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ORIGINAL ARTICLE

Efficacy and safety of baloxavir marboxil versus neuraminidase inhibitors in the treatment of influenza virus infection in high-risk and uncomplicated patients – a Bayesian network meta-analysis

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ABSTRACT

Objectives: Previous network meta-analysis (NMA) demonstrated advantageous or similar efficacy of baloxavir marboxil (baloxavir) over neuraminidase inhibitors in otherwise healthy (OwH) influenza patients. This analysis assessed the efficacy and safety of baloxavir in the subgroup of high-risk (HR) patients and in the population of uncomplicated influenza consisting of OwH and HR patients with influenza.

Methods: A systematic literature review (SLR) was performed in Medline, Embase, CENTRAL and ICHUSHI up to August 8th, 2018. A Bayesian NMA was conducted to compare baloxavir with oseltamivir, zanamivir, laninamivir and peramivir in HR patients and all uncomplicated patients.

Results: Based on the SLR, a total of 32 studies were identified as pertinent for the analysis, including 7 studies on HR patients, 13 trials on OwH patients and 14 studies on OwH + HR population. NMA of 10 trials assessing HR patients demonstrated comparable time to alleviation of symptoms for all treatments. Mean decline in virus titer from baseline at 24 h after treatment was significantly greater for baloxavir compared with oseltamivir and peramivir. The risks of total complications and drug-related adverse events were comparable between baloxavir and zanamivir, oseltamivir and laninamivir. These findings were highly consistent with results of the NMA using pooled evidence on the uncomplicated population of OwH and HR patients.

Conclusions: Baloxavir was significantly more effective than placebo regarding all outcomes except for the risk of pneumonia. Besides, baloxavir was associated with similar clinical efficacy and safety, and superior antiviral activity compared to other antivirals in HR patients, as well as in the entire population of uncomplicated patients with influenza.

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Network meta-analysis; baloxavir; influenza; high-risk patients

Introduction

Influenza is an acute viral infection of the respiratory tract, which occurs seasonally. It is a frequent cause of mild to severe illness, but it can also lead to death. The symptoms of influenza are often similar to those caused by other respiratory viruses circulating in temperate climates, including some or all of the following: fever or feeling feverish/chills, cough, sore throat, runny or stuffy nose, muscle or body aches, headaches, and fatigue (tiredness)[1]. Therefore, epidemiologists often use the term "influenza-like illness" (ILI) to refer to them[2]. The World Health Organization (WHO) defines ILI as an acute respiratory infection with a measured fever of $\geq$38 °C and cough; with an onset within the last 10 days[3]; however, other definitions are also used in the literature.

Symptoms of influenza are most often mild, and patients recover within 2 weeks without the need for medical care. In some patients, however, influenza leads to the development of a variety of complications, including life-threatening conditions, which require inpatient care. For this reason, influenza does not only impose a huge economic burden due to sick leave among patients but is responsible for humanistic burden in terms of mortality and lost quality of life. Molinari et al. predicted that the total economic burden of influenza would reach $87 billion in the US[4]. In Japan, the number of influenza patients in the 2018/19 season reached a near epidemic level of around 12 million infected[5]. Also in the 2018/19 season, the hospitalized influenza surveillance reported a total of 20,389 hospitalized influenza patients, similarly as in the preceding season (20,584 in 2017/18) but much higher compared to previous seasons (15,405 in 2016/17; 12,275 in 2015/16)[5–8].

The US Centers for Disease Control and Prevention (CDC) defines patients who are at particularly high risk of developing complications following ILI[9]. This group consists of

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Table 1. Inclusion and exclusion criteria of SLR and NMA.

Inclusion/Exclusion elements	Inclusion criteria	Exclusion criteria
Population	Patients $\geq$ 12 years with flu symptoms (influenza-like illness or confirmed influenza).	- Studies on hospitalized patients only or patients outside 48 h of symptom onset.
Interventions	• Baloxavir marboxil 40 mg • Oseltamivir 75mg • Zanamivir 10 mg • Laninamivir 40 mg • Peramivir 600 mg • Peramivir 300 mg	
Comparators	Any comparator	
Outcomes of interest	Efficacy: • Time to alleviation of all symptoms, defined as the time from the start of treatment to the time when all influenza symptoms are rated as absent or mild • Time to resolution of fever • Time to improvement of influenza symptoms • Change in virus titer from the baseline at 24h after treatment • Change in virus titer from the baseline at 48h after treatment • Total complications • Pneumonia • Bronchitis Safety: • Total Adverse Events (AEs) • Total DRAEs	
Study designs	Randomized Controlled Trials	Case reports, letters and historical articles

Abbreviations. AE: adverse event; NMA: network meta-analysis; SLR: systematic literature review.

people with a variety of underlying health complications, including asthma, diabetes, cancer, cardiovascular diseases, AIDS/HIV or children with neurologic conditions and others. Older age (>64 years old), children <2 years old, pregnancy and gestation have also been recognized by CDC as independent risk factors for developing ILI-associated complications[9]. At an individual level, high-risk (HR) patients, such as young children, elderly, pregnant women and patients with comorbidities, can experience much more severe symptoms than otherwise healthy patients. The population at risk infected with influenza occasionally develop complications including pneumonia, otitis media and dehydration or encephalopathy with or without liver failure[1].

Antiviral therapies have been developed to shorten the disease duration, improve recovery and reduce the risk of ILI-associated complications. The recent clinical practice guidelines issued by the Infectious Diseases Society of America recommend immediate initiation of antiviral treatment in hospitalized patients, people with progressing diseases and subjects with a high underlying risk of ILI complications[10]. A study conducted by Havers et al., however, showed that antiviral drugs are under-utilized in the group of HR patients with an acute respiratory illness[11].

The most commonly used antivirals include neuraminidase inhibitors. They interfere with the release of progeny influenza virus from infected host cells via blocking of neuraminidase activity; therefore, they prevent infection of new host cells and stop the spread of infection[12]. Nevertheless, there is a need to create new, more effective drugs since the development of resistance to already existing drugs has been identified during treatment of seasonal influenza[4]. A cap-dependent endonuclease inhibitor baloxavir marboxil (further referred as baloxavir) was developed as a single-dose, oral drug, with the purpose to target viral replication of influenza A and B. In the CAPSTONE-1 trial, baloxavir demonstrated superior efficacy to the placebo in alleviating influenza symptoms, and superior to both oseltamivir and the placebo in virologic outcomes[13]. A recently revealed CAPSTONE-2 trial demonstrated that baloxavir administered in HR patients was associated with a significantly shorter time to improvement of influenza symptoms compared with the placebo (median 73.2 h vs. 102.3 h, $p<.0001$) and numerically shorter than oseltamivir (81.0 h, $p=.8347$). The median time to cessation of viral shedding in baloxavir patients was 48 h– significantly less than 96 h in both the placebo and oseltamivir patients. Baloxavir compared with the placebo reduced the frequency of influenza-related complications (2.8 and 10.4%) and the need for systemic antibiotic use (3.4 vs. 7.5%)[14]. A recent network meta-analysis by Taieb et al. demonstrated that in the otherwise healthy (OwH) population, baloxavir was associated with a reduced time to alleviation of all symptoms compared to zanamivir, whereas time to cessation of viral shedding was significantly shorter for baloxavir than zanamivir and oseltamivir[15]. The mean decline in virus titer from the baseline at 24 h after treatment was significantly greater for baloxavir than for other drugs[15]. Baloxavir demonstrated a comparable safety profile to other antivirals, except for total drug-related adverse events (DRAE) where it demonstrated a decrease compared to oseltamivir and laninamivir[15].

This study was conducted to assess the comparative efficacy and safety profile of baloxavir in the subset of high-risk patients, as well as in the entire population of uncomplicated patients with influenza.

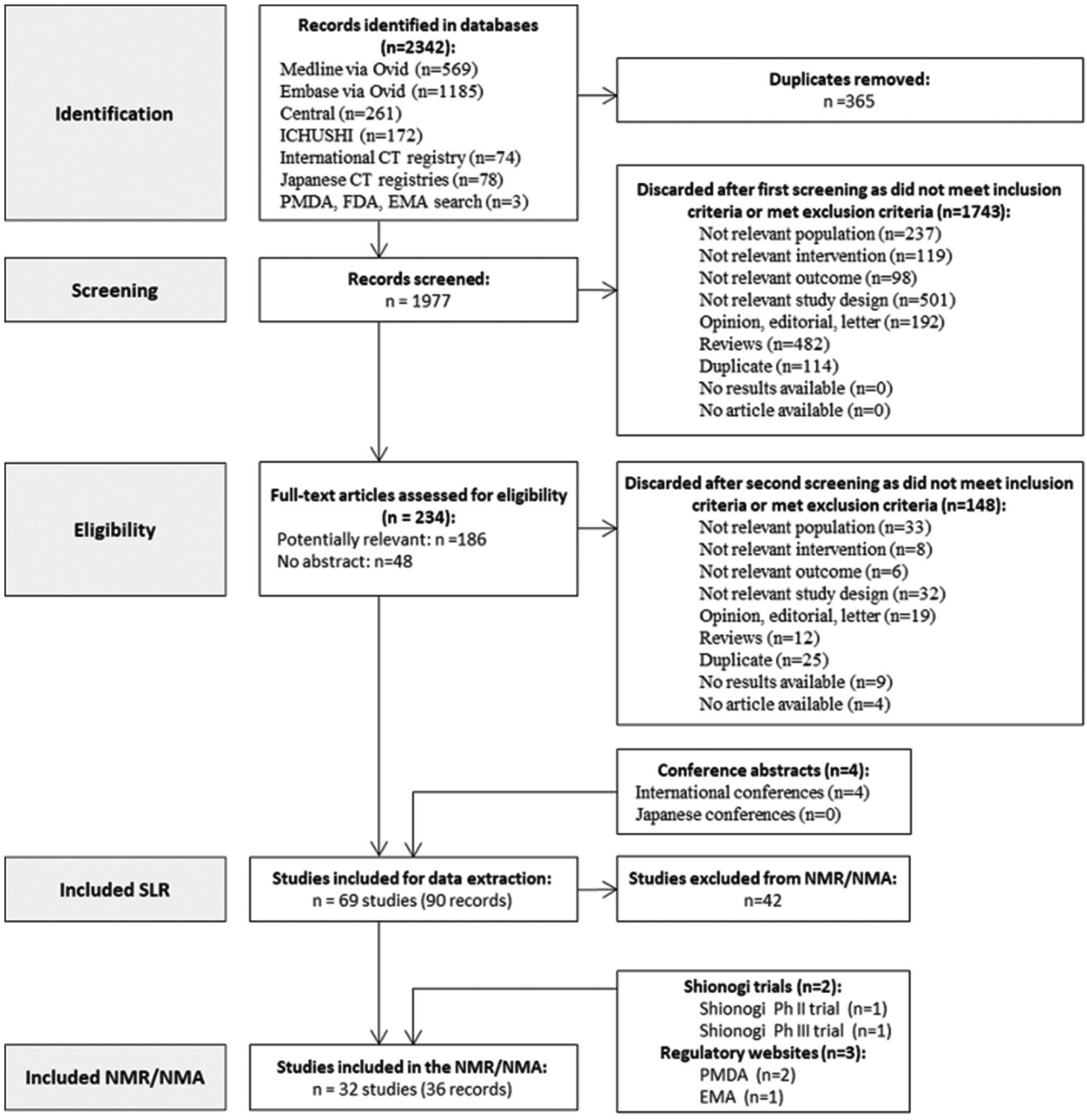

Figure 1. PRISMA flowchart of selected studies. Abbreviations. CT, clinical trials; EMA, European Medicines Agency; FDA, Food and Drug Administration; NMA, network meta-analysis; PMDA, Pharmaceuticals and Medical Devices Agency; SLR, systematic literature review.

