EMA/114965/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tamiflu

International non-proprietary name: oseltamivir

Procedure No. EMEA/H/C/000402/II/0142

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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ABBREVIATIONS

AE	Adverse event
ALL	Acute lymphoid leukaemia
AML	Acute myeloid leukaemia
AUC	Area under the concentration–time curve
AUC_{τ}	Area under the curve over dosing interval at steady state
AUC_{50}	Exposure at half-maximal inhibition
BID	Bis In Die (Twice A Day)
BLQ	Below the limit of quantification
BSA	Body surface area
BSV	Between-subject variability
CARIFS	Canadian acute respiratory infections scale
CDS	Core data sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Oseltamivir clearance (L/hr)
CL_M	Apparent oseltamivir carboxylate clearance (L/hr)
C_{max}	Maximum concentration at steady state
C_{min}	Minimum concentration at steady state
CRCL	Calculated creatinine clearance (mL/min)
CrCL	Creatinine clearance
CSR	Clinical Study Report
C_{trough}	Trough concentration at the end of the dosing interval
CPH	Cox proportional hazards
CULAUCVT	AUC of the viral titre for culture
CULPVT	Peak viral titre for culture
CV	Coefficient of variation
EOT	End of treatment
ER	Exposure-response
EU	European Union
FUM	Follow-up Measure
GCP	Good Clinical Practice
GvHD	Graft-versus-host disease
HA	Hemagglutinin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSCT	Haematopoietic stem cell transplant
I	Infected cells
IC	Immunocompromised

ICU	Intensive care unit
INH	Inhibition effect
IRIS	Influenza Resistance Information Study
ITT	Intent to treat
ITTi	Intent to treat influenza-infected patient population
IV	Intravenous
k_a	Absorption rate constant
k_{met}	Metabolism rate constant
LRTC	Lower respiratory tract complications
MAH	Marketing Authorization Holder
MD	Multiple dose
mITTi	Modified intent to treat infected
NA	Neuraminidase
OC	Oseltamivir carboxylate
OP	Oseltamivir (phosphate)
OR	Odds ratio
OwH	Otherwise healthy
PCR	Polymerase chain reaction
PCRPVT	Peak viral load for RT-PCR
PD	Pharmacodynamic
PDCO	Paediatric Committee
PE	Parameter Estimate
PI	Prediction interval
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PKEP	Pharmacokinetic evaluable patient
pNT	Rate of free virus production in the absence of drug inhibition
PSUR	Periodic Safety Update Report
Q	Inter-compartment clearance
RMP	Risk Management Plan
RSE	Relative standard error
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious adverse reactiion
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCR	Serum creatinine
SCS	Summary of Clinical Safety
SD	Standard deviation
SOT	Solid organ transplantation
SmPC	Summary of Product Characteristics
T	Target respiratory epithelial cells

TTR	Time to resolution
TTRAS	Time to resolution of all symptoms
TTRS	Time to resolution of symptoms
TTRF	Time to resolution of fever
TTCVS	Time to cessation of viral shedding
$TTCVS_{CUL}$	time to cessation of viral shedding by culture
$TTCVS_{PCR}$	Time to cessation of viral shedding by reverse-transcription polymerase chain reaction
US	United States
VK	Viral kinetics
vp/mL	Virus particles per millilitre

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 11 July 2019 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC following completion of the paediatric studies NV25719 and NV20234 and downstream population PK and PK/PD analysis, listed in the approved Tamiflu Paediatric Investigation Plan (PIP) (EMEA-000365-PIP01-08-M10).

The study NV25719 was a prospective, open-label, randomized study, which investigated PK and PD of two weight adjusted oseltamivir doses for the treatment of influenza-infected immunocompromised (IC) children less than 13 years of age. The study NV20234 was a prospective, double blind, randomized trial, which investigated safety and viral resistance to oseltamivir treatment in influenza-infected IC adults, adolescents and children.

The purpose of this variation is to establish a dose recommendation for the treatment of paediatric IC patients.

The Package Leaflet is updated accordingly.

The updated RMP version 19 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

In the present type II variation the MAH proposes a dosage recommendation of Tamiflu for immunocompromised (IC) children with influenza. SmPC, PL and labelling is proposed to be updated.

The currently approved SmPC does not preclude use in IC subjects in any age group, but there is no recommended dose for IC paediatric patients. For IC adults, the recommended posology is 75 mg twice daily for 10 days. The MAH now proposes the posology for IC paediatric patients <18 years of age: 75 mg (weight-adjusted in children < 13 years of age) twice daily for 10 days. The proposed dose is the same as in otherwise healthy paediatric subjects, but the duration of treatment is prolonged from 5 to 10 days. Treatment should be initiated before 48 hours. This proposal is deemed acceptable.

Notably, as the use of oseltamivir in IC patients is not currently excluded in Section 4.1 Indications or included in Section 4.3 Contraindications of the SmPC of Tamiflu, this variation concerns the evaluation of data defining the appropriate posology for IC children for guidance to treating physicians (in Section 4.2 Posology and method of administration). It is to be noted, however, that the MAH does not propose to delete from Section 4.4 of the SmPC the text "The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established." The currently submitted data is not robust enough for fully filling out the gap in scientific knowledge on efficacy of oseltamivir in IC patients.

Nevertheless, the obtained data is considered sufficient for dose recommendation to be followed when treatment of influenza is clinically warranted for paediatric IC patients.

Two interventional studies (NV20234 and NV25719) were carried out to establish the oseltamivir dose recommendation for the treatment of immunocompromised (IC) children with influenza. Study reports have been assessed in previous procedures (EMA/H/C/402/P46/105, EMA/H/C/402/ P46/106 and EMEA/H/C/000402/II/0136). Both studies compared the conventional dose of oseltamivir with higher doses. In study NV20234, the conventional daily dose was compared with the double dose of oseltamivir, and in study NV25719, the conventional daily dose was compared with a triple daily dose.

The background conditions and concomitant medications of the study population were multiple. In study NV20234, patients had either primary immunodeficiency at risk for viral infections or secondary immunodeficiency due to solid organ transplant (SOT), haematopoietic stem cell transplant (HSCT), HIV, haematological malignancies or systemic immunosuppressive therapy regardless of indication. Study NV25719 included children (below 13 years of age) who had undergone a conditioning regimen prior to HSCT or less than 6 months after HSCT or received induction, consolidation, or re-intensification chemotherapy for haematological malignancy.

Study NV20234 included both IC adults (>18 years old, n=207) and paediatric (1 year to <18 years old, n=20) patients. Study NV25719 included IC children <13 years of age (n=30). Even though enrolling infants was allowed by protocol, only patients above 1 year of age were finally included. There was a small number of patients with each different underlying IC condition. Even though the manifold background conditions cause large variability, it is on the other hand a benefit that the results obtained in this population can more easily be extrapolated to IC patients in general than would be the case if the studies had been performed in a uniform patient population.

Time to clearance of viral shedding (TTCVS) and time to resolution of all symptoms (TTRAS) varied markedly in both studies. The observed large inter-individual variation in virological and clinical efficacy measures was likely due to the variable background conditions and due to chance, taking in account the small number of patients.

For this reason, an extrapolation approach has been carried out using also the data sets that led to the original approval in OwH patients under 1 year old (Study NV25118, procedure EMEA/H/C/000402/II/110/G, May 2015) (see Section 8 Extrapolation of this AR).

The extrapolation plan to determine dosing in IC children was endorsed in PIP-M10. The specific steps to determine dosing in immunocompromised children were:

1) Using sparse PK data generated primarily from NV25719 together with any paediatric PK data collected from NV20234, if necessary, adapt and validate the existing population PK model in immunocompetent paediatric patients to describe the disposition of oseltamivir and OC in immunocompromised children.

2) Use model-simulated key exposure parameters, e.g. AUC, across the range of exposures studied in NV25719 to confirm the assumption that oseltamivir and OC PK does not differ to a clinically important extent based solely on immune status.

Steps 1 and 2 of the plan have been carried out adequately. The observed PK data in IC paediatric patients 1 to ≤18 years of age were used in population PK modelling and simulations. There was a reasonable number (n=22) of children from one to <10 years of age in the dataset. The previously developed PK model "Healthy Paediatric and Young Adult Subjects" was selected as the structural model. The final model indicated that in IC paediatric subjects ≥ 10 years of age the apparent clearances of oseltamivir and OC were decreased by 44.4% (95%CI: 26.8−62.0%) and 49.1% (95%CI: 34.5−63.8%), respectively, compared to OwH subjects

in the same age range, whereas in younger children (1 to <10 years) the PK of oseltamivir and OC were comparable in IC and OwH subjects.

The conducted PK simulations included comparison of predicted oseltamivir and OC exposures between IC patients of study NV25719 and OwH patients of study WV15758, stratified by age. The results indicated that the predicted OC exposures in paediatric IC subjects ≥ 10 years of age were approximately 2.1−2.2 fold higher than in OwH subjects in the same age range. One IC patient with nephrectomy was found to be an outlier, having more than 2 times higher AUC compared with all other IC paediatric patients from NV25719 study. When this outlier was excluded, the predicted OC exposures in IC patients were approximately 1.7−1.8 fold higher than in OwH subjects. This increase in exposure is comparable with that observed in IC adults (see procedure EMEA/H/C/000402/II/0136) and it is not expected to be associated with safety problems, taking into account the known safety profile of oseltamivir. In IC subjects < 10 years of age, the predicted exposures were similar as in otherwise healthy subjects in the same age range.

3) Examine the relationship between simulated exposure parameters and observed PD measures to determine if any PK/PD relationship exists. This relationship could form the basis of a dose recommendation at least for children up to 13 years and potentially up to 18 years. For adolescents, consideration could also be given to adult data from NV20234.

Step 3 of the plan has been carried out adequately. Relationships between predicted exposure and observed PD parameters (e.g. viral shedding and resolution of symptoms) were explored in 22 subjects with PK and PD data. No relationships between predicted exposure and viral parameters, such as time to cessation of viral shedding and viral titre/load measures were found. Treatment-emergent resistance developed in four patients with PK and PD data. There were no differences in exposures between patients that developed and did not develop resistance, indicating that higher than conventional dose and higher exposure to OC is not expected to decrease the incidence of resistance. Time to resolution of symptoms was the only parameter suggesting a potential benefit of a high exposure. This finding should be interpreted with caution because of limited number of subjects in the dataset.

Furthermore, the collected CARIFS symptom score (in patients below 13 years of age) contains several items that are not specific for respiratory tract infections. CARIFS was developed in paediatric population that did not have underlying disease requiring daily medication and it is uncertain whether it is reliable in IC children. The results of exposure-response analyses for IC adults of study NV20234 did not suggest any relationships between predicted OC exposure and virologic PD parameters or time to resolution of clinical symptoms. The overall results of exposure-response analyses did not provide robust evidence to support benefit of higher than conventional oseltamivir dose in IC paediatric patients. This is not surprising, because OC trough concentrations achieved with conventional dose are above inhibitory concentrations of tested influenza strains.

In studies NV20234 and NV25719, all doses (conventional, double and triple) of oseltamivir were relatively well tolerated. No new safety signals were observed in these studies. The nature and severity of AEs were consistent with established safety profile of oseltamivir. Hence, no need for amending the safety information in the Product Information of Tamiflu was identified.

As the variation concerns dosage to IC paediatric patients and as multiple PIP measures are involved in the variation, this AR was sent for comments to the PDCO in addition to the CHMP; no comments were received from PDCO. The type II variation proposal concerns PIP measure 2: NV20234, PIP measure 5: NV25179; and PIP measure 3: Population PK modelling study (data from PIP studies 2 and 5).

Some modifications to the proposed Product Information were requested during the variation procedure. The final submitted Product Information is considered acceptable.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 5.1 and 6.6 of the SmPC following completion of the paediatric studies NV25719 and NV20234 and downstream population PK and PK/PD and disease modelling analyses, listed in the approved Tamiflu Paediatric Investigation Plan (PIP) (EMEA-000365-PIP01-08-M10). The study NV25719 was a prospective, open-label, randomized study, which investigated PK and PD of two weight adjusted oseltamivir doses for the treatment of influenza-infected immunocompromised (IC) children less than 13 years of age. The study NV20234 was a prospective, double blind, randomized trial, which investigated safety and viral resistance to oseltamivir treatment in influenza-infected IC adults, adolescents and children. The purpose of this variation is to establish a dose recommendation for the treatment of paediatric IC patients.

The Package Leaflet is updated accordingly.

The RMP version 19.1 has also been submitted.

☒is recommended for approval

Grounds for refusal:

N/A

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Annex: CHMP assessment comments on the type II variation

4. Introduction

Influenza is an acute respiratory infection caused by viruses of the orthomyxoviridae family. Influenza serotypes A and B infect humans, and are responsible for acute infection of the respiratory tract characterized by the sudden onset of fever, malaise, headache, myalgia, and cough. Influenza is a seasonal illness, with epidemic infections occurring annually during cooler months. Although difficult to assess, annual influenza epidemics are thought to result in between 3 and 5 million cases of severe illness and between 250,000 and 500,000 deaths every year around the world (*World Health Organization. Influenza. Fact Sheet. November 2018; Iuliano al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 2018; 391, 1285-1300*). The clinical manifestations of influenza in paediatric patients are similar to those seen in adults; however, the rate of severe influenza infection is higher than in adults (*Wong et al. Influenza-associated pediatric deaths in the United States, 2004–2012. Pediatrics. 2013;132:796-804*). Influenza can cause serious complications resulting in substantial morbidity and mortality, particularly in higher-risk populations such as children, the elderly, and the immunocompromised (IC).

Tamiflu was initially approved in year 2002 for the treatment of influenza in adults and children one year of age or older and for post-exposure prevention in adults and adolescents 13 years of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. Thereafter, the indication has been several times extended due to need (especially during pandemic influenza) and based on studies performed during marketing of the product. Use for prevention of influenza in children of 1−12 years was approved in 2005 (variation II/0020), treatment of children between 6 and 12 months of age in case of pandemic influenza in 2009 (II/0068), treatment of children between 0 and 6 months of age and prophylaxis for children less than 1 year of age in case of pandemic influenza in 2009 (II/0070), treatment of infants <1year without restriction to pandemic in 2015 (II/0110/G), post-exposure prophylaxis of children below 1 year of age during a pandemic (II/0118). Finally, specific posology for treatment of IC adults was approved in 2019 (II/0136), see below; the SmPC has never explicitly precluded use in IC patients from the indication.

One concern has been prolonged viral shedding in IC patients treated with oseltamivir compared with immunocompetent patients, which has been feared to cause development of antiviral resistance against neuraminidase inhibitors. Some clinical practice guidelines have proposed a double-dose regimen of oseltamivir for 10 days in IC population (*Manuel et al. Influenza and other respiratory virus infections in solid organ transplant recipients. Clin Microbiol Infect. 2014;20 Suppl 7:102-108., Engelhard et al. European guidelines for prevention and management of influenza in hematopoietic stem cell transplantation and leukemia patients: summary of ECIL-4 (2011), on behalf of ECIL, a joint venture of EBMT, EORTC, ICHS, and ELN Transpl Infect Dis. 2013;15:219-232*). Data from observational studies indicate that this approach is widely used (*Watcharananan et al. Influenza A/H1N1 2009 pneumonia in kidney transplant recipients: characteristics and outcomes following high-dose oseltamivir exposure. Transpl Infect Dis. 2010;12:127-131; Kumar et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. Lancet Infect Dis. 2010;10:521-526*). However, only limited observational and retrospective evidence have supported these recommendations.

The requirement for the MAH to evaluate the use of oseltamivir for treatment and prophylaxis in immunocompromised (IC) patients was originally issued in 2002 with Follow-up Measure (FUM) 8 (subsequently as FUM-008.5), which later became post-approval measures MEA 75 and MEA 102. Studies NV20234 and NV20235 were designed to evaluate the treatment and prophylaxis of IC patients respectively, and were agreed as appropriate to address FUM-008.5 by the CHMP in November 2006. Study NV20235 for

the prophylaxis of influenza with oseltamivir was completed in June 2008 and the data added to the EU SmPC.

In 2010 (II/0069) it was added in the SmPC of Tamiflu that the efficacy of oseltamivir in IC population remains uncertain, as two studies conducted in IC patients failed to show significant benefit in seasonal prophylaxis with oseltamivir. These comprised 1) a prospective, randomised, double-blind, stratified (by transplant type, vaccination status, and age), multicentre trial of oseltamivir versus placebo for seasonal influenza prophylaxis for 12 weeks in IC adults and children aged above one year (NV20235); and 2) a prospective, non-randomised, open-label multicentre study to evaluate the safety of oseltamivir for seasonal influenza prophylaxis for 6 weeks in 52 children (1 to 12 years of age) considered at risk for infection or having susceptible individuals in their household (NV20236). However, safety of oseltamivir in the long-term administration was consistent with the known safety profile of oseltamivir.

