Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review)

Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ

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[Intervention Review]

Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

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ABSTRACT

Background

Planning for outbreaks of influenza is a high priority public health issue for national governments. Neuraminidase inhibitors (NIs) are thought to help reduce the symptoms of influenza with several possible mechanisms proposed. NIs have been stockpiled with a view to their widespread use in the event of a pandemic. However, the evidence base for this class of agents remains a source of debate. In a previous review we have documented substantial risks of publication bias of trials of NIs for influenza (60% of patient data from phase III treatment trials of oseltamivir have never been published) and reporting bias in the published trials. Our confidence in the conclusions of previous versions of this review has been subsequently undermined. Since we have become aware of a large number of unpublished trials of NIs in the management of influenza, this review updates and merges existing reviews in this area.

Objectives

To review clinical study reports of placebo-controlled randomised trials, regulatory comments and reviews ('regulatory information') of the effects of the NIs oseltamivir and zanamivir for influenza in all age groups and appraise trial programmes, rather than single studies.

Clinical study reports are very detailed, unpublished clinical trial data containing in-depth descriptions of protocol rationale, methods analysis plans, trial results and organisational documents (such as contracts). A series of clinical studies designed and conducted by one sponsor represents a trial programme of a drug indication (for example treatment of influenza).

Search methods

We searched trial registries, cross-referencing published and unpublished sources and corresponded with manufacturers and regulators. We searched the archives of the US Food and Drug Administration (FDA) and European and Japanese regulators. The evidence in this review reflects searches to obtain relevant information up to 12 April 2011.

Selection criteria

We included regulatory information based on assessments of randomised controlled trials (RCTs) conducted in people of any age who had either confirmed or suspected influenza, or who had been exposed to influenza in the local community or place of residence. We included information which had been made available by our deadline.

Data collection and analysis

We indexed regulatory information in two purpose-built instruments and reconstructed trials using CONSORT statement-based templates. To progress to Stage 2 (full analysis) we sought manufacturer explanations of discrepancies in the data. GlaxoSmithKline (GSK) offered us individual patient data and responded to our queries, but Roche did not provide us with complete clinical study reports. In Stage 2 we intended to analyse trials with validated data (i.e. assuming our validation questions aimed at clarifying omissions and discrepancies were resolved). No studies progressed to Stage 2. We carried out analyses of the effects of oseltamivir on time to first alleviation of symptoms and hospitalisations using the intention-to-treat (ITT) population and tested five hypotheses generated post-protocol publication.

Main results

We included and analysed data from 25 studies (15 oseltamivir and 10 zanamivir studies). We could not use data from a further 42 studies due to insufficient information or unresolved discrepancies in their data. The included trials were predominantly conducted in adults during influenza seasons in both hemispheres. A small number of studies were conducted in older people residing in care homes and in people with underlying respiratory diseases. The studies had adequate randomisation and blinding procedures, but imbalances in the analysis populations available (ITT influenza-infected) left many of the studies at risk of attrition bias. All the studies were sponsored by manufacturers of NIs. Time to first alleviation of symptoms in people with influenza-like illness symptoms (i.e. ITT population) was a median of 160 hours (range 125 to 192 hours) in the placebo groups and oseltamivir shortened this by around 21 hours (95% confidence interval (CI) -29.5 to -12.9 hours, $P < 0.001$; five studies) but there was no evidence of effect on hospitalisations based on seven studies with a median placebo group event rate of 0.84% (range 0% to 11%): odds ratio (OR) 0.95; 95% CI 0.57 to 1.61, $P = 0.86$). These results are based on the comprehensive ITT population data and are unlikely to be biased. A post-protocol analysis showed that participants randomised to oseltamivir in treatment trials had a reduced odds being diagnosed with influenza (OR 0.83; 95% CI 0.73 to 0.94, $P = 0.003$; eight studies), probably due to an altered antibody response. Zanamivir trials showed no evidence of this. Due to limitations in the design, conduct and reporting of the trial programme, the data available to us lacked sufficient detail to credibly assess a possible effect of oseltamivir on complications and viral transmission. We postponed analysis of zanamivir evidence because of the offer of individual patient data (IPD) from its manufacturer. The authors have been unable to obtain the full set of clinical study reports or obtain verification of data from the manufacturer of oseltamivir (Roche) despite five requests between June 2010 and February 2011. No substantial comments were made by Roche on the protocol of our Cochrane Review which has been publicly available since December 2010.

Authors' conclusions

We found a high risk of publication and reporting biases in the trial programme of oseltamivir. Sub-population analyses of the influenza infected population in the oseltamivir trial programme are not possible because the two arms are non-comparable due to oseltamivir's apparent interference with antibody production. The evidence supports a direct oseltamivir mechanism of action on symptoms but we are unable to draw conclusions about its effect on complications or transmission. We expect full clinical study reports containing study protocol, reporting analysis plan, statistical analysis plan and individual patient data to clarify outstanding issues. These full clinical study reports are at present unavailable to us.

PLAIN LANGUAGE SUMMARY

A review of unpublished regulatory information from trials of neuraminidase inhibitors (Tamiflu - oseltamivir and Relenza - zanamivir) for influenza

We decided to update and amalgamate our reviews on the antiviral drugs zanamivir and oseltamivir for influenza on the basis of the manufacturers' reports to regulators (called clinical study reports) and regulators' comments (which we called regulatory information). Clinical study reports are extensive documents with exhaustive details of the trial protocol, methods and results. In view of the unresolved discrepancies in the data presented in published trial reports and of the substantial risk publication bias in this area, we elected not to use data from journal articles. Availability of documents generated by national and regional regulatory bodies during licensing processes in the UK, USA, continental Europe and Japan, partial trial reports from the manufacturers of oseltamivir and from the European regulator European Medicines Agency (EMA), enabled us to verify information from the trials. The authors have been unable to obtain the full set of clinical study reports or obtain verification of data from the manufacturer of oseltamivir (Roche) despite five requests between June 2010 and February 2011. No substantial comments were made by Roche on the protocol of our Cochrane Review which has been publicly available since December 2010. Based on our assessments of the documents we could obtain, we came to the conclusion that

there were substantial problems with the design, conduct and availability of information from many of the trials. Due to these concerns we decided not to proceed with a meta-analysis of all the oseltamivir data as we had intended. Instead we carried out analyses of effects on symptoms (shortens them by 21 hours or so) and hospitalisations (no evidence of effect) of people with influenza-like illness ('flu') on data from all the people enrolled in treatment trials of oseltamivir. Other outcomes could not be assessed due to unavailability of data for all the people enrolled in treatment trials of oseltamivir. Our independent analysis concurs with the conservative conclusions regarding the effects of both drugs by the US Food and Drug Administration (FDA). The FDA only allowed claims of effectiveness of both drugs for the prevention and treatment of symptoms of influenza and not on other effects (such as interruption of person-to-person spread of the influenza virus or prevention of pneumonia). There is evidence to suggest that both drugs are associated with harms (oseltamivir: nausea, vomiting; zanamivir: probably asthma). The FDA described the overall performance of both drugs as "modest". We expect full clinical study reports containing study protocol, reporting analysis plan, statistical analysis plan and individual patient data to clarify outstanding issues. These full clinical study reports are at present unavailable to us.

BACKGROUND

In the midst of the A/H1N1 outbreak in June 2009, the Australian and UK governments commissioned an update of our long-standing Cochrane review on neuraminidase inhibitors (NIs) for influenza in (otherwise) healthy adults. The review had first been published in 1999 and had a major update in 2006 and a minor update in 2008. At the same time a similar review on children had also been published (Shun-Shin 2009).

We initially anticipated that the update of the review would likely reflect only updated pharmacovigilance data and not the incorporation of new trial evidence. This was because NIs (especially oseltamivir, better known as Tamiflu) had become an established public health drug (see Glossary in Appendix 1).

In the end, the 2009 update was inconclusive (Jefferson 2010a) as we were unable to verify the data underlying manufacturer and government claims about the effectiveness of oseltamivir. The claims were based on clinical trial evidence included in a published non-systematic meta-analysis of 10 manufacturer-funded clinical trials of oseltamivir for the treatment of influenza in people of all ages (Kaiser 2003). Eight of the 10 trials in the Kaiser et al meta-analysis have never been published (Jefferson 2009a) and their complete data sets are not available from either the authors or the manufacturers. This review reports our efforts to get to the bottom of the issue of the effects of NIs by appraising evidence from unpublished clinical study reports (see Glossary Appendix 1) and regulatory documents containing comments and reviews. We have called the body of clinical studies and regulatory comments 'regulatory information'.

Description of the condition

Influenza is mostly a mild, self limiting infection of the upper airways with local symptoms, including sniffles, nasal discharge, dry cough, sore throat and systemic symptoms such as fever, headache, aches and pains, malaise and tiredness.

Occasionally patients with influenza develop complications such as pneumonia, otitis media and dehydration or encephalopathy with or without liver failure, that may be due to effects of the influenza virus itself or associated secondary bacterial infections and/or adverse effects of drugs such as antipyretics (including salicylates and other non-steroidal anti-inflammatory drugs) (Hama 2008).

Influenza is not clinically distinguishable from influenza-like illness (ILI) (Call 2005). Epidemic influenza in humans is caused by influenza A and B viruses. Currently, influenza A/H1N1, influenza A/H3N2 and influenza B cause most influenza infections worldwide (CDC 2010).

Description of the intervention

NIs comprise inhaled zanamivir (*Relenza*, GlaxoSmithKline), oral oseltamivir (*Tamiflu*, Gilead Sciences and F. Hoffman-La Roche), parenteral *Peramivir* (BioCryst Ltd), inhaled *Laninamivir* (Daiichi Sankyo Co. Ltd) (Sugaya 2010) and others still under development (Hayden 2009). The use of NIs has increased dramatically since the outbreak of A/H1N1 in April 2009, partly because of the rise in amantadine/rimantadine resistance and, in the early stages of the outbreak, the lack of a vaccine, which meant that NIs became a widespread public health intervention. The World Health Organization (WHO) had previously encouraged member states to stockpile and gain experience of using NIs (WHO 2002a; WHO 2002b; WHO 2004).

How the intervention might work

Although NIs may reduce the ability of the virus to penetrate the mucus in the very early stage of infection (Bhatia 2007;

Matrosovich 2004; Moscona 2005; Ohuchi 2006), their main mechanism of action is thought to lie in their ability to inhibit influenza viruses to exit host cells (Liu 1995; Moscona 2005). The manufacturers state that oseltamivir does not prevent infection, nor affect antibody production (Smith 2006) but reduces symptom duration probably by reducing viral load, spread and release of cytokines (Hayden 1999b; WV15670), diminishing the chance of complications and interrupting person-to-person viral spread.

Oseltamivir phosphate (OP) (*Tamiflu*) is the pro-drug of oseltamivir carboxylate (OC), the effective form. OP dissociates in the gastrointestinal tract to form oseltamivir (OT) which is absorbed and metabolised into OC by hepatic carboxylesterase (hCE). OT may induce hypothermia (Ono 2008), possibly due to a central depressant action (Hama 2008) and may also inhibit human sialidase (Li 2007), causing abnormal behaviour.

Inhaled zanamivir reaches a far lower plasma concentration compared to its intravenous administration (Cass 1999).

Any treatment that reduces the complications of influenza (for example, pneumonia) and the excretion of virus from infected people might be a useful public health measure to contain an epidemic by limiting the impact and spread of the virus. In addition to symptomatic treatment, prophylactic use for interrupting the spread of disease has informed pandemic planning over the past decade.

Why it is important to do this review

There are three major reasons for conducting this review.

1. Oseltamivir is a commonly used and stockpiled drug against past and future pandemics on the basis of international and national recommendations. These recommendations are based on the claimed and assumed ability of oseltamivir to reduce complications and transmission (HHS 2005; WHO 2007).
2. There are now legitimate reasons to doubt these claims and the results of previous Cochrane reviews of NIs in adults and children due to the risk of reporting bias, including the risk of publication bias.
3. Oseltamivir is now on the list of WHO essential drugs.

Most attention has been focused on oseltamivir because it is used as a prescription drug for patients suffering from influenza and for prophylaxis and interruption of person-to-person spread (transmission) during epidemics and pandemics. In line with the WHO recommendation (WHO 2002a; WHO 2002b), governments around the world spent billions of dollars stockpiling it as a public health measure, under the assumption that in an emergency such as a pandemic, there would be insufficient time to manufacture sufficient quantities of antivirals to meet demand. Oseltamivir is one of the key interventions in the WHO's 2007 influenza pandemic rapid containment plan. Its key role rests on its assumed ability to contain the spread of influenza, either buying time for an organised response with longer-term interventions (such as vaccines) which take time to produce, or completely stopping an emergent pandemic (WHO 2007).

Prior to the emergence of influenza A/H1N1 in 2009, governments worldwide stockpiled nearly CHF 7.6 billion worth of oseltamivir (Jack 2009). The WHO has recently recommended oseltamivir be added to the list of essential medicines (WHO 2011) and oseltamivir has been prescribed for the treatment of influenza worldwide after the outbreak of 2009 A/H1N1 influenza.

Oseltamivir has been prescribed far more than zanamivir, most likely because of its ease of administration and storage. Another key manufacturer claim of the effects of oseltamivir is its ability to prevent complications of influenza (for example, pneumonia) if taken within 48 hours of influenza symptoms appearing. This claim is based on the Kaiser et al meta-analysis (Kaiser 2003).

The US Health and Human Services (HHS) Pandemic Influenza Plan assumed oseltamivir would greatly reduce complications, hospitalisations and mortality (HHS 2005). No evidence was provided for this critical assumption. The 2004 draft version of the Pandemic Plan indicates that the claim was based exclusively on the Kaiser et al meta-analysis (HHS 2004). However a more recent HHS publication anachronistically references additional, more recent studies as the rationale for the 2005 recommendation for the use of antivirals (HHS 2008). Since 2005 the Kaiser et al meta-analysis has also been the sole publication that the US Centers for Disease Control and Prevention (CDC) cited in support of similar claims about the effectiveness of oseltamivir in its influenza treatment guidelines (CDC 2005; CDC 2011). The Kaiser meta-analysis was supported by the manufacturer (Kaiser 2003).

Process

This review is focused on healthy adults and children. It represents the amalgamation of two long-standing Cochrane reviews on the effects of NIs for influenza in healthy adults (Jefferson 2010a, also published as Jefferson 2009a) and children (Matheson 2007). The reviews were combined to pool our collective expertise and time in extracting and assessing data from clinical study reports, which in the case of some oseltamivir trials, report both adult and paediatric outcomes. Cochrane reviews of NIs in both children and adults generated intense interest from clinicians and media during the influenza outbreak declared a pandemic by the WHO in 2009. The Cochrane review of NIs in healthy adults highlighted the high risk of publication bias (Jefferson 2010a).

In 2009, a reader posted a comment in response to the (then current) 2006 version of this review (Jefferson 2006). He pointed out that the review had endorsed the claim regarding a reduction in complications based on the uncritical inclusion of the Kaiser meta-analysis (Doshi 2009). The reader pointed out that only two of the 10 'Kaiser trials' had been published (Nicholson 2000; Treanor 2000) and the information provided by the Kaiser text about the remaining eight was insufficient for their appraisal. Our subsequent efforts to retrieve and review the eight unpublished

trials (representing 2691 patients) were unsuccessful, raising the possibility that the findings of our previous review were not an accurate estimate of the benefits and safety of the drug. In addition, we found clear evidence of possible publication bias (see below) amid concern that some evaluations have not been available to scrutiny by the scientific community (Cohen 2009; Doshi 2009; Freemantle 2009; Godlee 2009).

Our attempts to reconcile published and unpublished evidence by contacting the manufacturer and study authors failed (the latter were unable to provide us with the necessary data; some were not in possession of the data and others may have been restricted by confidentiality agreements). Together with the *British Medical Journal* (BMJ) we ascertained that ghost writers had been involved, which means the named authors may not have been in full control of the trial publications (Cohen 2009). We also identified several key differences in licensed indications for oseltamivir between regulatory systems (mainly between the US, Europe and Japan) and under-reporting of harms. The differences are detailed elsewhere (Doshi 2009) but of particular concern was the insistence of the FDA that oseltamivir has not been shown to reduce complications (FDA 2011a). The FDA has also not allowed an indication for interference of viral transmission within households (the key concept behind post-exposure prophylaxis). This undermined our confidence in published data and in the findings of our previous Cochrane reviews. In the background of all this were suggestions that NIs may not be as safe as previously assumed, with associations between oseltamivir use and neuropsychiatric adverse reactions of particular concern (Hama 2008).

In response to the 2009 update of our Cochrane review of NIs in healthy adults (Jefferson 2009a), oseltamivir's manufacturer pledged to make "full study reports" available for the 10 Kaiser treatment trials (Smith 2009). These reports, known as clinical study reports, are unabridged reports of clinical trials generated by trial sponsors primarily as part of submissions to regulators (see Glossary, Appendix 1). An individual clinical study report can be hundreds or even thousands of pages in length, containing far more detail than journal publications.

We decided that in the face of uncertainty over the published evidence base of the drug, obtaining unpublished clinical study reports should allow us to clarify the effects. We therefore decided to update our review using clinical study reports as well as regulatory documents that could be obtained either through already available sources or through requests under US and European Freedom of Information (FOI) laws (see Glossary, Appendix 1). We reasoned that regulatory data could help contextualise trial data, providing deeper insight than clinical study reports alone (Jefferson 2011).

Examples of discrepancies and publication bias

The release in January 2010 of partial clinical study reports by Roche allowed us to undertake an initial comparison of these reports with what was already published and in the public domain. While Roche only released a portion of its full clinical study reports (Module 1), these reports nonetheless contained a summary of the study methods and results, totaling over 3000 pages and indicated inconsistencies in the published record of trials. For example, the two most cited published trials of oseltamivir either did not mention serious adverse events (Nicholson 2000), or stated that "... there were no drug-related serious adverse events" (Treanor 2000). This finding has been repeated by bodies such as the UK National Health Service (NHS) ("No serious adverse events were noted in the major trials and no significant changes were noted in laboratory parameters") (UKMIPG 2001). However, the clinical study reports' Module 1 describe 10 serious adverse events (in nine participants) in the two trials (WV15670; WV15671), three of which were classified as possibly related to the study drug (oseltamivir). Similarly, a published prophylaxis trial (Hayden 1999a, known by its trial ID WV15673/WV15697) describes headache as having "occurred in similar proportions of subjects in the three groups (39 to 47 per cent)." However, for this trial, data within Japanese regulatory documents (JSBA; see Glossary, Appendix 1) show that 75 mg twice daily (bid) oseltamivir (high-dose group) versus placebo group yielded an odds ratio (OR) for headache of 1.37 (95% confidence interval (CI) 1.06 to 1.76, P = 0.014 by Fisher's exact test; two-sided) and evidence of a dose response effect of oseltamivir on headache: Chi^2 test for linear trend = 6.148 (P = 0.013). In addition, JSBA documents show a total of 584 (314 in oseltamivir group, 270 in placebo group) nervous system-related adverse events and 37 (24 and 13, respectively) psychiatric adverse events during the on-treatment period in three prophylaxis trials. However, we found no published paper of an oseltamivir trial which reported nervous or psychiatric adverse events, except headache.

We identified that 60% (3145/5267) of patient data from randomised, placebo-controlled phase III treatment trials of oseltamivir have never been published. This includes M76001, the biggest treatment trial ever undertaken on oseltamivir (with just over 1400 people of all ages). Exclusion of unpublished data changed our previous findings regarding oseltamivir's ability to reduce complications of influenza (Doshi 2009; Jefferson 2009a).

A modified approach

During the preparation of the 2010 review and of the current review, we realised that there were multiple sources and different levels of granularity of clinical trial data (see 'The Scope of Clinical Trial Data' table in Jefferson 2011). We decided that clinical study reports and regulatory comments were likely to provide the least biased, most complete and most insightful set of data for our review.

We have modified the routine Cochrane processes to improve our previous inadequate methods. To resolve inconsistencies and under-reporting, we changed our approach by no longer including trial data as reported in papers published in biomedical journals.

Instead, we treated clinical study reports as our basic unit of analysis. Clinical study reports are often sent to national drug regulators such as the FDA and the European Medicines Agency (EMA), formerly EMEA, which require far more stringent standards for completeness and accuracy of reporting than biomedical journals. Journal articles can be regarded as a very succinct synthesis of a clinical study report. In addition to seeking clinical study reports, we decided to read and review regulatory documentation. The FDA, in particular, and the EMA to a far lesser extent, make many of its scientific reviews available on its web site. Unlike Cochrane review authors, regulators can have access to the whole data set and their comments can provide useful insight, helping achieve a better understanding of trial programmes.

Clinical study reports generally remain hidden from public view and are not readily available for wider scientific scrutiny, despite the wealth of information they contain for those willing and able to spend the time reading them and despite calls to make all relevant trial data public (Godlee 2009) and the known problems with reporting biases (McGauran 2010).

In the case of oseltamivir, after Roche offered to make available full study reports for the ten treatment trials appearing in the Kaiser meta-analysis (Smith 2009), Roche expressed in email correspondence a willingness to consider making information for additional trials available as well (personal correspondence, 20 August 2010). GSK gave a similarly positive response to our enquiries. We therefore requested original clinical study reports for all trials identified meeting our inclusion criteria. We made similar FOI requests to the FDA and EMA. We also contacted BioCryst Ltd, makers of peramivir, for similar information. As BioCryst indicated that no clinical study reports would be available until FDA registration of its drug, we did not seek any further information and have restricted the scope of this review to the oseltamivir and zanamivir.

Implications

This modified approach to a Cochrane review aims to provide patients, clinicians and policy-makers with the most transparent and independent information possible about NIs for influenza. In addition it should contribute to a European regulatory and pharmacovigilance legal framework which commentators declare to be weak (Cohen 2009; Godlee 2009). We believe that as NIs have become public health drugs, recommended and stockpiled globally, independent scrutiny of all the evidence relating to harms and effects on complications is necessary to provide a complete and unbiased view of their performance.

Implication for A/H1N1 (2009) influenza

In response to our 2010 review (Jefferson 2009a; Jefferson 2010a), some have argued that its findings cannot be applied to the 2009 A/H1N1, suggesting that it is a new virus and thus we need new evidence (JAID 2010; Maugh 2009; Nebehay 2009; NHS 2009; NHS 2010). Novel A/H1N1 is a new strain of a subtype that has been circulating since 1977, but it also resembles the A/H1N1 strain that has been circulating before 1957 (CDC 2009) or before the 1918 pandemic (Itoh 2009). Influenza subtype A/H1N1 was indeed circulating in the clinical trials we have included in our previous reviews. In addition, oseltamivir and zanamivir were approved by regulators worldwide for the treatment and prevention of influenza types A and B, not specific subtypes or strains of influenza A and B. The expectation of regulatory approval is thus that the effects of these drugs demonstrated in clinical trials will apply to future strains of influenza A and B. Use of these drugs during the pandemic was not off-label. It was approved use because of the assumption that the clinical trial evidence underpinning regulatory approval applied to novel A/H1N1. We reviewed the clinical trial evidence with the expectation that our results, similar to regulators, will apply to all influenza viruses.

Wider implications

The modified approach in this Cochrane review grew out of a realisation that prior methods employed to review NIs were inadequate. There seems no compelling reason to think that the lessons learned are limited to these particular drugs (Godlee 2009). For this reason, our independent scrutiny using all possible trial information may inform the wider debate on the adequacy of existing regulatory frameworks in the adoption of new drugs and whether other systematic reviews should move to this new more rigorous approach which focuses on trial programmes rather than single trials (Eyding 2010; Ioannadis 2010) (see Glossary, Appendix 1). Although there is substantial evidence for the effects of reporting bias in estimates of effectiveness, less is known of its impact on the evidence of harms (Chou 2005). We decided to quantify the additional resources required to follow our modified methodological approach to assess the feasibility of other systematic reviews proceeding in a similar fashion.

See the Differences between protocol and review section for the previous version of the objectives of this review.

OBJECTIVES

To review clinical study reports identified from published and unpublished randomised controlled trials (RCTs) and relevant regulatory data on effectiveness and harms of NIs for influenza in all age groups.

METHODS

Criteria for considering studies for this review

Types of studies

We included evidence from RCTs testing the effects of NIs for prophylaxis, post-exposure prophylaxis (PEP) and treatment of influenza. Prophylaxis is the mode of use of NIs when there is expectation of possible near-future exposure to influenza. PEP is the use of NIs following probable exposure to influenza but before symptoms develop. Treatment is the use of NIs in persons showing probable signs of influenza.

Due to discrepancies between published and unpublished reports of the same trials, we decided to include only those trials for which we had unabridged clinical study reports (for example, with consecutively numbered pages), even though they may be parts of clinical study reports (i.e. Module 1 only) and information on reports of trials which were considered 'pivotal' (i.e. first or second-line evidence to regulators in support of the registration application).

Types of participants

We included previously healthy people (children and adults). 'Previously healthy' includes people with chronic illness (such as asthma, diabetes, hypertension) but excluding illnesses affecting the immune response (such as cancer and AIDS). We included only trials on people exposed to naturally occurring influenza with or without symptoms.

Types of interventions

NIs administered by any route compared with placebo or standard care during the period in which medication was assumed and during the follow-up (on and off-treatment (on-t and off-t) periods.

Types of outcome measures

Primary outcomes

Primary outcome measures for treatment studies.

1. Symptom relief
2. Hospitalisation and complications
3. Harms

Primary outcome measures for prophylaxis studies.

1. Influenza (both symptomatic and asymptomatic and laboratory-confirmed) and influenza-like illness (ILI)
2. Hospitalisation and complications
3. Interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts)
4. Harms

Secondary outcomes

Secondary outcome measures for treatment studies.

1. Symptom relapse after finishing treatment
2. Drug resistance
3. Viral excretion
4. Mortality

Secondary outcome measures for prophylaxis studies.

1. Drug resistance
2. Viral excretion
3. Mortality

We wanted to assess listed secondary outcomes, although recognising that these may be less relevant, less reliably measured, or analysed with multiple statistical tests or may have been inadequately powered to detect an effect on mortality.

Whilst overall symptom reduction is well documented, our interest was particularly focused on complications and adverse events, as this is where evidence is currently scarce or inconclusive (Jefferson 2009a; Shun-Shin 2009). Our preliminary examination of some regulatory documents and some published versions of the studies had identified that some symptoms and sequelae of influenza (such as pneumonia) had been classified as either a 'complication of influenza' or as an adverse event of the treatment'. This is somewhat confusing and we intended to analyse 'compliharms' (see Glossary, Appendix 1) irrespective of the classification as a 'complication of influenza' or as an 'adverse event of the treatment' (Appendix 2) in oseltamivir trials. In post-exposure prophylaxis trials we focused on evidence of interference with viral transmission. A positive balance of effects on complications and viral spread versus harm profile is the main reason for using NIs, especially oseltamivir.

Search methods for identification of studies

Searching an unpublished and hitherto unseen data set requires constructing a reasonably accurate list of all studies of the drug in question. The obvious source of such information would be trial registries but most trials of both NIs were carried out before inception or wide acceptance of centralised registries. As single, authoritative, up-to-date and complete lists of all clinical trials conducted on humans using a given drug are rarely available in the public domain, there was no alternative to constructing our own. We decided to do so by using multiple, cross-referencing methods. We constructed a list beginning with clinical trials identified from previous review updates. To this end, we added additional trials in humans from multiple sources, including manufacturer submissions to regulators, drug product information sheets, previous published reviews, Health Technology Assessment (HTA) documents and public and manufacturers' registers (Burch 2009; Cooper 2003; Jefferson 2006; Tappenden 2009; Turner 2003), such as www.ClinicalTrials.gov and www.roche-trials.com. Regulatory documents also aided the identification of unknown trials (see also Searching other resources). Finally, we also conducted

traditional database searches (Appendix 3) and searches of grey literature to identify previously unknown trials.

To ensure the list did not include duplicate entries, we assigned each trial a Unique Trial ID. 'Author' is not a good choice of Unique Trial ID, as different authors can be present across different versions of the same trial (that is, the authors of clinical study reports can be different from publications arising from the same clinical trial). Nor are any other details connected to publications a good option for Unique Trial ID because not all studies are published. Some trials will have company-specific codes and some will have public clinical trial registry numbers, or both or neither. The majority of trials cited in this review are manufacturer-funded (with corresponding manufacturer protocol IDs) and to simplify recognition and terminology we have used the manufacturer protocol ID as our Unique Trial ID.

A list is only helpful so long as it has sufficient details to enable us to decide whether it meets our inclusion criteria. For each Unique Trial ID, we gathered the following details.

1. Unique Trial ID
2. Other IDs
3. Phase of study
4. Sponsor
5. Short description
6. Official trial title
7. First authors (name and email)
8. Type of trial
9. Comparator
10. Outcomes assessed
11. Date of trial
12. Study period (days)
13. Population
14. Number of participants planned
15. Number of participants enrolled
16. Number of participants completing
17. Trial status (for example, completed, ongoing or early termination)
18. Publication status (a citation or understanding of why it was not published)
19. How identified (to record how the trial was discovered)
20. Notes

Once we had as complete a list of trials as possible, we contacted manufacturers and sent them our draft list, asking them to check accuracy and completeness of our list. Roche, GSK and BioCryst all did so, and in doing so we learned of hitherto unknown trials. Occasionally, the existence of other hitherto unknown trials was detected weeks and months after we thought we had a 'complete' list. We feel this is inevitable given that trial identification often takes place in unpredictable ways, for example while reading through detailed regulatory reports. We engaged in prolonged correspondence with both manufacturers and requested a series of regulatory documents under FOI law from both the FDA and EMA.

Electronic searches

We updated our searches of the electronic databases of published studies previously carried out for the Cochrane reviews on NIs in children (Matheson 2007) and healthy adults (Jefferson 2010a). The purpose of the searches was to identify trials previously unknown to the review authors. See Appendix 3 for details.

Searching other resources

We searched the following sources.

1. The FDA
2. The EMEA
3. Roche
4. Japanese regulator (PMDA) SBA
5. National Institute for Health and Clinical Excellence (NICE) 2000 submission by Roche and GSK

We conducted a search of the FDA regulatory documentation of the New Drug Applications (NDA) and supplementary New Drug Applications (sNDA) of both drugs (FDA 2011b). The FDA NDA documentation includes medical, statistical, microbiological and other reviews, product labels, reports of site inspections, meetings with manufacturers and records of the decision-making leading to registration and post-marketing requirements. We also searched 'Warning Letters' dispatched by the FDA (FDA 2011c).

To organise receipt of FDA materials, we created a Table of Contents (TOC) listing all the regulatory and pharmaceuticals documents accessible to us. The TOC's function was that of an index, searchable quick reference guide, and research tool to enable us to carry out quantitative (e.g. citation density analysis) and qualitative analyses (e.g. theme summaries) of the content. We also needed a rapid aide memoir with brief summaries of the evidence contained in each regulatory document listed in the TOC. We called this aide memoir the TOCE (Table of Contents-Evidence). As the TOCE contains copious working personal notes aimed to understand the regulatory narrative, we have not reproduced it here, but its content is woven into the narrative of this review.

Due to the length and format of regulatory documents, we realised in building the TOC that there was a need to formalise the search and identification methods of trials referenced in the FDA documentation. We concentrated on where each trial is mentioned in the documentation by its pharmaceutical code. So, for example if trial WV15670 is mentioned 60 times by that code in a particular file, then the TOC will report the page numbers in which it is cited, which could be any number up to 60. The unit of search was the file, as a FDA PDF file can contain many different types of documents scanned into the same file. TOC and TOCE are among the tools we specifically constructed for the review (Appendix 1).

We wanted to validate our new methods, therefore we compared the yield of Optical Character Recognition (OCR) searching and handsearching of the PDF files of the FDA regulatory material using the same trial ID as a working example.

We also searched the material sent to us by Roche for our 2009 update, Roche's and GSK's 2000 submissions to the UK National Institute for Health and Clinical Excellence (NICE).

We searched the web site of the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) http://www.info.pmda.go.jp/shinyaku/shinyaku_previous_index.html for data relating to NIs approved in 1999 and 2000, and http://www.info.pmda.go.jp/approvalSrch/PharmacySrchInit for NIs approved since 2001. We identified 1575 pages of documents relating to the regulatory review by the PMDA and the Japanese Ministry of Health, Labor and Welfare (JMHLW) and the Japanese SBA of oseltamivir treatment and prophylaxis of children and capsules for prophylaxis of influenza and their re-examination results. The Japanese regulatory body introduced the system to disclose their examination results and SBA in 1999 instead of the prior system, 'full disclosure requirement system', which had been introduced in 1967. Although these documents included preclinical, methodological, clinical, (pharmacological, toxicity and pharmacokinetic) data and clinical (phase I to phase III) studies and contain more precise data than the published papers, no complete clinical study reports were publicly available. Therefore, one review author (RH) asked the JMHLW on 29 July 2010 to disclose all documents reporting the evidence base for the approval of oseltamivir for these indications. The JMHLW sent RH a letter of refusal dated 2 September 2010, with the explanation "because the disclosure of such documents might hurt the right, position or other fair benefit in the competition of the corporation concerned". We waited six months to take further action hoping that the required clinical study reports would be forthcoming from the manufacturers. When this did not happen, RH filed a petition to overturn the JMHLW decision with the Osaka (Japan) District court on 28 February 2011. At the time of writing no decision has been made yet.

Data collection and analysis

Collection and inventory of the evidence base was facilitated by the tools specifically developed for the review (Appendix 1). The overall risk of bias is presented graphically in Figure 1 and summarised in Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies."Other bias" includes potentially active placebos.

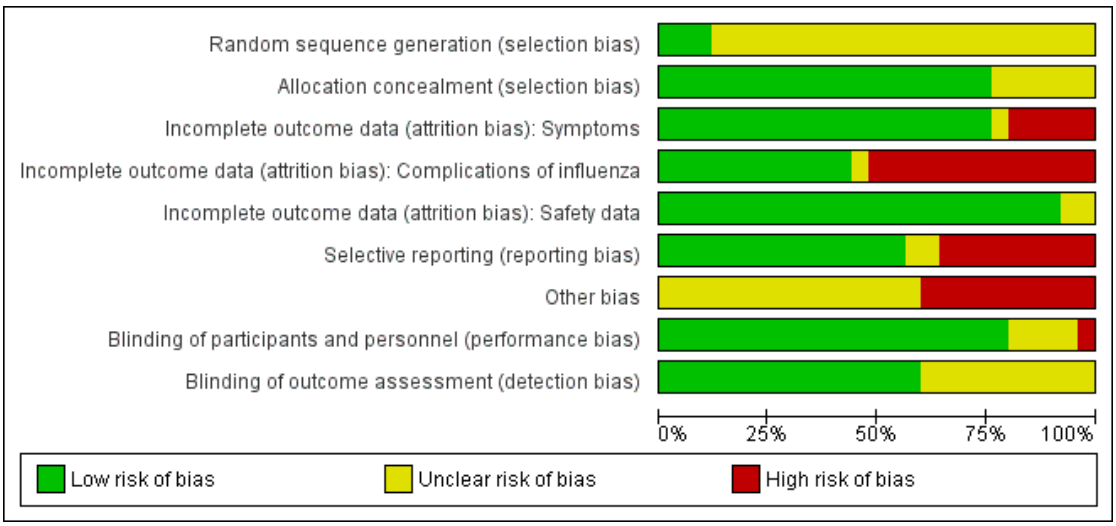
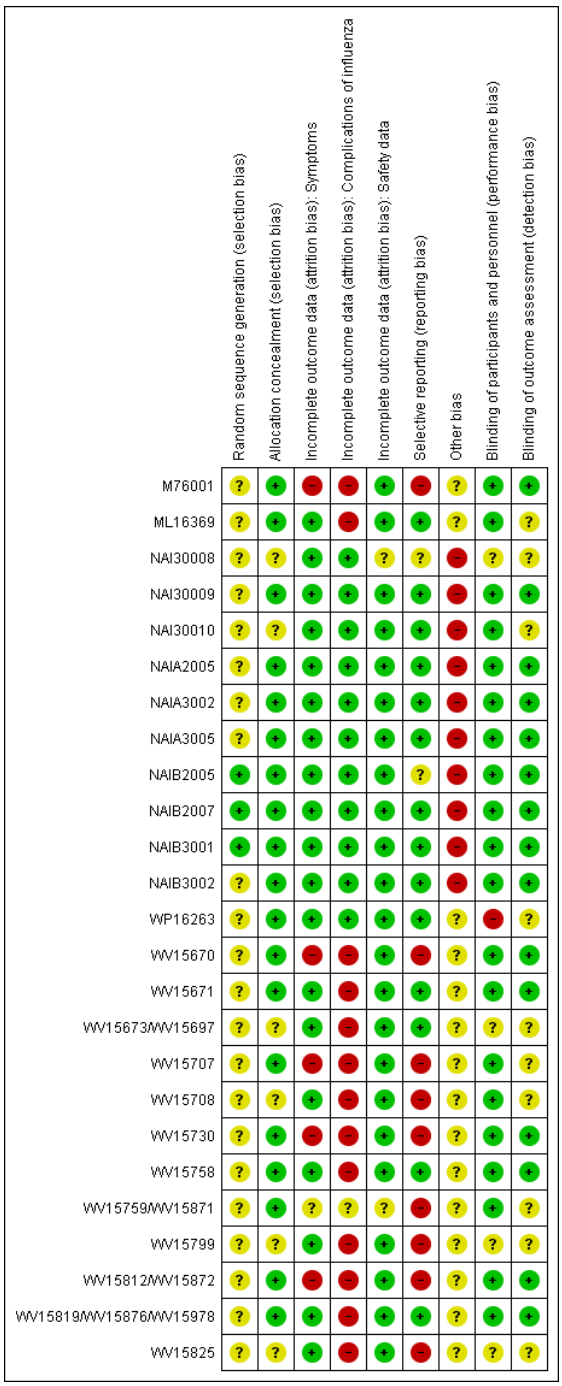


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study."Other bias" includes potentially active placebos.



Selection of studies

Two review authors (CDM, MT) independently scanned the titles and abstracts identified from the searches of the published literature. None of the identified items were published versions of trials unknown to us. Four review authors (TJ, CH, MJ, RH) independently read all data relating to the studies on the list constructed during our search and selected studies that seemingly fulfilled our inclusion criteria. One review author (PD) compiled the assessments into a single sheet for another review author (CDM). One review author (CDM) resolved disagreements by discussion.

We assigned three categories to identified trials from our complete list:

1. definitely included;
2. definitely excluded; and
3. trials for which we needed further information.

We excluded studies definitely not meeting inclusion criteria on the basis of available information (e.g. the title described the trial as a pharmacokinetic study). Where appropriate we requested further information from the trials' sponsor, usually copies of the clinical study reports (minus participant identification) for each trial that was definitely included or for which we needed further information. We did not contact first/corresponding authors of published versions of the trials on the basis of our experience with the 2009 review.

Data extraction and management

We subdivided the extraction, appraisal and analysis of the data into a two-stage exercise. In Stage 1 we assessed the reliability and completeness of the identified trial data. We decided to only include data in Stage 2 of the review (full analysis following standard Cochrane methods) if they satisfied the following three criteria.

1. Completeness. Clinical study reports/unpublished reports include both identifiable CONSORT statement-specified methods to enable replication of the study. Identifiable CONSORT statement-specified results (primary outcomes, tables, appendices) must be available.
2. Internal consistency. All parts (for example, denominators) of the same clinical study reports/unpublished report are broadly consistent.
3. External consistency. Consistency of data as reported in regulatory documents, other versions of the same clinical study reports/unpublished reports and other references, to be established by cross-checking.

Assessing aspects 2 and 3 was part of our data validation strategy. We reasoned that unclear or inconsistent items would have to be clarified with the manufacturers. Unclear, inconsistent or no answers would lead to the exclusion of the study from Stage 2 of the review. As we had decided to review trial programmes, instead of single trials, we would also have to make a decision as to whether exclusion of one or more trials from Stage 2 of the review would negate any attempt at a fair assessment of the relevant trial programme.

Stage 1

Two review authors assessed each study (with studies allocated randomly to three pairs of review authors). The lists of included studies (33 for oseltamivir, 30 for zanamivir, six for peramivir) were randomly created by the program Edgar II (Brown 2011). Every study was openly allocated to each group according to its number.

We initially included six peramivir trials in the randomisation/allocation sequence but subsequently decided not to proceed further, as we were informed by the manufacturers that no clinical study reports would be available until after registration with the FDA (correspondence with Bill Sheridan, 20 August 2010). One review author (TJ) was assigned to the attempted reconstruction of clinical study reports from the FDA documents.

Two weeks before 'time lock' (see Glossary in Appendix 1) we received the first batch of clinical study reports from the EMA (formerly EMEA), containing an additional four clinical study reports (including one complete four-module clinical study reports) of studies we wanted to include. This time random allocation was achieved by writing trial IDs on one set of tickets and asking an external researcher to allocate them to groups, the names of which had been written on another set of tickets.

Authors in pairs separately extracted data from the same clinical study reports of studies included in Stage 1 of the review. When we had more than one copy of the same clinical study reports from different sources (for example, clinical study reports submitted to a regulatory body and clinical study reports from a pharmaceutical company) we independently extracted data from each of the copies and then compared the results. We aimed to record and tabulate disagreements between data extracted from the same source and between different sources. We extracted data using a modified CONSORT statement-based extraction template (Appendix 4).

The modified CONSORT-based extraction template aimed to assemble a concise version of the clinical study reports which will include all important methods as well as define and extract all relevant outcomes. The CONSORT-based extraction template includes the features that would be expected to be found in a published trial report but in far greater detail. Our reconstructions do not include introduction or discussion sections. We extracted the following for each trial.

1. Background and objectives.
2. Methods: including trial design, important changes to methods after trial commencement (such as eligibility criteria),

with reasons.

3. Participants: including eligibility criteria for participants and settings and locations where the data were collected.

4. Interventions: the interventions for each group with sufficient details to allow replication, including how and when they were actually administered.

5. Outcomes: pre-specified primary and secondary outcome measures, including how and when they were assessed and changes to trial outcomes after the trial commenced, with reasons.

6. Sample size: how it was determined and explanation of any interim analyses and stopping guidelines.

7. Randomisation: including sequence generation and method used to generate the random allocation sequence.

8. Blinding: who was blinded after assignment to treatment groups.

9. Statistical methods: methods used to compare groups for primary and secondary outcomes and methods for additional analyses, such as subgroup analyses and adjusted analyses.

10. Results: participant flow, numbers of participants randomly assigned, losses and exclusions after randomisation, together with reasons. Baseline demographic and clinical characteristics for each group.

11. Outcomes: primary and secondary outcome results for each group.

12. Ancillary analyses: results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory.

13. Harms: all important harms or unintended effects in each group.

One review author completed the CONSORT-based extraction on the template in full (Appendix 4) with the name and date of completion and a statement of conflict of interests. A second review author checked the extraction. We extracted data, text, tables and figures directly from the relevant sections of the clinical study reports into the appropriate section of the template. We did not change the text in any way apart from clarifying abbreviations or spellings, but we highlighted some text. We used three types of text highlighting in the document.

Yellow: where text, figures or tables need to be checked with further information (for example, if an adverse event is referred to in appendices or a further clinical study reports module).

Red: where text or comments were inserted by one or both review authors but required an additional opinion due to concerns that there is the potential for discrepancies in the clinical study reports.

Green: any text or tables added by us to the template (for example, a reconstructed table of adverse events).

Two review authors (CH, MT) independently piloted the reconstruction method on oseltamivir trial WV15671 with data from Module 1 of the clinical study report from Roche and data submitted to UK NICE. We discussed the pilot reconstruction amongst the whole review team for clarification. At a face-to-face meeting we discussed the reliability and completeness of each reconstructed trial in the light of comments and other information from regulatory sources with a view to inclusion of the trial in Stage 2. We resolved all differences in opinion by consensus. We reached decisions on whether a trial moved to Stage 2 by consensus. We planned to record dissent when consensus was not possible.

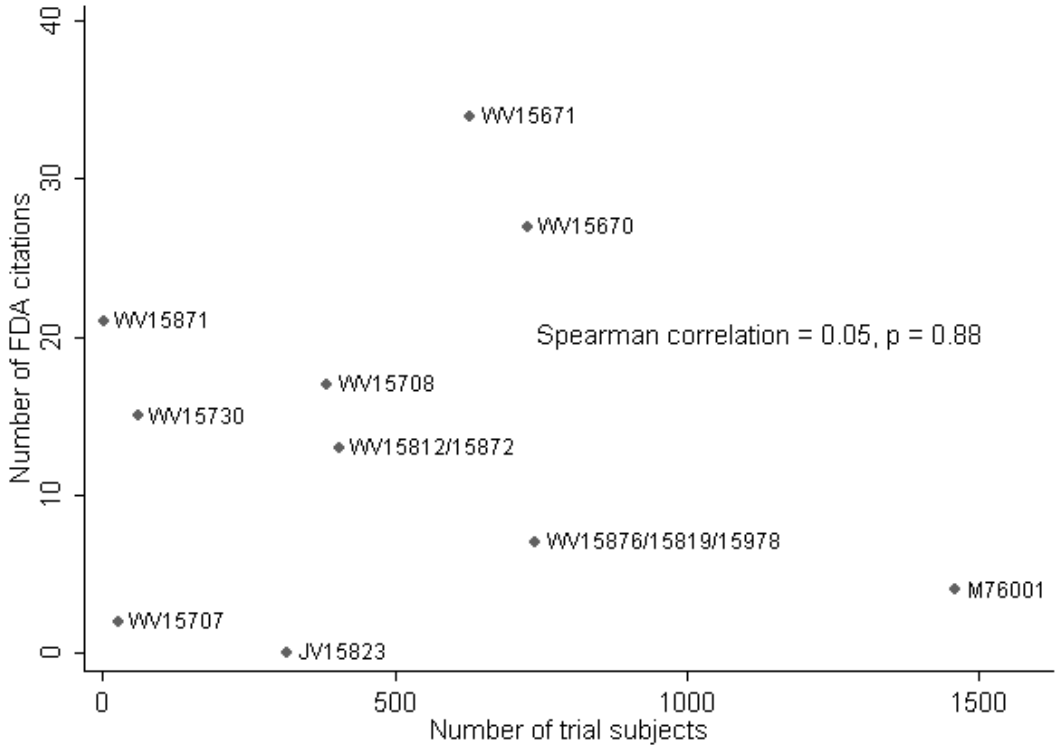
Stage 2

We intended to carry out Stage 2 on the basis of standard Cochrane methods for extracting, appraising and synthesising the evidence (two review authors independently extracting data, with a third review author arbitrating). Data would be extracted onto standard forms, checked and recorded. As no studies reached Stage 2, none of these procedures were carried out.

Regulatory information

We used regulatory information listed in the TOC to assess possible correlation between citation incidence of oseltamivir treatment trials in the FDA regulatory documents and trial characteristics, chiefly size. We found that there was no correlation. The biggest treatment trial, M76001, is cited only four times in three documents, while other contemporary treatment trials (WV15670; WV15671; WV15730; WV15812/WV15872; WV15707) are cited far more (Figure 3). WV15670, for example, is cited 46 times in the FDA documents. However, the combined enrolled denominator of the four treatment trials completed at the time (WV15670; WV15671; WV15707; WV15730) was 1442, smaller than M76001 (1459). This suggested that the FDA's regulatory evaluation of Roche's New Drug Application was based predominantly on what Roche had offered them as 'pivotal' or trials which best demonstrated the properties of oseltamivir, not the complete evidence base of all oseltamivir trials. One possible alternative explanation for this observation could have been the interval between trial completion, generation of the report and New Drug Applications (NDA) submission. This explanation is supported by the relatively brief interval between completion of the M76001 trial (19 February 1999) and submission (on 30 April 1999) of NDA 021087 to FDA. However, the core part of the submission (the clinical development programme) contains data from two (at the time) ongoing trials (WV15819/WV15876/WV15978; WV15812/WV15872).

Figure 3. Citation rate by oseltamivir treatment trial size in FDA documents.



The basis of the selection of trials to regulators is therefore unclear but must be dictated by criteria other than availability and size. The importance of trials (to manufacturers and possibly to regulators) may not be based on the same criteria that we would use (i.e. the capability of the trial to answer questions).

Due to the vast size of FDA documents, sometimes hundreds of pages long, it was difficult to determine by reading alone important emerging themes. To identify items of interest in the FDA comments we used word clouds (Feinberg 2009). Word clouds give greater prominence to words that appear more frequently in the source document. The resulting graphic representation showed words such as 'diary' and 'baseline' to be heavily mentioned in the relevant (abridged) text from the FDA's Medical Officer Review (FDA 1999c, PDF page 19). Examining the 'diary' entry in more detail, we found the following FDA comment:

"The majority of subjects participating in the treatment trials had only used the first diary card. The second diary card was issued in 15% to 20% of participants. In response to FDA's request, the applicant provided a summary of diary card dispensing in the 8/6/99 submission. It became apparent that instructions on when to start a second diary card were not uniformly followed in WV15670, WV15671, and WV15730 trials. There were examples of patients who had alleviated symptoms yet also received a second diary card. Conversely, there were also examples of patients who did not alleviate all symptoms but did not receive a second diary card. Thus the second diary card was used inconsistently which is viewed as a flaw of these trials. The lack of consistency in collecting symptom information after alleviation precluded a complete documentation of symptom fluctuation. Also missing second diary cards in subjects who had not alleviated symptoms were responsible for the majority of censored data which may have potentially influenced the results of efficacy analysis. In order to address the impact of censoring, the applicant performed several sensitivity analyses which will be summarized in the Integrated Summary of Efficacy".

The comment highlights problems with the follow-up treatment trials set which may have impaired their capacity to draw conclusions from the follow-up on duration of effect of oseltamivir. It also provides a good example of how graphic methods can help identify crucial comments in vast regulatory files.

Several other experiments with text from the same FDA document showed that the choice of text to be represented as a Word cloud heavily influenced cloud construction, visibility of words and hence our ability to detect important comments. It is for this

reason that we decided to adopt a mixed approach: mapping citations while reading FDA comments and integrating such comments in our appraisal of the evidence. Regulatory comments were all the more important, because at the time we developed this method we had few clinical study reports, and comments helped to identify the gaps in our knowledge of the trial programmes.

Based on the findings of the bias assessment and concerns identified during the process over the reliability of the data (see results of post-protocol Hypothesis 2 and 3) we did not proceed with meta-analysing the outcomes of primary interest to the review apart from two analyses on the ITT population: time to first symptom alleviation and hospitalisations.

We compared the time to first symptom alleviation between the active and placebo groups based on the ITT population. We attempted to include all of the treatment trials for which we have clinical study reports Module 1, however three trials did not report the data we require for the ITT population.

For hospitalisations we compared the incidence of all events at any time throughout the trial (on-treatment and off-treatment periods) between the active and placebo groups. We included all of the treatment trials for which we have clinical study reports Module 1.

Post-protocol analyses

After posting the review protocol (December 2010) but before validation of our CONSORT-based extractions, we decided to carry out analyses (which we called post-protocol analyses) to test five null hypotheses that we had formulated while reading, summarising and reconstructing the clinical study reports. The hypotheses originated from our observations of discrepancies and other unexpected observations in the clinical study reports data and were informed by reading regulatory information. We believe these additional analyses are all important for understanding the overall effectiveness of NIs and decided that an answer to the hypotheses would facilitate reaching consensus on the interpretation of the data at our disposal. The hypotheses (expressed as null hypotheses) are listed below, in order of their generation (not necessarily importance). Their rationale is explained further down the text.

Hypothesis 1. Incidence of certain harms is not associated with placebo content.

Hypothesis 2. Oseltamivir (or zanamivir) does not affect antibody production in treatment trials.

Hypothesis 3. Oseltamivir does not affect antibody production in post-exposure (or secondary prophylaxis) trials.

Hypothesis 4. The number of trial centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size).

Hypothesis 5. In oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection.