Methods

Systematic literature review (SLR)

This analysis was preceded by a systematic literature review (SLR) of randomized controlled trials (RCT) assessing the efficacy and safety of antiviral medications administered in patients with influenza symptoms and ILI. The identification of studies was based on SLR conducted on the 14November 2016 and further updated on the 8August 2018. The systematic search was conducted in the following electronic databases: MEDLINE, MEDLINE In-Process, EMBASE, CENTRAL, and ICHUSHI. Websites of conferences/congresses related to infectious diseases were screened for relevant clinical data. Additional sources were consulted in order to capture relevant documents for the review (e.g. ClinicalTrials.gov, Shionogi proprietary unpublished data). No geographical restrictions were applied. The search strategies are reported in the Supplementary Appendix. Clinical trials were selected by two reviewers working independently and the discrepancies were resolved by a third reviewer. Extracted data included publication characteristics, study details, patient characteristics, results and study limitations. All extracted data were quality-checked by a second reviewer. The eligibility criteria are summarized in Table 1.

Table 2. List of studies included in the analysis – HR population.

Author, year	Diagnosis	Intervention/Comparator	Sample size	Age (years)	Risk factors	Assumed HR patients (%)
Baloxavir						
Shionogi Ph 3 (Phase 3 trial HR)	CI	Baloxavir 40/80 mg (single administration) Oseltamivir 75 mg (BID, for 5 days) Placebo	2184	≥12	Age ≥ 65 years, chronic respiratory, endocrine, CV, renal, hematologic neurologic or renal disease, women within 2 weeks postpartum, BMI ≥ 40, residents of long-term care facilities, immunocompromised	100
Laninamivir						
PMDA Laninamivir Report 9, 2010	CI	Laninamivir (NR) Oseltamivir (NR)	26	≥65	Age ≥ 65 years	100
Watanabe, 2013	CI	Laninamivir 40 mg (single administration) Oseltamivir 75 mg (BID, for 5 days)	203	Range: 20–77	Chronic respiratory disease	100
Oseltamivir						
PMDA Tamiflu Interview Form 3	ILI	Oseltamivir 150 mg Placebo	284	≥65	Elderly	100
Peramivir						
Kohno, 2011	CI	Peramivir iv 300 mg (QD for 1–5days as needed) Peramivir iv 600 mg (QD for 1–5 days as needed)	18 19	Mean (SD): 51.5 (16.2) Mean (SD): 50.4 (16.7)	Poorly controlled diabetes, respiratory tract disease, use of immunosuppressive drugs, use of steroids due to asthma.	100
Nakamura, 2017	CI	Peramivir iv 600 mg (single administration, repeated if necessary) Oseltamivir 75 mg (BID, for 5 days)	92	Range: 33–92	Age ≥ 65 years, chronic CV, neurological, respiratory, kidney or metabolic disease, immunocompromised	100
Zanamivir						
Murphy, 2000	ILI	Zanamivir 10mg (BID, for 5 days) Placebo	525	≥12	Chronic respiratory disease	100

Abbreviations. BID, twice a day; CI, confirmed; CV, cardiovascular; ILI, influenza-like illness; NR, not reported; PMDA, Pharmaceuticals and Medical Devices Agency; QD, once daily; SD, standard deviation.

Table 3. List of studies included in the analysis – OwH population.

Author, year	Diagnosis	Intervention/Comparator	Sample size	Age (years)	Comorbidities (%)	Assumed HR patients (%)
Baloxavir						
Shionogi Ph 2 (Phase 2 trial OwH)	CI	Baloxavir 40 mg(single administration)	100	Range: 20–63	Excluded: heart, neurological diseases etc. (patients without risk factors and underlying diseases)	0
		Placebo	100	Range: 20–64		
Shionogi Ph 3 (Phase 3 trial OwH)	CI	Baloxavir 40/80 mg (single administration)	376	Range: 20–64	OwH patients with influenza	0
		Oseltamivir 75 mg (BID, for 5 days) + Placebo	377			
		Placebo	192			
Laninamivir						
NCT01793883[#]	ILI	Laninamivir: 40 mg (single administration)	213	Range: 18–64	HR excluded	0
		Placebo	212			
Watanabe, 2010	CI	Laninamivir 40 mg (single administration)	334	Range: 20–73 Mean (SD): 34.9 (11.5)	Excluded: chronic respiratory disease, renal dysfunction	0.4*
		Oseltamivir 75 mg (BID, for 5 days)	336	Range: 20–77 Mean (SD): 34.7 (11.3)		
Oseltamivir						
Nicholson, 2000	ILI	Oseltamivir 75 mg (BID, for 5 days)	158	Range: 18–65	Excluded: chronic illness or known HIV-1 infection, receiving steroids or immunosuppressants	0
		Placebo	161			
Treanor, 2000	ILI	Oseltamivir 75 mg (BID, for 5 days)	124	Range: 18–65	Excluded: chronic illness or HIV disease; receiving systemic steroids immunosuppressants	0
		Placebo	129			
Li Longyun, 2003	ILI	Oseltamivir 75 mg (BID, for 5 days)	134	Range: 18–65	Excluded: taking steroids or immune-suppressant therapies	0
		Placebo	139			
McBride, 2017[#]	CI	Oseltamivir 75 mg (BID, for 5 days)	8	Range: 20–43	HR excluded	0
		Placebo	32	Range: 20–43		
NCT02469298[#]	CI	Oseltamivir 75 mg (BID, for 5 days) + Placebo	7	Range: 18–64	HR excluded	0
		Placebo	7			
Kashiwagi 2000	ILI	Oseltamivir 75 mg (BID, for 5 days)	122	Range 16–69 ($n = 118$) Range: 70–89 ($n = 4$) Mean (SD): 35.5 (14.6)	Excluded: patients with transplantation, treated with steroids, immunosuppressants	1.5*
		Placebo	130	Range: 16–69 ($n = 127$) Range: 70–89 ($n = 3$) Mean (SD): 33.6 (13.9)		
Peramivir						
Kohno, 2010	CI	Peramivir 300 mg (single administration)	99	Range: 20–64	Excluded: respiratory dysfunction or chronic respiratory disorders, active clinically important chronic illness or known infection with HIV, renal impairment requiring, treatment with steroids or other immunosuppressants, allergy	0
		Peramivir 600 mg (single administration)	97			
		Placebo	100			
Kohno, 2011	CI	Peramivir 300 mg (single administration)	364	Range: 20–78 Mean (SD): 34.9 (11.7)	Excluded: impaired respiratory function, congestive cardiac failure, poorly controlled diabetes mellitus, immunosuppressive therapy, AIDS, renal disorder, ischemic heart disease or serious arrhythmia	0.6*
		Peramivir 600 mg (single administration)	362	Range: 20–78 Mean (SD): 35.9 (12.0)		
		Oseltamivir 75 mg (BID, for 5 days)	365	Range: 20–80 Mean (SD): 34.6 (11.7)		
NCT00419263, 2007	CI	Peramivir 300 mg (single administration)	115	Range 18–57 ($n = 106$) $\geq$ 58 ($n = 9$) Mean (SD): 36.2 (13.25)	Excluded: COPD, severe persistent asthma, chronic renal impairment, CHF, immunocompromised status due to illness or previous organ transplant, acute respiratory/	1.5*
		Placebo	114			

(*continued*)

Table 3. Continued.

Author, year	Diagnosis	Intervention/Comparator	Sample size	Age (years)	Comorbidities (%)	Assumed HR patients (%)
				Range 18–57 ($n = 106$) ≥ 58 ($n = 8$) Mean (SD): 33.9 (12.05)	cardiac disease, history of hepatitis B, hepatitis C, or HIV infection	
Zanamivir Puhakka, 2003	ILI	Zanamivir 10 mg (BID, for 5 days)	222	Range: 17–27	Chronic respiratory disease: 2% (ITT)	2
		Placebo	213	Range: 18–29		
Duval, 2010	CI	Zanamivir 10 mg (BID, for 5 days) + Placebo	173	Range: 18–84.2 Mean (SD): 39.9 (13.8)	Excluded: COPD, asthma or severe chronic disease	3*
		Oseltamivir 75 mg (BID, for 5 days) + Placebo	176	Range: 18.1–76.3 Mean (SD): 39.5 (13.1)		

*calculated from mean age; #studies which were not included in previous NMAs.
Abbreviations. BID, twice a day; CHF, chronic heart failure; CI, confirmed; COPD, chronic obstructive pulmonary disease; HR, high risk; ILI, influenza-like illness; ITT, intention to treat; NMA, network meta-analysis; OwH, otherwise healthy; QD, once daily; SD, standard deviation.

Statistical analysis

The CAPSTONE-2 trial was designed to compare between baloxavir and the placebo or oseltamivir regarding the time to the improvement of influenza symptoms as the primary endpoint, while the time to alleviation of all symptoms (TTAS) was assessed as the secondary efficacy measure. Since all identified trials for comparators assessed only TTAS, it was chosen as the primary efficacy outcome of this analysis. A sensitivity analysis was also carried out, in which the primary outcome from the CAPSTONE-2 trial was pooled together with TTAS reported in the remaining trials.

Network meta-analysis (NMA) was performed to compare baloxavir with antivirals [oseltamivir 75 mg twice a day (BID) for 5 days, zanamivir 10 mg BID for 5 days, laninamivir 40 mg single administration, peramivir 600 mg single or repeated administration] and the placebo in terms of efficacy and safety in HR patients.

The analyses were conducted in Bayesian framework, using the Markov Chain Monte Carlo (MCMC) method, as outlined by the National Institute for Health and Care Excellence Decision Support Unit (NICE DSU) guidelines[16]. The analyses of efficacy outcomes were conducted in the influenza-infected population and the analyses of safety outcomes were conducted in the total population. For continuous outcomes, the mean change from the baseline for each treatment and associated standard errors (SE) were used as inputs. For binary outcomes, the number of patients experiencing the outcomes and the total numbers of patients by study arm were used. For time to event outcomes, the analysis was conducted assuming that the survival function for time to recovery outcomes followed an exponential distribution, the input of the analysis was the logarithm of the hazard rate [log(λ)] and associated SE.