The increased morbidity of influenza in IC patients is associated with increased viral load and increased duration of virus shedding compared to that in healthy patients. Therefore, a key objective of anti-viral therapy in this population is to reduce the duration of viral shedding, which in turn should reduce influenza -associated morbidity. It has been demonstrated earlier that paediatric patients and immunocompromised population are susceptible to prolonged viral shedding and post-baseline viral resistance. The previous MAH-sponsored data on this issue is briefly reviewed below.

- The Influenza Resistance Information Study (IRIS, NV20237) was set up by the MAH in response to the emergence of naturally occurring neuraminidase resistance among seasonal influenza H1N1 viruses in 2008. The study enrolled 4553 patients from year 2008 to 2015, of whom 2578 were treated with oseltamivir either alone or combined with other antiviral medication(s). Over the first 5 years, patients of any age were eligible for enrolment. In years 6 and 7 of the study, recruitment was focused on children aged <12 years, since results of the first 5 years had indicated that this group had higher rates of resistance than adults and adolescents. The cumulative resistance rate against influenza A (H1N1pdm09 and H3N2 viruses combined) was 3.5%. Incidence of treatment-emergent resistance increased with decreasing age: 1.1% in adults and adolescents, 1.6% in children aged 6-12 years, 8.0% in children aged 1–5 years and 20.0% in infants aged <1 (although only 20 patients were assessed in this age group). Incidence of treatment-emergent resistance varied yearly. Children who were found to carry oseltamivir-resistant virus in general shed the virus for a prolonged period compared with subjects with susceptible virus. However, treatment-emergent resistance to oseltamivir did not affect treatment response and caused no prolongation of influenza symptoms. The results of IRIS were implemented in the PI of Tamiflu in variation II-122.
- During the variation II-122, the MAH submitted upon request an integrated analysis of viral resistance from all MAH-sponsored clinical trials with resistance data. The integrated analysis pooled data from 6/11 studies, as phenotypic and genotypic resistance was not available in all studies. The incidence of adult and adolescent patients found to carry oseltamivir-resistant virus was 0.62% (14/2253) by phenotyping alone and 0.67% (15/2253) by genotyping and phenotyping. For children aged 1-12 years the updated incidence was 3.89% (66/1698) by phenotyping and 4.24% (72/1698) by genotyping and phenotyping. For infants aged less than 1 year the resistance incidence was 18.31% (13/71) both by phenotyping alone and by a combination of genotyping and phenotyping.
- During years 4 and 5 of IRIS, a substudy was introduced to collect data in patients who were immunocompromised. The results of this sub-study were assessed separately (MEA 075.11-CHMP outcome 2 July 2014). In the substudy, 42 hospitalised IC patients aged from 1 to 73 years were recruited, of whom 29 were influenza-positive by RT-PCR. 25/29 had Influenza A, subtypes H1N1pdm09 (n= 15), H3N2 (n=14), mixed H1N1pdm09+H3N2 (n=1), and 4 had influenza B. No resistant viruses were detected at baseline. The H275Y resistance mutation was detected in post-Day-1 samples from 4 adult patients infected with H1N1pdm09 viruses who received

oseltamivir. No other resistance mutations were detected. Two patients with influenza A had prolonged viral shedding up to 15 days; one with H1N1pdm09 (H275Y mutant strain) and one with H3N2 (no antiviral resistance).

The purpose of the current variation is to establish a dose recommendation for the treatment of paediatric immunocompromised (IC) patients, who are currently not excluded from the indication, but for whom no prior recommendation of dosage exists in the PI of Tamiflu. The MAH is proposing update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC, and to update the PL accordingly.

The dosing recommendation for IC paediatric patients aged below 18 years is mainly based on pharmacokinetic (PK), pharmacodynamic (PD), PK/PD evaluation and disease modelling analysis in addition to observed resistance, efficacy and safety (see section 6 Clinical Pharmacology aspects of this AR). The key PK, PD, PK/PD and disease modelling results are derived from the following analyses conducted by the MAH:

- **Population PK Report: Population Pharmacokinetic and Exposure-Response Analyses of Oseltamivir and Oseltamivir Carboxylate in Pediatric Immunocompromised Patients with Influenza (Studies NV25719, NV20234), Report Number: 1093512. May 27. 2019.**

The report contains **population PK analyses** to 1) establish a predictive population model that describes the PK of OP and OC following multi-dose oral administration in IC paediatric patients from birth to less than 18 years of age for the treatment of influenza; and 2) to estimate individual OP and OC steady-state exposures ($AUC_{0\text{-}12}$, C_{max}, C_{trough}) in paediatric IC patients from studies NV20234 and NV25719 for the treatment of influenza; and **exposure-response (ER) analyses** to explore relationships between OP and OC systemic exposure and the pharmacodynamic endpoints on the viral and clinical course of influenza in these patients.

- **Analysis and Simulation Report. Viral Kinetics Modeling and Simulation to Evaluate Oseltamivir (Tamiflu®) in the Treatment of Immunocompromised Pediatric Patients (< 18 Years) with Influenza. Report number: 1093513, May 31, 2019.**

The purpose of the analysis was to characterize the kinetics of naturally occurring influenza infections and the treatment effect of oseltamivir in IC paediatric subjects. Data for the analyses comprised of 166 IC patients from study NV20234 (150 adult patients aged ≥18 years and 16 paediatric patients aged<18 years), 20 paediatric IC patients below 13 years from study NV25719, and 6 IC patients (aged 13 to 69 years) from study NV25118.

The studies used as source data for the above-mentioned analyses and prior regulatory procedures based on the studies are briefly described below.

Study NV20234 was originally designed to compare the efficacy of the conventional and double daily dose of oseltamivir administered for 10 days (double the conventional duration) in IC patients. However, due to recruitment problems, the power of the study was not expected to be sufficient for the original efficacy endpoint, and the primary endpoint was changed into investigation of safety and resistance profile of these two regimens. This study was initiated in 2007 and incorporated into the initial oseltamivir Paediatric Investigation Plan (PIP) on 02 October 2009 [measure 2 of current PIP]. The NV20234 study was a Phase III, double blind, randomized, stratified, multicentre study of conventional and double dose oseltamivir for the treatment of influenza in IC patients. Study NV20234 enrolled mainly adults (≥18 years of age) patients, although some paediatric patients were also enrolled (see Section 7.1 of this AR).

The final primary objective of study NV20234 was to evaluate prospectively the safety and tolerability of oseltamivir for the treatment of influenza in IC patients (adults and paediatric patients) and characterize the

effects of oseltamivir in IC patients on the development of resistant influenza virus. Secondary objectives evaluated the effects of conventional and double dose of oseltamivir on the population pharmacokinetics (PK) of oseltamivir and oseltamivir carboxylate (OC) in IC patients with confirmed influenza infection, through the application of established population pharmacokinetic (PK) models to the sparse plasma concentration data generated; the virologic course of influenza (proportion shedding and viral loads at different timepoints; the time to resolution of influenza symptoms; the clinical course of influenza (fever, symptoms, secondary illnesses as evidenced by otitis media, bronchitis, pneumonia, or sinusitis), and to explore the relationship of metrics of exposure (e.g., area under the concentration-time curve [AUC], trough plasma concentration [C_{min}]) to relevant pharmacodynamic (PD) endpoints.

The target population for study NV20234 were patients with primary immunodeficiency at risk for viral infections or secondary immunodeficiency due to ongoing immunosuppression due to solid organ transplant (SOT), allogenic haematopoietic stem cell transplant (HSCT) or human immunodeficiency virus [HIV] infection with CD4 count <500/mm3 (or <25% in children < 5 years old), haematological malignancies or systemic immunosuppressive therapy.

The dose recommendation for adult IC patients was implemented in the Product Information (PI) in January 2019 [Type II variation procedure No. EMEA/H/C/000402/II/0136 (EMA/CHMP/PRAC/487212/2018)]. The variation was based on the results on adult IC patients in study NV20234; a population PK analysis utilising data from IC patients (study NV20234) and otherwise healthy (OwH) patients (study NV25118); and an Influenza disease PK/VK model. The conclusion was that the double dose (150 mg BID) was not more efficacious than the standard dose (75 mg BID) in adult IC patients. There was no difference in incidence of secondary illnesses or hospitalisations. Adult IC patients treated with standard dose (75 mg BID) had mean steady-state OC levels comparable to OwH subjects treated with 150 mg BID, which was attributed to background conditions and to lower estimated creatinine clearance in the IC population. Treatment emergent resistance was more likely in the conventional compared with the double-dose group in IC adults; and when resistance was present, the time to cessation of viral shedding was prolonged. However, the number of adult patients with oseltamivir-resistant influenza was small: 10/73 patients in the conventional dose group and 2/78 in the double-dose group. Previous data, including the IRIS (Influenza Resistance Information Study) in 3725 immunocompetent patients, include no reports of further transmission of oseltamivir resistant viruses from a case with treatment-emergent oseltamivir resistance. As no clinical benefit was observed with double daily dose in IC adults, the daily dose of oseltamivir for adult IC subjects was accepted to be the conventional 75 mg BID. The duration of oseltamivir treatment in NV20234 was 10 days in both study arms (conventional and double dose). Modelling results suggested that with a 5-day treatment regimen of 75 mg BID there is a risk of viral re-growth, which can be reduced using a 10-day treatment regimen of 75 mg BID, therefore, the approved duration of treatment with oseltamivir in IC adults was accepted to be 10 days instead of the conventional 5 days. It was also noted that the time to resolution of all symptoms was markedly better in patients who were administered oseltamivir within 48 hours from onset of symptoms (69.0 hours, 95% CI: 44.4, 103.4) vs. 122.7 hours, 95% CI: 57.1, 169.0) in subjects who received oseltamivir >48 hours after onset of symptoms; although the 95% CIs overlapped.

Study NV25719 [measure 5 of PIP] and downstream population PK and PK/PD model [measure 3 of PIP] were intended to guide in appropriate posology of oseltamivir in the treatment of influenza in immunocompromised children less than 13 years of age with confirmed influenza infection. The final study report of NV25719 was assessed and accepted in the procedure no. EMA/H/C/402/P46/106 (April 2019). That procedure did not involve update of PI regarding dosage of oseltamivir for IC children, as the currently submitted results of the population PK and influenza disease modelling reports were awaited for that purpose.

The objectives of the study NV25719 were to generate data for the purpose of extrapolation of efficacy from adults with immunodeficiency and to compare and/or integrate exposure and response observations in the paediatric IC population to that seen in other, non-IC populations; to estimate the exposure achieved with

each of different dose levels of oseltamivir through the application of an established population PK (popPK) model to the sparse concentration data generated; and to examine the duration of treatment, of viral shedding, and of fever and to examine the safety, tolerability, incidence of influenza-associated complications and of resistance observed with different doses and duration of treatment and characterize any resistant virus isolate in terms of sequence and phenotype.

Study NV25719 recruited paediatric IC patients less than 13 years of age with a laboratory-confirmed diagnosis of influenza who were receiving induction, consolidation, or reintensification chemotherapy for a haematological malignancy or were undergoing a conditioning regimen either prior to hematopoietic stem cell transplant (HSCT) or less than 6 months after HSCT. The manifold background conditions of the subjects caused large variation in the viral and clinical outcome measures. On the other hand, the variability of the studied population supports generalisation of the obtained results in paediatric IC patients regardless of the reason for compromised immune response.

The duration of treatment tested in study NV20234 was 10 days. In study NV25719, the duration of treatment was adaptive and depended on clearance of viral shedding: mean duration of exposure to oseltamivir was 9.2 days (range: 4 to 19 days) in the conventional dose group and 8.5 days (range: 2 to 19 days) in the triple dose group.

Study NV25118 was a multicentre study of the safety of oseltamivir administered intravenously for the treatment of influenza in patients aged ≥13 years, conducted over 3 influenza seasons (2009/2010, 2010/2011 and 2011/2012). The study was initiated as the emergence of the pandemic (H1N1)2009 virus, created an urgent unmet medical need for an intravenous (IV) neuraminidase inhibitor to treat seasonal and pandemic influenza in critically ill patients and others unable to tolerate, swallow or absorb orally administered medications. Investigational product in this study was oseltamivir phosphate lyophilisate to be prepared for IV infusion; additionally oral capsule were used to complete the treatment course. The development of the IV formulation however was discontinued, and the IV compassionate use program was closed down as the requests to participate declined since the pandemic. Study NV25118 was therefore terminated early. The CSR of this study was assessed in 2013 (EMEA/H/K/002287). Of the 118 patients in NV25118, 6 were PD-evaluable IC patients (≥13 years of age), and their data has been used in the viral kinetics modelling and simulation analysis performed by the MAH for the current variation.

The results on the paediatric patients included in studies NV20234 and NV25719 are included and discussed in this AR in the extent that is considered relevant for the current variation, even though the CSRs for these studies were assessed previously.

In paediatric drug development, extrapolation is frequently used to address uncertainties due to gaps in knowledge (*Reflection paper on the use of extrapolation in the development of medicines for paediatrics. 7 October 2018. EMA/189724/2018*). E.g., the extension of use of oseltamivir in the treatment of influenza in infants below 1 year of age (II/0110/G) was based on extrapolation of efficacy from adults and older children and PK/PD modelling from studies CASG114 (children with influenza aged < 2 years) and WP22849 (infants with influenza <1 year of age). Due to the small number of subjects in the clinical studies on IC children, the recommended dosage cannot be based on robust efficacy data in this population. Therefore, extrapolation is needed from otherwise healthy (OwH) children and from IC adults.

The MAHs extrapolation plan as presented to the Paediatric committee of EMA (PDCO) during the most recent modification procedure (EMEA-000365-PIP01-08-M10, 29 June 2018) consists of data from immunocompetent and immunocompromised adults, immunocompetent and IC paediatric patients, and modelling and simulation (see section 8 Extrapolation of this AR). As use of oseltamivir in immunocompromised patients is not currently excluded in Section 4.1 Indications or included in Section 4.3

Contraindications of the SmPC of Tamiflu, this variation is not an extension of indication, but concerns evaluation of the data for defining appropriate posology for IC children for guidance to treating physicians (in Section 4.2 Posology and method of administration). It is to be noted, however, that the MAH does not propose to delete from Section 4.4 of the SmPC the text "The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established." The currently submitted data is not robust enough for filling out the gap in scientific knowledge on efficacy of oseltamivir in IC patients. Nevertheless, the obtained data is considered sufficient for dose recommendation to be followed when treatment of influenza is clinically warranted for paediatric IC patients.

In addition to the above-described modelling reports and the resubmitted CSRs for the clinical studies providing source data for the modelling, the MAH has submitted a Clinical overview, Clinical summary (Summary of clinical efficacy, Summary of clinical safety, Summary of clinical pharmacology), literature references with 65 references, synopses of individual studies and Risk Management Plan (RMP version 19.).

5. Clinical Pharmacology aspects

Introduction

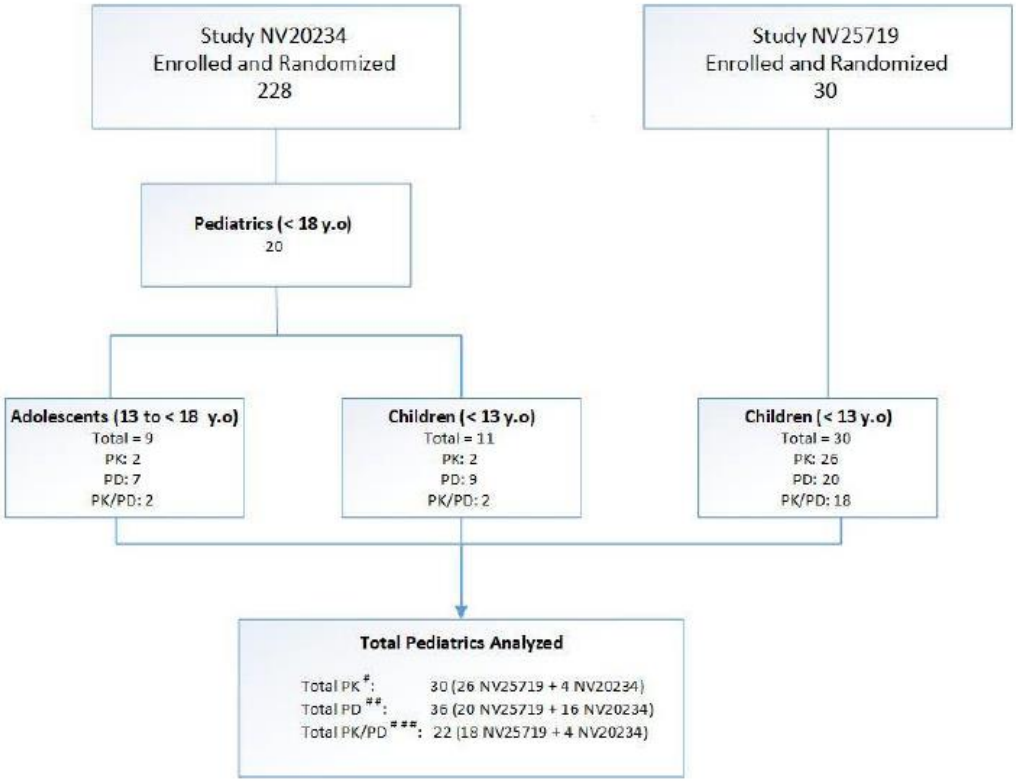
The active moiety of Tamiflu is the pro-drug oseltamivir (as oseltamivir phosphate). Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration and is extensively converted by hepatic carboxyl-esterase 1 to the active metabolite oseltamivir carboxylate (OC). At least 75% of an oral dose reaches the systemic circulation as active metabolite. Exposure to oseltamivir (in terms of AUC) is less than 5% of the exposure to OC. Plasma concentrations of both oseltamivir and OC are proportional to dose.