Hypothesis 1. Incidence of certain harms is not associated with placebo content.

Rationale. While reviewing the FDA critique of zanamivir, we noted the regulators' concern over the apparent drop in forced expiratory volume (FEV) following zanamivir inhalation (FDA 1999a) which appeared to be enhanced by the lactose powder excipient content of the active blister (FDA 1999b). The powder which causes bronchospasm in susceptible individuals was contained in both the active and the placebo blisters. This principle of using a matching placebo is of course correct, but may have had the effect of increasing the incidence of bronchospasm (or asthma-related episodes) in both arms. This is clearly reported as a warning in the 1999 FDA label "Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation" (FDA 2000b p.10).

We reasoned by analogy and reviewed the medication content of the available clinical study reports of oseltamivir trials. The detailed information comparing content and physical characteristics and batch numbers is in Table 1. Roche's use of the word 'matching' is not strictly correct as two principles present in the placebo capsules (dehydrocholic acid and dibasic calcium phosphate dihydrate) are not listed as being present in the active oseltamivir capsules. We could not locate the reason for such a choice in the clinical study reports but both substances may have gastrointestinal action if consumed in large enough quantities.

On this basis we formulated two **hypotheses**:

1a. There is no association between incidence of gastrointestinal harms and a placebo containing dehydrocholic acid in oseltamivir trials.

1b. There is no association between incidence of asthma-related events and a placebo containing lactose powder in zanamivir trials.

To test hypothesis 1a we assessed the oseltamivir trials for which we had clinical study reports Module 1 (M76001; WV15670; WV15671; WV15707; WV15812/WV15872; WV15730; WV15819/WV15876/WV15978; WV15758; WV15799) for gastrointestinal tract (GIT) harms including nausea, vomiting and diarrhoea as well as participants withdrawing from the studies due to adverse events. We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the Chi^2 test and used Tau^2 to estimate between-study variance. To investigate whether placebo containing dehydrocholic acid may be associated with gastrointestinal harms we compared adverse event rates in placebo groups from the oseltamivir trials (where placebo contained dehydrocholic acid) with adverse event rates in the placebo groups from the zanamivir trials (where placebo did not contain dehydrocholic acid). This comparison was done informally using 1) data obtained from the FDA labels of oseltamivir and zanamivir (FDA 2000b, FDA 2011a) as

well as 2) the trials for which we have clinical study reports. As a sensitivity analysis we assumed a similar gastrointestinal adverse event rate in the placebo groups of the oseltamivir trials as was observed in the placebo groups of the zanamivir trials and then repeated the meta-analysis (as described above). We also speculated that withdrawals in the placebo groups due to gastrointestinal adverse events were possibly related to dehydrocholic acid and removed these for the sensitivity analysis.

For hypothesis 1b we assessed asthma-related events in nine zanamivir trials for which we had clinical study reports (NAIA3002; NAIB3002; NAIA2005; NAIB2005; NAIB2007; NAIB3001; NAIA3005; NAI30010; NAI30009). We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the Chi^2 test and used Tau^2 to estimate between-study variance. To investigate whether placebo containing lactose powder may be associated with asthma-related events we informally compared event rates in placebo groups from the zanamivir trials (where placebo contained lactose powder) with event rates in the placebo groups from the oseltamivir trials (where placebo did not contain lactose powder). As a sensitivity analysis we assumed a similar asthma-related event rate in the placebo groups of the zanamivir trials as was observed in the placebo groups of the oseltamivir trials and then repeated the meta-analysis (as described above).

Hypothesis 2. Oseltamivir (or zanamivir) does not affect antibody production in treatment trials.

Rationale. All oseltamivir influenza treatment trials specify the primary efficacy analysis population as the influenza infected population, not the randomised intention-to-treat (ITT) base population. The influenza infected population (known as ITTI, or intention-to-treat-infected in clinical study reports) is determined post-randomisation based on the results of laboratory testing by culture and/or antibody rise (comparing paired sera from the same participant). The sample for culture and the first sample of sera are taken before commencement of trial product, but the second or the third sera are taken after patients are treated with trial medication. It is vital that placebo and active groups of patients have the same odds of being classified as influenza infected, otherwise any comparison between influenza infected groups will be potentially affected by bias and will essentially be a non-randomised comparison. If trial medication affects the production of antibodies, the selection of the influenza infected population (which is partly based on antibody production) is confounded by taking the trial medication.

Roche have stated on multiple occasions (Smith 2006; Ward 2005; section 3.2.4.2 Serology WV15799) that ingestion of oseltamivir does not affect antibody production and the FDA supports this, stating that "In studies of naturally acquired and experimental influenza, treatment with TAMIFLU did not impair normal humoral antibody response to infection" (FDA 2011a).

However, we noticed unequal numbers of individuals in the influenza infected population subgroup in numerous trials. In addition, Takahashi et al reported that oseltamivir significantly suppressed respiratory mucosal secretory immunoglobulin (Ig) A responses to antigen (Ag)-specific antibody (Ab) production and also the induction of Ag-specific IgA Ab-forming cells in an animal experiment (Takahashi 2010). If taking oseltamivir affects the production of IgG antibody as well, it may affect the selection of the influenza infected population.

We are also unsure of the implication for immunisation with influenza vaccine. According to the FDA, no influenza vaccine interaction study has been conducted with oseltamivir (FDA 2011a).

To test the hypothesis we compared: (1) the odds of participants in the ITT population subsequently classified as influenza infected; and (2) the odds of participants in the ITT population with four-fold or more rise of antibody between the placebo and active arms of the trials. If ingestion of oseltamivir does not affect antibody production then we expect the odds of being classified as influenza infected to be the same for the placebo and active arms. Therefore, we tested a null hypothesis that the odds of having a four-fold or more rise of antibody to be the same for the placebo and active arms. We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the Chi^2 test and used Tau^2 to estimate between-study variance. The trials included in this analysis were the 10 oseltamivir treatment trials analysed by Kaiser 2003 plus WV15758 for oseltamivir and NAIA3002, NAIB3002, NAIA2005, NAIB2005, NAIB2007, NAIB3001, NAI30009 for zanamivir. These are all the treatment trials for which we have clinical study reports Module 1. In an additional analysis we also assessed the oseltamivir trial conducted in China by Shanghai Roche Pharmaceutical Ltd for which we have a partial clinical study report (ML16369).

Hypothesis 3. Oseltamivir does not affect antibody production in post-exposure (or secondary prophylaxis) trials.

Rationale. According to the clinical study report of WV15799, the trial programme assessing the effects of oseltamivir in post-exposure prophylaxis (PEP) consisted of two trials: WV15799 and WV16139. The Module 1s of both trials together with copious FDA notes on trial WV15799 were available to us at 'time lock'. However the PEP trial WV16139 was not standard care or placebo-controlled and so we excluded it from the review.

WV15799 was a double-blind, cluster-randomised trial in which contact clusters of index cases were randomised to oseltamivir 75 mg a day or placebo for seven days. The trial formed an integral part of the pivotal trials package for the supplementary application and review for prophylaxis use of oseltamivir 75 mg in people aged more than 13 years of age, submitted to the FDA on 22 May 2000, approved on 20 November 2000 (FDA 2000c). In the clinical study report Module 1 the manufacturer claimed that the trial provided evidence of the drug's capacity to prevent influenza in contacts by interrupting its transmission from index cases. Since all index cases were left untreated except for a paracetamol rescue pack, it is hard to see how such a claim can be made. The interruption of transmission claim has two components: reduction of viral

spread from index cases (measured by nasal shedding of influenza viruses) and prevention of onset of influenza in contacts. This latter claim was based on the definition of (prevented) influenza cases: a mixture of symptoms signs and 'laboratory confirmation' (i.e. viral culture from the upper airways and/or at least a four-fold rise in antibody titres measured between baseline and two to three weeks later). The results of the trial later formed the basis for claims of the drug's effectiveness in interrupting transmission from person to person (WHO 2007) and allow time before the arrival of vaccines in the event of a pandemic. The interruption of transmission claim provided a powerful rationale for stockpiling oseltamivir (see for example vol 8, p.61-62 NICE 2000: "Ro 64-0796 successfully interrupts the transmission of influenza within households ... and suggests that Ro 64-0796 [oseltamivir] would control the spread of influenza in other closed communities associated with high risk of transmission, such as nursing homes" … "Ro 64-0796 also effectively interrupted virus transmission within households.")

The interruption of transmission indication was accepted by agencies such as the WHO and the US CDC, but the US FDA refused to register and allow publicity based on any further indication beyond treatment and prophylactic effects on symptoms (FDA 2000f). Review of the evidence from the study protocol and Module 1 together with the FDA criticism explains the rationale for the FDA not supporting the manufacturers' claims. The design of the trial did not allow for comparison of the effects of treating index cases with oseltamivir versus placebo (as all index cases were not medicated) and a repeat viral culture was not performed for all participants. Viral culture was performed at baseline for all participants and thereafter only in participants with ILI symptoms (see Schedule of assessment for the contact case, WV15799 and the FDA Medical Officer report (FDA 1999c)). Any participants presenting at follow-up with symptoms of influenza had throat and nasal swabs taken in order to confirm the presence or absence of influenza infection; FDA 2000c), thereby missing out on potential asymptomatic infected people. However, a recent review of transmission studies has found no convincing evidence of spread from pre-symptomatic or asymptomatic subjects (Patrozou 2009) which might explain the FDA's caution in sanctioning any such claim for oseltamivir.

Our review of the clinical study report's Module 1 identified further problems with the conduct and reporting of the trial and discrepancies both within the clinical study reports and between the study and its protocol. In the protocol (version H) there is no mention of viral shedding measurement. This appears to be a post-protocol addition which would explain the unsystematic nature of the viral excretion measurement remarked on by the FDA (i.e. taken from symptomatic contacts only). The primary population of analysis is the so called ITTIINAB population (contacts of ITT influenza-infected index cases who had negative virology at baseline). Although defined in the protocol, the selection and presentation of results for the intention-to-treat contacts of the influenza infected index case not infected at baseline (ITTIINAB) population has the effect of excluding 57% of the placebo (200/456) and 59% of the oseltamivir (205/497) participants. The effect of selection on the clustering was not formally tested in a sensitivity analysis. Nor is the potential weakness of such a choice discussed in the WV15799 clinical study report. We carried out an analysis using Fisher's exact test which showed that there was no statistical evidence that the placebo and oseltamivir groups' cluster sizes were distributed differently based on households with an infected index case (P = 0.56) (Table 2). By analysing the population by influenza status of the index case, instead of unit of randomisations (all index cases), the beneficial effects of the cluster-randomisations are potentially lost, introducing unknown biases into the analysis. In addition, the generalisability of the conclusions may not be easily applied to clinical practice where testing of suspected influenza cases is often not practical. Cross-checking the definition of ITTIINAB with that reported in the protocol of the other PEP trial, WV16193 (excluded from this review) yields a different definition (PDF page 589) "The primary outcome in this study (WV15799) was the incidence of influenza occurring among contacts of influenza infected index cases (the intent-to-treat-index-infected population)".

Throughout the clinical study report of trial WV15799 there are many other apparently contradictory statements on important aspects of the trial, for example, on how many viral swabs and paired sera tests were carried out. The text at page 50 of the Module 1 reports that "For 21 of the 26 contacts with laboratory-confirmed clinical influenza in the ITTIINAB population the diagnosis was confirmed by culture" but Table 19 shows the 26 contacts as shedding virus at days two to eight. The same table reports that 178 placebo contacts and 201 oseltamivir contacts were negative for virology (which suggests that they were tested) at days two and eight. However, viral testing only took place at baseline and thereafter only in symptomatic participants. The number of contacts in which influenza was diagnosed only by serology is unclear, but it appears to be five (26 minus 21). These inconsistencies highlight one of the fundamental conceptual problems in understanding the whole oseltamivir prophylaxis trial programme: the mode of action of the drug. Our interpretation of the text suggests that oseltamivir does not prevent infection and does not affect influenza antibody response. As stated above, the claim that oseltamivir does not affect antibody responses has been made by the manufacturers. However, an antibody response is part of the definition of influenza. We are unsure how it is possible that oseltamivir could prevent influenza by stopping symptoms appearing and antibodies rising while at the same time leaving antibody production unaffected.

It is for this reason that we decided to test whether administration of oseltamivir for PEP affected the production of antibodies to influenza viruses. The distribution of change in antibodies from baseline to follow-up was compared between the arms of the trials for contacts of the index cases. Analysis was performed using

Wilcoxon two-sample test separately for each type of antibody in each trial. An additional analysis of proportion of contacts having a four-fold or greater rise in influenza-specific antibody titre in antibodies was compared between groups using the Chi^2 test. Antibody data were not available for index cases, who were left untreated. In WV15799, antibody testing may have been undertaken at day 1, day 8 and at day 21 ± 4 days for all contacts. Day 8 blood samples for influenza antibody analysis were stored to measure influenza antibody levels only in those contacts who did not attend the follow-up visit (day 17 to 25). Analysis was based on data from the ITTIINAB population at pages 59-60 and Appendix 60 of the clinical study report's Module 1.

Hypothesis 4. The number of trial centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size) and **Hypothesis 5.** In oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size).

Rationale. The proportion of ITT population in the treatment trials of NIs that are subsequently diagnosed as infected with influenza is higher (~ 50% to 80%) than is usually seen in the course of the winter season in routine clinical care, although high peaks can occur for a very limited period. We know that in some treatment trials such as WV15670 and WV15671 centres were activated to "recruit subjects during an influenza outbreak in the locality, detected using standardized surveillance techniques." We postulated that unreported procedures may also have been used in the trials to obtain these high proportions of influenza to ILI cases. Two procedures that may have been used are: 1) use of rapid influenza tests to screen out patients based on negative results; 2) dropping of centres that recruited low proportions of infected patients. The use of rapid testing of patients prior to randomisation has been reported in at least one of the zanamivir treatment trials (NAIB3001), in oseltamivir trial WV15670 as a means of excluding infection with H5N1 in the Hong Kong Centre, as a pilot surveillance in suburban London during the 1998 to 1999 winter (NICE 2000 vol.1) and in most oseltamivir paediatric trials to exclude respiratory syncytial virus (RSV) infection. In addition, the schedule of testing varies by trial for the oseltamivir trials with swabbing performed either before randomisation or after randomisation. In at least one oseltamivir treatment trial (WV15730) it was reported that no viral culture was performed at centres from South America (FDA 1999c). As a result of these observations we reformulated **Hypothesis 4** as follows: the number of centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was primary outcome effect size) in oseltamivir treatment trials and **Hypothesis 5** as in oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection.

To test **hypothesis 4**, we used Spearman's rank method to estimate the correlation between average number of patients recruited per centre and the proportion of placebo patients subsequently diagnosed with influenza infection. The placebo patients were used for the proportion of patients subsequently diagnosed with influenza infection because, as we show later in the review, there is evidence that oseltamivir interferes with antibody production and antibody response was used to diagnose influenza infection. We did not analyse the number of centres dropped from studies because information on this variable was not available in Module 1s of the clinical study reports for the included trials (information on patients recruited to each centre is reported in Module 2 which we do not currently have access to).

Hypothesis 5 was generated to attempt to explain the seemingly high proportion of influenza infected influenza-like illness cases in treatment trials. However we did not formally test this hypothesis as there was only one clinical study report (WV15819/WV15876/WV15978) reporting randomisation first then swabbing second (see also Appendix 5).

Assessment of risk of bias in included studies

Previous studies comparing regulatory with published or internal company sources of evidence have reported a variety of different biases that affect medical knowledge (Chou 2005; MacLean 2003; McGauran 2010). We were unable to assess risk of bias using established criteria for single trials (Higgins 2011) and for trial programmes (Table 3 and Table 4) due to the lack of complete clinical study report availability.

Measures of treatment effect

We initially planned to analyse the ITT and ITTI (ITT influenza-infected) populations. However following our post-protocol analysis of Hypothesis 2 using available data which showed non-comparability of ITTI arms we now believe the ITT population is the most methodologically rigorous and clinically relevant population. For our analysis of symptom alleviation we had previously used hazard ratios as the measure of treatment effect for this outcome. However, hazard ratios (HRs) may not be appropriate due to non-proportional hazards over the follow-up period. In addition, hazard ratios are not reported in the clinical study reports Module 1 and need to be estimated using indirect methods. Therefore we used means and standard deviations (SDs) to estimate treatment effects. We used the random-effects approach of DerSimonian and Laird based on mean differences (MDs) for analysis with sensitivity analysis performed using the inverse variance fixed-effect method. For our analysis of hospitalisations we used the random-

effects approach for binary data of DerSimonian and Laird, where Tau^2 was estimated using the inverse variance method. We performed sensitivity analysis using the Mantel-Haenszel fixed-effect method.

We planned to use the tri-dimensional dose-relatedness, timing and patient susceptibility (DoTS) methodology to assess likelihood of harms causality (Aronson 2003) but the quality of the data available did not allow this.

Unit of analysis issues

Problems with unit of analysis are described in the 'Risk of bias' and 'Post-protocol hypotheses' sections.

Dealing with missing data

We developed a comprehensive strategy for dealing with data which we know are missing at the trial level, i.e. unpublished trials (see Search methods for identification of studies section) and unreliable published records which are a very concentrated summary of clinical study reports. For example in the oseltamivir trial programme, some trials' clinical study reports (e.g. WP16263) consist of 8545 pages. This has a 1000-fold greater length compared to its published version (Dutkowski 2010) which consists of 7 pages. Indeed the purpose of this review is to provide as complete a picture as possible of trial programmes, without reliance on the published literature.

Assessment of heterogeneity

We used Tau^2 (inverse variance method) to estimate between-study variance as a measure of the level of statistical heterogeneity and the Chi^2 test to test for heterogeneity.

Assessment of reporting biases

We aimed to carry out assessment of reporting biases based on the empirical framework in Table 3. We indicated that "Biases will be assessed depending on available data and order of priority". However, as we do not yet have access to the full set of clinical study reports we did not carry out a detailed assessment but left it for a further iteration of the review.

Data synthesis

We used the inverse variance and as a sensitivity analysis we used the fixed-effect method of Mantel and Haenszel.

Subgroup analysis and investigation of heterogeneity

We investigated the robustness of subgroup analysis by ITT, ITTI and ITTIINAB (intention-to-treat contacts of the influenza-infected index case not infected at baseline) for prophylaxis trial populations. Additional analyses were reported as 'post-protocol'.

Sensitivity analysis

Sensitivity analyses applicable to our post-protocol analyses have been specified earlier in the methods section of this review. We used the fixed-effect method of Mantel and Haenszel as a sensitivity analysis to supplement our primary analyses using the random-effects method of DerSimonian and Laird.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Regulatory files. We were able to download 2673 pages from the FDA web site. The TOC is at Table 5, Table 6, Table 7 and Table 8. It facilitated recognition of studies making up the programmes in the review.

Once the TOC had been constructed, we postulated that given the huge work involved in reviewing lots of regulatory files, our new instrument could also help us by indicating which parts were more important than others, thus focusing our efforts. We experimented with a variety of methods reported in the Data collection and analysis section.

Clinical study reports. At the date of completion of data searches (12 April 2011), Roche had only provided us with partial clinical study reports despite five requests for full clinical study reports. The material obtained from Roche included the first section (or so-called 'Module 1' or 'Core Report') of a full clinical study report, each of which contain four to five Modules (Appendix 6) for the 10 oseltamivir treatment trials included in the Kaiser 2003 meta-analysis. Not contained in the provided Module 1s are trial protocols with the list of amendments and original reporting analysis plans. These Module 1s comprise 3195 pages. Two Module 1s were also partly reproduced in the NICE submission, a PEP trial (WV15799) (253 pages) and the paediatric treatment trial WV15758 (513 pages). Roche has not made available any further material. In addition we had a 53-page report in English of the treatment trial ML16369 sponsored by Shanghai Roche Pharmaceutical Ltd. Regardless of success with our requests to obtain full clinical study reports, we decided to update our review with available material and subsequently update it as and when additional data becomes available.

Following a change of policy at the EMA prompted by similar efforts of the Nordic Cochrane Centre (Gotzsche 2011), we received an additional eight clinical study reports (10,737 pages) in response to a freedom of information request. An additional

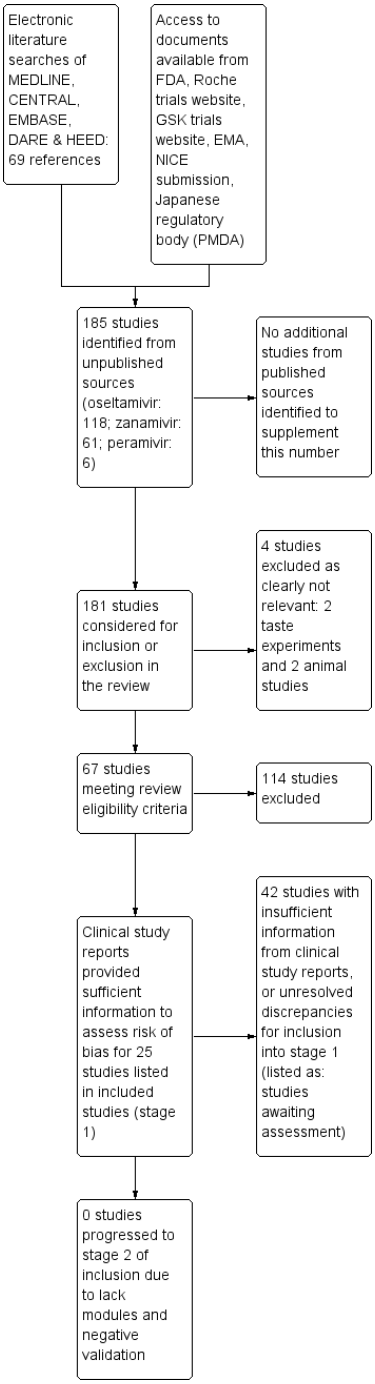
14,700 pages of further clinical study reports and 33 pages of regulators' comments arrived after our search deadline. All of the materials received from the EMA are related to oseltamivir. The EMA has no access to information for zanamivir, as it is a nationally authorised product in Europe (correspondence with Xavier Luria, 23 March 2011 and David Mackay 20 July 2011). At present we hold all Modules 1 and 2 of oseltamivir trials we have requested. From GSK we have received the promise of individual patient data. Many of the clinical study reports used in this review were obtained via FOI requests.

Our searches of electronic databases identified 69 possible titles. Two review authors (CDM, MT) independently scanned the titles and abstracts. None of the identified items were published versions of trials unknown to us.

Included studies

The included trials were predominantly conducted in adults during influenza seasons in both hemispheres. A small number of studies were conducted in older people residing in care homes and in people with underlying respiratory diseases. A flowchart presented in Figure 4 illustrates the study selection process for this review. The inclusion into Stage 1 was carried out using the clinical study reports (when available), titles, abstracts and any other relevant information. Through this process we identified 185 potentially relevant studies (118 oseltamivir trials, 61 zanamivir trials and six peramivir trials). Following the exclusion of four studies we considered 181 trials for inclusion in the review. We excluded 114 studies (listed in the table 'Characteristics of excluded studies') and we assessed 67 different studies for inclusion in our review at Stage 1. Thirty-one studies of oseltamivir (ML21776; WP16263; MV22940; WV15673/WV15697; NV20236; WV15708; WV15799; MV21737; JV15824; WV15825; WV15671; WV15758; ML16369; WV15812/WV15872; WV15730; WV15731; ML20910; JV16284; WV15707; M76001; MV21879; WV15670; WV15759/WV15871; WV15819/WV15876/WV15978; NV16871; MV22841; MV21118; WV16277; NCT00555893; ML20589; JV15823) and 30 for zanamivir (167-101; 167T3-11; JNAI-01; JNAI-04; JNAI-07; NAI30008; NAI30009; NAI30010; NAI30011; NAI30012; NAI30015; NAI30020; NAI30028; NAI30031; NAI30034; NAIA/B2008; NAIA/B2009; NAIA2005; NAIA2006; NAIA2010; NAIA3002; NAIA3003; NAIA3004; NAIA3005; NAIB2005; NAIB2006; NAIB2007; NAIB3001; NAIB3002; PE-01) appeared to fit criteria and had sufficient information for inclusion into Stage 1 (Table 9; Table 10). We also identified six completed or ongoing studies of peramivir in dose response or placebo-controlled studies (NCT00419263; NCT00453999; NCT00486980; NCT00610935; NCT00705406; NCT00958776).

Figure 4. Flow diagram describing the number of studies identified, inclusion, exclusion and progression from stage 1 to stage 2 of the review.



It was not uncommon for more than one trial to be reported in the same clinical study reports. This was either due to the amalgamation of two or more trials because of low influenza virus circulation and difficulties in recruitment (for example WV15812/WV15872) or because the trials bore different ID numbers when in reality they followed the same protocol, albeit in two different hemispheres (for example WV15759/WV15871).
We initially included one secondary prophylaxis trial (WV16193) in the review. Once its Module 1 had become available however, we excluded it as the comparator was not placebo/standard care. We initially excluded the cardiotoxicity trial WP16263 due to lack of information, but subsequently included it after discussion. It remains the only trial for which we have a full clinical study report (8545 pages).
We included thirty-six oseltamivir trials in our preliminary Stage 1 list for CONSORT-based extraction (Table 9) and for 26 of these (including the subsequently excluded trial WV16193) we had sufficient information from clinical study reports to enable us to generate a CONSORT statement-based extraction. We finally included fifteen oseltamivir studies (M76001; ML16369; WP16263; WV15670; WV15671; WV15673/WV15697; WV15707; WV15708; WV15730; WV15758; WV15759/WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/WV15978; WV15825) and 10 zanamivir studies (NAI30008; NAI30009; NAI30010; NAIA2005; NAIA3002; NAIA3005; NAIB2005; NAIB2007; NAIB3001; NAIB3002) in Stage 1 for assessment for progression to Stage 2. For 42 studies we were unable to obtain sufficient information to determine their suitability for further assessment and analysis in our review (see Characteristics of studies awaiting classification). Rather than exclude these studies outright we have decided to retain them pending confirmation of data from the additional clinical study report modules. For the oseltamivir trials (WV15799; WV16193; WV15759/WV15871; WV15819/WV15876/WV15978; MV21737; JV15824; NV16871; MV22841; WV15825; MV21118; JV15823; WV16277; ML20589) we wrote to the manufacturers seeking validation of aspects of methods and results of the trials but received no answer. According to our rules these trials had not been validated and we have excluded them from entering Stage 2 of the review.
Table 11 shows a breakdown of studies by relevant trial programme (primary prophylaxis, treatment, secondary prophylaxis and safety).
Given the GSK individual patient data offer and the extent of data received through our FOI request to the EMA, we decided to assess zanamivir trials in detail in a separate review.
Our attempt at collecting sufficient information from regulatory files to reconstruct missing clinical study reports also failed because the information appeared insufficient for a reliable reconstruction.

Excluded studies

We excluded 114 studies from entering Stage 1 for various reasons. Some were pharmacokinetic studies, or had an active comparator, or compared higher- versus lower-dose schedules or were ongoing trials. We did not include any studies in Stage 2.

Risk of bias in included studies

Study level assessments are reported in the 'Risk of bias' tables. As we ignored published trial reports but directed our attention to clinical study reports and regulatory information, failing to report outcomes or key details of a trial on the basis of their implications (a frequent cause of reporting bias) did not appear to be an issue. Our problem in reviewing the copious material at our disposal was how to identify and analyse important details in the midst of thousands of pages of information and how to construct a coherent appraisal of a large and complex trial programme.
In the following paragraphs we report some of the salient findings using the current Cochrane format but applying the logic of reviewing regulatory data and then we will try to give an overview of our findings. For the reasons explained this will mostly concern the oseltamivir trial programme.
In general, randomisation appeared adequate, although not described in detail in some clinical study reports. However, concealment was inadequate in at least one case (WP16263).

Allocation

All studies in the three programmes (treatment, prophylaxis and PEP) used a randomised, double-blind, placebo-controlled design in which either the enrolled individual or the healthy household contacts (aged 13 or older) with all index cases (in trial WV15799, see post-protocol Hypothesis 3) formed the unit of randomisation and subsequent allocation to study medication. However, the subsequent analyses for the primary population (the so called ITTI and ITTIINAB, respectively, in treatment and PEP trials) were different. These observations formed part of two of our post-protocol tested hypotheses in which we strived to understand the effects of this allocation/analysis 'fork'.

Blinding

Blinding appeared to have been formally maintained, but in at least one case (Table 1), the cardiotoxicity phase II trial WP16263, the cap of the placebo capsule was of a different colour from that of the active oseltamivir capsule, presumably making it readily recognisable by the volunteer participants. From the information at our disposal before 'time lock' (Appendix 1) it would not appear that other placebo capsules were visually distinguishable from the

active capsules, but a further analysis will have to wait our appraisal of the clinical study report modules received outside 'time lock' (Appendix 1).

Incomplete outcome data

We identified a report of a site inspection for the adult prophylaxis trial WV15673/WV15697. The inspection was carried out by the FDA in September 2000 at various trial sites in the US including the West Virginia site (which was responsible for enrolling many hundreds of participants). An FDA official letter reported several violations including failure to report serious harms to the sponsor (Roche) as the protocol required and in addition stated: "we view the statement in the payment section of the consent form used in the study that subjects '...will receive $300.00 for participating in and completing the study. No payment will be made to you if you withdraw from the study for personal reasons...' to be an improper procedure. When subjects are to be paid for participating in a study, the payment should be prorated for the subject's actual participation in the study in order to avoid the possibility of coercion" (FDA 2000e, PDF page 177). The FDA allowed the data (which had been published a year earlier in a prime journal) to stand in support of Roche's application for the prophylaxis indication. We do not know whether the participant contract was standard (i.e. whether the observation of possible improper procedures could be generalised to other sites and other trials) but the document cited by the FDA inspector is the subject of one of our FOI requests. The possibility of financial pressure, if confirmed, could seriously confound dropout rates because of harms or any other causes in prophylaxis trials.

The significantly higher incidence of diarrhoea in placebo recipients of treatment trial WV15671 was identified by the FDA reviewers who remarked "Diarrhea was reported more frequently among subjects receiving placebo than among subjects receiving Ro 64-0796 [oseltamivir]. Diarrhea, although not specified as an inclusion criterion, has been documented to be a clinical manifestation of influenza infection. The reduction in the incidence of diarrhoea for the treatment groups compared with the placebo group could be considered as a possible treatment effect of Ro 64-0796" (FDA 1999c). However, according to the J-SBA of oseltamivir capsules for prophylaxis, diarrhoea was reported more frequently in the oseltamivir arm (49/986) than in the placebo group (38/973) on the summarised table of adverse events from three trials (WV15673/WV15697; WV15708; WV15825). Our findings are inconsistent with the explanation by the FDA.

Selective reporting

The major issue still requiring further investigation is that of harms and especially serious harms. In treatment trials we had difficulty in following the logic of compliharms, even with access to most Module 1s. The definition of adverse events in the randomised controlled studies of oseltamivir and zanamivir is different from the ordinary definition of ICH E2D which is as follows: "An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product".
(http://www.ich.org/fileadmin/Public˙Web˙Site/ICH˙Products/Guidelines/Efficacy/E2D/Step4/E2D˙Guideline.pdf)

As an example the definition of adverse events in the WV15670 (page 22) study is as follows: "An adverse event was defined as **any adverse change from the subject's baseline (pre-treatment) condition**, which occurred during the course of the study after treatment had started, whether considered related to treatment or not. 'Treatment' included **all** investigational agents (including placebo and comparative agents) administered during the course of the study)" (our emphasis).

As a consequence, adverse events that are similar to the symptoms of influenza (such as headache, and mild gastrointestinal adverse events) tend to be excluded from the treatment trials.

We found evidence of possible selective reporting when we analysed the JSBA data on prophylaxis. The regulatory data reports tables for individual trials as well as 10 pages of summarised tables for three trials for prophylaxis (WV15673/WV15697; WV15708; WV15825). Tables for individual trials include data for high-dose arms but report few psychiatric adverse events overall. However, the summarised tables list a variety of psychiatric adverse events including psychotic and suicidal adverse events but not adverse events from the high-dose group. As a preliminary exploratory analysis we combined the following suspected serious adverse events collectively: hallucination and delusion that are classified grade 3 (serious) by the National Cancer Institute-Common Toxicity Criteria Version 2.0 (NCI-CTC V2.0), psychosis (hallucination and delusion are the two major symptoms of this disease), suicidal attempt that is classified grade 3 (serious) by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (CTCAE V4.0) and hostility that includes aggression, hostility, violence, murder and commonly considered as serious events though not listed in the NCI-CTC V2.0 or CTCAE V4.0. Numbers of suspected serious psychotic/suicidal adverse events (including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide) were five in the oseltamivir group and zero in the placebo group during the on-treatment period. When the off-treatment period data are added the total was eight versus one.

The prophylaxis programme is crucial in understanding the harms profile of the drug as the potential for harms witnessed to be confounded by the apparently proteiform symptoms and signs of influenza infection is far less, as many participants do not become infected with influenza. This makes a causality assessment more

straightforward.

We decided to delay the analysis of serious harms and dropouts from the trial programme until we had access to the detailed case reports. We plan to carry out a blinded assessment of possible causality by programme, and integrate it with up to date data from the FDA Adverse Events Reporting System (AERS).

Other potential sources of bias

We believe that the correct sequence of reviewing documents should begin with each study protocol and its relative amendments (usually listed in sequence by a letter suffix, i.e. WV15799H), followed by the reporting analysis plan (RAP) and end with the core report and sundry papers (such as study form templates and clinical report forms) including whenever available, regulators' reviews. In the next phase of the review we will assess the presence of other potential biases.

Effects of interventions

Table 12 summarises the data available at 13 April 2011 by outcome and trial population in the oseltamivir treatment trials.

Analysis of time to first symptom alleviation (ITT population)

Table 13 reports the raw data extracted from the clinical study reports Module 1 by trial and treatment group. The median time to first symptom alleviation in people with influenza-like illness symptoms was 160 hours (range 125 to 192 hours) in the placebo groups and the pooled mean difference (MD) due to oseltamivir was -21.3 hours with 95% confidence interval (CI) -29.6 to -13.0, P < 0.001. There was no evidence of heterogeneity: Chi^2 test = 3.00 (df = 4) P = 0.56, and the estimate of between-study variance Tau^2 = 0.00. Using the inverse variance fixed-effect method of meta-analysis gave the same result.

There is a clear treatment effect for time to first symptom alleviation in favour of oseltamivir of around 21 hours. However, limitations of this analysis are that three eligible trials could not be included due to unavailability of data and the outcome is time to first symptom alleviation hence it does not take into account patients who relapsed (an individual was censored once they reported an alleviation of symptoms, irrespective of the fact their symptoms may return at any point during the illness). In addition the outcome did not include confirmation that the symptom alleviation was sustained for any clinically important period. Of the three excluded trials, two were very small. However, a third trial was in chronically ill patients that showed no evidence of a difference in time to first symptom alleviation in the intention-to-treat-infected (ITTI) population (WV15812/WV15872). In addition, we excluded other trials that we do not have clinical study reports for, including the Chinese trial ML16369 which showed a treatment effect of only four hours based on median difference in the intention-to-treat (ITT) population. As a consequence the estimate of 21 hours is possibly an over-estimate of the true treatment effect. However it is unlikely that inclusion of the additional trials would change the statistical significance of the comparison.

Analysis of hospitalisations

Table 14 reports the raw data extracted from the clinical study reports Module 1 by trial and treatment group. Random-effects meta-analysis showed no evidence of a difference between treatment groups: odds ratio (OR) 0.95; 95% CI 0.57 to 1.61, P = 0.86. There was no evidence of heterogeneity: Chi^2 test = 1.43 (df = 6) P = 0.96 and the estimate of between-study variance Tau^2 = 0.00. A fixed-effect analysis gave a similar result: OR 0.97; 95% CI 0.58 to 1.63, P = 0.91. There was no evidence of a difference in the absolute risk of hospitalisation between treatment groups (risk difference 0.00; 95% CI -0.01 to 0.01).

Based on the safety population of all the trials for which we have clinical study reports Module 1, we have found no evidence of a difference between treatment groups in the incidence of hospitalisations throughout the entire treatment period.

Analysis of influenza complications

The issue which triggered our major change of methods, that of whether oseltamivir is capable of preventing serious complications of influenza, will remain unresolved. No standard definitions of complications in either paediatric, elderly or adult trials were ever prepared and incorporated in the trials. The reporting of cases of 'otitis media', 'pneumonia' or 'bronchitis' was based on local centre definitions making it impossible to attribute a cause and draw conclusions (FDA 2000d). This is probably why the US Food and Drug Administration (FDA)-approved oseltamivir package insert since 17 November 2000 has consistently stated: "serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications." The original product label did not contain such a statement, but on 14 April 2000, after oseltamivir was approved for sale in the United States, the FDA sent Roche a warning letter about "Misleading Efficacy Claims" the FDA had noted in Roche's promotional materials (FDA 2000a, pdf page 3). One of the statements that Roche made was: "Tamiflu reduces incidence of secondary complications (i.e. bacterial infections) by 45%." The FDA commented: "Further, you have claimed reductions in severity and incidence of secondary infections with Tamiflu that are misleading because they are not supported by substantial evidence" (FDA 2000a, pdf page 3). We do not know how Roche responded to the FDA, but in subsequently available Roche promotional material information, Roche's statements were consistent with the FDA's demands (Doshi 2009).

Contrary to the FDA, the European Medicines Agency (EMA)'s oseltamivir 'Summary of Product Characteristics' states that oseltamivir significantly reduces the incidence of lower respiratory tract complications in individuals 13 years of age and older. This claim is based on "a pooled analysis of all influenza-positive adults and adolescents (N = 2413) enrolled into treatment studies", of which 1063 were in the placebo group and 1350 were in the oseltamivir-treated population (EMA 2010). This statement appears in the EMA files as early as 2001 (EMEA 2001). These exact denominators appear in the Kaiser 2003 meta-analysis.

The results of our post-protocol analyses are also reported in Figure and or Table format.

Hypothesis 1a tested in a sensitivity analysis whether the incidence of gastrointestinal harms may be associated with exposure of participants to a placebo containing dehydrocholic acid. The data obtained from the oseltamivir trials clinical study reports is shown in Table 15.

Overall the crude adverse event incidence in the placebo groups of the oseltamivir trials was 5.5% for nausea; 3.6% for vomiting; and 7.0% for diarrhoea. This compares with crude incidence in the nine zanamivir treatment trials placebo groups of 4.1% for nausea and vomiting (reported as a combined outcome in the clinical study reports); and 2.8% for diarrhoea. Two studies (WV15670; WV15671) compared three treatment groups: oseltamivir 150 mg bid; oseltamivir 75 mg bid; and placebo. To maintain the blinding in these trials, each participant took two pills twice daily. Therefore the participants in the oseltamivir 75 mg bid group took one placebo tablet twice daily. We note that in trial WV15671 there was evidence of a dose response effect of placebo on incidence of diarrhoea: oseltamivir 150 mg bid (5.9%); oseltamivir 75 mg bid (8.7%); and placebo (11.8%) (P = 0.036). However, there was no evidence found of a similar trend in trial WV15670 (P = 0.88). We were unable to carry out a similar analysis for paediatric treatment trial WV15758 because a detailed content of the placebo preparations is not available (see Table 1).

Random-effects meta-analysis of the data in Table 15 provided the following results.

Nausea: increased odds of adverse events due to oseltamivir (OR 1.62; 95% CI 1.17 to 2.26, P = 0.004).

Vomiting: increased odds of adverse events due to oseltamivir (OR 2.32; 95% CI 1.62 to 3.31, P < 0.001).

Diarrhoea: decreased odds of adverse events due to oseltamivir (OR 0.72; 95% CI 0.53 to 0.97, P = 0.03).

Withdrawal from treatment due to adverse events: no evidence of a difference between treatment groups (OR 1.08; 95% CI 0.66 to 1.76, P = 0.75).

We carried out a sensitivity analysis by assuming placebo rates of gastrointestinal adverse events in oseltamivir trials based on those observed in placebo groups of similar zanamivir trials. Overall rates of nausea, vomiting and diarrhoea in placebo groups of zanamivir treatment trials for adults and adolescents were 3%, 2% and 4% compared to oseltamivir treatment trials for adults and adolescents where rates were 6%, 3% and 10% respectively based on FDA-reported data (FDA 2000b; FDA 2011a). Conversely, other common adverse events such as headaches, cough and dizziness had similar incidences of 2% to 3% in the placebo groups of zanamivir and oseltamivir treatment trials (FDA 2000b; FDA 2011a). In the treatment trials of children the rates of nausea, vomiting and diarrhoea in placebo groups of zanamivir treatment trials were 2%, 3% and 2% compared to oseltamivir treatment trials of children where rates were 4%, 9% and 11% respectively. Our conservative estimate is that the oseltamivir placebo increased rates of nausea two-fold (risk ratio (RR) = 2), vomiting (RR = 1.5) and diarrhoea (RR = 2.5) compared to the placebo arms in zanamivir trials. Based on the adult and adolescent trials we could conservatively speculate that the substances in the oseltamivir trials placebo increase nausea, vomiting and diarrhoea by 100% (6%/3%), 50% (3%/2%) and 150% (10%/4%) respectively. This could also be considered a conservative assumption because it is plausible that the lactose powder used as the placebo in the zanamivir trials also induced gastrointestinal symptoms, especially in patients that were lactose intolerant. Adjusting the actual rates of these events in the oseltamivir trials placebo groups to be consistent with the zanamivir trials placebo group rates (as reported by FDA: FDA 2000b; FDA 2011a) and re-running the random-effects meta-analysis we obtained the following results.

Nausea: increased odds of adverse events due to oseltamivir (OR 3.33; 95% CI 2.44 to 4.54, P < 0.001; test for heterogeneity P = 0.33).

Vomiting: increased odds of adverse events due to oseltamivir (OR 3.46; 95% CI 2.51 to 4.78, P < 0.001; test for heterogeneity P = 0.37).

Diarrhoea: increased odds of adverse events due to oseltamivir (OR 1.86; 95% CI 1.39 to 2.50, P < 0.001; test for heterogeneity P = 0.50)

The estimated effect sizes for nausea and vomiting have increased based on the sensitivity analysis. The effect on diarrhoea has reversed, indicating oseltamivir is possibly associated with increased odds of this adverse event. The results of our analysis support an alternative interpretation to that of the FDA.

Finally, we carried out a sensitivity analysis of withdrawal from treatment due to adverse events by assuming no withdrawals due to gastrointestinal events in the placebo group. In total there were nine patients in the oseltamivir trials' placebo groups that withdrew due to gastrointestinal events. When these withdrawals are not included the following result is obtained based on random-effects meta-analysis:

Withdrawal from treatment due to adverse events: no evidence of a difference between treatment groups (OR 1.48; 95% CI 0.87 to 2.51, P = 0.15; test for heterogeneity P = 0.40).

We conclude that participants in placebo arms of oseltamivir treatment trials experience a higher rate of gastrointestinal adverse events compared to their zanamivir counterparts. As the zanamivir trials' inclusion criteria were similar to the oseltamivir trials (fever

and two additional symptoms of influenza-like illness (ILI)) this observation cannot plausibly be explained by an incremental role of influenza infection in the genesis of such heterogeneity. It is possible that the difference in reported gastrointestinal adverse events in the placebo groups of zanamivir and oseltamivir trials is due to differences in the collection of these events. However, other common adverse events such as headaches, cough and dizziness had very similar rates in the placebo groups of zanamivir and oseltamivir trials. Despite the results of this sensitivity analysis it is impossible without a clear statement of dosage and rationale of use to assess the role of dehydrocholic acid and possibly calcium phosphate in the causation of such a high incidence of gastrointestinal adverse events.

For **hypothesis 1b** the data obtained from the zanamivir treatment trials clinical study reports are shown in Table 16.

Over all the nine zanamivir trials the incidence of asthma (including asthma exacerbation) in the placebo groups was 2.1% compared to 0.9% in the placebo groups of the oseltamivir trials. Random-effects meta-analysis of the data in Table 16 provided the following results for the combined outcome of any asthma event:

Asthma: decreased odds of adverse events due to zanamivir (OR 0.54; 95% CI 0.34 to 0.86, P = 0.01).

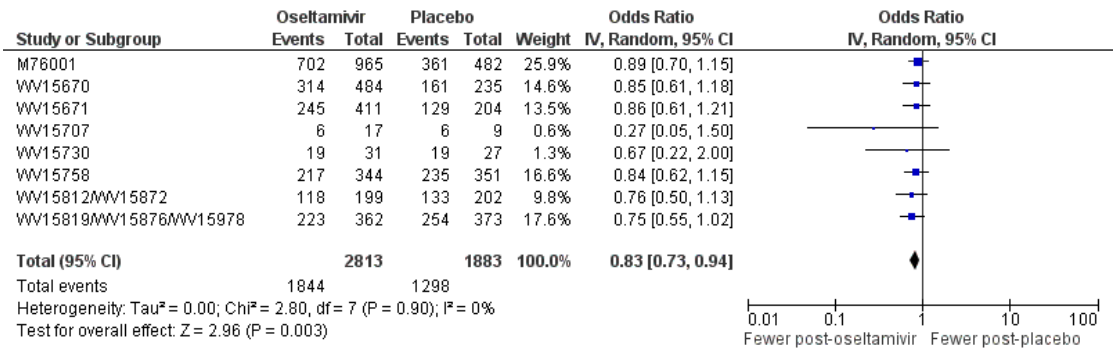
We carried out a sensitivity analysis by assuming placebo rates of asthma-related adverse events in zanamivir trials based on those observed in similar oseltamivir trials. If we assume a rate of asthma events in the placebo groups of the nine zanamivir trials similar to that observed in the oseltamivir trials we obtain the following result based on random-effects meta-analysis:

Asthma: no evidence of a difference between treatment groups (OR 1.27; 95% CI 0.71 to 2.26, P = 0.42; test for heterogeneity P = 0.68).

We conclude that zanamivir trial placebo recipients appear to have a higher incidence of asthma-related events than their oseltamivir counterparts. Again, as the inclusion criteria were similar for both trial programmes this finding is not likely to be due to severity of influenza infections but associated with exposure to lactose powder and possibly to the active principle. This is a point remarked on by the FDA.

For **hypothesis 2** (oseltamivir (or zanamivir) does not affect antibody production in treatment trials) the relevant trials showed strong and consistent evidence that patients randomised to active treatment had reduced odds of being classified as influenza infected (OR 0.83; 95% CI 0.73 to 0.94, P = 0.003) with no evidence of heterogeneity (heterogeneity Chi^2 test = 2.80 (df = 7) P = 0.90; estimate of between-study variance Tau^2 = 0.00) (see Table 17; Figure 5). There was also strong evidence that patients randomised to active treatment had reduced odds of having four-fold or higher rise in antibody titers (OR 0.79; 95% CI 0.70 to 0.90, P < 0.001) with no evidence of heterogeneity (heterogeneity Chi^2 test = 4.61 (df = 7) P = 0.71; estimate of between-study variance Tau^2 = 0.00) (see Table 17).

Figure 5. Forest plot of comparison: 1 Oseltamivir versus placebo, outcome: 1.3 Defined as influenza-infected at baseline.



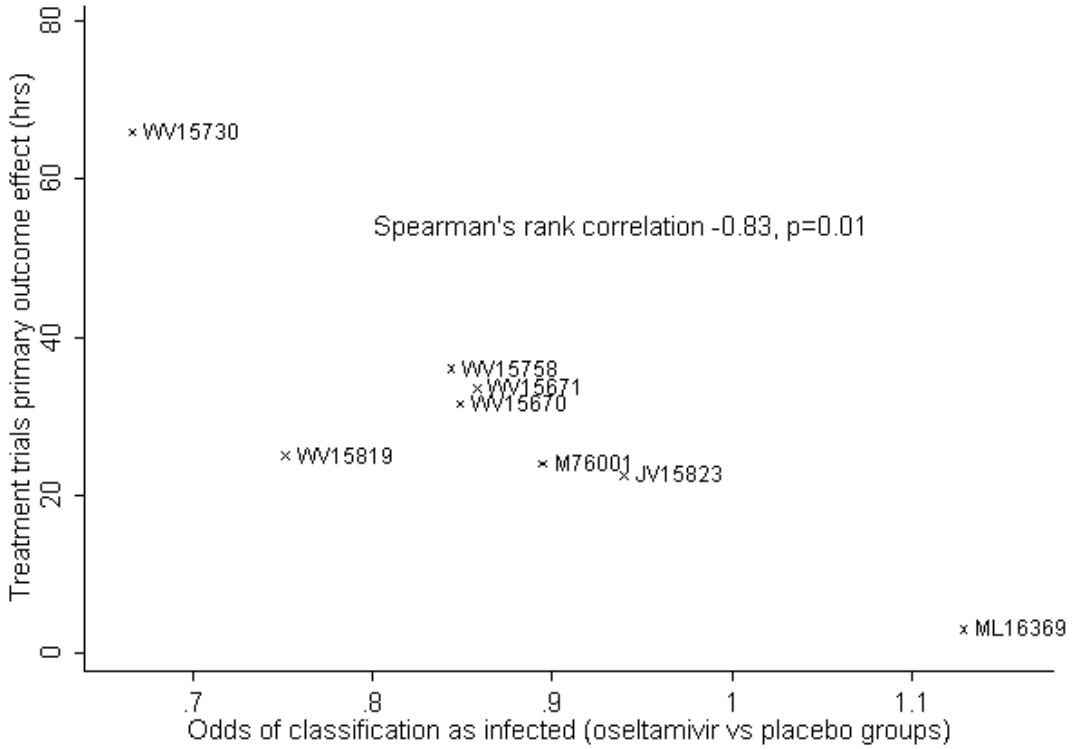
In contrast, the zanamivir trials showed no evidence that patients randomised to active treatment had reduced odds of being classified as influenza infected (OR 1.05; 95% CI 0.90 to 1.24, P = 0.52) with no evidence of heterogeneity (heterogeneity Chi^2 test = 3.03 (df = 6) P = 0.81; estimate of between-study variance Tau^2 = 0.00) (see Table 18).

These results have important implications for the oseltamivir treatment trials programme and for all ongoing trials. All influenza infected populations are selected post-randomisation and post-trial termination on the basis of laboratory findings (all ITT participants being symptomatic at entry, with etiology unknown).

However, as oseltamivir appears to affect antibody production (or perhaps testing, or both), there may be some participants in the oseltamivir group who were infected with influenza but not diagnosed by the antibody rise and were therefore not counted in the influenza infected population. These may have subsequently been excluded from the efficacy analysis. It is also possible that the strength of the antibody production limit to qualify for an influenza infection-induced antibody rise (four-four fold and above from baseline) had the effect of selecting the 'stronger' responders into the influenza infected subgroup of the oseltamivir arm. This would mean that the best antibody producers were selected and this may have led to inflated treatment estimates of efficacy in influenza infected populations.

To investigate this possibility we calculated the correlation between odds of being classified as infected in the oseltamivir group compared to the placebo group and the size of the primary treatment effect (time to alleviation of symptoms in the ITTI population). In treatment trials all participants are recruited on the basis of symptoms of influenza-like illness. According to the mechanism of action proposed by the manufacturer, infected participants given oseltamivir up to 48 hours from symptom onset should have an antibody response which, given the effects of randomisation, should be similar to that of placebo recipients. Non-responders or weak responders should be spread evenly across the trial arms. All treatment trials of oseltamivir showing evidence of a treatment effect on the primary outcome of the study were included in the analysis. This included two trials for which we did not have clinical full study reports (ML16369; JV15823). We included these trials to increase variation in the two variables used for the analysis. In addition, two trials were excluded: WV15707 which had a total ITTI sample size of 12 participants; and WV15812/WV15872 which was a treatment trial in chronically ill adults that showed no evidence of a treatment effect. Results showed strong evidence of a correlation (Spearman rank correlation = -0.83, P = 0.01) (Table 19; Figure 6). The correlation was highly negative, indicating that lower odds of being classified as ITTI in the oseltamivir group compared to the placebo group is associated with larger treatment effects for the primary outcome of the studies. In contrast there was no evidence of a correlation between the odds of being classified as infected in the oseltamivir group compared to the placebo group (Table 19) and the size of the treatment effect in the ITT population (Spearman rank correlation = -0.23, P = 0.66). A limitation of this analysis is that data for the ITT population for two trials were not available (WV15730; JV15823) (Table 19).