Vague prior distributions were used for the model parameters. The between-treatment differences regarding estimates of virus titer and time to event endpoints were considered statistically significant when the associated 95% credibility intervals (CrI) did not include zero. An odds ratio was considered statistically significant if the associated 95% CrI did not include 1. All data regarding time to alleviation of symptoms and time to resolution of fever were converted to hours for the analysis.

Fixed-effects (FE) and random-effects (RE) models were fitted for the NMA. The final model was selected based on the deviance information criterion (DICs). The RE model was chosen if DIC was reduced by >5 compared to the FE model[17].

Analyses were conducted using R 3.5.0 statistical software and WinBUGS 1.4.3.

Results

SLR results

The SLR yielded a total of 2342 references, of which 365 were duplicates, and the remaining 1977 were included in the title and abstract screening. Of those, 1743 records were excluded based on pre-defined selection criteria and 234 were considered for full-text analysis. Finally, 90 records

Table 4. List of studies included in the analysis – uncomplicated population.

Author, year	Diagnosis	Intervention/Comparator	Sample size	Age (years)	Comorbidities (%)	Assumed HR patients (%)
Laninamivir						
PMDA Laninamivir Report 7 (10/09/2010)	NR	Laninamivir: 40 mg (single administration)	519	NR	NR	14**
		Oseltamivir 150 mg + Placebo	575			
Ikematsu, 2011	CI	Laninamivir: 40 mg (single administration)	100	NR	NR	14**
		Zanamivir 10 mg (BID, for 5 days)	88			
Yoshino, 2016[#]	CI	Laninamivir: 40 mg (single administration)	12	Mean (SD): 36.2 (10.0)	Diabetes (8.3%); chronic renal failure (8.3%); bronchial asthma (8.3%)	
		Peramivir 300 mg (single administration)	13	Mean (SD): 43.6 (15.3)	Diabetes (15.4%); chronic renal failure (15.4%); other respiratory diseases (7.7%)	
		Oseltamivir 75 mg (BID, for 5 days)	9	Mean (SD): 40.4 (9.84)	Immunosuppressive diseases (11.1%)	
Oseltamivir						
EMA oseltamivir	CI	Oseltamivir 150 mg	724	>13 years	NR	14**
		Placebo	716			
Peramivir						
NCT00705406, 2008[#]	CI	Peramivir 600 mg (single administration)	202	Mean (SD): 35 (12.1)	NR	
		Placebo	203	Mean (SD): 35 (11.3)		
Zanamivir						
Boivin, 2000	ILI	Zanamivir 10 mg (BID, for 5 days)	17	≥ 12 years	HR 6%	11
		Placebo	10	≥ 12 years	HR 20%	
Makela, 2000	ILI	Zanamivir 10 mg (BID, for 5 days)	136	Range: 12-81	HR 9%	11
		Placebo	141	Mean: 37.2	HR 13%	
Hayden, 1997-1	ILI	Zanamivir 10 mg (BID, for 5 days)	85	≥ 13 years Mean (SD): 31 (11)	NR	14*
		Placebo	89	≥ 13 years Mean (SD): 33 (12)		
Matsumoto, 1999	ILI	Zanamivir 10 mg (BID, for 5 days)	22	Range: 16-65	NR	14*
		Placebo	29			
Monto, 1999	ILI	Zanamivir 10 mg (BID, for 5 days)	419	≥ 13 years	HR 11%	14
		Placebo	422		HR 16%	
PMDA Zanamivir	CI	Zanamivir 20 mg	412	NR	NR	14**
		Placebo	365			
Campion, 1998	ILI	Zanamivir 10 mg (BID, for 5 days)	161	≥ 12 years Mean (SD): 35.7 (13.4)	HR 15%	16
		Placebo	160	≥ 12 years Mean (SD): 37.7 (13.5)	HR 18%	

**weighted average based on studies which report the percentage of patients with high risk; [#]studies which were not included in previous NMAs.

Abbreviations. BID, twice a day; CI, confirmed; European Medicines Agency; HR, high risk; ILI, influenza-like illness; NMA, network meta-analysis; NR, nor reported; PMDA, Pharmaceuticals and Medical Devices Agency; QD, once daily; SD, standard deviation.

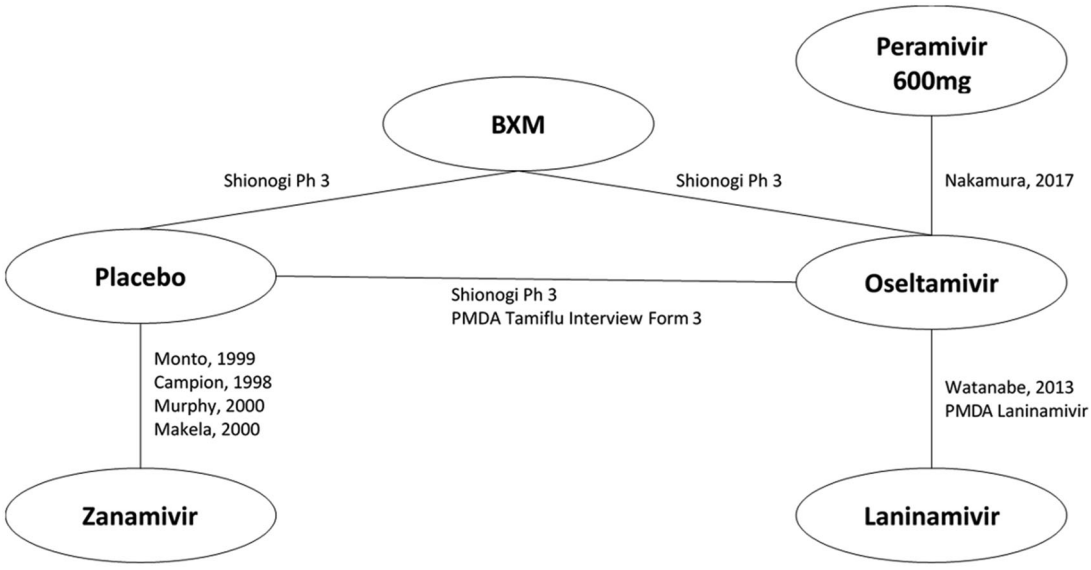

Figure 2. Network of evidence – HR population. Abbreviations. BXM, Baloxavir; HR, high risk; PMDA, Pharmaceuticals and Medical Devices Agency.

related to 69 studies were identified, of which 32 studies (36 records) reported data pertinent for the NMA, including:

- 5 studies (7 records) recruiting HR patients only;
- 14 studies (14 records) recruiting a general uncomplicated population (HR + OwH);
- 13 studies (15 records) studies recruiting OwH only population.

The study selection process is presented in Figure 1. An overview of the studies included in the analysis is reported in Table 2 (HR population), Table 3 (OwH population) and Table 4 (uncomplicated population).

NMA results

The network of evidence for the HR population is reported in Figure 2, and a summary of available evidence for each outcome of interest is provided in Table 5. The network of evidence for the entire evidence set (HR + OwH) is presented in Figure 3, and a summary of the available evidence is provided in Table 6.

Efficacy outcomes

Time to alleviation of symptoms (TTAS). There were 6 studies (6 treatments; 1931patients) included in the analysis of the median TTAS in HR population.

A fixed-effect model NMA revealed that baloxavir was associated with a significantly shorter TTAS compared with the placebo [difference in median of 33.17 h (13.67; 63.44)]. The effect of baloxavir did not differ significantly from zanamivir 20 mg [difference in median of 2.75 h (−21.39; 29.36)], laninamivir [difference in median of 21.62 h (−11.85; 71.75)], oseltamivir [difference in median of 11.14 h (−3.40; 30.90)] and peramivir 600 mg [difference in median of 11.17 h (−31.91; 71.82)] (Figure 4; Table 7).

A total of 23 RCTs (8265 patients) were included in the analysis pooling all evidence regardless of underlying risk, of which 7 studies were conducted on HR patients, 7 on OwH patients and the remaining 9 on a mixed population of OwH and HR patients.

The results of the FE model NMA pooling all available evidence were consistent with the outcomes of the NMA, including HR patients, except that baloxavir was associated with significantly shortened TTAS compared with zanamivir 20 mg [19.04 h (5.78, 39,71)] (Figure 4; Tables 8 and 9).

Time to resolution of fever (TTRF). There were 3 studies (5 treatments; 1438 patients) included in the analysis of the median TTRF in HR population.

An FE model NMA revealed that baloxavir was associated with a significantly lower TTRF compared to the placebo [difference in median of 21.18 h (13.77; 30.25)]. The effect of baloxavir did not differ significantly from laninamivir [difference in median of 8.49 h (−2.96; 22.25)], oseltamivir [difference in median of 3.63 h (−1.24; 8.31)]) and peramivir 600 mg [difference in median of 6.55 h (−8.34; 26.36)] (Figure 5; Table 7).

There were 16 studies (7 treatments; 5931 patients) included in the pooled analysis of all RCTs for the median TTRF, among which 4 studies were conducted on HR patients, 5 on OwH patients and remaining 7 trials on a mixed population of HR and OwH patients (Figure 5).

The results of the RE model NMA pooling all available evidence were consistent with the outcomes of the NMA, including HR patients (Figure 5; Tables 8 and 9).

Time to improvement of influenza symptoms. There were 6 studies (6 treatments; 1931 patients) included in the analysis of the median time to the improvement of influenza symptoms in the HR population. In the CAPSTONE-2 study, the endpoint was defined as time to the improvement of influenza symptoms, while in the remaining trials, TTAS of influenza was reported.

Table 5. Summary of evidence for efficacy and safety outcome measures – high-risk population.

Outcome	Number of studies included	Number of treatments included	Number of patients included	References
Efficacy				
Time to alleviation of all symptoms	6	6	1,931	Campion 1998, Shionogi Ph 3 (HR), Nakamura 2017, Watanabe 2013, Monto 1999, Murphy 2000
Time to resolution of fever	3	5	1,438	Shionogi Ph 3 (HR), Nakamura 2017, Watanabe 2013
Time to improvement of influenza symptoms	6	6	1,931	Campion 1998, Shionogi Ph 3 (HR), Nakamura 2017, Watanabe 2013, Monto 1999, Murphy 2000
Change in virus titer from baseline at 24 h after treatment	2	4	1,115	Shionogi Ph 3 (HR), Nakamura 2017
Change in virus titer from baseline at 48 h after treatment	2	4	1,208	Shionogi Ph 3 (HR), Watanabe, 2013
Total complications	4	6	1,486	Shionogi Ph 3 (HR), Nakamura 2017, Watanabe 2013, Makela 2000
Pneumonia	3	4	1,539	Shionogi Ph 3 (HR), Nakamura 2017, PDMA Tamiflu Interview Form 3
Bronchitis	3	5	1,456	Shionogi Ph 3 (HR), Nakamura 2017, Watanabe 2013
Safety				
Total adverse events	4	5	2,870	Campion 1998, Shionogi Ph 3 (HR), Murphy 2000, Nakamura 2017
Drug-related adverse events	4	6	2,820	Shionogi Ph 3 (HR), Murphy 2000, Nakamura 2017, PDMA Laninamivir [Report (10/09/2010) 9]

Abbreviations. HR, high risk.