The volume of distribution of intravenously dosed OC is approximately 23 to 26 litres (~0.3 l/kg) in healthy adults. The binding of OC to human plasma proteins is negligible (approximately 3%).

Absorbed oseltamivir is primarily (>90%) eliminated by conversion to OC, which is not further metabolised. OC is eliminated by renal excretion (glomerular filtration and tubular secretion). Clearance of intravenously dosed OC is approximately 20 l/h in healthy adults. Elimination half-life (t½) of OC after oral dosing of oseltamivir is approximately 6 to 10 hours in adults with normal renal function. This is significantly longer than the t½ of intravenously administered OC (approximately 1 to 2 hours), which indicates that release of OC from the liver is the rate-limiting step in the elimination of OC after oral administration of oseltamivir.

Pharmacokinetic (PK) and pharmacodynamic (PD) properties of the pro-drug oseltamivir and the active metabolite oseltamivir carboxylate are established. The new clinical pharmacology data supporting the current application are oseltamivir and OC concentrations and viral/clinical PD data for immunocompromised (IC) paediatric subjects in studies NV25719 and NV20234 (Figure 5.1.1) and subsequent population PK and exposure-response modelling and simulations. A disease model (viral kinetics modelling and simulation) is also presented.

Figure 5.1.1. Patient Disposition (PK/PD analyses and Disease Modelling in IC Paediatric Patients)



\# Pop PK population
\## PD and Disease Modeling population
\### PK/PD population

Sources: NV20234 CSR, Report 1078105, NV25719 CSR, Report 1084847, Pop PK/PD, Report 1093512, Disease Modeling, Report 1093513. For a more details on patient distribution by age for the PK and PK/PD analyses, refer to Appendix 1.

5.1 Methods – analysis of data submitted

Bioanalytics

Plasma concentrations of oseltamivir (RO0640796) and oseltamivir carboxylate (RO0640802) were determined in human EDTA plasma according to the validated LC-MS/MS method (PRA-US-0017). Quantification was accomplished by means of the internal standard method using isotopically labelled internal standards for both oseltamivir and oseltamivir carboxylate. The method employed protein precipitation for sample preparation and gradient elution on HPLC followed by mass spectrometric detection. The bioanalytical method of study NV20234 has been previously assessed in the procedure EMEA/H/C/000402/II/0136. The assessment of bioanalytical methods used in study NV25719 is shown below.

Bioanalytics of oseltamivir and oseltamivir carboxylate (Study NV25719)

Plasma concentrations of oseltamivir (RO0640796) and oseltamivir carboxylate were determined in human EDTA plasma according to the validated LC-MS/MS method (RPU664UL-116647-B). Quantification was accomplished by means of the internal standard method using isotopically labelled internal standards for both oseltamivir and oseltamivir carboxylate. The method employed protein precipitation for sample preparation and gradient elution on HPLC followed by mass spectrometric detection.

The human plasma samples were collected in tubes containing K_3-EDTA. The samples were initially stored at -20°C, but were later relocated to −70°C on 16-May-2018 according to the Study Plan Amendment No. 01. The calibration standards and quality control (QC) samples were prepared in K_2-EDTA.

The total number of received samples was 108 and concentrations of oseltamivir and oseltamivir carboxylate were successfully determined in all 108 samples within the documented long-term stability of 1197 days at −70 °C and 1014 days at −20 °C.

Tandem mass spectrometric detection was applied using a mass spectrometer operating in positive ion mode with electrospray ionization. The data was collected using multiple reaction monitoring (MRM). The selected transitions (m/z) were 313.1 → 166.0 for oseltamivir, 285.1 → 138.0 for oseltamivir carboxylate, 316.2 → 167.2 for oseltamivir internal standard (RO0640796-d_3) and, 288.2 → 139.1 for oseltamivir carboxylate internal standard (RO0640802-d_3). Quantification was accomplished by using internal standard method.

The calibration standards were prepared in human K_2-EDTA plasma. Eight different concentrations of calibration standards were included ranging from 1.00 ng/ml to 500 ng/ml for RO0640796 and 10.0 ng/ml to 5000 ng/ml for RO0640802. The calibration curves were established by weighted ($1/x^2$) linear regression from peak area ratios (peak area of analyte/peak area of internal standard) versus nominal concentrations. The back calculated concentrations of the calibration standards and the calibration curve parameters are presented.

The performance of sample analysis was monitored by quality control (QC) samples in K_2-EDTA plasma spiked with 3 different concentrations of the analytes, 3.00, 50.00 and 400 ng/ml for RO0640796 and 30.0, 500 and 4000 ng/ml for RO0640802. The individual results for the QC samples including the corresponding precision and accuracy data are presented.

In each analytical run, a blank sample and a zero sample were analysed to assess the selectivity of the analytical method. Selectivity was acceptable if the response of co-eluting peaks (peak area) did not exceed 20.0% of the peak response at the LLOQ level of the analyte and did not exceed 5.0% of the peak response (peak area) of the internal standard found in the sample at the LLOQ level analysed in the same run.

In run AN-11, two blanks had peaks > LLOQ for both analytes, 716% and 241% for RO0640796, and 692% and 206% for RO0640802. Results were not consistent with carryover but rather attributed to isolated interfering peaks. The run was rejected for both analytes out of precaution and the samples were reanalysed.

A total of 3 samples for RO0640796 and 2 samples for RO0640802 were reanalysed for analytical reasons. For RO0640796, 2 original results were not reportable due to abnormal internal standard response and 1 original result was not reportable due to out of range concentration (>500 ng/mL) where the sample was reanalysed after dilution. For RO0640802, the original results were not reportable for 2 samples due to abnormal internal standard response.

Dilution integrity (10-fold) was evaluated.

Incurred sample reanalysis (ISR) was done for a total of 15 study samples. Three of the ISR samples for RO0640796 showed variability greater than 20%. None of the ISR samples for RO0640802 had variability greater than 20%.

Representative chromatograms of blank, zero, calibration, QC and study samples are presented.

Assessor's comments on bioanalytics

The bioanalytical method used to quantitate oseltamivir (RO0640796) and oseltamivir carboxylate (RO0640802) has been validated according to the Guideline on bioanalytical method validation (EMEA/CHPM/EWP/192217/2009 Rev.1). The current submission did not contain the validation report. However, the validation report including the amendments 01 and 02 has been provided earlier. The validation is considered acceptable.

The samples were originally stored at −20 °C and later (16 May 2018) moved to −70 °C. The stability results presented in Amendment 02 to the validation report (Table 17 of the Amendment 2, not shown in this AR) show that oseltamivir is stable up to 1197 days at −70 °C but not at −20 °C. It is stated in the bioanalytical report that the samples were analysed within the documented stability of 1197 days at −70 °C and 1014 days at −20 °C. Maximum storage time of the samples at −20 °C before analysis has not been stated but it appears to be significantly shorter than the documented stability of 1014 days.

Tables of all analytical runs are included in the report. The back-calculated concentrations of the calibration standards and calibration curve parameters of acceptable runs are presented and they are acceptable.

The criteria for selectivity was met and the bioanalytical results were not affected by carry-over.

The individual results for the QC samples including the corresponding precision and accuracy data have been presented. One QC sample result for RO0640802 was outside the acceptance criteria but was included in statistical evaluation. The intra-assay precision of QC samples ranged from 2.9% to 5.5% for RO0640796 and from 2.7% to 6.8% for RO0640802. There was no marked inaccuracy in the results of QC samples.

Reanalysis of the samples has been discussed adequately.

The results of incurred samples reanalysis are acceptable.

Population Pharmacokinetic and Exposure-Response Analyses

Population PK and exposure-response (ER) analyses (Report Number 1093512; May 27, 2019) were performed to describe the PK characteristics of oseltamivir and oseltamivir carboxylate (OC) in IC patients following oral administration of oseltamivir.

Population PK model

The objectives of the population PK analysis were:

- To establish a predictive population model that describes the pharmacokinetics of oseltamivir and OC following multi-dose oral administration in immunocompromised paediatric patients from birth to less than 18 years of age for the treatment of influenza;
- To estimate individual oseltamivir and OC steady-state exposures ($AUC_{0\text{-}12}$, C_{max}, C_{trough}) in paediatric IC patients from studies NV20234 and NV25719 for the treatment of influenza.

The data available for the current population PK analysis were limited (sparse sampling from 30 subjects). Therefore, new PK model was not developed. Instead, two previously developed population PK models were tested with model parameters fixed to prior estimates, and study effect parameters were added to oseltamivir and OC apparent clearances to account for differences between paediatric IC patients and otherwise healthy (OwH) subjects. The models are summarised below.

Model in Healthy Paediatric and Young Adult Subjects (Prior Model 1)

The model in healthy paediatric and young adult subjects (*Ravva et al. Mechanistic Population Pharmacokinetics of Oseltamivir in neonates to young adult patients with normal renal function, Abstract T-59, American Conference on Pharmacometrics 7, 2016.*), further called Prior Model 1, was developed to assess the effects of renal and hepatic maturation in this population. The model was developed using oseltamivir (3100 samples) and OC (3560 samples) concentration-time data following oseltamivir oral and IV administration in 313 paediatric subjects and 123 young adult subjects (≤40 years) with normal renal function (creatinine clearance > 90 ml/min). The model has been assessed by the CHMP in the procedure EMEA/H/C/000402/II/0118 (Scope: to update the pharmacokinetic information to include information regarding use in post-exposure prophylaxis of children below 1 year of age during a pandemic).

Model structure and parameters are presented in Figure 5.1.2 and Table 5.1.1, respectively. The model takes developmental physiological changes into account.

Figure 5.1.2 Population PK Model for Oseltamivir (Prior Model 1)

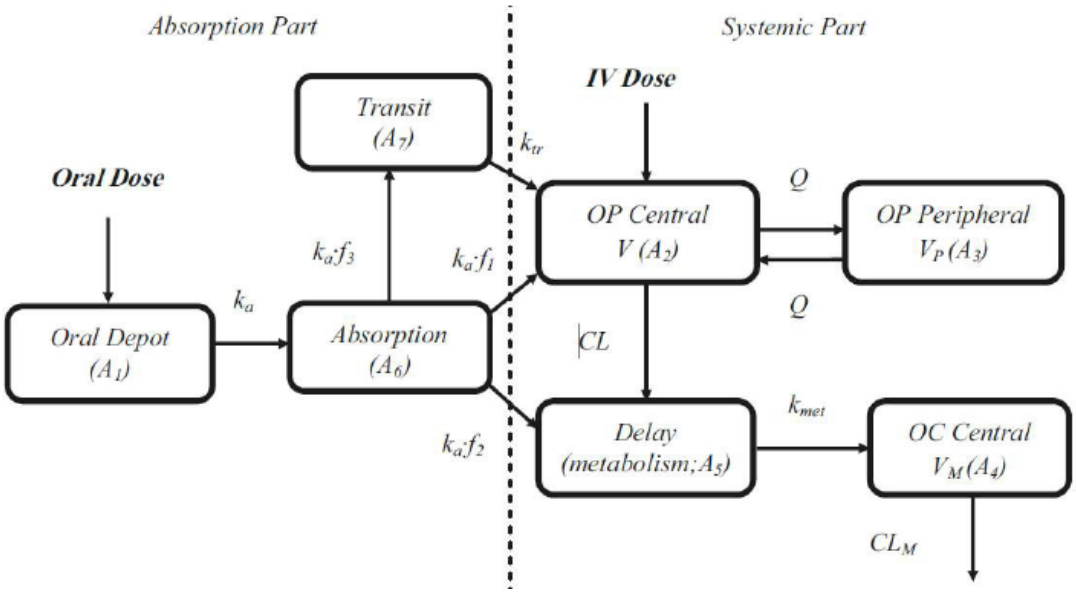


Table 5.1.1. Parameter Estimates of Oseltamivir Population PK Model (Prior Model 1).

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
CL (L/hr)	θ_1	197	4.62	180 - 215		
V_C (L)	θ_2	20.6	7.74	17.5 - 23.7		
Q (L/hr)	θ_3	83.2	4.12	76.5 - 89.9		
V_P (L)	θ_4	131	3.11	123 - 139		
CL_M (L/hr)	θ_5	27.4	3.58	25.4 - 29.3		
V_M (L)	θ_6	6.31	3.37	5.89 - 6.73		
k_{met} (1/hr)	θ_7	0.0941	2.32	0.0898 - 0.0984		
k_a (1/hr)	θ_8	0.861	2.73	0.815 - 0.907		
FF_2 [a]	θ_9	2.11	7.19	1.81 - 2.41		
FF_3 [a]	θ_{10}	0.251	2.1	0.24 - 0.261		
k_{tr} (1/hr)	θ_{11}	0.0515	6.25	0.0452 - 0.0578		
AGE_{50}	θ_{12}	45.6	4.48	41.6 - 49.6		
γ	θ_{13}	2.35	14.9	1.67 - 3.04		
$CL_{25138,25139}$	θ_{14}	0.488	14	0.354 - 0.622		
$CLM_{25138,25139}$	θ_{15}	0.49	9.4	0.4 - 0.58		
$k_{a,AGE\geq18}$	θ_{16}	1.71	7.05	1.47 - 1.95		
CL_{WT}	θ_{17}	1.03	3.15	0.967 - 1.09		
$V_{C,WT}$	θ_{18}	0.65	13.2	0.481 - 0.819		
Q_{WT}	θ_{19}	1.95	5.81	1.73 - 2.17		
$V_{P,WT}$	θ_{20}	1.58	4.69	1.44 - 1.73		
$CL_{M,WT}$	θ_{21}	0.75	Fixed			
$V_{M,WT}$	θ_{22}	1.44	7.87	1.22 - 1.67		
$k_{a,15826}$	θ_{23}	1.7	14.8	1.21 - 2.2		
WT_{ref}	θ_{24}	43.0	4.15	39.5 - 46.5		
ω^2_{CL}	$\Omega(1,1)$	0.119	7.14	0.103 - 0.136	CV=34.5%	11.9%
ω^2_{CLM}	$\Omega(2,2)$	0.118	5.83	0.105 - 0.132	CV=34.4%	3.9%
ω^2_{kmet}	$\Omega(3,3)$	0.0922	12.4	0.0697 - 0.115	CV=30.4%	26.0%
ω^2_{ka}	$\Omega(4,4)$	0.116	12.9	0.087 - 0.146	CV=34.1%	17.5%
$\sigma^2_{OP,prop}$	$\Sigma(1,1)$	0.206	1.96	0.198 - 0.214	CV=45.4%	5.7%
$\sigma^2_{OC,prop}$	$\Sigma(2,2)$	0.0264	1.17	0.0258 - 0.027	CV=16.2%	10.4%
$\sigma^2_{OC,add}$	$\Sigma(3,3)$	25.4	22.2	14.3 - 36.4	SD=5.04	

a. f1 = 1/(1+FF2+ FF3), f2 = FF2/(1+FF2+ FF3), f3 = FF3/(1+FF2+ FF3).

PE: Parameter Estimate; **SE**: Standard Error: **RSE**: Relative Standard Error, RSE=100·SE/PE; **95% CI**: 95% confidence interval; **SD**: Standard Deviation; **CV**: coefficient of variation, CV = 100*SD%.

