Oseltamivir plus usual care versus usual care for influenza-like illness in primary care : an open-label, pragmatic, randomised controlled trial

Oseltamivir plus usual care versus usual care for influenza-like-illness: An open-label, pragmatic, randomized controlled trial in primary care

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Keywords

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Panel

Research in context

Evidence before this study

At the conception of this trial in February, 2015, we searched PubMed for systematic reviews in any language using the following MEDLINE subject heading keywords: “neuraminidase inhibitors” and “influenza”. A systematic review of placebo controlled randomized trials found that oseltamivir improved the median time to alleviation of symptoms over placebo by 17.8 (95% CI: -27.1 to -9.3) hours, and a Cochrane systematic review found oseltamivir improved time to first alleviation of symptoms by 16.8 (95% CI: -21.8 to -8.4) hours, both in intention to treat (ITT) populations with influenza-like-illness (ILI). A systematic review and meta-analysis of published and unpublished placebo controlled trials in adults with suspected or confirmed infleunzafound a mean reduction in duration of symptoms from oseltamivir of 20.7 hours (95% CI: 13.3-28.0) in 5 studies that included 3833 participants in an ITT population, and a mean reduction of 25.4 hours (95% CI: 17.2-33.5) in the intention to treat infected (ITTI) population (7 studies, 2690 patients), a difference of about 5 hours. Trials have found relatively greater benefits in those treated within 24 hours of symptom onset, and guidelines recommend initiating oseltamivir within 48 hours of symptom onset. Some of the trials included in the systematic reviews have been criticized for under-recruiting, selective reporting of outcomes, not including sufficient children or older people, and recruiting in a single season. In addition, the impact of antiviral treatment on return to daily activities, quality of life and care-seeking in key subgroups is largely unknown.

Added value of this study

In an open-label, publicly funded, pragmatic, randomized controlled trial that included 3266 adults and children consulting in primary care with ILI, patients treated with oseltamivir

recovered sooner, irrespective of influenza virus test results. Older, sicker, patients with comorbidities and longer prior illness duration showed greater absolute benefit.

Implications of all the available evidence

Adding oseltamivir to usual primary care for patients with ILI accelerates recovery by a mean of about one day and slightly longer in those with risk factors; this appears to be irrespective of influenza status. Initiating oseltamivir 48 to 72 hours after illness onset appears to give similar benefit to earlier initiation.

Summary (word count 226)

Background

Antivirals are infrequently prescribed in European primary care for influenza-like-illness (ILI), mostly because of perceived ineffectiveness in real world primary care, and as individuals who will especially benefit have not been identified in independent trials. We aimed to determine whether adding antiviral treatment to usual primary care for patients with ILI reduces time to recovery overall and in key subgroups.

Methods

We conducted an open-label, pragmatic, adaptive, randomized controlled trial of adding oseltamivir to usual care in patients aged one year and older consulting with ILI in primary care. The primary endpoint was time to recovery (return to usual activities, with fever, head- and muscle-ache minor/absent), following a Bayesian piece-wise exponential model. Baseline nasopharyngeal swabs were analyzed after study completion. The trial is registered with the ISRCTN Registry number ISRCTN 27908921

Findings

We recruited 3266 participants in 15 European countries during three seasonal influenza seasons (2015-2018), allocated 1629 to usual care plus oseltamivir, and 1637 to usual care, and ascertained the primary outcome in 1533 and 1526, respectively; 52% (1590/3059) had PCR-confirmed influenza infection. Time to recovery was shorter in those given oseltamivir (Hazard Ratio (HR) 1.29 (95% Bayesian CI: 1.20-1.39)). Regarding harms, there was evidence of increased burden of vomiting and/or nausea in the oseltamivir arm.

Interpretation

Primary care patients with ILI treated with oseltamivir recovered sooner than those managed by usual care alone.

Funding

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Registration

ISRCTN27908921; EudraCT Number: 2014-004471-23

Background

Guidelines recommend antiviral treatment for individuals presenting with suspected or confirmed influenza who have high-risk features. [1 2] However, antivirals are not often prescribed in primary care in many European countries,[3] partly because clinical and cost-effectiveness overall, potential side effects such as nausea and vomiting, and because individuals who will especially benefit have not been identified in prospective, non-industry funded and pragmatic studies.[4] It is unclear whether treatment should be initiated only after a positive test for influenza, or whether it should be based on syndromic presentation alone. Currently, oseltamivir treatment is recommended by the CDC as early as possible for patients with confirmed or suspected influenza who are hospitalized, severely ill, or have higher risk for influenza complications, and treatment can be considered for symptomatic outpatients with suspected influenza if treatment can be initiated within 48 hours of illness onset, which is similar to European recommendations.[1 2 5]

Meta-analyses have found that oseltamivir improves the median time to alleviation of symptoms over placebo among adults by 17.8 (95% CI: -27.1 to -9.3) hours,[6] and time to first alleviation of symptoms by 16.8 (95% CI: -21.8 to -8.4) hours.[7] Some of the included trials have been criticized for under-recruiting, selective reporting of outcomes, not including sufficient children or older people, and recruiting in a single season.[7 8] In addition, the impact of antiviral treatment on return to daily activities, quality of life and care-seeking is largely unknown, which is pivotal to assessing cost-effectiveness. We therefore set out to determine whether adding antiviral treatment to usual primary care for patients with ILI is effective in reducing time to recovery both overall and in key subgroups.

Methods

Study design

ALIC^{4}E (A randomized Controlled trial of Clinical and Cost effectiveness in primary CarE) was an investigator initiated, open-label, publicly funded, pragmatic, response-adaptive, platform, randomized controlled trial (RCT). The trial protocol has been published previously.[9]

Independent Trial Steering, Data Monitoring and Ethics Committees provided study oversight. The funder (European Commission's Seventh Framework Programme) had no influence on the design or conduct of the trial. The trial protocol, available online, was approved by NRES Committee South Central (Oxford B). Clinical Trial Authority (CTA) approval was obtained from The UK Medicines and Healthcare products Regulatory Agency. All participating countries gained national research ethics committees and CTA approval as required.

Participants

Potential participants were identified when they presented with symptoms of ILI, or when they telephoned for an appointment or advice about their symptoms to medical practices that were part of primary care research networks that had agreed to participate in the trial. ILI was defined as a sudden onset of self-reported fever, with at least one respiratory symptom (cough, sore throat, running or congested nose) and one systemic symptom (headache, muscle ache, sweats or chills, or tiredness), with symptom duration of 72 hours or less during a seasonal influenza epidemic.[10] Those with ILI aged >1 year, for whom informed, written

consent was provided, could comply with study requirements, and who agreed to take an antiviral agent according to randomization were eligible.

Randomisation

Participants were randomized at the point of care using a remote online electronic data capture (EDC) system (Research Online 2), with a 1:1 ratio between the two arms. The trial design was adaptive only with respect to the randomization ratio, in which adaptive randomization would be implemented if certain criteria were satisfied (see Web Extra materials), but such criteria were never met and the trial maintained 1:1 randomization throughout the trial. The trial design did not contain any adaptive stopping rules (e.g. early success or futility); rather the trial sought to enrol as many patients as possible across 3 consecutive winters (targeting between 2500 and 4500 participants). Stratified block randomization was implemented, with stratification by age (<12, 12-<65, ≥65 years), overall ILI severity (rated by the responsible clinician as mild, moderate, severe), any relevant comorbidity (yes/no, for any of heart disease; diabetes; chronic respiratory condition; hepatic, hematologic, neurological, neurodevelopmental condition; stroke/transient ischemic attack; overnight hospital stay in previous year), and prior duration of symptoms since onset (≤48 hours/>48-72 hours: based on recommendations that oseltamivir should be started within 48 hours of symptom onset).

Procedures

Participants were randomized to either usual primary care according to GPs' normal preferences -without prescription of oseltamivir- (control), or usual primary care plus oseltamivir (intervention). Adults and children weighing >40 kg who were randomized to the intervention and able to swallow capsules were given 75 mg oral oseltamivir twice daily for

five days. For those <13 years, oseltamivir was given in oral suspension, according to weight: 10-15 kg=30 mg; >15-23 kg=45 mg; >23-40 kg=60 mg; >40 kg=75 mg.

A baseline case report form was completed covering overall clinician-rated ILI severity (GPs' global impression of mild, moderate or severe illness without provided, predefined criteria), duration of symptoms, comorbidity, temperature, pulse, individual ILI symptom severities (patient-reported at inclusion), and usual care advice (registered by GP). An oropharyngeal and a nasal swab (COPAN®) were taken from those <16 years of age and a nasopharyngeal swab (COPAN®) from those ≥16 years of age. Clinicians were trained in nasopharyngeal and nasal swabbing techniques using face-to-face and online video methods. The Fast Track Diagnostics Respiratory Pathogens 21 plus real-time PCR assay was used to determine the aetiology, including influenza A and B status after each season, or after study completion, but results were not available for clinicians to inform management.[11]

Patients were asked to complete a symptom diary for 14 days in order to indicate when they had returned to their usual daily activities and to evaluate fever, running/congested nose, sore throat, headache, cough, shortness of breath (adults only item), muscle ache, sweats/chills (adults only item), diarrhea, nausea/vomiting, abdominal pain, low energy/tired (adults only item), not sleeping well, dizziness, feeling generally unwell, as 'no,' 'minor,' 'moderate,' or 'major' problem. These were supplemented with child-specific questions so that the Canadian Acute Respiratory Illness Flu Scale was completed for children ≤12 years of age.[12] Patients were contacted via telephone between days 2-4, days 14-28, and after 28 days to support study participation and diary completion, monitor intervention adherence, and ascertain a minimal outcome data set.

Outcomes

The primary outcome was patient-reported time to recovery, defined as having 'returned to usual daily activity', and 'fever', 'headache' and 'muscle ache' rated as minor or no problem. For non-verbal children, 'clinginess' replaced 'headache' and 'muscle ache', when both were unanswered. Secondary outcomes were: cost effectiveness of adding antiviral treatment to usual primary care (to be reported separately); incidence of hospital admissions; complications related to influenza-like illness; repeat attendance in general practice; time to alleviation of ILI symptoms; incidence of new or worsening symptoms; time to initial reduction in severity of symptoms; use of additional symptomatic and prescribed medication, including antibiotic; transmission of infection within household; self-management of ILI symptoms; and, whether the intervention benefits certain subgroups of patients more than others. These outcomes, together with reports of individual symptoms such as nausea and vomiting, which may be both side effects of oseltamivir as well as symptoms of influenza, were also considered in relation to possible harms from the intervention.[9]

Statistical Analysis

Full details and explanation of the statistical design are provided in the Web Extra material, section 1. Given the platform trial,[13] the statistical design explicitly addressed the estimation of a treatment effect in multiple pre-specified subgroups and allowed for an additional treatment during trial conduction. This latter feature was not implemented. The trial aimed to recruit between 2500 and 4500 participants over three consecutive winters. Extensive simulations in the design stage ensured this sample size was sufficient to provide at least 80% power for detecting a mean 1-2 day oseltamivir benefit in each of the subgroups. The pre-specified design required that response adaptive randomization be activated at an interim time point if either of the following pre-specified criteria were met: 1) an interim conclusion of "super-superiority" within a subgroup; or 2) the addition of a second antiviral arm. Neither criterion was met, so a 1:1 randomization ratio was maintained throughout the trial.

The pre-specified primary analysis was based on a Bayesian piece-wise exponential time-to-event model; the intention-to-treat (ITT) population included all randomized patients in the arm they were assigned regardless of treatment received. For the primary endpoint, where diary data was unavailable, data from the day 14-28 telephone call was used, and if that was unavailable, data from the call after 28 days. When data was incomplete, participants were censored at their last contact date or at 28 days.