Figure 6. Oseltamivir treatment trials primary outcome effect size in hours (i.e. difference between oseltamivir and placebo groups in median time to first alleviation of symptoms) by magnitude of selection bias (i.e. odds ratio of classification as infected in oseltamivir compared to placebo groups).



Thus, all influenza infected comparisons are potentially confounded by the action of the drug (oseltamivir, but probably not zanamivir) and are essentially non-randomised comparisons. Any analyses should be based on ITT populations in oseltamivir treatment trials. Analyses and data considered for inclusion in systematic reviews should be based on the ITT (or safety) populations only.

Our analysis of **Hypothesis 3** shows that the odds of having a four-fold rise in antibodies is 0.33 (95% CI 0.16 to 0.67) for the oseltamivir group compared to placebo (hence a much bigger effect compared to the treatment trials). Due to insufficient information provided in the clinical study report we were unable to take account of the clustering in this analysis, hence the confidence intervals are possibly under-estimated; however an analysis that takes into account clustering is unlikely to change the conclusions. These results show that oseltamivir prophylaxis is associated with lower odds of a four-fold rise in antibodies and this appears to be due to a difference in the distribution of antibody rise in HIAAH3 antibodies but not HIAAH1 or HIB antibodies (see Table 20, Table 21, Table 22 and Table 23). In summary no conclusions can be drawn from available evidence on the effects of the drug on viral transmission. The mode of action in prophylaxis appears mainly to be ascribed to symptom suppression or control. There is uncertainty around other possible effects of the drug especially given its interaction with the production of antibodies.

We rejected **Hypothesis 4** and are currently unable to test **Hypothesis 5** (Appendix 5).

DISCUSSION

Reconstructing trial lists and indexing regulatory comments

Calls for incorporating unpublished data to supplement published trial data in systematic reviews and meta-analyses highlight current methods for obtaining the most complete understanding of a drug's effects (Godlee 2010). Our methodological approach en-

tailed comprehensive searching of unpublished sources, with a particular emphasis on obtaining unpublished and internal reports from drug manufacturers intended for regulatory submission and comments from national regulatory bodies. Our decision not to use published evidence as a basis for trial appraisal and data extraction meant that we had to reconcile and synthesise information from multiple unpublished sources. We had to devise a new method of searching, indexing, retrieving and reviewing trial data and to combine this understanding with regulatory comments to produce an informative review. We were convinced that the first step in this process entailed the need to develop our own reconstruction of the trial programme without initial help from outside sources. The reconstructed list of trials and then programmes took a whole-time-equivalent (WTE) researcher 20 days to compile. Due to the complexity of the task we suggest that some of the essential phases, such as trial ID checking, be conducted in pairs. One of the comments received on our protocol suggested that discrepancies between published and unpublished versions of the same data set could be due to mistakes in the non-peer reviewed, unedited clinical study reports (which may be corrected by the time of publication). Our experience, especially with the non-reporting of serious adverse events, points to the opposite being the case (Jefferson 2011). Considering the fact that unintentional errors can occur, we believe the response should not be a resort to published papers as 'most accurate' and best unit of analysis, but rather that clinical study reports - as by far the most comprehensive record of a trial - remain the key unit of analysis with the expectation that they be amended and kept as accurate as possible over time, with complete documentation of reasons for any amendments.

We believed that the results of our review would be undermined without accessing a more complete body of evidence which we knew to be outside the public domain.

In theory trial registers would be expected to provide a comprehensive picture of a drug's trial programme. However, registers were not our primary instruments to reconstruct zanamivir and oseltamivir trial programmes. Both drugs' programmes were mainly run in the late 1990s, before trial registration became the norm. In addition registers may suffer from some of the problems that we were trying to address, as reported by Bourgeois 2011. The researchers audited entries for 546 trials of five major classes of drugs on ClinicalTrials.gov, the biggest prospective register of clinical trials, and found evidence of risk of reporting bias and delay in reporting of results (Bourgeois 2011). Another recent review of 152 trials found that the description of 123 (or 81%) of the trials in the sample had been changed in at least one key element in the time between registration and publication. The most frequent changes regarded outcomes (Huic 2011). Despite the current limits of registers, both specifically to this review and in the way they are run and updated, we believe that registers are an obvious first choice to start reconstruction of trials programmes. Searching for unpublished material has not yet become standard practice in conducting Cochrane reviews (Van Driel 2009) and is currently variably reported (Ghersi 2010).

The indexing and review of regulatory files was also a very laborious task. It took a WTE researcher three days to review the US Food and Drug Administration (FDA) regulator's comments and gain a basic understanding of the content. Four additional days were needed to read and annotate the FDA zanamivir files and 28 days for reading and annotating the oseltamivir files and building the Table of Contents-Evidence (TOCE). The exercise had to be repeated several times to cross-check content and expand annotations. Construction of the Table of Contents (TOC) was laborious. A first attempt at electronic mapping the TOC content took 12 and 8 hours respectively for the FDA and National Institute for Health and Clinical Excellence (NICE) regulatory documents. This was carried out using the Adobe Acrobat Optical Character Recognition (OCR) search facility, which enabled mapping of citation counts by document and by trial ID. Initially we used the trial prefix followed by the serial number ('WV15670') as ID. This procedure, however, had one major drawback linked to the nature of regulatory documents. As regulatory documents consist of notes, correspondence and reviews, the same trial is cited in a non-standardised way. For example, trial WV15670 is cited as 'WV15670' 15 times, as 'WV˙15670' 12 times and simply as '15670' 19 times). Thorough searches must be conducted using all the different terms. As this can be very time-consuming, we decided to compare an Acrobat search with a Boolean string strategy containing all possible citation formats (for example WV15758 OR WV 15758 OR Trial 15758 OR Trial15758 OR Trials 15758 OR Trials15758 OR 15758 OR study 15758 OR study15758) (this is logically equivalent to 'WV 15758 OR WV 15758') with a term-by-term search (i.e. separately searching for WV15758 and then for WV 15758 and so on). We reasoned that if the yield were comparable, the Boolean strategy would have been faster. The yield of citations of the two strategies was the same for six of seven 'tracker' studies but use of a Boolean string was considerably faster (an average of 3 versus 14 hours) than the term-by-term strategy. NICE submission citations took two hours to list on TOC using a Boolean strategy. We adopted the Boolean search strategy to construct our TOC. Ultimately it is possible that a search with the trial numerals ('15670') may be sufficient to identify the vast majority of citations. To further validate this method of searching our methods should be repeated on other sets of regulatory documents.

Once we had reconstructed the trial programmes we submitted the results to GlaxoSmithKline (GSK) and Roche for their input. We received detailed feedback from both but Roche's list of trials was incomplete, and did not include 15 trials possibly fitting our inclusion criteria. We identified these from a variety of sources including regulators and personal correspondence with authors of published studies. Our current best estimate is that there are 116 oseltamivir and 59 zanamivir trials with complete or partial industry support. Despite the laboriousness of the methods, we believe we ended up with a far more comprehensive and less biased set of

evidence than that available through the current system of journal-based publications. This shift in our data synthesis paradigm was made necessary by the numerous and documented discrepancies between regulatory and published evidence and by the sizeable risk of publication bias of the oseltamivir trial programme. The importance of reconstructing the trial programme by first generating a complete trial list was further reinforced upon discovering bias and oversights in regulators' handling of the trial programme. Trial M76001 is a good example: it is the largest oseltamivir treatment trial, conducted prior to initial registration of the drug (and still unpublished), but was largely ignored by regulators. One explanation could be that the manufacturer did not put it forward as a "pivotal trial", whereas far smaller and even ongoing studies were included in the evidence base to support Roche's year 1999 New Drug Application number 021087 (Treatment of uncomplicated acute illness due to influenza infections in adults who have been symptomatic for no more than two days).

The effects of neuraminidase inhibitors (what the evidence shows)

Oseltamivir shortens duration of symptoms by less than a day in people with influenza-like illness (ILI) (the intention-to-treat (ITT) population) but there is no evidence of an effect on hospitalisations. However, we found it difficult to draw hard conclusions regarding the other effects of neuraminidase inhibitors on the efficacy outcomes of key importance to this review (viral transmission and complications of influenza). For oseltamivir, many outcomes could not be assessed due to the unavailable of data for the full trial (ITT) population.

In the oseltamivir and some of the zanamivir treatment trials the primary analyses have been conducted by the manufacturers on the influenza infected subpopulation (the so-called intention-to-treat infected subgroup, ITTI). This is not, nor does it approximate, an ITT analysis because between 25% to 40% of the participants in each trial have been excluded from the analysis as they did not test positive for influenza. We found that oseltamivir likely interacted with antibody production and therefore the placebo and oseltamivir treatment arms of the influenza infected subpopulation (defined in part by a rise in antibody titer) were not comparable. The evidence, across numerous trials, demonstrating an apparent effect of oseltamivir to reduce antibody production deserves a more detailed discussion. In 11 manufacturer-sponsored oseltamivir trials, participants in the oseltamivir group had a decreased odds of being classed as influenza infected (odds ratio (OR) 0.83; 95% confidence interval (CI) 0.73 to 0.94). By contrast, in the Chinese oseltamivir treatment trial ML16369, for which we have a partial clinical study report, information reported showed that all participants had a culture test, whereas antibody testing was performed on 306 out of 478 participants. In this trial, there was a somewhat higher odds of participants classified as influenza infected in the oseltamivir group compared to the placebo group (134 out of 216 in the oseltamivir group compared to 139 of 235 in the placebo group: OR 1.12; 95% CI 0.76 to 1.67). This difference leads us to speculate that the 11 manufacturer-sponsored oseltamivir trials relied primarily on antibody testing to determine classification into the influenza infected (ITTI) subgroup. Classification into ITTI was generally described as based on culture test at baseline and/or four-fold increase in antibody titers from baseline to 21-day follow-up. However, details on exactly what proportion of patients had each test was not provided in the portions of clinical study reports available to us for these trials. So, unlike the Chinese trial ML16369, we were unable to reconstruct the denominators of participants who had antibody responses measured, or of those who had viral culture, or of those who had both.

The seeming incomparability between arms of the influenza infected subpopulation raises the question of how an appropriate analysis should be conducted. If influenza infected groups are comparable (as appears to be the case in zanamivir treatment trials) then an appropriate analysis strategy (based on Senn 2004) would be to first determine the effect of treatment in the ITT population. If there is evidence of a treatment effect, then treatment by infected status interaction could be tested. If there was evidence of an interaction, then estimates of treatment effect could be derived separately for the influenza infected and non-influenza infected subpopulations. However, this analysis should be conducted on the ITT population using a single appropriate statistical model, obviating the need to conduct separate analysis on the influenza infected subpopulation. Roche used geometric mean titres indicating antibody responses to support their statement that oseltamivir does not affect antibody responses (for example at Table 20 and linked text of Module 1 of trial WV15799). However, use of such measures can be misleading. What are required for such an analysis are data on how many participants responded by arm at what level of antibody response and how many were tested. Such data are likely to be included in the individual efficacy listings in Module 3s of the relevant clinical study reports which we requested but do not have access to. A further effect of choosing a subpopulation analysis (ITTI in treatment trials and ITTIINAB (ITT influenza-infected index cases who had negative virology at baseline) in prophylaxis trials) as the primary analysis is to restrict generalisability of results. This is especially so in the case of design flaws (for example, in the case of the post-exposure prophylaxis trial WV15799 where all index cases were not treated and around 55% of participants were dropped from the ITTIINAB analysis). In this cluster-trial design households should be included as random-effects in the analysis to take account of within-household correlations.

Evidence from treatment trials shows that oseltamivir may shorten duration of illness but the mechanism by which it may achieve this effect remains unexplained. Given its other possible properties (weak interference with viral nasal voidance and antibody production and symptom rebound in a proportion of people upon cessation of treatment) we speculate that its mode of action is chiefly directed to the central nervous system by a non-specific,

antipyretic, rather than antiviral, action. Symptom amelioration has been consistently observed if taken within 36 to 48 hours from symptom onset, perhaps because the natural history of influenza is benign and self limiting in the vast majority of cases. This non-specific mode of action is shown in prophylaxis trials where oseltamivir prevents symptoms onset but we did not find credible evidence supporting any action on transmission because of study design problems and lack of systematic viral sampling. In addition, the mix up in diary card dispensing in 'pivotal' treatment trials WV15670, WV15671 and WV15730 means that no clear picture of possible symptom rebound on cessation of treatment (FDA 1999c) from data at our disposal can be defined. Similar uncertainty is present on the effects of oseltamivir on duration of nasal shedding of influenza viruses because of partial and inconsistent measurement in the trials (FDA 1999c, page 21).

Following our findings from the testing of Hypotheses 2 and 3 we sought published evidence and results by the Examination Center (PMDA) and Japanese SBA of oseltamivir and zanamivir's effects on the immune response. The evidence comes from animal models and in some cases from viral challenge studies in humans (Hayden 1999b). It is possible the low immune response with a low level of pro-inflammatory cytokines induced by the action of oseltamivir carboxylate may reduce symptoms of influenza. If so, this action is unrelated to influenza virus replication inhibition.

Sufficient plasma concentration of oseltamivir carboxylate from orally administered oseltamivir phosphate may act directly on the host endogenous neuraminidase to reduce (or suppress) the immune response. However, plasma concentration of zanamivir does not reach a high enough concentration to reduce the immune response because of the inhaled administration. The potential hypothermic or antipyretic effect of free oseltamivir as a central nervous system depressant may also contribute to the apparent reduction of host symptoms. Interestingly, we found evidence that administration of oseltamivir showed symptom-relieving effect (decreased weight loss) and inhibition of viral clearance in animals challenged by respiratory syncytial virus (RSV) that lacks a neuraminidase gene. These effects were accompanied with decreased response of CD^{+8} T cell surface sialoglycosphingolipid GM1 level that is regulated by the endogenous sialidase/neuraminidase in response to viral challenge along with suppression of cytokines expression (Moore 2007). The finding from animal experiments on the reduction of cytokine production in response to infection was confirmed by experimental influenza infection on humans (Hayden 1999a).

Takahashi et al found that risk of re-infection may increase in patients showing a low mucosal response following oseltamivir administration (Takahashi 2010). Our findings that IgG antibody response was decreased by oseltamivir administration support Takahashi's findings. The findings of the study by Moore et al (Moore 2007) suggest a risk of infection and exacerbation of infection by pathogens other than influenza virus in spite of the apparent reduction of symptoms from infection. The findings from animal studies require replication in humans.

The quality of the trials poses significant challenges to drawing meaningful inferences about the effect of neuraminidase inhibitors on complications of influenza. It is notable that in the two treatment studies of chronically ill patients (WV15812/WV15872) a quarter of the ITTI population were diagnosed with a specified secondary illness (complication) with no difference between treatment arms (oseltamivir: 25% versus placebo: 25%). In addition, there was no evidence of a difference in the primary outcome (time to alleviation of symptoms in the ITTI population) for these trials. Given that oseltamivir is now recommended as an essential medicine for treatment of seriously ill patients or those in higher-risk groups (WHO 2011), this is of some concern.

In a primary or secondary prophylaxis indication the postulated central effect of oseltamivir is confined to suppressing symptoms, as infection is not prevented. However, the central problem remains the incompatibility of the two contrasting claims on its activity against antibody production. If, as reported in many documents, oseltamivir does not interfere with antibody production (see for example FDA 2011a; Smith 2006), how is it possible that oseltamivir prevents cases of influenza when part of the definition of prevented cases in oseltamivir trials was based on absence of antibody response?

The apparent ability of oseltamivir to interfere with antibody response calls into question the mode of action of the drug and puts in doubt the proposed effects of oseltamivir. One possibility in treatment trials is that oseltamivir administration, by interfering with antibody production, has the effect of selecting the strongest antibody responders in the ITTI subpopulation. These individuals are classified as influenza cases and are included in the oseltamivir arm of the ITTI population. This selected subpopulation probably represents the healthiest or those least likely to experience complications. An alternative consequence could be that interference with antibody production in the oseltamivir arm led to active arm participants being more likely to develop complications due to impaired immune function. Data presented in Figure 6 show that the odds of being classified as infected in the oseltamivir arms (compared to the placebo arms) vary between trials. The Figure also shows the size of the primary treatment effect (time to symptom alleviation in the ITTI population) varies considerably by trial. In addition there is evidence of a negative correlation ($P = 0.01$) where lower odds of being classified as infected in the oseltamivir arms (compared to the placebo arms) is associated with a larger primary outcome treatment effect. This association supports the possibility of selection of healthier (those with the strongest immunological response) participants in the ITTI oseltamivir arms. Without detailed clinical report forms and standardised definitions of complications (which were never provided) we will never know which of the hypotheses is correct.

A similar mode of action would also fit with the evidence from prophylaxis and secondary prophylaxis trials. The participants who become positive (i.e. who are subsequently classified as cases of

influenza) in the oseltamivir arms are the few who mount a strong response despite oseltamivir interference. The remainder (who are significantly fewer than in the placebo arm) are classified as prevented or avoided cases. However as prophylaxis clinical study reports do not report antibody responses and viral isolate results for the ITT populations either, it is impossible to tell whether this proposed mode of action fits all evidence. The effect of oseltamivir on nasal shedding is unclear, but problems with sampling and culture undermine any claims as to its secondary prophylactic properties, as the FDA made clear in its response (FDA 1999c).

Oseltamivir in all indications and in all populations appears to be associated with nausea, vomiting and probably diarrhoea. We have not been able to assess reliably the effects of oseltamivir on harms in treatment trials because of the ambiguous nature of their classification into compliharms (Appendix 1). It is our intention to tackle the issue of neurotoxicity in the next iteration of this review, with assessment of individual patient case report forms (Module 2) of the Roche clinical study reports and a full and updated set of pharmacovigilance reports.

Our new method

Reviewing huge quantities of complicated data and linked comments is a very difficult and delicate business. The main problem is not so much the appraisal following standard rules and possible synthesis of data (as when we review published information), but the reconstructions and logical threading of a trial programme in the absence of visibility of a narrative of the complete programme (i.e. the manufacturer's full regulatory submission which remains confidential). Most of the essential data required are likely to be available in clinical study reports, together with masses of less important data. Manufacturers are under obligation to provide regulators with all data requested to enable them to reach a decision. In doing so they produce vast submissions. None of us had any experience of reviewing regulatory information. Our random allocation of studies to pairs of authors for CONSORT-based extraction had the drawback of parcelling trials from the same programme or sub-programme (for example, treatment in healthy adults) across the whole review team, but the main gain was familiarisation of each review author with different programmes of both drugs. We tried to identify a quicker and equally reliable way of reviewing regulatory information but could not find any obvious shortcuts. However, we believe that providing a critical overview of a trial programme rather than minute dissection of each trial is necessary. This can be done by identifying the important topics in the trial programme (such as the effects of the drug on symptoms, infection, complications, transmission and well being) and following them throughout the programme, knitting the evidence into a coherent narrative. In practice this means carrying out a high-level overview of the mode of action of the drug in different populations for different indications. Understanding any drug's mode of action is core to correct reporting of its strengths and limitations.

In addition, a large part of the regulatory submission is made up of chemistry, microbiological, animal model pharmacodynamic and pharmacokinetic studies which are important for shedding light on the trial programme but which seldom feature in systematic reviews. We are unsure as to whether this information could be considered as core information but an exhaustive review of a trial programme should include reviews dedicated to such topics.

The methodological problems identified while reviewing the oseltamivir trial programme may be partly resolved one way or the other when we access the other modules contained in full clinical study reports. The authors have been unable to obtain the full set of clinical study reports or obtain verification of data from the manufacturer of oseltamivir (Roche) despite five requests. No substantial comments were made by Roche on the protocol of our Cochrane Review which has been publicly available since December 2010. Individual efficacy data are listed under the contents of Module 3. If such data include antibody responses for the complete ITT population we should be able to test our mode of action hypothesis in a definitive way. Individual patient data may also provide the opportunity to present important subgroup analyses, such as the effects of NIs on children. We requested Modules 3, 4 and 5 (the statistical analysis report) from EMA. Of note, for most oseltamivir trials, EMA do not have the relevant documents and neither apparently do National Competent Authorities (email from EMA, 24 May 2011; email from Dutch regulator MEB, 20 July 2011). This means that the modules do not appear to have been either submitted to or requested by regulators, raising questions as to the extent of appraisal of the clinical trials during the regulatory review of oseltamivir in Europe.

The lack of comparability between arms induced by subset analysis and by the randomisation-analysis fork, high positivity rate of influenza, high gastrointestinal events in the placebo arms, unjustified choice of placebo content and possible procedural breach in one trial do not inspire confidence. Overall the safest and more conservative option appears to carry out analyses on the basis of the ITT population, in which units of randomisations and analysis are the same and many of the potential problems listed are either not present or minimised.

Our novel methodology remains a work in progress; we welcome any comments and input.

Regulatory comments

Reviewing regulatory comments was on the whole an exceptional way to deepen our understanding of the trial programme. From early on in our review we hoped that a close reading of regulatory material would allow us to finally understand the reason for discrepancies between US and European regulators' conclusions regarding the effects of oseltamivir, particularly (but not limited to) their purported effect on complications (Doshi 2009). We wondered what led the FDA to have far more cautious and conservative statements - as witnessed in the Tamiflu product label and FDA

Warning Letters - in comparison to European regulators. Our access to huge amounts of FDA regulatory data allowed for many insights, but gave us little visibility of manufacturers' responses.
Some of the statements made by the manufacturer in the clinical study reports and subsequently in publications and advertisements appeared unsupported by the evidence provided. The FDA drug regulatory reviewers' comments, although laborious to summarise and contextualise (because of the non-availability of the whole pharmaceutical submission), were confirmed by our reading of the clinical study reports. However, we looked in vain for a statement explaining how the FDA reviewed each New Drug Application (NDA). FDA reviewing methods appeared to be a mixture of spot checks, re-run of statistical analyses and on-site inspections. An FDA methods volume or standard operational procedure may be among the documents not available from the web but accessible through a Freedom of Information (FOI) request. Neither the FDA nor the EMA have inventories of held documents, making it very difficult to know what to ask for under FOI rules. We stuck to downloading or asking for specific clinical study reports and related documents or reviewers' comments on a particular NDA. The quantity of information held by regulators is likely to be large. For example, New Drug Application 21-246, the use of Tamiflu in the treatment of influenza in children submitted to the FDA on 15 June 2000 consisted of 137 volumes of study documents and possibly several electronic files. Although we do not know exactly how long a volume was, we have seen references to up to hundreds of pages in each volume.
Requesting specific documents and packages of information is especially important to allow a more efficient and timely reviewing process when confronted with a large volume of evidence, most of which could be of peripheral value. A request for a specific document is likely to be dealt with far more efficiently than a generic request for "all documentation relative to oseltamivir". This is one of the reasons why developing a TOC for any drug or family of drugs (no matter how time-consuming) is an absolute pre-requisite for any serious attempt at reviewing regulatory evidence. This introduces another very difficult problem: how to handle huge quantities of structured information and the ethics of drawing conclusions from what is still a fragmentary (albeit sizeable) evidence base.
Overall the FDA assessment of the performance of oseltamivir was "modest". The adjective appears six times in a 50-page review document (FDA 1999c). For example in the Division Director Memorandum " dated 25 October 1999 under the heading "Public health role of antiviral treatment" the FDA states: "The clinical relevance of the modest treatment benefit is a highly subjective question" (FDA 1999c pdf page 3). The FDA refused to accept claims on oseltamivir's effects on influenza complications as "false or misleading" statements in promotional materials (FDA 2000f). An FDA warning letter seems to imply, for example, that oseltamivir's mode of action is "proposed" or "possibly" [that proposed by the manufacturers] i.e. not certain (FDA 2000f). However, FDA reviewers appear to have missed important problems in Roche's clinical trials (such as the imbalance in numbers of individuals classified as influenza infected in oseltamivir treatment trials). Most of all, no one seems to have questioned the coherence of the evidence with the proposed mode of action of the drug.
There is still a considerable amount of work to be done to obtain a stable picture of the oseltamivir trial programme. First, we have to compare trial protocols and their amendments with analyses plans (both contained in Module 2, which we have yet to review) and also with full studies (only the latter are contained in Module 1s). Second, we have to shed light on serious adverse events and attrition from trials. Again, the detailed information to enable us to do this is contained in Modules 2 to 5.

Summary of main results

We found that subset analysis in oseltamivir treatment trials introduced selection bias and subsequent non-comparability of arms in the entire programme. In treatment trials and the post-exposure prophylaxis trial (WV15799) the difference between unit of randomisation and unit of primary population analysis excluded up to half of the participants, thereby breaking the intention-to-treat schedule and limiting generalisability of results.
We reconstructed the programme with a copious but incomplete regulatory evidence base. Oseltamivir may interfere with antibody production. As an antibody rise (or lack of, in prophylaxis trials) is part of the influenza outcome definition, the construction of the various influenza infected populations on the basis of antibody responses may select the strongest antibody responders who are likely to be the fittest, recover quicker and have fewer sequelae. While the FDA reported that oseltamivir is effective in preventing the incidence of laboratory-confirmed clinical influenza, the manufacturer has reported that the drug does not prevent influenza infection (Smith 2006). We have constructed an alternative oseltamivir mode of action hypothesis according to which oseltamivir suppresses symptoms acting on the central nervous system, does not prevent viral infection but interferes with antibody production. To test this fully we need the data from the missing trial modules.
The inhaled usual dose of zanamivir does not appear to affect antibody production.
A potentially active placebo may have masked the occurrence of asthma in zanamivir trials.
Statements made on the capacity of oseltamivir to interrupt viral transmission and reduce complications are not supported by any data we have been able to access.
We also have documented one possible procedural breach in a prophylaxis oseltamivir trial, a variable and at times perfunctory regulatory review and flaws in the design and execution of oseltamivir drugs' trial programmes.
We analysed clinical study reports and regulatory comments, rather than published trials. This has led us to raise serious con-

cerns about the design, conduct and reporting of studies in the oseltamivir trial programme.

Overall completeness and applicability of evidence

The majority of modules in clinical study reports were inaccessible to us and we were therefore unable to complete the review in some of its most important aspects, such as serious harms. We have major reservations as to whether the evidence from the trial programmes we have reviewed so far is applicable in any way to clinical practice.

In the case of treatment trials, conclusions and generalisations are drawn from a subpopulation in which the two arms do not appear comparable due to the apparent ability of oseltamivir to interfere with influenza antibody production. The effect of oseltamivir on the gastrointestinal tract appears to be notable although a definitive statement will only be possible once mode of action and dosage of dibasic calcium phosphate dihydrate and dehydrocholic acid have been clarified. The high percentage of influenza infections appears in contrast with the need to pool or delay several trials and the small recruitment size of others because of lack of influenza circulation. In the case of post-exposure prophylaxis (PEP) trials, the selection of the infected population has the effect of excluding from the analysis large percentages (in some cases over 50%) of participants. This brings the generalisability of the results of these trials into question.

Much has been made in the trial programmes of viral nasal voidance as a marker of effect. However, its measurement was unreliable in treatment trials as this verbatim quote from the FDA review shows: "Duration of viral shedding was measured from treatment initiation to the time of the first negative virus culture with no subsequent positive cultures. Upon reviewing a list of viral shedding patterns provided by the applicant on 8/16/99, two problems emerged: (1) the pattern of virus shedding was fluctuating in at least 33 subjects (i.e. pos-neg-pos-neg, with or without a subsequent negative result). (2) In at least 100 subjects, the last virus shedding sample was the first negative sample in sequence, meaning there was not a subsequent negative confirmation. Given the fluctuating pattern of virus shedding, to estimate the duration of viral shedding based on the occurrence of a single first negative data poses a high level of uncertainty") (FDA 1999c).

In all programmes the effect of complications is based on outcomes which have been left to the discretion of the local clinician without microbiological proof, which makes generalisation impossible. This per se would not be a big problem in randomised trial designs as it is the difference between arms of these events which is the important measure. We have shown, however, that the comparison arms in the primary population were likely to be non-comparable, de facto cancelling the effects of randomisation. In the case of trial WV15799 nasal voidance was measured only in symptomatic subjects as an adjunct to protocol version H. However, this does not prevent the manufacturers from making claims of effect on all these outcomes.

Other general requirements, such as presentation within 36-48 hours, raises questions about the generalisability of the research evidence. However, underlying all our doubts is the conflicting evidence on the mode of action of the drug.

Our review conclusions are limited by our incomplete data set. For example, we are not able to test fully the effect of oseltamivir on antibodies because we do not have separate data for influenza-negative symptomatic participants. We also have no definitive idea of how many participants were diagnosed on the basis of serology, viral culture or both. In addition we do not have data from the ITT population for a number of important outcomes, e.g. complications. Finally we do not yet have access to Case Report Forms for all serious adverse events. All these shortcomings have entailed the drawing of provisional and not definitive conclusions. We expect full clinical study reports containing study protocol, reporting analysis plan, statistical analysis plan, and individual patient data to clarify outstanding issues. These full clinical study reports are at present unavailable to us.

Quality of the evidence

The body of evidence at our disposal does not allow us to draw robust and unequivocal conclusions. Out of 31 oseltamivir and 30 zanamivir trials included in Stage 1, 17 oseltamivir trials and nine zanamivir trials had study reports. The oseltamivir clinical study reports all have Module 2s which mostly remain to be assessed as they fell outside our time lock (Appendix 1). However, our partial evidence base has copious details which allow outline reconstruction of the three oseltamivir trial programmes. Analyses of these has shown a number of problems which are consistent across the programmes, chief of which is the discrepancy between the evidence we saw and the drug's mode of action proposed by its manufacturers (no effect on infection or antibody production and symptom amelioration thanks to failure to release virions from infected cells). The design and reporting problems and our inability to access all the clinical study evidence mean that we should not draw fast conclusions but continue in our attempts to access the missing Modules.

Missing data in the treatment programme was a particular worry for the FDA's Medical Officer reviewers who had the option of checking and re-running the follow-up analysis. An apparent mix-up in the pivotal treatment trials WV15670, WV15671 and WV15730 in the distribution of symptom cards (on which participants recorded duration of symptoms in relation to duration of the trial) had the effect of producing an incomplete documentation of symptom fluctuation and perhaps impacted on the conclusions (FDA 1999c). This point, which may at first glance seem to be of only superficial or academic interest, actually impacts on our understanding of the mode of action of oseltamivir. We do not know whether cessation of treatment after five days of a stan-

dard course of treatment in infected symptomatic people results in symptom rebound. If it does, this observation would point to a symptomatic mode of action of the drug, not specific to influenza virus.

Potential biases in the review process

We are conscious that we have carried out a high-level review of regulatory data and documents without necessarily having a complete data set nor even knowing how much regulatory information is available worldwide. High-level means that given the amount of data at our disposal we had to restrict the degree of detail we reported for each trial and restrict the focus of the review to deliver on time. This fitted well with our stated intention to appraise trial programmes and not single trials. However, even with such a huge amount of data available, we acknowledge that we still do not have and cannot convey the full picture. There is, in other words, still a notable amount of uncertainty as to the real mode of action of both drugs. We are also conscious that we have concentrated mainly on the appraisal of oseltamivir, in light of its far greater market share and substantial role played in seasonal and pandemic influenza control policies. We believe that this is appropriate in view of its status as a WHO essential drug (WHO 2011). However, we hope to be able to redress the balance by being able to carry out an individual patient data meta-analysis of zanamivir. Zanamivir is an important drug as it is the first neuraminidase inhibitor (NI) to be registered and may be the first of a rapidly expanding family of compounds.

We think we have succeeded in creating methods and procedures to address the risk of reporting bias we knew to be likely in published literature. We do not believe we have all the answers, but we leave readers to judge.

Agreements and disagreements with other studies or reviews

Several reviews of NIs are now available (Burch 2009; Cooper 2003; Falagas 2010; Tappenden 2009; Turner 2003), including several separate versions of our previous reviews (Jefferson 2006; Jefferson 2009a; Matheson 2007; Shun-Shin 2009). All are mainly based on published information and reach similar conclusions to our 2006 review which sparked the reader's comment and subsequent investigation and change of methods.

Following publication of our review update in December 2009, Roche asked the US academics Hernan and Lipsitch to repeat the Kaiser analysis to confirm or reject Kaiser's conclusions (Hernan 2011). Roche provided individual patient data and Module 1 for the 10 Kaiser trials and one more treatment trial (WV16277). Their conclusions are similar to Kaiser's but notably report a reduced effect size in favour of oseltamivir. In view of our findings, we suggest that these results should be interpreted with caution. We have published our preliminary comments (Cochrane Neuraminidase Inhibitors Review Team 2011). This approach to analysing data reinforces the importance of detailed, critical assessment of entire trial programmes, with access to full-length study reports. Our analysis questions the fit between the evidence and the proposed mode of action of oseltamivir.

AUTHORS' CONCLUSIONS

Implications for practice

The mechanism of action of oseltamivir should be independently researched, with special regard to any direct central action of the drug Tamiflu, until a clear picture of its effects on influenza complications, transmission and action on antibodies can be clarified. However, use of the drugs in serious or compassionate cases is probably justified while there is uncertainty.

Regulators should post an inventory of their documentary holdings on their web sites with a brief description of the main content and size of each file.

Regulators should make all information available shortly after making a registration decision on a drug. Publication and the information should be in electronic format and anonymised (i.e. participants' details should be removed to prevent each person being identified, but no further). Redactions should be kept to the minimum. The concept of commercially sensitive information should be inapplicable to public health drugs. 'Available' information should mean within a week of a request being lodged or directly accessible from the web site (we prefer the latter).

Supervision with a random sampling procedure of public trial registries should be implemented by their sponsors. Clear instructions for the reporting and updating of their content should be promulgated and heavy fines levied on trespassers. Registration should be made compulsory for all studies in which human beings are randomly assigned to experimental arms. Ethical and consent procedures for all trials should include obligations of the trial sponsor to ensure results are made public.

Registration of a trial should include the latest version of a trial protocol with a full list of amendments.

Implications for research

We believe that methods for systematic reviews of regulatory information should be urgently developed. However, the resource implications of our method are not slight. It took a whole time equivalent (WTE) researcher three days to glance over the US Food and Drug Administration (FDA) regulator's comments and gain a basic understanding of the content. Four additional days were needed to read and annotate the FDA zanamivir files and 28 days for reading and annotating the oseltamivir files and building

the Table of Contents-Evidence (TOCE). The exercise had to be repeated several times to cross-check content and expand annotations.

Given the resources involved in the methods used, a system to prioritise reviews of important drugs should be put into place (perhaps defined as first drugs of a new family or drugs considered to be innovative or that are likely to have a big market impact). Such reviews should be publicly funded, but be at arms' length from both regulators and manufacturers. Reviewers with no recent ties to either government or the pharmaceutical industry should be chosen.

The Cochrane Collaboration should consider whether our methods and findings may be applicable to other drugs and whether perhaps similar experimental reviews should be carried out on prioritised drugs.

We next aim to complete the review of Module 2s and other comments and evidence available to us after our time lock (Appendix 1), but even this is still incomplete.

The missing trial modules should be made available to enable independent assessment of the remaining effects in the ITT population stratified by age group (especially children) and influenza risk categories, harms using standard definitions and to clarify any discrepancies or missing information such as the rationale for using dehydrocholic acid in the placebo capsule.

We will continue to pursue access to full (not partial) clinical study reports.

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ML16369 *{published data only}*
A double-blind, randomized, placebo-controlled multicenter study of oseltamivir phosphate in the treatment of influenza infection in China.

NAI30008 *{published data only}*
A double-blind, randomized, placebo-controlled, parallel group, multi-center study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for five days in the treatment of influenza in patients 12 years or over diagnosed with asthma or chronic obstructive pulmonary disease.

NAI30009 *{published data only}*
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NAI30010 *{published data only}*
Hunter S, Reilly L, Sharp S, West M, Alfors S, Hammond

J, et al.A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within families.

NAIA2005 *{published data only}*
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NAIA3002 *{published data only}*
Elliott M, Flack N, Keene O, Szymborski P, Vega R (PharmaResearch, Inc). A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults.

NAIA3005 *{published data only}*
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NAIB3002 *{published data only}*
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WP16263 *{published data only}*
A randomized, double blind, parallel group, placebo controlled study of the effect of oseltamivir on ECG intervals in healthy subjects.

WV15670 *{published data only}*
Dorkings J. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomized controlled trial.

WV15671 *{published data only}*
Dorkings J. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial.

WV15673/WV15697 *{published data only}*
Efficacy of Ro 64-0796 when used as chemoprophylaxis against natural influenza infection.

WV15707 *{published data only}*
Grosse M. A multi-center, randomized, double-blind, placebo-controlled, parallel group study of oseltamivir treatment in elderly patients with influenza.

WV15708 *{published data only}*
A double-blind randomised placebo controlled study of Ro 64-0796 (also known as GS4104) used in elderly subjects for the prevention of clinical influenza during influenza season.

WV15730 *{published data only}*
Dorkings J. A double-blind, stratified, randomized, placebo controlled study of Ro 64-0796 (GS4104) in the treatment of influenza infection in adults.

WV15758 *{published data only}*
A double-blind, randomized, stratified, placebo-controlled study of Ro 64-0796 (also known as GS 4104) in the treatment of children with influenza.

WV15759/WV15871 *{published data only}*
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WV15799 *{published data only}*
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WV15819/WV15876/WV15978 *{published data only}*
A double-blind, randomized, stratified, placebo-controlled study of Ro 64-0796 (also known as GS4104) in the treatment of influenza infection in elderly patients.

WV15825 *{published data only}*
A double-blind, randomised, placebo-controlled study of Ro 64-0796 (also known as GS4104) used in elderly subjects for the prevention of clinical influenza during the influenza season.

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105934 *{published data only}*
A post-marketing surveillance to monitor the safety of RELENZA (zanamivir) administered in Korean subjects according to the prescribing information.

107485 *{published data only}*
An open label, single-dose, five-way crossover study examining relative oral bioavailability of zanamivir with bioenhancing excipients following direct release into mid-small intestine using gamma scintigraphy and the InteliSite Companion Capsule in healthy subjects.

108127 *{published data only}*
An open-label, non-randomized, single-dose study to evaluate serum zanamivir pharmacokinetics following intravenous administration to human subjects with renal impairment compared to subjects without renal impairment.

112311 *{published data only}*
Special drug use investigation for Relenza (resistant appearance).

112312 *{published data only}*
Special drug use investigation for Relenza (efficacy).

113268 *{published data only}*
Drug use investigation for Relenza.

113502 *{published data only}*
Prophylactic efficacy of Relenza against influenza A and B.

113625 *{published data only}*
A randomized, placebo controlled, 3-way crossover study to investigate the safety, tolerability, and pharmacokinetics of repeat dose zanamivir/placebo 10 mg administered twice daily for 5 days by a rotahaler compared to the diskhaler in healthy subjects.

113678 *{published data only}*
An open-label, multi-center, single arm study to evaluate the safety and tolerability of intravenous zanamivir in the treatment of hospitalized adult, adolescent and pediatric subjects with confirmed influenza infection.

114045 *{published data only}*
Collection of patients' background information Relenza® sentinel site monitoring program in Japan.

114373 *{published data only}*
A phase III international, randomized, double-blind, double-dummy study to evaluate the efficacy and safety of 300 mg or 600 mg of intravenous zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily in the treatment of hospitalized adults and adolescents with influenza.

167-02 *{published data only}*
(Zanamivir trial. Title unknown).

167-03 *{published data only}*
(Zanamivir trial. Title unknown).

167-04 *{published data only}*
(Zanamivir trial. Title unknown).

167-05 *{published data only}*
(Zanamivir trial. Title unknown).

ADS-TCAD-PO206 *{published data only}*
A randomized open label study comparing the efficacy, safety, and tolerability of oral administration of amantadine and ribavirin with oseltamivir versus oseltamivir to influenza A virus infected immunocompromised subjects.

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JNAI-02 *{published data only}*
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JNAI-03 *{published data only}*
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JP15734 *{published data only}*
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JP15735 *{published data only}*
Japanese MD study.

M76006 *{published data only}*
Early administration of oral oseltamivir increases the benefits of influenza treatment.

ML17713 *{published data only}*
Phase IV study on Tamiflu® capsule 75 in the elderly aged 80 years or older (a single dose oral administration study for assessing pharmacokinetics in the elderly not infected with influenza virus).

ML20542 *{published data only}*
Evaluation of combination therapy with oseltamivir and zanamivir versus monotherapy in the treatment of virologically confirmed influenza in primary care a randomised double blind controlled trial study.

ML21954 *{published data only}*
Efficacy and safety of combination therapies with oseltamivir & zanamivir or oseltamivir & amantadine versus oseltamivir monotherapy in the treatment of seasonal influenza A infection.

ML22789 *{published data only}*
An unblinded, comparative, randomized study of influenza A/H1N1 2009 resistance in patients with standard and double dose oseltamivir treatment.

ML22872 *{published data only}*
Viral shedding/resistance with double duration oseltamivir in infected patients (New Zealand).

ML22879 *{published data only}*
Viral shedding/resistance with standard dose/duration oseltamivir in infected patients (UK).

ML25018 *{published data only}*
A study of the relative oral bioavailability of the antiflu medicine oseltamivir (Tamiflu®) in patients in the intensive care unit.

ML25087 *{published data only}*
Viral shedding/resistance with double dose oseltamivir in infected patients (Australia).

ML25094 *{published data only}*
Nasogastric administration of OP in infected patients with respiratory failure.

ML25157 *{published data only}*
Oseltamivir pharmacokinetics in morbid obesity.

ML25176 *{published data only}*
Open-label pharmacokinetic of oseltamivir in healthy obese Thai adult subjects.

ML25179 *{published data only}*
A randomized, double-blinded controlled trial comparing high vs standard dose oseltamivir in severe, influenza infection in ICU. "ROSII Study".

ML25265 *{published data only}*
Probing the functional expression of carboxyl esterase in preterm neonates using oseltamivir: a pragmatic observational study.

ML25266 *{published data only}*
Plasma levels of oseltamivir in H1N1 infected patients supported by extracorporeal membrane oxygenation: a single-centre cohort study.

MP20691 *{published data only}*
Effect of probenecid on the pharmacokinetics of oseltamivir.

MV20043 *{published data only}*
A prospective study to assess household transmission of influenza and emergence and transmissibility of drug resistance to oseltamivir following treatment of children with influenza A and B.

MV20050 *{published data only}*
High-dose versus standard-dose oseltamivir for the treatment of severe influenza and Avian influenza: a phase II double-blind, randomized clinical trial.

MV22926 *{published data only}*
A study on higher-dose oseltamivir treatment's impact on viral clearance and clinical recovery in adults hospitalized with influenza.

MV22949 *{published data only}*
A study of the pharmacology of oseltamivir (Tamiflu) in pregnancy.

MV22951 *{published data only}*
Pharmacokinetics of Tamiflu® (oseltamivir) in patients receiving extracorporeal membrane oxygenation (ECMO) and or continuous venovenous hemodialysis (CVVHD).

MV22963 *{published data only}*
Pharmacokinetics of oseltamivir in critically ill adult patients.

MV22970 *{published data only}*
Observational study on the pharmacokinetics of oseltamivir in the treatment of influenza during lactation.

NAI106784 *{published data only}*
Phase I, open-label study to evaluate steady-state serum and pulmonary pharmacokinetics following intravenous administration of zanamivir in healthy adult subjects.

NAI108166 *{published data only}*
Phase 1, open-label study to evaluate potential pharmacokinetic interactions between orally-administered oseltamivir and intravenous zanamivir in healthy Thai adult subjects.

NAI10901 *{published data only}*
A double-blind, randomised, placebo-controlled study to evaluate the effect of inhaled zanamivir 10 mg od for 28 days on anti-haemagglutinin antibody production (HAI titre) following co-administration with Fluvirin™ trivalent influenza vaccine in healthy adult subjects.

NAI10902 *{published data only}*
An open label, randomized evaluation of the direct measurement of zanamivir concentrations in respiratory secretions following a single dose inhalation of 10 mg RELENZA™ via DISKHALER in health volunteers.

NAI40012 *{published data only}*
An open-label, multi-center study of the patient instructional leaflet for RELENZA DISKHALER.

NAIA1009 *{published data only}*
Pharmacokinetics of zanamivir (GG167) following inhaled administration in pediatric subjects with signs and symptoms of respiratory illness.

NAIB1001 *{published data only}*
(Zanamivir trial. Title unknown).

NAIB1002 *{published data only}*
A study to evaluate the effect of repeat doses of GG167 dry powder on pulmonary function and bronchial hyper-responsiveness in asthmatic subjects.

NAIB1007 *{published data only}*
(Zanamivir trial. Title unknown).

NCT00297050 *{published data only}*
A phase I double-blind, placebo-controlled, dose-escalating study to evaluate the safety and tolerability of intravenous peramivir in healthy subjects.

NCT00416962 *{published data only}*
An open-label, multiple dose, randomized, three-period crossover study in healthy volunteers to evaluate the effect of co-administration of amantadine 100 mg BID and oseltamivir 75 mg BID on the pharmacokinetic properties of amantadine and oseltamivir.

NCT00867139 *{published data only}*
TCAD vs. monotherapy for influenza A in immunocompromised patients.

NCT00957996 *{published data only}*
A phase 3, open-label, randomized study of the antiviral activity, safety, and tolerability of intravenous peramivir in

hospitalized subjects with confirmed or suspected influenza infection.

NCT01063933 *{published data only}*
A pharmacokinetic/pharmacodynamic and safety evaluation of investigational intravenous peramivir in children with influenza disease (CASG 117).

Not applicable (registry) *{published data only}*
(Oseltamivir trial. Title unknown).

NP15525 *{published data only}*
(Oseltamivir trial. Title unknown).

NP15717 *{published data only}*
Study of the PD and PK of the neuraminidase inhibitor Ro 64-0796 (GS4104) in the treatment of volunteers experimentally infected with human influenza B virus.

NP15718 *{published data only}*
An excretion balance and pharmacokinetic study of Ro 64-0796 after a single oral dose of 14C-labelled Ro 64-0796 and an intravenous dose of 14C-labelled Ro 64-0802 in healthy male subjects.

NP15719 *{published data only}*
Study of the pharmacokinetics and absolute bioavailability of the neuraminidase inhibitor Ro 64-0796.

NP15728 *{published data only}*
An open-label study of the effect of cimetidine and probenecid on the pharmacokinetics of Ro 64-0796/GS4104 in healthy subjects.

NP15729 *{published data only}*
An open-label bioequivalence and food effect study of the clinical trial and market formulations of Ro 64-0796 in healthy subjects.

NP15757 *{published data only}*
Study of the pharmacokinetics and pharmacodynamics of the neuraminidase inhibitor Ro 64-0796 (GS4104) in the prophylaxis of experimental infection of volunteers with the human influenza B virus.

NP15810 *{published data only}*
An open-label bioequivalence and food effect study of the clinical trial and market formulations of Ro 64-0796 in healthy subjects.

NP15826 *{published data only}*
An open-label study of pharmacokinetics of Ro 64-0796/GS4104 in children.

NP15827 *{published data only}*
Study of the pharmacodynamics of the neuraminidase inhibitor in the treatment of subjects experimentally infected with the human influenza B virus.

NP15881 *{published data only}*
(Oseltamivir trial. Title unknown).

NP15901 *{published data only}*
An open-label, two-way crossover pharmacokinetic drug interaction study of neuraminidase inhibitor Ro 64-0796/GS4104 and amoxicillin in healthy volunteers.

NP15912 *{published data only}*
(Oseltamivir trial. Title unknown).

NP16472 *{published data only}*
A single center, open label, multiple dose oral oseltamivir suspension study in end-stage-renal disease (ESRD) patients on hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD).

NP22770 *{published data only}*
An open-label, multiple dose, randomized, three-period crossover study in healthy subjects to evaluate the effect of co-administration of oseltamivir (RO0640796) 75 mg twice daily and rimantadine 100 mg twice daily on the pharmacokinetic properties of oseltamivir and rimantadine.

NP25138 *{published data only}*
A study of intravenous oseltamivir [Tamiflu] in infants with influenza.

NP25139 *{published data only}*
A study of intravenous Tamiflu (oseltamivir) in children with influenza.

NP25140 *{published data only}*
PK and safety of multiple ascending doses of iv oseltamivir in healthy adults.

NV20234 *{published data only}*
A randomized, double-blind trial evaluating conventional and high dose Tamiflu in the treatment of influenza in immunocompromised patients.

NV20235 *{published data only}*
A double-blind, randomized, placebo controlled multicenter trial of oseltamivir for the seasonal prophylaxis of influenza in immunocompromised patients.

NV20237 *{published data only}*
An influenza resistance information study (IRIS).

NV22155 *{published data only}*
A randomized, multicenter trial of oseltamivir [Tamiflu] doses of 75 mg for 5 or 10 days versus 150 mg for 5 or 10 days to evaluate the effect on the duration of viral shedding in influenza patients with pandemic (H1N1) 2009.

NV22158 *{published data only}*
Registry avian/pandemic study.

NV25118 *{published data only}*
A randomized, multicenter, parallel study of the safety, pharmacokinetics and the effect on viral activity of intravenously administered Tamiflu [oseltamivir] in patients with influenza over 13 years of age.

NV25182 *{published data only}*
Infant Tamiflu safety study.

PP15974 *{published data only}*
A single oral dose, multi-center, open label study of the pharmacokinetics, safety and tolerability of Ro 64-0796/GS4104 in ESRD subjects on hemodialysis and peritoneal dialysis.

PP16351 *{published data only}*
An open label study of the pharmacokinetics of oseltamivir (Ro 64-0796) in children aged 0 - 5 years old after a single dose.

PP16361 *{published data only}*
Double-blind, randomized, placebo controlled, single ascending i.v. dose study of the tolerability (with emphasis of nausea and vomiting), safety, pharmacokinetics of oseltamivir (Ro 64-0796) and its active metabolite oseltamivir carboxylate (Ro 64-0802) in healthy male volunteers.

PV15615 *{published data only}*
GS97802 - challenge flu A treatment.

PV15616 *{published data only}*
GS-97801 challenge flu A treatment.

WP15517 *{published data only}*
Single ascending oral dose study of the tolerability, safety and pharmacokinetics (including effect of food) of the neuraminidase inhibitor GS4104 in healthy volunteers.

WP15525 *{published data only}*
Multiple ascending oral dose study of the tolerability, safety and pharmacokinetics of the neuraminidase inhibitor, GS4104 in healthy volunteers.

WP15647 *{published data only}*
Multiple ascending oral dose study of the tolerability, safety and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 in healthy elderly volunteers.

WP15648 *{published data only}*
Multiple oral dose study of the pharmacokinetics, tolerability and safety of the neuraminidase inhibitor Ro 64-0796 in patients with renal impairment.

WP15676 *{published data only}*
Study of the safety and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 in healthy volunteers when administered concomitantly with paracetamol (acetaminophen).

WP15979 *{published data only}*
An open-label, relative bioavailability study of the phase III pediatric clinical trial and market formulations of Ro 64-0796 in healthy volunteers.

WP16094 *{published data only}*
An open-label, three-way crossover, pharmacokinetic drug interaction study of neuraminidase inhibitor Ro 64-0796 and aspirin in healthy subjects.

WP16134 *{published data only}*
An open label bioequivalence and food effect study of the enteric coated and immediate release formulations of oseltamivir in healthy subjects.

WP16137 *{published data only}*
An open-label, bioequivalence study of the phase III pediatric clinical trial and market oral suspension formulations of Ro 64-0796 in healthy volunteers.