Paediatrics through Geriatrics Population PK Model (Prior Model 2)

Paediatrics through geriatrics model (further called Prior Model 2) describes oseltamivir PK in healthy subjects and subjects with renal impairment, in paediatric and adult subjects of all ages. This model uses calculated creatinine clearance (CRCL) as a covariate, but a non-standard way of computing CRCL was used during development of this model (refer to *Kamal et al. Population pharmacokinetics of oseltamivir: paediatrics through geriatrics. Antimicrob Agents Chemother. 2013;57(8):3470–3477*). Therefore, two

versions of the model were evaluated, with CRCL computed using the original way (Kamal et al. 2013) and by the modified Schwartz equations in paediatric subjects:

- CRCL = 0.45 * HTCM [Height (cm)]/SCR [serum creatinine; mg/dL)] if Age ≤ 1 year;
- CRCL = 0.55*HTCM/SCR (mg/dL) if Age >1 and ≤ 17 years.

Model structure and parameters (from Kamal et al. 2013) are presented in Figure 5.1.3 and Table 5.1.2, respectively.

Figure 5.1.3. Structural PK model for oseltamivir (OP) and oseltamivir carboxylate (OC) (Prior Model 2).

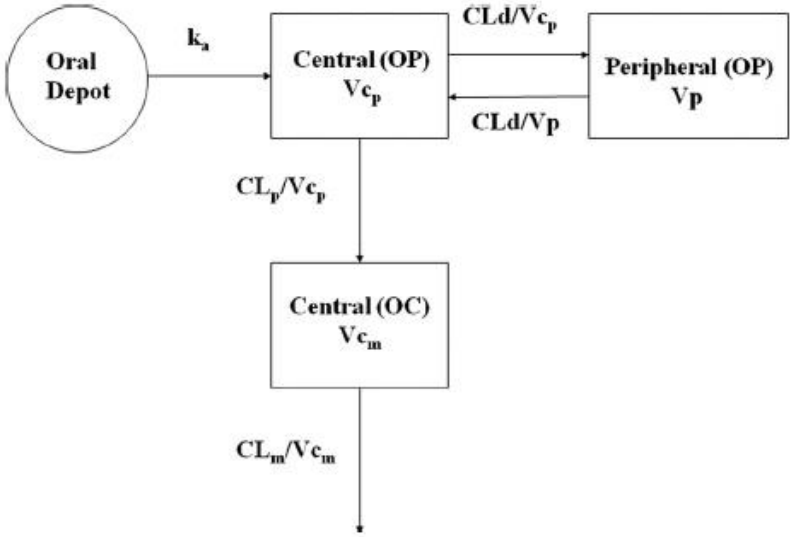


Table 5.1.2. Oseltamivir and OC population PK model parameter estimates[a] (Prior Model 2)

Parameter	Value for parameter	
	Final estimate	%SEM
k_a (h^{-1})	0.775	3.74
CL_p/F (liters/h) = $519(WT/70)^{0.838}$		
Coefficient	519	3.99
Power of WT	0.838	4.67
Vc_p/F (liters)	421	6.05
CLd/F (liters/h)	120	4.95
Vp/F (liters)	2,800	7.46
CL_m/F (liters/h) = $20.7(WT/70)^{0.560}(CL_{CR}/95)^{0.487}$		
Coefficient	20.7	3.36
Power of WT	0.560	6.63
Power of CL_{CR}	0.487	9.01
Vc_m/F (liters) = $238(WT/70)^{0.830} - 2.25(age - 21)$		
Coefficient	238	5.16
Power of WT	0.830	18.7
Slope of age	−2.25	31.2
ω^2 for k_a	30.7% CV	18.1
ω^2 for CL_p/F	42.1% CV	7.57
ω^2 for Vc_p/F	69.3% CV	15.6
ω^2 for CLd/F	62.1% CV	13.5
ω^2 for Vp/F	63.7% CV	27.5
ω^2 for CL_m/F	38.3% CV	5.71
ω^2 for Vc_m/F	65.3% CV	9.84
Covariance (CL_p/F, CL_m/F)	0.0987 ($r^2 = 0.372$)	10.4
Covariance (Vp/F, Vc_m/F)	0.218 ($r^2 = 0.274$)	23.7
σ^2_{CCV} for oseltamivir	40.5% CV	2.42
σ^2_{CCV} for OC	14.0% CV	1.49
σ^2_{ADD} for OC	17.9 ng/ml	4.96

[a] Abbreviations: k_a, first-order oseltamivir absorption rate; CL_p/F, apparent oseltamivir clearance; Vc_p/F, apparent oseltamivir central volume of distribution; CLd/F, apparent oseltamivir distribution clearance; Vp/F, apparent oseltamivir peripheral volume of distribution; CL_m/F, apparent OC clearance; Vc_m/F, apparent OC central volume of distribution; WT, weight; CL_{CR}, creatinine clearance; r^2, coefficient of determination; CV, coefficient of variation; ω^2, interindividual variability; σ^2, residual variability (CCV subscript indicates constant coefficient of variation; ADD subscript indicates additive).

The two models described above were first tested with all parameters fixed to the prior values. Then, additional effects of immunocompromised status (implemented as the multiplicative study effects) on oseltamivir and OC clearance parameters (CL and CL_M, respectively) were added and estimated while the rest of the parameters remained fixed.

Diagnostic plots and the objective function value were used for comparison of the models. The ability of the model to predict the exposure was characterized by its ability to predict individual values of OC AUC (that are inversely proportional to OC clearance). Therefore, standard deviation of inter-individual error on CL_M (CV=sd(ηi CL_M)) that characterizes the discrepancy between the population and individual predictions of CL_M was computed and used as an additional measure of goodness of fit (as OC clearance is not dependent on the dose). Finally, model performance was verified with visual predictive check (VPC) plots and normalized prediction distribution errors (NPDE) plots.

The population PK analysis was conducted via nonlinear mixed-effects modelling with the NONMEM software, Version 7.4.3. The first-order conditional estimation with INTERACTION option (FOCEI) method in NONMEM was employed for all model runs. Model-based simulations were performed by a combination of R (version 3.5.1) and NONMEM software.

The selected final population PK model was used to estimate the individual PK parameters and exposures. Specifically, steady-state C_{max}, C_{trough}, and AUC_{τ}, were computed for oseltamivir and OC following nominal BID dosing regimen for each subject. AUC_{τ} and C_{trough} values were computed over the 12-hr period. The summaries of individual PK parameters and exposure estimates (mean, standard deviation [SD], geometric mean, coefficient of variation [CV], median and range) were computed by dosing group and study. Individual estimates of exposure were used in exposure-response analyses.

Furthermore, individual exposure estimates for IC adult subjects were used to compare IC effects in adult and paediatric populations. The model for immunocompromised adult subjects was previously selected in procedure EMEA/H/C/000402/II/0136 (scope: to guide prescribers on the use of Tamiflu for treatment in immunocompromised adult patients).

Exposure-response analyses

Exposure-response (ER) relationships were investigated in 22 IC paediatric patients who had both PK and PD data. Predicted oseltamivir carboxylate steady-state exposure measures ($C_{min,OC}$ and $AUC_{12,OC}$) were highly correlated (R=0.989), therefore, only predicted OC trough concentration ($C_{min,OC}$) was used for the ER analyses.

Time-to-Event analyses. The following time-to-event endpoints were investigated:

- Time to cessation of viral shedding by culture [$TTCVS_{CUL}$] and by reverse-transcription polymerase chain reaction (RT-PCR) [$TTCVS_{PCR}$]
- Time to resolution of influenza symptoms (including fever) (TTRS) and of fever (TTRF)

Two analyses were performed for each time-to-event endpoint. In the first analysis, subjects were divided in two exposure categories (defined by the median value of exposure) and Kaplan-Meier plots were constructed for each of the two exposure categories. In the second analysis, ER relationships were described by semi-parametric Cox proportional hazards (CPH) models that aimed to evaluate the effect of exposure on the probability of events. The hazard function in the CPH model is expressed as:

$$\lambda(t) = \lambda_0(t)exp(\boldsymbol{\beta}^T \boldsymbol{X}_i),$$

where $\lambda_0(t)$ is the baseline hazard function and X_i is a vector of predictor variables that included continuous exposure ($C_{min,OC}$ or natural logarithm of $C_{min,OC}$) or exposure category (defined by median of $C_{min,OC}$). The parameter vector β was estimated by maximum partial-likelihood.

Analyses of Viral Titre/Load Measures. A linear regression model was implemented to assess the correlation between each viral titre/load measure [AUC of the viral load for RT-PCR (PCRAUCVT); AUC of the viral titre for culture (CULAUCVT); Peak viral load for RT-PCR (PCRPVT); Peak viral titre for culture (CULPVT)] with exposure ($C_{min,OC}$ and $\log C_{min,OC}$). To define confidence interval for the linear regression function, 1000 bootstrap samples were drawn with replacement from the analysis population, and linear regression was fitted to each of these samples.

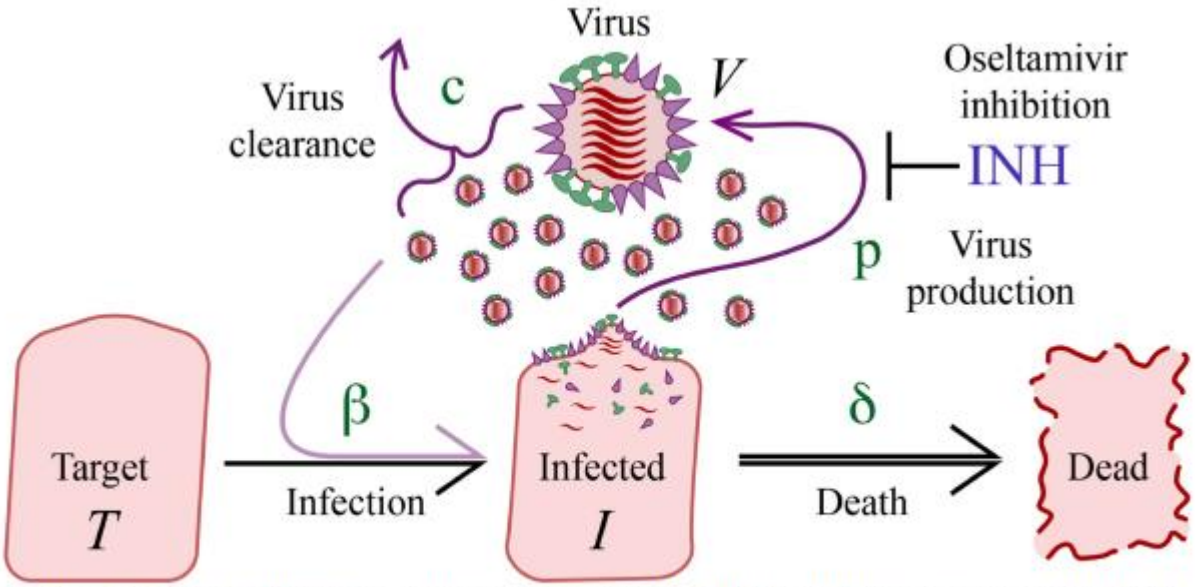
Analyses of Treatment-Emergent Resistance. Logistic regression models were implemented to assess the correlation of the probability of treatment-emergent genotypic or phenotypic resistance with exposure. To define confidence interval for the logistic regression function, 1000 bootstrap samples were drawn with replacement from the analysis population, and the logistic regression was fitted to each of these samples.

Disease modelling

A mechanistic viral kinetic model was developed for IC paediatric and adult patients receiving treatment with oseltamivir based on a drug-disease model previously developed for immunocompromised adult patients (procedure EMEA/H/C/000402/II/0136), which was based on a published 3-compartment model

representing uninfected target epithelial cells (T), infected cells (I) and pool of free virus (V) [*Baccam et al.. J Virol. 2006; 80(15): 7590–9; Kamal et al. Antimicrob Agents Chemother. 2015; 59(9): 5388–95*]. The model structure is summarised in Figure 5.1.4.

Figure 5.1.4. Structure of the influenza viral kinetic and drug inhibition model.



A simple mechanistic model describing influenza virus progression ([3]). A pool of target respiratory epithelial cells (T) are infected by a pool of free virus (V) described by a second-order rate constant, β. Infected cells (I) shed virus at a production rate p. Free virus is cleared by a rate c, and infected cells are cleared by rate δ. Oseltamivir acts by inhibiting viral production from infected cells.

The key objectives of the disease modelling analysis were:

- Extend a viral kinetic model developed from longitudinal viral load data and oseltamivir carboxylate exposures in immunocompromised adult patients to immunocompromised paediatric patients to characterize the viral kinetics of influenza following oseltamivir dosing.
- Exploration of biologically relevant covariates that may explain inter-individual variability and antiviral treatment effect.
- Identification and characterization of potential population differences impacting the influenza kinetics and oseltamivir effects between adult (≥ 18 years) and paediatric(< 18 years) immunocompromised subjects
- To simulate the effects of oseltamivir dose regimens in the immunocompromised paediatric population to characterize the impact of dose, time from symptom onset to treatment initiation, and the duration of treatment post-infection on viral kinetics

The viral kinetics of this model are described by the following differential equations:

$$\frac{dT}{dt} = -\beta TV \quad (1)$$

$$\frac{dI}{dt} = \beta TV - \delta I \quad (2)$$

$$\frac{dV}{dt} = pI - cV \quad (3)$$

where a pool of target respiratory epithelial cells (T) are infected by a pool of free virus (V) described by a second-order rate constant (β). Infected cells (I) shed virus at a production rate (p). Free virus is cleared by rate (c), and infected cells are cleared by rate (δ).

The antiviral effect of oseltamivir was modelled according to its known mechanism of action for p inhibition, and was described by:

$$INH = \frac{AUC}{AUC_{50} + AUC} \quad (4)$$

$$p = pNT \cdot (1 - INH) \quad (5)$$

where AUC is the area under the concentration-time curve for oseltamivir within a dosing interval at steady state; AUC_{50} is the exposure at half-maximal inhibition and pNT is the rate of free virus production in the absence of drug inhibition. The inhibition effect is set to zero (i.e. INH = 0) during the absence of treatment (pre- or post-treatment).

Model assumptions included:

- The initial amount of uninfected target epithelial cells (T_0) was assumed as 4 x 10^8 cells, based on known respiratory physiology in healthy human adults. There was no replenishment of dead cells.
- The initial conditions for infected cells (I_0) and free virus (V_0) were assumed as 0 cells and 1 vp/mL, respectively. For free virus, a positive viral load (but BLQ) was required for initialization and model stability. An initial condition of 1 vp/mL for V_0 was therefore arbitrarily assumed.
- The time of viral infection was assumed to occur at 36 hours prior to symptom onset.
- Drug inhibition was driven by post-hoc individual estimates for the AUC of oseltamivir carboxylate that were derived from the population PK model. The inhibition effect was implemented only for the treatment duration, and was negated before and after the dosing period. Thus, in the absence of treatment, the rate of viral production is defined by pNT (where INH = 0).

Data manipulation, visualization, and simulations were conducted using version 3.5 of R. Population viral kinetics analyses were conducted via nonlinear mixed effects modelling with the NONMEM software, Version 7.4. Missing post-baseline genotypic and phenotypic resistance covariate values were imputed to be non-resistant, the most common value. Given the large number (618 of 1202; 51.4%) of viral load observations below the limit of quantification (BLQ), the Beal "M3" method was applied.

The base structural model (Figure 5.1.4.) was implemented in Monolix during the previous (IC adult) modelling effort. The initial conditions, population time since infection estimate, and parameter estimates from the previous IC adult analysis were used as the initial conditions and initial parameter estimates for translation into NONMEM. The Bayesian estimation method in NONMEM (METHOD=BAYES) with ADVAN13 and TOL=9 was used. Random effects (ETAs) were placed on parameters β, δ, pNT, AUC_{50}, and c, and a

proportional log-additive error model was implemented, modelled as a SIGMA-like THETA. Random effect covariances were set to 0 to maintain consistency with the original IC adult modelling work.

Following implementation of the initial base structural model in NONMEM, extension to the paediatric population was explored. Paediatric population scaling was examined for potential inclusion on the free virus and infected cell clearance rate parameters (c and δ, respectively) to account for potential differences in immune response between IC adults and IC paediatric patients. Population covariate (paediatric vs. adult) on viral production rate and infection rate was not considered, as these parameters are inherent to viral strains and not expected to differ between patient populations.

The final IC adult and paediatric viral kinetics model was used to simulate oseltamivir treatment scenarios of interest. For each treatment arm in these scenarios, 500 simulated trials, each with 250 IC adult and 250 IC paediatric patients were conducted. For each trial and each patient random draws from the posterior distribution were used for all estimated model parameters (fixed effects (THETAs), random effects (ETAs) and residual error (EPS) effects). For each patient and simulated trial, the viral load time course was then simulated using the mrgsolve R package. Then, the median and 90% prediction interval around the median were calculated on a per treatment arm basis after binning simulated viral load measurements by time, and patient group (IC adult or IC paediatric).