An FE model NMA revealed no significant differences between baloxavir and any other treatments. Baloxavir was found significantly more effective only when compared to the placebo, with a difference of median time to improvement equal to 37.57 h (16.59; 70.53). The analysis of the entire evidence set (HR + OwH) was not feasible due to the lack of data for the OwH population (Table 7).

Time to cessation of viral shedding. The analysis of this outcome on the HR population was not feasible due to the lack of evidence for this population.

Change in virus titer from baseline at 24 h after treatment. There were 2 studies (4 treatments; 1115 patients) included in the analysis of change in virus titer from the baseline at 24 h after treatment in the HR population.

An FE model NMA revealed that baloxavir showed a significantly greater change in virus titer from the baseline at 24 h after treatment when compared with all treatments: oseltamivir [difference in mean of 1.60 (1.27; 1.93) $\log_{10}$TCID50/mL], peramivir 600 mg [difference in mean of 1.46 (0.65; 2.26) $\log_{10}$TCID50/mL) and the placebo [difference in mean of 2.11 (1.77; 2.45) $\log_{10}$TCID50/mL] (Figure 6; Table 7).

There were 11 studies (6 treatments; 4755 patients) included in the pooled analysis of all RCTs for the change in virus titer from the baseline at 24 h after treatment, among which 2 studies were conducted on HR patients, 5 on OwH patients and remaining 4 on a mixed population of HR and OwH patients.

The results of the RE model NMA pooling all available evidence were consistent with the outcomes of the NMA, including HR patients (Figure 6; Tables 8 and 9).

Change in virus titer from the baseline at 48 h after treatment. There were 2 studies (4 treatments; 1208 patients) included in the analysis of change in virus titer from the baseline at 48 h after treatment in the HR population.

An FE model NMA revealed that the effect of baloxavir in a change in virus titer from the baseline at 48 h after treatment was significantly better compared to all other treatments: oseltamivir [difference in mean of 0.66 (0.31; 1.02) $\log_{10}$TCID50/mL], laninamivir [difference in mean 0.91 (0.14; 1.68) $\log_{10}$TCID50/mL] and the placebo [difference in mean of 0.93 (0.57; 1.29) $\log_{10}$TCID50/mL] (Figure 7; Table 7).

There were 13 studies (7 treatments; 4,974 patients) included in the pooled analysis of all RCTs for the change in virus titer from the baseline at 48 h after treatment, among which, 3 studies were conducted on HR patients, 3 on OwH patients and remaining 7 trials on a mixed population consisted of HR and OwH patients.

The results of RE model NMA pooling all available evidence were consistent with the outcomes of the NMA, including HR patients, except that baloxavir did not differ significantly from laninamivir [0.94 (−0.34; 2.25)] (Figure 7; Tables 8 and 9).

Total complications. There were 4 studies (6 treatments; 1486 patients) which reported the number of patients with complications.

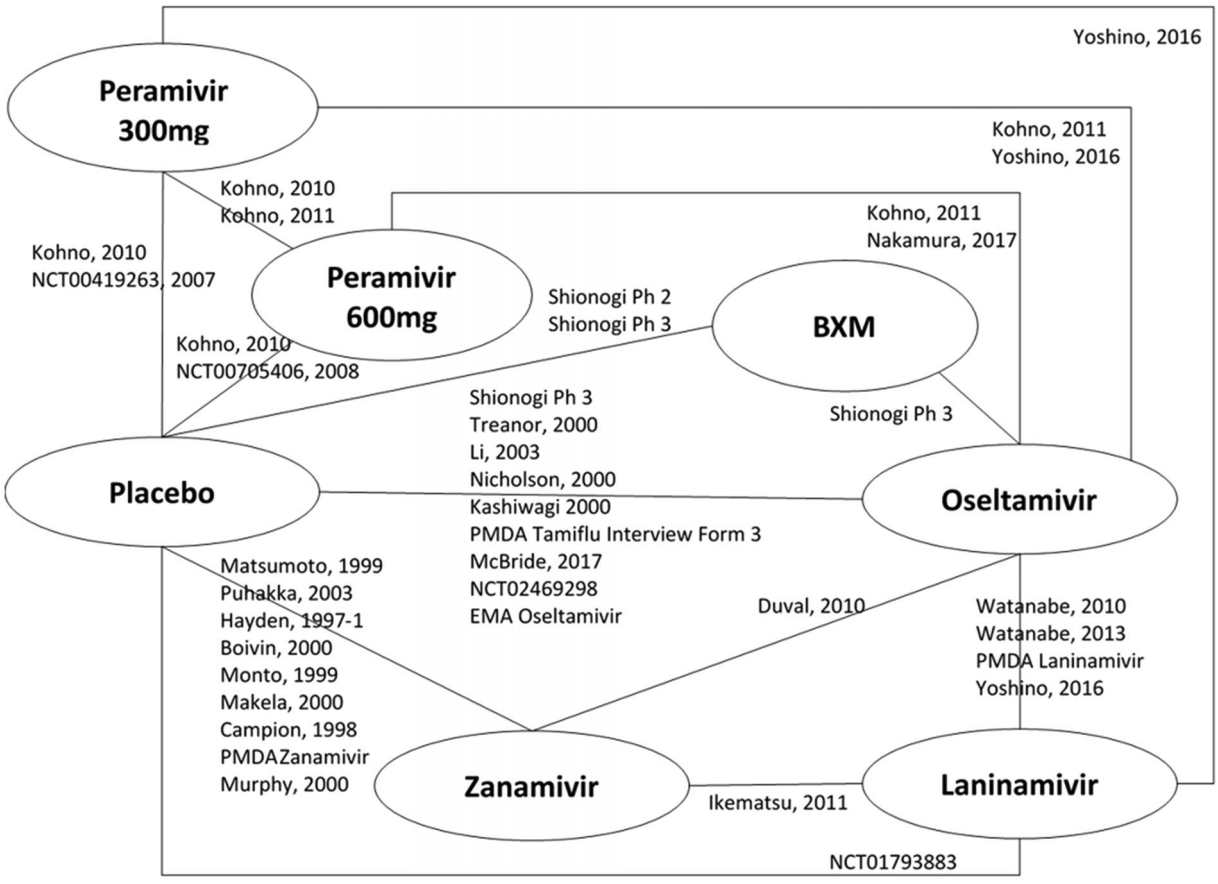

Figure 3. Network of evidence – entire evidence set (HR + OwH). Abbreviations. BXM, Baloxavir; HR, high risk; OwH, otherwise healthy.

An FE model NMA revealed that in terms of the risk of total complications, baloxavir did not differ significantly from zanamivir [odds ratio in median of 1.20 (0.20; 6.59)], oseltamivir [odds ratio in median of 1.68 (0.79; 3.72)], peramivir [odds ratio in median of 1.03 (0.20; 4.94)] and laninamivir [odds ratio in median of 1.41 (0.35; 5.74)]. A significant difference was recorded when baloxavir was compared with the placebo [odds ratio in the median of 4.04 (2.10; 8.41)] (Table 7).

The analysis of the entire evidence set (HR + OwH) was not feasible due to the lack of evidence for the OwH population.

Incidence of pneumonia. There were 4 studies (5 treatments; 1740 patients) that reported the number of patients with pneumonia in the HR population. However, one study (Watanabe 2013) was excluded from the analysis due to the lack of events in both study arms. As a result, 3 studies (4 treatments; 1539 patients) were included in the NMA.

An FE model revealed no significant differences between baloxavir and oseltamivir [odds ratio in median of 9.56 (0.62; 4275.03)], peramivir [odds ratio in median of 4.15 (0.05; 2625.25)] and the placebo [odds ratio in median of 14.20 (0.99; 6170.20)] in incidence of pneumonia. Since the number of events was very low in all treatments arms, NMA results were associated with a high credible interval and subjected to instability (Figure 8; Table 7).

There were 10 studies (6 treatments; 4409 patients) included in the pooled analysis of all RCTs for the risk of pneumonia, among which 4 studies were conducted on HR patients, 3 on OwH patients and remaining 3 studies on a mixed population consisted of HR and OwH patients.

The results of the FE model NMA pooling all available evidence were consistent with the outcomes of the NMA including HR patients (Figure 8; Tables 8 and 9).

Incidence of bronchitis. There were 3 studies (5 treatments; 1456 patients) reported the number of patients with bronchitis in the HR population.

An FE model NMA revealed no significant differences between baloxavir and oseltamivir [odds ratio in the median of 1.31 (0.47; 3.76)], peramivir [odds ratio in the median of 0.25 (0.001; 8.65)]. A significant difference between baloxavir and the placebo was recorded [odds ratio in the median of 3.56 (1.57; 9.23)] (Table 7).

The analysis of the entire evidence set (HR + OwH) was not feasible due to the lack of evidence for the OwH population.

Safety outcomes

Adverse events (AEs). There were 4 studies (5 treatments; 2870 patients) that reported the number of patients with adverse events in the HR population.

An FE model NMA revealed that the risk of total adverse events (AE) for baloxavir was significantly lower than for the placebo [odds ratio in median of 1.26 (1.002; 1.59)], but did not differ significantly when baloxavir was compared with

Table 6. Summary of evidence for efficacy and safety outcome measures – entire evidence set (HR + OwH).