WP16225 *{published data only}*
An open-label, relative bioavailability study of the market suspension (with improved process), the clinical trial suspension and market capsule formulation of Ro 64-0796 (Tamiflu, oseltamivir) in healthy subjects.

WP16226 *{published data only}*
A study of the pharmacokinetics of oseltamivir (Ro 64-796) and its active metabolite Ro 64-0802 following single oral dosing of Ro 64-0796 to healthy volunteers and patients with moderate hepatic impairment.

WP16254 *{published data only}*
A pharmacokinetic drug interaction study of oseltamivir (Ro 64-0796) and antacid in healthy volunteers.

WP17721 *{published data only}*
Clinical pharmacokinetics of cyclosporine or mycophenolate with and without a concurrent single dose of oseltamivir phosphate in patients with a renal transplant.

WP18308 *{published data only}*
Comparison of the pharmacokinetics of Ro 64-0802 following a single dose of oseltamivir phosphate either in a capsule or a drinking solution.

WP20727 *{published data only}*
A combined single ascending dose, multiple ascending dose and exploratory bioavailability study to investigate the safety, tolerability and pharmacokinetics of intravenous Ro 64-0796 in healthy volunteers.

WP20749 *{published data only}*
Oseltamivir treatment for children less than 24 months of age with influenza.

WP21272 *{published data only}*
An open-label, randomized 2-period crossover study to investigate the pharmacodynamics, pharmacokinetics, safety and tolerability of warfarin, and the pharmacokinetics, safety and tolerability of oseltamivir, when given in combination.

WP22849 *{published data only}*
An open label, prospective, pharmacokinetic/ pharmacodynamic and safety evaluation of oseltamivir (Tamiflu®) in the treatment of infants 0 to < 12 months of age with confirmed influenza infection.

WV16139 *{published data only}*
(Oseltamivir trial. Title unknown).

WV16193 *{published data only}*
A randomized, open-label, parallel group study of oseltamivir used for management of influenza in households.

References to studies awaiting assessment

167-101 *{published data only}*
(Zanamivir trial. Title unknown).

167T3-11 *{published data only}*
(Zanamivir trial. Title unknown).

JNAI-01 *{published data only}*
(Zanamivir trial. Title unknown).

JNAI-04 *{published data only}*
(Zanamivir trial. Title unknown).

JNAI-07 *{published data only}*
(Zanamivir trial. Title unknown).

JV15823 *{published data only}*
Phase 3 study for treatment of influenza with Ro64-0796.

JV15824 *{published data only}*
Phase 3 study for prophylaxis of influenza with Ro64-0796.

JV16284 *{published data only}*
An open trial of Ro64-0796 for treatment in children with influenza.

ML20589 *{published data only}*
Economic and social benefits of treating and preventing influenza in aged care facilities.

ML20910 *{published data only}*
A randomized, open label study to evaluate the effect of Tamiflu on viral shedding and on serum and cytoplasmic inflammatory cytokine concentrations in patients with laboratory-confirmed influenza.

ML21776 *{published data only}*
Pilot study to develop a model to evaluate nosocomial transmission of influenza.

MV21118 *{published data only}*
A double-blind, randomized, placebo-controlled study of early oseltamivir treatment of influenza in children 1-3 years of age.

MV21737 *{published data only}*
A phase 4, multi-center, randomized, double blind, placebo controlled study, to evaluate the safety of inhaled zanamivir 10 mg versus placebo and oral oseltamivir 75 mg versus placebo for influenza prophylaxis in healthy volunteers for 16 weeks.

MV21879 *{published data only}*
Efficacy of oseltamivir in reducing the duration of clinical illness, viral shedding, and transmissibility reduction within households among participants in an influenza disease burden surveillance cohort in urban Dhaka, Bangladesh.

MV22841 *{published data only}*
Viral shedding/resistance with standard dose/duration oseltamivir in infected patients (South Africa).

MV22940 *{published data only}*
A randomised controlled trial on the effect of post-exposure oseltamivir prophylaxis on influenza transmission in nursing homes (PEPpIE).

NAI30011 *{published data only}*
A randomised, double-blind, placebo-controlled study to evaluate the impact of inhaled zanamivir treatment on workplace attendance due to influenza A and B infections.

NAI30012 *{published data only}*
A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for five days in the treatment of symptomatic influenza A and B viral infections in subjects aged over 65 years.

NAI30015 *{published data only}*
A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10mg administered twice daily for five days in the treatment of symptomatic influenza A and B viral infections in armed services personnel.

NAI30020 *{published data only}*
A double-blind, randomised, placebo-controlled, multicenter study in 2 parallel groups, to investigate the efficacy and safety of inhaled zanamivir (10 mg bd. via Diskhaler), for 5 days, in high risk patients with symptomatic influenza A and / or B infection.

NAI30028 *{published data only}*
A double-blind, randomised, placebo-controlled, multicenter study in 2 parallel groups, to investigate the efficacy and safety of inhaled zanamivir (10 mg bd via Diskhaler), for 5 days, in children aged 5 to 12 years with symptomatic influenza A and / or B infection.

NAI30031 *{published data only}*
A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within households.

NAI30034 *{published data only}*
A double-blind, randomized, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day for 28 days in the prevention of symptomatic influenza A and B viral infections in community-dwelling high-risk populations.

NAIA/B2008 *{published data only}*
(Zanamivir trial. Title unknown).

NAIA/B2009 *{published data only}*
(Zanamivir trial. Title unknown).

NAIA2006 *{published data only}*
(Zanamivir trial. Title unknown).

NAIA2010 *{published data only}*
(Zanamivir trial. Title unknown).

NAIA3003 *{published data only}*
A double-blind, randomized, parallel-group, multi-center study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day compared to the standard of care in controlling nursing home influenza outbreaks.

NAIA3004 *{published data only}*
A double-blind, randomized, placebo-controlled, parallel-group, multi-center study to investigate the efficacy and safety of inhaled zanamivir 10 mg once a day in controlling nursing home influenza outbreaks.

NAIB2006 *{published data only}*
(Zanamivir trial. Title unknown).

NCT00419263 *{published data only}*
A phase II, multicenter, randomized, double-mask, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza.

NCT00453999 *{published data only}*
A phase II, multicenter, randomized, double-mask, double-dummy study comparing the efficacy and safety of peramivir

administered intravenously once daily versus oseltamivir administered orally twice daily in adults with acute serious or potentially life-threatening influenza.

NCT00486980 *{published data only}*
A phase 3 multicenter, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza.

NCT00555893 *{published data only}*
Monitoring influenza severity and transmission on Tamiflu (MISTT).

NCT00610935 *{published data only}*
A phase 3 multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza.

NCT00705406 *{published data only}*
A phase II, multicenter, randomized, placebo-controlled, study to evaluate the efficacy and safety of intramuscular peramivir 600 mg in subjects with uncomplicated acute influenza.

NCT00958776 *{published data only}*
A phase 3, multicenter, randomized, double-blind, controlled study to evaluate the efficacy and safety of peramivir administered intravenously in addition to standard of care compared to standard of care alone in adults and adolescents who are hospitalized due to serious influenza.

NV16871 *{published data only}*
A double-blind, randomized, stratified, placebo-controlled study of oseltamivir in the treatment of influenza in children with asthma.

NV20236 *{published data only}*
An open label, multicenter trial of oseltamivir prophylaxis of seasonal influenza in children.

PE-01 *{published data only}*
(Zanamivir trial. Title unknown).

WV15731 *{published data only}*
A double-blind, randomized, stratified pilot study of Ro 64-0796 (also known as GS4104) in children with influenza.

WV16277 *{published data only}*
A double-blind, randomised, stratified, placebo-controlled study of oseltamivir in the treatment of influenza infection in patients.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

M76001

Methods	Study design: randomised, double-blind, placebo-controlled, parallel study stratified by onset of influenza symptoms. Influenza surveillance programme set up to track outbreak of virus across the continental United States Location, number of centres: USA (164 centres) Duration of study: 21 (+/-4) days
Participants	Number screened: not available Number randomised: 1459 (oseltamivir: 965; placebo: 482. N randomised but did not receive study drug: 12) Number completed: 1344 M = 44% F = 56% Mean age: 35 years Baseline details: 81% Caucasian Inclusion criteria 1. Ambulatory male and female outpatients, aged ≥ 13 to 80 years of age 2. Symptoms consistent with influenza 3. Fever ≥ 100 °F (documented in the office/clinic) PLUS at least 1 respiratory symptom (cough, sore throat, nasal congestion) PLUS at least 1 constitutional symptom (chills/sweats (feeling feverish), headache, myalgia (aches and pains), fatigue) 4. No more than 36 hours post onset of feeling unwell 5. Negative urine pregnancy test in women of childbearing potential 6. Willing and able to comprehend and give written informed consent Exclusion criteria 1. Patients with unstable or uncontrolled renal, cardiac, pulmonary, vascular, neurologic or diabetes, thyroid disorders, adrenal disease) disease, hepatitis or cirrhosis. Stable disease is defined as disease not requiring a major change of therapy or hospitalisation for 8 weeks prior to the first dose of study drug 2. Transplant recipients 3. Patients taking systemic steroids or immunosuppressant therapies 4. Active cancer at any site (patients with basal cell carcinoma or a previous history of cancer in remission and not requiring therapy were eligible) 5. Known HIV infection 6. Pregnant or breast-feeding females 7. Female patients of childbearing potential unable to use an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study therapy 8. Allergy to any excipients in the capsule (Section Oseltamivir/Ro 64-0796) or acetaminophen (paracetamol) 9. Patients who experienced a previous episode of acute upper respiratory tract infection (URTI), otitis, bronchitis or sinusitis within 2 weeks prior to study Day 1 10. Received antiviral therapy for influenza within 2 weeks prior to study Day 1 11. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry

	12. A clinically relevant history of abuse of alcohol or other drugs **Definition of patient populations for analysis** ***Intention-to-treat (ITT) infected population (N = 1063)*** This population was the primary analysis population and was used for summaries and analyses of efficacy parameters and consisted of the same patients as the ITT population, but excluded patients who did not have laboratory-confirmed infections. Patients were analysed according to the groups to which they were randomised ***ITT population (N = 1447)*** The ITT population consisted of all patients who took at least 1 dose of study medication and had at least 1 efficacy measurement. Patients with protocol violations or deviations were retained in the ITT population. Patients were analysed according to the groups to which they were randomised ***Safety population (N = 1447)*** Not defined ***Standard population (N = 932)*** This population was used for summaries of selected efficacy parameters. It included all patients who were randomised, who had no major protocol violations or deviations, who had laboratory-confirmed influenza and who received at least the first 6 scheduled doses
Interventions	Intervention Oseltamivir (size 2 capsules) 75 mg bid Control Matching placebo (size 2 capsules) bid For each treatment arm, patients were provided with a blister pack containing 12 capsules for 10 doses (2 extra capsules in case of damage or mishandling) Treatment period 5 days Follow-up period 12 to 18 days post-treatment Co-interventions Acetaminophen 500 mg was also provided for symptomatic relief, if necessary
Outcomes	***Primary outcome*** Duration of illness Length of time until alleviation of the symptoms of influenza (nasal congestion, sore throat, cough, aches and pains, fatigue, headaches and chills/sweats). The time to alleviation of all 7 symptoms correspond to the duration over which subsequent area under the curve (AUC) calculations were made ***Secondary outcomes*** 1. Severity of illness 2. Duration of symptoms 3. Sequelae/complications due to Influenza 4. Tertiary efficacy parameters

	5. Serology 6. Use of symptom relief medications 7. Quality of life 8. Adverse events
Notes	The final Protocol is dated 2 October 1998. There were no amendments to the Protocol. The first patients received treatment on 24 December 1998

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	"The randomisation numbers were allocated by a central randomisation service, ICTI (Interactive Clinical Technologies Inc., Princeton, NJ)." "The investigator or study coordinator telephoned the Randomization Center to report their centre's identification number, the patient's initials, date of birth and time from the onset of flu symptoms. The Randomization Center then assigned a unique patient identification number and a corresponding medication number for each patient. The investigator or coordinator entered these numbers in the appropriate place on the case report form."
Incomplete outcome data (attrition bias) Symptoms	High risk	Data from study participants without influenza (i.e. the ITT population) were not included in the analysis of symptoms
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all participants irrespective of compliance with treatment or infection status
Selective reporting (reporting bias)	High risk	Summary statistics for ITT population reported in a separate CSR module not made available to the review authors

M76001 (*Continued*)

Other bias	Unclear risk	No information available on placebo contents
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"No open key to the randomisations code was available at the Study Center (...). A scratch-off, double-blind tear-off label was attached to the study medication. This blinded label indicated the treatment identity for the drug dispensed. These sealed labels were torn off prior to distribution to the patient, and then placed on the CRF. A duplicate set of sealed codes was kept by Roche Laboratories, Inc. In the event of a medical emergency the blind could be broken, if this was considered absolutely necessary to properly manage the patient."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the randomisations code was available (...) to the Roche Monitors, statisticians or at Roche Headquarters."

ML16369

Methods	Study design: a randomised, double-blind, placebo-controlled trial conducted during the influenza epidemic season Location, number of centres: Beijing and Shanghai, China; 7 study centres Duration of study: 21 days
Participants	Number screened: not available Number randomised: 478 (baseline data on ITTI population only: 273 (oseltamivir: 134; placebo: 139)) Number completed: 451 M = (ITTI) 50% F = (ITTI) 50% Mean age: 31 years Baseline details: baseline information only available for the ITTI population Smoking history: 20%; influenza virus: A (62%); B (36.5%); unknown (1.5%) Inclusion criteria 1. Male/female patients with symptoms consistent with influenza: fever $\geq$ 37.8 °C PLUS at least 2 of the following symptoms (coryza/nasal congestion, sore throat, cough, myalgia/muscles aches and pain, fatigue, headache or chills/sweats) during an influenza outbreak in the community 2. No more than 36 hours post onset of feeling unwell 3. Aged $\geq$18 and $\leq$65 years of age 4. Willing and able to comprehend and give written informed consent 5. Patients must agree to utilise an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study therapy and females of childbearing potential must have a negative urine pregnancy test prior to

	drug dosing Exclusion criteria 1. Presentation > 36 hours post onset of feeling unwell 2. Patients with active clinically significant renal, cardiac, pulmonary, vascular, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease), immunodeficiency disorders, cancer, hepatitis or cirrhosis 3. High likelihood of bacterial infection, based on signs, symptoms or laboratory tests, e.g. WBC ³ 10.0 ´ 10^9/L or N ≥ 90% 4. Patients taking steroids or immuno-suppressant therapies 5. Allergy to any excipients in the capsule (see section 8.1.) or paracetamol/ acetaminophen 6. Asthmatics and patients with COPD 7. Patients who experienced a previous episode of acute upper respiratory tract infection (URTI), otitis, bronchitis or sinusitis or received antibiotics for URTI, otitis, sinusitis or bronchitis or antiviral therapy for influenza, e.g. amantadine or rimantadine, within 2 weeks prior to study day 1 8. Dementia or other psychiatric condition that might interfere with the patient's ability to assess influenza symptomatology 9. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry 10. Administration of influenza vaccine less than 12 months prior to study day 1 11. A clinically relevant history of abuse of alcohol or other drugs 12. Pregnant or breast-feeding females 13. Transplant recipients 14. Known HIV infection **Definition of patient populations for analysis** ***ITT infected population (N = 273)*** The population for primary efficacy analyses was the intention-to-treat-infected (ITTI) population comprising randomised participants who received at least 1 dose of study drug and had laboratory-confirmed influenza (a positive culture on day 1 and/or ≥ 4 fold increase in HAI antibody between baseline and day 21 of the study) ***ITT population (N = 451)*** The ITT population consisted of all participants who took at least 1 dose of study medication. The safety population included all participants who received at least 1 dose of study medication and who had at least 1 safety follow-up, whether or not withdrawn prematurely ***Safety population (N = 459)*** Not defined
Interventions	Intervention Oseltamivir 75 mg (Ro 64-0796) bid Control Matching placebo bid Treatment period 5 days Follow-up period Up to day 21

	Co-interventions Contents of rescue pack of medication provided to study participants not reported
Outcomes	***Primary outcome*** Duration of illness: the median duration was presented for each treatment group together with 95% confidence intervals. Kaplan-Meier graphs of duration of symptoms according to treatment group were provided. Although the primary analysis for the primary parameter was done using the ITTI population, an additional analysis for the primary parameter was done using the ITT population ***Secondary outcomes*** 1. Extent and severity of Illness 2. Symptoms 3. Symptom relief medications consumption 4. Secondary illness 5. Adverse events
Notes	Conducted during influenza season from January to April 2001

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	"In each centre, the eligible patient was assigned sequentially by the investigator a randomisation number which corresponded to either oseltamivir phosphate or placebo (...) The randomisation code was prepared and designed by Roche, Basal."
Incomplete outcome data (attrition bias) Symptoms	Low risk	ITT population outcome data reported in CONSORT-based extraction
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all participants irrespective of compliance with treatment or infection status
Selective reporting (reporting bias)	Low risk	Symptoms and outcomes of primary interest were available for ITT population

ML16369 (*Continued*)

Other bias	Unclear risk	No information available on placebo contents
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants and staff remained blinded to allocation status throughout the study. The investigator received a sealed envelope for each subject in the trial, for use in emergencies. Each envelope contained the identity of a subject's treatment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment

NAI30008

Methods	Study design: double-blind, randomised, placebo-controlled, parallel-group, multi centre study in people with asthma or COPD Location, number of centres: USA (46 centres); UK (36); France (23); South Africa (11); Norway (10); Canada (9); Australia (6); Germany (5); Slovakia (3); Austria (2); Belgium (2); Denmark (2); Sweden (2) Chile (1); Israel (1) Duration of study: 4 weeks
Participants	Number screened: not available Number randomised: 525 (zanamivir: 262; placebo: 263) Number completed: 488 M = 58% F = 42% Mean age: 39.4 years Baseline details Inclusion criteria 1. ≥ 12 years of age with influenza-like illness (temp. ≥ 37.8 °C and 2/4 symptoms of headache, sore throat, cough, muscle/joint pains) 2. Diagnosed asthma or COPD 3. Influenza must have been circulating in the community 4. Participants had to take the first dose of study medication within 36 hours (1.5 days) of the onset of their influenza-like symptoms Exclusion criteria 1. Bacterial infection 2. Antivirals in 7 days prior to study **Definition of patient populations for analysis** ***Influenza-positive population (N = 313)*** Participants who took at least 1 dose of study drug and confirmed influenza. Confirmation of influenza was based on a positive result by baseline virus culture or PCR assay, or seroconversion ***ITT (N = 525)***

NAI30008 (*Continued*)

	All participants randomised ***Safety population (N = 524)*** All participants randomised to treatment who took at least 1 dose of study medication
Interventions	Intervention Inhaled zanamivir via diskhaler/rota disk, 5 mg 2 inhalations bid (20 mg total) Control Placebo Treatment period 5 days Follow-up period 3.3 weeks post-treatment Co-interventions Pack of relief medication (paracetamol and cough mixture)
Outcomes	***Primary outcomes*** Alleviation of influenza symptoms. Measured in half-day intervals and defined as no fever (temperature < 37.8 °C and a feverishness score of 'none') and headache, muscle/joint aches and pains, sore throat and cough recorded as 'none' or 'mild'. Alleviation had to be maintained for a further 24 h ***Secondary outcomes*** 1. Lung function 2. Complications of influenza 3. Adverse events
Notes	Study period: June 1998 to April 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Unclear risk	Described as randomised, no other details were available
Incomplete outcome data (attrition bias) Symptoms	Low risk	Data presented on both the ITT and IP populations
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The

NAI30008 (*Continued*)

		influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Unclear risk	Safety population based on randomised participants
Selective reporting (reporting bias)	Unclear risk	Symptoms and outcomes of primary interest were available for ITT population
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo described; further description not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details available

NAI30009

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group, multi centre study in children Location, number of centres: USA (36 centres); Canada (6); France (7); Germany (6); Belgium (2); Finland (2); Spain (2); Russia (2); Sweden (2); Israel (1) United Kingdom (1) Duration of study: 14 to 28 days
Participants	Number screened: not described Number randomised: 471 (zanamivir: 224; placebo: 247) Number completed: 458 M = 57 F = 43 Mean age: 8.71 years Baseline details: 90% Caucasian; 2% current vaccination Inclusion criteria 1. 5 to 12 years old 2. Females were of non-childbearing potential or had a negative pregnancy test (urine) at study entry 3. Participants with influenza-like illness (ILI) as defined by the presence of fever (temperature $\geq$ 37.8 °C) and no other clinical evidence of bacterial infection. Fever documented at clinic during the first treatment visit. Where possible, consideration was given to delaying anti-pyretic medication until study entry 4. Participants able to take the first dose of study medication in the first 36 hours (1.5 days) of ILI 5. Influenza was circulating in the community (according to the guidelines agreed with each centre)

	6. Ability to use diskhaler as assessed during screening 7. Participant's parents were willing and able to adhere to protocol (diary card and health outcome questionnaires were completed by subject's parent) 8. Participants could be managed as outpatients according to investigator opinion 9. Parents were willing and able to give written informed consent to have their child participate in the study. Written assent also obtained from child as appropriate Exclusion criteria 1. Pregnancy, lactation or at risk of becoming pregnant during the study 2. Participants known or suspected to be hypersensitive to any component of study medication/relief medications 3. Participants who had received any influenza antiviral therapy in the previous 7 days, e.g. rimantadine, amantadine or ribavirin 4. Participants who received an investigational drug in the previous 30 days 5. Participants with psychiatric disorders/any medical condition that could affect completion of the study/confound safety or efficacy data 6. Immunocompromised participants (e.g. HIV infection or systemic chemotherapy) 7. Cystic fibrosis **Definition of patient populations for analysis** ***Safety population (N = 471)*** All participants who took at least 1 dose of study medication ***Influenza-positive population (N = 346)*** All participants in the safety population with confirmed influenza
Interventions	Intervention Inhaled zanamivir 5 mg 2 inhalations bid (20 mg total) via rota disk/diskhaler Control Matching placebo Treatment period 5 days Follow-up period 9 to 23 days post-treatment Co-interventions Relief medication (cough suppressant and paracetamol)
Outcomes	***Primary outcomes*** Time to alleviation of clinically significant symptoms of influenza. Defined as no fever (temperature < 37.8 °C), cough recorded as "none" or "mild" and muscle/joint aches and pains, sore throat, feverishness/chills and headache recorded as "absent or minimal". All of these had to be maintained for 24 hours ***Secondary outcomes*** 1. Time to alleviation of clinically significant symptoms of influenza and no use of relief medication 2. Mean overall influenza score (Days 2 to 5) 3. Body temperature

	4. Health resource use (e.g. hospitalisation) 5. Virology 6. Adverse events 7. Use of relief medication	
Notes	Study conducted: 11 January 1999 to 19 April 1999	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Low risk	"Subjects were assigned to study treatment in accordance with the randomisations schedule provided by the Sponsor. An unblocked randomisations schedule was used."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Data presented on both the ITT and IP populations
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Safety population based on randomised participants
Selective reporting (reporting bias)	Low risk	Symptoms and outcomes of primary interest were available for ITT population
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding maintained at level of sponsor

NAI30010

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group study. Families were randomised as a unit when an index case was detected Location, number of centres: USA (11 centres); Canada (2); Finland (1); UK (1) Duration of study: 11 days
Participants	Number screened: not available Number randomised: 337 families (1167 participants in total; zanamivir: 169 (577 participants); placebo: 168 families (590 participants)) Number completed: 1167 M = 44% F = 56% Mean age: 24.3 years Baseline details: 89% Caucasian; 14% vaccinated Inclusion criteria: 1. Families were randomised to treatment when a member of the family living in the household (index case) developed influenza defined by presence of at least 2 from: fever >= 37.8 °C, cough, headache, sore throat, myalgia, feverishness; when influenza was known to be circulating in the community 2. Contacts and index cases had to start treatment within 36 hours of the index case 3. Becoming ill 4. Families had to have 2 to 5 members living at home for the study period 5. At least 1 adult, ≥18 years of age, and 1 child, 5 to 17 years of age had to be part of the family unit 6. Index case >= 5 years with at least 2 of: fever >= 37.8 °C, cough, headache, sore throat, myalgia, feverishness Exclusion criteria Not specified **Definition of patient populations for analysis** ***ITT population (N = 1158)*** Index cases ≥ 5 years and contact cases ≥ 5 years randomised to treatment. Index cases and contact cases < 5 years of age who did not receive treatment, were excluded from the ITT analysis. The family was included if at least 1 randomised family member was in the population ***Safety population (N = 1158)*** Index cases and contact cases who took at least 1 dose of study medication. Randomised participants excluded if there was clear evidence of failure to take study medication
Interventions	Intervention Inhaled zanamivir 5 mg, 2 inhalations, via rota disk/diskhaler bid (total dose of 20 mg daily) Control Matching placebo Treatment period 10 days Follow-up period

NAI30010 (*Continued*)

	1 day post-treatment Co-interventions Relief medication pack (contents not specified)
Outcomes	***Primary outcomes*** Proportion of families with at least 1 randomised contact developing symptomatic, laboratory-confirmed influenza A or B infection. Defined as presence of at least 2 of the following symptoms: fever ≥ 37.8 °C, cough, headache, sore throat, myalgia, feverishness and laboratory confirmation ***Secondary outcomes*** 1. Proportion of families with 1 contact who developed laboratory-confirmed influenza infection 2. Proportion of families with 1 randomised contact developed symptomatic, laboratory-confirmed influenza infection and where the symptoms began any time from the start of treatment to Day 11 3. Proportion of randomised families with 1 randomised contact who developed a temperature ≥ 37.8 °C during Days 1 to 11 4. Proportion of randomised families with at least 1 contact case (including non-treated contact cases < 5 years of age) who developed symptomatic, laboratory-confirmed influenza infection 5. Proportion of randomised families in whom at least 1 randomised member developed a secondary complication of influenza 6. Adverse events
Notes	Study Period: October 1998 to May 1999

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Unclear risk	Inadequate information available to ascertain concealment of allocation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Not applicable to this study design (prophylaxis study)
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Safety population based on randomised participants

NAI30010 (*Continued*)

Selective reporting (reporting bias)	Low risk	Outcomes of primary interest to post-exposure prophylaxis were available from the study report
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo delivered in same inhaler device as treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment

NAIA2005

Methods	Study design: randomised, double-blind, placebo-controlled trial Location, number of centres: USA (30 centres); Canada (8) Duration of study: 21 days
Participants	Number screened: not specified Number randomised: 220 (inhaled zanamivir: 68; inhaled and intranasal zanamivir: 71; placebo: 81) Number completed: 204 M = 61% F = 39% Mean age: 32 years Baseline details: 83% Caucasian; 25% smokers Inclusion criteria 1. Male or female > 13 years 2. Females of childbearing potential/pre-menarchal females with negative pregnancy test. Those at risk of pregnancy had to be taking adequate contraceptive precautions 3. Otherwise in good health 4. Influenza-like illness (ILI) for 48 hours: fever (≥ 37.8 °C or 100.1 °F) and at least 2 of: headache, myalgia, cough, sore throat 5. Influenza was circulating in the community 6. Willing and able to adhere to protocol 7. Willing and able to use diskhaler and aqueous nasal spray devices 8. Willing and able to give informed consent to participate in the studies Exclusion criteria 1. Suspected bacterial infection 2. Use of anti-infective agents within previous 7 days 3. Received influenza vaccine since 1 October 1994 (study published in 1997) 4. Unable/unwilling to take relief medications provided if needed 5. Risk of developing complications from influenza infections (e.g. chronic active disorders of the cardiovascular (except uncomplicated hypertension) or pulmonary systems (including asthma), chronic metabolic disease (including diabetes mellitus),

	hepatic or renal dysfunction, or immunosuppression) 6. Unstable chronic illness 7. Concurrent medical condition that could interfere with evaluations of safety or efficacy 8. Currently receiving intranasal or inhaled medication 9. Pregnant or breast-feeding females or those likely to become pregnant during the study 10. Use of investigational drug in the previous 30 days 11. Evidence or history of abuse of any drug substance **Definition of patient populations for analysis** ***Influenza-positive population (N = 111)*** All participants in the ITT population with confirmed influenza. This was the secondary population for analysis of efficacy. Participants were included in this population who had a positive confirmation of influenza from any pre-treatment diagnostic sample or from the serology results. If the diagnostic sample and the serology were both positive but indicated different influenza types, the influenza type was assigned according to the diagnostic sample result ***ITT population (N = 220)*** All randomised participants, regardless of whether the study drug was actually taken or whether the patient completed the study medication as per the protocol. This was the primary population for assessing efficacy. Data for patients who did not take study medication as per the randomisations schedule was, for the purposes of analysis, included in the treatment group to which the patient was randomised ***Safety population (N = 220)*** All participants randomised to treatment who took at least 1 dose of study medication. This was the primary population for safety analysis. Safety population did not include anyone if there was clear evidence of failure to take any study medication
Interventions	Intervention 1. Inhaled zanamivir 2 inhalations (5 mg per inhalation) twice daily via diskhaler plus placebo 2 sprays per nostril twice daily (total daily dose 20 mg) 2. Inhaled zanamivir 2 inhalations (5 mg per inhalation) twice daily via diskhaler plus zanamivir 2 intranasal sprays (1.6 mg per spray) per nostril twice daily (total daily dose 20 mg inhaled and 6.4 mg intranasal) Control Inhaled placebo 2 inhalations twice daily, plus placebo 2 sprays per nostril twice daily Treatment period 5 days Follow-up period 16 days post-treatment Co-interventions Acetaminophen, dextromethorphan hydrobromide and pseudoephedrine hydrochloride
Outcomes	***Primary outcomes*** Time to alleviation of major influenza symptoms. Defined according to "feverishness" if

	headache, myalgia, cough and sore throat were recorded as none or mild AND a feverishness score recorded as none. Alleviation could also be defined according to "temperature" if headache, myalgia, cough and sore throat were recorded as none or mild AND a temperature recorded as < 37.8 °C. All of these had to be maintained for a further 24 hours for both definitions ***Secondary outcomes*** 1. Time to alleviation of feverishness, headache and myalgia 2. Time to eradication of major signs and symptoms of influenza 3. Time to alleviation and eradication of individual symptoms of influenza 4. Mean symptom score for 5 symptoms of feverishness, headache, myalgia, cough and sore throat 5. Mean daily temperature 6. Return to normal activities 7. Number of days that a symptom recorded as 'moderate' or 'severe' 8. Number of days that overall symptom assessment recorded as 'moderate' or 'severe' 9. Number of days that sleep disturbance recorded as 'moderate' or 'severe' 10. Use of relief medication 11. Investigator global assessment of symptoms 12. Day at which viral shedding fell below limit of quantitation (core centres only) 13. Area under the viral shedding curve (core centres only) 14. Adverse events
Notes	Major protocol amendments 1. Modified the inclusion criteria to specify fever as a temperature ≥ 37.8 °C or 100.1 °F 2. Changed patient populations from S = subset of patients at centres with experience in virology and X = all patients to C = core centre patients (centres with experience in virology), T = target patients (patients with whom symptom assessments and diary cards were reviewed by study site personnel) and X = all patients 3. Defined target patient population as 1 out of every 6 patients (except core centre patients) who was targeted for additional face-to-face diary card review and clinical symptom assessment by site study staff on Days 2, 4 and 8 4. Modified adverse events to include those that were temporally related to study drug administration 5. Clarified the clinical symptom assessment and the diary card review for the core centre and target patients 6. Added section on unscheduled visits and clarified the withdrawal information 7. Revised statistical methods section 8. Changed 1 exclusion criterion from patients with influenza vaccines administered since August 1993 to patients with influenza vaccines administered since 1 October 1994 Study period: not specified in CONSORT-based extraction

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

NAIA2005 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Low risk	"…randomisations code was supplied to the GWRD Pharmaceutical Supplies Department by the GWI Medical Data Sciences Department." "Each investigator was provided with a sealed envelope containing the individual code break envelopes for patients in their centre."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Data from infected and non-infected participants were available
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Safety population based on randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes of primary interest to the review available from the study report
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo described "The investigator, all study staff, patients (…) were blinded as to the study treatment (zanamivir or placebo) administered."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"…the monitors were blinded as to the study treatment (zanamivir or placebo) administered."

NAIA3002

Methods	Study design: double-blind, randomised placebo-controlled study Location, number of centres: USA (72 centres); Canada (12) Duration of study: 28 days

Participants	Number screened: not specified Number randomised: 777 (zanamivir: 412; placebo: 365) Number completed: 735 M = 48% F = 52% Mean age: 35 years Baseline details: 86% Caucasian; 21% smokers Inclusion criteria 1. Males/females aged ≥12 years 2. Women of childbearing potential had to have a negative pregnancy test before receiving study medication. Those at risk of pregnancy must have taken adequate contraceptive precautions during the study period 3. Influenza-like illness (ILI) defined by temperature 37.8 °C and at least 2 of the following 4 symptoms: headache, muscle/joint aches and pains (e.g. myalgia/arthralgia) , sore throat and/or cough. Participants aged 65 years could have a lower temperature (≥ 37.2 °C) 4. Participants able to take first dose of study medication on first or second calendar day of their influenza-like symptoms 5. Influenza was circulating in the community 6. Ability to use diskhaler 7. Willing and able to adhere protocol 8. Could be managed on an outpatient basis 9. Participants who were willing and able to give written informed consent to participate in the study (if the subject was younger than the legal age of consent, the legally acceptable representative also provided consent) 10. Participants who were fluent and literate in the language spoken by the investigator and staff Exclusion criteria 1. Females who were pregnant, breast-feeding or at risk of becoming pregnant during the study 2. Participants known/suspected to be hypersensitive to study medication or relief medications 3. Participants who had received any influenza antiviral therapy in the previous 7 days (e.g. rimantadine or amantadine) 4. Participants who had received an investigational drug in the previous 30 days 5. Participants with evidence/history of alcoholism, drug abuse, psychiatric disorders, or any other medical condition that could affect study completion or safety or efficacy data 6. Participants who were immunocompromised (e.g. HIV infection or systemic chemotherapy treatment) 7. Participants who had received influenza vaccine for current season could be recruited into the study. However, there had to be laboratory confirmation of their influenza infection (e.g. rapid test) prior to the first dose of study medication being administered **Definition of patient populations for analysis** ***Influenza-positive population (N = 569)***

	Participants were influenza-positive if a positive result was obtained by any 1 of the following methods: baseline culture/polymerase chain reaction assay/seroconversion (≥ 4-fold increase in convalescent antibody titres compared with baseline demonstrated by haemagglutination inhibition) ***ITT population (N = 777)*** All randomised participants irrespective of study drug use or study completion. Participants analysed in groups they were assigned to irrespective of treatment received. This was the secondary population for assessing efficacy ***Safety (N = 777)*** All participants randomised to treatment who took at least 1 dose of study medication. Randomised participants were only to be excluded from the safety population if there was clear evidence of failure to take study medication. Participants retained in group of treatment that they received. This was the primary population for the analysis of safety data ***High risk (N = 109)*** Participants who, as a result of age/underlying medical condition, might experience more prolonged and/or severe course of illness or suffer complications as a result of an influenza virus infection
Interventions	Intervention Inhaled zanamivir (5 mg per inhalation), 2 inhalations bid via rota disk/diskhaler (total daily dose 20 mg) Control Placebo, 2 inhalations twice daily, via rota disk/diskhaler Treatment period 5 days Follow-up period 23 days post-treatment Co-interventions Relief pack of medication (paracetamol and cough mixture)
Outcomes	***Primary outcomes*** Time until alleviation of clinically significant symptoms of influenza. Clinically significant symptoms of influenza were defined as fever, headache, muscle/joint aches and pains (e.g. arthralgia/myalgia), sore throat and cough ***Secondary outcomes*** 1. Time to alleviation of clinically significant symptoms and no use of relief medication 2. Return to normal activities 3. Time to alleviation of each individual symptom score 4. Mean overall influenza score 5. Mean symptom score for each of the individual symptoms collected on the diary card 6. Maximum daily temperature 7. Relief medication use

	8. Global assessment of symptoms at the post treatment visit 9. Incidence of complications of influenza and associated antibiotic use 10. Viral titre 11. Adverse events
Notes	Major protocol amendments 1. Reference to 5 mL spoonfuls of dextromethorphan was deleted 2. Study personnel recorded in CRF, instead of diary card, whether first dose of study medication was given before or after 14:00 hours 3. Secondary complications would be recorded in the CRF 4. Second diary card was to be completed twice a day 5. Appendix 4 defined categories of influenza complications Study period: October 1997 to April 1998

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Low risk	"...packs containing zanamivir or matching placebo were provided by the Pharmaceutical Supplies Department of Glaxo Wellcome Research and Development to Glaxo Wellcome Inc. The supplies were labelled and packed in Clinical Supply Operations at GWI for distribution to the study centres by Simirex, Inc., Mt. Laurel, NJ."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Data for ITT and IP populations available
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Safety population based on randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes of primary interest to the review were available from the study report
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events

NAIA3002 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The investigator, all staff, subjects (...) were blinded as to the study treatment administered. Each carton, which contained four Rotadisks, was labelled with a 2-part, 3-panel, double blind label containing protocol number, treatment number, contents, instructions for use, and storage conditions."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...study monitors were blinded as to the study treatment administered Each carton, which contained four Rotadisks, was labelled with a 2-part, 3-panel, double blind label containing protocol number, treatment number, contents, instructions for use, and storage conditions."

NAIA3005

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group, multi centre study to assess effect of zanamivir in preventing symptomatic disease caused by influenza A and B viral infections in community-dwelling adults. Participants were entered in to the study and administered the study drug when influenza was detected in the local university community Location, number of centres: USA, 2 centres Duration of study: 35 days
Participants	Number screened: not available. Number randomised: 1107 (zanamivir: 553; placebo: 554) Number completed: 1080 M = 41% F = 59% Mean age: 29 years Baseline details: 83% Caucasian Inclusion criteria 1. Males or females ≥ 18 years from a university community 2. Women of childbearing potential had to have a negative pregnancy test before receiving study medication and those at risk of pregnancy taking adequate contraceptive precautions throughout the study period 3. Participants were able to take first dose of study medication within 72 hours following notification of an influenza outbreak and complete 4 weeks of treatment while at university 4. Able to use the diskhaler 5. Participants were willing and able to adhere to protocol 6. Participants could be managed on an outpatient basis and would not be medically compromised by study participation 7. Participants were willing and able to give written informed consent to participate

	8. Participants were fluent and literate in the language spoken by the investigator and staff 9. Eligibility for randomisation to study drug if all of the above criteria were met and an influenza outbreak was declared in the university community (according to guidelines) Exclusion criteria 1. Pregnancy, lactation or risk of becoming pregnant during the study 2. Hypersensitivity to any component of study medication 3. Evidence/history of alcoholism, drug abuse, psychiatric disorders, or any other medical condition that would affect their ability to complete the study or confound the evaluation of safety or efficacy data 4. Participants who were immunocompromised (e.g. HIV infection or systemic chemotherapy treatment) Participants were not eligible for randomisation to study drug if 1 of these criteria applied 1. Pregnancy, lactation or risk of becoming pregnant during the study 2. Influenza antiviral therapy in previous 7 days (e.g. rimantadine or amantadine) 3. Exposure to an investigational drug in the previous 30 days 4. Symptoms indicative of influenza prior to the prophylaxis phase of the study **Definition of patient populations for analysis** ***Intention-to-treat population (N = 1107)*** Not specified. ***Safety (N = 1107)*** All randomised participants who took 1 dose of study drug. Primary population for analysis of safety data ***Non-vaccinated population (N = 948)*** All non-vaccinated randomised participants who took at least 1 dose of study drug. Primary population for the analysis of efficacy ***Per-protocol (N = 891)*** Not specified
Interventions	Intervention Inhaled zanamivir (5 mg per inhalation), 2 inhalations once a day via rota disk/diskhaler (total daily dose 10 mg) Control Placebo, 2 inhalations once a day, via rota disk/diskhaler Treatment period 28 days Follow-up period 7 days post-treatment Co-interventions Relief medication provided as paracetamol and cough mixture

NAIA3005 (*Continued*)

Outcomes	***Primary outcomes*** Proportion of non-vaccinated randomised participants who developed symptomatic, laboratory-confirmed influenza A or B infection. Defined as presence of at least 2 of: temperature ≥ 37.8 °C, cough, headache, sore throat, myalgia, feverishness. Symptoms had to be present concurrently for 3 consecutive diary card entries. Laboratory confirmation of influenza infection by culture or seroconversion ***Secondary outcomes*** 1. Laboratory-confirmed influenza infection 2. Acquisition of symptomatic, laboratory-confirmed influenza infection during prophylaxis period 3. Development of febrile illness (defined as a temperature of 37.8 °C) with laboratory confirmation of influenza infection during prophylaxis period 4. Development of febrile illness irrespective of laboratory confirmation of influenza during prophylaxis period 5. Maximum recorded score on diary card 6. Inability to perform normal activities 7. Recorded use of relief medication 8. Development of a secondary complication of influenza and subsequent associated laboratory confirmation of influenza infection 9. Development of secondary complication of influenza irrespective of laboratory confirmation of influenza 10. Antibiotic requirement 11. Requirement for over-the-counter medication 12. Requirement for a prescribed medication 13. Unscheduled healthcare contact 14. Confinement to bed/incapacitated plus the mean duration of incapacity because of influenza 15. Absence from 1/2 day work/school because of influenza and the mean duration missed from work/school 16. Adverse events
Notes	Major protocol amendments 1. Vaccination against influenza not an exclusion criterion 2. Stratification in randomisation by vaccination status 3. CPK added to chemical laboratory tests performed 4. Participants asked to complete a questionnaire at screening visit to determine occupational status and tobacco use 5. Statistical methods section revised to allow for stratification of vaccinated participants 6. In the efficacy evaluations, nasal symptoms (nasal congestion, rhinorrhoea) were changed to nasal congestion (blocked, runny nose) 7. Blood for haemagglutination inhibition would only be collected at the screening visit and at Day 35 8. Randomisation of participants would begin within 3 working days of the influenza outbreak and must have been completed within 5 working days of the outbreak Study performed prior to influenza season in 1997
Risk of bias	

NAIA3005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	"When the influenza outbreak was declared, subjects that continued to meet the inclusion/exclusion criteria would be stratified according to their vaccination status and randomly assigned to a treatment number in accordance with the randomisation schedule provided by Glaxo Wellcome."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Not applicable to study design (prophylaxis)
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes of primary interest to the review are available in the CONSORT-based extraction
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The investigator, all staff, subjects (...) were blinded as to the study treatment administered. Each carton, which contained four Rotadisks, was labelled with a 2-part, 3-panel, double blind label containing protocol number, treatment number, contents, instructions for use, and storage conditions."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...study monitors were blinded as to the study treatment administered."

NAIB2005

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group, multi centre study to evaluate effect of zanamivir in treating influenza A and B viral infections Location, number of centres: Belgium (3 centres); Finland (1); France (5); Germany (1) ; Italy (2); Netherlands (1); Norway (6); Spain (5); Sweden (4); UK (4) Duration of study: 28 days
Participants	Number screened: not available Number randomised: 197 (zanamivir (inhaled): 64; zanamivir (inhaled and intranasal): 70; placebo: 63) Number completed: 185 M = 53 F = 47 Mean age: 34 years Baseline details: 96% Caucasian; 24% smokers Inclusion criteria 1. Male or female ≥ 18 years 2. Duration of ILI ≤ 48 hours (i.e. feverish and at least 2 of the following symptoms: headache, myalgia, cough, sore throat) 3. In good health except for current respiratory illness 4. Able to use diskhaler and aqueous nasal spray devices 5. Willing and able to adhere to protocol 6. Willing and able to give informed consent to participate in the study 7. Fluent and literate in the language spoken by the investigator and staff Exclusion criteria 1. Suspected bacterial infection 2. Influenza vaccine administered within previous year 3. At risk of developing complications from influenza infections (e.g. chronic active disorders of cardiovascular or pulmonary systems, chronic metabolic disease, hepatic or renal dysfunction, or immunosuppression 4. Unstable chronic illness 5. Concurrent medical condition that could interfere with evaluations of safety or efficacy, e.g. perennial rhinitis, vasomotor rhinitis 6. Currently receiving intranasal or inhaled medication 7. Influenza antiviral therapy in previous 7 days 8. Pregnancy/lactation or likely to become pregnant during study 9. Received investigational drug in previous 30 days 10. Evidence or history of abuse of any drug substance 11. Use of antibiotic within the previous 7 days 12. Intolerance to lactose **Definition of patient populations for analysis** ***Influenza-positive population (N = 151)*** All participants in the ITT population with laboratory-confirmed influenza determined either from pre-treatment diagnostic sample or a positive serology result. If diagnostic sample and serology were both positive but indicated different influenza types, influenza type was assigned according to diagnostic sample result. Secondary population for assessment of efficacy ***Intention-to-treat population (N = 197)***

	All randomised participants included in the treatment group to which they were assigned even if no medication was taken. Primary population for assessment of efficacy ***Safety (N = 196)*** Participants randomised to treatment who took at least 1 dose of study medication. Participants excluded if there was clear evidence of failure to take any study medication. Used for safety data
Interventions	Intervention 1. Inhaled zanamivir (5 mg per inhalation) 2 inhalations twice a day plus placebo 2 sprays per nostril (0.1 mL per spray) twice a day (total daily dose 20 mg) 2. Inhaled zanamivir (5 mg per inhalation) 2 inhalations twice a day plus zanamivir (16 mg/mL) 2 sprays per nostril (1.6 mg zanamivir) twice a day (total daily dose of inhaled zanamivir: 20 mg; intranasal zanamivir: 10.4 mg) Control Matching placebo for inhaled and intranasal administration Treatment period 5 days Follow-up period 23 days post-treatment Co-interventions Relief medication described and measured as an outcome, but not clear whether this was administered as co-intervention
Outcomes	***Primary outcomes*** Time to alleviation of symptoms. Calculated in days from diary card entries. Treatment failure defined as no positive evidence of symptom alleviation, if they withdrew or had missing diary card data. Mean time to alleviation of symptoms calculated for each treatment group using value 10 for patients with no positive evidence of alleviation before Day 10 *Secondary outcomes* 1. Time to eradication of major signs and symptoms of influenza 2. Time to alleviation of headache/myalgia and eradication of feverishness 3. Time to alleviation and eradication of symptoms of influenza 4. Combined symptoms 5. Mean daily temperature 6. Return to normal activities 7. Patient assessment of symptoms 8. Sleep 9. Relief medication use 10. Investigator assessment of symptoms 11. Viral shedding 12. Adverse events 13. Vital signs

NAIB2005 (*Continued*)

Notes	Protocol amendments 1. Protocol amendment 1 applied to centres in France and made protocol consistent with the requirements of French law 2. Protocol amendment 2 (dated 31 August 1994) referred to centres in Ireland only. Participants in Ireland were excluded if they had received any other investigational drug in the previous 16 weeks before the study in accordance with Irish law Study period: November 1994 to April 1995

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomisation code was (...) generated using the GWRD program Patient Allocation in Clinical Trials (PACT)."
Allocation concealment (selection bias)	Low risk	"The randomisation code was supplied to the GWRD Pharmaceutical Supplies Department by the GWRD Medical Statistics Department."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Data from ITT and IP populations available
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on randomised participants
Selective reporting (reporting bias)	Unclear risk	Authors note that complications do not appear to have been investigated. It is not clear whether these were measured but not reported
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo "The investigator, all study staff, patients (…) were blinded as to the study treatment administered."

NAIB2005 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"…the monitors were blinded as to the study treatment administered."

NAIB2007

Methods	Study design: randomised, double-blind, placebo-controlled study to investigate combination inhaled and intranasal zanamivir in the treatment of influenza A and B viral infections Location, number of centres: Australia, New Zealand, South Africa (24 centres) Duration of study: 28 days
Participants	Number screened: not available Number randomised: 554 (inhaled zanamivir: 188; inhaled and intranasal zanamivir: 183; placebo: 183) Number completed: 456 M = 52% F = 48% Mean age: 30 years Baseline details: 92% Caucasian; 23% smokers Inclusion criteria 1. Male or female, ≥ 13 years (aged 16 and above, or aged 18 and above in some centres). Women of childbearing potential had a negative pregnancy test before receiving study medication. Those at risk of pregnancy were, in the opinion of the investigator, taking adequate contraceptive precautions 2. Patients with laboratory-confirmed influenza or influenza-like illness defined as feverishness and at least 2 of: headache, myalgia, cough, sore throat of less than or equal to 48 hours duration 3. Ability to use diskhaler and aqueous nasal spray devices 4. Willingness to adhere to protocol 5. Consent to participate in the study 6. Fluency and literacy in language spoken by investigator and staff Exclusion criteria 1. Patients with asthma (applicable to all centres recruiting in 1995 and applied to some centres in 1996) 2. Suspected bacterial respiratory infection 3. Unstable chronic illness. Patients currently hospitalised, on dialysis or those who were experiencing a worsening of their condition 4. Influenza antiviral therapy in previous 7 days 5. Pregnancy, lactation or likely to become pregnant during the study 6. Consumption of investigational drug in previous 30 days. Those who had received influenza vaccine for current season were recruited, however, laboratory-confirmation of influenza infection was required prior to administration of the first dose of study medication 7. Abuse or history of abuse of any drug substance 8. Known or suspected hypersensitivity to any component of study medication **Definition of patient populations for analysis**

	Influenza-positive population (N = 348) All members of the safety population with confirmed influenza. This was secondary population for assessing efficacy. Participants included in this population if diagnostic test or baseline culture was positive, or if there was a 4-fold increase in influenza antibody from Day 1 to Day 28. If more than 1 sample was positive but different influenza types indicated, influenza type was assigned firstly according to baseline culture result and otherwise according to additional diagnostic test sample ***ITT population (N not specified)*** All randomised patients, regardless of whether study drug actually taken or study completion as per the protocol. Primary population for assessing efficacy. Participants were analysed in the treatment group to which they were allocated ***Safety population (N = 549)*** All randomised participants who took at least 1 dose of study medication. This was the primary population for safety analysis. Randomised patients were excluded only if there was clear evidence of failure to take any study medication ***High risk population (N = 66)*** Participants in the safety population at greater risk of complications following influenza infection. Not included for study in original protocol or subsequent protocol amendments. Criteria for inclusion were 1 or more of 1. Aged 65 or over 2. Concurrent cardiovascular condition (excluding hypertension) 3. Concurrent respiratory condition 4. Diabetes
Interventions	Intervention 1. Inhaled zanamivir (5 mg) 2 inhalations bid via diskhaler plus placebo 2 sprays per nostril (0.1 mL per spray) twice daily (total daily dose: 20 mg) 2. Inhaled zanamivir (5 mg) 2 inhalations bid via diskhaler plus zanamivir (16 mg/mL) 2 sprays per nostril (0.1 mL per spray) twice daily (total daily dose: 26.4 mg) Control Matching placebo Treatment period 5 days Follow-up period 23 days post-treatment Co-interventions Paracetamol was provided for symptomatic relief
Outcomes	***Primary outcomes*** Time to alleviation of clinically significant symptoms of influenza. Clinically significant symptoms of influenza defined as fever, headache, myalgia, cough and sore throat. Alleviation defined as no fever (temperature < 37.8 °C and feverishness recorded as 'none') and a score of 'none' or 'mild' for headache, myalgia, cough and sore throat. Scores had to be maintained over next 24 hours. Time to alleviation of influenza symptoms measured in days from the start of treatment

	Secondary outcomes 1. Time to alleviation of individual symptoms of influenza 2. Return to normal activities 3. Return to usual daily activities and perform these as well as normal 4. Mean symptom score (based on 5 symptoms of feverishness, headache, myalgia, cough and sore throat), summarised over treatment period 5. Number of days that symptoms rated as 'moderate' or 'severe' 6. Number of days that at least 1 symptom rated as 'moderate' or 'severe' 7. Number of days that sleep disturbance recorded as 'moderate' or 'severe' 8. Maximum daily temperature summarised over the study treatment period 9. Paracetamol use over study treatment period 10. Investigator-rated symptoms. Influenza-infection status of patients rated by the investigator at post-treatment visit as 'none', 'mild', 'moderate' or 'severe' 11. Incidence of secondary infections 12. Adverse events
Notes	Protocol amendments 1. Protocol amendment 1 led to the exclusion of patients with asthma due to a delay in availability of bronchial reactivity study 2. Protocol amendment 2 re-instated the criterion for including people with asthma and lowering the age limit of those eligible for the study to 13 years 3. Protocol amendment 3 led to the revision of the definition of serious adverse events and timeline changes for reporting adverse events. Amendments were also made to definitions for primary and secondary efficacy parameters, and statistical analyses were modified 4. Protocol amendments 4 to 7 varied the age range included between study centres (13 to 65 years, 16 to 65 years and 18 to 65 years, respectively) and the inclusion or exclusion of patients with asthma in order to meet local regulatory and ethics committee requirements Study period: May 1995 to May 1996

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"This code was generated with a block size of six using the GWRD program PACT (Patient Allocation in Clinical Trials)."
Allocation concealment (selection bias)	Low risk	"The randomisation code was supplied to the Pharmaceutical Supplies Department (GWRD) by the Medical Statistics Department (GWRD)."
Incomplete outcome data (attrition bias) Symptoms	Low risk	ITT and IP population data available for symptom relief

NAIB2007 (*Continued*)

Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes of primary importance to the review reported in CONSORT-based extraction reconstruction
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo "The investigator, all staff, patients (...) were blinded as to the study treatment administered."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...the monitors were blinded as to the study treatment administered."