5.2 Results

Population PK model

Dataset. The data included 116 and 120 quantifiable plasma concentrations of oseltamivir and OC, respectively, collected from 30 immunocompromised subjects (26 and 4 subjects from studies NV25719 and NV20234, respectively). For oseltamivir, 3 samples were below the limit of quantification and excluded, as well as 1 evaluable data point that was not consistent with the dosing history. No OC samples were excluded. Figure 5.2.1 and Figure 5.2.2 display the individual plasma concentration profiles for oseltamivir and OC, respectively, versus time (time after first dose) and time after dose for both studies.

Figure 5.2.1. Individual Plasma Concentrations of Oseltamivir versus Time and Time after Dose, by Dose Group.

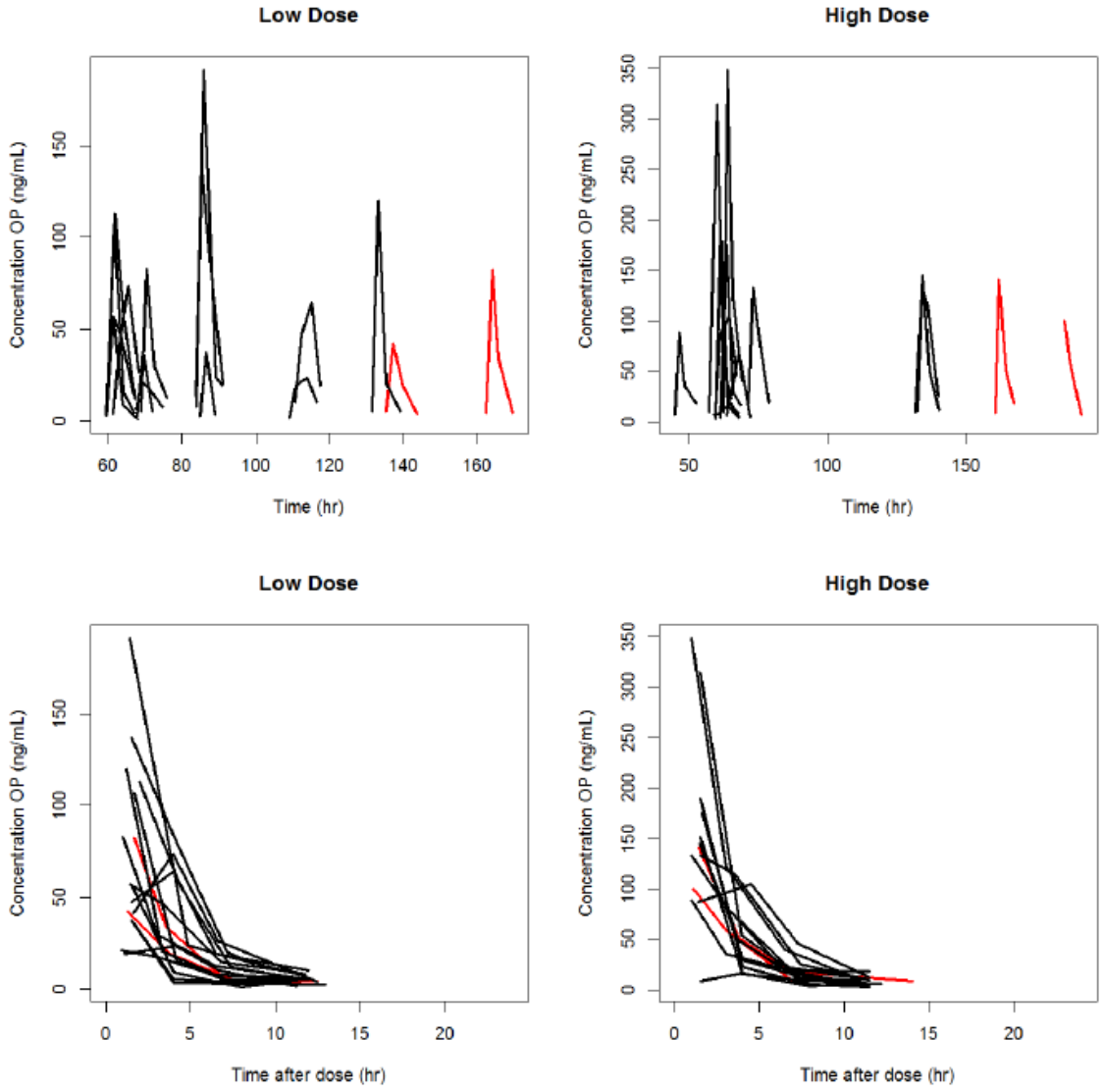
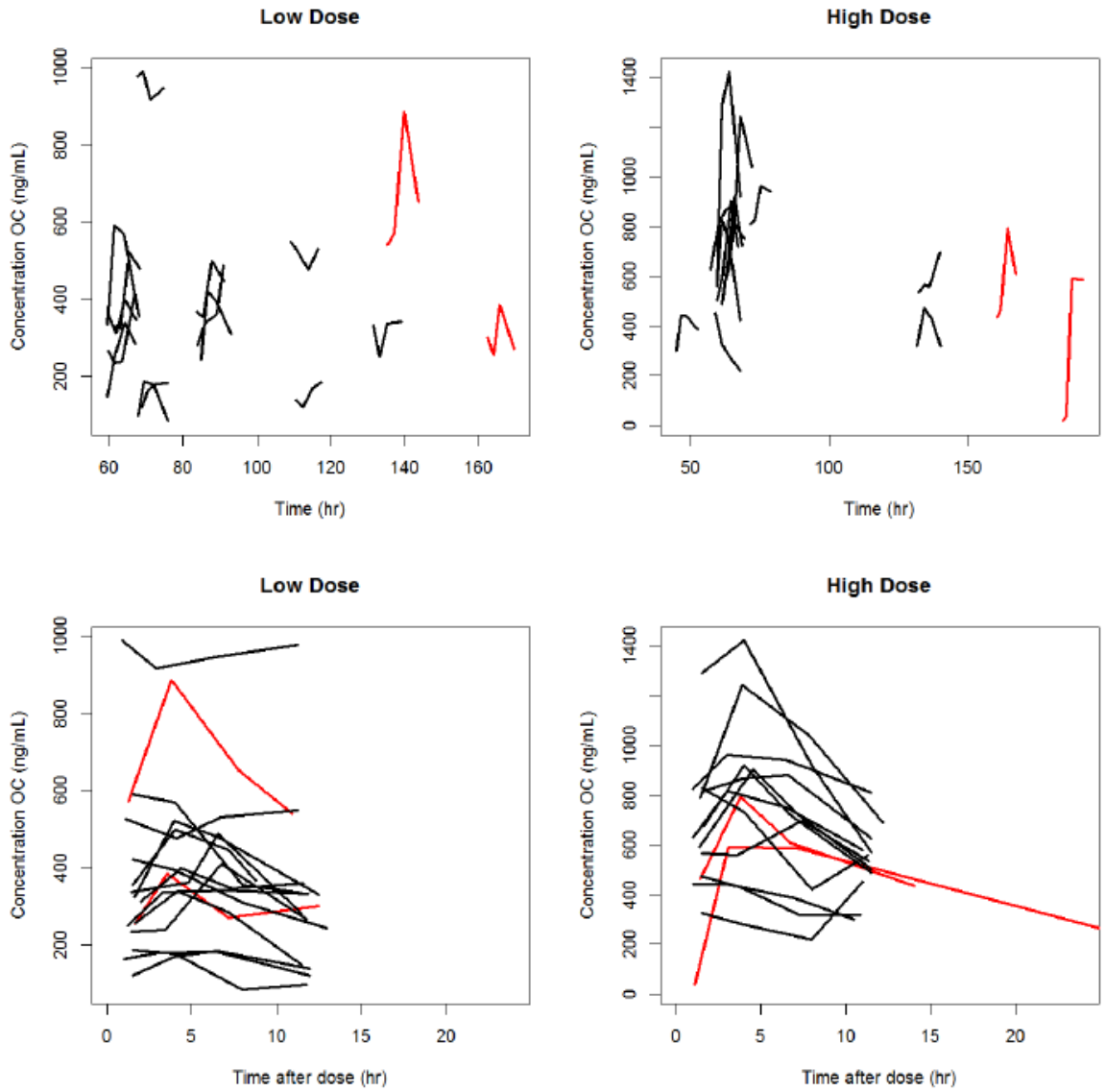


Figure 5.2.2. Individual Plasma Concentrations of Oseltamivir Carboxylate versus Time and Time after Dose, by Dose Group.



The analysis included paediatric subjects from 1 to <18 years old with a wide range of weights (from 9.4 kg to 60.6 kg). Of 30 subjects with PK, there were 10 (33%) females and 3 (10%) had transplantation. Approximately equal number received the low (16/30; 53%) and high (14/30; 47%) doses. Majority of subjects were younger than 13 years old (28/30; 93%) and approximately equal number (9, 7, 9) were in the first three weight groups (< 15 kg, 15-23 kg, and 23-40 kg respectively). The summaries of covariates, by study and dose group are presented in Table 5.2.1 and Table 5.2.2.

Table 5.2.1. Summary of Continuous Covariates

Covariate	Statistic	Total	Study NV25719		Study NV20234 [a]	
			Low Dose	High Dose	Low Dose	High Dose
	N	30	14	12	2	2
Age (years)	**mean**	6.37	7.14	4.25		
	SD	4.3	4.26	2.3		
	median	5	6.5	3		
	range	1 ; 17	1 ; 12	2 ; 8	4 ; 14	5 ; 17
Weight (kg)	**mean**	24.7	26.6	19		
	SD	12.6	12.4	8.53		
	median	21.1	27.2	14.8		
	range	9.4 ; 60.6	9.4 ; 49.8	12.2 ; 41	27 ; 32.7	18 ; 60.6
CLCR (mL/min)	**mean**	147	137	147		
	SD	31.4	24.8	29.2		
	median	139	129	144		
	range	98.9 ; 229	110 ; 192	98.9 ; 216	191 ; 229	138 ; 176
Height (cm)	**mean**	115	118	105		
	SD	23.6	25.7	16.9		
	median	112	118	102		
	range	80 ; 159	80 ; 156	85 ; 137	110 ; 151	112 ; 159
BSA (m^2)	**mean**	0.868	0.915	0.732		
	SD	0.307	0.314	0.215		
	median	0.787	0.865	0.651		
	range	0.446 ; 1.62	0.446 ; 1.43	0.521 ; 1.23	0.88 ; 1.2	0.751 ; 1.62
SCR (mg/dL)	**mean**	0.349	0.367	0.305		
	SD	0.101	0.0994	0.0725		
	median	0.335	0.37	0.30		
	range	0.2 ; 0.633	0.2 ; 0.5	0.21 ; 0.447	0.317 ; 0.362	0.351 ; 0.633

a There are only 2 subjects in each dose group, therefore only individual values (i.e. range) are reported.
BSA = body surface area; **CRCL** = creatinine clearance; **SCR** = serum creatinine; **SD**= standard deviation.

Table 5.2.2. Summary of Categorical Covariates

Covariate	Level	Total	Study 25719		Study 20234	
			Low Dose	High Dose	Low Dose	High Dose
Dose (DOSE)	30	3 (10%)	3 (21.4%)	NA	NA	NA
	45	3 (10%)	3 (21.4%)	NA	NA	NA
	60	7 (23.3%)	6 (42.9%)	NA	1 (50%)	NA
	75	3 (10%)	2 (14.3%)	NA	1 (50%)	NA
	90	7 (23.3%)	NA	6 (50%)	NA	1 (50%)
	135	3 (10%)	NA	3 (25%)	NA	NA
	150	1 (3.3%)	NA	NA	NA	1 (50%)
	180	2 (6.7%)	NA	2 (16.7%)	NA	NA
	225	1 (3.3%)	NA	1 (8.3%)	NA	NA
Race (RACE)	Caucasian	22 (73.3%)	8 (57.1%)	10 (83.3%)	2 (100%)	2 (100%)
	Asian	1 (3.3%)	NA	1 (8.3%)	NA	NA
	American Indian or Alaska Native	1 (3.3%)	1 (7.1%)	NA	NA	NA
	Other	6 (20%)	5 (35.7%)	1 (8.3%)	NA	NA
Sex (SEXF)	Male	20 (66.7%)	9 (64.3%)	8 (66.7%)	2 (100%)	1 (50%)
	Female	10 (33.3%)	5 (35.7%)	4 (33.3%)	NA	1 (50%)
Transplantation status (TRSPST)	No	27 (90%)	12 (85.7%)	12 (100%)	1 (50%)	2 (100%)
	Yes	3 (10%)	2 (14.3%)	NA	1 (50%)	NA
Dose Group (DSGRP)	Low	16 (53.3%)	14 (100%)	NA	2 (100%)	NA
	High	14 (46.7%)	NA	12 (100%)	NA	2 (100%)
Weight/Age Group (WAGRP)	≤ 15 kg	9 (30%)	3 (21.4%)	6 (50%)	NA	NA
	15-23kg	7 (23.3%)	3 (21.4%)	3 (25%)	NA	1 (50%)
	23-40kg	9 (30%)	6 (42.9%)	2 (16.7%)	1 (50%)	NA
	> 40 kg and <13yrs	3 (10%)	2 (14.3%)	1 (8.3%)	NA	NA
	≥13 yrs	2 (6.7%)	NA	NA	1 (50%)	1 (50%)

Population PK model runs. For each model type, first the model with all parameters fixed to the values in the corresponding Prior Model was tested. Then, 2 additional effects, multiplicative study effects on OP and OC

clearance were added; the parameters for these effects were estimated while all other parameters remained fixed. The summary of model runs is presented in Table 5.2.3. Each run converged successfully and provided estimates of standard errors. Of tested models, the Prior Model 1 (Run 013; OFV 2047.351) had lower objective function value than Prior Model 2 (Run 102 and Run 112; OFV 2072.955 and 2072.877), while the values of standard deviation for the random effect on OC apparent clearance (CL_M) were similar between the models. The Prior Model 1 (Run 013) was selected for further analyses.

Table 5.2.3. Summary of NONMEM Runs for Model Development.

Run	Description	OFV*	Comment
Prior Model 1: Model in Healthy Pediatric and Young Adult Subjects			
012	Prior Model 1 with fixed parameters	2052.912	
013	As 012 with study effects on CL and CL_M	2047.351	Fr_{CL}=0.901; Fr_{CLM}=0.887; CV=0.500
Prior Model 2: Pediatrics through Geriatrics Model: CLCR computed as in the manuscript was used			
101	Prior Model 2 with fixed parameters	2076.877	
102	As 201 with study effects on CL and CL_M	2072.955	Fr_{CL}=1.16; Fr_{CLM}=1.02; CV = 0.436
Prior Model 2: Pediatrics through Geriatrics Model: CLCR computed using standard Cockcroft and Gault formula was used			
111	Prior Model 2 with fixed parameters	2077.022	
112	As 211 with study effects on CL and CL_M	2072.877	Fr_{CL}: 1.16; Fr_{CLM}: 1.01; CV = 0.436
Model 013 Refinement			
018	As 013 but different effects for AGE < 10 and AGE ≥ 10 years	2003.967	$Fr_{CL,<10}$=1.08; $Fr_{CLM,<10}$=1.08; $Fr_{CL,\geq 10}$=0.556; $Fr_{CLM,\geq 10}$=0.509
019	As 018 but no effects for AGE < 10	2005.993	$Fr_{CL,\geq 10}$=0.556 (0.380-0.732) $Fr_{CLM,\geq 10}$=0.509 (0.362-0.655)

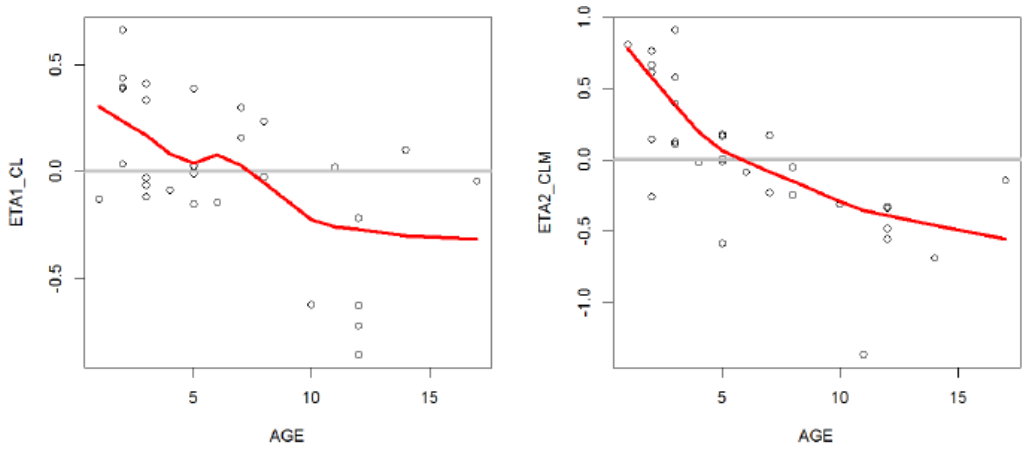
CL = Clearance of oseltamivir; CL_M = clearance of oseltamivir carboxylate; CV = coefficient of variation; Fr = fraction.