Per the pre-specified design, the model evaluated the benefit of oseltamivir in the overall study population, within each marginal subgroup by each stratification factor, and within each of the 36 stratification factor subgroup combinations. The model included parameters for season, intervention group, age, severity, any comorbidity, symptom duration and the corresponding two-way interaction terms between the intervention and each of the four stratification variables. Based on the pre-specified design, the oseltamivir arm was declared superior for a specific population if the Bayesian posterior probability exceeded 0.975 for that population. To protect against false positives, the model used prior distributions that favour homogeneity in response between the various subgroups, unless data suggested otherwise. For subgroups with small sample size, this implies the estimates of treatment benefit were driven by the observed results in similar subgroups and the overall study population. Extensive simulations were conducted in the trial design phase to ensure adequate control of false positive conclusions; the simulated Type I error was between 0.001 and 0.04 for each of the hypotheses in the global null setting (i.e. when no oseltamivir benefit in all populations). Complete details are provided in the Web Extra materials. Estimates in the primary analysis were not adjusted for any interim analyses, as there was no evidence of bias resulting from adaptations in trial design simulations.

An exploratory analysis not specified in our original statistical analysis plan evaluated the interaction between the intervention and PCR-confirmed influenza status with respect to the

primary outcome. All analyses were based on complete case analyses, in which patients with unknown influenza status were ignored.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We randomised 3266 participants (data from 7 patients needed to be deleted) from 21 networks covering 209 primary care practices in 15 European countries over three consecutive influenza seasons: 495 in 2015-16, 1225 in 2016-17, and 1546 in 2017-18 (Web Extra materials, Table 1). Each season's start/end of recruitment was based on reports of national ILI presentation incidences rising above/falling below country-specific thresholds, using information from the European Centre of Disease Prevention and Control [14] and regional sources for each network.

Overall, 51% (1672/3259) of patients had confirmed influenza, and randomization occurred within 48 hours of symptom onset for 66% (2151/3259).

After randomization, 33 withdrew/were withdrawn, 162 were lost to follow-up, and 5 had too many missing/conflicting data to determine the composite primary outcome. The primary outcome was ascertained for 94% (3059/3259, Figure 1). No relevant differences in demographic or clinical characteristics were noted between the randomization groups (Table 1) or between flu seasons (Web Extra materials, Table 2). The low vaccination rate reflects recommendations in European countries that seasonal vaccination be given to those at risk for complications, for example children with asthma, and those aged over 65 with comorbidity. Regarding adherence, 1477 (96%) of those randomized to oseltamivir and included in the primary outcome analysis reported having initiated treatment, and 1232 (80%) reported having used the complete course; 80% (657/818) of those randomized to oseltamivir with confirmed influenza infection reported completing the course. No participant in the usual care group was prescribed oseltamivir.

The model-based estimated mean number of days to recovery for patients in the ITT usual care group was 6.73 days; recovery took longer for patients who were older, for patients with a comorbid condition, and for patients with severe symptoms (Figure 2). The estimated mean oseltamivir benefit was 1.02 days (95% Bayesian credible interval [BCI]: 0.74-1.31), corresponding to an estimated mean of 5.71 days to recovery in the ITT oseltamivir population.

The corresponding hazard ratio (HR) for all patients was 1.29 (95% BCI: 1.20-1.39), indicating faster recovery with oseltamivir (for Kaplan-Meier plot, see Web Extra Materials, Figure 1). Estimated HRs for each marginal subgroup within the four stratification factors (e.g., stratification group age has 3 marginal subgroups) showed similar oseltamivir benefit, with estimated HRs ranging from 1.26 to 1.41. For each of these 10 marginal subgroups, the Bayesian posterior probability that adding oseltamivir was superior to usual care alone exceeded the 0.975 pre-determined threshold to declare superiority (Web Extra materials, Figure 2A). In addition, the primary analysis model showed relatively similar HRs across the 36 subgroup combinations (all possible combinations of the 4 stratification factors), with estimated HRs ranging from 1.13 to 1.72. The Bayesian posterior probability of superiority exceeded the 0.975 threshold for 30 of the 36 subgroups (Web Extra materials, Figure 2B).

These estimated HRs indicate similar proportionate benefits of oseltamivir, and when applied to the varying absolute numbers of days to recovery in the usual care subgroups (Figure 2), might translate to meaningful differences between the estimated absolute numbers of days of oseltamivir benefit in the 36 subgroups (Figure 3). For instance, in patients <12 years old, without comorbidities and low severity symptoms ≤48 hours, a HR of 1.31 gives an

oseltamivir benefit of 0.70 days over the usual 5.1 days to recovery. However, in patients ≥65 years old, with comorbidities and moderate to severe symptoms >48 hours, HRs of 1.38 to 1.52 give an oseltamivir benefit of 2-3 days over the usual 11-13 days to recovery (Figure 3). In general, more absolute benefit of oseltamivir was observed with increasing age, more severe illness, comorbidity, and when presenting after 48 hours (Web Extra materials, Figure 3).

Additionally, the estimated HR for oseltamivir benefit in influenza-infected patients was 1.27 (95% BCI: 1.15-1.41), compared to 1.31 (95% BCI: 1.18-1.46) for patients negative influenza (Figure 4), indicating a similar oseltamivir benefit regardless of influenza status. Additional sensitivity analyses, some of which were not pre-specified, were conducted to evaluate the robustness of the primary analysis findings, with similar conclusions: no evidence of differential benefit between those found to be infected with influenza A versus influenza B, no evidence of differential benefit by season, and no evidence of differential benefit by infection with influenza versus any confirmed other viral infection (Web Extra materials, section 2). For example, the estimated benefit of oseltamivir versus usual care was approximately 1.2, 0.9, and 1.1 days for seasons 1, 2, and 3 (respectively) with overlapping credible intervals.

Slightly fewer antibiotics were used by the oseltamivir group, 9% of patients, compared to 13% in the usual care group, and there was a lower proportion of reported new household infections in the oseltamivir group, 39% of patients, compared to 45% in the usual care group (Table 2).

Harms

Secondary analyses did not identify differences in patient-reported repeat visits with health care services, hospitalizations, X-ray confirmed pneumonia, or over-the-counter (OTC) and acetaminophen/ibuprofen containing medication use (Table 2). Initial worsening of vomiting and/or nausea appeared more common (21% vs 16%) in the oseltamivir group compared to the usual care group (Web Extra materials, Table 3), and lasted longer in the oseltamivir arm (HR for time to symptom alleviation 0.94; 95% CI: 0.86-1.01). All other symptoms resolved faster in the oseltamivir arm (Web Extra materials, Figure 4). The number of patients missing usual activities and the number of hours of usual activities missed was similar in both groups (Web Extra materials, Table 4).

Of the 29 serious adverse events (SAEs) reported, 17 were in the usual care arm and 12 in the oseltamivir arm. Of the 12 events in the oseltamivir arm, one was assessed as a Serious Adverse Reaction (SAR) (known adverse reaction related to oseltamivir) – Urticaria; and one was assessed as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (thought to be possibly related to oseltamivir because of a temporal relationship, but not expected from current information) - Ischaemic left leg, requiring below knee amputation. Of the remaining 10 SAEs in the oseltamivir arm, three were reported as pneumonia; one suspected meningitis; one acute tonsillitis; one hip fracture; one hypertension; one ovarian cyst; one planned hospitalisation; and one shortness of breath and chest pain.

In the usual care arm, five SAE's were described as pneumonia; two as influenza; two asthma; one broken leg; one Guillain-Barré syndrome; one laryngospasms causing breathing difficulty; one leukocytoclastic vasculitis; one lung carcinoma; one paracetamol overdose; one peritonsillar abscess; and one viral meningitis.

No serious breaches were reported. There were 74 protocol deviations: the most common reasons were: medication storage temperature excursions (n=13); issues with lost or incorrectly labelled swabs (n=9); back-up randomisations being performed (n=9); incorrect participant identifiers being used for randomisation (n=7); and, issues with consent - some countries required both parents to provide consent for their child and whilst one parent gave consent at the time of the baseline visit, sometimes consent from the second parent was not granted (n=6).

Discussion

The ALIC^{4}E Trial was a large-scale, international, publicly-funded, pragmatic, randomized trial of effectiveness of adding oseltamivir to usual primary care for people with ILI over three influenza seasons powered to detect effects in key clinical subgroups.

Overall, these patients returned to their usual activities with mild residual symptoms minimally interfering after about 6.5 days, and about one day earlier with oseltamivir addition, which is consistent with previous placebo-controlled evidence in adults and children.[6 7 15 16] Moreover, we found that those at higher risk of adverse outcome -older, sicker, with comorbid conditions, or longer prior illness duration- might expect to return 2-3 days earlier with oseltamivir.

Those with confirmed influenza did not benefit more than those testing negative in our study. Furthermore, we found no evidence of a differential effect between those who were influenza positive and those positive for other viruses, or between those infected with influenza A or B. A systematic review and meta-analysis of published and unpublished placebo controlled studies of oseltamivir for ILI found a clinically unimportant difference of less than five hours in the mean reduction of symptom duration between those in the ITT population (5 studies, 3833 patients) and those with confirmed influenza infection (7 studies, 2690 patients).[15] As we asked participants to complete the symptom diary once a day, we may have not detected such a small difference. Other possible explanations include that oseltamivir's mode of action may include some generalized non-specific mechanisms, and/or an action on a wider range of viruses[6]; that we may have missed cases of influenza infection due to variable virus shedding over time (the Flu Watch study found that only a quarter of people with serologically confirmed influenza had PCR confirmed disease,[17] and a study in intensive care units found

that nucleic acid testing underestimated pandemic (H1Na) influenza when compared to paired serology by about a third[18]); possibly inconsistent swabbing techniques (which seems unlikely given the recent data from the recruiting Network[11]); that our primary outcome captured a range of factors, such as deterioration after initial recovery, and social influences such as thresholds for returning to work that might be less influenced by antiviral activity earlier on in the illness; or, that we found a placebo effect. However, there was no evidence of a differential relative benefit in subgroups such as those with lower illness severity where systematic reviews suggest a more marked placebo response.[19] Moreover, our overall estimate is similar to effects found in placebo-controlled trials. [6 7 15 16] The inclusion criterion of fever means we have not been able to document benefit in some elderly individuals where the febrile response can be less marked. Predicting the impact in a more highly vaccinated population is difficult. There could be a lesser effect (due to partial protection), but the impact could also plausibly be greater (those presenting with ILI would be more likely to be vulnerable individuals with a poor vaccine response).

Some might consider the lack of a placebo control as a limitation. We deliberately chose to perform an open-label trial in the context of everyday practice as effect sizes identified by placebo-controlled, efficacy studies with tight inclusion criteria may not be reproduced in routine care, and because we wished to estimate time to patient-reported recovery from the addition of an antiviral agent to usual care rather than benefit from oseltamivir treatment compared to placebo.[20] This pragmatic, open trial design makes our findings likely to reflect real world effects in primary care, since knowledge of what medication one is taking may influence subsequent help seeking and health behaviour, and use of symptomatic medications.[21 22] However, the design did not allow us to be sure of mechanisms, or how much of the observed effect can be attributed to specific oseltamivir or other possible effects,

and the relative contribution of such possible effects which might differ for the various subgroups.