NAIB3001

Methods	Study design: randomised, double-blind, multi centre study comparing efficacy and safety of zanamivir with placebo in treating influenza infection Location, number of centres: Australia (6 centres); New Zealand (4); South Africa (3) Duration of study: 28 days
Participants	Number screened: not specified Number randomised: 455 (zanamivir: 227; placebo: 228) Number completed: 428 M = 53% F = 47% Mean age: 37 years Baseline details: 95% Caucasian; 6% vaccinated for current season Inclusion criteria 1. Males/females ≥ 12 years. Females of childbearing potential had to have a negative pregnancy test before receiving study medication. Those at risk of pregnancy were required to be taking adequate contraceptive precautions 2. Patients with laboratory-confirmed influenza or influenza-like illness defined as symptoms of fever (≥ 37.8 °C) and/or feverishness and at least 2 of: headache, myalgia, cough, sore throat (first dose of study medication administered within 36 hours (1.5 days) of the onset of symptoms) 3. Influenza circulating in community

	4. Ability to use diskhaler satisfactorily 5. Willingness to adhere to protocol 6. Willing to give written informed consent to participate in the study 7. Fluency and literacy in language spoken by study personnel Exclusion criteria 1. Suspected bacterial respiratory infection 2. Pregnancy, lactation or likely to become pregnant during study 3. Known/suspected hypersensitivity to any component of the study medication 4. Amantadine or any other influenza antiviral therapy in previous 7 days 5. Anyone who could be medically compromised if they participated in the study 6. Use of investigational drug in the previous 30 days **Definition of patient populations for analysis** ***Influenza-positive population (N = 321)*** Secondary population for assessing efficacy. Defined as all participants the safety population who had confirmed influenza. Participants were included in this population if baseline culture test was positive or if rapid diagnostic test was positive or if serology results confirmed influenza infection ($\geq$ 4-fold increase in influenza antibody from Day 1 to Day 28) Sensitivity analysis also performed for primary endpoint on population of patients confirmed as influenza-positive by either culture or serology ***ITT population (N = 455)*** Primary population for assessing efficacy. All randomised patients, regardless of whether or not the study drug was actually taken or completion of study. Participants analysed according to assigned treatment group irrespective of which medication they took during the study ***Safety population (N = 455)*** Primary population for the analysis of safety data. Defined as all participants randomised to treatment who took at least 1 dose of study medication. Randomised patients were excluded if there was clear evidence of failure to take study medication. Participants were analysed according to treatment group of the actual medication they took the majority of the time ***High risk population (N = 76)*** All patients in safety population at greater risk of complications if they became infected with influenza. Analysis of 'high risk' population restricted to primary endpoint, complications, adverse event incidence and serious adverse event incidence All participants $\geq$ 65 years were in this population. In addition, conditions thought to pre-dispose patients to greater risk of complications from influenza included concurrent cardiovascular conditions (excluding hypertension), concurrent respiratory conditions (asthmatics excluded if un-medicated), concurrent metabolic conditions and those who were immunocompromised
Interventions	Intervention Inhaled zanamivir (5 mg per inhalation) 2 inhalations bid via diskhaler (total daily dose 20 mg) Control Matching placebo

NAIB3001 (*Continued*)

	Treatment period 5 days Follow-up period 23 days post-treatment Co-interventions Paracetamol and cough mixture were provided for symptomatic relief
Outcomes	***Primary outcomes*** Time until alleviation of major signs and symptoms of influenza. Defined as fever, headache, myalgia, sore throat and cough. Alleviation defined as no fever (temperature < 37.8 °C and feverish recorded as 'none') and headache, myalgia, cough and sore throat recorded as 'none' or 'mild'. All of these were required to have been maintained for 24 hours ***Secondary outcomes*** 1. Time to alleviation of each diary card symptom calculated separately 2. Return to normal; activities. Required to be maintained for 2 consecutive diary card entries 3. Mean symptom score over post-treatment (assessed on day 1 to 5 and on day 1 to 14) 4. Maximum daily temperature 5. Sleep disturbance (mean number of days when sleep was disturbed 'not at all' or 'slightly') changed to number of days out of Days 2 to 14 for which patient recorded 'moderate', 'quite a bit' or 'severe' sleep disturbance 6. Paracetamol use 7. Use of cough mixture 8. Investigator assessment of symptoms 9. Complications of influenza and associated antibiotic use 10. Adverse events
Notes	Protocol amendment At 3 Australian centres an additional study protocol designed to collect pharmacoeconomic data was instigated. This involved interviews with influenza-positive patients after their Day 28 visit Study period: recruitment commenced in May 1997 and rolled over to 1998

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation code was supplied to the Clinical Trials Pharmacist at Glaxo Wellcome Australia by the GWRD Clinical Statistics Department. This code was generated using the GWRD program Patient Allocation in Clinical Trials (PACT). "

NAIB3001 (*Continued*)

Allocation concealment (selection bias)	Low risk	"The randomisation code was supplied to the Clinical Trials Pharmacist at Glaxo Wellcome Australia by the GWRD Clinical Statistics Department." "Each investigator was provided with a sealed envelope containing the individual code-break envelopes for patients in their centre. These were only to be opened in a medical emergency, where knowledge of the study treatment was essential for further management of the patient."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Based on ITT and IP populations
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes of primary interest to the review were available in the study report
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The investigator, study staff, patients (...) were blinded as to the study treatment administered."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...the monitors were blinded as to the study treatment administered."

NAIB3002

Methods	Study design: randomised, double-blind, placebo-controlled, multi centre study designed to evaluate zanamivir in the treatment of symptomatic influenza in adolescents and adults Location, number of centres: multi centre study in Europe: Belgium (2 centres); Denmark (3); Finland (2); France (10); Germany (5); Holland (1); Italy (2); Norway (7); Spain (1); Sweden (6); UK (3) Duration of study: 28 days
Participants	Number screened: not available Number randomised: 356 (zanamivir: 174; placebo: 182) Number completed: 349 M = 52% F = 48% Mean age: 37 years Baseline details: 99% Caucasian; 4% vaccinated Inclusion criteria 1. Males or females aged ≥ 12 years. Women of childbearing potential had to have a negative pregnancy test before receiving study medication. Those at risk of pregnancy must have taken adequate contraceptive precautions during the study period 2. Influenza-like illness defined by the presence of fever (temperature ≥ 37.8 °C) and at least 2 of: headache, muscle/joint aches and pains (e.g. myalgia/arthralgia), sore throat and/or cough. For those aged ≥ 65 years, fever was defined as temperature ≥ 37.2 °C. Participants encouraged not to take anti-pyretic medication prior to study entry 3. Able to take first dose of study medication on first/second calendar day of influenza-like symptoms 4. Influenza circulating in community 5. Ability to use diskhaler 6. Willing to adhere to protocol 7. Participants had to be managed on outpatient basis and not medically compromised by study participation 8. Written informed consent to participate 9. Fluency and literacy in language spoken by the investigator and staff 10. In some centres where facilities permitted participants were only included if they were influenza-positive according to a (usually rapid) diagnostic test Exclusion criteria 1. Pregnancy, lactation or risk of pregnancy during study 2. Known or suspected hypersensitivity to any component of study or relief medications 3. Influenza antiviral therapy in previous 7 days (e.g. rimantadine or amantadine) 4. Use of investigational drug in previous 30 days 5. Evidence or history of alcoholism, drug abuse, psychiatric disorders or any other medical condition that would affect completion of the study or confound evaluation of safety or efficacy data 6. Participants who were immunocompromised, because of HIV infection or systemic chemotherapy treatment 7. Influenza vaccination for current season was not an exclusion criterion. However, there had to be laboratory-confirmed influenza infection (e.g. rapid test) **Definition of patient populations for analysis**

	Influenza-positive population (N = 277) Primary population for assessing efficacy. Defined as all participants in safety population with confirmed influenza. Participants considered influenza-positive if positive result obtained from any of: baseline culture or polymerase chain reaction (PCR) assay, or if participants showed seroconversion (≥ 4-fold increase in convalescent antibody titres compared with baseline demonstrated by haemagglutination inhibition) ***ITT population (N = 356)*** All randomised participants, regardless of whether study drug was taken or study completion. Participants who did not take medication to which they were randomised included in treatment group assigned. This was the secondary population for assessing efficacy ***Safety population (N = 356)*** All participants who took at least 1 dose of study medication. Participants only excluded from safety population if clear evidence of failure to take study medication. Participants who did not take medication to which they were randomised would have been included in the treatment group of the actual medication they took the majority of the time. This was the primary population for the analysis of safety data ***High risk (N = 32)*** Defined as those who could experience more prolonged or severe illness, or suffer complications from influenza due to age or underlying medical condition
Interventions	Intervention Inhaled zanamivir (5 mg per inhalation) 2 inhalations bid via diskhaler (total daily dose 20 mg) Control Matching placebo Treatment period 5 days Follow-up period 23 days post-treatment Co-interventions Paracetamol and cough mixture were provided for symptomatic relief
Outcomes	***Primary outcomes*** Time to alleviation of clinically significant symptoms of influenza. Alleviation defined as no fever (temperature < 37.8 °C and feverish recorded as 'none') and headache, muscle/joint aches and pains, cough and sore throat recorded as 'none' or 'mild'. Alleviation had to be maintained for a further 24 hours. For temperature, this meant 5 consecutive readings during treatment or 3 consecutive measurements following treatment. For other symptoms, 3 consecutive recordings were required ***Secondary outcomes*** 1. Time to alleviation of clinically significant symptoms of influenza and no use of relief medication 2. Maximum daily temperature over the treatment period 3. Return to normal activities. This had to be maintained for 2 consecutive diary card entries

	4. Time to alleviation of each individual symptom 5. Mean overall influenza score 6. Mean symptom score for individual symptoms collected on diary card 7. Relief medication consumption (paracetamol and cough mixture) 8. Global assessment of symptoms at post-treatment visit 9. Incidence of complications of influenza 10. Viral titre 11. Productivity and healthcare resource utilisation 12. Adverse events
Notes	Protocol amendments 1. Reference to '5 mL' spoonfuls of dextromethorphan deleted 2. Study personnel recorded whether first dose of study medication given before or after 14:00 hours 3. Secondary complications were to be recorded in the CRF 4. The second diary card including symptom assessments and relief medication use, to be completed twice a day. Questions relating to productivity and normal activities completed once a day 5. Consent form amended to include statement that subject's doctor/nurse would also need to take a throat swab on Day 6 6. Categories to be used to document influenza complications were defined 7. Protocol amendment 2 applied to all centres in Denmark, France, Holland, Italy and Norway: minimum age for inclusion was to be 18 years in response to Ethics/ Regulatory issues in those countries 8. Protocol amendment 3 was standard administrative amendment to meet requirements of French law no. 88-1138, of 20 December 1988, and modified by French Law No. 94-630, of 25 July 1994 Study period: recruitment planned for between October 1997 and April 1998

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	"The treatments were packed according to an unblocked randomisation schedule supplied by the GWRD Medical Data Sciences Department (...)The principal investigator was provided with sealed envelopes for each treatment number, containing details of the treatment assignation. It was the responsibility of the investigator to ensure that these envelopes were stored safely and readily available to study staff."

NAIB3002 (*Continued*)

Incomplete outcome data (attrition bias) Symptoms	Low risk	Based on ITT and IP populations
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes of primary interest to the review were available in the study report
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo "The investigator, all staff, subjects (...) were blinded as to the study treatment administered."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...study monitors were blinded as to the study treatment administered."

WP16263

Methods	Study design: randomised, double-blind study conducted in healthy volunteers Location, number of centres: USA, UK and New Zealand, 9 centres Duration of study: 9 to 22 days (variable screening phase of between 2 and 15 days)
Participants	Number screened: 976 Number randomised: 391 (oseltamivir (75 mg): 95; oseltamivir (225 mg): 97; oseltamivir (450 mg): 99; placebo: 100) Number completed: 384 M = 52% F = 48% Mean age: 34 years Baseline details: healthy volunteers Inclusion criteria 1. Male/female volunteers of any race 2. Aged 18 to 65 years (inclusive) 3. In good health 4. Body weight within ± 40% of accepted normal weight for height, as defined by the Metropolitan Life Insurance 5. Participants able to participate and willing to give informed consent and comply

	with the study restrictions 6. Negative urine pregnancy test for all females of childbearing potential 7. Both male and female participants must agree to utilise an effective method of contraception during the study Exclusion criteria 1. Administration of any new prescription medicine within 2 weeks of study day 2. Myocardial infarction or invasive cardiac procedure within 3 months of study day -1 3. Clinically significant renal, cardiac, bronchopulmonary, vascular, gastrointestinal, allergic, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease), immunodeficiency disorders (including HIV infection), cancer, hepatitis (including hepatitis B) or cirrhosis determined by medical history, clinical examination or screening laboratory evaluations. 4. Allergy to oseltamivir or to any of the excipients in the study medication capsule (which were described in the Protocol, which is included in Module 2 of this report) 5. Participation in a clinical study with an investigational drug within 6 weeks of study day -1 6. Donation/ loss of more than 700 mL of blood in the 6-week period prior to the screening examination 7. Any clinically relevant abnormal laboratory test results, including positive test results for drugs of abuse test in urine 8. Pregnant or lactating female 9. Fever > 37.8 °C or other evidence of acute infection of any type on study day -1 10. Any history of congenital QTc prolongation 11. Any of the following on screening or baseline ECG: atrial fibrillation/flutter/ (right/left) bundle branch block/Wolff-Parkinson White syndrome. Cardiac pacemaker fitted 12. In receipt of concomitant medication known to cause torsade de pointes **Definition of patient populations for analysis** ***ITTI population*** Not applicable ***ITT population*** Not identified
Interventions	Intervention 1. Oseltamivir 75 mg bid (total daily dose 150 mg) 2. Oseltamivir 225 mg bid (total daily dose 450 mg) 3. Oseltamivir 450 mg bid (total daily dose 900 mg) Control Matching placebo bid Treatment period 5 days Follow-up period 2 days post-treatment

	Co-interventions NA
Outcomes	Change from baseline (study Day -1) in the following ECG measures, which were collected using an average of 3 readings from sequential cardiac cycles in lead II,: R-R interval (heart rate), P-R interval, QRS interval and QT interval. The QT intervals were corrected using the Fridericia (QTcF), Bazett (QTcB), and Framingham (QTcL) formulas. T-wave morphology and U-waves Incidence of adverse events Mean change from screening and incidence of significant shift from screening to follow-up in biochemistry, haematology and urinalysis tests Mean change from baseline and incidence of significant shift from baseline in vital signs
Notes	Study period: 22 August 2000 to 25 September 2000

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	"The central randomisation was arranged by ICTI, UK."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Not applicable to this study (healthy volunteers)
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Not applicable to this study (healthy volunteers)
Incomplete outcome data (attrition bias) Safety data	Low risk	Attrition was low between the study groups and unlikely to affect the outcomes of interest to the review
Selective reporting (reporting bias)	Low risk	Outcomes were available in the full set of modules from the clinical study reports
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo and oseltamivir capsules were described as having non-identical appearances from the certificate of analysis: oseltamivir: "Body: grey, opaque; cap: light yellow, opaque" placebo: "Body: grey, opaque; cap: ivory, opaque"

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information was presented to ascertain this

WV15670

Methods	Study design: randomised, double-blind, placebo-controlled study in people with symptoms of influenza. Centres were activated to recruit participants during an influenza outbreak in the locality, detected using standardised surveillance techniques Location, number of centres: 51 centres in Europe, 11 in Canada and 1 in Hong Kong Duration of study: 21 (+/- 4 days)
Participants	Number screened: not available Number randomised: 719 (oseltamivir 75 mg: 242; oseltamivir 150 mg: 242; placebo: 235) Number completed: 688 M = 51% F = 49% Mean age: 37.4 Baseline details Inclusion criteria 1. Fever ≥ 38 °C 2. At least 1 respiratory symptom (cough, sore throat, nasal symptoms) 3. At least 1 constitutional symptom (headache, myalgia (aches/pains), sweats/chills (feeling feverish), prostration (fatigue)) 4. No more than 36 hours post onset of feeling unwell 5. Aged ≥18 and ≤ 65 years of age 6. Willing and able to comprehend and give written, informed consent 7. Willing to utilise an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study therapy 8. Negative urine pregnancy test prior to drug treatment (females of childbearing potential) For the purposes of analysis and definition of the study populations, the criteria were adjusted to accept a baseline temperature of 37.8 °C and entry into the studies up to 40 hours post onset of illness thereby accounting for differences between criteria evaluated at time of entry and criteria at time of first dose Exclusion criteria 1. Active, clinically significant, renal, cardiac, pulmonary, vascular, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease) or immunodeficiency disorders, cancer, hepatitis or cirrhosis 2. Transplant recipients 3. Use of steroids or immuno-suppressant therapies 4. Pregnant or breast-feeding females 5. Known HIV infection 6. Allergy to any excipients in the capsule or paracetamol (acetaminophen) 7. Asthmatics in receipt of chronic therapy for asthma 8. Participants who experienced a previous episode of acute upper respiratory tract

	infection (URTI), otitis, bronchitis or sinusitis within 2 weeks prior to study Day 1 9. Receipt of antibiotics for URTI, otitis, sinusitis or bronchitis or antiviral therapy for influenza within 2 weeks prior to study Day 1 10. Participation in a clinical study with an investigational drug within 4 weeks prior to screen/study Day 1 11. Administration of influenza vaccine less than 12 months prior to study Day 1 12. A clinically relevant history of abuse of alcohol or other drugs 13. Presentation > 36 hours post onset of feeling unwell **Definition of patient populations for analysis** ***ITTI population (N = 425)*** Participants who were discovered to have been infected with laboratory-confirmed influenza ***ITT population (N = 726)*** All randomised participants irrespective of influenza status
Interventions	Intervention 1. Oseltamivir 75 mg bid, given as size 2 capsules (total daily dose 150 mg) 2. Oseltamivir 150 mg bid, given as size 2 capsules (total daily dose 300 mg) Control Placebo size 2 capsules Treatment period 5 days Follow-up period 12 to 20 days post-treatment Co-interventions Participants were provided with a rescue pack of paracetamol (500 mg) for symptomatic relief. The amount of medication was noted on the participant's diary card. Participants were requested not to use any other medication for the relief of symptoms during the study treatment period. However, if any other medication was taken, this was to be recorded
Outcomes	***Primary outcome*** Duration of illness, defined as the length of time to first alleviation of the symptoms of influenza (nasal congestion, sore throat, cough, aches and pains, fatigue, headaches and chills/sweats). This was calculated from 'time 0' (study drug initiation) to the time at which all 7 symptoms were alleviated ***Secondary outcomes*** 1. Severity of symptoms 2. Virus shedding 3. Serology 4. Symptoms 5. Temperature 6. Proportion of participants with fever 7. Symptom relief medication use

	8. Secondary illnesses, pre-defined as sinusitis, otitis, bronchitis, pneumonia and other chest infections (as well as recurring symptoms noted on the diary card once alleviation of that symptom had been considered to occur 9. Proportion of household contacts who developed an influenza-like illness following the illness of the trial participant 10. Virology 11. Return to baseline health status (i.e. pre-flu health) 12. Virus type (e.g. A/H1N1, A/H3N2, B, etc.) 13. Time to afebrile state 14. Symptom relief medication usage over the dosing period 15. Viral resistance 16. Proportion with infection 17. Pharmacokinetic evaluation: plasma and urine samples 18. Adverse events
Notes	Protocol amendments 1. (7 January 1998) defined the exclusion and withdrawal criteria for subjects participating in the study at the Hong Kong centre who were found to be infected with the influenza A/H5N1 virus. Since May 1997, 18 individuals have been diagnosed with influenza infection caused by a new human pathogen influenza A/H5N1, of whom 6 have died as a result. This virus, previously associated with avian influenza, has apparently crossed species and resulted in a pathogenic infection in man. The vast majority of influenza infections occurring in Hong Kong at the time of the study were of the non-virulent strain types influenza A/H1N1, H3/N2 or influenza B. However, it was considered that in view of the apparent virulence of the A/H5N1 strain type, participants enrolled into this study, which was placebo-controlled, might be placed at undue risk. This risk was specific to Hong Kong, as this strain type has not so far been identified outside of this region 2. The influenza A/H5N1 virus type is known to be sensitive to amantadine. Throat swabs were taken from all participants entered into the trial prior to the first dose of study drug. In the Hong Kong region, a rapid diagnostic technique (the Polymerase Chain Reaction, PCR) was used to test the swab eluates for the presence or absence of influenza A/H5N1. If any subject was found to be harbouring this strain type, they were to be withdrawn from the study without breaking the blind and offered amantadine at the discretion of the investigator and if the participants condition merited such intervention 3. (16 February 1998) revised the analyses and definition of secondary and tertiary parameters in the study. Following an experiment to assess the use of a standardised protocol for quantitative viral culture, significant variability was detected between the 2 virology laboratories with respect to these assays. Further work continued in order to elucidate the mechanisms of this variability and to further validate the methods. However, due to the lengthy period of time required to complete this work, virus titre was removed as a secondary parameter in this study and the information analysed post-database close. The major virology parameter in these studies thus became the duration of virus shedding following inclusion into the trial. It was also believed that peak virus titre might have occurred prior to baseline for a significant number of participants entering the trial and hence this particular parameter was not analysed Study period: December 1997 to April 1998

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	"The randomisation numbers were generated by a central randomisation service, ICTI (Interactive Clinical Technologies inc., Princeton, NJ, USA)." "The investigator telephoned the centre to report the subject's initials, date of birth and smoking history. The randomisation number was then supplied by the centre in the form of a message on an interactive voice response system (IVRS). The investigator entered the randomisation number in the appropriate place on the case report form."
Incomplete outcome data (attrition bias) Symptoms	High risk	Available data analysed by ITTI population and not ITT.
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all participants irrespective of compliance with treatment or infection status
Selective reporting (reporting bias)	High risk	Outcomes of primary interest for the ITT population not made available to the review authors
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"In order to maintain blinding, each subject had 2 bottles of medication for each dose interval. 1 capsule was administered from each bottle twice per day at approximately 12 hour intervals. The first dose was

WV15670 (*Continued*)

		administered during the first (day 1) visit Each bottle was labelled with the subject number and contained identical capsules of either active compound or placebo. Those subjects receiving 75 mg bid received one capsule containing 75 mg from one bottle and a matching capsule containing placebo from the other bottle at each dosing. Subjects receiving doses of 150 mg bid received one capsule containing 75 mg active drug from each bottle at each dosing."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the randomisation code was available at the Study Center, to the Roche Monitors, Statisticians or at Roche Headquarters. In the event of a medical emergency the blind could be broken, if this was considered absolutely necessary to properly manage the subject, by contacting the randomisation centre The blinding was not required to be broken for any subject during the study."

WV15671

Methods	Study design: multi centre, double-blind, randomised, placebo-controlled, parallel-group study design in participants presenting with influenza-like illness Location, number of centres: USA, 57 centres Duration of study: 12 days (+/- 4 days)
Participants	Number screened: not described Number randomised: 627 (oseltamivir 75 mg bid: 209; oseltamivir 150 mg bid: 210; placebo: 208) Number completed: 581 M = 49% F = 51% Mean age: 32.6 Baseline details Inclusion criteria Fever $\geq$ 100 °F plus 1. 1 of cough, sore throat or nasal symptoms, plus: 2. 1 constitutional symptom (headache, malaise, (feeling unwell), myalgia (aches and pains), sweats/chills (feeling feverish), prostration (fatigue)) 3. No more than 36 hours post onset of feeling unwell (protocol violation up to 40 hours) 4. $\geq$18 and $\leq$ 65 years

	5. Comprehension/willingness to give written consent 6. Agreement to utilise an effective method of contraception throughout study period and for 1 reproductive cycle following cessation of study therapy. Negative urine pregnancy test prior to dosing Exclusion criteria 1. Clinically significant disorders/conditions (renal, cardiac, pulmonary, vascular, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease), immunodeficiency disorders, cancer, hepatitis or cirrhosis) 2. Receipt of transplant 3. Steroids/immuno-suppressant therapies 4. Pregnant or breast-feeding females 5. HIV infection 6. Allergy to any excipients in the capsule or acetaminophen 7. Chronic therapy for asthma 8. Previous episode of acute upper respiratory tract infection (URTI), otitis, bronchitis or sinusitis or received antibiotics for URTI, otitis, bronchitis or sinusitis or antiviral therapy for influenza within 2 weeks prior to study day 1 9. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry 10. Vaccination against influenza less than 12 months prior to study day 1 11. Clinically relevant history of abuse of alcohol or other drugs 12. Presentation > 36 hours post onset of symptoms **Definition of patient populations for analysis** ***Intention-to-treat infected population (N = 375)*** All participants who took 1 dose of the study drug, and were subsequently discovered to have laboratory-confirmed influenza ***Standard population (N not presented)*** As for the ITTI population, except that this was further restricted to those who took at least 5 doses of the study drug ***ITT population (N = 615)*** All participants who took at least 1 dose of the study drug. Following request from regulators this population was included in hypothesis testing for the primary efficacy endpoint
Interventions	Intervention 1. Oseltamivir 75 mg bid, given as size 2 capsules (total daily dose 150 mg) 2. Oseltamivir 150 mg bid, given as size 2 capsules (total daily dose 300 mg) Control Matching placebo capsules (2) for Ro 64-0796 (GS 4104) orally bid for 5 days Treatment period 5 days Follow-up period 12 to 20 days post-treatment Co-interventions Rescue pack consisting of acetaminophen (500 mg) for symptomatic relief

Outcomes	***Primary outcomes*** Time to alleviation of symptoms (nasal congestion, sore throat, cough, aches and pains, fatigue, headache and chills/sweats) as derived from subject symptom questionnaire. Calculated from time 0 (study drug initiation) to the time at which all 7 symptoms were alleviated. Participants who withdrew prior to the alleviation of symptoms were censored at the time of withdrawal ***Secondary outcomes*** 1. Extent and severity of Illness 2. Viral shedding 3. Serology 4. Symptoms 5. Temperature 6. Proportion of participants with fever 7. Symptom relief medication usage 8. Adverse events
Notes	Protocol amendments Protocol amendment D (16 February 1998) revised the analyses and definition of secondary and tertiary parameters in the study. Vitus titre was removed as a secondary outcome following the detection of significant variability between 2 virology laboratories with respect to these assays. The major virology parameter in these studies thus became the duration of virus shedding following inclusion into the trial. It was also believed that peak virus titre might have occurred prior to baseline for a significant number of participants entering the trial and hence this particular parameter was not analysed Study period: December 1997 to April 1998

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	"Randomisation was conducted by a central randomisation service by telephone. The investigator/study coordinator telephoned the randomisation centre giving the subjects initials, date of birth and smoking history and the treatment number was then supplied by the centre. The randomisation number was entered in the appropriate place on the subject's Case Report Form by the investigator."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Data from study participants without influenza were available for symptom relief

WV15671 (*Continued*)

Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all participants irrespective of compliance with treatment or infection status
Selective reporting (reporting bias)	Low risk	Outcomes of primary interest for the ITT population available in the CONSORT reconstruction
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo used "In order to maintain the double blind nature of the study, subjects received 2 capsules twice daily for all treatments." "The identification number was added by the investigator at the time of randomisation" "No open key to the code was available at the Study Center..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The identification number was added by the investigator at the time of randomisation." "No open key to the code was available at the Study Center, to the Monitors, Statisticians or at Gilead/Roche Headquarters"

WV15673/WV15697

Methods	Study design: combined analysis of 2 randomised, double-blind, placebo-controlled trials. Participants were requested to return to the clinic when investigators determined that influenza was present in the community Location, number of centres: USA; 6 centres Duration of study: 8 weeks
Participants	Number screened: not specified. Number randomised: 1562 (oseltamivir 75 mg: 520; oseltamivir 150 mg: 521; placebo: 521) Number completed: 1505 M = 37% F = 63%

	Mean age: 34 years. Baseline details: 80% Caucasian; 11% African-American; 3% Hispanic Inclusion criteria 1. Healthy adults 2. 18 to 65 years of age Exclusion criteria 1. Recent vaccination **Definition of patient populations for analysis** ***ITTI population*** Not applicable ***ITT population (N = 1559)*** All participants randomised to treatment and who took at least 1 dose of study medication
Interventions	Intervention 1. Oseltamivir 75 mg once daily plus placebo (total daily dose: 75 mg) 2. Oseltamivir 75 mg twice daily (total daily dose: 150 mg) Control Placebo twice daily Treatment period 6 weeks Follow-up period 2 weeks post-treatment Co-interventions None specified
Outcomes	***Primary outcome*** Laboratory-confirmed clinical influenza during the 6-week treatment period ***Secondary outcomes*** 1. Asymptomatic influenza infection (virus shedding/4-fold increase in antibody to influenza virus in the absence of clinical symptoms of influenza) 2. Non-clinical influenza (symptoms not meeting the criteria for clinical influenza but confirmed to be influenza virus infection through detection of influenza virus shedding/4-fold increase in antibody to influenza virus) 3. Influenza-like illness not caused by influenza virus 4. On and off-treatment adverse events
Notes	Study period not specified

Risk of bias

Bias	Authors' judgement	Support for judgement

WV15673/WV15697 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Unclear risk	Inadequate information available to ascertain concealment of allocation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Not applicable to the study design (prophylaxis)
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes of primary interest for the ITT population available in the CONSORT-based extraction reconstruction
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Inadequate information available to ascertain presentation of placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment

WV15707

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group study. Stratification by vaccination status (current season or not) and chronic obstructive airways disease (present/absent) Location, number of centres: Australia, South Africa and South America, 13 centres Duration of study: 21 +/-4 days
Participants	Number screened: not described Number randomised: 26 (oseltamivir: 17; placebo: 9) Number completed: 25 M = 59% F = 41% Mean age: 71.5 years

	Baseline details Inclusion criteria 1. Male or female patients 2. ≥ 65 years 3. Symptoms of influenza, including temperature (> 37.5 °C) 4. At least 1 respiratory symptom (cough, sore throat or nasal congestion) 5. At least 1 constitutional symptom (chills/sweats, headache, myalgia (aches and pains) fatigue) Exclusion criteria Not described **Definition of patient populations for analysis** ***ITTI population (N = 12)*** Analysis of participants according to the groups to which they were randomised, having received at least 1 dose of study treatment and laboratory-confirmed influenza virus infection ***ITT population (N = 26)*** Analysis of participants according to the groups to which they were randomised, having received at least 1 dose of study treatment, irrespective of influenza infection status ***Standard population (N not reported)*** Population with no major protocol violations or deviations and laboratory-confirmed influenza, who received at least the first 6 scheduled doses within 72 hours/first 5 doses within 72 hours and went on to take 9 or 10 doses. Analysis according to treatment received
Interventions	Intervention Oseltamivir 75 mg bid (total daily dose 150 mg) Control Placebo (provided as size 2 capsule containing dehydrocholic acid, dibasic calcium phosphate dihydrate and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate) Treatment period 10 days Follow-up period 7 to 15 days post-treatment Co-interventions Not specified
Outcomes	***Primary outcomes*** Duration of illness (time to alleviation of symptoms) ***Secondary outcomes*** 1. Area under the curve (AUC) of the composite symptom score 2. Virus shedding 3. Quality of life 4. Adverse events

Notes	Study period not specified No viral swab data was collected on South American patients. This population was therefore excluded from the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Low risk	"Randomization was performed by a central randomisations service. The investigator telephoned the centre to report the subject's date of birth, vaccination status and history of COAD. The treatment number was then supplied by the randomisations centre."
Incomplete outcome data (attrition bias) Symptoms	High risk	Available data analysed by ITTI population and not ITT
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all randomised participants
Selective reporting (reporting bias)	High risk	Outcomes of primary interest for the ITT population not made available to the review authors
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Presentation of placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment

WV15708

Methods	Study design: multi centre, stratified and randomised, double-blind, placebo-controlled, parallel-group study carried out in elderly persons residential homes. Participants were randomised to treatment when a local outbreak was detected. Stratification factors were vaccine status and presence or absence of chronic obstructive airway disease Location, number of centres: Australia, New Zealand, South Africa, Brazil (14 centres) Duration of study: 8 weeks
Participants	Number screened: not described Number randomised: 372 (oseltamivir: 190; placebo: 182) Number completed: 335 M = 41% F = 59% Mean age: 79 years Baseline details: 99% Caucasian; 69% vaccinated against influenza; 12% had COPD. 90% participants had other pre-existing diseases, of which diabetes was more common in oseltamivir than placebo (17.4% versus 8.8% respectively) Inclusion criteria Resident in care home Exclusion criteria Not listed **Definition of patient populations for analysis** ***ITT population*** Not described. Incidence of influenza was low
Interventions	Intervention Oseltamivir 75 mg od (total daily dose: 75 mg) Control Matching placebo Treatment period 6 weeks Follow-up period 2 weeks post-treatment Co-interventions Not specified
Outcomes	***Primary outcomes*** Laboratory-confirmed clinical influenza, defined as: fever (temperature > 99 °F) plus 1 respiratory symptom (cough, sore throat, nasal symptoms) and 1 constitutional symptom (headache, myalgia, sweats/chills, fatigue). Laboratory confirmation by either virus shedding within 2 days of symptom onset or 4-fold increase in influenza antibody ***Secondary outcomes*** 1. Adverse events 2. Mortality

Notes	Study period not specified	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Unclear risk	Inadequate information available to ascertain concealment of allocation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Not applicable to the study design (prophylaxis)
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all randomised participants
Selective reporting (reporting bias)	High risk	Harms data provided as a narrative description without adequate reporting of outcome data
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment

WV15730

Methods	Study design: randomised, double blind, placebo-controlled, parallel-group study. Participants were stratified by current smoking behaviour (smoker/non smoker). Centres activated to recruit participants during an influenza outbreak in the locality, detected using standardised surveillance techniques Location, number of centres: Australia and South Africa, 12 centres Duration of study: 21 +/- 4 days
Participants	Number screened: not described Number randomised: 58 (oseltamivir: 31; placebo: 27) Number completed: 56 M = 52% F = 48% Mean age: 35 years Baseline details: 93% Caucasian; 21% smoking history Inclusion criteria 1. Fever ≥ 38 °C 2. 1 or more respiratory symptom (cough, sore throat, nasal symptoms). 3. 1 or more constitutional symptom (headache, myalgia, (aches and pains), sweat/chills (feeling feverish), prostration (fatigue)) 4. ≤ 36 hours post onset of feeling unwell 5. Between 18 and 65 years of age 6. Willing and able to comprehend and give written informed consent 7. Participants were to utilise an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study drug 8. Females of childbearing potential had to have negative urine pregnancy test prior to drug dosing Exclusion criteria 1. Active clinically significant renal, cardiac, pulmonary, vascular, neurologic, metabolic (diabetes, thyroid disorder, adrenal disease) disease, immunodeficiency disorders, cancer, hepatitis or cirrhosis 2. Receipt of transplant 3. Steroids or immuno-suppressant therapy 4. Pregnant or breast-feeding females 5. Known HIV infection 6. Allergy to any excipients in capsule or paracetamol 7. Chronic therapy for asthma 8. Previous episode of acute upper respiratory tract infection (URTI): otitis, bronchitis or sinusitis; or received antibiotics for URTI, otitis, sinusitis or bronchitis, or antiviral therapy for influenza within 2 weeks prior to study entry 9. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry 10. Administrations of influenza vaccine less than 12 months prior to study entry 11. The use of the antiviral drugs for influenza such as rimantadine, ribavirin, zanamivir and amantadine was not permitted during this study 12. A clinically relevant history of abuse of alcohol or other drugs 13. Presentation > 36 hours post the onset of feeling unwell **Definition of patient populations for analysis** ***ITTI population (N = 38)***

	Participants analysed according to groups to which they were randomised providing they had received at least 1 dose of study treatment and had laboratory-confirmed influenza virus infection ***ITT population (N = 58)*** The ITT population consisted of the same participants as the ITTI population, also included participants who did not have laboratory-confirmed influenza but took at least 1 dose of study medication. Participants analysed by groups to which they were randomised ***Safety population (N = 58)*** All participants randomised, who received at least 1 dose of study medication and at least 1 safety follow-up, whether or not they had withdrawn prematurely. Participants who receive therapy other than intended were analysed according to therapy received ***Standard population (N = 38)*** All randomised participants without major protocol violations or deviations, with laboratory-confirmed influenza and who received at least the first 6 scheduled doses within 72 hours or who received the first 5 doses within 72 hours and went on to take 9 or 10 doses. Participants analysed according to treatment received
Interventions	Intervention Oseltamivir 75 mg bid (total daily dose: 150 mg), given as size 2 capsule Control Placebo, given as size 2 capsule Treatment period 5 days Follow-up period Between 12 and 20 days post-treatment Co-interventions Rescue medication pack
Outcomes	***Primary outcomes*** Time to alleviation of symptoms. Assessed as alleviation of nasal congestion, sore throat, cough, aches and pains, fatigue, headache and feeling feverish. Time to alleviation of symptoms calculated from study drug initiation to time at which all symptoms were alleviated. Participants withdrawing prior to alleviation of all symptoms were censored at the time of withdrawal ***Secondary outcomes*** 1. Extent and severity of illness 2. Duration of viral shedding 3. Serology 4. Symptoms 5. Rescue medication consumption 6. Household contacts developing ILI 7. Viral resistance 8. Quality of life 9. Pharmacokinetics

	10. Adverse events	
Notes	Study period not specified	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Low risk	"Randomization was performed by a central randomisations service. The investigator telephoned the centre to report the subject's date of birth, vaccination status and smoking status. The treatment number was then supplied by the randomisations centre."
Incomplete outcome data (attrition bias) Symptoms	High risk	Available data analysed by ITTI population and not ITT
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all randomised participants
Selective reporting (reporting bias)	High risk	Outcomes of primary interest for the ITT population not made available to the review authors
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the code was available at the study centre, to the monitors, statistician or at Roche Headquarters. In the event of a medical emergency the blinding was to be broken if considered absolutely mandatory to properly manage the patient

		by contacting the randomisations centre. The blinding was not broken for any subject during the study."

WV15758

Methods	Study design: randomised, double-blind, placebo-controlled study stratified for the presence of acute otitis media Location, number of centres: USA and Canada, 80 centres Duration of study: 28 +/-4 days
Participants	Number screened: not described Number randomised: 698 (oseltamivir: 342; placebo: 356) Number completed: 655 M = 50% F = 50% Mean age: 5.34 years Baseline details: 65% Caucasian; 18% otitis media Inclusion criteria 1. Temperature ≥ 100 °F or 37.8 °C PLUS at least 1 respiratory symptom (either cough or coryza) 2. Between 1 and 12 years 3. Less than 48 hours between onset of feeling unwell and administration of first dose of study medication 4. Parent/guardian willing and able to comply with study requirements and give consent 5. Subject able to comply with study requirements and willing to give assent, if appropriate Exclusion criteria 1. RSV positive, using a rapid diagnostic test 2. Steroids or immuno-suppressant therapy 3. HIV infection 4. Uncontrolled significant diseases (renal, vascular, neurologic or metabolic disease (diabetes, thyroid disorders, adrenal disease), hepatitis, cirrhosis or pulmonary disease (other than mild asthma), or participants with known chronic renal failure). Uncontrolled defined as requiring change of therapy (increased dose or change of medication) or hospitalisation 4 weeks or less before first dose of study drug 5. Active cancer 6. Hospitalised participants (participants hospitalised for less than 24 hours were not excluded) 7. Major transplant recipients 8. Allergy to study drug or paracetamol/acetaminophen 9. Antiviral treatment for influenza in the previous 2 weeks 10. Females of childbearing potential 11. Participation in a clinical trial with an investigational drug within 4 weeks prior to study entry **Definition of patient populations for analysis**

	ITTI infected population (N = 452) Participants analysed according assigned treatment provided they received at least 1 dose of study treatment with some follow-up efficacy data and had laboratory-confirmed influenza virus infection as determined post entry into the study ***ITT population (N = 695)*** All participants who took at least 1 dose of study medication with some follow-up efficacy data irrespective of influenza virus infection. Participants analysed according to the groups to which they were randomised ***Safety population (N = 695)*** Participants who received at least 1 dose of study medication and who received at least 1 safety follow-up, whether or not withdrawn prematurely. Participants analysed according to treatment received ***Standard population (N = 396)*** Used for summaries of efficacy parameters. All participants who had no major protocol violations or deviations, who had laboratory-confirmed influenza and who received at least the first 6 scheduled doses within 72 hours or who received the first 5 doses within 72 hours but went on to take 9/10 doses. Participants analysed according to the treatment received
Interventions	Intervention Oseltamivir 2 mg/kg (not exceeding a maximum of 100 mg/dose) bid Control Placebo bid Study drugs administered as dry powder to be reconstituted with water Treatment period 5 days Follow-up period 19 to 27 days post-treatment Co-interventions Relief medication was provided but details not specified
Outcomes	***Primary outcomes*** Time to freedom from illness: defined as the length of time taken from the start of treatment to the point at which all of the following criteria were met 1. A score of '0' (no problem) or '1' (minor problem) for cough and nasal symptoms (items 14 and 15 of the CARIFS scale) 2. Return to normal activities 3. Return to afebrile state The duration of the event was calculated from 'time 0' (study drug initiation) to the time at which all the above 3 conditions were simultaneously met and remained true for a minimum of 24 hours ***Secondary outcomes*** 1. Time to return to normal health and activity 2. Duration of symptoms

	3. Extent and severity of symptoms 4. Secondary illnesses and associated antibiotic use 5. Symptom relief medication use 6. Medically attended visits and hospitalisation 7. Serology 8. Virology and viral resistance 9. Adverse events
Notes	Protocol amendments 1. Eligibility: temperature at entry into the study from 101.3 °F to 100.0 °F (38.5 °C to 37.8 °C) so as not to exclude several febrile children who otherwise met the entry criteria at baseline since parents had administered antipyretic medication prior to the clinic (screening) visit 2. Composite outcome: normal health was based on combination of parental global assessment and the absence or alleviation of the key objective signs/symptoms including fever, cough and coryza which defined the illness for the purposes of inclusion into the protocol Study period: December 1998 to April 1999

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Low risk	"Randomization was conducted by a central randomisations service, ICTI (Interactive Clinical Technologies Inc., Princeton, NJ). The investigator telephoned the centre to report the subject's date of birth, sex, and weight. The randomisations number was then supplied by the centre in the form of a message on an interactive voice response system (IVRS). The investigator entered the randomisations number in the appropriate place on the case report form. The subject randomisations numbers were allocated sequentially within a stratum in the order in which subjects were enrolled."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Data available for both influenza infected and non-infected study populations
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-compa-

WV15758 (*Continued*)

		rable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes of primary interest to the review for ITT population available in the CONSORT-based extraction reconstruction
Other bias	Unclear risk	Unable to ascertain placebo capsule contents
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"No open key to the code was available at the study centre..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the code was available (...) to the Roche monitors, statisticians or at Roche Headquarters."

WV15759/WV15871

Methods	Study design: randomised, double-blind, stratified placebo-controlled study. Stratification by asthma severity Location, number of centres: not available Duration of study: not available
Participants	Number screened: not provided Number randomised: not provided (oseltamivir: NA; placebo: NA) Number completed: not provided M = NA F = NA Mean age: NA Baseline details: NA Inclusion criteria 1. Chronic asthma 2. 6 to 12 years 3. Symptoms of influenza (as fever (≥ 37.8 °C or ≥ 100.0 °F), plus 1 respiratory symptom (cough or coryza) Exclusion criteria None specified **Definition of patient populations for analysis** ***ITTI population (N = NA)*** Not specified ***ITT population (N = NA)*** Not specified

Interventions	Intervention Oseltamivir: 2.0 mg/kg bid Control Matching placebo bid Study drugs administered as dry powder Treatment period 5 days Follow-up period Not specified Co-interventions Not specified
Outcomes	***Primary outcomes*** Composite of all of the following: 1. First alleviation of cough and nasal congestion segment of the CARIFS score 2. First return to normal health and activity 3. First return to afebrile state (temperature < 37.2 °C or 98.9 °F) ***Secondary outcomes*** 1. Return to normal health and activity 2. Duration of symptoms 3. Extent and severity of symptoms 4. Secondary illnesses 5. Lung function 6. Symptoms 7. Adverse events
Notes	Study period not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Low risk	"The subject randomizations numbers will be generated by Roche or its designee and incorporated into double-blind labelling. Randomization will be conducted by a central randomisations service by telephone."

WV15759/WV15871 (*Continued*)

Incomplete outcome data (attrition bias) Symptoms	Unclear risk	Insufficient information was available to ascertain populations for analysis and judge risk of bias
Incomplete outcome data (attrition bias) Complications of influenza	Unclear risk	Insufficient information was available to ascertain populations for analysis and judge risk of bias
Incomplete outcome data (attrition bias) Safety data	Unclear risk	Insufficient information was available to ascertain populations for analysis and judge risk of bias
Selective reporting (reporting bias)	High risk	No outcome data were provided in the study CONSORT-based extraction reconstruction
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment

WV15799

Methods	Study design: randomised, double-blind, placebo-controlled cluster trial recruiting families of 3 to 8 members. Households recruited if any member developed an influenza-like illness during an influenza outbreak within the community (index case) Location, number of centres: USA (35 centres); Canada (11 centres); Denmark (1 centre) ; Finland (6 centres); Germany (6 centres); Netherlands (3 centres); Norway (2 centres) ; Switzerland (1 centre); UK (8 centres) Duration of study: 21 +/- 4 days
Participants	Number screened: not described Number randomised: 962 (oseltamivir: 498; placebo: 464) Number completed: 944 M = not reported F = not reported Mean age: range from 1 to 76 years Baseline details: 13% contacts had received influenza vaccination in the same season. 40% contacts had pre-existing diseases (most frequently reported: asthma (3.0%), hypertension (5.7%), drug hypersensitivity (3.9%) and depression (2.9%)) Inclusion criteria 1. Household contact of someone who developed ILI

	2. Participants had to live in same home for at least 2 days before and 3 days after index case identification 3. Maintain daily contact with the index case Exclusion criteria Not specified **Definition of patient populations for analysis** ***ITT (contacts: N = 550; index cases: 370)*** People residing in the same house an index case (someone with ILI, irrespective of baseline infection status) ***ITTI (contacts: N = 405; index cases: 163)*** People residing in the same house as a positive index case (somebody with confirmed influenza at baseline) ***Standard population: N = unclear*** Mentioned but not described
Interventions	Intervention Oseltamivir 75 mg od (total daily dose: 75 mg) Control Placebo Treatment period 7 days Follow-up period 10 to 18 days post-treatment Co-interventions Index case received paracetamol/acetaminophen
Outcomes	***Primary outcomes*** Incidence of laboratory-confirmed clinical influenza in contacts of the index case. Defined as fever plus at least 1 respiratory symptom (cough, sore throat, nasal congestion) and 1 constitutional symptom (fatigue, aches and pains, headache, feeling feverish), all recorded on the same day (either by the investigator as an illness visit report on the CRF, or by the participant on their diary card) plus laboratory confirmation of influenza infection ***Secondary outcomes*** 1. Incidence of laboratory-confirmed non-clinical influenza 2. Laboratory-confirmed asymptomatic influenza 3. Laboratory-confirmed influenza infection 4. The incidence of viral shedding irrespective of whether participants had symptoms of influenza or not
Notes	Study period not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

WV15799 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Unclear risk	Inadequate information available to ascertain concealment of allocation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Not applicable to the study design (prophylaxis)
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all randomised participants
Selective reporting (reporting bias)	High risk	Outcome data for ITT population were not available to the review authors
Other bias	Unclear risk	No information available on placebo contents
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Inadequate information available to ascertain presentation of placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment

WV15812/WV15872

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group design. Stratification performed by presence of chronic obstructive airways disease (COAD) Location, number of centres: northern hemisphere (80 centres) and southern hemisphere (20 centres) during influenza seasons Duration of study: 21 +/- 4 days
Participants	Number screened: not reported Number randomised: 404 (oseltamivir: 200; placebo: 204) Number completed: 393 M = 44% F = 56% Mean age: 52 years Baseline details: COAD 76%; vaccination: 28%; smoking: 22%

	Inclusion criteria 1. Adults (≥13 years of age (Norway and Sweden ≥ 18 years of age) with chronic cardiac (excluding chronic idiopathic hypertension) or pulmonary disorders (including bronchopulmonary dysplasia, and asthma but excluding cystic fibrosis) severe enough to require regular medical follow-up or hospital care. In study WV15872 the following clarification was also given: pulmonary disorders were defined as COAD which permanently reduces the FEV1. Asymptomatic patients with a previous valve replacement or bypass surgery were also eligible 2. Symptoms consistent with influenza: fever ≥ 38 °C (100 °F) if patients aged < 65 years or fever ≥ 37.5 °C (99.5 °F) if patients aged ≥ 65 years plus 1 respiratory symptom (cough, sore throat, nasal symptoms) and 1 constitutional symptom (chills/sweats (feeling feverish), malaise (feeling unwell), headache, myalgia (aches and pains), prostration (fatigue)) 3. Presentation such that the first dose may be taken no later than 36 hours post onset of feeling unwell 4. Legally effective written informed consent available 5. Mental Status Questionnaire (MSQ) ≥7 6. Not in need of or awaiting residential care 7. Women of childbearing potential provided they had a negative urine pregnancy test prior to drug dosing and they agreed to utilise an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study therapy. (Male patients whose partners were of childbearing potential were to agree to use an effective method of contraception throughout the study and for 3 months after completing the trial - added by amendment to protocol WV15872) Exclusion criteria 1. Uncontrolled disease (renal, vascular, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease), hepatitis or cirrhosis, defined as disease requiring change of therapy or hospitalisation within 4 weeks preceding the first dose of study drug 2. Creatinine clearance (measured or estimated) ≤ 30 mL/min 3. Frank jaundice or with transaminase values within or greater than grade III of the WHO scale 4. New York Heart Association (NYHA) class IV 5. COAD stage III 6. Major transplant recipients 7. Immuno-suppressant therapy (inhaled steroids or systemic steroids less than or equivalent to 5 mg/day prednisolone were allowed) 8. Pregnant or breast-feeding females 9. Active cancer (basal cell carcinoma, squamous cell carcinoma of the skin or a previous history of cancer in remission and not requiring therapy were permitted) 10. HIV infection 11. Allergy to any excipients in capsule or paracetamol/acetaminophen 12. Previous episode of acute upper respiratory tract infection (URTI), otitis, bronchitis or sinusitis or received antibiotics for URTI, otitis, sinusitis or bronchitis or antiviral therapy for influenza within 2 weeks prior to study day 1 13. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry 14. A clinically relevant history of abuse of alcohol or other drugs

	15. Presentation > 36 hours post the onset of feeling unwell **Definition of patient populations for analysis** ***ITTI population (N = 231)*** All patients who had at least 1 dose of study medication and who had a laboratory-confirmed influenza virus infection. Data were analysed according to treatment assignment at randomisation ***ITT population (N = 402)*** All randomised patients who received at least 1 dose of study medication ***Safety population (N = 401)*** Randomised participants who received at least 1 dose of study medication and had at least 1 post-baseline safety assessment ***Standard population (N = 236)*** Participants from ITTI population without major protocol violations, and who received at least the first 6 scheduled doses within 72 hours, or received the first 5 doses within 72 hours and went on to take 9 out of the 10 doses
Interventions	Intervention Oseltamivir 75 mg bid (total daily dose 150 mg) Control Placebo bid Treatment period 10 days Follow-up period 7 to 15 days Co-interventions Pack of paracetamol/acetaminophen (500 mg)
Outcomes	***Primary outcomes*** Time to alleviation of illness (derived from a patient-rated symptom questionnaire). The 7 symptoms assessed in the questionnaire were 1. Nasal congestion 2. Sore throat 3. Cough 4. Aches and pains 5. Fatigue 6. Headache 7. Chills/sweats ***Secondary outcomes*** 1. Extent and severity of symptoms 2. AUC of individual symptoms 3. Use of symptom relief medication 4. Quality of life 5. Virology

	6. Adverse events	
Notes	Study period: WV15812: January to April, 1999; WV15872: June to October, 1999	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Low risk	"Randomisation was performed by a central randomisation service."
Incomplete outcome data (attrition bias) Symptoms	High risk	Available data analysed by ITTI population and not ITT
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all randomised participants
Selective reporting (reporting bias)	High risk	Outcomes of primary interest to the review for the ITT population were not available to the review authors
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the code was available at the Study Centre, to the Monitors, Statisticians or at Roche Headquarters. The blind was to be broken only in the event of a medical emergency if considered absolutely necessary to manage the patient."