Outcome	Number of studies included	Number of treatments included	Number of patients included	References
Efficacy				
Time to alleviation of all symptoms	23	7	8,265	Campion, 1998; Shionogi Ph 3 (OwH, HR); Shionogi Ph 2; Nakamura, 2017; Watanabe, 2013; Monto, 1999; Murphy, 2000; Treanor, 2000; Kohno, 2011 (OwH, HR); Duval, 2010; Watanabe, 2010; Kohno, 2010; Li, 2004; Nicholson, 2000; Matsumoto, 1999; Hayden, 1997; NCT00419263, 2007; Kashiwagi, 2000; PDMA Zanamivir; NCT01793883; NCT00705406, 2008
Time to resolution of fever	16	7	5,931	Kohno, 2011 (OwH, HR); Watanabe, 2010; Li, 2004; Nicholson, 2000; NCT00419263, 2007; NCT00705406, 2008; Ikematsu, 2011; Kashiwagi, 2000; Shionogi Ph 2; Shionogi Ph 3 (OwH, HR); NCT02469298; Yoshino, 2016; Nakamura, 2017; Watanabe, 2013
Change in virus titer from baseline at 24 h after treatment	11	6	4,755	Treanor, 2000; Puhakka, 2003; Nicholson, 2000; Boivin, 2000; NCT00419263, 2007; Shionogi Ph 3 (OwH, HR); Shionogi Ph 2; Kohno, 2010; Kohno, 2011; Nakamura, 2017
Change in virus titer from baseline at 48 h after treatment	13	7	4,974	Duval, 2010; Puhakka, 2003; Boivin, 2000; NCT00419263, 2007; Shionogi Ph 3 (OwH, HR); Shionogi Ph 2; Kohno, 2010; Kohno, 2011 (OwH, HR); Kashiwagi, 2000; NCT00705406, 2008; Watanabe, 2013
Pneumonia	10	6	4,409	Treanor, 2000; Duval, 2010; Nicholson, 2000; NCT00705406, 2008; Shionogi Ph 3 (OwH, HR); PDMA Peramivir; Nakamura, 2017; PDMA Tamiflu; Kohno (HR), 2011; NCT02469298
Safety				
Total adverse events	18	7	9,806	Kohno, 2010; Kohno, 2011 (OwH, HR); Puhakka, 2003; Makela, 2000; Monto, 1999; Campion, 1998; NCT00705406, 2008;Kashiwagi, 2000; Shionogi Ph 2; Shionogi Ph 3 (OwH, HR); PDMA Laninamivir 10/09/2010 (Report 6); McBride, 2017; NCT02469298; NCT01793883; Murphy, 2000; Nakamura, 2017
Drug-related adverse events	13	7	7,754	Kohno, 2011 (OwH, HR); Li, 2003; Monto, 1999; Matsumoto, 1999; Hayden, 1997; Shionogi Ph 2; Shionogi Ph 3 (OwH, HR); PDMA Laninamivir [10/09/2010 (Report 6, Report 9)]; Murphy, 2000; Nakamura, 2017

Abbreviations. HR, high risk; OwH, otherwise healthy.

Table 7. Results summary in HR population – Efficacy and safety outcomes versus baloxavir.

Treatment	Model	Efficacy outcomes								Safety outcomes	
		Time to alleviation of all symptoms (median time difference, [95% CI])	Time to resolution of fever (median time difference, [95% CI])	Time to improvement of influenza symptoms (median time difference)	Change in virus titer from the baseline at 24h after treatment (mean difference, [95% CI])	Change in virus titer from the baseline at 48h after treatment (mean difference, [95% CI])	Total complications (OR [95% CI])	Pneumonia (OR [95% CI])	Bronchitis (OR [95% CI])	Adverse events (OR, [95% CI])	Drug-related adverse events (OR, [95% CI])
Placebo	NMA	**33.17 [13.67; 63.44]**	**21.18 [13.77; 30.25]**	**37.57 [16.59; 70.53]**	**2.11 [1.77; 2.45]**	**0.93 [0.57; 1.29]**	**4.04 [2.10; 8.41]**	14.20 [0.99; 6170.20]	**3.56 [1.57; 9.23]**	**1.26 [1.002; 1.59]**	**1.52 [1.002; 2.30]**
Zanamivir 20 mg	NMA	2.75 [−21.39; 29.36]	–	7.21 [−15.70; 34.80]	–	–	1.20 [0.20; 6.59]	–	–	0.98 [0.66; 1.46]	1.53 [0.74; 3.22]
Laninamivir 40 mg	NMA	21.62 [−11.85; 71.75]	8.49 [−2.96; 22.25]	20.08 [−11.75; 67.63]	–	**0.91 [0.14; 1.68]**	1.41 [0.35; 5.74]	–	1.01 [0.17; 5.90]	–	5.20 [0.51; 170.90]
Oseltamivir 150 mg	NMA	11.14 [−3.40; 30.90]	3.63 [−1.24; 8.31]	10.14 [−3.69; 28.80]	**1.60 [1.27; 1.93]**	**0.66 [0.31; 1.02]**	1.68 [0.79; 3.72]	9.56 [0.62; 4275.03]	1.31 [0.47; 3.76]	1.16 [0.92; 1.47]	1.45 [0.96; 2.21]
Peramivir 600 mg	NMA	11.17 [−31.91; 71.82]	6.55 [−8.34; 26.36]	10.16 [−30.86; 67.70]	**1.46 [0.65; 2.26]**	–	1.03 [0.20; 4.94]	4.15 [0.05; 2625.25]	0.25 [0.001; 8.65]	0.34 [0.10; 1.06]	0.10 [0.0002; 1.69]

*Results in **bold** suggest statistical significance in favor of baloxavir.
Abbreviations. CI, credibility intervals; NMA, network meta-analysis; OR, odd ratio.

Table 8. Values of DIC for NMA on HR + OwH population.

Outcome	NMA	
	Fixed-effect DIC	Random-effect DIC
Time to alleviation of all symptoms	**−79.31**	−77.84
Time to resolution of fever	−24.66	**−40.25**
Change in virus titer from the baseline at 24 h after treatment	27.02	**1.45**
Change in virus titer from the baseline at 48 h after treatment	39.56	**11.31**
Pneumonia	**86.94**	88.24
Total adverse events	**270.60**	272.72
Drug-related adverse events	**182.25**	182.89

DIC value given **in bold** reflects the selected model.
Abbreviations. CrI, credibility intervals; DIC, deviance information criterion; HR, high risk; NMA, network meta-analysis.

Table 9. Results summary in HR + OwH population – Efficacy and safety outcomes versus baloxavir.

Treatment	Model	Efficacy outcomes					Safety outcomes	
		Time to alleviation of all symptoms (median time difference, [95% CI])	Time to resolution of fever (median time difference, [95% CI])	Change in virus titer from the baseline at 24h after treatment (mean difference, [95% CI])	Change in virus titer from the baseline at 48h after treatment (mean difference, [95% CI])	Pneumonia (OR [95% CI])	Adverse events (OR, [95% CI])	Drug-related adverse events (OR, [95% CI])
Placebo	NMA	**32.69 [16.37; 58.75]**	**19.61 [9.62; 32.77]**	**2.66 [2.10; 3.25]**	**1.40 [0.84; 1.99]**	2.27 [0.53; 13.93]	**1.24 [1.04; 1.48]**	1.36 [0.98; 1.89]
Zanamivir 20 mg	NMA	**19.04 [5.78; 39.71]**	6.64 [−13.01; 35.53]	**2.17 [1.15; 3.20]**	**1.00 [0.19; 1.84]**	0.31 [0.001; 15.52]	0.99 [0.78; 1.26]	1.25 [0.81; 1.93]
Laninamivir 40 mg	NMA	10.67 [−2.92; 29.41]	2.78 [−9.65; 17.04]	–	0.94 [−0.34; 2.25]	–	1.24 [0.88; 1.73]	**1.80 [1.05; 3.12]**
Oseltamivir 150 mg	NMA	6.21 [−1.73; 16.68]	1.64 [−6.79; 9.90]	**2.01 [1.41; 2.64]**	**0.69 [0.10; 1.30]**	1.68 [0.39; 10.64]	1.17 [0.98; 1.39]	**1.64 [1.20; 2.26]**
Peramivir 300 mg	NMA	6.70 [−5.73; 22.48]	1.13 [−10.05; 13.74]	**2.00 [1.22; 2.81]**	**1.00 [0.26; 1.82]**	4.12 [0.47; 49.24]	1.04 [0.76; 1.43]	1.04 [0.63; 1.70]
Peramivir 600 mg	NMA	6.21 [−5.67; 21.29]	3.06 [−8.25; 15.70]	**1.87 [1.07; 2.70]**	**1.01 [0.24; 1.79]**	3.25 [0.42; 31.72]	1.12 [0.84; 1.49]	1.40 [0.87; 2.26]

*Results in **bold** suggest statistical significance in favor of baloxavir.
Abbreviations. CI, credibility intervals; NMA, network meta-analysis; OR, odd ratio.

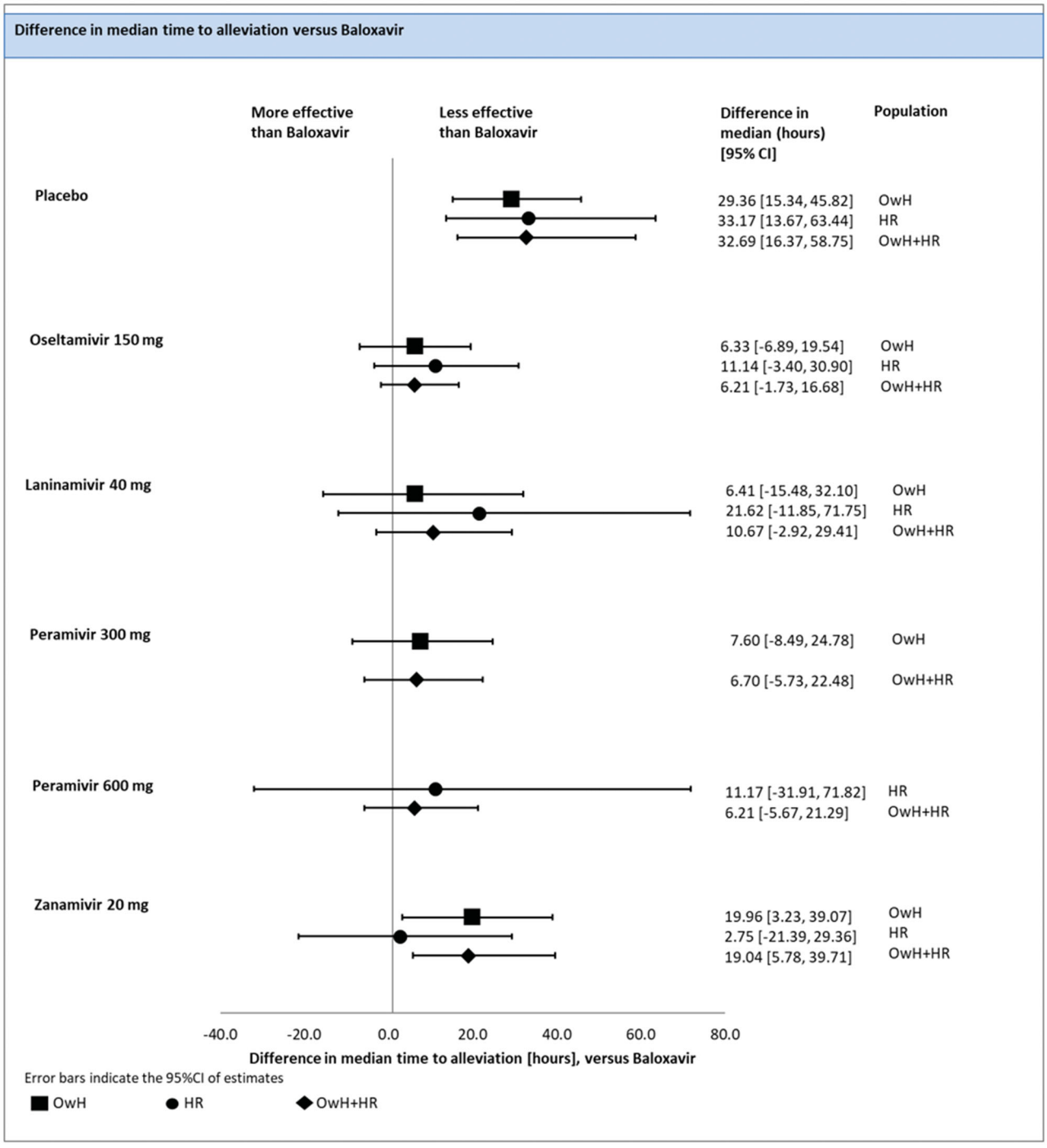

Figure 4. Time to alleviation of symptoms – NMAs on OwH/HR/OwH + HR. Abbreviations. CI, credibility interval; HR, high risk; NMA, network meta-analysis; OwH, otherwise healthy.

zanamivir [odds ratio in median of 0.98 (0.66; 1.46)], oseltamivir [odds ratio in median of 1.16 (0.92; 1.47)] and peramivir [odds ratio in median of 0.34 (0.10; 1.06)] (Figure 9; Table 7).