Previous trials have found relatively greater benefits in those treated within 24 hours of symptom onset;[5 23] additional benefit from earlier treatment was not apparent in our trial, but our trial was specifically powered to detect subgroup effects in a representative primary care population. A recent community-based trial of oseltamivir for uncomplicated influenza found a similar effect to our study overall, and observed reductions in the duration of symptoms and virus shedding even when treatment was started >48h after illness onset.[24]An open, randomised trial of oseltamivir added to usual care in adults hospitalized with influenza-associated lower respiratory tract infections with a median time to oseltamivir initiation of 6 days found no reductions in terms of clinical failures.[25] In our population those presenting with longer prior duration (>48h) had a longer natural history, so although there was no difference in relative benefit, there was greater absolute benefit. In those with a shorter natural course of ILI, there may also be a ceiling effect, so that impact on viral replication may be too brief for benefit to become apparent, especially in a largely healthy primary care population. A possible explanation for the greatest impact in the subgroups who were older and at higher risk,[26] is that viral replication continues for longer, with a longer natural history of the illness in such individuals.

Meta-analyses have found that oseltamivir reduced the risk of self-reported pneumonia but not of clinically diagnosed pneumonia, [6 7] and that treatment with oseltamivir might reduce the risk of complications and hospitalization in patients tested positive for influenza.[6] Although our study was not powered on secondary outcomes, we found no evidence of an

effect on pneumonia or hospitalization, although oseltamivir was associated with slightly lower antibiotic use and reported new infections in household members.

Regarding harms, we did not identify meaningful differences in patient-reported repeat visits with health care services, hospitalizations, or serious adverse events, but found evidence for increased burden of vomiting and/or nausea in the oseltamivir arm, which is a common side effect of oseltamivir. One participant underwent a below knee amputation following arterial occlusion after having started oseltamivir five days previously. A search by the study team and also by an independent medicines information service found did not find reports of arterial thrombosis linked with oseltamivir: we did find reports of thrombotic events related to influenza . We decided to err on the side of caution by classifying this event as a "possible" SUSAR due to the temporal relationship between oseltamivir and the thrombosis. One SAE (urticaria) was considered related, and a further ten unrelated.

Previous trials have generally reported either time to first alleviation of symptoms or return to usual activities as their primary outcome. Our composite outcome captured both specific ILI symptoms and return to usual activities. Baseline body temperature was lower in our participants than reported in hospital-based studies, suggesting applicability to a typical primary care population. As in many other studies, children and older people were under-represented, but this may reflect consulting behaviour.

In conclusion, adding oseltamivir to usual primary care for ILI is likely to accelerate recovery by about a day in those with ILI and slightly more in those with risk factors. The effect does not appear to be mediated by influenza virus status as measured using PCR analysis of swabs, and is unlikely to be due to a placebo effect alone; while the reason for this effect is unclear,

the real world estimates are what patients and clinician can anticipate will occur in daily practice. Furthermore, oseltamivir started after 48 hours of symptom onset has a similar effect. Although the average benefit for many patients is modest, and therefore it is difficult to advocate widespread use of oseltamivir, given concerns about possible side-effects and also the 'medicalization' of largely self-limiting illness for most otherwise well people, clinicians and patients may wish to consider adding oseltamivir to routine treatment where a day less of illness is particularly important for patients. Clinicians may especially want to consider treatment in older patients, and those, including children, with more severe illness and comorbidities in whom the absolute benefit may increase recovery time by as much as 2-3 days.

Contributors

CCB and TJV were co-chief investigators of this trial and act as guarantors of the study in its entirety. CCB and TJV led the development of the research question, study design and obtaining the funding along with AWV, JC, HG, MDJ, PO and PL. EB, AWV and JC managed the trial and coordinated the operational delivery of the study protocol to the networks coordinating centres. SaC and NAF, members of the Trial Management Group, provided scientific and practical input. BRS, JH, RJL, and JTC were the trial statisticians. MI and VM led the microbiological analysis. MGC, CL, SłC, CL, BS, PDS, AC, RA, LB, NJH, ML, DG, HCB, BK, RRJ, PTL, AWM, AS represented the collaborating coordinating centres responsible for their network's participation in the trial. CCB led and produced the first draft of this manuscript. All authors provided critical review and final approval of the manuscript.

Declarations of interests

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boards form GSK, Vertex, Janssen, other from Roche, from Cidara Therapeutics; Heiner C. Bucher or his institute has received in the 36 months prior to the submission of this manuscript grants, support for travelling, consultancy fees and honorarium from Gilead, BMS, Viiv Healthcare, Idorsia and Roche that were not related to this project. He serves as the president of the association contre le HIV et autres infections transmissibles. In this function he has received support for the Swiss HIV Cohort Study from ViiV Healthcare, Gilead, BMS, MSD and Abbvie; Dr. Lewis is the Senior Medical Scientist at Berry Consultants, LLC. Berry Consultants, LLC was compensated for work related to the design and implementation of the clinical trial; Prof Verheij reports grants from the NIHR, grants from Netherlands Organization of Health Research and Development and a grant from the EU IMI which has Janssen Pharmaceuticals, Biocartis, Janssen, BioMerieux and Berry Consultants as partners, all outside the submitted work.

Data Sharing

After publication of the full trial report, formal requests for study data should be made to the corresponding author (CCB) using a bespoke data request form delineating research aim(s), methods and the variables needed. Such requests will be considered by the core ALIC^{4}E team (CCB, TV, BS, AWV, EB) and the PREPARE coordinator (HG). If research question(s) and methods are considered relevant and valid, the Data Management Department of the Julius Center, UMCU, will securely transfer the requested, fully anonymized data in the desired format to the party under data transfer agreements. The ALIC^{4}E team will decide about co-authorships, after discussion with the interested party about this. The Study protocol, statistical analysis plan and informed consent from will be made available.“

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Trial Status

Recruitment started 15 January 2016 and ended 12 April 2018. The current protocol is version 4.1 02-DEC-2017.

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Figure 1: Patient flow in the ALIC^{4}E trial.

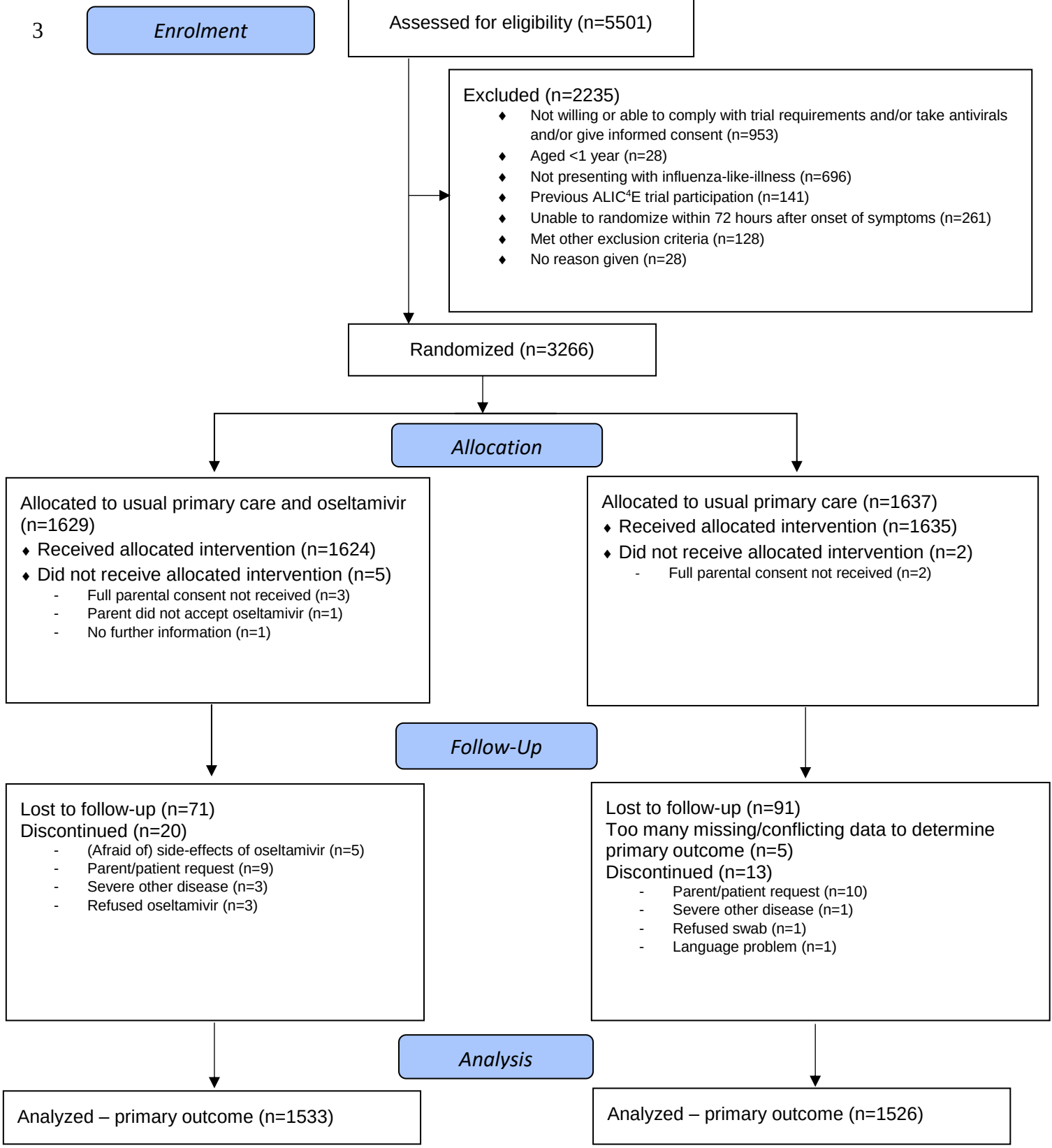


Figure 2: Estimated mean days to recovery for all subgroups in the usual care ITT population.