WV15819/WV15876/WV15978

Methods	Study design: randomised, double-blind, placebo-controlled, parallel-group design. Participants were stratified according to vaccination status (vaccinated in the current influenza season or not), and coexistence or not of chronic obstructive airways disease (COAD) Location, number of centres: France, the Netherlands, Belgium, Germany, Switzerland, United Kingdom, Norway, Sweden, Denmark, Israel, Lithuania, Estonia, Poland, Canada USA, Canada, South Africa, New Zealand, Australia; 169 centres Duration of study: 21 +/- 4 days
Participants	Number screened: not reported Number randomised: 726 (oseltamivir: 362; placebo: 374) Number completed: 715 M = 43% F = 57% Mean age: 73 years Baseline details: 98% Caucasian; COAD: 8%; vaccination: 43% Inclusion criteria 1. Age ≥ 65 years 2. Symptoms consistent with influenza: fever ≥ 37.5 °C (≥ 97.5 °F) *plus* 1 respiratory symptom (cough, sore throat, nasal symptoms), *plus* 1 constitutional symptom (headache, myalgia (aches and pains), sweats/chills (feeling feverish), fatigue) 3. No more than 36 hours since onset of feeling unwell 4. Willingness and ability to understand and give written informed consent 5. Mental Status Questionnaire (MSQ) score ≥ 7 6. Living independently, capable of self care, ambulant, and not in need of or awaiting residential care (residents of retirement homes were eligible provided they fulfilled these criteria) 7. If male with a partner of childbearing potential, agreement to use an effective method of contraception throughout the study and for 3 months after completing the trial Exclusion criteria 1. Unstable or uncontrolled disease (renal, cardiac, pulmonary, vascular, neurologic or metabolic disease, hepatitis or cirrhosis 2. Creatinine clearance < 30 ml/min 3. Known significant liver dysfunction associated with frank jaundice or transaminase 4. Concentrations of WHO grade 3 or greater 5. Significant cardiac failure resulting in limitation of physical activity and clinical signs of cardiac failure including pitting oedema, elevated jugular venous pressure and/or evidence of pulmonary oedema 6. Transplant recipient 7. Active cancer at any site 8. HIV infection 9. Allergy to any excipients in the capsules/paracetamol (acetaminophen) 10. Acute upper respiratory tract infection (URTI), otitis media, bronchitis or sinusitis, or antibiotic therapy for URTI, otitis media, bronchitis or sinusitis, or antiviral therapy for influenza, within 2 weeks before study entry 11. Use of the antiviral drugs rimantadine, ribavirin, zanamivir and amantadine 12. Previous or concomitant treatment with neuraminidase inhibitor (inhaled or oral)

	13. Participation in a clinical study of an investigational drug within 4 weeks before study entry 14. Clinically relevant history of abuse of alcohol or other drugs **Definition of patient populations for analysis** ***ITTI population (N = 477)*** Primary analysis population for efficacy. Participants analysed according to the groups to which they were randomised, provided they received at least 1 dose of study treatment and had laboratory-confirmed influenza virus infection. Participants with protocol violations or deviations were retained in the ITTI population ***ITT population (N = 735)*** All participants who took at least 1 dose of study medication. Participants analysed according to groups to which they were randomised ***Safety population (N = 736)*** All randomised participants who received at least 1 dose of study medication and who had at least 1 safety follow-up, whether or not withdrawn prematurely. Data from participants were analysed according to therapy they received ***Standard population (N = 445)*** All randomised participants who had no major protocol violations or deviations, laboratory-confirmed influenza virus infection, and who received at least the first 6 scheduled doses within 72 hours or who received the first 5 doses within 72 hours but went on to take 9 out of 10 total doses. Participants were analysed according to treatment received
Interventions	Intervention Oseltamivir 75 mg bid (total daily dose 150 mg) given as size 2 capsules Control Matching placebo size 2 capsules Treatment period 5 days Follow-up period 12 to 20 days post-treatment Co-interventions Rescue pack of paracetamol
Outcomes	***Primary outcomes*** Duration of illness given as summary measures from Kaplan-Meier survival curves ***Secondary outcomes*** 1. Extent and severity of illness 2. Virus shedding 3. Serology 4. Symptoms 5. Temperature and fever 6. Rescue medication use 7. Secondary illness 8. Hospitalisation

	9. Quality of life 10. Adverse events 11. Vital signs (blood pressure, heart rate, respiratory rate)
Notes	Protocol amendments 1. Protocol WV15819 amendment B and Protocol WV15876 amendment B. Originally, symptoms, signs and common sequelae of influenza were to be reported as adverse events. After this protocol amendment, such symptoms, signs and common complications were excluded from reporting as adverse events, unless they fulfilled the criteria for reporting as serious adverse events or the criteria for secondary illness 2. Protocol WV15876 Amendment B also added a requirement for male participants whose partners were of childbearing potential to use effective contraception during the study and for 3 months after completing the study, to follow Roche current standard operating procedures 3. Protocol WV15819 Amendment D and Protocol WV15876 Amendment C made changes to the secondary efficacy parameters. The secondary efficacy parameter reflecting the antiviral effect of treatment was changed from the duration of viral shedding to the proportion of participants shedding virus on day 3. This change was made because the intermittent sampling schedule used in the study meant that the true duration of viral shedding could not be assessed exactly, whereas the proportion of participants shedding virus could be determined. The incidence of secondary illnesses requiring antibiotics was included as a new secondary endpoint, and the secondary illnesses were defined as sinusitis, LRTI, otitis media, bronchitis and pneumonia. The method of analysis of the proportion of participants shedding virus and for the proportion of participants with predefined secondary illnesses (Fisher's 2-tailed exact test) was added to the statistical methods. Protocol WV15978 included an additional exclusion criterion around previous or concomitant treatment with a neuraminidase inhibitor Study period: Northern Hemisphere centres recruited during flu seasons in 1998 and 1999; Southern Hemisphere centres recruited during flu seasons in 1999

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	"Randomization was conducted by a central randomisation service via telephone. The investigator or study coordinator telephoned the randomisation centre giving the subject's date of birth, vaccination status and history of COAD, and the treatment number was then supplied by the centre. The randomisation number was entered in the appropriate place on the subject's Case Report Form by the investigator.

		"
Incomplete outcome data (attrition bias) Symptoms	Low risk	Available data analysed for both by ITTI and ITT populations
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes of primary interest to the review are available in the CONSORT-based extraction reconstruction
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the code was available at the study centres, to the monitors, statisticians or at Roche headquarters. In the event of a medical emergency the blind could be broken, if considered absolutely mandatory to properly manage the subject, by contacting the randomisations centre."

WV15825

Methods	Study design: randomised, double-blind, placebo-controlled trial in residential homes for elderly people. Participants were recruited when a local outbreak was detected, defined as 2 cases in immediate vicinity within 7 days or 1 case in the home itself Location, number of centres: USA (16 centres), UK (1 centre), France (4 centres), Belgium (2 centres), and the Netherlands (3 centres) Duration of study: 8 weeks
Participants	Number screened: not reported Number randomised: 548 (oseltamivir: 276; placebo: 272) Number completed: 493 M = 31% F = 69% Mean age: 82 years Baseline details: 92% Caucasian; 4% Black; 4% Hispanic. 80% vaccinated; 14% COAD

	Inclusion criteria No inclusion criteria detailed. Study conducted in residential homes for the elderly Exclusion criteria Not specified ***Definition of patient populations for analysis*** Prophylaxis study, differentiation between populations at baseline not undertaken
Interventions	Intervention Oseltamivir 75 mg (frequency of administration not specified) Control Placebo Treatment period Not specified Follow-up period 8 weeks Co-interventions Not specified
Outcomes	***Primary outcomes*** Laboratory-confirmed clinical influenza. Defined as fever (temperature > 99 °F) plus 1 respiratory symptom (cough, sore throat, nasal symptoms) plus 1 constitutional symptom (headache, myalgia, sweats/chills, fatigue) confirmed by either virus shedding within 2 days of symptom onset or 4-fold increase in influenza antibody ***Secondary outcomes*** Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised; procedure generating randomisations schedule not available
Allocation concealment (selection bias)	Unclear risk	Inadequate information available to ascertain concealment of allocation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Not applicable to the study design (prophylaxis)
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-compa-

WV15825 (*Continued*)

		rable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all randomised participants
Selective reporting (reporting bias)	High risk	Outcome data relating to complications were not available for the CONSORT-based extraction reconstruction
Other bias	Unclear risk	Placebo contained dehydrocholic acid. Dosage not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Inadequate information available to ascertain presentation of placebo capsules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment

AUC: area under the curve
bid: twice daily
CSR: clinical study report
CARIF: severity score
CDC = US Centers for Disease Control and Prevention
COAD: chronic obstructive airways disease
CONSORT: Consolidated Standards of Reporting Trials
COPD: chronic obstructive pulmonary disease
CPK: inflammation marker
CRF: clinical report form
ECG: electro cardio gram
EMA = European Medicines Agency
EMEA = see EMA
FEV1: forced expiratory volume (at interval 1 in spirometry testing)
FDA = US Food and Drug Administration
h: hour
HAI: anti-haemagglutinin antibody
ILI: influenza-like illness
IP: electronic address
ITT: intention-to-treat (population)
ITTI: intention-to-treat (influenza)-infected (population)
LRTI: lower respiratory tract infection
NA: not applicable
od: once daily
PCR: polymerase chain reaction
P-R: one of the segments of the ECG trace
QRS: one of the segments of the ECG trace
QT: one of the segments of the ECG trace

QTc: one of the segments of the ECG trace
R-R: risk ratio
RSV: respiratory syncytial virus
URTI: upper respiratory tract infection
WBC: white blood cell
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
105934	Post-marketing study
107485	Dose-ranging study
108127	Non-randomised study
112311	Pharmacoavailability study
112312	Pharmacoavailability study
113268	Pharmacoavailability study
113502	Non-comparative study
113625	Pharmacokinetics study
113678	Non-comparative study
114045	Survey
114373	Not placebo/do-nothing controlled
167-02	Unknown study. Only ID traced
167-03	Unknown study. Only ID traced
167-04	Unknown study. Only ID traced
167-05	Unknown study. Only ID traced
ADS-TCAD-PO206	Not placebo/do-nothing controlled
BP21288	Pharmacokinetics study
C94-009	Unknown study. Only ID traced

(*Continued*)

C94-085	Unknown study. Only ID traced
GCP/95/045	Pharmacokinetics study
GS-97-801	Unknown study. Only ID traced
GS97-802	Unknown study. Only ID traced
JNAI-02	Unknown study. Only ID traced
JNAI-03	Unknown study. Only ID traced
JP15734	Pharmacokinetics non-comparative study
JP15735	Dose-ranging study
M76006	Not placebo/do-nothing controlled
ML17713	Non-comparative study
ML20542	Not placebo/do-nothing controlled
ML21954	Not placebo/do-nothing controlled
ML22789	Not placebo/do-nothing controlled
ML22872	Not placebo/do-nothing controlled
ML22879	Not placebo/do-nothing controlled
ML25018	Bioavailability study
ML25087	Not placebo/do-nothing controlled
ML25094	Non-comparative study
ML25157	Pharmacokinetics study
ML25176	Pharmacokinetics study
ML25179	Not placebo/do-nothing controlled
ML25265	Non-comparative observational study
ML25266	Pharmacokinetics study

(*Continued*)

MP20691	Pharmacokinetics study
MV20043	Transmission study
MV20050	Dose-ranging study
MV22926	Non-comparative study
MV22949	Pharmacokinetics study
MV22951	Pharmacokinetics study
MV22963	Pharmacokinetics study
MV22970	Pharmacokinetics study
NAI106784	Pharmacokinetics study
NAI108166	Pharmacokinetics study
NAI10901	Comparator is vaccine
NAI10902	Pharmacokinetics study
NAI40012	Instructional leaflet study
NAIA1009	Pharmacokinetics study
NAIB1001	Unknown study. Only ID traced
NAIB1002	Pharmacokinetics study
NAIB1007	Unknown study. Only ID traced
NCT00297050	Dose-ranging study
NCT00416962	Not placebo/do-nothing controlled
NCT00867139	Not placebo/do-nothing controlled in immunocompromised people
NCT00957996	Peramivir study - does not have placebo/do nothing comparator
NCT01063933	Pharmacokinetics study
Not applicable (registry)	Unknown study. Only ID traced

(*Continued*)

NP15525	Unknown study. Only ID traced
NP15717	Pharmacokinetics study
NP15718	Pharmacokinetics study
NP15719	Pharmacokinetics study
NP15728	Pharmacokinetics study
NP15729	Pharmacokinetics study
NP15757	Pharmacokinetics study
NP15810	Pharmacokinetics study
NP15826	Pharmacokinetics study
NP15827	Pharmacodynamics study
NP15881	Unknown study. Only ID traced
NP15901	Pharmacokinetics study
NP15912	Unknown study. Only ID traced
NP16472	Not placebo/do-nothing controlled
NP22770	Pharmacokinetics study
NP25138	Not placebo/do-nothing controlled
NP25139	Not placebo/do-nothing controlled
NP25140	Pharmacokinetics study
NV20234	Immunocompromised participants
NV20235	Immunocompromised participants
NV20237	Resistance study
NV22155	Not placebo/do-nothing controlled
NV22158	Registry study

(*Continued*)

NV25118	Pharmacokinetics study
NV25182	Not placebo/do-nothing controlled
PP15974	Pharmacokinetics study
PP16351	Pharmacokinetics study
PP16361	Pharmacokinetics study
PV15615	Viral challenge study
PV15616	Viral challenge study
WP15517	Pharmacokinetics study
WP15525	Pharmacokinetics study
WP15647	Pharmacokinetics study
WP15648	Pharmacokinetics study
WP15676	Pharmacokinetics study
WP15979	Bioavailability study
WP16094	Pharmacokinetics study
WP16134	Bioequivalence study
WP16137	Bioequivalence study
WP16225	Bioequivalence study
WP16226	Pharmacokinetics study
WP16254	Pharmacokinetics study
WP17721	Pharmacokinetics study
WP18308	Pharmacokinetics study
WP20727	Pharmacokinetics study
WP20749	Not placebo/do-nothing controlled

(*Continued*)

WP21272	Pharmacokinetics study
WP22849	Pharmacokinetics study
WV16139	Unknown study. Only ID traced. ID Could be a typo.
WV16193	Not placebo/do-nothing controlled

DATA AND ANALYSES

Comparison 1. Oseltamivir versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to alleviation of symptoms (ITT population)	5	3713	Mean Difference (IV, Random, 95% CI)	-21.29 [-29.59, -12.98]
2 Hospital admission (safety population)	8	4696	Odds Ratio (IV, Random, 95% CI)	0.95 [0.57, 1.61]
3 Defined as influenza-infected at baseline	8	4696	Odds Ratio (IV, Random, 95% CI)	0.83 [0.73, 0.94]
4 Antibody rise four-fold or greater	8	4696	Odds Ratio (IV, Random, 95% CI)	0.79 [0.70, 0.90]
5 Adverse events - Nausea	9	5651	Odds Ratio (IV, Random, 95% CI)	1.62 [1.17, 2.26]
6 Adverse events - Vomiting	9	5651	Odds Ratio (IV, Random, 95% CI)	2.32 [1.62, 3.31]
7 Adverse events - Diarrhoea	9	5651	Odds Ratio (IV, Random, 95% CI)	0.72 [0.53, 0.97]
8 Withdrawal from trial due to adverse events	9	5651	Odds Ratio (IV, Random, 95% CI)	1.08 [0.66, 1.76]

Comparison 2. Zanamivir versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Defined as influenza-infected at baseline	7	3029	Odds Ratio (IV, Random, 95% CI)	1.05 [0.90, 1.24]
2 Adverse event - asthma	9	5269	Odds Ratio (IV, Random, 95% CI)	0.54 [0.34, 0.86]

Analysis 1.1. Comparison 1 Oseltamivir versus placebo, Outcome 1 Time to alleviation of symptoms (ITT population).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 1 Oseltamivir versus placebo

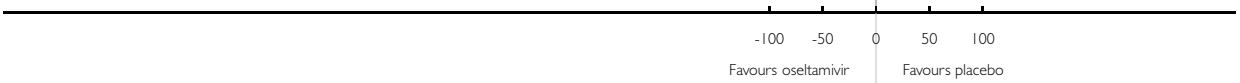
Outcome: 1 Time to alleviation of symptoms (ITT population)

Study or subgroup	Oseltamivir N	Mean(SD)[hours]	Placebo N	Mean(SD)[hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
M76001	933	140.6 (125.2)	473	165.5 (156.5)		26.2 %	-24.90 [-41.13, -8.67]
WV15670	240	129 (114.6)	235	144.5 (118)		15.8 %	-15.50 [-36.42, 5.42]
WV15671	204	102.4 (89.9)	200	125.3 (98.9)		20.3 %	-22.90 [-41.34, -4.46]
WV15758	344	130.2 (109.4)	351	159.6 (127.3)		22.2 %	-29.40 [-47.04, -11.76]
WV15819/WV15876/WV15978	358	185 (145.6)	375	192.4 (145.2)		15.6 %	-7.40 [-28.46, 13.66]
Total (95% CI)	**2079**		**1634**			**100.0 %**	**-21.29 [-29.59, -12.98]**

Heterogeneity: Tau?? = 0.0; Chi?? = 3.00, df = 4 (P = 0.56); I?? =0.0%

Test for overall effect: Z = 5.02 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Oseltamivir versus placebo, Outcome 2 Hospital admission (safety population).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 1 Oseltamivir versus placebo

Outcome: 2 Hospital admission (safety population)

Study or subgroup	Oseltamivir n/N	Placebo n/N	Odds Ratio IV,Random,95% CI	Odds Ratio IV,Random,95% CI
M76001	7/965	4/482		0.87 [0.25, 3.00]
WV15670	1/484	1/235		0.48 [0.03, 7.78]
WV15671	5/411	1/204		2.50 [0.29, 21.54]
WV15707	2/17	1/9		1.07 [0.08, 13.65]
WV15730	0/31	0/27		0.0 [0.0, 0.0]
WV15758	4/344	3/351		1.36 [0.30, 6.14]
WV15812/WV15872	6/199	8/202		0.75 [0.26, 2.21]
WV15819/WV15876/WV15978	9/362	10/373		0.93 [0.37, 2.30]
Total (95% CI)	**2813**	**1883**		**0.95 [0.57, 1.61]**

Total events: 34 (Oseltamivir), 28 (Placebo)

Heterogeneity: Tau?? = 0.0; Chi?? = 1.43, df = 6 (P = 0.96); I?? =0.0%

Test for overall effect: Z = 0.18 (P = 0.86)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Oseltamivir versus placebo, Outcome 3 Defined as influenza-infected at baseline.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 1 Oseltamivir versus placebo

Outcome: 3 Defined as influenza-infected at baseline

Study or subgroup	Oseltamivir n/N	Placebo n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
M76001	702/965	361/482		25.9 %	0.89 [0.70, 1.15]
WV15670	314/484	161/235		14.6 %	0.85 [0.61, 1.18]
WV15671	245/411	129/204		13.5 %	0.86 [0.61, 1.21]
WV15707	6/17	6/9		0.6 %	0.27 [0.05, 1.50]
WV15730	19/31	19/27		1.3 %	0.67 [0.22, 2.00]
WV15758	217/344	235/351		16.6 %	0.84 [0.62, 1.15]
WV15812/WV15872	118/199	133/202		9.8 %	0.76 [0.50, 1.13]
WV15819/WV15876/WV15978	223/362	254/373		17.6 %	0.75 [0.55, 1.02]
Total (95% CI)	**2813**	**1883**		**100.0 %**	**0.83 [0.73, 0.94]**

Total events: 1844 (Oseltamivir), 1298 (Placebo)

Heterogeneity: Tau?? = 0.0; Chi?? = 2.80, df = 7 (P = 0.90); I?? =0.0%

Test for overall effect: Z = 2.96 (P = 0.0031)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Oseltamivir versus placebo, Outcome 4 Antibody rise four-fold or greater.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 1 Oseltamivir versus placebo

Outcome: 4 Antibody rise four-fold or greater

Study or subgroup	Oseltamivir n/N	Placebo n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
M76001	519/965	275/482		30.2 %	0.88 [0.70, 1.09]
WV15670	297/484	151/235		14.0 %	0.88 [0.64, 1.22]
WV15671	206/411	115/204		12.9 %	0.78 [0.55, 1.09]
WV15707	5/17	6/9		0.5 %	0.21 [0.04, 1.18]
WV15730	18/31	17/27		1.3 %	0.81 [0.28, 2.35]
WV15758	203/344	229/351		15.5 %	0.77 [0.56, 1.04]
WV15812/WV15872	109/199	130/202		9.1 %	0.67 [0.45, 1.00]
WV15819/WV15876/WV15978	212/362	247/373		16.4 %	0.72 [0.53, 0.97]
Total (95% CI)	**2813**	**1883**		**100.0 %**	**0.79 [0.70, 0.90]**

Total events: 1569 (Oseltamivir), 1170 (Placebo)

Heterogeneity: Tau?? = 0.0; Chi?? = 4.61, df = 7 (P = 0.71); I?? =0.0%

Test for overall effect: Z = 3.74 (P = 0.00018)

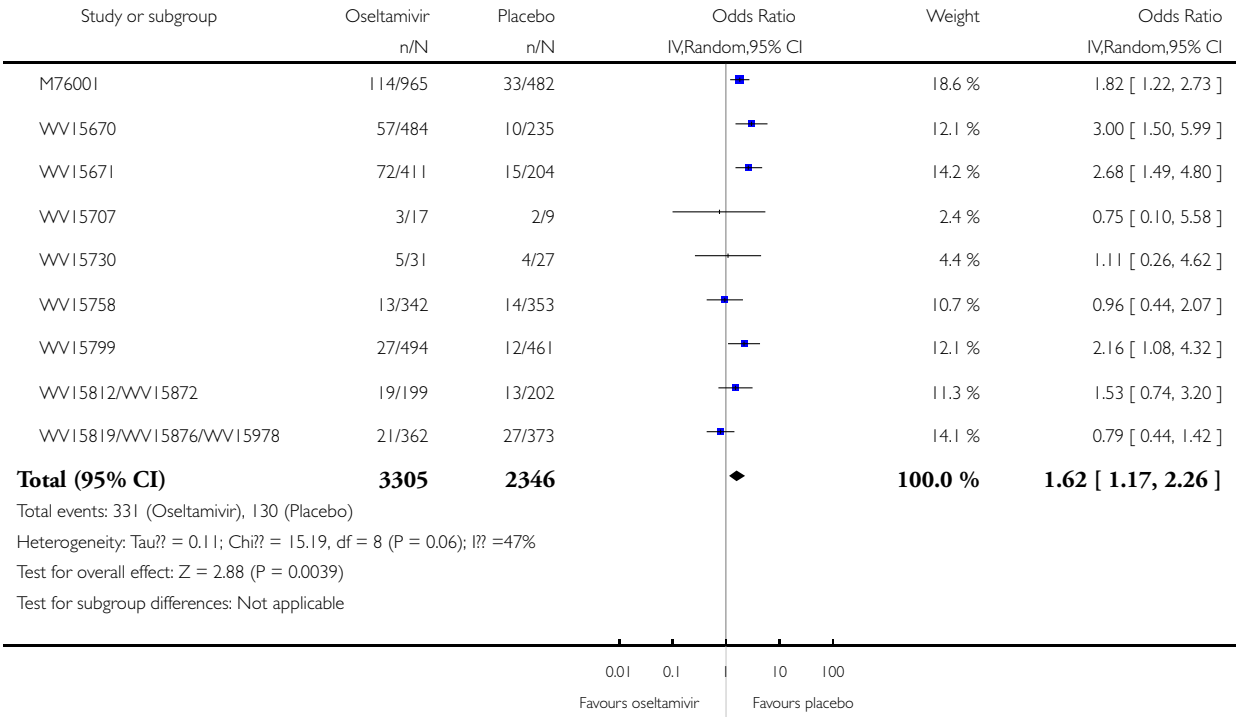
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Oseltamivir versus placebo, Outcome 5 Adverse events - Nausea.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 1 Oseltamivir versus placebo

Outcome: 5 Adverse events - Nausea



Analysis 1.6. Comparison 1 Oseltamivir versus placebo, Outcome 6 Adverse events - Vomiting.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 1 Oseltamivir versus placebo

Outcome: 6 Adverse events - Vomiting

Study or subgroup	Oseltamivir n/N	Placebo n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
M76001	100/965	17/482		20.3 %	3.16 [1.87, 5.35]
WV15670	46/484	7/235		12.6 %	3.42 [1.52, 7.70]
WV15671	56/411	7/204		12.8 %	4.44 [1.99, 9.93]
WV15707	2/17	0/9		1.2 %	3.06 [0.13, 70.94]
WV15730	6/31	1/27		2.5 %	6.24 [0.70, 55.59]
WV15758	49/342	30/353		21.9 %	1.80 [1.11, 2.91]
WV15799	4/494	6/461		6.5 %	0.62 [0.17, 2.21]
WV15812/WV15872	9/199	6/202		8.8 %	1.55 [0.54, 4.43]
WV15819/WV15876/WV15978	17/362	11/373		13.5 %	1.62 [0.75, 3.51]
Total (95% CI)	**3305**	**2346**		**100.0 %**	**2.32 [1.62, 3.31]**

Total events: 289 (Oseltamivir), 85 (Placebo)

Heterogeneity: Tau?? = 0.09; Chi?? = 12.13, df = 8 (P = 0.15); I?? =34%

Test for overall effect: Z = 4.60 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Oseltamivir versus placebo, Outcome 7 Adverse events - Diarrhoea.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 1 Oseltamivir versus placebo

Outcome: 7 Adverse events - Diarrhoea

Study or subgroup	Oseltamivir n/N	Placebo n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
M76001	80/965	37/482		22.9 %	1.09 [0.72, 1.63]
WV15670	24/484	10/235		11.2 %	1.17 [0.55, 2.50]
WV15671	30/411	24/204		16.4 %	0.59 [0.34, 1.04]
WV15707	1/17	0/9		0.8 %	1.73 [0.06, 46.77]
WV15730	2/31	4/27		2.6 %	0.40 [0.07, 2.36]
WV15758	30/342	37/353		18.5 %	0.82 [0.49, 1.36]
WV15799	7/494	11/461		7.8 %	0.59 [0.23, 1.53]
WV15812/WV15872	8/199	23/202		9.7 %	0.33 [0.14, 0.75]
WV15819/WV15876/WV15978	9/362	19/373		10.1 %	0.48 [0.21, 1.06]
Total (95% CI)	**3305**	**2346**		**100.0 %**	**0.72 [0.53, 0.97]**

Total events: 191 (Oseltamivir), 165 (Placebo)

Heterogeneity: Tau?? = 0.06; Chi?? = 11.44, df = 8 (P = 0.18); I?? =30%

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Oseltamivir versus placebo, Outcome 8 Withdrawal from trial due to adverse events.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 1 Oseltamivir versus placebo

Outcome: 8 Withdrawal from trial due to adverse events

Study or subgroup	Oseltamivir n/N	Placebo n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
M76001	25/965	9/482		33.8 %	1.40 [0.65, 3.02]
WV15670	9/484	6/235		19.8 %	0.72 [0.25, 2.06]
WV15671	8/411	1/204		5.4 %	4.03 [0.50, 32.44]
WV15707	1/17	0/9		2.2 %	1.73 [0.06, 46.77]
WV15730	0/31	1/27		2.3 %	0.28 [0.01, 7.17]
WV15758	6/342	4/353		13.8 %	1.56 [0.44, 5.57]
WV15799	5/494	0/461		2.8 %	10.37 [0.57, 188.08]
WV15812/WV15872	2/199	5/202		8.4 %	0.40 [0.08, 2.09]
WV15819/WV15876/WV15978	3/362	6/373		11.6 %	0.51 [0.13, 2.06]
Total (95% CI)	**3305**	**2346**		**100.0 %**	**1.08 [0.66, 1.76]**

Total events: 59 (Oseltamivir), 32 (Placebo)

Heterogeneity: Tau?? = 0.03; Chi?? = 8.42, df = 8 (P = 0.39); I?? =5%

Test for overall effect: Z = 0.31 (P = 0.75)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Zanamivir versus placebo, Outcome 1 Defined as influenza-infected at baseline.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 2 Zanamivir versus placebo

Outcome: 1 Defined as influenza-infected at baseline

Study or subgroup	Zanamivir n/N	Placebo n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
NAI30009	164/224	182/247		15.5 %	0.98 [0.65, 1.47]
NAIA2005	71/139	40/81		8.6 %	1.07 [0.62, 1.85]
NAIA3002	312/412	257/365		25.6 %	1.31 [0.95, 1.80]
NAIB2005	102/134	49/62		4.9 %	0.85 [0.41, 1.75]
NAIB2007	230/371	118/183		19.1 %	0.90 [0.62, 1.30]
NAIB3001	161/227	160/228		15.9 %	1.04 [0.69, 1.55]
NAIB3002	136/174	141/182		10.4 %	1.04 [0.63, 1.72]
Total (95% CI)	**1681**	**1348**		**100.0 %**	**1.05 [0.90, 1.24]**

Total events: 1176 (Zanamivir), 947 (Placebo)

Heterogeneity: Tau?? = 0.0; Chi?? = 3.03, df = 6 (P = 0.81); I?? =0.0%

Test for overall effect: Z = 0.64 (P = 0.52)

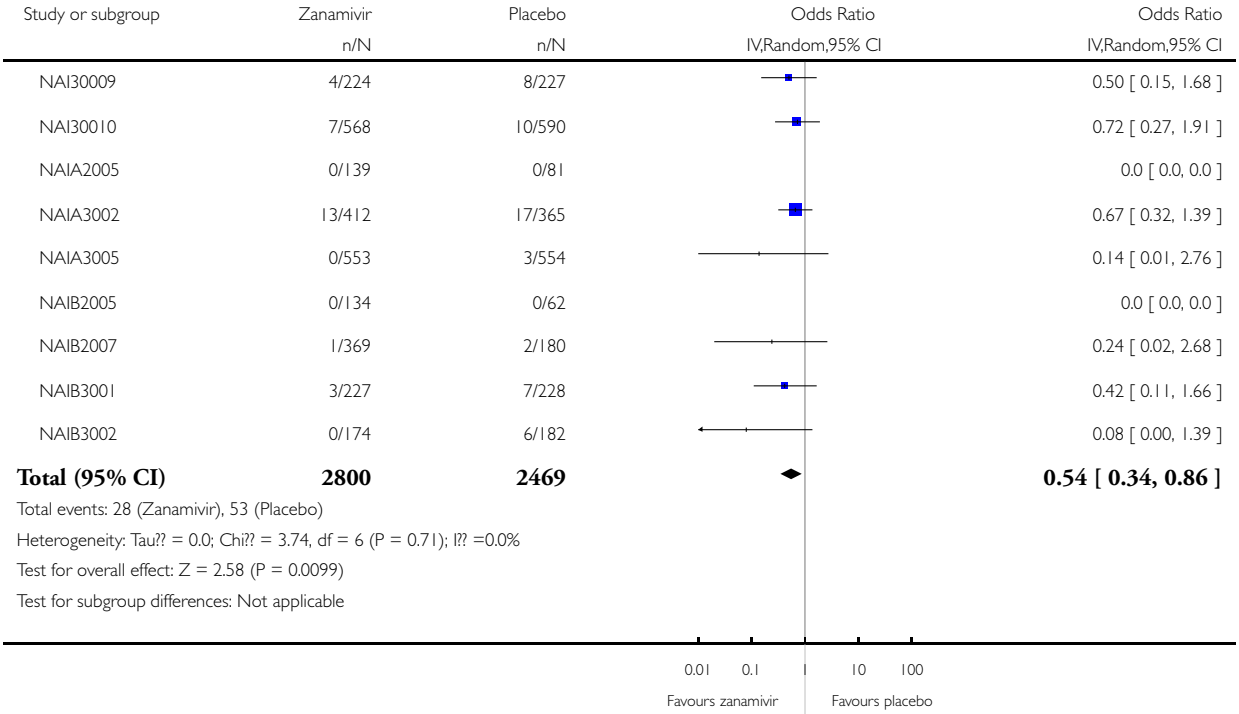
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Zanamivir versus placebo, Outcome 2 Adverse event - asthma.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Comparison: 2 Zanamivir versus placebo

Outcome: 2 Adverse event - asthma



ADDITIONAL TABLES

Table 1. Oseltamivir placebo contents by trial

Trial ID	Description oseltamivir/batch no	Description placebo/batch no	Certified content (oseltamivir)	Certified content (placebo)	Ref (PDF page number)
M76001	Size 2 capsules containing 75 mg oseltamivir/ V01-00 (GS 4104) , batch number G MZ 0082	Size 2 placebo capsules for oseltamivir/ V02-00 (GS 4104) , batch number G MZ 0083			20
ML16369					

Table 1. Oseltamivir placebo contents by trial (*Continued*)

ML20542					
MV21879					
NV25118					
WP16263	Grey opaque body, light yellow opaque cap/PT2247C01	Grey opaque body, Ivory opaque cap/G MZ 0163	Oseltamivir 97.5mg	Dehydrocholic acid	19 and 422
WV15670	Size 2 capsules containing 75 mg Ro 64-0796/ V01-00 (GS 4104) , batch number G MZ 0067	Size 2 placebo capsules for Ro 64-0796/V02-00 (GS 4104), batch number G MZ 0066			13
WV15671	Capsules (size 2) containing 75 mg Ro 64-0796 (GS 4104) /V01; batch number G MZ 0067/ G MZ 0065	Matching placebo capsules (size 2) for Ro 64-0796 (GS 4104)/ V02; batch number G MZ 0066			13
WV15673/ WV15697					
WV15707	Ro 64-0796 was provided as a size 2 capsule containing 75mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Ro 64-0796 (GS4104)/ V01-00 batch number GMZ 0082	Placebo was provided as a size 2 capsule containing dehydrocholic acid, dibasic calcium phosphate dihydrate and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Placebo Ro 64-0796/V02-00 batch number GMZ 0066			16
WV15708					

Table 1. Oseltamivir placebo contents by trial (*Continued*)

WV15730	Ro 64-0796 was provided as a caramel, opaque, size 2 capsule containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Ro 64-0796 (GS4104)/V01-00 batch number GMZ 0082	Placebo was provided as a caramel, opaque, size 2 capsule containing dehydrocholic acid, dibasic (calcium phosphate dihydrate and packaging material consisting of pregelatinized starch, povidone, talc and sodium stearyl fumarate. Placebo Ro 64-0796/V02-00 batch number GMZ 0083			17
WV15758	2 batches of the paediatric formulation were used in the present study: 1. Ro 64-0796/V20-01 (0.6% syrup); batch no. G HK 0180/05 2. Ro 64-0796/V20-01 (0.6% syrup); batch no. G HK 0180/06	2 batches of the corresponding placebo formulation were used: 1. Ro 64-0796/V19-01; batch no. G HK 0179/04 2. Ro 64-0796/V19-01; batch no. G HK 0179/05			27
WV15759/15871	Ro 64-0796 was to be provided as a dry powder for reconstitution with water. The powdered formulation contains the active ingredient, sorbitol and saccharin sodium (sweeteners), betacarotene (coloring agent), permageal 31 tutti frutti (flavor), cellulose, xanthan gum and				36

Table 1. Oseltamivir placebo contents by trial (*Continued*)

	methylhydroxy/ propylhydroxybenzoate.				
WV15799	Ro 64-0796 was provided as ivory, opaque, size 2 capsule containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Ro 64-0796 (GS4104)/ V14-00 batch numbers GMZ 0124/03 and GMZ 0129/03	Placebo was provided as a ivory, opaque, size 2 capsule containing dehydrocholic acid, dibasic calcium phosphate dihydrate and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Placebo Ro 64-0796/V16-00 batch number GMZ 0136			24
WV15812/15872	Ro 64-0976 was provided as size 2, capsules containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate	Matching placebo was provided as size 2, capsules, containing dehydrocholic acid, dibasic calcium phosphate dihydrate, pregelatinised starch, povidone, talc, sodium stearyl fumarate			18
WV15876/15819/ 15978	Capsules (size 2) containing 95.8 mg oseltamivir phosphate, equivalent to 75 mg oseltamivir: Formulation V14; batch numbers G MZ 0124/ 03, G MZ 0129/03 The following statement appears after the desription of the placebo; whether it ap-	Matching placebo capsules (size 2) for oseltamivir: formulation V16; batch numbers G MZ 0136, G MZ 0163 The following statement appears after the desription of the placebo; whether it applies to oseltamivir capsules is unclear: "Excipients for each capsule consisted of			21

Table 1. Oseltamivir placebo contents by trial (*Continued*)

	plies to oseltamivir capsules is unclear: "Excipients for each capsule consisted of dehydrocholic acid, dibasic calcium diphosphate dihydrate, pregelatinized starch, povidone, talc, sodium stearyl fumarate."	dehydrocholic acid, dibasic calcium diphosphate dihydrate, pregelatinized starch, povidone, talc, sodium stearyl fumarate."			
WV16193	For participants over the age of 12 years: Ro 64-0796/V35 (batch no. B1020) Capsules containing 75 mg of active drug and packaging material consisting of pregelatinized starch, povidone, talc, and sodium stearyl fumarate. For participants under the age of 12 years: Ro 64-0796/V37 (batch numbers: PT 9409C31A, PT 9409C32A, PT 9409C33A, PT 9409C31B, PT9409C32B and PT 9409C33B). A powder for reconstitution with water into a pediatric suspension containing 12 mg oseltamivir per mL of reconstituted solution and the following excipients: sorbitol, titanium dioxide, sodium ben-				26

Table 1. Oseltamivir placebo contents by trial (*Continued*)

	zoate, xanthan gum, monosodium citrate, saccharin sodium and Permaseal 11900-31 Tutti Frutti (flavor)				
WV16277					-
NV16871	Capsules containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. All participants over the age of 13 or who weigh > 40 kg will receive this dosage form. 2. A paediatric suspension containing 12 mg oseltamivir per ml of reconstituted solution and the following excipients: sorbitol, titanium dioxide, sodium benzoate, xanthan gum, monosodium citrate, saccharin sodium and Permaseal11900-31 Tutti Frutti (flavour). All participants of 12 years and under or who weigh ≤ 40 kg will receive this dosage form or 10 doses	Matching placebo was to be provided as capsules and as suspension			29

NB Most content dosage unavailable at review time lock.

Table 2. Distribution of cluster sizes in WV15799 (ITTIINAB population)

	Placebo	Oseltamivir	Overall
INFECTED INDEX CASE N clusters	**79**	**84**	**163**
N contacts	**200**	**205**	**405**
Cluster size: 2 contacts	**79 (39.5%)**	**101 (49.3%)**	**180 (44.4%)**
3 contacts	**84 (42.0%)**	**72 (35.1%)**	**156 (38.5%)**
4 contacts	**31 (15.5%)**	**32 (15.6%)**	**63 (15.6%)**
6 contacts	**6 (3.0%)**	**0 (0.0%)**	**6 (1.5%)**

Table 3. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries and published trials for the following outcomes: harms, complications and compliharms, by priority of testing. First priority null hypotheses to test.

Null hypothesis	Definition	Potential impact	Framework to test hypothesis
There is no under-reporting (overview hypothesis) (Hopewell 2009; McGauran 2010)	Under-reporting is an overall term including all types of bias when there is an association between results and what is presented to the target audience	Tailoring methods and results to the target audience may be misleading. The direction of the effect could change or the statistical significance of the effect could change or the magnitude of the effect could change from clinically worthwhile to not clinically worthwhile and vice versa	1. Is there evidence of under-reporting? 2. What types of under-reporting are apparent (list and describe them)? 3. What is the overall impact of the under-reporting on the results of a meta-analysis (compare estimates of effects using (under)reported data and all data)? 4. What is the impact of under-reporting on the conclusions of a meta-analysis, i.e. are conclusions changed when all data are reported?
There is no difference between analysis plan in the protocol and final report (or the differences are listed and annotated) (McGauran 2010)	When protocol violations, especially if not reported and justified, are not associated with study results	Post hoc analyses and changes of plan lead to manipulation of reporting and choice of what is and not reported	1. List any discrepancies between what is pre-specified in protocol and what was actually done 2. Can these discrepancies be explained by documented changes or amendments to the protocol? 3. Were these changes made

Table 3. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries and published trials for the following outcomes: harms, complications and compliharms, by priority of testing. First priority null hypotheses to test. (*Continued*)

			prior to observing the data? 4. What is the perceived impact of these changes on the results and conclusions?
There is no difference between published and unpublished conclusions of the same study (McGauran 2010)	A specific bias relating to the selective reporting of data in association with target audience	Results have been tailored to the intended recipient audience	1. Compare reporting of important outcomes (harms, complications) between published reports and other reports such as those to regulatory bodies, e.g. FDA 2. Document any differences in conclusions based on separate reports of the same studies
Presentation of same data set is not associated with differences in spelling, incomplete, discrepant, contradictory or duplicate entries (Doshi 2009; Golder 2010; Jefferson 2009a)	Different versions of the same data set are associated with discrepancies	Raises questions of whether these discrepancies are mistakes or deliberate?	1. Document any differences or similarities in separate reports of important outcomes (harms, complications) based on the same studies 2. Report any discrepancies to the manufacturer and ask them to clarify and correct any errors 3. What is the impact on the evidence base of including or excluding material with similar discrepancies?
There is no evidence of publication bias (Hopewell 2009; McGauran 2010)	Publication status is not associated with size and direction of results	Negative or positive publication bias can have major impact on the interpretation of the data at all levels	1. Are there studies that have not been published (yes/no)? 2. How many studies have not been published (number and proportion of trials not published and proportion of patients not published)? 3. Construct a list of all known studies indicating which are published and which are not 4. What is the impact on the evidence base of including or excluding unpublished material?
There is no evidence of outcome emphasis bias (McGauran 2010)	When over or under emphasis of outcomes is not associated with size or direction of results	Can lead to wrong conclusions because over emphasis on certain outcomes	1. Are all of the pre-specified outcomes in the study protocol reported? 2. Are the outcomes reported in the same way as specified in the study protocol?

Table 3. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries and published trials for the following outcomes: harms, complications and compliharms, by priority of testing. First priority null hypotheses to test. (*Continued*)

			3. Are there any documented changes to outcome reporting listed in the study protocol? 4. What is the impact on the evidence base of including or excluding emphasised outcomes?
There is no evidence of relative versus absolute measure bias (McGauran 2010)	When choice of effect estimates is not associated with size or direction of results	Can lead to wrong conclusions because of apparent under or overestimation of effects (e.g. in the use of relative instead of absolute measures of risk)	1. Are both relative and absolute measures of effect size used to report the results? 2. Is the incidence of each event reported for each treatment group? 3. What is the impact on the evidence base of including estimates of effect expressed either in relative and absolute measures?
There is no evidence of follow-up bias (McGauran 2010)	When there is no evidence that length of follow-up is related to size and direction of results	Can lead to wrong conclusions due to over or under emphasis of results	1. Are reported results based on the complete follow-up of each patient? 2. Are important events (harms, complications) unreported because they occurred in the off-treatment period? 3. What is the impact on the evidence base of including or excluding material with complete follow-up?
There is no evidence of data source bias (Chou 2005; McGauran 2010)	There is no difference between the evidence base presented to regulators (for approval for an indication) and that produced by or in possession of the drug's manufacturer (Chou 2005)	Can lead to approved indications inconsistent with full data set	1. Have regulators been presented with all data sets resulting from trials sponsored by the drug's manufacturer? 2. Have all national regulatory agencies been presented with the same trial data sets? 3. Can differences between national regulatory agencies be explained by access to different data sets?

FDA: Food and Drug Administration

Table 4. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries and published trials for the following outcomes: harms, complications and compliharms, by priority of testing. Second priority null hypotheses to test.

Null hypothesis	Definition	Potential impact	Framework to test hypothesis
There is no difference by funder (Jefferson 2009b; McGauran 2010)	When results and tone of conclusions are associated with type of funder	Funder influences results, conclusions and study visibility	1. Are there substantial numbers of comparable trials with different funding? 2. Is type of funder associated with quality, relationship between conclusions and data presented and prestige of the journal of publication? 3. Is the type of funder associated with publication status?
There is no evidence of authorship musical chairs bias (Cohen 2009; Doshi 2009; Jefferson 2009a; MacLean 2003)	When different authors for the same data set are presented to different target audiences	Raises an accountability question: who is responsible for the study?	1. Are the names of the people responsible for the unpublished report the same as those of the published reports? 2. Is the responsibility for conducting the trial clear?
There is no evidence of time lag bias (McGauran 2010)	When result reporting time frame is not associated with size or direction of results	Can lead to wrong conclusions	1. Are there significant differences in on-t and off-t treatment data? 2. Does the reporting or not reporting of on-t and off-t treatment data impact on the conclusions?
There is no evidence of location bias (Higgins 2011)	The publication of research findings in journals with different ease of access or levels of indexing in standard databases, depending on the nature and direction of results	Can lead to wrong conclusions in a specific setting or mislead generalisation to another context	1. Is there an association between publishing trials in journals with similar ease of access and data basing and size or direction of results? 2. How does this relate to unpublished material?
There is no evidence of disclosure pressure bias (McGauran 2010)	When external stimuli to publish or not are not associated with size or direction of results	Can lead to wrong conclusions because of blocks on what is reported or not	1. Why were some data and/or studies not published? 2. What impact do these motives have on interpretation of the evidence base?
There is no evidence of off-label bias (McGauran 2010)	When reporting is not associated with a higher or lower probability of unregistered indications use or recommendations thereof	Can lead to wrong conclusions because of reporting of data which leads to off-label use or is a product of off-label use	1. Is there any difference in the on-label indications and dosage between published and unpublished clinical study reports?

Table 4. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries and published trials for the following outcomes: harms, complications and compliharms, by priority of testing. Second priority null hypotheses to test. (*Continued*)

			2. If so, how does the inclusion or exclusion of off-label data impact conclusions from the evidence base of this drug?
There is no evidence of commercial confidentiality bias (McGauran 2010)	When commercial confidentiality rules do not impact on presentation of results	Can lead to wrong conclusions because IPR or commercial confidentiality prevent full disclosure of results	1. Is there evidence of commercial confidentiality being invoked for the decision to publish or otherwise. 2. If so, how do the inclusion or exclusion of commercial confidentiality restricted data impact conclusions from the evidence base of this drug?
There is no evidence of inclusion of previously unpublished data bias (Golder 2010; McGauran 2010)	When there is no evidence of inclusion of heterogeneous unpublished data of variable quality and sometimes difficult to interpret either because of swamping or absence of methods chapters	Can lead to wrong conclusions because of the inclusion of biased data not clearly identified as such	1. Is there any evidence of published review studies (particularly meta-analyses) containing previously unpublished data? 2. If so what is the impact of including or excluding unpublished data on the conclusions from the evidence base of this drug?
There is no evidence of blank cheque bias	When there is no evidence that third-party independent researchers agree to having a trial's sponsor fill in their data extraction sheets for unpublished data	Can lead to wrong conclusions because of the impossibility of independently assessing data. If the practice is not declared, it can mislead readers, giving conclusions a spurious impression of robustness	1. Are there unpublished data included in the third-party data set or meta-analysis that were gained without independent verification? 2. If so, how does the inclusion or exclusion of trusted data impact conclusions from the evidence base of this drug?
There is no evidence of competition bias (McGauran 2010)	When there is no evidence that any type of reporting bias is related to market competition, leading to a better positioning of the drug	Can lead to wrong conclusions because what you see may be due to market pressures	1. Do the types of bias detected (outcome emphasis, time lag, etc) favour NIs versus other drugs or interventions in particular ways? 2. Do they present a picture or tell a story which is different from all the evidence and position the NI favourably or the competitor unfavourably? 3. How does competition bias impact conclusions from the evidence base of this drug?

Table 4. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries and published trials for the following outcomes: harms, complications and compliharms, by priority of testing. Second priority null hypotheses to test. (*Continued*)

There is no evidence of language bias (Higgins 2011)	When there is no evidence that reporting is associated with language of target audience	Can lead to wrong conclusions because what you see may be due to the type of market being targeted	1. Is there evidence of presentation of unpublished (e.g. slide shows, product inserts) or published evidence in a particular language? 2. If so does the text in the source language differ from destination language? 3. If so, how does language bias impact conclusions from the evidence base of this drug?
There is no evidence of differences in methodological quality (McGauran 2010)	When there is no evidence of difference on methodological quality by source and outcome	Can lead to wrong conclusions because methodological quality affects estimates of effect, so if quality is not in fact equivalent, then differences ascribed to drug performance may be false	1. Is there difference in methodological quality between published and unpublished data? 2. How do differences in methodological quality impact conclusions from the evidence base of this drug?
There is no evidence of differences in sample size bias (McGauran 2010)	When there is no evidence of the presence of differences in sample in association with size and direction of results	Same potential impact as methodological quality, but with respect to sample size	1. Are there significant differences in sample sizes between published and unpublished material? 2. If so, do these impact on conclusions drawn from the evidence base?
There is no evidence of multicentre status bias (McGauran 2010)	When there is no evidence that there the presence of many or few centres is associated with size and direction of results	Can lead to wrong conclusions because what you see may be due to selection of centres and may not be generalisable	1. Are the methods used different from centre to centre? 2. If so, how do different methods impact conclusions from the evidence base of this drug?
There is no evidence of citation bias	When there is no evidence that citation of a selected study is associated with size and direction of results	Pressure is placed on authors of reports of study to provide an unbalanced interpretation or perspective by selecting citations or misreporting their content	1. Are the references in the published studies comprehensive? 2. Do they refer to unpublished material? 3. If so, how do the inclusion or exclusion of cited unpublished material impact conclusions from the evidence base of this drug?
There is no association between affiliation of authors and positive research conclusions (	When there is no evidence that differences in affiliation/ employer of authors may be	This form of bias is particularly dangerous when readers' understanding or policy are based	Are there differences in study conclusions associated with affiliation of authors?