There were 18 studies (7 treatments; 9,806 patients) included in the pooled analysis of all RCTs for the risk of AEs, among which 4 studies were conducted on HR patients, 6 on OwH patients and remaining 8 trials on a mixed population consisted of HR and OwH patients.

The results of the FE model NMA pooling all available evidence were consistent with the outcomes of the NMA, including HR patients (Figure 9; Tables 8 and 9).

Drug-related adverse events (DRAEs). There were 4 studies (6 treatments; 2820 patients) reported the number of patients with drug-related adverse events in the HR population.

An FE model NMA revealed that the risk of DRAEs was significantly lower for baloxavir compared with the placebo [median odds ratio of 1.52 (1.002; 2.30)]. Baloxavir did not differ significantly from zanamivir [median odds ratio of 1.53 (0.74; 3.22)], peramivir [median odds ratio of 0.10 (0.0002; 1.69)] and laninamivir [median odds ratio of 5.20 (0.51; 170.90)] (Figure 10; Table 7).

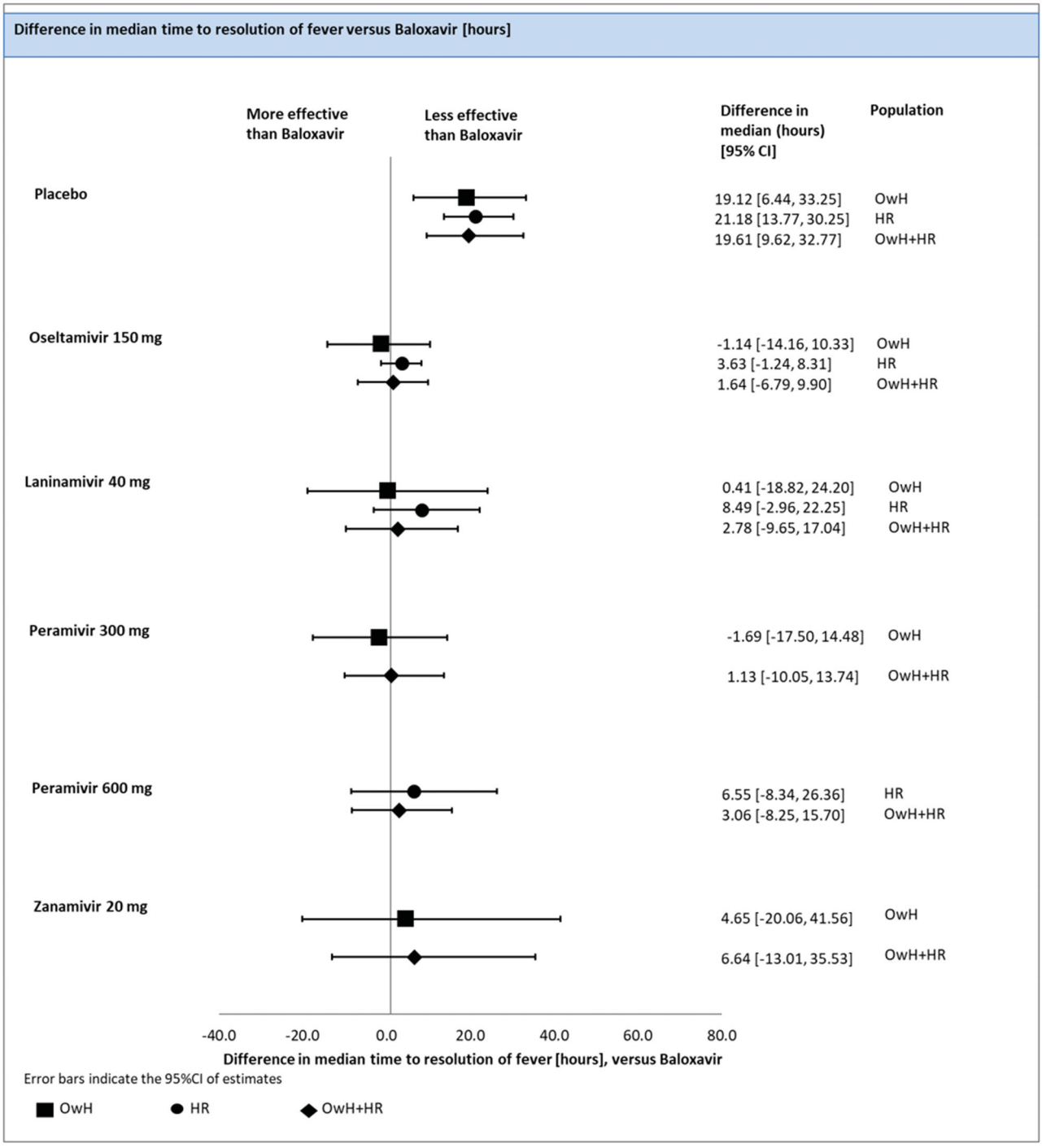

Figure 5. Time to resolution of fever – NMAs on OwH/HR/OwH + HR. Abbreviations. CI, credibility interval; HR, high risk; NMA, network meta-analysis; OwH, otherwise healthy.

There were 13 studies (7 treatments; 7,754 patients) included in the pooled analysis of all RCTs for the risk of DRAEs, among which 5 studies were conducted on HR patients, 3 on OwH patients and the remaining 5 on a mixed population that consisted of HR and OwH patients.

The results of FE model NMA pooling all available evidence were consistent with the outcomes of the NMA including HR patients, except that baloxavir was significantly better than oseltamivir [odds ratio in the median of 1.64 (1.20; 2.26)] and laninamivir [1.80 (1.05; 3.12)] (Figure 10; Tables 8 and 9).

Discussion

This study provides a comprehensive comparison of treatment outcomes between baloxavir and neuraminidase inhibitors in terms of safety conducted in patients with ILI and efficacy conducted in the influenza-infected population. In the primary analysis, the relative between-treatment differences were assessed in the subset of patients with the underlying high risk of complications. According to the up to date clinical practice guidelines, these patients should be treated with antivirals following diagnosis without any delays to prevent severe and life-threatening conditions.

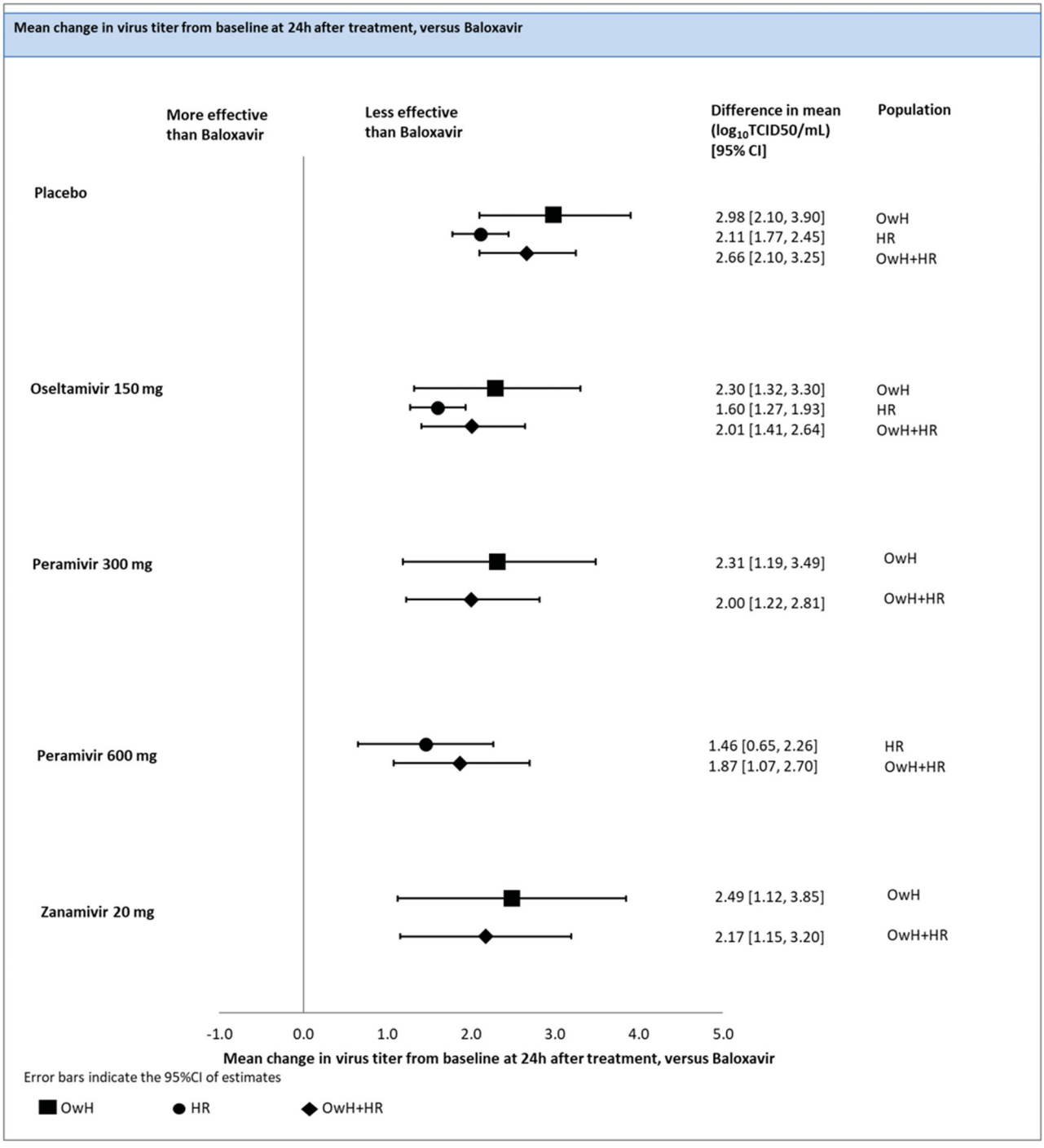

Figure 6. Change in virus titer from baseline at 24 h after treatment – NMAs on OwH/HR/OwH + HR. Abbreviations. CI, credibility interval; HR, high risk; NMA, network meta-analysis; OwH, otherwise healthy.Comparison with laninamivir 40 mg was infeasible due to lack of data on change in virus titer from baseline to 24 h.