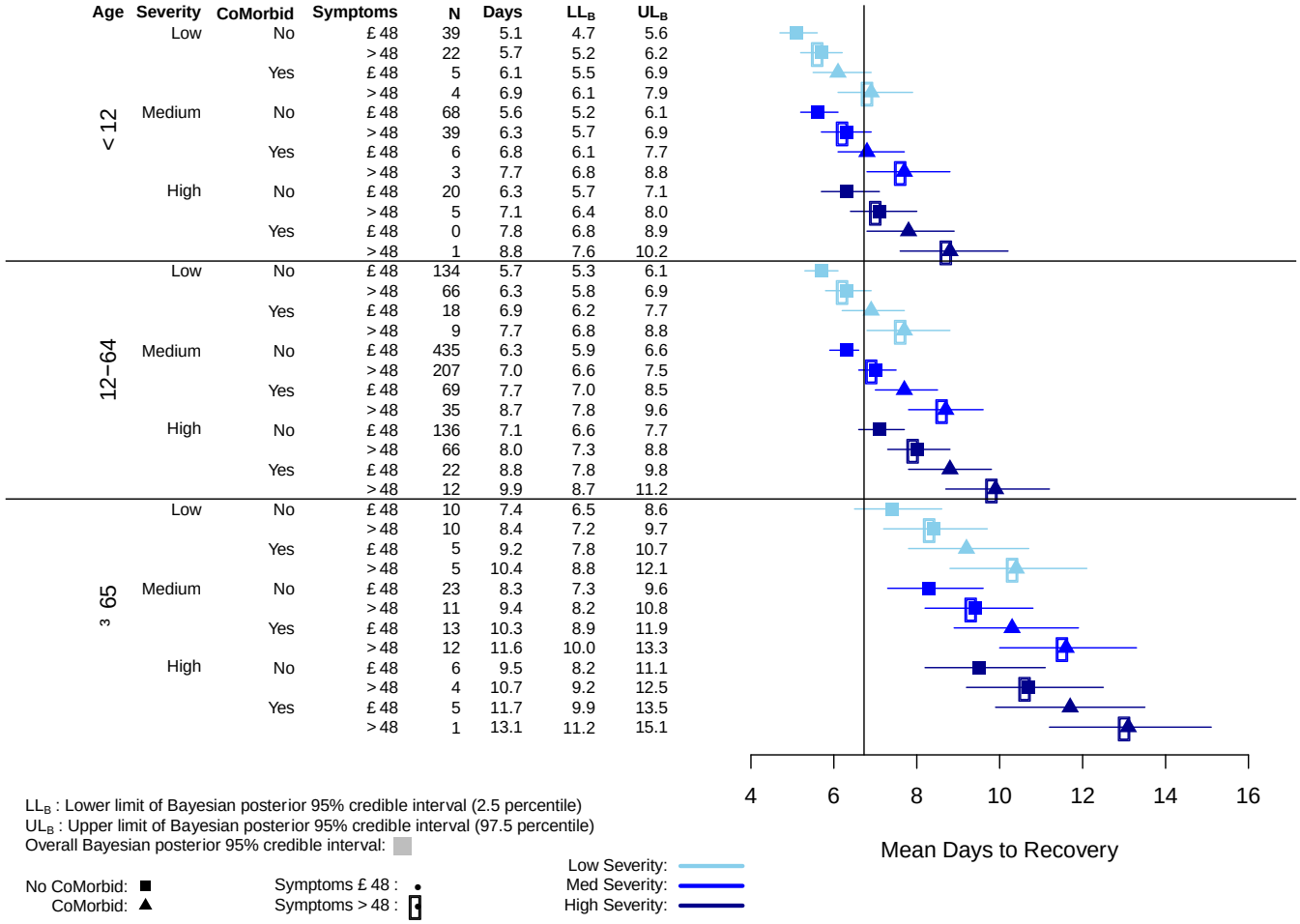


Figure 3: Estimated mean days of oseltamivir benefit for all subgroups in the ITT population.

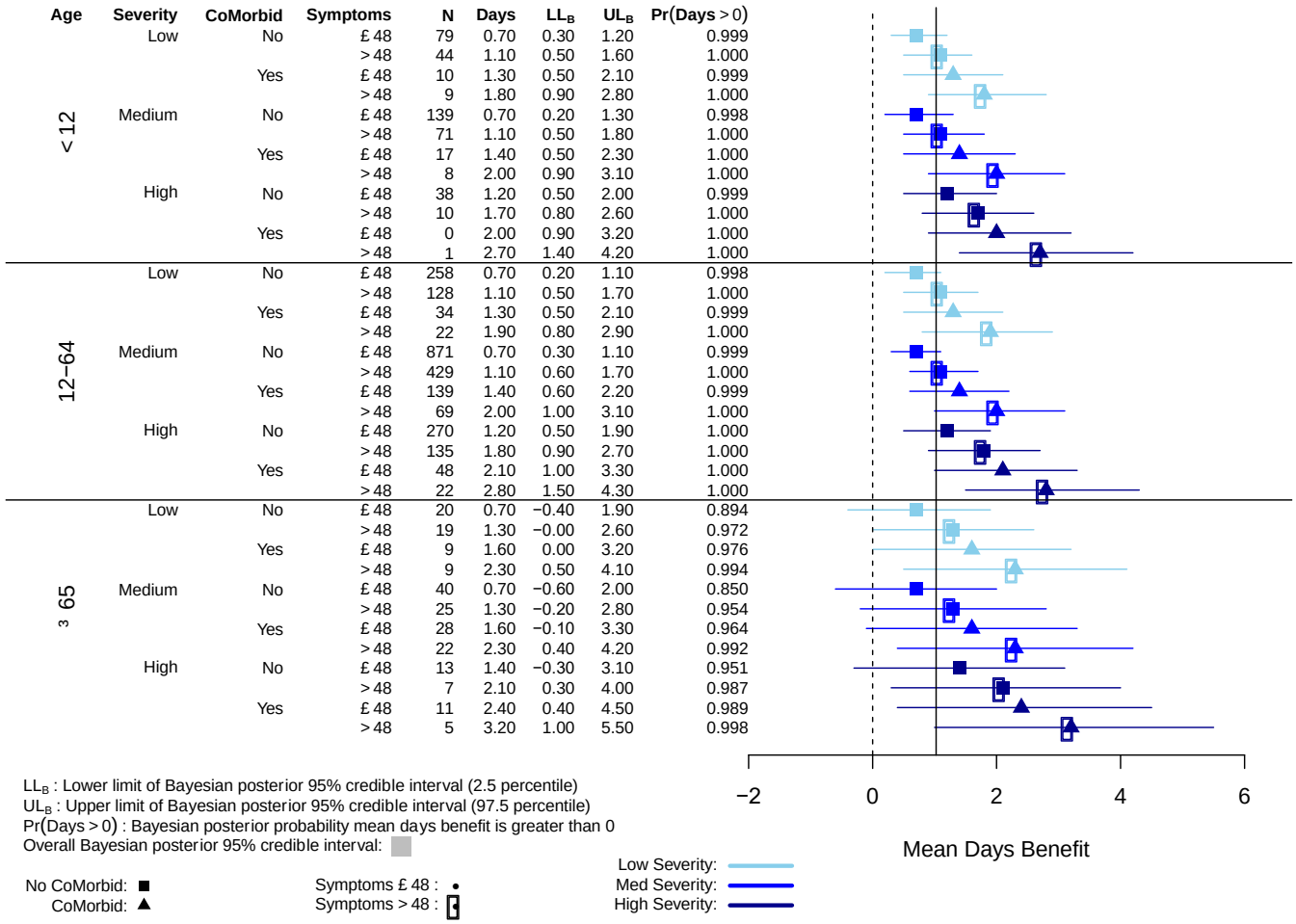
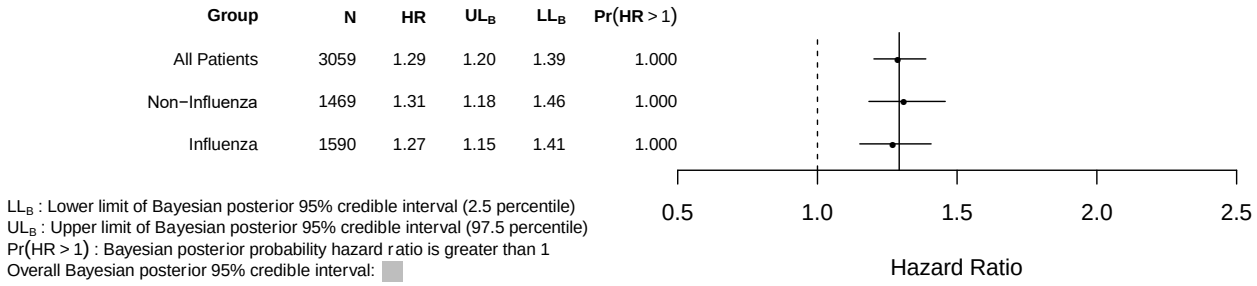


Figure 4: Modelled oseltamivir benefit by influenza status in the ITT population.



LL_B : Lower limit of Bayesian posterior 95% credible interval (2.5 percentile)
UL_B : Upper limit of Bayesian posterior 95% credible interval (97.5 percentile)
Pr(HR > 1) : Bayesian posterior probability hazard ratio is greater than 1
Overall Bayesian posterior 95% credible interval:

Table 1: Baseline demographic and clinical characteristics by treatment group in the ITT population (n=3259*).

	Usual care n=1635	**Usual care plus oseltamivir n=1624**
Sex (male)	731 (45%)	707 (44%)
Age		
<12 years	223 (14%)	225 (14%)
12-65 years	1306 (80%)	1296 (80%)
>65 years	106 (6%)	103 (6%)
Comorbidity		
Heart disease	76 (5%)	71 (4%)
Diabetes	42 (3%)	40 (2%)
Chronic respiratory condition	92 (6%)	104 (6%)
Hepatic, hematologic, neurological, neurodevelopmental condition	11 (1%)	21 (1%)
Stroke/Transient ischemic attack	9 (1%)	4 (0%)
Overnight hospital stay in preceding year	45 (3%)	51 (3%)
At least one of the above	239 (15%)	251 (15%)
Severity of ILI		
Mild	353 (22%)	340 (21%)
Moderate	985 (60%)	983 (61%)
Severe	297 (18%)	301 (19%)
Prior symptom duration		
≤24h	454 (28%)	448 (28%)
>24-≤48h	633 (39%)	616 (38%)
>48-≤72h	548 (34%)	560 (34%)

Signs and symptoms (major+moderate)		
Fever	1264 (77%)	1287 (79%)
Running or congested nose	990 (61%)	1001 (62%)
Sore throat	968 (59%)	946 (58%)
Headache	1190 (73%)	1189 (73%)
Cough	1134 (69%)	1093 (67%)
Shortness of breath[$]	387 (24%)	381 (23%)
Muscle ache and pains	1147 (70%)	1139 (70%)
Sweats/chills[$]	1109 (68%)	1103 (68%)
Diarrhea	97 (6%)	73 (4%)
Nausea and/or vomiting	171 (10%)	154 (9%)
Abdominal pain[$]	161 (10%)	149 (9%)
Low energy/tired	1334 (82%)	1336 (82%)
Not sleeping well	881 (54%)	852 (52%)
Dizziness	362 (22%)	417 (26%) [≠]
Feeling generally unwell	1428 (87%)	1413 (87%)
Poor appetite [#]	143 (60%)	144 (60%)
Crying more [#]	81 (34%)	84 (35%)
Needing extra care [#]	121 (51%)	135 (56%)
Clinginess [#]	121 (51%)	120 (50%)
Not playing well [#]	102 (43%)	119 (49%)
Irritable, cranky, fuzzy [#]	105 (44%)	114 (47%)
Not interested in what is going on [#]	73 (31%)	76 (32%)
Unable to get out of bed [#]	36 (15%)	49 (20%)
Temperature, Celsius, mean (SD)	37.5 (0.89)	37.6 (0.91) [≠]
Pulse rate, per minute, mean (SD)	87.4 (15)	87.7 (16)
Smoker (yes + occasionally)	257+65 (20%)	240+78 (20%)
Flu vaccination	156 (10%)	151 (9%)
Pneumococcal vaccination	86 (5%)	86 (5%)

PCR Evidence of influenza overall	820 (50%)	852 (52%)
Influenza A	452 (28%)	496 (31%)
Influenza B	369 (23%)	357 (22%)

* 7 patients withdrawn before any data collection, or data had to be deleted. # symptoms answered by participants ≤12 years of age (n=238 for usual care, and n=241 for usual care plus oseltamivir).

Missing data was no more than 3% for any variable, except for the symptom variables which were only answered by children, where missing was not more than 12%.

$ symptoms answered by participants >12 years of age

Table 2: Secondary outcomes by treatment group (n=3064).