Table 4. Reporting bias testing framework for comparing evidence from multiple regulators, manufacturer clinical study reports, trial registries and published trials for the following outcomes: harms, complications and compliharms, by priority of testing. Second priority null hypotheses to test. (*Continued*)

McGauran 2010)	associated with differences size and direction of results or conclusions drawn	solely on the abstracts or conclusions of studies	
There is no evidence of publication constraints (McGauran 2010)	When there is no evidence that obstacles to publication are associated with size and direction of results	What you see has been filtered on the basis of its results	1. If unpublished studies exist, why were they not published? 2. Were data presented to regulators not published? If so, why?
There is no evidence of study design bias	When there is no evidence that there may be differences in design to emphasise size and direction of selected results	Can be misleading as design affects results and generalisability and the choice of design is influenced by considerations other than study objective and ethics	1. Is there any relationship between study design and study conclusions? 2. If so, how does the relationship impact conclusions from the evidence base of this drug?

NI: neuraminidase inhibitor
on-t: on-time frame
off-t: off-time frame
IPR: intellectual property rights

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA)

Mentioned study	File name	Pages where study is mentioned (separated by commas)	Note
113502			
113625			
113678			
114045			
NAI108166			
105934			
NAI106784			
107485			
108127			
112311			
112312			

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

113268			
GCP/95/045			
NAI10901	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	15.15	
NAI10902			
NAI30008	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	15	7 documents with 14 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	13	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	19,19,20	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	1,1,3,4,4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/21036ltr.pdf	2	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_MEDR.pdf	33	
NAI30009	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	1.2	7 documents with 110 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P1.pdf	10,10,12,13,13,14,14,17,29,42,61,62,64,64,65,65,68	

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P2.pdf	33,34,36,43,43,43,43,52,52,52,53,53,56,57	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5,5,5,6,6,8,8	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_MEDR.pdf	3,3,3,3,3,3,3,4,4,5,8,9,9,10,10,11,11,11,14,14,15,16,17,19,19,19,20,20,22,23,23,23,24,24,24,25,25,25,25,25,25,26,26,26,27,27,28,28,28,29,29,31,31,31,31	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_MICROBR.pdf	3,3,4,4,4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_STATR.pdf	2,2,2,4,7,12,18,18,18,19	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P1.pdf	31.56	1 document with 2 instances
NAI30010	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	1.2	6 documents with 65 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P1.pdf	10,12,13,14,14, 15,17,62, 62,62,64	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P2.pdf	34,34,36,43,53	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_	5,5,6,6	

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	BIOPHARMR.pdf		
	Tam- iflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21- 036-S001_RELENZA_MEDR.pdf	3,3,3,3,3,4,5,18,19,21,21,22,23, 23,23,23,24,25,25,25,26,26,26, 26,27,27,27,28,28,29,29,29,30, 31,31,31,32	
	Tam- iflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21- 036-S001_RELENZA_STATR.pdf	2,2,13,13,13,19	
	Tamiflu and Relenza/Relenza/Re- lenza - NDA 021036/20000426_ 001/21-036-S001_RELENZA_ BIOPHARMR.pdf	6	1 document with 1 instance
NAI30012	Tamiflu and Relenza/Relenza/Re- lenza - NDA 021036/19990726_ 000/021036-medreview7.pdf	1	1 document with 1 instance
NAI30015			
NAI30020			
NAI30028			
NAI30034			
NAI40012			
NAIA1009	Tamiflu and Relenza/Relenza/Re- lenza - NDA 021036/20000426_ 001/21-036-S001_RELENZA_ ADMINCORRES_P1.pdf	56	4 documents with 17 instances
	Tamiflu and Relenza/Relenza/Re- lenza - NDA 021036/20000426_ 001/21-036-S001_RELENZA_ ADMINCORRES_P2.pdf	1,1,1,48,49,52	
	Tamiflu and Relenza/Relenza/Re- lenza - NDA 021036/20000426_ 001/21-036-S001_RELENZA_ BIOPHARMR.pdf	5,5,6	
	Tam- iflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-	3,3,6,7,20,31,31	

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	036-S001_RELENZA_MEDR.pdf		
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	18	5 documents with 5 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	9	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P2.pdf	52	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	11	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_STATR.pdf	2	
NAIA3002	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	13 documents with 122 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	6,6,7,7,14,15,22,22,23	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	1,4,4,12,12,12,12,17	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	4,14,14,14,14,14,15,15,15,15,16	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview2.pdf	1,2,3,4,4,5,6,6,6,8,8,9,9,9,12,12,15,16,16,16,17	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview3.pdf	5,5,6,6,6,7,7,7,8,8,9,9,9,10,11,12,13,13,14,15,15,17,18,18,19,20,21	

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	1,1,1,1,2,6	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	4,5,10,12	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	1,1,2,2,2,2,3,3,4,4,5,5,7,8,10,11,12,14,16,16,16,16,16,17	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	2,2,6,6,8,8,9,10	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	10	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-stats.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	15	1 document with 1 instance
NAIA3003	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	17,17,18	3 documents with 6 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	4.4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	22	
NAIA3004	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	14	4 documents with 8 instances

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	18,18,19	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	4,4,4	
NAIA3005	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	14	5 documents with 12 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	12,12,12,13,14,15,15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	14.15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P2.pdf	38	
NAIB1002			
NAIB3002	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	14 documents with 99 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	14,15,15,15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	11.12	

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	4,14,14,14,14,14,14,14,14	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview2.pdf	9,9,9,9,9,9,10,11,12,12,12,12,13,13,13,14,14,14,15,15,16,16,16,17	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview3.pdf	4,5,6,6,6,7,7,7,8,8,8,9,9,11,12,12,13,13,14,15,17,18,18,19,20,21	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	1,1,1,1,2	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	4,5,10,12	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	2,3,3,7,8,10,11,14,15,16,16,16	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	7,8,8,8,9,9	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	10.2	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-stats.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5.5	
NAI30011			

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

NAIB2007	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	7 documents with 18 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	14,15,15,16,16,17,17,17,18	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	3	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	8,10,10,15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	2	
NAIA2006			
NAIB2006			
NAIB1007			
C94-009	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	17	1 document with 1 instance
C94-085	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	17	2 documents with 2 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	22	
NAIB1001	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_	17	1 document with 1 instance

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	001/21-036-S001_RELENZA_BIOPHARMR.pdf		
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	6	1 document with 1 instance
NAIA2005	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	10 documents with 44 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	7,17,10	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	2.4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	4.5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	2,2,3,3,3,3,5,6,6,6,6,8,8,8,9,11,12,12,13,14,14,14,14,14,15,18	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	3.4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	2,5,9,15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	10	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-microbiology.pdf	21	

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

NAIB2005	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	9 documents with 43 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	17,20,20,22,23	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	5.5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	3,3,3,7,8,8,8,9,10,11,11,11,11,11,12,12,12,13,14,14,14,14,14,14,14,15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	3.4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	2,9,15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	2	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-microbiology.pdf	21	
NAIA/B2008	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	4	1 document with 1 instance
NAIA2010	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	16	1 document with 1 instance
NAIA/B2009			
167-02			

Table 5. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*Continued*)

167-03			
167-05			
167-04			
JNAI-03			
JNAI-02			
JNAI-01			
JNAI-07			
JNAI-04			
PE-01			
167-101			
167T3-11			

Zanamivir trials citation by trial ID and source FDA file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which regulatory file. Blank spaces indicate no citation for known trials.

All the studies have been searched in the folder "Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726˙000/021036". File name is left blank when the study was not present in that folder.

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA)

Referenced study	File name	Pages where study is mentioned (separated by commas)	Note
NP15717	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	46.46	6 documents with 13 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	14,15,15	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tam- iflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21- 246_Tamiflu_Admindocs_P2.pdf	2	
	Tamiflu and Relenza/Tamiflu/Tam- i- flu - NDA 021246/20001214_000/ 21-246_Tamiflu_BioPharmr.pdf	5,8,10,13,31	
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021246/20040624_ 010/021087_S016_TAM- IFLU CAPSULES - DRY POW- DER_BIOPHARMR.pdf	3	
NP15718	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021087/19991027_ 000/21087_Tamiflu_bior.pdf	17	1 document with 1 instance
NP15728	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021087/19991027_ 000/21087_Tamiflu_bior.pdf	16.35	3 documents with 6 instances
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021087/19991027_ 000/21087_Tamiflu_medr_P1.pdf	11	
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021087/19991027_ 000/21087_Tamiflu_medr_P2.pdf	45,46,47	
NP15757	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021087/20001117_ 002/21-087SE1-002_review.pdf	92,93,104,122,126,131,144,144, 145	1 document with 9 instances
NP15826	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021087/19991027_ 000/21087_Tamiflu_medr_P2.pdf	47	9 documents with 26 instances
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021087/20040624_ 016/021087_S016_TAM- IFLU CAPSULES - DRY POW- DER_ADMINCORRES.pdf	6	

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	2	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_BioPharmr.pdf	4,5,5,8,8,8,10,17,29,30,30,30,30,30,31,31	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	9.1	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	9.1	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
NP15827	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	10.12	2 documents with 7 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	16,16,17,17,17	
WP15525	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	21,25,26,27,27,27,27,42,42,44	3 document with 13 instances

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tam- iflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	2.2	
	Tamiflu and Relenza/Tamiflu/Tam-i- flu - NDA 021246/20001214_000/21-246_Tamiflu_BioPharmr.pdf	29	
WP15647	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	24,27,27	2 documents with 4 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	44	
WP15648	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	39	3 documents with 8 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	44.44	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	94,128,153,153,154	
WP15676	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	28.33	3 documents with 4 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	11	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	45	
WV15670	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	2,44,44	6 documents with 45 instances

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6,19,37,38,39,39,39,39,40,41,41,42,43,44,48,48,49,49	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	1,25,25,35,35,39,39,47	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	3,3,4,4,5,5,5,8,9,10,17,17,21,22,	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	189	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
WV15671	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	2,44,44	7 documents with 50 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6,16,19,24,24,25,25,26,27,27,28,32,34,35,36,37,38,39,39,39,40,41,46,49,49	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	1,25,25,35,38,47	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	3,4,4,5,5,5,5,9,10,10,15,17,21	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	189	

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
WV15673	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3	3 documents with 50 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	18,18,18,20,21,21,21,22,39	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	58,59,71,71,71,71,71,72,72,73,73,76,76,76,76,76,77,77,79,82,83,83,84,122,124,125,126,128,131,131,132,133,134,134,145,145,156,169,177,189	
WV15697	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	39	2 documents with 40 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	58,59,71,71,71,71,71,72,72,73,73,76,76,76,76,76,77,77,79,82,83,83,84,122,126,128,131,131,131,132,133,134,145,145,152,153,156,162,189	
WV15708	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3	3 documents with 39 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	23,35,39,41	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	71,71,71,71,71,72,72,72,72,75,75,75,75,77,77,78,79,79,82,82,122,125,125,126,131,134,134,135,135,149,151,152,152,153	

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

WV15708D	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3	2 documents with 3 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	23.35	
WV15730	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	44.44	5 documents with 15 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6,9,19,49,50,50	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	1,1,25,25,27	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	189	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
WV15731	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	17	4 documents with 9 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	5,30,37	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Microbr.pdf	5.6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	5,30,37	

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

WV15758	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P1.pdf	12,19,19,36	9 documents with 92 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	2,8,17,39,39,57,57	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_BioPharmr.pdf	3,4,5,5,5,8,10,17,27,30	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Corres.pdf	6.9	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	5,5,9,9,10,11,12,12,16,18,18,18, 19,19,31,31,31,33,33,35,36,37, 37,37,37,37,37,37,40,43	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Microbr.pdf	2,4,5,6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	5,5,9,9,10,11,12,12,16,18,18,18, 19,19,31,31,31,33,33,35,36,37, 37,37,37,37,37,37,40,43	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6,6,8	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	2.3	
WV15759	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P1.pdf	12.13	7 documents with 44 instances

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tam- iflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21- 246_Tamiflu_Admindocs_P2.pdf	39	
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021246/20001214_ 000/21-246_Tamiflu_Medr.pdf	5,10,30,30,30,30,31,32,32,33,34, 37,37,37,40,44	
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021246/20001214_ 000/21-246_Tamiflu_Microbr.pdf	2,4,4,5,6	
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021246/20001214_ 000/21-246_Tamiflu_Statr.pdf	5,10,30,30,30,30,31,32,32,33,34, 37,37,37,40,44	
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021087/20040624_ 016/021087_S016_TAM- IFLU CAPSULES - DRY POW- DER_ADMINCORRES.pdf	6,6,9	
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021246/20040624_ 010/021087_S016_TAM- IFLU CAPSULES - DRY POW- DER_BIOPHARMR.pdf	2	
WV15799	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021087/20001117_ 002/21-087SE1-002_review.pdf	28,28,28,28,28,29,29,30,30,30, 30,30,31,31,31,31,32,32,32,32, 32,33,33,34,34,35,35,35,36,37, 37,37,37,37,38,38,38,39,39,40, 40,40,40,40,58,60,71,71,71,71, 71,72,72,73,76,76,76,77,78,79, 84,85,122,125,125,126,126,128, 131,140,140,140,143,147,149, 156,162,169,175,187,203,208, 208	4 documents with 89 instances
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021246/20001214_ 000/21-246_Tamiflu_Medr.pdf	10.11	
	Tamiflu and Relenza/Tamiflu/Tam- iflu - NDA 021246/20001214_ 000/21-246_Tamiflu_Statr.pdf	10.11	

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6.7	
WV15812	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3,6,10,12	2 documents with 9 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	6,8,10,25,35	
WV15819	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6,10,12,15	2 documents with 8 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	2,6,6,39	
WV15825	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	41,41,41,41,42,42,42,42,42,42, 43,44,58,59,71,71,71,71,71,72, 72,72,72,73,73,75,75,77,77,78, 79,79,79,80,80,80,81,82,85,125, 125,126,126,128,131,134,134, 135,135,137,137,138,145,150, 151,152,152,155,156,162,169, 180,204,211	1 document with 64 instances
WV15871	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P1.pdf	12.13	7 documents with 42 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	39	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	5,11,30,31,31,32,32,32,33,34,37, 37,37,37,37,37,40	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Microbr.pdf	2,5,6	

Table 6. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*Continued*)

	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	5,11,30,31,31,32,32,32,33,34,37,37,37,37,37,37,40	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	2	
WV15872	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	11.33	2 documents with 4 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	11.33	

Oseltamivir trials citation by trial ID and source FDA file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which regulatory file. Blank spaces indicate no citation for known trials.

Search strategy:

WV15758 OR WV 15758 OR Trial 15758 OR Trial15758 OR Trials 15758 OR Trials15758 OR 15758 OR study 15758 OR study15758

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK)

Mentioned study	File name	Pages where study is mentioned (separated by commas)	Note
NAI106784			
107485			
108127			
112311			
112312			
113268			

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

GCP/95/045			
NAI10901			
NAI10902			
NAI30008	Relenza treatment submission executive summary.pdf	4	3 documents with 10 instances
	Relenza treatment submission full document.pdf	5,26,26,26,146	
	Relenza treatment submission main text.pdf	5,26,26,26	
NAI30009	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	7 documents with 461 instances
	NAI30009 study report pdf\CSR30009.pdf		
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf		
	NAI30009 study report pdf\suptables.pdf		
	NAI30009 study report pdf\tables.pdf		
	Relenza treatment submission full document.pdf	16,16,17,18,18,18,18,19,27,30, 31,	
	Relenza treatment submission main text.pdf	16,16,17,18,18,18,18,19,27,30, 31,76,128,130,132,134,144	
NAI30010	NAI30010 study report\Final NAI30010 for sign-off.pdf		7 documents with 399 instances
	NAI30010 study report pdf\NAI30010 HO final FSR.pdf		
	NAI30010 study report pdf\suptables.pdf		

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

	NAI30010 study report pdf\tables.pdf		
	Relenza prophylaxis submission.pdf	2,5,8,11,12,19,20,21,23,24	
	Relenza treatment submission full document.pdf	16,16,17,18,18,18,27,30,31,76,135,137,139,141,143,144	
	Relenza treatment submission main text.pdf	16,16,17,18,18,18,27,30,31	
NAI30012	Relenza treatment submission executive summary.pdf	4	3 documents with 8 instances
NAI30012	Relenza treatment submission full document.pdf	5,26,26,146	
NAI30012	Relenza treatment submission main text.pdf	5,26,26	
NAI30015	Relenza treatment submission full document.pdf	146	1 document with 1 instance
NAI30020			
NAI30028			
NAI30031			
NAI30034			
NAI40012			
NAIA1009	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	101	2 documents with 3 instances
	NAI30009 study report pdf\CSR30009.pdf	28.34	
NAIA3002	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	9 documents with 513 instances

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

	NAI30009 study report pdf\CSR30009.pdf	34.95	
	NAI30009 study report pdf\NAI30009 HO final FSR.pdf	22	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf		
	NAIA3002 study report pdf\NAIA3002 supporting tables 2.pdf		
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28,47,49	
	Relenza treatment submission full document.pdf	16,16,17,17,18,19,27,30,31,63,63,63,76,106,106,107,107,109,109,112,112,114,114,115,115,144	
	Relenza treatment submission main text.pdf	16,16,17,17,18,19,27,30,31	
NAIA3003	Relenza prophylaxis submission.pdf	10	1 document with 1 instance
NAIA3004	Relenza prophylaxis submission.pdf	10	1 document with 1 instance
NAIA3005	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	36,94,94,94,95,96,96,101	5 documents with 310 instances
	NAI30010 study report pdf\NAI30010 HO FSR.pdf	6.18	
	NAIA3005 study report pdf\A3005cr01.pdf		

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

	NAIA3005 study report pdf\TABS.pdf		
	Relenza prophylaxis submission. pdf	2,5,6,12,13,13,15,15,16,16,17, 17,18,18	
NAIB1002			
NAIB3001	NAI30009 study report pdf\CSR30009.pdf	34,50,95	11 documents with 374 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10.22	
	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	
	NAI30010 study report pdf \NAI30010 HO FSR.pdf	17.17	
	NAIA3002 study report pdf\NAIA3002 full study report. pdf	28	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3001 study report pdf\NAIB3001 full study report. pdf		
	NAIB3001 study report pdf\NAIB3001 supporting tables 1.pdf		
	NAIB3002 study report pdf\NAIB3002 full study report. pdf	28	
	Relenza treatment submission full document.pdf	16,16,17,18,18,18,18,27,30,31, 32,63,63,63,76,99,99,101,101, 103,103,105,105,144,162	
	Relenza treatment submission main text.pdf	16,16,17,18,18,18,18,27,30,31, 32	

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

NAIB3002	NAI30009 study report pdf\CSR30009.pdf	34.95	10 documents with 579 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	22	
	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	
	NAIA3002 study report pdf\NAIA3002 full study report. pdf	28,48,50	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report. pdf		
	NAIB3002 study report pdf\NAIB3002supporting tables 1.pdf		
	NAIB3002 study report pdf\NAIB3002supporting tables 2.pdf		
	Relenza treatment submission full document.pdf	16,16,17,17,18,19,27,30,31,63, 63,63,76,117,117,117,118,118, 120,120,122,122,124,124,125, 125,127,127,144	
	Relenza treatment submission main text.pdf	16,16,17,17,18,19,27,30,31	
NAI30011	Relenza treatment submission full document.pdf	146	1 document with 1 instance
NAIB2007	NAI30009 study report pdf\CSR30009.pdf	95	10 documents with 379 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10	

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28,28,29	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2007 study report pdf\b2007cr.pdf		
	NAIB2007 study report pdf\TABLES.pdf		
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25.26	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28,28,29	
	Relenza treatment submission full document.pdf	16,16,17,18,18,19,27,30,31,76,91,91,92,92,94,94,96,96,98,98,144	
	Relenza treatment submission main text.pdf	16,16,17,18,18,19,27,30,31	
NAIA2006	NAIA2005 study report pdf\a2005cr.pdf	38,73,74	4 documents wiht 6 instances
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
NAIB2006	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	3 documents with 3 instances
	NAIA3005 study report pdf\A3005cr01.pdf	25	

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
NAIB1007			
C94-009			
C94-085			
NAIB1001			
NAIB_1001			
NAIA2005	NAI30009 study report pdf\CSR30009.pdf	95	12 documents with 895 instances
	NAIA2005 study report pdf\a2005cr.pdf		
	NAIA2005 study report pdf\APPS_ALL.pdf		
	NAIA2005 study report pdf\TBS_ALL.pdf		
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28,28,48,48	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2005 study report pdf\b2005cr.pdf	7,7,22,25,26,34,34,42,71,72,72	
	NAIB2007 study report pdf\b2007cr.pdf	76	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28,28,47,47	

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

	Relenza treatment submission full document.pdf	16,16,16,16,17,18,27,30,76,77,77,77,79,79,80,80,82,82,84,84,85,144,144	
	Relenza treatment submission main text.pdf	16,16,16,16,17,18,27,30	
NAIB2005	NAI30009 study report pdf\CSR30009.pdf	95	12 documents with 838 instances
	NAIA2005 study report pdf\a2005cr.pdf	7,8,8,24,24,25,43,70,74,74	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28,28,48,48	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2005 study report pdf\APPSNEW.pdf		
	NAIB2005 study report pdf\b2005cr.pdf		
	NAIB2005 study report pdf\TBS_ALL.pdf		
	NAIB2007 study report pdf\b2007cr.pdf	76	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28,28,47,47	
	Relenza treatment submission full document.pdf	16,16,16,16,17,18,27,30,76,77,79,79,85,85,85,86,86,88,88,90,90,144,144	
	Relenza treatment submission main text.pdf	16,16,16,16,17,18,27,30	

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

NAIA/B2008	NAI30009 study report pdf\CSR30009.pdf	95	6 documents with 16 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10	
	NAIA3002 study report pdf\NAIA3002 full study report. pdf	28,28,29,29	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3001 study report pdf\NAIB3001 full study report. pdf	25,26,26,26,77	
	NAIB3002 study report pdf\NAIB3002 full study report. pdf	28,28,29,29	
NAIA2010	NAIA3005 study report pdf\A3005cr01.pdf	25	1 document with 1 instance
NAIA/B2009	NAIA3002 study report pdf\NAIA3002 full study report. pdf	28	3 documents with 3 instances
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report. pdf	28	
167-02			
167-03			
167-05			
167-04			
JNAI-03			
JNAI-02			
JNAI-01			

Table 7. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*Continued*)

JNAI-07			
JNAI-04			
PE-01			
167-101			
167T3-11			

Zanamivir trials citation by trial ID and source NICE file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which file. Blank spaces indicate no citation for known trials

Table 8. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK)

Referenced study	File name volume*	Pages where study is mentioned (separated by commas)	Note
133312			
GS97-802			
133312			
GS-97-801			
JP15734			
JP15735			
JV15823			
JV15824			
JV16284			
M76001	1	33,36,37,37,38,38,39,67,68,94,95,224	1 document with 12 instances
M76006			
ML20910			
ML22789			
ML22879			
MV21118			

Table 8. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*Continued*)

MV22841			
NCT00298233			
NCT00555893			
NCT00707941			
NCT00799760			
NCT00830323			
ML25018			
NCT00867139			
NCT00873886			
NCT01002729			
NP15717	6	32,75,76,77	2 documents with 5 instances
	8	68	
	6	73.98	1 document with 2 instances
NP15718			
NP15728			
NP15757	8	68	1 document with 1 instance
NP15826	6	32,75,75,75,76,76,77,78,79,80,98	1 document with 11 instances
NP15827	8	68	1 document with 1 instance
NP22770			
NP25138			
NP25139			
NV16871			
NV20234			
NV20235			
NV20236			

Table 8. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*Continued*)

NV20237			
NV22155			
NV25118			
NV25182			
PP16351			
WP15517	1	185.245	1 document with 2 instances
WP15525	1	185.245	1 document with 2 instances
WP15647			
WP15648			
WP15676			
WP15901			
WP22849			
WV144181			
WV15670	1	33,36,37,37,38,38,39,47,48,48,49,49,50,53,54,54,55,163,171188,207,209,224,245,245,252,253,253	7 documents with 1193 instances
	10	7,36,37,37	
	2		
	3		
	4	90	
	6	35.98	
	8	65	
	2	20,20,20,20,20	1 document with 5 instances
WV15671	1	33,36,37,37,38,38,39,47,48,49,49,50,53,54,54,55,163,171,188,207,209,224,245,245	7 documents with 1222 instances
	10	7,36,37,37	

Table 8. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*Continued*)

	2	82	
	4		
	5		
	6	35.98	
	8	66	
WV15673	8	66	1 document with 1 instance
WV15673D	8	66	1 document with 1 instance
WV15697	8		1 document with 1 instance
WV15697D	8		1 document with 1 instance
WV15707	1	33,36,37,37,38,67,68,224,245,245,245,246	1 document with 12 instances
WV15708			
WV15708D			
WV15730	1	33,36,37,37,38,38,39,47,53,54,55,186,207,224,245,245,246	4 documents with 22 instances
	10	7,36,37	
	2	82	
	4	90	
WV15731	6	98	1 document with 1 instance
WV15758	1	36,37,82,83,84,85,86,92,94,95,97,106,224,246	4 documents with 424 instances
	6		
	7		
	8	68	
WV15759	1	36,37,94,95,95,109,113,114,121,122,224,246	1 document with 12 instances
WV15799	1	137,139,139,232,233	3 documents with 499 instances

Table 8. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*Continued*)

	8		
	9		
WV15812	1	36,37,37,38,38,39,67,68,68,107,107, 107,108,108,121,121,122,123,224,246	2 documents with 197 instances
	10		
WV15819	1	33,36,37,37,38,58,58,59,59,60,61,62,62, 65,65,67,68,224,246	2 documents with 173 instances
	10		
WV15825	8	66.66	1 document with 2 instances
WV15871	1	109.246	1 document with 2 instances
WV15872	1	36,37,37,38,38,39,67,68,68,107,107, 108,108,121,121,122,123,224	1 document with 18 instances
WV15876	1	246.246	1 document with 2 instances
WV15978	1	67,70,175,246,246	1 document with 5 instances
WV16193			
ML16369			

Oseltamivir trials citation by trial ID and source NICE file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which file. Blank spaces indicate no citation for known trials.
All the studies have been searched in the folder "Roche submission".
When there is the number of the volume but no pages are mentioned, it means that the code of the study is cited more than 100 times.
*Number of the volume of the Tamiflu NICE Submission.

Table 9. Publication details for oseltamivir trials included in Stage 1

Type	Trial ID	CSR (Y/N)	Primary publication	Secondary publication	Conference abstract, poster or other publication
?	ML21776	N			
Safety	WP16263	Yes. M1-4			
PEP	MV22940	N			

Table 9. Publication details for oseltamivir trials included in Stage 1 (*Continued*)

PX	WV15673/ WV15697	Yes. M1-2	Hayden 1999a		
PX	NV20236	N	Manuscript in submission		Reisinger et al. 5th Annual Meeting of the World Society for Paediatric Infectious Diseases (WSPID), Bangkok, Thailand, 15-18 November 2007 -- with Reisinger et al
PX	WV15708	N			
PX	WV15799	Yes. M1	Welliver 2001		
PX	MV21737	N			
PX	JV15824	N	Kashiwagi 2000a		
PX	WV15825	Yes. M 1-2	Peters 2001		
TX	WV15671	Yes. M1	Treanor 2000	Kaiser 2003; Hernan 2011	
TX	WV15758	Yes. M1	Whitley 2001	Winther 2010	
TX	ML16369	Abridged M1	Li 2003		
TX	WV15812/ WV15872	Yes. M1		Kaiser 2003; Hernan 2011	
TX	WV15730	Yes. M1		Kaiser 2003; Hernan 2011	Robson et al. 9th International Congress on Infectious Diseases, 10-13 April 2000, Buenos Aires, Argentina; Abstract 80.019
?	WV15731	N			Garcia et al. European Respiratory Society 12th Annual Congress, Stockholm, 2002
TX	ML20910	N			

Table 9. Publication details for oseltamivir trials included in Stage 1 (*Continued*)

TX	JV16284	N		Schentag 2007	Gieschke et al. Options for the Control of Influenza VI, Toronto, Canada, September 2007 (Abstract P921)
TX	WV15707	Yes. M1		Kaiser 2003; Hernan 2011	
TX	M76001	Yes. M1		Kaiser 2003; Hernan 2011	Treanor et al. 38th Annual Meeting of the Infectious Disease Society of America, 7-10 September 2000, New Orleans, USA; Abstract 611
TX	MV21879	N			
TX	WV15670	Yes. M1	Nicholson 2000	Kaiser 2003; Hernan 2011	
TX	WV15759/ WV15871	Yes. M2	Johnston 2005		
TX	WV15819/ WV15876/ WV15978	Yes. M1		Kaiser 2003; Hernan 2011	
TX	NV16871	Yes. M1+			
TX	MV22841	N			Durigon et al. XII International Symposium on Respiratory Viral Infections (ISRVI), 11-14 March 2010, Taiwan, China
TX	MV21118	N	Heinonen et al. *Clinical Infectious Diseases* (submitted)		
TX	WV16277	N		Hernan 2011	
TX and PX	NCT00555893	N			
TX and PX	ML20589	N	Booy et al. Manuscript in preparation		

Table 9. Publication details for oseltamivir trials included in Stage 1 (*Continued*)

TX	JV15823	N	Kashiwagi 2000b		

? = trial type unknown; CSR = availability of clinical study report; TX = treatment trial; PX = prophylaxis trial; PEP = post-exposure (or secondary) prophylaxis trial; Safety = safety trial; M (in 'CSR' column) = 'Modules' of Roche's clinical study reports.

Table 10. Publication details for zanamivir trials included in Stage 1

Type	Trial ID	CSR (Y/N)	Primary publication	Secondary publication	Conference abstract, poster or other publication
?	167T3-11	N	None	None	None
?	NAI30011	N	None	None	None
?	NAIA2006	N	None	None	None
PEP	NAIB2006	N	None	None	None
PX	167-101	N	None	None	None
PX	NAI30010	Y	Hayden 2000		Hayden FG, Gubareva L, Klein T, Elliott MJ, Hammond J, Ossi M, et al. Inhaled zanamivir for preventing transmission of influenza in families. ICAAC 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, USA, 26 Sep 1999 to 29 Sep 1999
PX	NAI30031	N	Monto 2002		
PX	NAI30034	N	LaForce 2007		Campbell FM, Greos LS, Kudule L, Yoxall S, Man CY. Safety and efficacy of zanamivir in the prevention of influenza in community-dwelling high-risk subjects. Poster presentation at European Congress of Clinical Gerontology, 18-21 June 2002
PX	NAIA/B2009	N	Kaiser 2000		
PX	NAIA2010	N	Schilling 1998		
PX	NAIA3003	N	Gravenstein 2005		

Table 10. Publication details for zanamivir trials included in Stage 1 (*Continued*)

PX	NAIA3004	N	Ambrozaitis 2001; Ambrozaitis 2005		
PX	NAIA3005	Y	Monto 1999c		
PX	PE-01	N	None	None	None
TX	JNAI-01	N	Matsumoto 1999		
TX	JNAI-04	N	None	None	None
TX	JNAI-07	N	GSK says: "Japanese language publication"		
TX	NAI30008	N	Murphy 2000		Berger W, Stein WJ, Sharp SJ, Szymborski PG. Effect of inhaled zanamivir on pulmonary function and illness duration in asthma and/or chronic obstructive pulmonary disease (COPD) patients with influenza. *Annals of Allergy, Asthma and Immunology* 2001;86 (1):85
TX	NAI30009	Y	Hedrick 2000		Hayden FG Gubareva L Klein T Elliott MJ Hammond J Ossi M Sharp S Monto AS. Inhaled zanamivir for preventing transmission of influenza in families. ICAAC 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA, USA, 26 Sep 1999 to 29 Sep 1999
TX	NAI30012	N			Arvydas M Ambrozaitis, Sally Yoxall, Fiona M Campbell. Safety and efficacy of zanamivir for the treatment of influenza in elderly subjects. Poster presentation at European Congress of Clinical Gerontology, 18-21 June 2002
TX	NAI30015	N	Puhakka 2003		
TX	NAI30020	N	None	None	None
TX	NAI30028	N	None	None	None

Table 10. Publication details for zanamivir trials included in Stage 1 (*Continued*)

TX	NAIA/B2008	N	Monto 1999a		
TX	NAIA2005	Y	Hayden 1997		
TX	NAIA3002	Y	None	Monto 1999b	Lalezari J, Klein T, Stapleton J, Elliott M, Flack N, Keene O. The efficacy and safety of inhaled zanamivir in the treatment of influenza in otherwise healthy and 'high risk' individuals in North America. Int Soc 21 Int Congr Chemother 1999; p8
TX	NAIB2005	Y	Hayden 1997		
TX	NAIB2007	Y	None	Monto 1999b	
TX	NAIB3001	Y	MIST Study Group 1998		Silagy CA, Campion KJ, Keene O. The efficacy and safety of zanamivir in the treatment of influenza in otherwise healthy and 'high risk' individuals. Abstr 38, Intersci Conf Antimicrob Agents Chemother 1998; 331
TX	NAIB3002	Y	Makela 2000		

? = trial type unknown; CSR = availability of clinical study report; TX = treatment trial; PX = prophylaxis trial; PEP = post-exposure prophylaxis trial

Table 11. Studies by trial programme

Prophylaxis	Treatment	Secondary prophylaxis	Safety (cardiotoxicity)
NAIA3005; WV15673/ WV15697; WV15708; WV15825	M76001; ML16369; NAI30008; NAI30009; NAIA2005; NAIA3002; NAIB2005; NAIB2007; NAIB3001; NAIB3002; WV15670; WV15671; WV15707; WV15730; WV15758; WV15759/ WV15871; WV15812/ WV15872; WV15819/ WV15876/WV15978	NAI30010; WV15799	WP 16263

Table 12. Outcome data available for oseltamivir treatment trials

Outcome	Data available in clinical study report?	Which populations?	Comments
Symptom relief	Yes	ITTI - all clinical study reports have included these data ITT - most clinical study reports have included these data	This outcome is time to FIRST symptom relief
Complications	Yes	ITTI - most clinical study reports have included these data ITT - no clinical study reports have included these data	Events occurring in the first 2 or 3 days not classified as complication Complications only reported for patients classified into ITTI population
Hospitalisation	Yes	These data are included under serious adverse events	Small numbers of patients hospitalised
Harms	Yes	Safety - all clinical study reports have included these data	Neuro-psychiatric events and other events considered related to influenza infection not reported unless serious
Symptom relapse	No		No data provided in clinical study report Module 1
Drug resistance	No		No data provided in clinical study report Module 1
Viral excretion	Some	ITTI - most clinical study reports have included these data ITT - no clinical study reports have included these data	High proportion of missing data/ data only reported by some centres
Mortality	Yes	All	Only one reported death

Clinical Study Reports Module 1 available are M76001, WV15670, WV15671, WV15707, WV15812/WV15872, WV15730, WV15819/WV15876/WV15978, WV15758

ITTI: intention-to-treat (influenza)-infected (population)

Table 13. Time to first symptom alleviation in ITT population

Trial	Treatment group	Number of participants	Mean	Standard error	Standard deviation
M76001	Oseltamivir	933	140.6	4.1	125.2
WV15670	Oseltamivir	240	129	7.4	114.6

Table 13. Time to first symptom alleviation in ITT population (*Continued*)

WV15671	Oseltamivir	204	102.4	6.3	89.9
WV15758	Oseltamivir	344	130.2	5.9	109.4
WV15819	Oseltamivir	358	185	7.7	145.6
M76001	Placebo	473	165.5	7.2	156.5
WV15670	Placebo	235	144.5	7.7	118.0
WV15671	Placebo	200	125.3	7	98.9
WV15758	Placebo	351	159.6	6.8	127.3
WV15819	Placebo	375	192.4	7.5	145.2

Table 14. Hospitalisation events in the safety population

Trial	Treatment group	Number of subjects	Hospitalisation events
M76001	Oseltamivir	965	7
WV15670	Oseltamivir	484	1
WV15671	Oseltamivir	411	5
WV15707	Oseltamivir	17	2
WV15730	Oseltamivir	31	0
WV15758	Oseltamivir	344	4
WV15812	Oseltamivir	199	6
WV15819	Oseltamivir	362	9
M76001	Placebo	482	4
WV15670	Placebo	235	1
WV15671	Placebo	204	1
WV15707	Placebo	9	1
WV15730	Placebo	27	0
WV15758	Placebo	351	3
WV15812	Placebo	202	8

Table 14. Hospitalisation events in the safety population (*Continued*)

WV15819	Placebo	373	10

Table 15. Gastrointestinal adverse events in oseltamivir trials

Trial	Type of trial	Group	Participants N	Nausea N (%)	Vomiting N (%)	Diarrhoea N (%)	Withdrew N (%)
M76001	Treatment Age 13 to 80	Oseltamivir	965	114 (11.8)	100 (10.4)	80 (8.3)	25 (2.6)
M76001	Treatment Age 13 to 80	Placebo	482	33 (6.8)	17 (3.5)	37 (7.7)	9 (1.9)
WV15670	Treatment Adults	Oseltamivir	484	57 (11.8)	46 (9.5)	24 (5.0)	9 (1.9)
WV15670	Treatment Adults	Placebo	235	10 (4.3)	7 (3.0)	10 (4.3)	6 (2.6)
WV15671	Treatment Adults	Oseltamivir	411	72 (17.5)	56 (13.6)	30 (7.3)	8 (1.9)
WV15671	Treatment Adults	Placebo	204	15 (7.4)	7 (3.4)	24 (11.8)	1 (0.5)
WV15707	Treatment Elderly	Oseltamivir	17	3 (17.6)	2 (11.8)	1 (5.9)	1 (5.9)
WV15707	Treatment Elderly	Placebo	9	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)
WV15730	Treatment Adults	Oseltamivir	31	5 (16.1)	6 (19.4)	2 (6.5)	0 (0.0)
WV15730	Treatment Adults	Placebo	27	4 (14.8)	1 (3.7)	4 (14.8)	1 (3.7)
WV15812	Treatment Ill adults	Oseltamivir	199	19 (9.5)	9 (4.5)	8 (4.0)	2 (1.0)
WV15812	Treatment Ill adults	Placebo	202	13 (6.4)	6 (3.0)	23 (11.4)	5 (2.5)
WV15819	Treatment Elderly	Oseltamivir	362	21 (5.8)	17 (4.7)	9 (2.5)	3 (0.8)
WV15819	Treatment Elderly	Placebo	373	27 (7.2)	11 (2.9)	19 (5.1)	6 (1.6)

Table 15. Gastrointestinal adverse events in oseltamivir trials (*Continued*)

WV15758	Treatment Children	Oseltamivir	342	13 (3.8)	49 (14.3)	30 (8.8)	6 (1.8)
WV15758	Treatment Children	Placebo	353	14 (4.0)	30 (8.4)	37 (10.5)	4 (1.1)
WV15799	PEP*	Oseltamivir	494	27 (5.5)	4 (0.8)	7 (1.4)	5 (1.0)
WV15799	PEP*	Placebo	461	12 (2.6)	6 (1.3)	11 (2.4)	0 (0.0)

*PEP = post-exposure prophylaxis in households

Table 16. Asthma-related events in zanamivir trials

Trial	Type of trial	Group	Subjects N	Asthma events N (%)	Asthma exacerbation N (%)
NAIA3002	Treatment Age ≥ 12	Zanamivir	412	7 (1.7)	6 (1.5)
NAIA3002	Treatment Age ≥ 12	Placebo	365	9 (2.5)	8 (2.2)
NAIB3002	Treatment Age ≥ 12	Zanamivir	174	0 (0.0)	0 (0.0)
NAIB3002	Treatment Age ≥ 12	Placebo	182	3 (1.6)	3 (1.6)
NAIA2005	Treatment Age ≥ 13	Zanamivir	139	0 (0.0)	0 (0.0)
NAIA2005	Treatment Age ≥ 13	Placebo	81	0 (0.0)	0 (0.0)
NAIB2005	Treatment Adults	Zanamivir	134	0 (0.0)	0 (0.0)
NAIB2005	Treatment Adults	Placebo	62	0 (0.0)	0 (0.0)
NAIB2007	Treatment Age ≥ 13	Zanamivir	369	1 (0.3)	0 (0.0)

Table 16. Asthma-related events in zanamivir trials (*Continued*)

NAIB2007	Treatment Age ≥ 13	Placebo	180	2 (1.1)	0 (0.0)
NAIB3001	Treatment Adults	Zanamivir	227	3 (1.3)	0 (0.0)
NAIB3001	Treatment Adults	Placebo	228	7 (3.1)	0 (0.0)
NAIA3005	Community prevention	Zanamivir	553	0 (0.0)	0 (0.0)
NAIA3005	Community prevention	Placebo	554	2 (0.4)	1 (0.2)
NAI30010	PEP*	Zanamivir	568	2 (0.4)	5 (0.9)
NAI30010	PEP*	Placebo	590	4 (0.7)	6 (1.0)
NAI30009	Treatment Children	Zanamivir	224	2 (0.9)	2 (0.9)
NAI30009	Treatment Children	Placebo	227	5 (2.2)	3 (1.3)

*PEP = post-exposure prophylaxis in families

Table 17. ITT and ITTI populations in oseltamivir trials

Trial	Group	Number participants (ITT)	Number infected (ITTI)	Percentage with influenza infection	Number with 4-fold rise in antibody titre	Proportion with 4-fold rise in antibody titre
M76001	TF	965	702	72.7%	519	53.8%
M76001	PL	482	361	74.9%	275	57.1%
WV15670	TF	484	314	64.9%	297	61.4%
WV15670	PL	235	161	68.5%	151	64.3%
WV15671	TF	411	245	59.6%	206	50.1%
WV15671	PL	204	129	63.2%	115	56.4%
WV15707	TF	17	6	35.3%	5	29.4%

Table 17. ITT and ITTI populations in oseltamivir trials (*Continued*)

WV15707	PL	9	6	66.7%	6	66.7%
WV15730	TF	31	19	61.3%	18	58.1%
WV15730	PL	27	19	70.4%	17	63.0%
WV15758	TF	344	217	63.1%	203	59.0%
WV15758	PL	351	235	67.0%	229	65.2%
WV15812	TF	199	118	59.3%	109	54.8%
WV15812	PL	202	133	65.8%	130	64.4%
WV15819	TF	362	223	61.6%	212	58.6%
WV15819	PL	373	254	68.1%	247	66.2%

TF = Tamiflu; PL = placebo

Table 18. ITT and ITTI populations in zanamivir trials

Trial	Group	Number participants (ITT)	Number infected (ITTI)	Percentage with influenza infection
NAI30009	RL	224	164	73.2%
NAI30009	PL	247	182	73.7%
NAIA2005	RL	139	71	51.1%
NAIA2005	PL	81	40	49.4%
NAIA3002	RL	412	312	75.7%
NAIA3002	PL	365	257	70.4%
NAIB2005	RL	134	102	76.1%
NAIB2005	PL	62	49	79.0%
NAIB2007	RL	371	230	62.0%
NAIB2007	PL	183	118	64.5%
NAIB3001	RL	227	161	70.9%
NAIB3001	PL	228	160	70.2%

Table 18. ITT and ITTI populations in zanamivir trials (*Continued*)

NAIB3002	RL	174	136	78.2%
NAIB3002	PL	182	141	77.5%

RL = Relenza; PL = placebo

Table 19. Effect of odds of being classified as infected on primary outcome

Trial	Odds ratio	Reduction symptom alleviation in hours (ITTI)	Reduction symptom alleviation in hours (ITT)
WV15730	0.67	66	*
WV15819	0.75	25	10
WV15758	0.84	36	21
WV15670	0.85	32	22
WV15671	0.86	33	22
M76001	0.89	24	17
JV15823	0.94	23	*
ML16369	1.13	3	4

*Data not reported

Table 20. Proportions of contacts with positive serology data (WV15799 ITTIINAB population)

Positive serology	Group		Total
	Placebo N %	Tamiflu N %	
No	166 83.0	192 93.7	358
Yes	34 17.0	13 6.3	47
Total	200	205	405

Chi^2 P = 0.001

Table 21. Distribution of HIAAH1 antibodies in trial WV15799

Antibody rise	Group		Total
	Placebo N %	Tamiflu N %	
No change	191 95.50	200 97.56	391
2-fold	7 3.50	5 2.44	12
4-fold	2 1.00	0 0.00	2
Total	200	205	405

Wilcoxon two-sample test P = 0.25

Table 22. Distribution of HIAAH3 antibodies in trial WV15799

Antibody rise	Group		Total
	Placebo N %	Tamiflu N %	
No change	157 78.50	179 87.32	336
2-fold	21 10.50	20 9.76	41
4-fold	4 2.00	3 1.46	7
8-fold	8 4.00	1 0.49	9
16-fold	5 2.50	1 0.49	6
32-fold	3 1.50	0 0.00	3
64-fold	1 0.50	1 0.49	2

Table 22. Distribution of HIAAH3 antibodies in trial WV15799 (*Continued*)

128-fold	1 0.50	0 0.00	1
Total	200	205	405

Wilcoxon two-sample test P = 0.01

Table 23. Distribution of HIB antibodies in trial WV15799

Antibody rise	**Group**		**Total**
	Placebo **N** **%**	**Tamiflu** **N** **%**	
No change	183 91.50	189 92.20	372
2-fold	7 3.50	8 3.90	15
4-fold	1 0.50	1 0.49	2
8-fold	4 2.00	2 0.98	6
16-fold	0 0.00	4 1.95	4
32-fold	3 1.50	1 0.49	4
64-fold	1 0.50	0 0.00	1
128-fold	1 0.50	0 0.00	1
Total	200	205	405

Wilcoxon two-sample test P = 0.77

Table 24. Descriptive data on centre recruitment in the oseltamivir treatment trials

Trial	# Centres	Proposed N	Actual N	Average participants per centre
M76001	164	1425	1447	8.8
WV15670	63	750	719	11.4
WV15671	57	750	615	10.8
WV15707	13	400	26	2.0
WV15730	12	500	58	4.8
WV15758	80	680	695	8.7
WV15812-872	100	500	401	4.0
WV15819-876-978	169	500	735	4.3

APPENDICES

Appendix 1. Glossary of terms used in this review

Public health drugs. Drugs in which a considerable quantity of public money has been invested and/or are on the WHO essential drugs list.

Clinical study reports. Detailed reports of a clinical trial usually submitted to regulators following a prescribed ICH format. Roche's follow a modular structure (see Appendix 5). Reports can be several hundred pages long and contain details both of the planned design, conduct (protocol), analysis (reporting analysis plan or RAP) and results of the trial.

Compliharm. Term describing events defined as either complications or harms according to ambiguous criteria that appeared to include time of analysis (with times either unspecified or inconsistent among trials) and whether participants were infected (by influenza) or not. In oseltamivir treatment trials some potential harms or complications could both be caused by medication or influenza infection (e.g. vomiting), hence our classification as a compliharm.

Time lock. Date (12^{th} April 2011) after which no documentation would be reviewed in this iteration of the review. A cutoff was made necessary by the sheer scale of our data holdings. We were initially funded to review the full clinical study reports of the 10 treatment trials included in the Kaiser et el paper. We were able to access the 10 Modules 1 and regulatory comments (approximately 6000 pages in total). As the funder-stipulated deadline to producing our review progressively shortened and our understanding of the issues evolved we received notification that while the balance of the ten study reports were unlikely to be accessible by our deadline, we would receive substantial quantities of regulatory documents from the EMA in four tranches. When we held our second face to face meeting in April 2011 we had just received our first tranche of clinical study reports consisting of just over 10 thousand pages, bring our total holdings to 16 thousand pages. We decided that we did not have the resources to review any further documentation within our current funding and imposed a data time lock. Any documentation received after this date would be reviewed if and when we had more resources. At the time of writing we are being granted an extension to our funding and plan to review the balance of documents (a further 14000 pages) in the next 18 months. The process is similar to that adopted in our 2009 review.

TOC. Table of content of regulatory reviews and comments on industry submissions. Our TOC indicates which trial is cited in which document in which page how many times.

TOCE. Annotated version of the TOC. Comments and annotation are preliminary and form the basis for the weaving of the important aspects into the review narrative. See also Table 5; Table 6; Table 7; Table 8.
Trial ID. Means of identifying a trial. Usually made up of letters and numbers (WV 15799). At times the ID bears a letter suffix indicating the last version of the protocol followed in the trial (e.g. WV 15799H, i.e. trial carried out following amendment H).
Regulatory information. Term comprising clinical study reports (data) and regulatory comments and reviews.
Modules. Basic structure of Roche's trial reports see (Appendix 5). Today, the term "modules" refers to the components of a regulatory submission, as set by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (ICH 2011). Clinical study reports are just one "module" of a regulatory submission.
FOI. Freedom of Information. Enshrined by law in the US and EMA policy in Europe. FOI requests in this review have been a means of access to clinical study reports and regulatory comments (regulatory information).
CONSORT-based extraction. Extraction, synthesis and appraisal method used in this review for data from clinical study reports. Reconstructions were done by pairs of review authors and assessed in the authors' plenary session to decide whether included trials could proceed to stage 2 of the analysis. The structure of the reconstruction follows that of the CONSORT statement.
Protocol. Document reporting the trial's planned design and conduct, with amendments (when relevant). Confusingly also used in submissions and regulatory documents as synonymous with study.
IPD. Individual patient data. Anonymised individual data listings of characteristics and results which form the basis for the synthetic analyses in clinical study reports.
Trial programme. Series of trials designed and carried out to achieve registration or to answer specific questions. Usually programmes of the same drug or intervention focus on the same indication or the same study population.
Reporting Analysis Plan (RAP). Plan of analysis usually linked to trial protocol explaining what and how the authors intend to analyse.
Japanese Summary Basis for Approval (of a drug) (JSBA). Summary of the application dossiers included as one of the documents prepared and attached by the sponsoring pharmaceutical company. These are submitted to the regulatory body for approval of a new drug.

Appendix 2. Compliharms: events alternatively recorded as complications or harms

Roche Clinical Study Report of oseltamivir treatment trial: "The following symptoms, signs and common sequelae associated with influenza were excluded from specific adverse event reporting if they occurred during the period of drug treatment provided their appearance was in conjunction with one or more other influenza-related symptoms. The recrudescence of single discrete signs/symptoms associated with influenza syndrome were recorded as adverse events."
[Event by body system]
Respiratory
Cough
Pneumonia
Bronchitis/tracheitis
Sinusitis
Dyspnoea/difficulty breathing
Cardiovascular
Tachycardia
Eyes, ears, nose and throat
Sore throat
Nasal obstruction
Earache
Otitis
Coryza
Conjunctivitis
Central nervous system
Headache
Fatigue
Musculo-skeletal
Myalgia
Other

Fever
Rigor
Malaise/asthenia
Chills
Source: "Appendix 1. Events Associated with Influenza Syndrome". Roche Clinical Study Report No. W-144117, Protocol WV15707, Module I-43
A 1999 FDA medical review of oseltamivir: "As symptoms and common sequelae of influenza were collected as endpoint data, these symptoms, signs and common complications were specifically excluded from reporting as adverse events. The following table [above] lists events associated with influenza syndrome which were excluded from adverse event reporting. … In addition, following the alleviation of influenza-like symptoms, the recurrence of a single respiratory or constitutional symptom was recorded as an adverse event; however, the reappearance of more than one symptom was recorded as influenza-like syndrome (i.e. secondary illness). Comment: As the applicant [Hoffman-La Roche] stated in a written response dated 6/11/99, some sites incorrectly reported symptoms occurring prior to the cessation of the primary illness as secondary illness."
Emphasis in the original. Oseltamivir Medical Review. US FDA Center for Drug Evaluation and Research, Application No. 021087, 25 October 1999, page 15. www.accessdata.fda.gov/drugsatfda˙docs/nda/99/21087˙Tamiflu˙medr˙P1.pdf

Appendix 3. Searches of the electronic databases

Although this review focuses on the primary data sources of manufacturers, to check that there were no published randomised controlled trials (RCTs) from non-pharmaceutical sources we ran electronic searches in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (eight search results); MEDLINE (Ovid) from 1 May 2009 to 12 April 2011 (31 search results); EMBASE from 1 January 2010 to 12 April 2011 (54 search results); DARE (five search results) and NHSEED (five search results). CENTRAL, DARE and NHSEED are part of *The Cochrane Library,* www.thecochranelibrary.com (Issue 2, 2011, accessed 1 June 2011). All search results were loaded to an electronic library (*EndNote*).
We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy for EMBASE. We imposed no publication or language restrictions.