The results of this NMA conducted among HR patients suggest that baloxavir was significantly more efficacious than the placebo for all efficacy outcomes, except pneumonia. Baloxavir was also associated with a significantly greater reduction of virus titer at 24 h since treatment initiation compared with oseltamivir 150 mg and peramivir 600 mg, and better reduction of viral titer at 48 h after treatment compared with oseltamivir 150 mg and laninamivir 40 mg. These results are consistent with previous findings reported in the NMA on OwH patients conducted by Taieb et al. showing that baloxavir was more effective than other antivirals regarding the reduction of viral titer within 24 h. Interestingly in the OwH population, baloxavir was more effective than zanamivir in the alleviation of influenza symptoms, which was not confirmed among the HR population[15].

A traditional NMA has also been conducted to pool all identified studies on uncomplicated population, including HR patients and OwH. The results of all conducted analyses (NMA on HR, NMA on the uncomplicated population) were highly consistent suggesting the superiority of baloxavir over

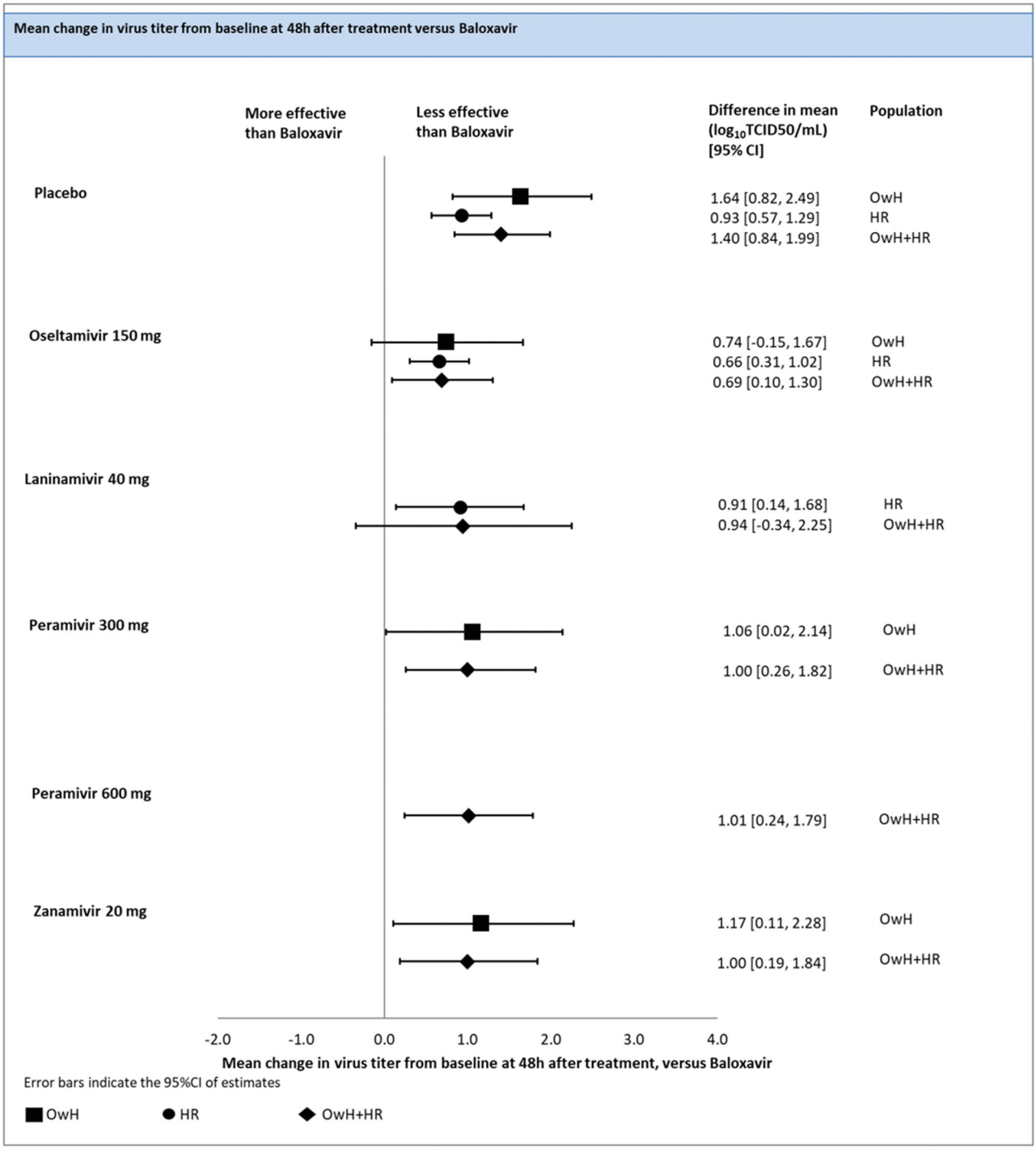

Figure 7. Change in virus titer from baseline at 48 h after treatment - NMAs on OwH/HR/OwH + HR. Abbreviations. CI, credibility interval; HR, high risk; NMA, network meta-analysis; OwH, otherwise healthy.

the placebo for all efficacy outcomes, except pneumonia. The analysis pooling all evidence regardless of underlying risk was consistent with the results presented by Taieb et al. showing that baloxavir was significantly better than zanamivir 20 mg for TTAS and significantly better than zanamivir 20 mg, oseltamivir 150 mg and both peramivir 300 mg and 600 mg in change in a virus titer from the baseline at 24 h and at 48 h after treatment[15]. Baloxavir was more efficacious in control of the virus load (change in virus titer from baseline at 24 h and 48 h after treatment) than all other comparators for which data were available, except laninamivir 40 mg in the change in virus titer from the baseline at 48 h after treatment. The safety profile of baloxavir was significantly better than the placebo regarding total AEs and significantly better than laninamivir 40 mg and oseltamivir 150 mg regarding DRAEs.

The emergence of drug-resistant strains of the influenza virus imposes a potential threat, in particular for

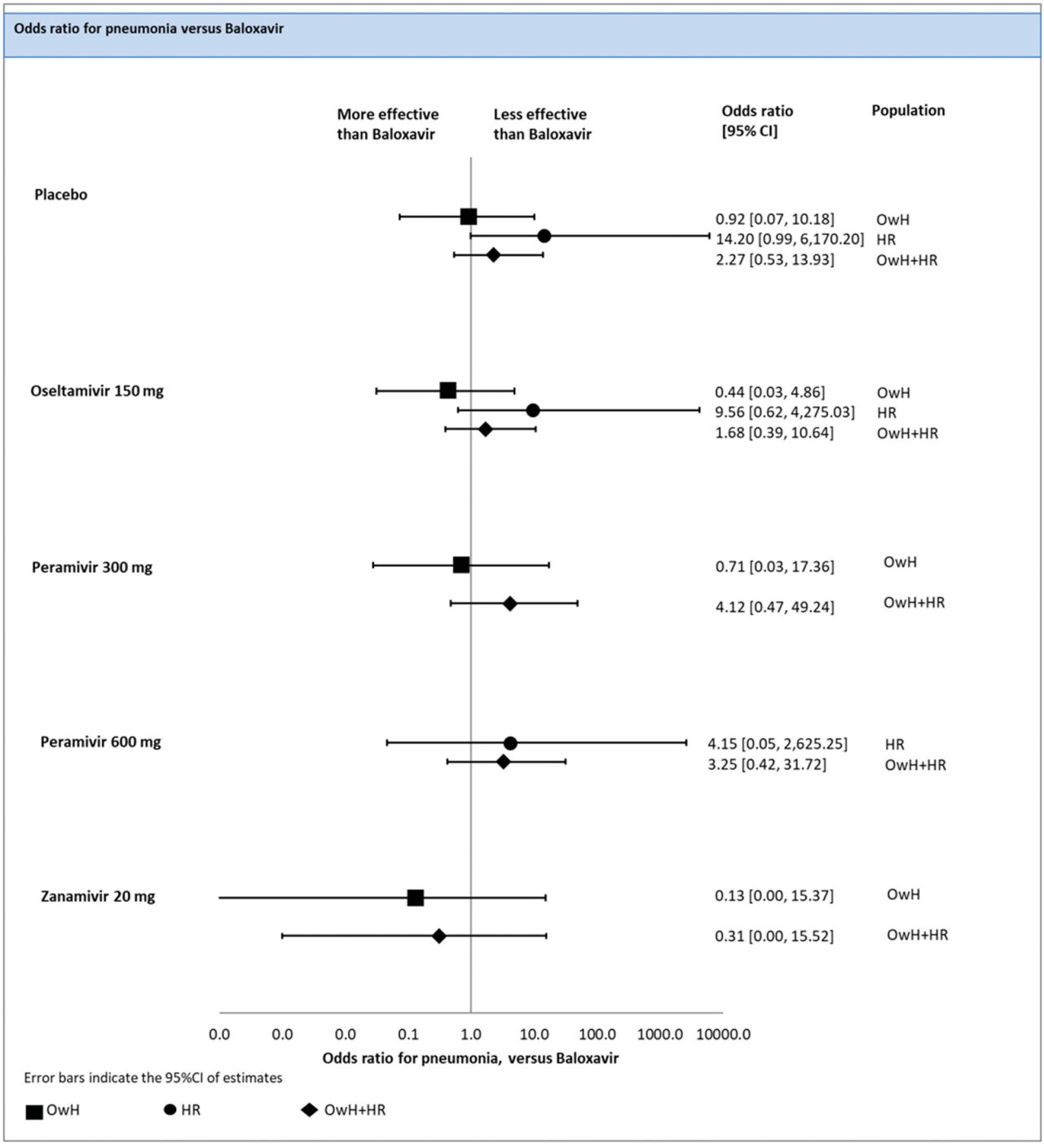

Figure 8. Incidence of pneumonia – NMAs on OwH/HR/OwH + HR. Abbreviations. CI, credibility interval; HR, high risk; NMA, network meta-analysis; OwH, otherwise healthy. Comparison with laninamivir 40 mg was infeasible due to lack of data on pneumonia. Zanamivir 20 mg was assessed in one trial (Duval, 2010) recruiting patients without respiratory complications, including recent exacerbations of chronic obstructive pulmonary disease, asthma or severe chronic disease. The proportion of HR patients was therefore estimated solely based on age distribution.