Outcome	Usual care (n=1529)[$]	Usual care plus oseltamivir (n=1535)[$]	Difference in % (95% CI)
Hospital attendance: week 1-2	52/1462 (4%)	43/1469 (3%)	0.6 (-0.7, 2)
Hospital overnight stay: week 1-2	14/51 (27%)	8/42 (19%)	8.4 (-10.8, 27.6)
X-ray confirmed pneumonia: week 1-2	12/21 (57%)	7/15 (47%)	10.5 (-28.2, 49.1)
Hospital attendance: week 3-4	22/1393 (2%)	19/1426 (1%)	0.2 (-0.7, 1.2)
Hospital overnight stay: week 3-4	4/22 (18%)	4/17 (24%)	-5.3 (-36.4, 25.7)
X-ray confirmed pneumonia: week 3-4	3/5 (60%)	0/0	
Repeat attendances with health care services (except hospital)*	805/1529 (53%)	796/1535 (52%)	0.8 (-2.8, 4.4)
Took over-the-counter/other medication*	1258/1529 (82%)	1254/1535 (82%)	0.6 (-2.2, 3.4)
Use of antibiotics* Median days on antibiotics (interquartile range)	202/1529 (13%) 7 (5, 8)	142/1535 (9%) 5 (3, 7)	4 (1.7, 6.3)
Use acetaminophen containing medicine*	974/1529 (64)	924/1535 (60)	3.5 (0, 7)
Use ibuprofen containing medicine*	621/1529 (41)	594/1535 (38%)	1.9 (-1.6, 5.4)
Reports of new infections within the household	553/1222 (45%)	485/1237 (39%)	6.0 (2.1, 10.0)

[$] For the calculation of secondary outcomes, denominator and percentages are those with information from patients' diaries; for hospital admission/overnight stay and pneumonia data is from phone data too. Overnight hospital stay was calculated for those who attended the hospital and X-ray confirmed pneumonia for those who have had an X-ray in the hospital.

* If a patients didn't give an answer to the questions for repeat attendances, OTC/other medication and antibiotic use it was assumed the answer to the question was 'no'. From OTC medication, acetaminophen, and ibuprofen (containing medication) use is shown separately.

Web Extra material: Oseltamivir plus usual care versus usual care for influenza-like-illness: An open-label, pragmatic, randomized controlled trial in primary care

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Section 1: Further details of the statistical methods

Full details of the statistical design and analysis plan are found in the protocol and the Statistical analysis plan (SAP), both of which are available online. Despite the great amount of detail in these documents, further explanation is warranted in order to assist the reader understand the trial design, analysis, and results. This Appendix provides a general overview of the statistical design and analysis plan, along with additional details to help clarify certain aspects of the statistical design.

Adaptive Platform Design
This trial was designed as an adaptive platform trial, in which randomization ratios could change based on accruing data, and new treatment arms could be added at a later time in the ongoing trial. Multiple interim analyses were scheduled to analyze the interim data and implement the pre-specified adaptations. These interims were scheduled to occur midway and at the completion of each flu season (5 total interims over 3 seasons). Procedures were created to mitigate the possibility of operational bias. For example, unblinded interim analysis data and results were restricted to only the statistical analysis committee (SAC) performing the analyses and the data monitoring committee. Study investigators, site physicians and patients were not allowed access to datasets or results that could allow comparisons of outcomes across treatment arms.

Initially the trial was to randomize patients to oseltamivir plus usual care (intervention) versus usual care alone (control). If a second antiviral arm was added during the course of the trial (per a steering committee and consideration of available antiviral agent becoming available that would be suitable for pragmatic evaluation in primary care and resources), the pre-specified design would trigger the implementation of response adaptive randomization, in which patients would be randomized to better performing arms with a higher probability within each of the pre-specified subgroups. However, a suitable antiviral agent did not become available for evaluation in the trial, so a second antiviral arm was never added to the trial, and this trigger for response adaptive randomization was never met.

In the setting of only two arms (intervention versus control), the pre-specified design would maintain 1:1 randomization within each subgroup, unless there was a conclusion of interim superiority within a subgroup. The interim superiority required a "super-superiority" threshold to be met (SAP 2.6.2), achieved if at least a 0.975 probability of a HR exceeding 1/0.7=1.43, at which point the randomization would allocate 90% of patients to the superior arm and 10% to the inferior arm. The reasoning for continuing randomization to an inferior arm is because of the potential for seasonal effects, and the desire to ensure generalizability of any treatment effect across all 3 seasons. Despite evidence of benefit of Oseltamivir throughout the trial, the "super-superiority" threshold was never met; hence the trial maintained 1:1 randomization in all subgroups throughout the trial.

Primary Analysis Model
The primary analysis compares the time to recovery between treatment groups using a Bayesian piece-wise exponential survival model. The mathematical structure of the model is provided in the SAP. Similar to a Cox proportional hazards model, the piecewise exponential model estimates a hazard ratio (HR) comparing the two treatment groups, in which the HR is proportional across time. This is done by fitting an exponential survival curve to the control group within multiple time segments. These pre-specified time segments were defined as 0-2 days, 3-5 days, 6-10 days, and 11 or more days, and allow flexibility in the estimation of the underlying survival curve. The primary focus of the model is the estimation of the treatment effect that is held constant across these various time segments (i.e. proportional hazards). Hence the time interval parameters are regarded as nuisance parameters, and simply aid in providing a more robust estimate of the proportional hazards across time.

There are two primary reasons for using a Bayesian model as the pre-specified primary analysis instead of a classical approach: 1) To implement response adaptive randomization in the case of 3 treatment groups (the original plan was to introduce a second antiviral treatment arm); and 2) to use prior distributions to control the false positive rate. The Bayesian model used non-informative prior distributions for the treatment effect, main effects of the stratification factors, season, and the piece-wise exponential time segments, which allowed the data to quickly dominate those priors in the estimation of the corresponding posterior distributions. The model included interaction parameters between the intervention and each of the four stratification factors, allowing a separate treatment hazard ratio for each of the 36 patient subgroups, as defined by all possible combinations of the 4 stratification factors. For these interaction parameters, the Bayesian model used informative prior distributions centered at 0 with a small variance to control the false positive rate. With this structure, the model

starts with the assumption that the 36 subgroups have a similar treatment effect, but with sufficient data the treatment effects within the subgroups can differ from each other. For subgroups with a small sample size, the model can still reach strong conclusions about benefit because it leverages data from other adjacent subgroups and the overall population. Extensive simulations were conducted in the design stage to calibrate these pre-specified prior distributions (see Statistical Appendix: Operating Characteristics), to ensure that the design protected against false positives, while providing sufficient power for detection of simulated treatment effects. The targeted sample size was 2500-4500 patients, but the study enrolled as many patients as possible over the 3 seasons.

The Bayesian primary analysis model was fit in R and JAGS software using Markov Chain Monte Carlo (MCMC) methods, with a burn-in of 5,000 samples followed by 15,000 posterior MCMC samples. Posterior convergence was monitored graphically and analytically. The model was fit on the scale of the log hazards ratio.

Bayesian Posterior Probabilities

A Bayesian posterior distribution is obtained for each parameter in the primary analysis model by combining the prior distributions with the observed data. Linear combinations of these parameters are used to obtain posterior distributions of the treatment effect within each of the 36 patient subgroups. These treatment effects are measured as a hazard ratio, where a value greater than 1.0 indicates a faster recovery (i.e. a better outcome). The posterior distributions of the hazard ratios provide evidence for a treatment effect in terms of probabilities, and are fundamentally different than a classical approach via p-values. Instead of requiring a small p-value to contradict a null hypothesis, a Bayesian posterior distribution can directly estimate the probability that the treatment group is superior to the control group, given as the probability the hazard ratio is greater than 1. Based on the pre-specified analysis plan, if this estimated posterior quantity is equal to or greater than the pre-specified 0.975 threshold in a given subgroup, then there is sufficient evidence to claim the alternative hypothesis of a superior treatment effect within that subgroup population. This posterior probability of superiority is estimated for each of the 36 patient subgroups. Each corresponding distribution is summarized by calculating a mean with a 95% Bayesian credible interval [BCI], taken as the 2.5^{th} and 97.5^{th} percentiles of the Bayesian posterior distribution. In addition, linear combinations of the primary analysis model parameters are used to obtain posterior distributions of the mean number of days to recovery for each of the respective subgroups (Figure 2).

Marginal subgroups

Per the Statistical Analysis Plan (Section 8.2), the primary analysis model provides estimates of treatment benefit in the following populations: 1) the overall participant population, 2) each pre-specified marginal subgroup, and 3) each of the 36 covariate subgroups. The 36 patient subgroups represent all possible combinations of the 4 stratification variables (age, severity, comorbid conditions, and duration of symptoms). The pre-specified "marginal" subgroups are classified by each level of the stratification factors (i.e. all 3 groups classified by age, all 3 groups classified by severity, 2 groups classified by comorbidities, and 2 groups classified by duration of symptoms), and two additional pre-specified marginal populations classified by 1) older participants without comorbidities (PreSpec1 in Figure S2A, S3), and 2) middle-aged participants with comorbidities (PreSpec2 in Figure S2A, S3). The use of the word "marginal" to describe these subgroups is intended to convey the message that the treatment effect is being collapsed over subset populations. For example, in Figure S2B, there are 12 subgroups in which age < 12 years. A marginal hazard ratio for children with age <12 years old can be estimated by collapsing all 12 of these subgroups using a weighted average of the respective hazard ratios. Similarly, the HRs can be collapsed for persons with ages 12-64 years and ages ≥ 65 years, respectively. These marginal hazard ratios (Figure S2A) show the estimated benefit of the treatment within the corresponding marginal subpopulation. Because this is a pragmatic trial, and persons <12 years are likely to have different profiles of severity, comorbid conditions, and duration of symptoms compared to persons ≥ 65 years, these marginal estimates do not attempt to "adjust for other variables" nor "hold the other variables constant". Rather, they can be regarded as the marginal treatment effect expected in patients within the given classification. In other words, one would expect to obtain similar estimates with a univariate model evaluating the association between age and time to recovery.

A secondary analysis was conducted to evaluate the interaction treatment with PCR confirmed influenza status with respect to the primary outcome. For this analysis, we used a Bayesian model identical to the Bayesian primary analysis model, except that we included two additional parameters corresponding to the main effect of confirmed influenza status, and the interaction of confirmed influenza status with treatment. Both parameters were assigned non-informative N(0,1) prior distributions. Using this fitted model, the marginal treatment effect was estimated in both confirmed and non-confirmed influenza groups, averaged over the subset populations (Figure 4). The two estimates were very similar, with sufficient precision to rule out large differences between the two populations.

Section 2: Sensitivity Analyses

The following sensitivity analyses were conducted to evaluate the robustness of the primary analysis findings:
1) We repeated the primary analysis on only those participants who have PCR confirmed influenza;
2) We repeated the primary analysis with a modified definition of the primary endpoint, given as "time to resolution of symptoms" (i.e. without the "return to usual activities" in the composite time-to-event endpoint);
3) We repeated the primary analysis using alternative time segment, e.g. 0-3, 4-7, 8-14, 15+ days;
4) We estimated Kaplan-Meier survival curves by treatment group;
5) We fit Cox proportional hazards models to the primary outcome. These models took various forms, but included a Cox model with the same variable structure as the primary analysis model; a Cox model with interactions of oseltamivir by PCR influenza status; a Cox model with interactions of oseltamivir by season; a Cox model with interactions of oseltamivir by PCR influenza type (A vs. B); and a Cox model with interactions of oseltamivir by PCR influenza positive (irrespective of co-infections) vs. PCR virus positive (and influenza negative).

In sensitivity analyses #1, 2, 3 above, the primary conclusions remained robust across the variations of the primary analysis model. In #4, the Kaplan Meier curves showed a proportional treatment effect across time. Although there were some differences in the estimation between Cox model and Bayesian model in #5, the overall conclusions were similar across the respective analyses. In addition, there was no evidence of differential oseltamivir benefit (i.e. interactions) with any of the investigated variables.

Table 1: Inclusions by networks and influenza seasons.