*OFV: Objective Function Value (-2 log likelihood)

The basic goodness of fit plots for Run 013 showed no major deficiencies. However, the plots of random effects versus age (Figure 5.2.3) and weight (Figure 5.2.4) revealed model misspecification, as the random effects on clearance of oseltamivir (CL) and oseltamivir carboxylate (CL_M) decreased with age and weight. The individual estimates of CL and CL_M for paediatric IC subjects plotted versus age and weight were superimposed with the respective estimates for otherwise healthy paediatric and adult subjects and adult IC subjects in Figure 5.2.5. Based on a visual inspection of the plot it was observed that the distributions of CL and CL_M for IC and otherwise healthy subjects were similar for young subjects (< 10 years of age). For patients 10 years and older, CL and CL_M were lower in IC patients as compared to the corresponding parameters for otherwise healthy subjects. Run 018 implemented this observation by allowing separate effects of IC status for subjects younger than 10 years and subjects of 10-years old or older (Table 5.2.3). The estimates of the IC effect in younger subjects were close to no-effect level and confidence intervals included 1. When these effects were fixed to 1 (Run 019), the objective function increased by only 2 points (Table 5.2.3). This model (Run 109) was selected as the final model.

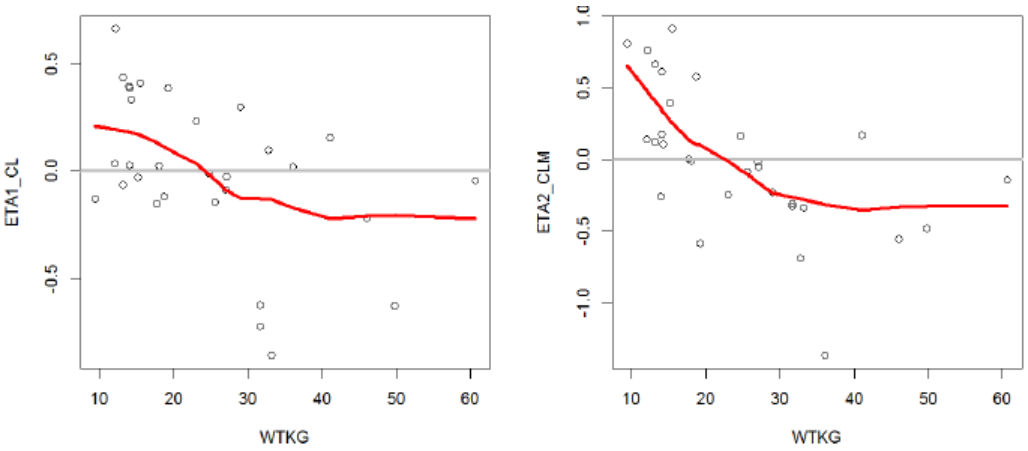
Results of the final model (Run 019) indicated that IC paediatric subjects younger than 10 years old appeared to have similar apparent clearances of oseltamivir and OC compared to otherwise healthy subjects in the same age range, whereas in IC paediatric subjects from 10 to 17 years of age the apparent clearances of oseltamivir and OC were decreased by 44.4% (95%CI: 26.8 - 62.0%) and 49.1% (95%CI: 34.5 - 63.8%), respectively, compared to otherwise healthy subjects in the same age range.

Figure 5.2.3 Relationships of the Inter-Individual Random Effects with Age (Run 013).



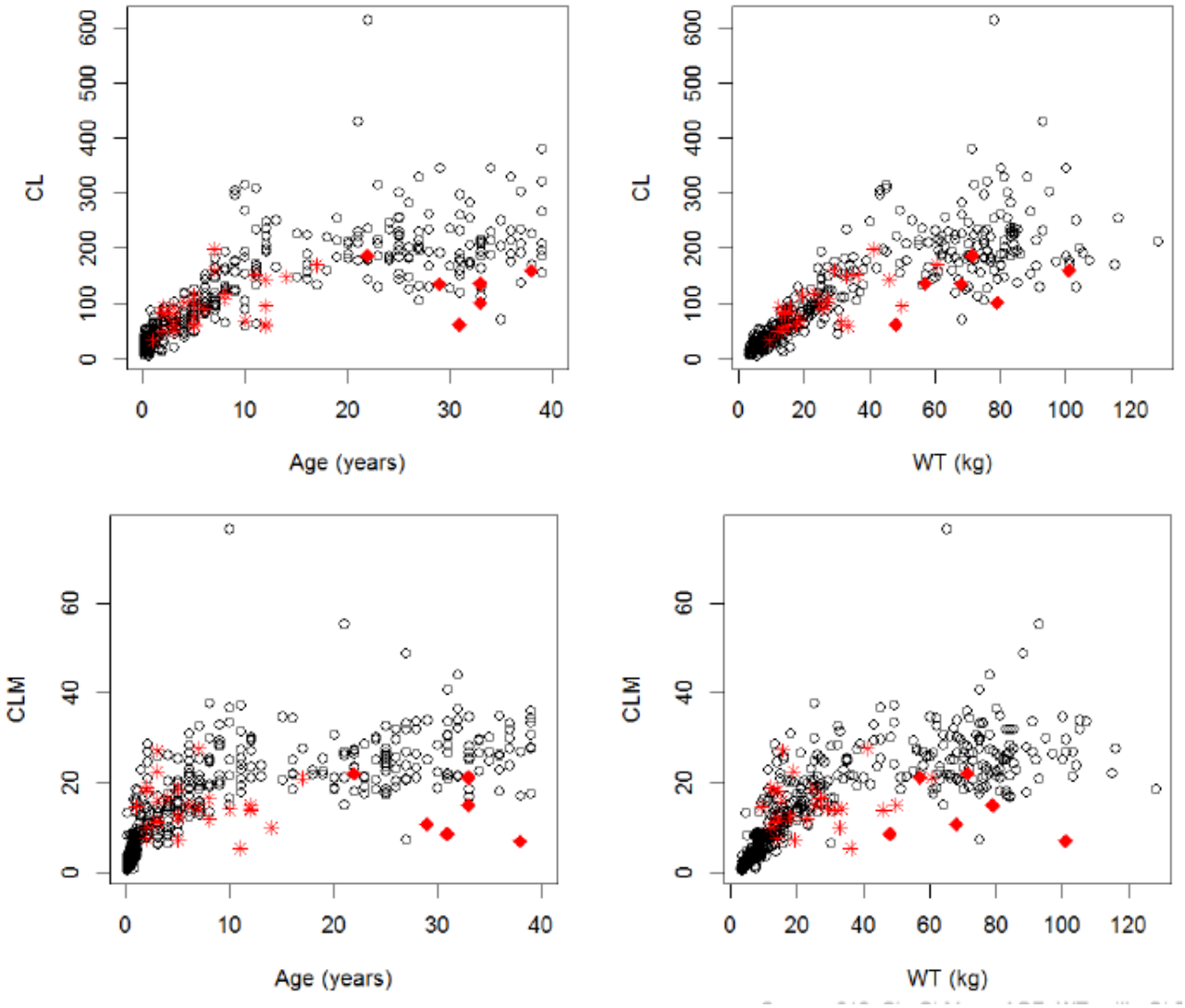
Left: Oseltamivir clearance vs. Age. **Right**: Oseltamivir carboxylate clearance vs. Age.

Figure 5.2.4 Relationships of the Inter-Individual Random Effects with Weight (Run 013).



Left: Oseltamivir clearance vs. Weight. **Right**: Oseltamivir carboxylate clearance vs. Weight.

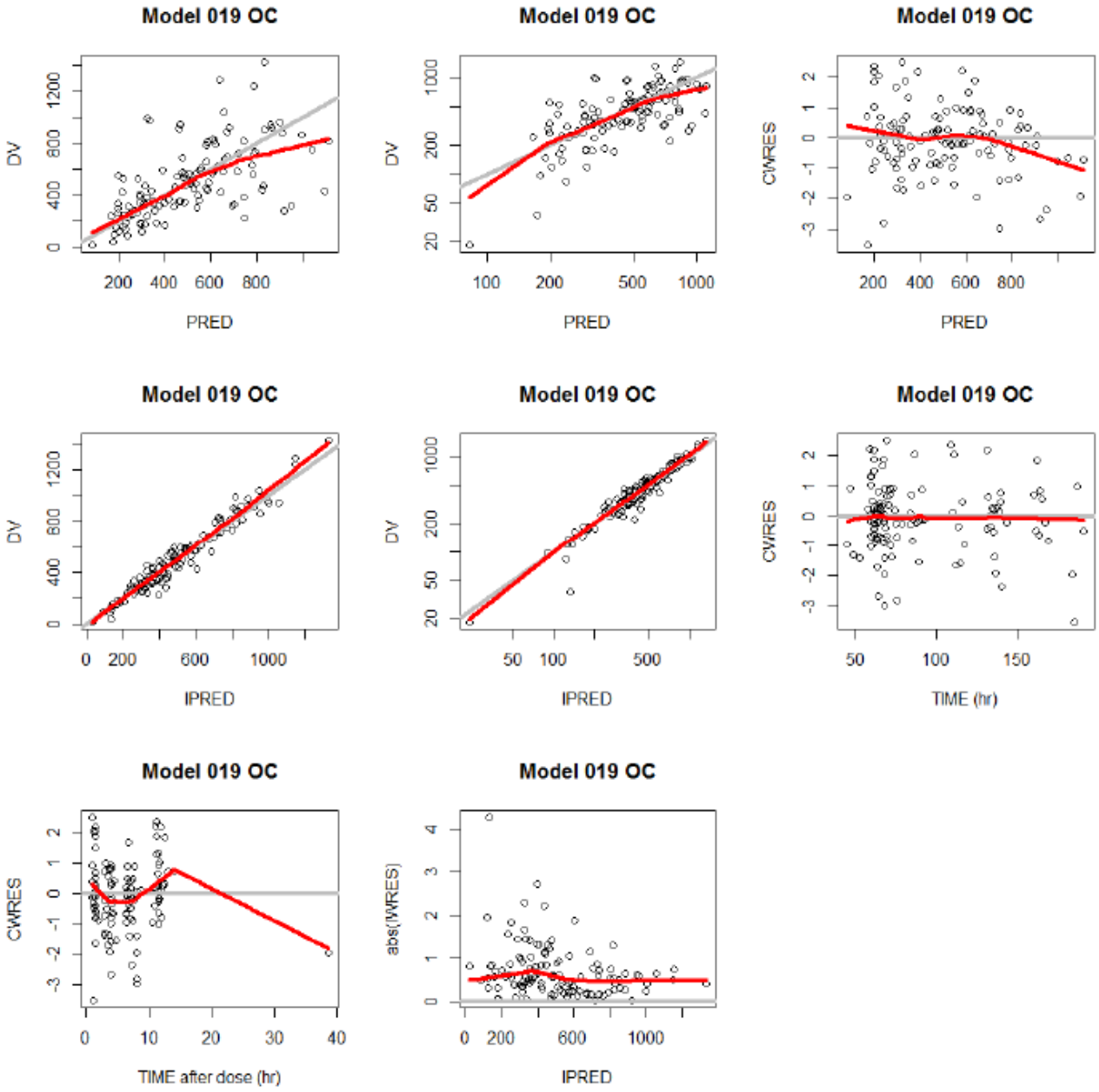
Figure 5.2.5. Individual Estimates of CL (top) and CL_M (bottom) in Paediatric IC Subjects, Adult IC subjects, and Otherwise Healthy Adult and Paediatric Subjects versus Age and Weight.



Individual estimates of CL and CL_M in: **black circles**: otherwise healthy adult and paediatric subjects from the established model, **red stars**: paediatric IC subjects of the current analysis data set, **red diamonds**: adult IC subjects of 18-40 years old from the established model.

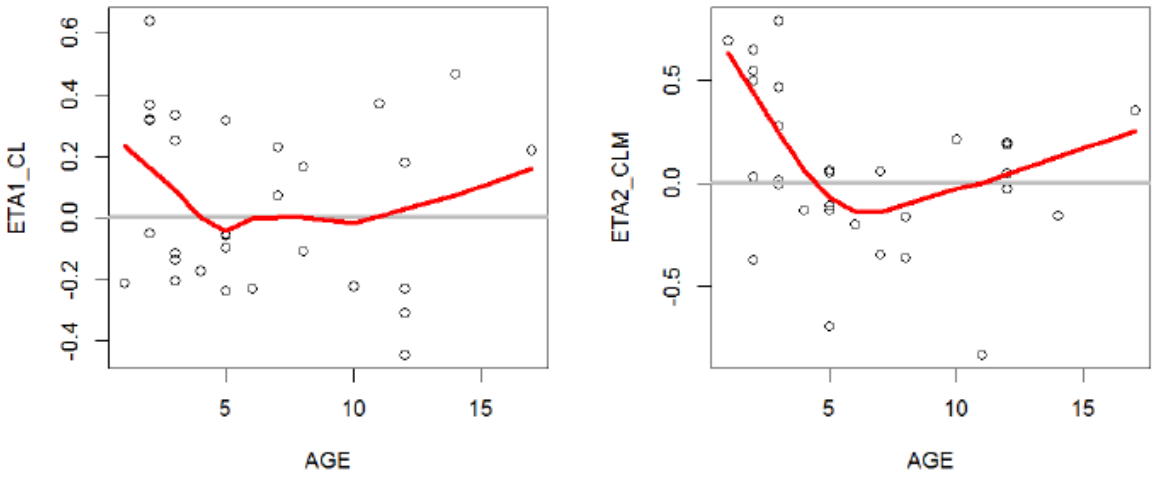
Run 019 goodness of fit plots for oseltamivir and OC did not reveal any major deficiencies; plots for OC are displayed in Figure 5.2.6. The plots of random effects versus age (Figure 5.2.7) and weight (Figure 5.2.8) indicated improved fit compared with Run 013. The normalized prediction distribution errors (NPDE) plots and visual predictive check (VPC) plots confirmed the ability of the model to predict the central tendency and variability of the observed data; plots for OC are shown in Figure 5.2.9 and Figure 5.2.10. Overall, the diagnostic plots demonstrated that the model could be used to predict oseltamivir and OC exposures in immunocompromised subjects and that individual predictions of exposure could be used for exposure-response analyses.

Figure 5.2.6. Goodness-of-Fit for Model 019: Oseltamivir Carboxylate.



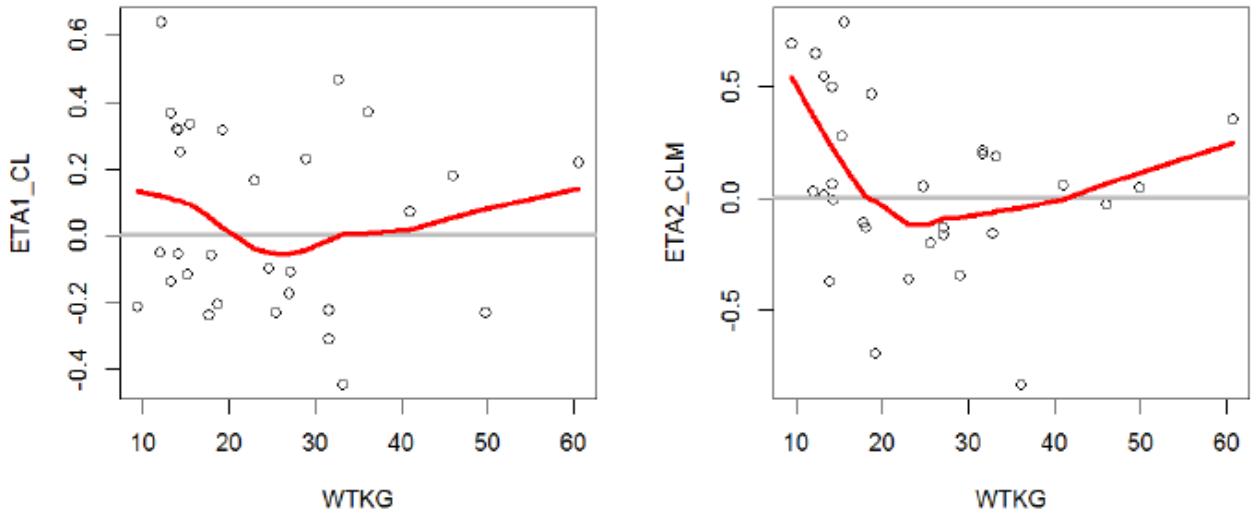
DV: Observed concentrations; **PRED**: population predictions of the model; **IPRED**: individual predictions of the model; **CWRES**: conditional weighted residuals; **IWRES**: individual weighted residuals; **TIME**: time after the first dose. The gray solid y=x or y=0 lines are included for reference. The bold red lines are the lowess (local regression smoother) trend lines.