immunocompromised patients and other seriously ill subjects. Although, the overall resistance to neuraminidase inhibitors is considered as low with around 3.5 and 1% of circulating viruses resistant to oseltamivir and zanamivir, respectively[18]. The survey of susceptibility patterns conducted in the 2018–2019 season indicated that 1% of A(H1N1)pdm09 strains were resistant to both oseltamivir and peramivir but sensitive to zanamivir[5,19]. Baloxavir, with its high antiviral activity, serves a promising option in the treatment of patients with influenza., however human-to-human transmission was detected in 5 patients in the antiviral resistance surveillance in Japan in 2018/2019 and it needs to be continuously monitored through the surveillance[19]. Substitutions of the 38th amino acid position in polymerase

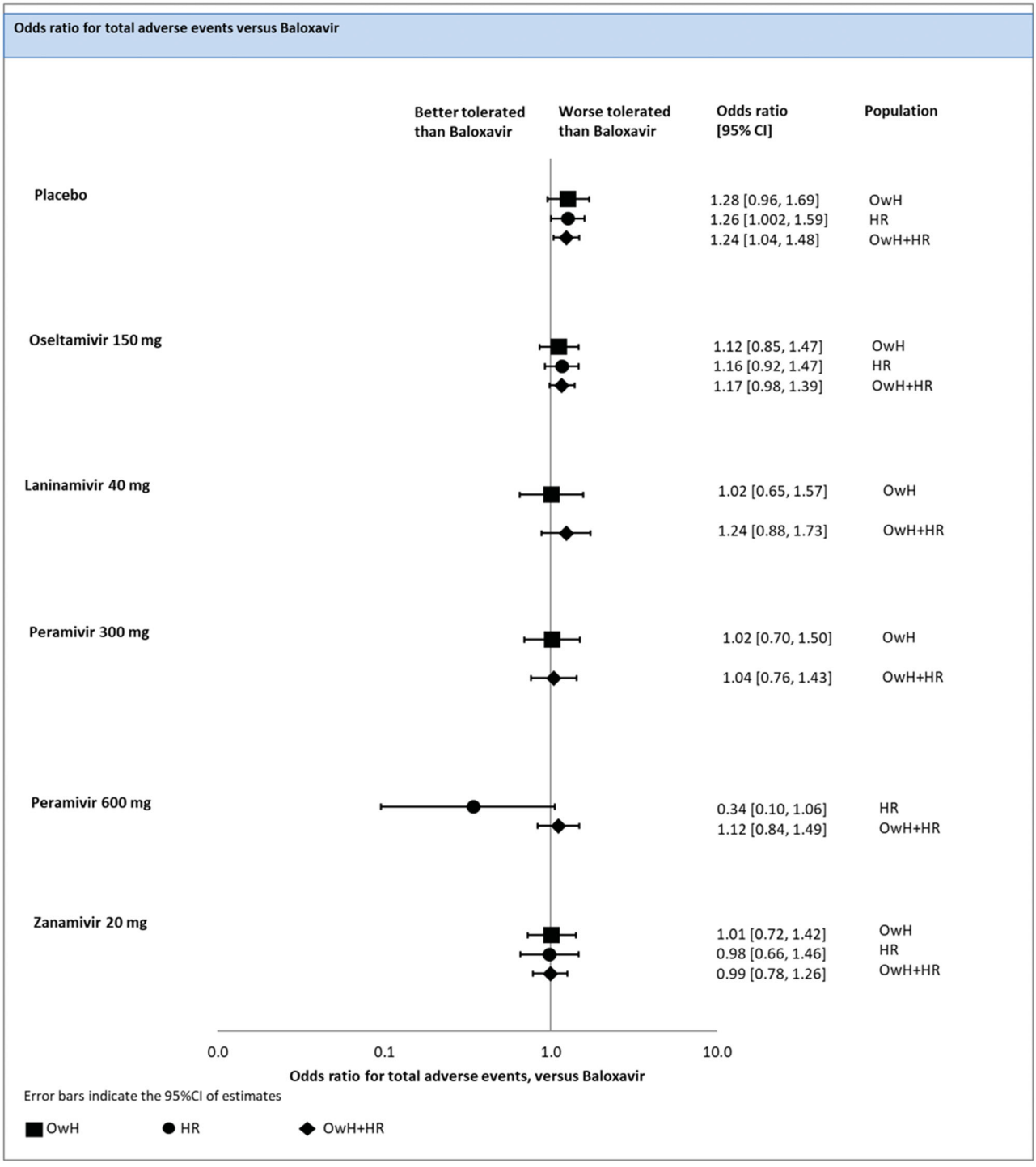

Figure 9. Total adverse events – NMAs on OwH/HR/OwH + HR. Abbreviations. CI, credibility interval; HR, high risk; NMA, network meta-analysis; OwH, otherwise healthy.

acidic protein conferring reduced baloxavir susceptibility emerged in 2.2 and 9.7% of patients in phase 2 and phase 3 of CAPSTONE-1 trial respectively, as well as in 5.2% of patients in phase 3 CAPSTONE-2 trial[13,14].

There are some potential limitations caused by considering studies that enrolled patients with a wide range of risk factors, as well as studies with single risk factors that may result in potential heterogeneity and inconsistency within the network of evidence in this analysis. The comparability of these populations was confirmed by the clinical expert. Another limiting factor is that the differences regarding the definition of the outcomes across the included studies cannot be excluded. Although the majority of studies assessed resolution of ILI symptoms, some papers did not specify which symptoms contributed to this endpoint. No evidence was collected that any of these differences would affect the

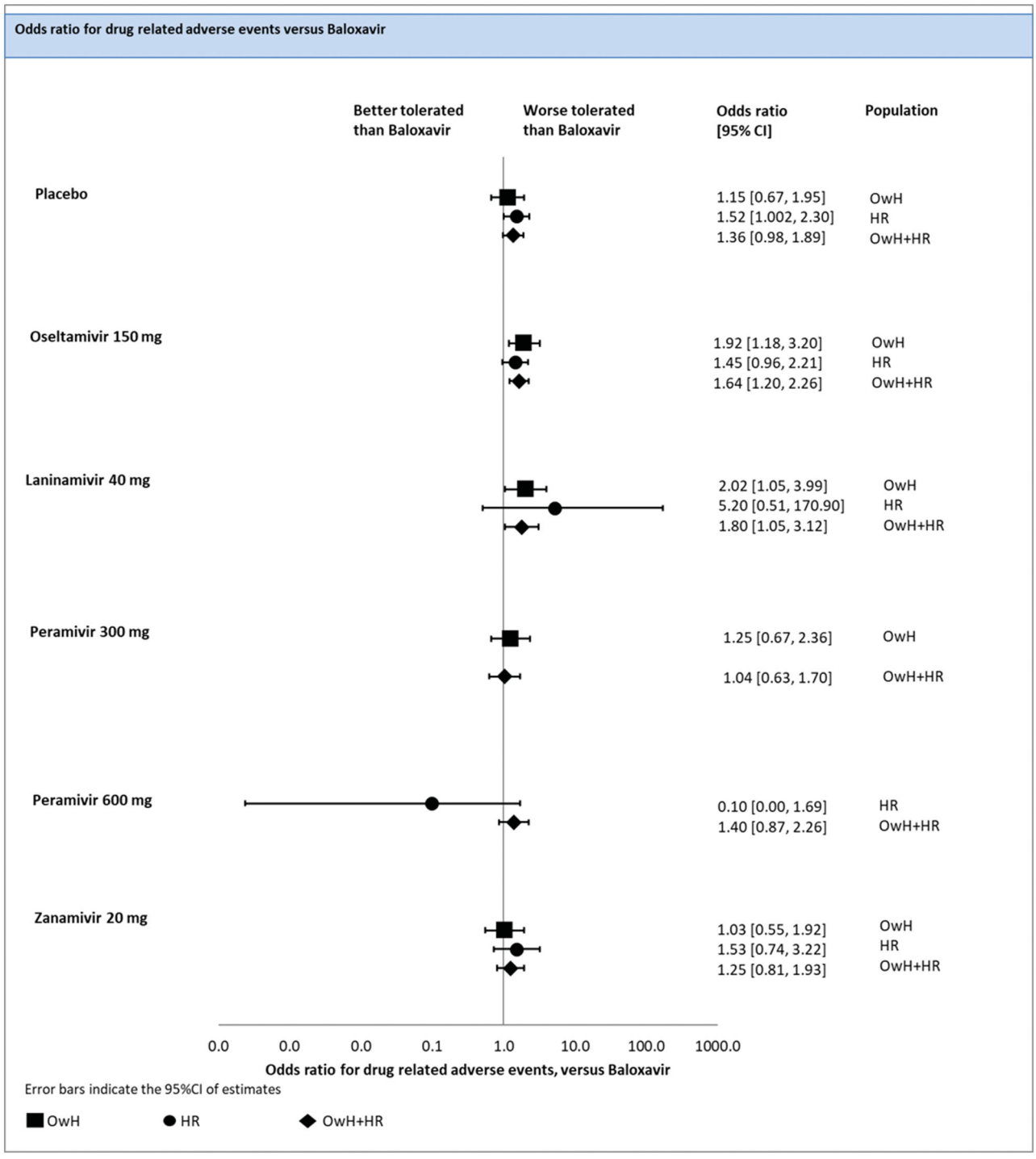

Figure 10. Drug-related adverse events – NMAs on OwH/HR/OwH + HR. Abbreviations. CI, credibility interval; HR, high risk; NMA, network meta-analysis; OwH, otherwise healthy.

relative treatment effect; therefore, the analysis was conducted despite heterogeneity in outcome definitions. The comparability between studies may be questioned due to the fact that the response to treatment could potentially vary between seasons and countries depending on circulating strains of the virus[20,21]. Finally, the pivotal studies assessing baloxavir were designed and powered to demonstrate clinical superiority versus placebo. Moreover, the number of eligible trials seems to be limited, given the complexity of the evidence networks. Therefore, this NMA is likely underpowered to demonstrate the difference between baloxavir and other antivirals regarding the time to alleviation of disease symptoms and other clinically relevant outcomes.

Transparency

Declaration of funding

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Declaration of financial/other relationships

VT, PW, KJ and SA report grant funding from Shionogi & Co., Ltd during the conduct of the study and outside of the submitted work. MH is an employee of Shionogi Limited. HI is an employee of Shionogi & Co., Ltd. NH reports personal fees and other from Shionogi & Co., Ltd., outside the submitted work.

Author contributions

Conception and design: HI, MH, VT, SA
Acquisition of data: VT, SA, PW, KJ
Analysis and interpretation of the data: HI, MH, VT, SA, PW, KJ, NH
Drafting of the manuscript: VT, SA, PW, KJ, HI, MH
Critical revision of the manuscript for important intellectual content: VT, SA, PW, KJ, HI, MH, NH
Obtaining funding: HI, MH

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