	Season 1	**Season 2**	**Season 3**	
Belgium (Antwerp)	88	109	161	358
Belgium (Ghent)	0	100	151	251
Czech Republic	3	40	52	95
Denmark	17	19	32	68
France	14	14	21	49
Greece	19	62	44	125
Hungary	55	91	70	216
Ireland	10	10	28	48
Lithuania	81	88	70	239
Netherlands	25	20	18	63
Norway	27	18	10	55
Poland (Lodz)	0	125	120	245
Poland (Bialystok)	0	218	169	387
Spain (Barcelona)	0	20	28	48
Spain (Santiago)	7	10	16	33
Spain (Catalonia)	0	95	332	427
Sweden	25	28	16	69
Switzerland	6	15	5	26
UK (Oxford)	50	60	89	199
UK (Southampton)	22	45	59	126
UK (Cardiff)	46	38	55	139
	495	1225	1546	3266

* 7 patients withdrawn before any data collection, or data had to be deleted. Not all networks contributed in the first season, and some received approvals later during a season.

Table 2: Baseline characteristics by flu season, ITT population.

	Season 1 n=492	Season 2 n=1222	Season 3 n=1545
Sex (male)	214 (43.5%)	526 (43%)	698 (45.2%)
Age			
< 12 years	82 (16.7%)	180 (14.7%)	186 (12%)
12-65 years	383 (77.8%)	963 (78.8%)	1256 (81.3%)
>65 years	27 (5.5%)	79 (6.5%)	103 (6.7%)
Comorbidity			
Heart disease	23 (4.7%)	61 (5%)	63 (4.1%)
Diabetes	15 (3%)	26 (2.1%)	41 (2.7%)
Chronic respiratory condition	41 (8.3%)	79 (6.5%)	76 (4.9%)
Hepatic, hematologic, neurological, neurodevelopmental condition	2 (0.4%)	9 (0.7%)	21 (1.4%)
Stroke/Transient ischemic attack	1 (0.2%)	4 (0.3%)	8 (0.5%)
Overnight hospital stay in preceeding year	18 (3.7%)	46 (3.8%)	32 (2.1%)
At least one of the above	88 (17.9%)	198 (16.2%)	204 (13.2%)
Severity of ILI			
Mild	104 (21.1%)	296 (24.2%)	293 (19%)
Moderate	321 (65.2%)	682 (55.8%)	965 (62.5%)

	Season 1 n=492	Season 2 n=1222	Season 3 n=1545
Severe	67 (13.6%)	244 (20%)	287 (18.6%)
Prior symptom duration			
≤ 24h	136 (27.6%)	344 (28.2%)	422 (27.3%)
>24 ≤ 48h	181 (36.8%)	471 (38.5%)	597 (38.6%)
>48 ≤ 72h	175 (35.6%)	407 (33.3%)	526 (34%)
Signs and symptoms (major+moderate)			
Fever	381 (77.4%)	944 (77.3%)	1226 (79.4%)
Running or congested nose	286 (58.1%)	821 (67.2%)	884 (57.2%)
Sore throat	290 (58.9%)	711 (58.2%)	913 (59.1%)
Headache	341 (69.3%)	882 (72.2%)	1156 (74.8%)
Cough	329 (66.9%)	827 (67.7%)	1071 (69.3%)
Shortness of breath*	124 (25.2%)	274 (22.4%)	370 (23.9%)
Muscle ache and pains	320 (65%)	826 (67.6%)	1140 (73.8%)
Sweats/chills*	342 (69.5%)	815 (66.7%)	1055 (68.3%)
Diarrhoea	27 (5.5%)	63 (5.2%)	80 (5.2%)
Nausea and/or vomiting	58 (11.8%)	104 (8.5%)	163 (10.6%)
Abdominal pain*	66 (13.4%)	106 (8.7%)	138 (8.9%)
Low energy/tired	402 (81.7%)	1000 (81.8%)	1268 (82.1%)

	Season 1 n=492	Season 2 n=1222	Season 3 n=1545
Not sleeping well	292 (59.3%)	637 (52.1%)	804 (52%)
Dizziness	127 (25.8%)	300 (24.5%)	352 (22.8%)
Feeling generally unwell	433 (88%)	1048 (85.8%)	1360 (88%)
Poor appetite[#]	52 (59.8%)	117 (61.3%)	118 (58.7%)
Crying more[#]	25 (28.7%)	71 (37.2%)	69 (34.3%)
Needing extra care[#]	49 (56.3%)	107 (56%)	100 (49.8%)
Clinginess[#]	38 (43.7%)	102 (53.4%)	101 (50.2%)
Not playing well[#]	45 (51.7%)	89 (46.6%)	87 (43.3%)
Irritable, cranky, fussy[#]	35 (40.2%)	103 (53.9%)	81 (40.3%)
Not interested in what's going on[#]	30 (34.5%)	64 (33.5%)	55 (27.4%)
Unable to get out of bed[#]	20 (23%)	35 (18.3%)	30 (14.9%)
Temperature, Celsius, mean (SD)	37.52 (0.89)	37.59 (0.9)	37.45 (0.9)
Pulse rate, per minute, mean (SD)	89 (16)	87 (16)	87 (15)
Smoker			
Yes	81 (16.5%)	167 (13.7%)	249 (16.1%)
Occasionally	17 (3.5%)	56 (4.6%)	70 (4.5%)
Flu vaccination	40 (8.1%)	122 (10%)	145 (9.4%)
Pneumococcal vaccination	31 (6.3%)	61 (5%)	80 (5.2%)

	Season 1 n=492	Season 2 n=1222	Season 3 n=1545
PCR Evidence of influenza overall			
Influenza A	123 (25%)	565 (46.2%)	260 (16.8%)
Influenza B	121 (24.6%)	20 (1.6%)	585 (37.9%)

* Adults only
# Children only

Table 3 Incidence of new or worsening symptoms, ITT population

Symptom	Oseltamivir (n=1535)			Standard care (n=1529)			Difference in % (95% CI)
	No (%)	Yes (%)	Missing (%)	No (%)	Yes (%)	Missing (%)	
Fever	1130 (74)	133 (9)	272 (18)	1038 (68)	218 (14)	273 (18)	6.8 (4.1, 9.6)
Headache	1000 (65)	248 (16)	287 (19)	937 (61)	309 (20)	283 (19)	4.9 (1.6, 8.3)
Muscle ache	1044 (68)	179 (12)	312 (20)	960 (63)	273 (18)	296 (19)	7.5 (4.4, 10.6)
Nausea and/or vomiting	872 (57)	325 (21)	338 (22)	944 (62)	248 (16)	337 (22)	-6.3 (-9.8, -2.8)
Nasal congestion or runny nose	836 (54)	438 (29)	261 (17)	772 (50)	493 (32)	264 (17)	4.6 (0.8, 8.4)
Sore throat	966 (63)	285 (19)	284 (19)	871 (57)	371 (24)	287 (19)	7.1 (3.6, 10.6)
Cough	896 (58)	381 (25)	258 (17)	837 (55)	439 (29)	253 (17)	4.6 (0.9, 8.3)
Shortness of breath*	720 (55)	323 (24)	278 (21)	682 (52)	373 (28)	262 (20)	4.4 (0.3, 8.5)
Sweats/chills*	894 (68)	166 (13)	261 (20)	866 (66)	199 (15)	252 (19)	3 (-0.3, 6.3)
Diarrhoea	880 (57)	311 (20)	344 (22)	892 (58)	295 (19)	342 (22)	-1.3 (-4.8, 2.3)
Abdominal pain*	756 (57)	274 (21)	291 (22)	744 (56)	289 (22)	284 (22)	1.4 (-2.6, 5.3)
Low energy	1011 (66)	258 (17)	266 (17)	955 (62)	310 (20)	264 (17)	4.2 (0.9, 7.5)
Not sleeping well	887 (58)	358 (23)	290 (19)	844 (55)	397 (26)	288 (19)	3.2 (-0.5, 6.9)
Dizziness- adults only	742 (56)	300 (23)	279 (21)	733 (56)	316 (24)	268 (20)	1.3 (-2.7, 5.3)
Feeling generally unwell	1058 (69)	195 (13)	282 (18)	1016 (66)	235 (15)	278 (18)	3.2 (0.2, 6.3)

Poor appetite[#]	125 (58)	44 (21)	45 (21)	106 (50)	64 (30)	42 (20)	11.6 (1.2, 22)
Irritable, cranky, fussy[#]	109 (51)	61 (29)	44 (21)	95 (45)	70 (33)	47 (22)	6.5 (-4.5, 17.6)
Not playing well[#]	106 (50)	59 (28)	49 (23)	92 (43)	77 (36)	43 (20)	9.8 (-1.3, 20.9)
Crying more than usual[#]	99 (46)	61 (29)	54 (25)	98 (46)	63 (30)	51 (24)	1 (-10.3, 12.3)
Needing extra care[#]	121 (57)	47 (22)	46 (21)	107 (50)	56 (26)	49 (23)	6.4 (-4.2, 16.9)
Not interested in what's going on[#]	127 (59)	34 (16)	53 (25)	115 (54)	42 (20)	55 (26)	5.6 (-4.4, 15.6)
Unable to get out of bed[#]	118 (55)	41 (19)	55 (26)	100 (47)	54 (26)	58 (27)	9.3 (-1.5, 20.1)

* Adults only
[#] Children only

Table 4: Hours of usual activities missed in the first two weeks comparison of usual care treatment and usual care plus oseltamivir, ITT population.

Outcome	Usual care (n=1529)	Usual care plus oseltamivir (n=1535)
Usual activities missed in the first week for those aged > 12 years Median hours (interquartile range)	797/1317 (61%) 36 (19, 52)	806/1321 (61%) 35 (18, 50)
Usual activities missed in the second week for those aged > 12 years Median hours (interquartile range)	337/1317 (26%) 20 (7, 40)	334/1321 (25%) 20 (8, 40)
Usual activities missed in the first week for those aged ≤ 12 years[#] Median hours (interquartile range)	113/212 (53%) 40 (22, 76)	102/214 (48%) 37.5 (16.9, 64)
Usual activities missed in the second week for those aged ≤12 years[#] Median hours (interquartile range)	54/212 (25%) 33 (14.2, 64)	34/214 (16%) 24.5 (20, 80)

[#] For children the number of hours of missed activities is the sum of the number of hours of activities missed by: themselves; the adult who filled in the form; and other carers.