MEDLINE (Ovid)

1. Influenza, Human/
2. exp Influenzavirus A/
3. exp Influenzavirus B/
4. (influenza* or flu).tw.
5. or/1-4
6. Oseltamivir/
7. Zanamivir/
8. Peramivir/
9. Laninamivir/
10. neuraminidase inhibitor*.tw.
11. (oseltamivir or zanamivir or tamiflu or relenza or peramivir or laninamivir or gs4071).tw,nm.
12. or /6-11
13. 5 and 12

EMBASE.com

17 #13 AND #16 285 25 Jan 2011
16 #14 OR #15 833616 25 Jan 2011
15 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti AND [embase]/lim 794617 25 Jan 2011
14 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim 235493 25 Jan 2011

13 #4 AND #12 4283 24 Jan 2011
12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 5170 24 Jan 2011
11 oseltamivir:ab,ti OR zanamivir:ab,ti OR tamiflu:ab,ti OR relenza:ab,ti OR peramivir:ab,ti OR laninamivir:ab,ti OR gs4071:ab,ti AND [embase]/lim1806 24 Jan 2011
10 'sialidase inhibitor':ab,ti OR 'sialidase inhibitors':ab,ti AND [embase]/lim 87 24 Jan 2011
9 'neuraminidase inhibitor':ab,ti OR 'neuraminidase inhibitors':ab,ti AND [embase]/lim 829 24 Jan 2011
8 'sialidase inhibitor'/exp AND [embase]/lim 5028 24 Jan 2011
7 'peramivir'/de AND [embase]/lim 322 24 Jan 2011
6 'zanamivir'/de AND [embase]/lim 2544 24 Jan 2011
5 'oseltamivir'/de AND [embase]/lim 3945 24 Jan 2011
4 #1 OR #2 OR #3 65548 24 Jan 2011
3 influenza*:ab,ti OR flu:ab,ti AND [embase]/lim 56510 24 Jan 2011
2 'influenza virus a'/exp OR 'influenza virus b'/de AND [embase]/lim 14985 24 Jan 2011
1 'influenza'/exp AND [embase]/lim 26330 24 Jan 2011

Appendix 4. Modified CONSORT statement-based extraction template for clinical study reports

Title and drug name **Include source documents used:**		
Modified CONSORT extraction template http://www.consort-statement.org/		
Introduction CONSORT number		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Insert text:		
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Insert text:		
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Insert text:		

(*Continued*)

Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Insert text:		
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Insert text:		
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Insert text:		
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Insert text:		
Results		

(*Continued*)

Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Insert text:		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Insert text:		
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Insert text:		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Insert text:		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
Insert text:		
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available

(*Continued*)

Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
Insert text:		
First author Date of completion Conflicts of interest Second author check Date of check Conflicts of interest		

Appendix 5. Hypotheses 4 and 5 - Results

We rejected **Hypothesis 4** as there was no evidence of correlation between average recruited subjects per centre and the proportion of placebo patients subsequently diagnosed with influenza infection (Spearman correlation = 0.26; P = 0.53). Table 24 shows that the average recruited participants per centre ranged from 2 to 11 which appears very low for international multicentre trials. Two studies failed to reach their recruitment target (WV15707 and WV15730) and two clinical study reports were made up of multiple trials due to the original trial's poor recruitment (WV15819/WV15876/WV15978 and WV15812/WV15872) (Table 24). In addition the proportion of placebo patients subsequently diagnosed with influenza infection ranged from 63% to 75%, implying little between-trial variation.

We are currently unable to test **Hypothesis 5** as only one oseltamivir clinical study report (of three trials) reported randomisation first then swabbing second (WV15819/WV15876/WV15978). In this study the proportion of placebo patients that were confirmed as influenza-infected was 68.1%. This compares with the other seven clinical study reports where swabbing was carried out first and randomisation second and the proportion of placebo patients that were confirmed as influenza-infected ranged from 63.2% to 74.9% with mean 68.1%. Hence it seems that swabbing after randomisation made no difference in the treatment trial programme where this practice is reported. However with only one clinical treatment study report randomising prior to swabbing available to us, the power to detect a difference in the proportion of placebo patients subsequently diagnosed with influenza infection is low. We hope to be able to retest this hypothesis as more data become available.

Appendix 6. Example of contents of a Clinical Study Report (from page 1 of WV15670 report)

Final study report modules

This report consists of five modules. Those not supplied in this submission were obtainable from the sponsor on request.

MODULE I: CORE REPORT AND STUDY PUBLICATIONS

Introduction
Rationale
Objectives
Methodology
Efficacy results
Safety results
Discussion/conclusions
Appendices

MODULE II: PRESTUDY DOCUMENTS AND STUDY METHODOLOGY

Protocol and amendment history
Blank CRF
Subject information sheet
Glossary of original and preferred terms
Randomisation list
Reporting analysis plan (RAP)
Certificates of analysis
List of investigators
List of responsible ethics committees

MODULE III: INDIVIDUAL SUBJECT LISTINGS OF DEMOGRAPHIC AND EFFICACY DATA

Demographic data listings
Previous and concomitant diseases
Previous and concomitant medications
Efficacy listings

MODULE IV: INDIVIDUAL SUBJECT LISTINGS OF SAFETY DATA

Laboratory parameters
Vital signs data

MODULE V: STATISTICAL REPORT

F E E D B A C K

From Michael Power, Sowerby Centre for Health Informatics at Newcastle, 15 December 2010

Summary

From: Michael Power <michael.power@schin.co.uk>
Date: 15 December 2010 18:51
Subject: Neuraminidase inhibitors for influenza - HTA project
To: "cdelmar@bond.edu.au" <cdelmar@bond.edu.au>, "jefferson.tom@gmail.com" <jefferson.tom@gmail.com>, Carl Heneghan <carl.heneghan@dphpc.ox.ac.uk>

Hi
I picked up Carl's Twitter request for comments on your draft protocol "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data". So, here are my two comments on the content.

The title confused me: I expected it to be a review of unpublished trials to complement your review of published trials. It would be longer but clearer if you could call it "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports for published and unpublished trials".

The section "How the intervention might work" could be reorganized along the lines of:
0) Metabolism: oseltamivir phosphate (OP), Tamiflu, is the pro-drug of oseltamivir carboxylate (OC), the effective form. OP dissociates in the gastrointestinal tract to form oseltamivir (OT) which is absorbed and metabolised into OC by hepatic carboxylesterase (h-CE).

1) Reducing the ability of the virus to penetrate the mucus in the very early stage of infection (Bhatia 2007; Matrosovich 2004; Moscona 2005; Ohuchi 2006).
2) Inhibiting neuraminidase, which enables influenza viruses to exit host cells (Liu 1995; Moscona 2005).
3) Central depression by OT (Hama 2008) may cause hypothermia (Ono 2008).
4) Inhibition by NIs of human sialidase may cause abnormal behaviour (Li 2007).
You have obviously put a huge amount of work and expertise into developing the protocol, and have an even bigger task ahead to complete the review. Congratulations for taking this on.

Best wishes
Michael

Reply

Thanks for the constructive comments.

1. We have re-titled the Protocol to address this concern (and that of feedback from GSK, see below);
2. We have re-examined the "How the intervention might work" section, but made only small adjustments in the interest of keeping this section short;
3. We are not sure what problems you might have had printing the pdf file, and hope they are resolved with this new version.

Contributors

Chris Del Mar

From Juan C. Vergara, Intensive Care, Hospital Cruces, 48901 Barakaldo, Spain, 24 February 2011

Summary

From: JUAN CARLOS VERGARA SERRANO <JUANCARLOS.VERGARASERRANO@osakidetza.net>
Date: 24 February 2011 12:48
Subject: oseltamivir
To: jefferson.tom@gmail.com

I've read your Intervention Protocol: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data. And may be you can be interested in this letter I wrote to de BMJ: http://www.bmj.com/content/340/bmj.c789.extract/reply
1. Early use of oseltamivir does not reduce swine flu mortality, Juan C. Vergara, MD. Intensive Care Unit, Hospital Cruces. 48901 Barakaldo. Spain

As you say, in July the National Pandemic Flu Service started providing oseltamivir to anybody who telephoned with a plausible set of symptoms. From 23rd July to 1st December, the National Pandemic Flu Service (NPFS) in the UK, has provided more than one million courses of antiviral medication. By that time the Spanish Health Secretary General, José Martínez Olmos, at the Congress of Deputies, announced that only 6.000 patients (most of them hospitalised) had received oseltamivir in Spain. At the end of January there have been 411 deaths reported due to pandemic (H1N1) 2009 in the UK, and about 300 in Spain. That means 6.7 and 6.5 deaths per million, respectively. These data create serious doubts about the real utility of early use of oseltamivir in preventing deaths from Influenza A H1N1.
http://www.nhsdirect.nhs.uk/article.aspx?name=SbSwineflu
http://www.congreso.es/public˙oficiales/L9/CONG/DS/CO/CO˙411.PDF

Competing interests: None declared

Yours sincerely;

J. C. Vergara

Reply

Thank you for your interest.

Contributors

Chris Del Mar

From Dr Helen Steel, GSK, UK, 30 March 2011

Summary

GSK comments on Cochrane Collaboration protocol: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data

General:

- The term **'unpublished data'** is used extensively in the protocol. However, it does not appear to be clearly defined either in the protocol or in Jefferson's comment in the 15 Jan 2011 edition of the BMJ. Additionally, the term **'unpublished data'** is misleading. It appears the Cochrane Group use this term interchangeably with Clinical Study Reports, regardless of whether a primary manuscript is available for a given study. We suggest this is clarified or preferably replaced, especially since the term appears extensively in the protocol including the title. Readers are likely to use the terms 'unpublished data' and 'unpublished trials' (trials for which no primary publication appears in the scientific press) interchangeably. A suggested replacement is 'Clinical Study Reports' since this term is not easily misinterpreted and is clearly defined in Jefferson's BMJ comment.

- The 'scope of clinical trial data' are defined in Jefferson's BMJ 15 Jan 2011 comment, as mentioned above (i.e. definitions for clinical study reports, raw data, unpublished trial, published trial, regulatory data). It would seem important that these and any other definitions introduced in the protocol are included in the protocol.

Description of Intervention

- This section incorrectly describes Relenza as 'nebulized zanamivir'. Relenza is formulated in Rotadisks containing foil blisters with a powder mixture of zanamivir and lactose. Relenza is administered by oral inhalation using a breath-activated device called the Diskhaler. Earlier clinical studies explored several methods of administration, including nebulized and intranasal routes, but marketing approval in nearly all countries is currently available only for oral inhalation via Rotadisk/Diskhaler.

Types of Studies

- To meet the objective of providing a comprehensive review of neuraminidase inhibitors in preventing and treating influenza, it would seem appropriate that clinical trials from all sources (including sponsors other than industry) be included in this meta-analysis. Please clarify if this is your intent.

Outcome Measures

More details should be provided on the outcome measures section in the final protocol.

- For example, broad outcome measures are stated in the protocol, but specific endpoints are not provided. The primary and secondary endpoints of the meta-analysis should be clearly defined in the final protocol.

    - e.g.1. A stated primary outcome in the treatment studies is 'symptom relief'. Does this refer to 'the time to alleviation of symptoms' or 'reduction in symptom score' or another endpoint? Time to alleviation of clinically significant symptoms was the primary endpoint used in the majority of GSK treatment studies.

    - e.g.2. Another stated primary outcome is 'Harms'. Please provide the specific endpoints. Will this refer to 'incidence of most common AEs' or 'incidence of common SAEs', 'incidence of complications' or another endpoint? It is not clear if 'harms' are the same as 'compliharms'. It is not clear what specific events will comprise compliharms.

- Prophylaxis studies: Several types of prophylaxis studies were conducted by GSK: household prophylaxis (post-exposure prophylaxis), community prophylaxis and outbreak control in nursing homes, and as such the designs and/or endpoints are different.

It is possible to measure 'prevention of onset of influenza in contacts' in these studies, but not 'reduction in viral spread from index cases' in the majority of prophylaxis studies.

- Hospitalizations: As studies were generally conducted in the setting of acute uncomplicated influenza, limited hospitalisation data were collected, and are available only for some studies.

- Extracting compliharms: There is a statement that 'AEs are reported for all participants while complications are only reported for infected subjects'. This statement is not accurate for GSK trials. AEs are reported for all study participants. However, AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness. Without knowing the specific safety endpoints, it is unclear whether this will affect the outcome of some of the harms analyses.

Data collection and analysis:

- The protocol indicates that clinical study reports will be requested (minus participant identification). In fact many documents for each study will need to be redacted not just to remove participant identification, but any personally identifiable information including author and investigator identification.

- Missing Data. The protocol states "*At the participant level (i.e. within a trial) we will not make any assumptions about missing data.*" This is not possible, because an analysis of data that is collected in a trial can only be done in the context of assumptions about potential mechanisms that led to data being missing (e.g., missing completely at random, or missing at random).

- Meta-analysis Method. Little detail is given in the protocol. The protocol states that "*Whether or not heterogeneity is detected, we will perform a random effects meta-analysis. Random-effects methods will be used to compare the dichotomised outcomes (RR and absolute risk reduction (ARR) for efficacy and safety).*" There are several different Random Effects methods available (Bayesian or frequentist, DerSimonian & Laird or Maximum-likelihood or REML), and different approaches to handling rare events (various "corrections" to include trials with zero counts). Furthermore, would random-effects methods also used to compare the continuous outcomes?

- Fixed-effects Model. The protocol also states that fixed-effects models will be used in a sensitivity analysis. No details are given with regard to which fixed-effects models will be used. There are several fixed-effects models available including Inverse Variance, Mantel-Haenszel, and Peto's method. The appropriate method used should also depend on the outcome measures (dichotomous vs. continuous; relative vs. absolute). The approach and choice of models for sparse data and rare events should be provided. Furthermore, various methods in the framework of fixed-effects model may be explored to evaluate the robustness of the results.

- Hazard Ratio. The protocol states "*We will convert medians of treatment groups into (log) hazard ratios (estimating the variance of these) to enable meta-analysis of time to event outcomes.*" Although hazard ratio (HR) is a standard analysis and widely recommended approach for time-to-event data in clinical trials, the HR analysis may not be suitable for the Relenza studies with relatively short follow-up time because the assumption of proportional hazards required for the proportional hazards model may not hold. GSK did not follow this approach for the original analysis due to the concern stated above. Further the clinical and regulatory interest centred on differences in the time to alleviation not in the relative hazard between treatments. The above issues would be best addressed by using subject level rather than summary data, which GSK have offered to provide to the Cochrane Group.

- Analysis Populations. The protocol does not specify which populations will be used for the various analyses, for example, intent-to-treat or influenza-positive or other. We believe that influenza positive population is appropriate, especially for the efficacy analysis using time to alleviation of influenza symptom as a primary endpoint consistent with the prescribing information for Relenza.

- Study Duration. No details are given in the protocol with regard to how studies with different follow-up times will be handled.

- Trials with no Events. No details are given in the protocol with regard to how to deal with trials in which there are no events (such as death). By excluding studies with no events will make the event appear more common than it actually is. There are various techniques: Bayesian approach, continuity correction, combining similar trials to avoid having any components of the analysis that have no events.

- Sensitivity Analyses. Sensitivity analyses using different outcome measures, statistical models and/or continuity correction factors to assess the robustness of the results are strongly encouraged.

Reply

General:

- **'unpublished data'**. We agree that this term is confusing, and are attracted to the proposal of using 'clinical study reports' instead.
- We have attempted to ensure all terms are clear.

Description of Intervention

- Description of zanamivir (Relenza): we have corrected 'nebulized zanamivir' to 'powder inhalation'.

Types of Studies

- Yes, we intend to comprehensively review clinical trials from all sources (including sponsors other than industry). This intent is clear from the subsection " ***Electronic Searching*** " under the "**Search methods for identification of studies**" Section.

Outcome Measures

- Our specified outcomes are those of interest to patients, and their clinicians and policy-makers. They are therefore likely to be broader than the more specific endpoints selected by trialists. The purpose of Cochrane Reviews are usually to set clinically relevant review questions, and search the literature (or other sources) for answers to them. Sometimes answers to some questions are not available, and this is also documented. Where possible we report outcomes as pre-specified in the trial protocols, or as pre-specified in the review protocol, or otherwise reported as a post-hoc analysis.

  - e.g.1. 'symptom relief' may refer to 'the time to alleviation of symptoms' or 'reduction in symptom score', or any other endpoint (including 'area under the curve of symptom score and time').

  - e.g.2. 'Harms' include common adverse events (AEs) as well as serious AEs. We agree about the confusion of harms and complications, and have tried to capture the totality of these with the neologism 'compliharms' to avoid classification errors between their different labellings.

- Prophylaxis studies: We understand that it is possible to measure 'prevention of onset of influenza in contacts' in some GSK studies, but not 'reduction in viral spread from index cases' in others.

- Hospitalisations: We understand that hospitalisation data may only be available for some studies. However patient hospitalisation is usually classified as a serious adverse event therefore we expect to identify hospitalisations (not reported separately) in that way.

- Extracting compliharms: Your statement that 'AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness' underlies the complexity of analysing AEs and complications (our 'compliharms'). We have noted in the protocol that the limitation of complications only reported for the infected patients is relevant to the Roche trials only.

Data collection and analysis:

- We are interested that not only subject identification would be required to be removed from any documents of clinical study reports, but also information personally identifying authors and investigators. We wonder why.

- Missing Data. We have removed this statement.

- Meta-analysis Method. DerSimonian & Laird method will be used. Note that in the case of zero cells (e.g. no events in one group) the RevMan software (which we will use for the analysis) automatically adds 0.5 to each cell of the 2×2 table for any such study. There are no continuous outcomes specified in this review.

- Fixed-effects Model. Mantel-Haenszel method will be used except in the case of sparse data, in which case Peto's method will be used (as recommended in the Cochrane handbook).

- Hazard Ratio. We note the concerns with this outcome hence we will also consider analysis of this outcome as a continuous outcome noting that the data is likely to be skewed. We will use the inverse-variance random-effects method for this analysis.

- Analysis Populations. All analysis will be using the intent-to-treat population as this is the most methodologically rigorous and clinically relevant.

- Study Duration. We have specified in the protocol, where appropriate, that we will report outcomes for the on-treatment and off treatment time periods. If data is not available in the clinical study reports for any time period of the study then we will write to the relevant manufacturer to request the missing data.

- Trials with no Events. As stated above the RevMan software automatically adds 0.5 to each cell of the 2×2 table for any such study.

- Sensitivity Analyses. We note this point and agree. Where appropriate, a realistic sensitivity analyses will be conducted.

Contributors

Chris Del Mar

From Frederick G. Hayden, M.D., 2 February 2012

Summary

I am writing to comment on the recently updated meta-analysis by Jefferson and colleagues published through the Cochrane Collaboration and to request clarifications on several points, as well as to suggest some additional analyses that would be helpful in terms of taking greater advantage of this useful database. While I fully support access of Jefferson and other interested investigators to all of the published and unpublished data from the RCTs of oseltamivir and zanamivir for further analyses, this analysis only focuses on RCTs in ambulatory patients with uncomplicated influenza (the vast majority of whom were previously healthy) and on the period before the 2009 H1N1 pandemic. Consequently, I would urge these investigators to extend their efforts to other populations and datasets examining the risks and benefits of using neuraminidase inhibitors (NAIs) for treatment and prophylaxis. Furthermore, the authors should acknowledge the limitations of their analyses more explicitly and avoid inappropriate extrapolation to populations and influenza events that the RCTs did not adequately address. Differences in disease pathogenesis related to virus and host factors, as well as time to treatment, have important effects on the utility of antiviral agent interventions. My specific comments and recommendations for additional analyses follow:

1. Use of Intention to Treat (ITT) and ITTI-Infected Groups. The exclusive focus in the current treatment analysis on the ITT population is a readily rectified shortcoming. Outcomes in all three groups of relevance (ITT, ITT-infected, and ITT-noninfected) should be presented, so that readers can examine both clinical effectiveness and efficacy for the key endpoints, as well as events in those without documented influenza. Because NAI treatment would not be expected to provide any benefit in non-influenza illness, not presenting the ITT-infected outcomes in the analysis underestimates possible beneficial drug effects. Assessment of the non-infected group provides a valuable control and also enables a determination of whether there was a potential drug-disease adverse interaction of NAI treatment in non-influenza patients. Of note, our earlier pooled analysis of physician-diagnosed lower respiratory tract complications leading to antibiotic use found a significant benefit of oseltamivir in the influenza-infected patients but not in those enrolled in whom influenza infection was not detected by culture or serology [Kaiser 2003].

2. Sample size considerations. Severe outcomes of influenza infection are sufficiently uncommon in previously healthy people that even large RCTs or combining multiple RCTs would be very unlikely to detect them with confidence. The same point applies to very uncommon endpoints like microbiologically documented bacterial complications and rare adverse effects of treatment. Consequently, conclusions that there is no evidence (from trials) that NAIs reduce the risk of pneumonia, hospitalizations, deaths are overstated, as the evidence considered in this analysis is insufficient to properly address these questions.

The US CDC has estimated age-related influenza-related hospitalization and mortality rates for both seasonal epidemics and the 2009 pandemic [Shrestha 2011]. Jefferson and colleagues should use such event estimates and others to make calculations of the necessary sample sizes to detect reductions in these severe outcomes with NAI therapy in a controlled RCT across a range of clinically relevant effect sizes (e.g., 20%, 35%, 50% reductions). In a related fashion, they should also provide more quantitative estimates for their ability to detect such outcomes with their existing database and comment more precisely on their power to capture particular endpoints.

3. Complications in ambulatory patients. Other clinically relevant endpoints in these previously healthy and at-risk persons warrant investigation. With regard to influenza-related complications, the most frequent in previously healthy children and adults are respiratory tract infections (otitis media, bronchitis) leading to antimicrobic use. These are usually not severe and typically not microbiologically documented with respect to etiologies, but physician-diagnosed complications leading to antibiotic use is an outcome that has important clinical and public health implications (i.e., cost, antibiotic resistance, side effects) and also is sufficiently frequent to demonstrate effects of antivirals. We showed such a benefit in adults in our earlier pooled analyses of the then available RCT data on inhaled zanamivir [Kaiser 2000] and oral oseltamivir [Kaiser 2003]. The oseltamivir effect was confirmed in a recent meta-analysis [Hernan 2011], and another recent Cochrane report confirms an effect on otitis media in children [Wang 2011].

Given the large amount of data available to the investigators, it would be a valuable contribution to also explore the clinical outcomes in greater detail and to clarify the use of terms like severe outcomes. Although uncommon in the populations enrolled in these RCTs, endpoints such as radiographically documented pneumonia, microbiologically documented infections, and hospitalization or death are clear and should be listed separately in those with or without proven influenza infection. Because of the importance of hospitalizations as an endpoint, it would be helpful to examine not only all-cause hospitalizations but also relevant subgroups based on likely causation (e.g., events in which influenza was documented or likely implicated including exacerbations of co-morbidities vs others like accidents, elective surgeries, conditions unlikely to be influenza-related). In addition to these events, exacerbations of underlying conditions (e.g., asthma, COPD, diabetes, CHF) are of medical importance in influenza outpatients with co-morbidities and should be examined.

4. Data from observational studies. Typically the patients who are most at risk of severe outcomes (older people, infants and young children, those with underlying chronic conditions) are not included in RCTs. In this regard, the current analysis is limited to placebo- or active-controlled RCTs largely done in previously healthy persons and does not consider the multiple observational studies from different countries that have consistently showed protective effects against severe outcomes like pneumonia and hospitalization, particularly in those with co-morbidities, as well as reduced mortality if patients have been hospitalized. A considerable amount of new treatment data was generated in many countries during the 2009 H1N1 pandemic that found timely NAI treatment to be associated with a lower risk for intensive care admission and death (reference list available upon request).

While such data and analyses are weaker than RCT data and subject to bias, these observational studies address key endpoints in at-risk and seriously ill populations, including patients admitted to a hospital at the time of initiating therapy, that the available RCTs cannot and do not address. Furthermore, the standard of care has evolved such that placebo-controlled RCT in such patient groups would not be acceptable to investigators or ethics committees. The decision by Jefferson and colleagues not to consider and critically analyze the large amount of observational data with modern techniques means that they are not incorporating key information and many important patient groups in which the available data suggests medically important benefits from early NAI therapy. Such findings from observational data can inform antiviral treatment in more severely ill patients when no other data are available. As discussed above, not to include observational data means that conclusions of no effect on uncommon events or no severe adverse events being detected are almost inevitable. This should be made explicit in the design and the conclusion of the current report.

4. Influenza diagnosis and serologic results. The Jefferson report raises questions about the possible inhibitory effects of oseltamivir therapy on influenza-specific serologic rises and introduction of bias into the outcomes analysis. Further analyses might help to assess these possibilities. They should compare the primary endpoint of illness alleviation between the oseltamivir and placebo subgroups that were culture-positive (irrespective of serologic findings) at enrollment, and separately those that were culture-negative but had serologic evidence of infection.

Of note, one prior study of oseltamivir treatment in pandemic 2009 H1N1 patients, although not in seasonal influenza patients, suggested that early treatment could reduce antibody responses [Cowling 2010]. Jefferson and colleagues should examine the age-related frequencies of HAI seroconversions and the GMT titer rises in those with influenza-culture positive illness and separately in those with such HAI rises in absence of culture positivity. Of course, if still available, it would be interesting to test the culture-negative enrollment samples by RT-PCR.

The RCT data were generated over multiple seasons in which different influenza A and B viruses were circulating. Influenza B neuraminidases are generally less susceptible to oseltamivir carboxylate and several observational studies indicate that oseltamivir is less effective in influenza B- than influenza A-infected children [Sugaya 2007; Sato 2008]. It would be useful to examine the primary outcome in relation to virus type (A vs. B) and if possible A subtype (H3 vs. H1) in those with documented infections to expand on this point.

5. Other treatment endpoints of interest. Since those enrolled in the RCTs were outpatients, it would be useful to explore other endpoints that reflect patient recovery and impacts on the healthcare system (e.g., nonscheduled return visits for complications or adverse events). Perhaps more important than the time to alleviation endpoint used in the registrational trials might be the times to resumption of usual activities and return to pre-morbid status.

The authors raise the possibility that oseltamivir might have non-specific antipyretic effects, and one animal model study has also suggested possible adverse immunomodulatory effects of oseltamivir in RSV infection [Moore 2007]. Consequently, it would be interesting to examine the course of fever resolution (a much earlier event than cough resolution) and of symptoms in oseltamivir- and placebo-treated patients with and without documented influenza infections. In addition, it would be valuable to examine the correspondence (or lack thereof) between influenza virologic measures (e.g., enrollment virus titer, time to culture negativity, change in viral titers over time) and symptom resolution measures in both oseltamivir and placebo groups.

Various cost-effectiveness analyses on NAI therapy in low-risk populations have been published with widely divergent outcomes, largely depending on the input assumptions. Using this large database, a more refined analysis that incorporates both the direct and indirect (productivity losses) costs of influenza would be informative.

6. Adverse events with treatment. With regard to drug tolerability, it is important to examine not only the frequencies of reported adverse events but also assess indicators of their severity and interference with compliance (e.g., symptom days, patient reported severity, premature cessation of study drug).

Comparisons of AEs in the placebo groups across zanamivir and oseltamivir studies need to be interpreted with caution, since these studies were performed in different influenza seasons viruses and locations, with different protocols and case record forms, and by different investigators. Only one head-head RCT of treatment comparing these drugs has been published to date to my knowledge but the design did not include placebo only groups [Duval 2010]. In particular, comparisons in children (page 24) need to be age-adjusted as there were major differences in those enrolled into the zanamivir (5 years and older) and oseltamivir trials (1 year and older), and the frequencies of gastrointestinal manifestations are much higher in younger children with influenza and other acute illnesses.

7. Prophylaxis endpoints of interest. The analysis of prophylaxis outcomes and the associated discussion requires clarification. The statement on page 5 says: "The FDA has also not allowed an indication for interference of viral transmission within households (the key concept behind post-exposure prophylaxis)." The key concept behind post-exposure prophylaxis is prevention of illness in exposed persons, and the primary endpoint in most prophylaxis studies has been symptomatic, laboratory-confirmed influenza illness. FDA and other regulatory agencies have approved both NAIs for post-exposure prophylaxis in households and also for longer duration pre-exposure chemoprophylaxis [reviewed in Khazemi 2009].

The Jefferson analysis seems to focus exclusively on the effect of chemoprophylaxis in "preventing the spread" of influenza, with endpoints presumably determined by evidence of culture or serologically confirmed infection irrespective of illness. While this is one endpoint of interest in such studies, the primary outcome of medical interest is prevention of influenza illness in those exposed. There is abundant RCT data, as well as observational data from the 2009 pandemic, that both inhaled zanamivir and oral oseltamivir have both statistically significant and medically important effects on preventing influenza-specific illness. Of note, the development of serologic evidence of infection without illness is advantageous in those receiving chemoprophylaxis, as it likely is an immunizing event that protects against future infection and illness by that strain. In addition several oseltamivir RCTs have shown significant but lesser effects on influenza infection in prophylaxis recipients [Welliver 2001; Hayden 1999]. The authors should present all of the relevant endpoints in their analysis of the prophylaxis trials.

8. Adverse effects with prophylaxis. The prophylaxis studies are particularly useful in assessing drug tolerability as symptoms of acute illness present in treatment studies are not confounders and there is a more prolonged duration of drug exposure. However, it is essential to examine not only the frequencies of reported adverse events but also indicators of their severity and possible interference with compliance (e.g., symptom days, patient reported severity, premature cessation of study drug).

For example, the Jefferson posting states that "Similarly, a published prophylaxis trial (Hayden 1999a, known by its trial ID WV15673/WV15697) describes headache as having "occurred in similar proportions of subjects in the three groups (39 to 47 per cent)." but indicates that Japanese regulatory documents reached a different conclusion. My own review of the adverse event tabulations from our 6-weeks prophylaxis study (tables provided by the sponsor) indicates that the proportions of subjects reporting headache (not otherwise specified) that might have been related to study drug (unrelated reports excluded) during the treatment phase were similar across the placebo (N=116, 22.4%), oseltamivir 75 mg once (N=124, 23.8%), and oseltamivir 75 mg twice (N=132, 25.4%) daily dose groups [Hayden 1999]. Most of these reports indicated mild or moderate intensity and were self-limited. As indicated in the published paper [Hayden 1999], study withdrawals for AEs or illness occurred infrequently across these same groups (N=10, 1.9%; N= 8, 1.5%; N= 7, 1.3%). Of note, the specified causes for AE-related withdrawals included three reports of headache associated with other symptoms in the placebo group. In contrast, there were no reports of headache as reason for the withdrawals receiving oseltamivir; gastrointestinal complaints accounted for withdrawals in 4 of 8 oseltamivir 75 mg and 3 of 7 oseltamivir 75 mg twice daily recipients. The total numbers of patients with premature study withdrawal for any reason was 21 (4.0%), 17 (3.3%), and 16 (3.1%) across the three groups, respectively. Overall, severe AEs were reported in 82 (15.8%) of placebo, 75 (14.4%) of oseltamivir 75 mg, and 77 (14.8%) of oseltamivir 75 mg twice daily recipients. We were unable to include these details in the paper because of space limitations, but my interpretation remains that no excess of clinically relevant oseltamivir-related headache occurred during this study. This type of detailed AE analysis incorporating severity measures provides necessary context in interpreting the possible importance of AEs.

9. Peer review. The questions raised and opinions expressed in this and earlier Cochrane reports on NAIs by Jefferson and colleagues have resulted in debate and sometimes confusion among practitioners and policy makers regarding the appropriate use of NAIs in seasonal and pandemic influenza responses. Given the importance of these issues, it would be helpful for any future updates to have proper independent review before posting or publication by the Collaboration, as the Cochrane methodology of publication and then independent peer review is not well understood by many people.

Thank you for the opportunity to provide comments. I look forward to seeing the responses from Dr. Jefferson and his colleagues on these points.

Sincerely,

Frederick G. Hayden, M.D.
Stuart S. Richardson Professor of Clinical Virology
Professor of Medicine
University of Virginia School of Medicine
Charlottesville, Virginia, USA

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Submitter has modified conflict of interest statement: Disclosures to BMJ (Updated 4 June 2012)

Dr. Hayden received lecture and/or consulting honoraria from GSK until 2002 and from Roche until 2005. Gilead Sciences from 1996-1999 and Roche from 1999-2005 provided grant support to the University of Virginia for oseltamivir studies on which he was PI. Similarly GSK provided grant support to the University of Virginia for zanamivir studies from 1994-2001. Dr. Hayden served as medical officer in the Global Influenza Programme from 2006-2008 with funding provided to the University of Virginia through the National Institute of Allergy and Infectious Diseases (NIAID). Since 2008 to present the University of Virginia has received funding from the Wellcome Trust for his part-time work as influenza research coordinator at the Trust and through NIAID for his work as consultant the Southeast Asia Infectious Diseases Clinical Research Network. From 2008-11 the University also received honoraria for his participation in the Neuraminidase Inhibitor Susceptibility Network which received funding from Roche and GSK. Since 2008 to present, Dr. Hayden has been an unpaid consultant to multiple companies engaged in the development or marketing of influenza antivirals including Roche and GSK.

Dr. John Treanor reports receiving compensation as a member of the scientific advisory boards of Novartis and Immune Targeting Systems, and has performed consulting work for Pfizer. Within the last 3 years, his group has been funded to perform laboratory assays or conduct clinical trials for Sanofi, GlaxoSmithKline, Protein Sciences Corp, Wyeth, PaxVax, Ligocyte, and Vaxinnate.

Dr. Kaiser reports no financial disclosures.

Reply

Response to Dr. Hayden's comments of 2 February 2012.

We thank Dr. Hayden for his detailed feedback. However nothing he writes allays our basic concerns that:

(1) Despite the 16,000 pages we analyzed, we currently only have access to a very limited dataset hence cannot carry out many of the analyses Dr. Hayden suggests;

(2) Analyzing the "influenza infected" population in Roche oseltamivir trials, as Dr. Hayden proposes, will lead to misleading results because the treatment groups are not comparable for this population;

(3) The observational studies Dr. Hayden urges us to consider are generally of poor quality and only represent the small proportion of patients who are hospitalized with influenza;

(4) the Kaiser et al (2003) analysis is seriously flawed;

(5) Data have been selectively reported.

Below, we provide point-by-point responses to Dr. Hayden's concerns. (Please note that point 4 appears twice, to follow the numbering in Dr. Hayden's letter.)

1. Use of Intention to Treat (ITT) and ITTI-Infected [sic] Groups.

We agree, in principle, to conduct analysis using the ITT-Infected (ITTI) sub-population provided that it is appropriately selected by the results of testing completed before the start of the trial (for example by using only the results of viral culture or rapid testing before randomization).

However we argue that this is not possible in Roche oseltamivir trials. In these trials, the selection of "infected" or "non-infected" was dependent on the results of serology that is affected by "use" and "non-use" of oseltamivir. And the selection of those with "serology-positive results" appears to have given advantage to the oseltamivir group. Hence the method of selecting the ITT-Infected population in the trials has fundamental flaws and therefore the results are less reliable than those obtained using the ITT population.

2. Sample size considerations.

The Kaiser et al analysis has a number of fundamental problems. First, analyses were performed on the ITT-Infected sub-population which we have shown to be non-comparable between treatment groups. Second, the authors analyzed an outcome that was different to that pre-specified in the trials. In the trials, complications included otitis media and sinusitis but in the Kaiser et al paper these were not included. This is an example of selective reporting or "cherry picking". Third, complications were not objectively or consistently measured in the trials. Fourth, outcomes such as pneumonia and bronchitis could be either reported as a complication or as an adverse event according to a classification criteria we do not understand and is not discussed in the Kaiser et al paper. And finally the data from the 10 trials was not meta-analysed, rather, it was combined as if generated from one single trial.

We could potentially address most of these limitations (except for the third) but we have not been given access to the data despite repeated requests to the manufacturer. However we were able to compare hospitalisations as those data were available to us for the ITT population.

We found no evidence of effect on hospitalisations based on seven studies with a median placebo group event rate of 0.84% (range 0% to 11%): odds ratio (OR) 0.95; 95% CI 0.57 to 1.61, P = 0.86). This result is quite different to that reported by Kaiser et al based on the (non-comparable) ITT Infected population.

In terms of power analysis, to detect a significant difference at this level of difference of 0.84% (placebo) vs 0.80 % (oseltamivir), with alpha of 0.05 and power of 0.8, a RCT with approximately 800,000 participants is required.

3. Complications in ambulatory patients.

As we have illustrated above the Kaiser et al (2003) analysis has fundamental flaws that we cannot address because the manufacturer refuses to provide us with the data necessary to conduct a proper analysis.

Analysis of the "population with proven influenza infection" (ITT-Infected population) is not appropriate (see above). Data for the analysis of "population without proven influenza infection" are not available to us.

As we have shown above, the power to detect a difference in all-cause hospitalization is very small hence to do a subgroup analysis on this outcome seems unwarranted.

The pharmacological/toxicological adverse effects of oseltamivir can be classified into two major types [3]. One is sudden type occurring during the hypercytokinemic state in the early phase of infection including sudden death [3,4], accidental death after abnormal behaviours and vomiting induced by the central depressing action of unchanged oseltamivir [4]. The second are delayed type of reactions including recurrence or exacerbation of influenza and/or other infection, diabetes, bleeding, renal impairment and delayed type neuropsychiatric reactions related to inhibition of the host's neuraminidase [3]. Sudden type adverse effects should be collected and analysed only during the early phase of influenza (for example, vomiting was only significantly increased within one day of treatment in

the pediatric RCTs). However, delayed type adverse effects should be collected and analysed for a longer period to detect those reactions after a full course of treatment (for example the increase of pneumonia in the off-treatment period in the pediatric RCTs).
A recently published proportional mortality study has indicated that oseltamivir increases sudden type of death (odds ratio: 5.9) compared with zanamivir users by analysing all death cases among approximately 20 million 2009A/H1N1 influenza patients in Japan. This effect was also true for the comparison of oseltamivir users with non-users of antivirals [4].

4. Data from observational studies.

Observational studies during the 2009 H1N1 influenza outbreak have assessed the effects of oseltamivir on a selected population of hospitalized patients. These represent a very small proportion of the total population who get influenza. While subgroup analyses are important, it is important to not lose sight of the fact that the use and governmental stockpiling of oseltamivir is for its routine use in asymptomatic and symptomatic members of the community. Our review thus considers the evidence base that applies to the vast majority of people.
In addition, the studies Dr. Hayden appears to be referring to are retrospective observational studies in which apparent treatment effects may be the result of an effective treatment but could also be due to confounding effects. Unfortunately there is no way to determine which of these possibilities is true. That is why drug regulators require evidence from RCTs to determine whether or not a drug is approved for use. According to the analysis by Jones and Hama [5], apparent protective effects against severe outcomes like pneumonia, hospitalization and mortality are possibly derived from survivor treatment selection bias (or immortal time-bias). This is not an issue for randomised controlled trials because follow up begins at the time of randomisation which is the same for patients allocated to active drug and patients allocated to placebo. However in the case of observational studies treatment can begin at varying times (up to several days) after the onset of symptoms. Therefore a naive comparison that compares a binary outcome, such as death (or other adverse event), or time to an event (survival time) is at high risk of survivor treatment selection bias (also referred to as immortal time bias or simply time dependent bias). This bias can occur, for example, because patients who die early are not given the opportunity to receive treatment. In addition patients who are extremely sick may not be given the opportunity to receive antivirals because other treatments and procedures take priority. This bias can be addressed with an appropriate analysis however this has not been done in any of the observational studies of antiviral use for influenza that we have seen.

4. Influenza diagnosis and serologic results.

We do not have access to the data required to conduct all these analyses.

5. Other treatment endpoints of interest.

We do not have access to the data required to conduct these analyses (time to resumption of usual activities and return to pre-morbid status) using the ITT population.
By mentioning the evidence and possible mechanism of action for oseltamivir, we are arguing that fever alleviation and symptom reduction may not be caused by the reduction of viral load but may be the result of inhibition of host's immune functions including induction of cytokines and antibody production by inhibition of the host's neuraminidase in addition to central depression by oseltamivir.
Analysis of the population with documented influenza infection (ITT-Infected population) is not valid (see above). Hence we are unable to conduct a valid analysis in the influenza positive population and data for the influenza negative population has not been provided.
Antibody titre is one of the ways of selecting only subjects infected with influenza. However we have shown that the production of antibodies was consistently lower in the oseltamivir group compared to the placebo group in the treatment trials. Therefore the use of antibody production to confirm influenza in prophylaxis trials is not valid. Moreover comparison of the proportion with confirmed infection between the oseltamivir group(s) and the placebo group will provide misleading results.
Nor are "virus titre", "time to culture negativity" or "change in viral titres over time" a true measure of viral load, because oseltamivir as a neuraminidase inhibitor may conceal positivity by inhibiting the influenza virus from leaving the surface of host respiratory cells (which are covered by a mucous layer on the surface of the cells).

6. Adverse events with treatment.

In principle we agree. However, there are many data that show the classification of severity is questionable: for example, we believe that *psychosis* or *hallucinations* should be classified as "severe" but this has not always been followed. Therefore, we are planning to propose using new classification methods for the analysis of adverse events in the next update of our review.
We agree that comparisons of adverse events in the placebo groups across zanamivir and oseltamivir studies need to be interpreted with caution.
We agree that the spectrum and severity of adverse events/reactions are different among age groups. Therefore, we propose analysing adverse events/reactions stratified by age, if possible, according to the data in the Clinical Study Reports or individual patients' data in the next step of our systematic review.

7. Prophylaxis endpoints of interest.

As described on page 7 of our systematic review, the primary outcome measures for prophylaxis studies are:

1. Influenza (both symptomatic and asymptomatic and laboratory-confirmed) and influenza-like illness (ILI);
2. Hospitalisation and complications;
3. Interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts);
4. Harms.

We did not meta-analyse data from the prophylaxis trials in this systematic review because the substantial documents for prophylaxis trials were obtained after the time-lock of April 12th 2011.

Due to the problems we have illustrated above on using virus titer to confirm influenza infection we plan to amend the primary endpoint for prophylaxis trials to influenza-like illness (ILI).

There is some fear that those with serologic negative infection without symptoms may be more easily infected with influenza virus in the future, because evidence from animal experiments shows that IgA antibody in the respiratory mucosa is reduced (to about 20% of the control group), while reduction of those of systemic IgG antibody (HI antibody) was slight and not statistically significant [6].

8. Adverse effects with prophylaxis.

We agree that the prophylaxis studies are particularly useful in assessing drug tolerability.

As we discussed above ("7. Adverse events with treatment"), there are many data that show the classification of severity is questionable. For example, we believe that psychosis or hallucinations should be classified as "severe" but this has not always been followed. Therefore, we are planning to propose using new classification methods for the analysis of adverse events in the next step of the review.

We mentioned the statement "occurred in similar proportions of subjects in the three groups (39 to 47 per cent)" as an example of reporting bias present in the paper (Dr. Hayden's reference no. 3; known by its trial ID WV15673/WV15697).

The numbers for headache are 47% (242/520) in high dose oseltamivir group, 43% (335/520) in low dose oseltamivir group and 39% (202/519) in placebo group. These proportions are not similar and show a significant linear trend of increase with oseltamivir dose (p=0.013).

In addition, we would be grateful if Dr. Hayden were to supply the definition of "drug related headache among headaches reported as adverse events"? In particular, how was it decided whether a headache was drug-related or not? We cannot suggest signs or symptoms to distinguish oseltamivir-induced headache from placebo-induced headache.

We propose analysing adverse events in clinical study reports, including those for prophylaxis trials.

9. Peer review.

We agree that there is confusion among policy-makers and practitioners but believe this to be justified: the data published and accessible to them appear to have some flaws that need to be resolved. We are encouraged by Dr Hayden's support for our obtaining all the data necessary to clear the confusion.

Cochrane systematic reviews are stringently peer-reviewed. Not only are they peer-reviewed by independent experts prior to publication, but the protocols are also peer-reviewed before being undertaken, to reduce a priori biases. In addition, protocols are available for comment from outside the internal review process - Dr Hayden himself, or employees of Roche the manufacturer of oseltamivir, could have provided input about suggested alterations to the protocol which we would have been glad to receive. To this extent the peer-review process is more stringent than that employed by most other scientific journals.

RH, MJ, TJ, CDM, PD

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Contributors

Frederick G. Hayden

Feedback from Wolfgang Becker-Brueser, 30 January 2012

Summary

Dear Tom Jefferson,
I read your review about NI for prevention and treating influenza with interest. It's an important work. In the chapter "Why it is important to do this review" I found a small mistake concerning the worldwide stockpiling of oseltamivir which is mentioned to be "CHF 7.6 billion worth of oseltamivir (JACK 2009)". This would be an enormous amount "prior (!) to the emergence of influenza A/H1N1 in 2009". But Andrew JACK wrote in the cited Financial Times (May 13, 2009): "Governments around the world had stockpiled 220m treatments to date, swelling sales since the start of 2003 to SFr7.6bn, largely on the basis of preparation for a pandemic virus that has yet to appear." So 7.6 billion SFr represent sales and not stockpiling.

Contributors

Wolfgang Becker-Brueser (physician and pharmacist)

WHAT'S NEW

Last assessed as up-to-date: 12 April 2011.

Date	Event	Description
7 September 2012	Amended	Conflict of interest statement updated for a Feedback submitter

HISTORY

Protocol first published: Issue 1, 2011

Review first published: Issue 1, 2012

Date	Event	Description
9 February 2012	Feedback has been incorporated	Feedback comments added to review.
4 May 2011	Feedback has been incorporated	Feedback from three contributors has been added to the review

CONTRIBUTIONS OF AUTHORS

All review authors (except RH) were authors of the separate relevant Cochrane reviews. The protocol was written by TJ, PD and CDM. All authors contributed to the writing of this protocol and devised the approach strategies to the data sources. CH provided logistical support. For this review all authors reconstructed clinical trials using the CONSORT statement-based extraction template, TJ reviewed regulatory material, TJ, MJ, CH, RH and CDM applied inclusion criteria. CDM supervised the process and arbitrated when necessary. MJ carried out the statistical analyses. RH reviewed Japanese data together with MJ and PD. TJ reviewed the FDA files. CDM and MT screened the electronic searches. TJ prepared the final text and all authors contributed to the final draft. Toby Lasserson contributed editorial support.

DECLARATIONS OF INTEREST

All review authors have applied for and received competitive research grants. All review authors are co-recipients of a NIHR grant to carry out this review. In addition:

Tom Jefferson was an ad hoc consultant for F. Hoffman-La Roche Ltd in 1998-1999. He receives royalties from his books published by Blackwell and Il Pensiero Scientifico Editore, none of which are on NIs. He is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 products unrelated to NIs.

Chris Del Mar provided expert advice to GlaxoSmithKline about vaccination against acute otitis media in 2008-2009. He receives royalties from books published through Blackwell BMJ Books and Elsevier.

Chris Del Mar and Tom Jefferson have recently updated their Cochrane review on physical interventions to prevent the spread of acute respiratory infections with World Health Organization (WHO) funds.

Rokuro Hama has written the following books:

1. Published in January 2008: “Tamiflu: harmful as feared” (Kin-yobi Publishing Co). Royalties were split between his institution and the Tamiflu sufferers group 7%-1%.

2. Published in November 2008: “In order to escape from drug-induced encephalopathy”. NPOJIP(Kusuri-no-Check). Royalties to his institution.

He provided scientific opinions and expert testimony on:

1. 11 adverse reaction cases related to oseltamivir where applications were made by their families for adverse reaction relief by PMDA (Pharmaceuticals and Medical Devices Agency). This is reported in: IJRSM 2008:20:5-36. Two cases were paid in May 2005 and others were not.

2. a law suit on the fatal adverse reactions to gefitinib against AstraZeneca and the Japanese Minister of Health Labor and Welfare. He argued that gefitinib’s fatal toxicity was known before approval in Japan as shown in “Gefitinib story”: http://npojip.org/english/The-gefitinib-story.pdf and in other articles: http://npojip.org/. Paid by the plaintiff’s lawyers.

Mark Jones and **Peter Doshi** have no conflicts of interest to declare.

Matthew Thompson received payment for running educational courses at the University of Oxford and University of Oxford ISIS consulting services for external teaching and training.

Carl Heneghan receives payment for running educational courses at the University of Oxford and University of Oxford ISIS consulting services for external teaching and training. He also receives royalties for books (Evidence Based Toolkit series by Blackwell BMJ Books).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR, UK.

The review has been prepared with support from a NIHR (UK) grant 10/80/01

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have made a number of changes to the text during the process of turning the protocol into the review. This reflects our evolving understanding of the issues, during the relatively long period when work on the review was underway.

We have changed the review title to reflect the nature of the evidence. The old title was: *Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports*.

We have also re-written the objective twice, tightening up the text to bring it in line with our initial intentions and clarifying its meaning. The old objectives were: "To review clinical study reports (CSRs) identified from published and unpublished randomised controlled trials (RCTs) and relevant regulatory data on effectiveness and harms of NIs for influenza in all age groups" and "To review published and unpublished clinical study reports and other relevant regulatory data on effectiveness and harms of NIs for influenza in all age groups (and compare them with our published review)."

We changed the emphasis of the objectives on unpublished study reports as we had decided from the start to concentrate on regulatory information. Similarly, comparison of published versus unpublished data is an important and worthwhile effort, but the original objective possibly misled readers as to its importance in our work. We had always conceptualised it as a low-priority task we could carry out only if we had time following our review of unpublished data. We have also avoided using acronyms which we thought cumbersome and confusing to the reader.

Our initial intention was to review clinical study reports and regulatory comments making up what we have subsequently called 'regulatory information'. The edits do not reflect a change on intent but our slowly evolving understanding of the problems we faced and our solutions to address these problems. As one of many examples, the transition from a world in which studies were identified by names and years (Nicholson 2000) to one in which the same trial is identified by a series of letters and numbers (WV15670) was not easy.

While the review was underway, we identified several unforeseen issues such as placebo content and the effect of oseltamivir on antibodies. To test the relevant hypotheses we carried out post-protocol analyses which had not been present in the original protocol, but were derived from our protocol-stated intention to assess programmes and not single trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [adverse effects; *therapeutic use]; Drug Evaluation; Enzyme Inhibitors [adverse effects; *therapeutic use]; Europe; Great Britain; Health Status; Influenza, Human [*drug therapy; *prevention & control]; Japan; Legislation, Drug; Neuraminidase [*antagonists & inhibitors]; Oseltamivir [adverse effects; *therapeutic use]; Publication Bias; Randomized Controlled Trials as Topic; United States; Zanamivir [adverse effects; *therapeutic use]

MeSH check words

Adult; Child; Humans