Figure 5.2.7. Relationships of the Inter-Individual Random Effects with Age (Run 019).



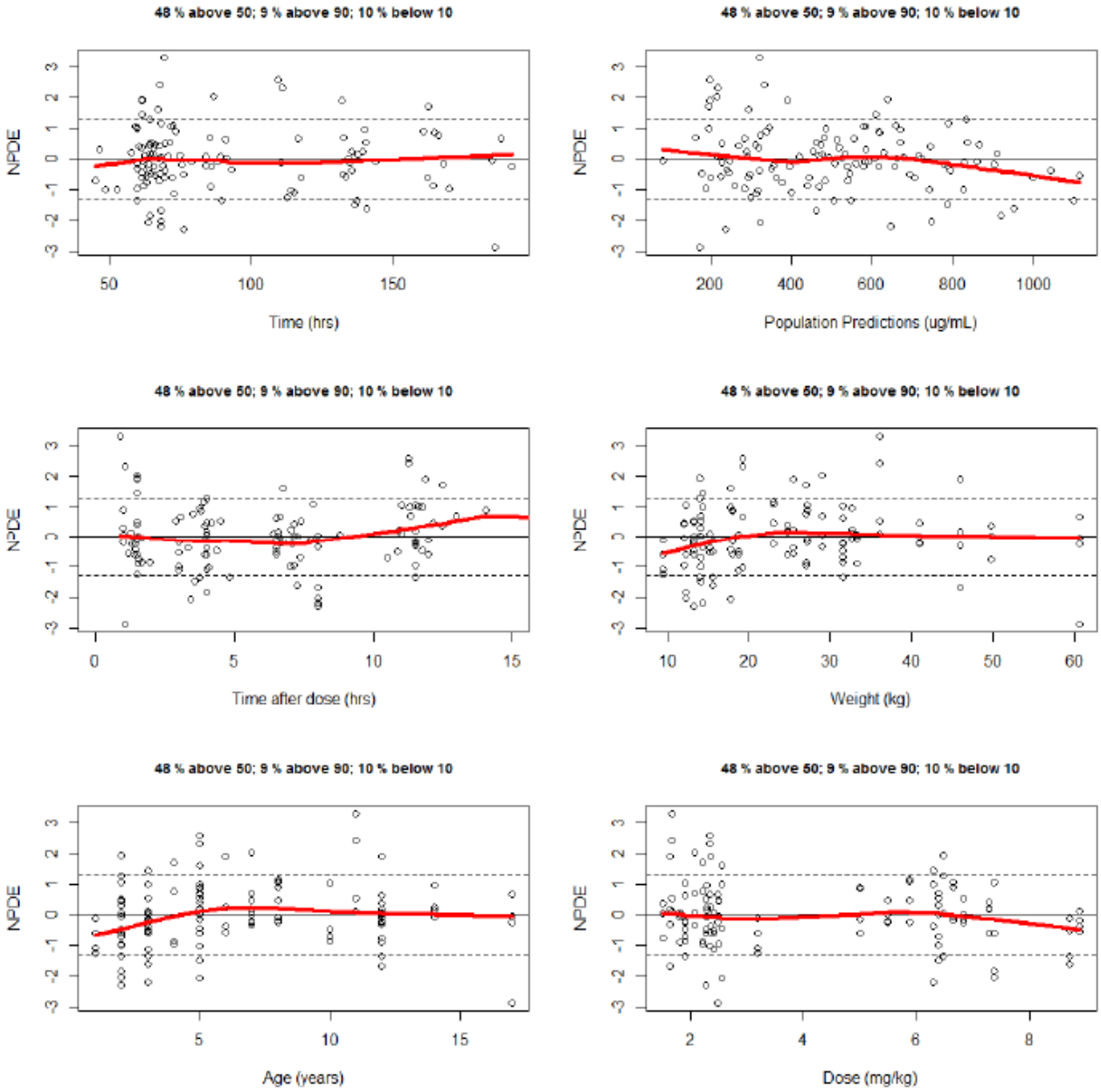
Left: Oseltamivir clearance vs. Age. **Right**: Oseltamivir carboxylate clearance vs. Age.

Figure 5.2.8. Relationships of the Inter-Individual Random Effects with Weight (Run 019).



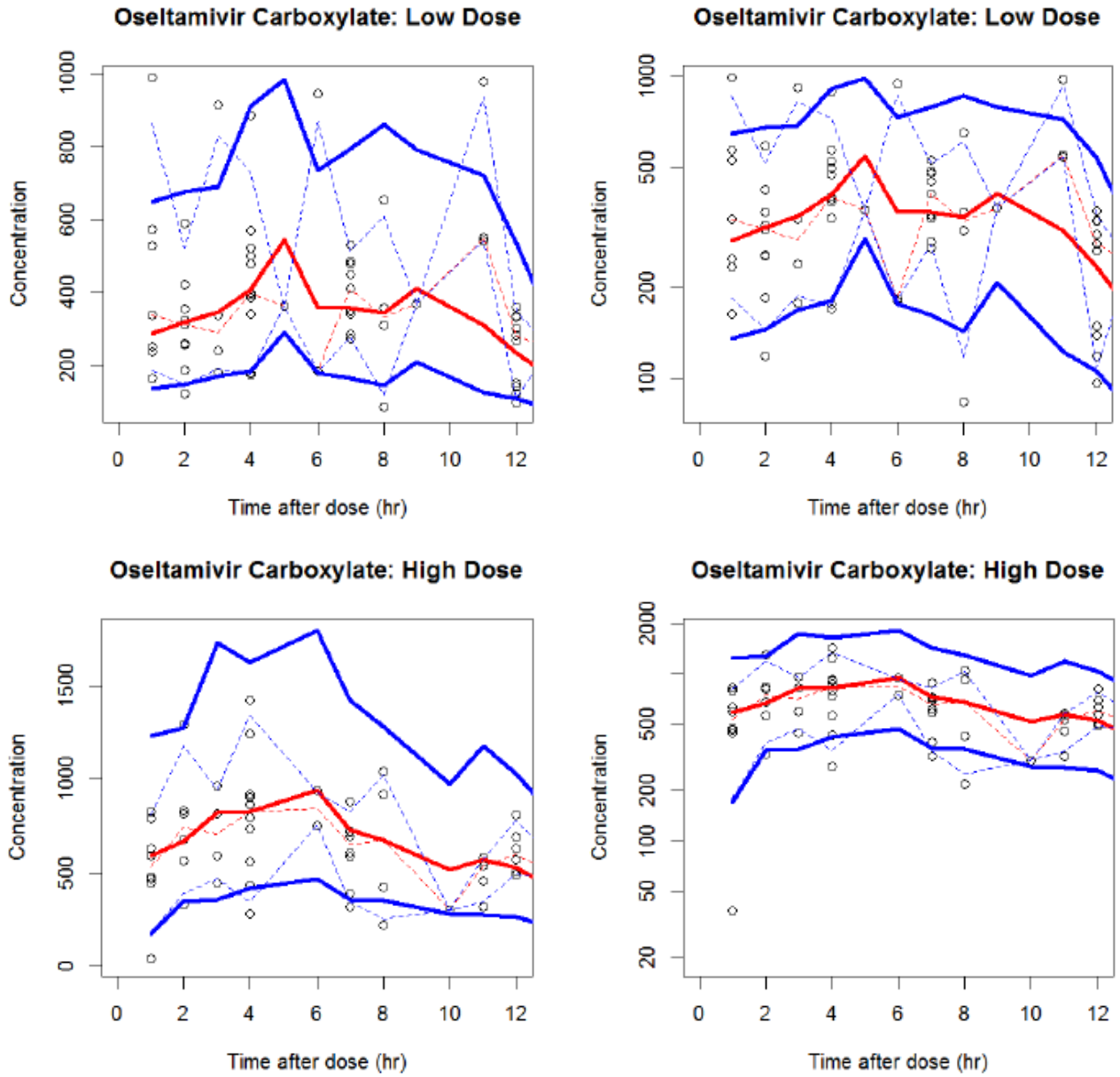
Left: Oseltamivir clearance vs. Weight. **Right**: Oseltamivir carboxylate clearance vs. Weight.

Figure 5.2.9. NPDE Plots for Model 019: Oseltamivir Carboxylate.



Circles: normalized prediction distribution errors; red lines: lowess (local regression smoother) trend lines.

Figure 5.2.10. Visual Predictive Check for Model 019: Oseltamivir Carboxylate.



The circles show the observed concentrations. The lines show median (red), and the 5th and 95th percentiles (blue) of the simulated (solid) and observed (dash) concentrations. The simulated values were computed from 1000 trials simulated using dosing, sampling, and the covariate values of the analysis dataset.

Model-Based PK Simulations. Model/Run 019 was used to simulate individual estimates of PK parameters and steady-state exposures for IC paediatric patients.

IC paediatric subjects in study NV25719 were treated with weight- and age-based conventional dose (N=14) or 3x conventional dose (N=12). Summary of model-predicted individual steady-state exposure estimates for oseltamivir and OC are presented in Table 5.2.4. Most exposure metrics indicated approximately 2 times higher exposure in the 3x conventional dose, i.e. less than proportional increase in exposure with increasing dose. None of the established oseltamivir PK models indicated non-linearity, thus the apparent nonlinearity of exposure observed in this study was considered to be related to an imbalance of covariates in the two dosing groups. There were 6 patients > 10 years of age (range: 10-12 years) in the conventional dose group

(mean age of 7 years, mean weight of 27 kg), whereas none of the patients in the 3x conventional dose group were > 10 years of age (mean age 4 years, mean weight of 19 kg). As estimated CL and CL_M were 44% and 49% lower in 10 to < 18 years old IC paediatric patients, whereas clearances were unchanged in IC paediatric patients < 10 years, this might explain the lower than dose-proportional increase of exposure with dose. Furthermore, there was one patient in the conventional dose group who had a history of nephrectomy and low estimated creatinine clearance (CrCl) (62 mL/min/1.73m^2) on the PK assessment day, but not at baseline.

Table 5.2.4 Model-Predicted Oseltamivir and Oseltamivir Carboxylate Steady-State Exposure Metrics by Dose Group (study NV25719).

Parameter	Statistics	Oseltamivir		Oseltamivir Carboxylate	
		Conventional Dose	3x Conventional Dose	Conventional Dose	3x Conventional Dose
C_{max} (ng/mL)	N	14	12	14	12
	mean	59.8	139	440	847
	SD	19.4	48	220	288
	median	60	124	430	845
	range	25.7 ; 97.4	68.7 ; 234	186 ; 1050	444 ; 1400
C_{min} (ng/mL)	N	14	12	14	12
	mean	4.96	8.19	279	483
	SD	2.46	2.79	177	135
	median	3.94	6.92	259	480
	range	1.82 ; 9.46	5.34 ; 12.7	84.6 ; 807	289 ; 710
AUC_{0-12h} (ng/mL*hr)	N	14	12	14	12
	mean	255	516	4410	8160
	SD	93.4	151	2400	2500
	median	245	468	4260	8100
	range	132 ; 414	327 ; 832	1640 ; 11300	4680 ; 11900

Subsequently, oseltamivir and OC exposures in IC paediatric subjects of study NV25719 were compared with exposures of otherwise healthy paediatric subjects of study WV15758. A stratification by age allows to further illustrate the model finding with similar or slightly higher predicted oseltamivir and OC exposures in IC subjects younger than 10 years old and in paediatric otherwise healthy subjects (Table 5.2.5), while in older paediatric IC subjects the predicted oseltamivir and OC exposures were approximately 2.1-2.2 fold higher than in paediatric otherwise healthy subjects (Table 5.2.6).

Table 5.2.5. Comparison of Predicted Steady-State Mean Exposures with Historical Data in Paediatric Subjects: Age < 10 years old.

Study	Dose group	N	Oseltamivir			Oseltamivir Carboxylate		
			C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-12} (ng/mL*hr)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-12} (ng/mL*hr)
NV25719	Low	8	45.5	2.96	172	281	172	2780
	High	12	40.3	2.38	150	254	145	2450
	All	20	42.4	2.61	159	265	156	2580
WV15758		75	36.1	2.84	161	243	146	2400
Percent difference between predicted exposure in Study NV25719 and Study WV15758 following 2 mg/kg dose								
			17%	-8%	-1%	9%	7%	4%

Predicted exposures for subjects with PK are compared with the respective values in immunocompetent paediatric subjects (Study WV15758). For both studies, exposures are normalized to 2 mg/kg dose.

Table 5.2.6. Comparison of Predicted Steady-State Mean Exposures with Historical Data in Paediatric Subjects: Age ≥ 10 years old

Study	Dose group	N	Oseltamivir			Oseltamivir Carboxylate		
			Cmax (ng/mL)	Cmin (ng/mL)	AUC0-12 (ng/mL*hr)	Cmax (ng/mL)	Cmin (ng/mL)	AUC0-12 (ng/mL*hr)
All subjects from this group								
NV25719	Low	6	74.9	7.54	352	683	442	6900
	High	0	-	-	-	-	-	-
	All	6	74.9	7.54	352	683	442	6900
One patient with low CRCL excluded (ID=701)								
NV25719	Low	5	83.6	8.09	382	567	336	5540
	High	0	-	-	-	-	-	-
	All	5	83.6	8.09	382	567	336	5540
WV15758		14	34.0	3.27	165	308	195	3090
Percent difference between predicted exposure in Study NV25719 and Study WV15758 following 2 mg/kg dose								
All patients			120%	130%	113%	122%	127%	123%
Five patients with normal CRCL			146%	147%	132%	84%	72%	79%

Predicted exposures for subjects with PK are compared with the respective values in immuno- competent paediatric subjects (Study WV15758). For both studies, exposures are normalized to 2 mg/kg dose.

IC paediatric subjects in study NV20234 were treated with weight- and age-based conventional dose or 2x conventional dose. There were only 2 subjects in each dose group. Summary of model-predicted individual steady-state exposure estimates for oseltamivir and OC are presented in Table 5.2.7.

Table 5.2.7. Model-Predicted Oseltamivir and Oseltamivir Carboxylate Steady-State Exposure Metrics by Dose Group (study NV20234)

Parameter	Statistic	Oseltamivir		Oseltamivir Carboxylate	
		Conventional Dose	2x Conventional Dose	Conventional Dose	2x Conventional Dose
C_{max} (ng/mL)	**N**	2	2	2	2
	values	53 ; 54.2	76.7 ; 111	356 ; 806	741 ; 825
C_{min} (ng/mL)	**N**	2	2	2	2
	values	3.36 ; 3.48	6.95 ; 7.96	230 ; 456	393 ; 436
AUC_{0-12h} (ng/mL*hr)	**N**	2	2	2	2
	values	211 ; 217	409 ; 441	3600 ; 7760	7260 ; 7560

Exposure-response analysis

Time-to-Event analyses. Notable ER relationships were not identified for time to cessation of viral shedding, determined by culture and RT-PCR (Figure 5.2.11), although a trend for faster resolution of symptoms (including fever) was observed for high exposure group (Figure 5.2.12).

Figure 5.2.11. Kaplan-Meier Plot of Time to Cessation of Viral Shedding by Culture (left) and RT-PCR (right) by Exposure Groups, defined by the Median of the Predicted OC Steady-State C_{min}.