Figure 1: Kaplan Meier estimates of probability of recovery across time by treatment group, ITT population

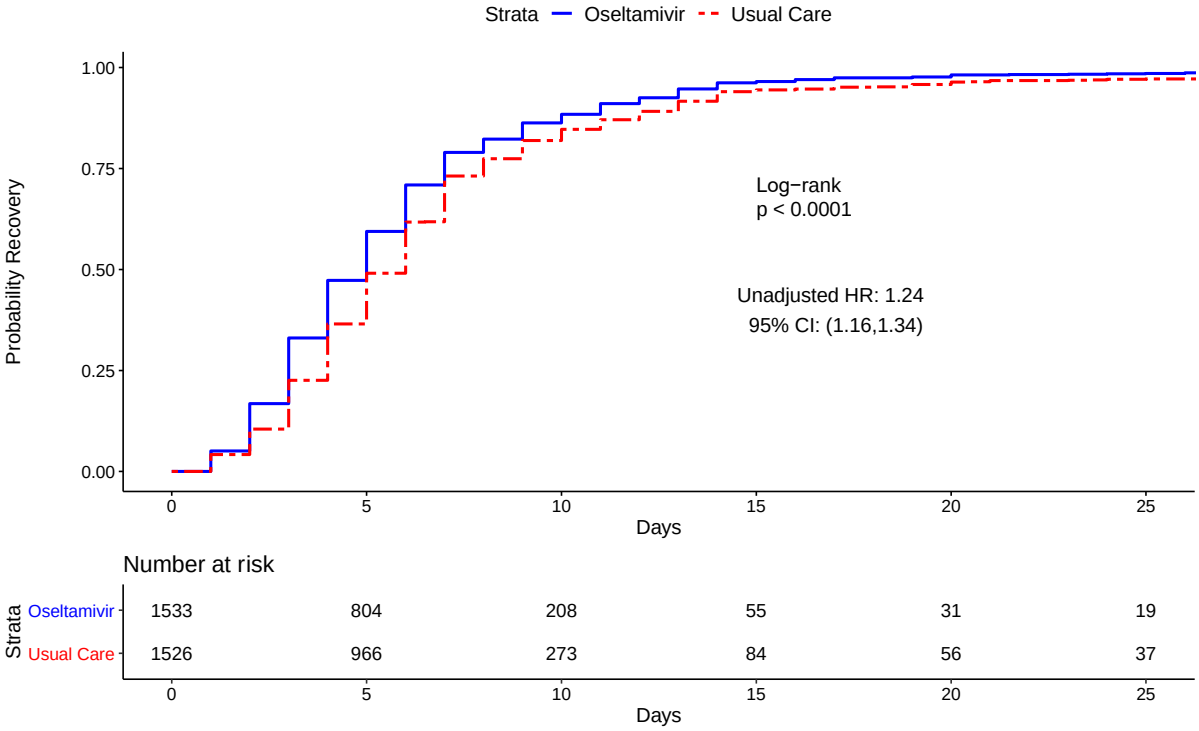
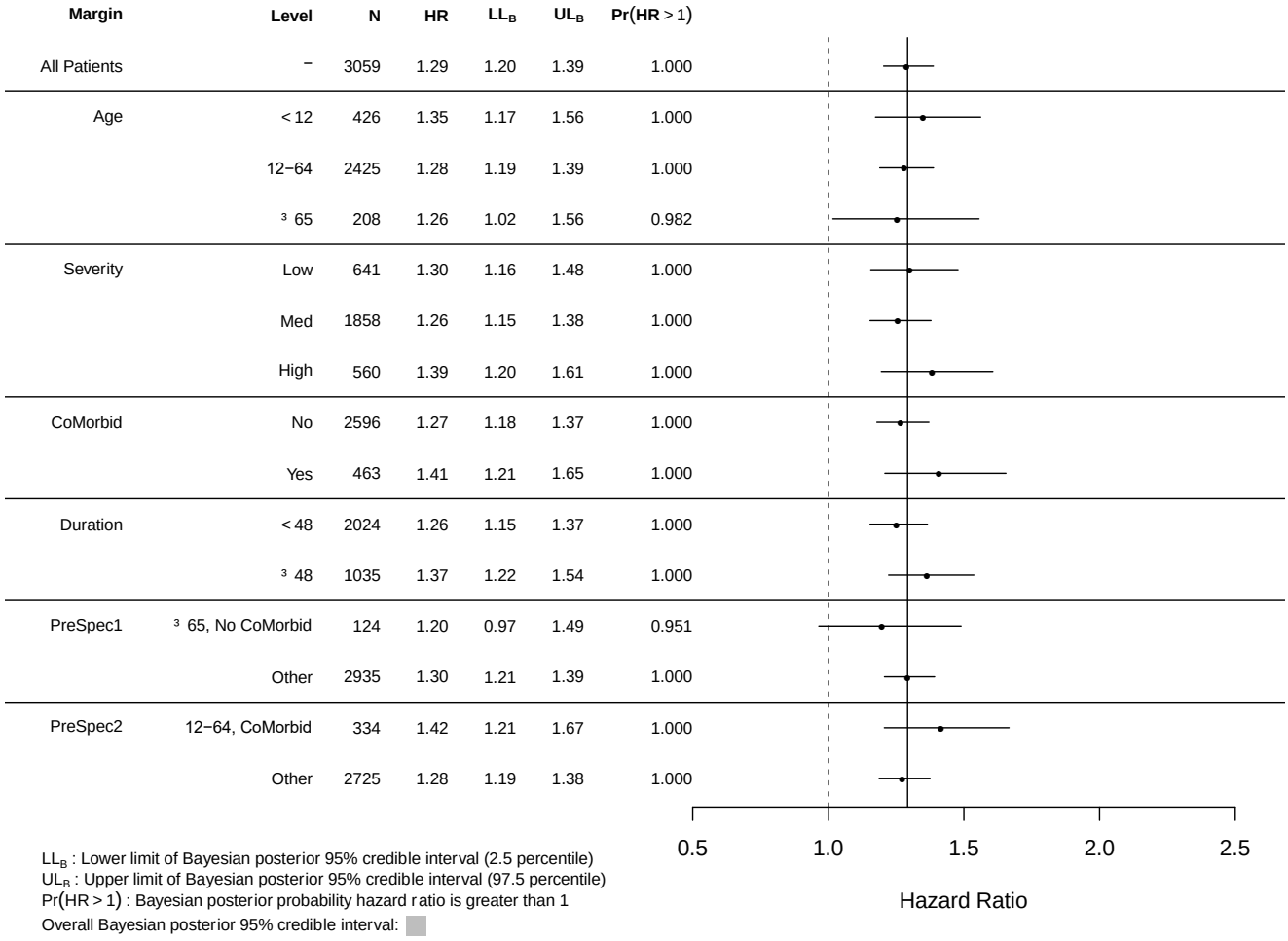
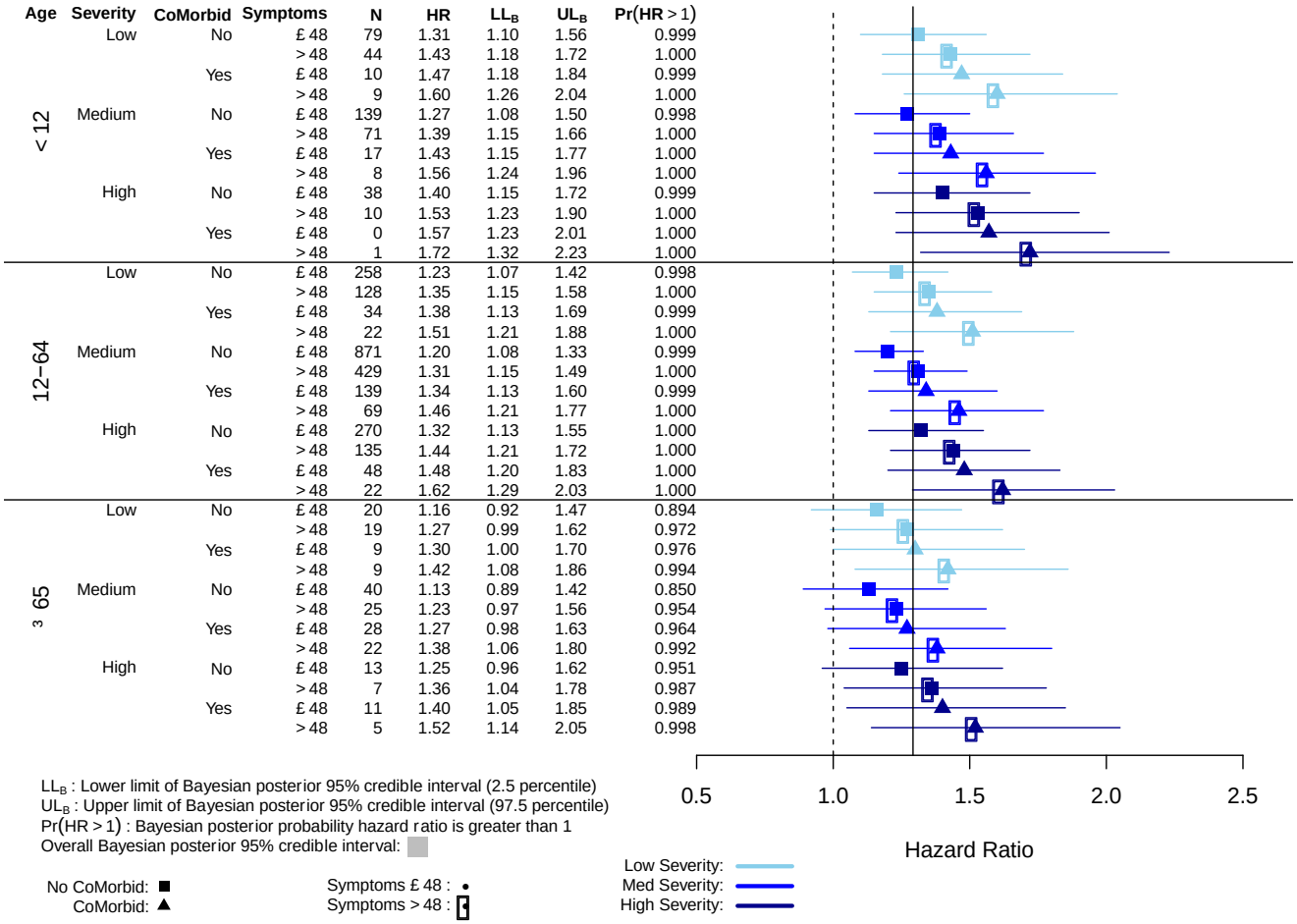


Figure 2A: Hazard Ratios of oseltamivir benefit in the 4 marginal stratification and pre-specified groups, ITT population



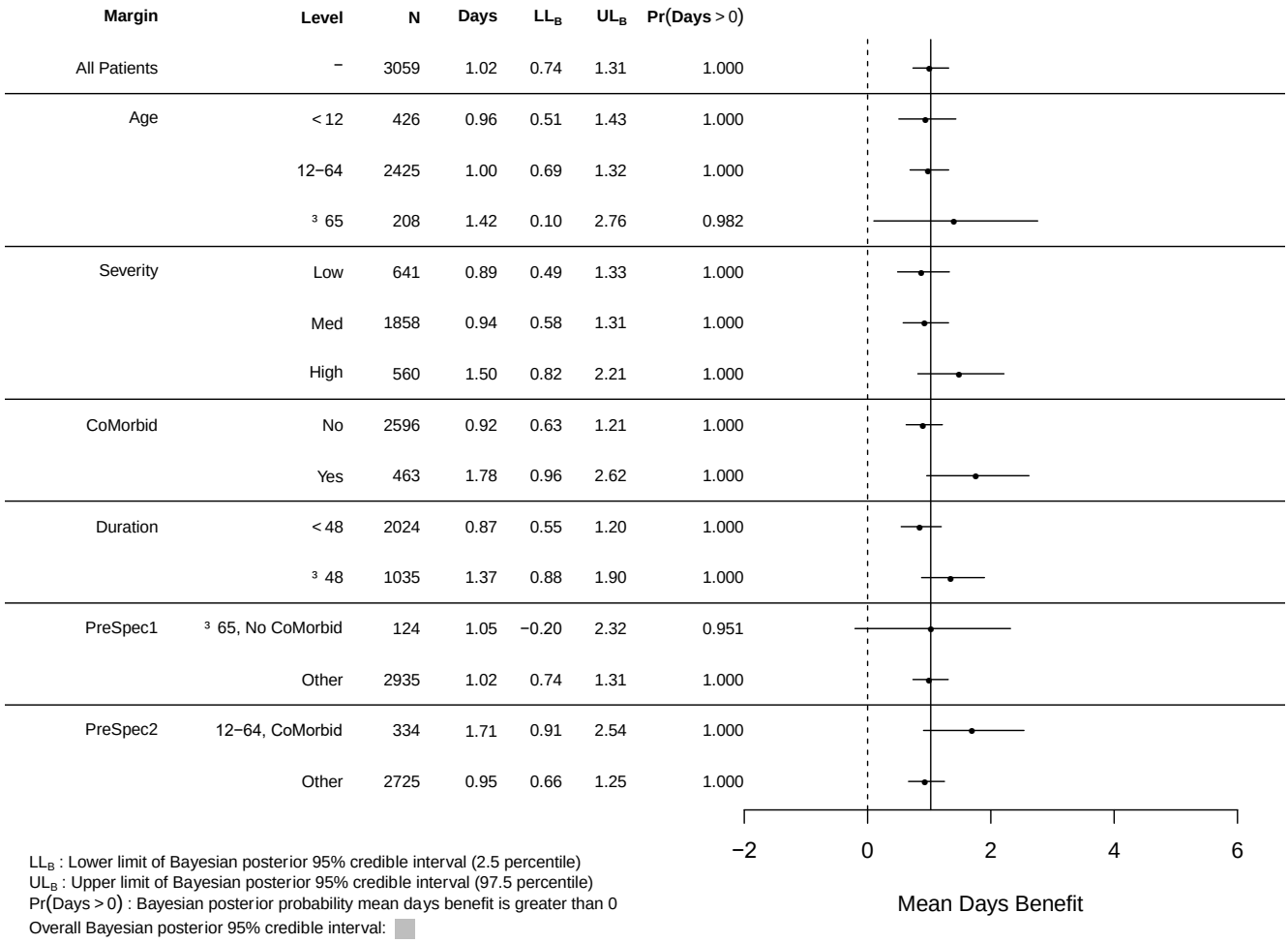
LL_B : Lower limit of Bayesian posterior 95% credible interval (2.5 percentile)
UL_B : Upper limit of Bayesian posterior 95% credible interval (97.5 percentile)
$Pr(HR > 1)$: Bayesian posterior probability hazard ratio is greater than 1
Overall Bayesian posterior 95% credible interval:

Figure 2B: Hazard Ratios of oseltamivir benefit in the 36 subgroups, ITT population



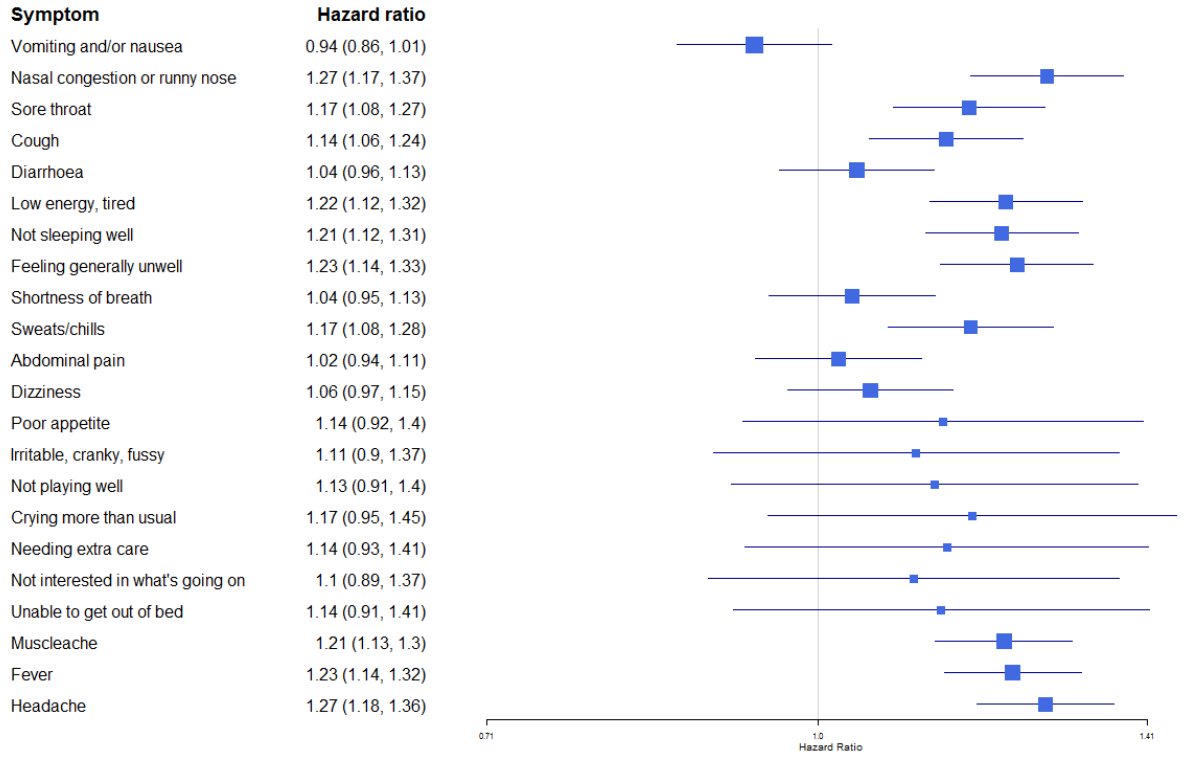
Age	Severity	CoMorbid	Symptoms	N	HR	LL_B	UL_B	Pr(HR > 1)
< 12	Low	No	£ 48	79	1.31	1.10	1.56	0.999
			> 48	44	1.43	1.18	1.72	1.000
		Yes	£ 48	10	1.47	1.18	1.84	0.999
			> 48	9	1.60	1.26	2.04	1.000
	Medium	No	£ 48	139	1.27	1.08	1.50	0.998
			> 48	71	1.39	1.15	1.66	1.000
		Yes	£ 48	17	1.43	1.15	1.77	1.000
			> 48	8	1.56	1.24	1.96	1.000
	High	No	£ 48	38	1.40	1.15	1.72	0.999
			> 48	10	1.53	1.23	1.90	1.000
		Yes	£ 48	0	1.57	1.23	2.01	1.000
			> 48	1	1.72	1.32	2.23	1.000
12–64	Low	No	£ 48	258	1.23	1.07	1.42	0.998
			> 48	128	1.35	1.15	1.58	1.000
		Yes	£ 48	34	1.38	1.13	1.69	0.999
			> 48	22	1.51	1.21	1.88	1.000
	Medium	No	£ 48	871	1.20	1.08	1.33	0.999
			> 48	429	1.31	1.15	1.49	1.000
		Yes	£ 48	139	1.34	1.13	1.60	0.999
			> 48	69	1.46	1.21	1.77	1.000
	High	No	£ 48	270	1.32	1.13	1.55	1.000
			> 48	135	1.44	1.21	1.72	1.000
		Yes	£ 48	48	1.48	1.20	1.83	1.000
			> 48	22	1.62	1.29	2.03	1.000
³ 65	Low	No	£ 48	20	1.16	0.92	1.47	0.894
			> 48	19	1.27	0.99	1.62	0.972
		Yes	£ 48	9	1.30	1.00	1.70	0.976
			> 48	9	1.42	1.08	1.86	0.994
	Medium	No	£ 48	40	1.13	0.89	1.42	0.850
			> 48	25	1.23	0.97	1.56	0.954
		Yes	£ 48	28	1.27	0.98	1.63	0.964
			> 48	22	1.38	1.06	1.80	0.992
	High	No	£ 48	13	1.25	0.96	1.62	0.951
			> 48	7	1.36	1.04	1.78	0.987
		Yes	£ 48	11	1.40	1.05	1.85	0.989
			> 48	5	1.52	1.14	2.05	0.998

Figure 3: Modelled mean days of oseltamivir benefit for the 4 marginal stratification and pre-specified groups, ITT population.



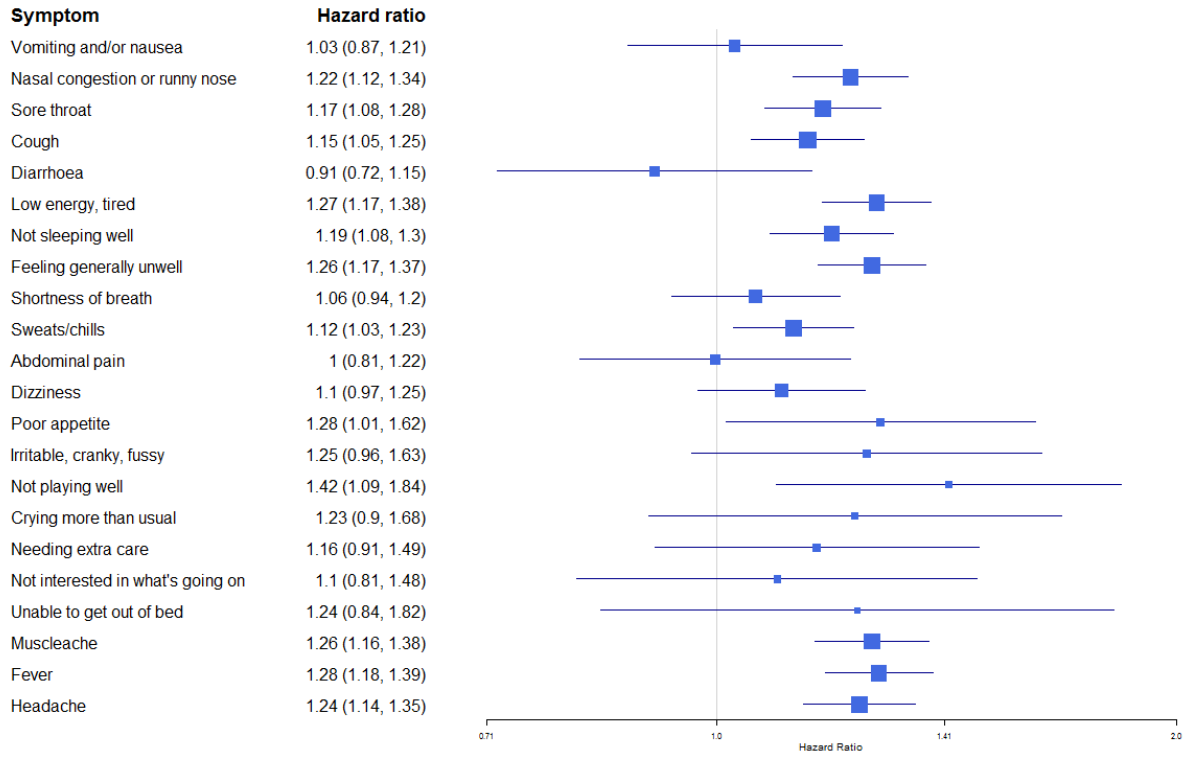
Pre-specified marginal subgroups are classified by each level of the 4 stratification variables. This includes all 3 groups defined by age, all 3 groups defined by severity, 2 groups defined by presence/absence of relevant comorbidities, 2 groups defined by duration of symptoms, and 2 additional marginal combinations of covariates, given by 1) older patients without comorbidities ("PreSpec1"), and 2) middle-aged patients with comorbidities ("PreSpec2").

Figure 4: Time to alleviation of individual ILI symptoms, comparison of usual care treatment and usual care plus oseltamivir, ITT population.



Hazard ratios and 95% CI from fitting Cox proportional hazards regression models to each symptom separately, adjusted for the stratification factors age group, co-morbidities, duration of symptoms and severity of symptoms, and also adjusted for treatment and season. A hazard ratio >1 indicates a shorter time for the symptom to be resolved (to no more than a minor problem) for patients randomized to oseltamivir compared to usual care.

Figure 5: Time to reduction in severity of individual ILI symptoms, comparison of usual care treatment and usual care plus oseltamivir, ITT population.



Hazard ratios and 95% CI from fitting Cox proportional hazards regression models to each symptom separately, adjusted for the stratification factors age group, co-morbidities, duration of symptoms and severity of symptoms, and also adjusted for treatment and season. A hazard ratio >1 indicates a shorter time for the symptom to reduce in severity by one level for patients randomized to oseltamivir compared to usual care.