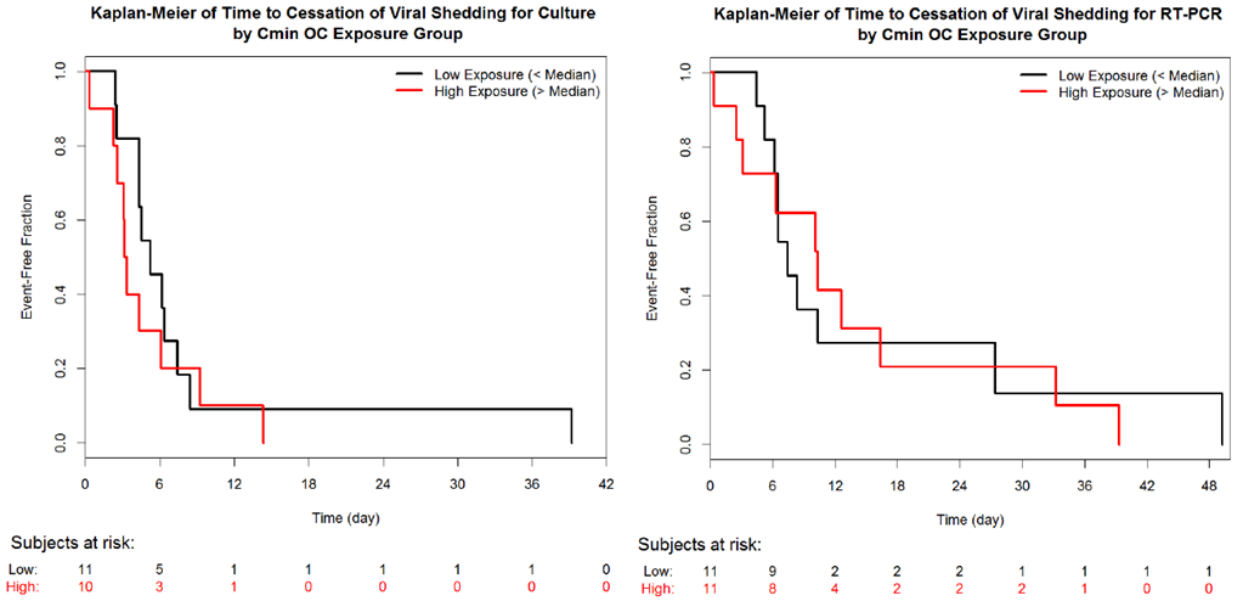
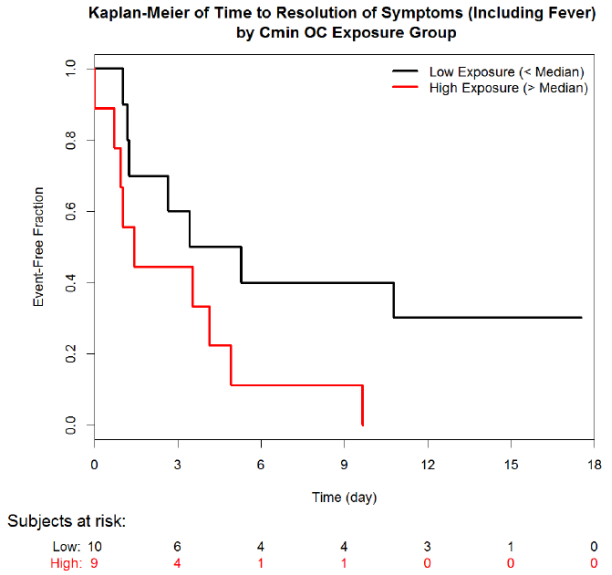


Figure 5.2.12. Time to Resolution of Symptoms (Including Fever) by Exposure Category.



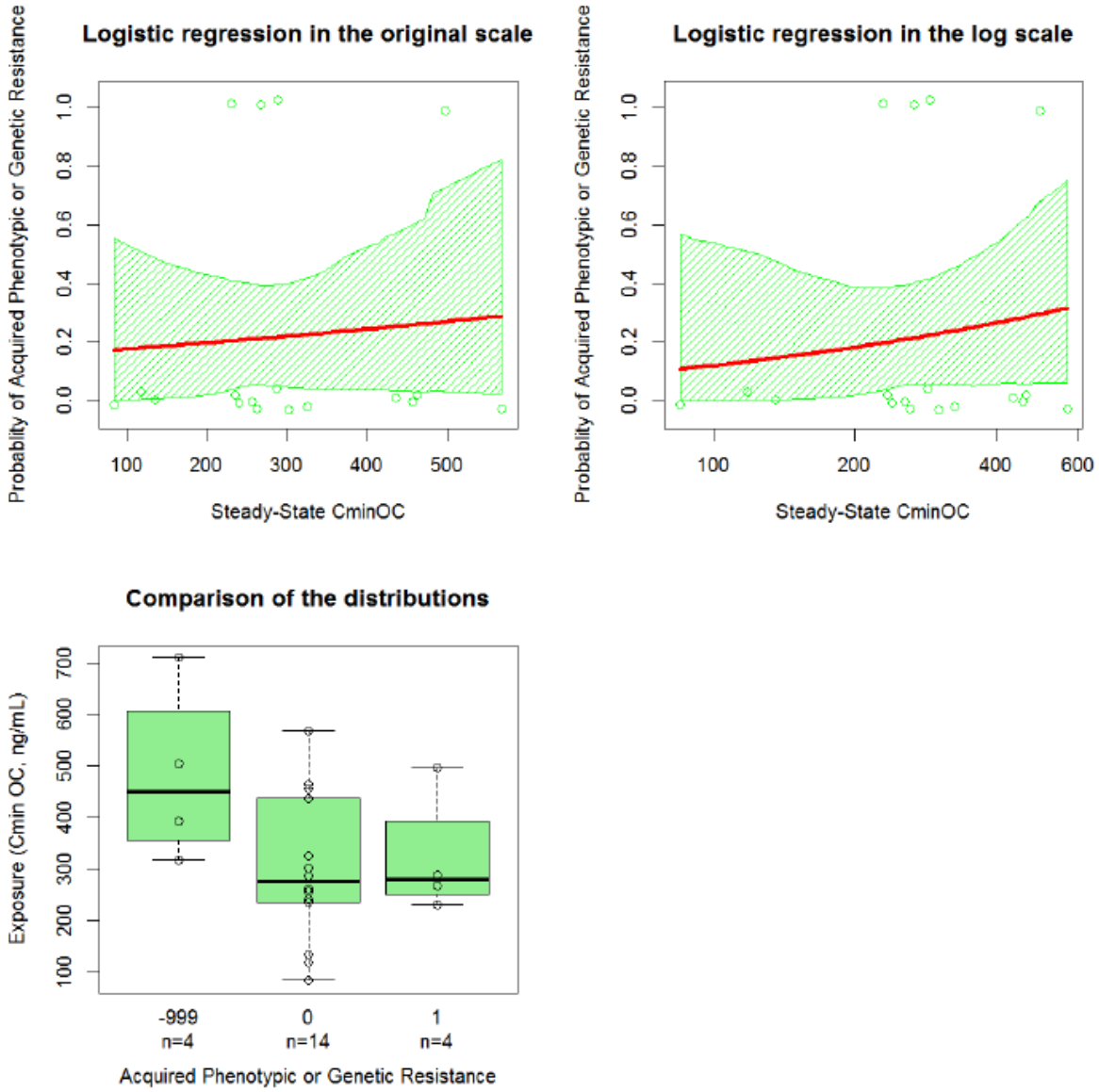
Analyses of Viral Titre/Load Measures. No relationship was observed between exposure and viral titre/load measures, as summarised in Table 5.2.8. Likewise, there were no correlations between viral kinetics (viral titres/loads and their change from baseline) and exposure.

Table 5.2.8. Summary of Linear Regression Models for Viral Titre/Load Measures

Formula	Intercept	Exposure Coefficient	P-value
CULAUCVT ~ $C_{min,OC}$	550	0.0652	0.941
CULAUCVT ~ log($C_{min,OC}$)	-181	132	0.616
CULAUCVT ~ $C_{min,OC}$>median	636	-128	0.629
CULPVT ~ $C_{min,OC}$	3.64	0.000369	0.867
CULPVT ~ log($C_{min,OC}$)	1.38	0.417	0.524
CULPVT ~ $C_{min,OC}$>median	4.02	-0.523	0.427
PCRAUCVT ~ $C_{min,OC}$	755	1.9	0.452
PCRAUCVT ~ log($C_{min,OC}$)	-2160	621	0.349
PCRAUCVT ~ $C_{min,OC}$>median	1400	-126	0.843
PCRPVT ~ $C_{min,OC}$	6.45	0.00103	0.5
PCRPVT ~ log($C_{min,OC}$)	4.8	0.35	0.44
PCRPVT ~ $C_{min,OC}$>median	6.86	-0.134	0.772

Analyses of Treatment-Emergent Resistance. There were 4 patients with treatment-emergent genetic resistance; these patients also developed treatment-emergent phenotypic resistances. No other patients had treatment-emergent phenotypic resistance. There were no differences in exposures between patients that developed and did not develop resistance (Figure 5.2.13). These results do not suggest a benefit (i.e. less viral resistance) coming from a higher exposure to OC.

Figure 5.2.13. Treatment-emergent Genetic or Phenotypic Resistance versus Exposure.



Red line: logistic regression line; **green region**: 90% confidence interval for the logistic regression line.
Treatment-emergent resistance: -999 = missing; 0 = No; 1 = Yes.

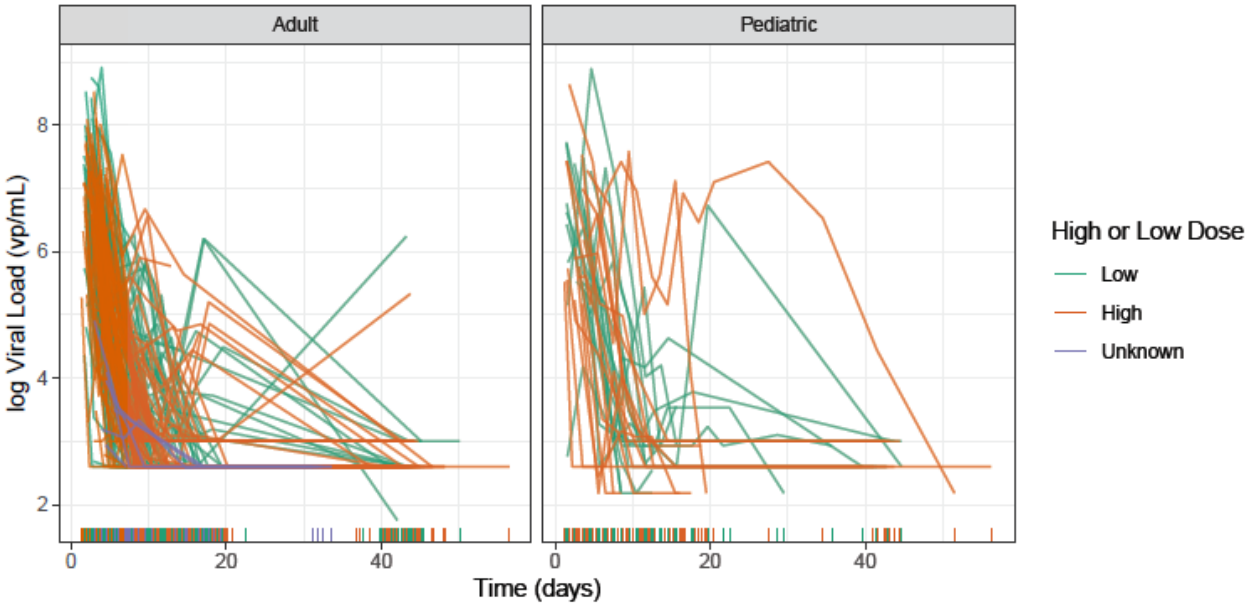
Disease modelling

Dataset: The IC paediatric population consisted of data from 36 patients (N = 20 from study NV25719 and N = 16 from study NV20234); the IC adult population consisted of data from 156 IC patients (N = 150 from study NV20234 and N = 6 from study NV25118). The model estimation dataset contained longitudinal influenza (type A or B) viral load observations from studies NV20234, NV25719, and NV25118. The combined model estimation data set consisted of 1,202 viral load observations taken from192 individuals. Across all studies, there were 618 viral load observations that were BLQ, comprising 51.4% of all observations in the data set. The BLQ observations were distributed evenly amongst all studies.

Observed viral kinetics: The majority of individuals in both IC adult and IC paediatric patient populations showed rapid declines in viral load as a result of treatment (Figure 5.2.14). IC adult and IC paediatric patients appear to qualitatively exhibit similar viral kinetics. Additionally, both IC paediatric and IC adult

patient populations contain a relatively small number of individuals who exhibited rebounding viral loads. The time courses of viral loads were visually explored against covariates to discern potential trends. In general, differences were not apparent either within or between IC adult and IC paediatric populations when stratified by virus type, transplant type, high or low (i.e. standard) oseltamivir dose (Figure 5.18), and treatment duration.

Figure 5.2.14. Time course of viral load profile by oseltamivir dose category.



Source code: EDAfigs.R
Source graphic: ./deliv/figure/EDAfigs_VK_AUCH.pdf

Viral load profile faceted by pediatric and adult patients. Colors indicate exposures at high (double or triple the conventional dose) or low (defined by F. Hoffmann-La Roche AG). The rug (below each panel) shows the sampling times. **Note:** lower limit of quantification (not shown here) is 2.6 for influenza type A and 3.0 for influenza type B.

Disease model: Models with paediatric population covariates outperformed the base model (Table 5.2.9). Models with paediatric population covariates on both δ and c and only on δ outperformed the model with paediatric population covariate only on c. For reasons of model parsimony, the model including only the paediatric population effect on δ was selected as the final base model. As no covariates were found to be significant sources of additional inter- or intra-subject variability in model parameters, this was the final model. Parameter estimates of the final model are summarised in Table 5.2.10.

Table 5.2.9. Key viral kinetics model development steps.

Model	OFV	BIC
Base Model	1363.130	1441.140
Base Model with pediatric population effect on δ and c	1358.922	1451.115
Base model with pediatric population effect on c, *only*	1361.456	1446.557
Final Model: Base model with pediatric population effect on δ, *only*	1356.600	1441.701

OFV is the Objective Function Value; BIC compares "goodness" of fit with model complexity; lower OFV and BIC values represent increasing model quality.

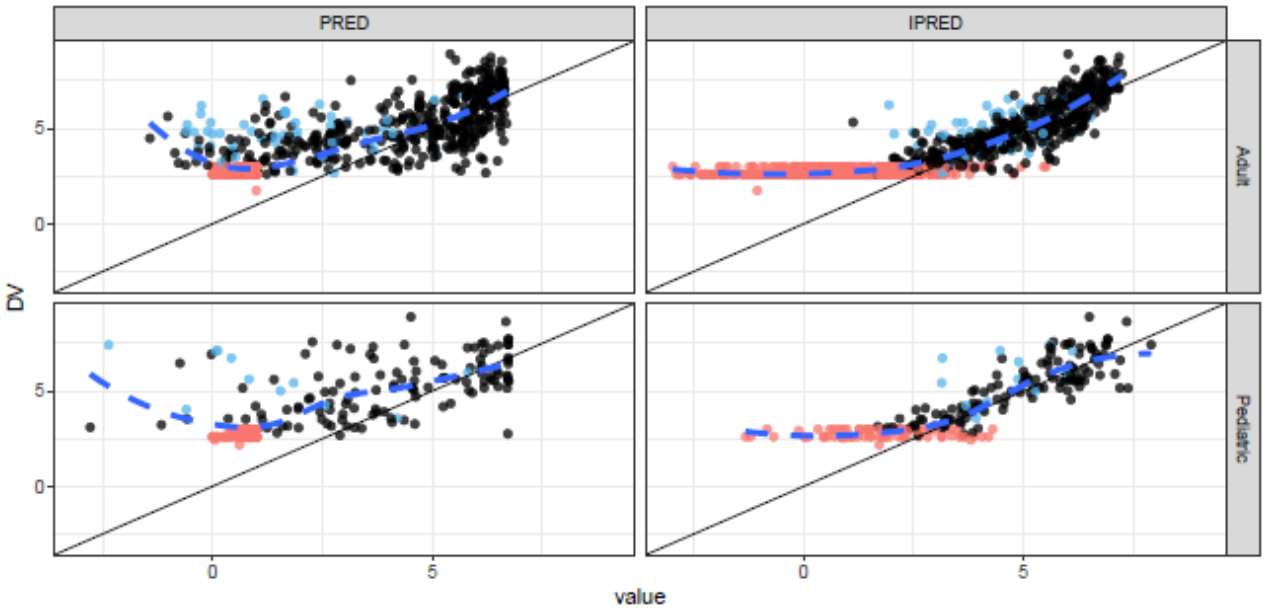
Table 5.2.10. Final viral kinetics and oseltamivir population parameter estimates for immunocompromised adult and paediatric patients: Mean (CV%) and 90% Credibility Interval.

Parameter	Parameter description	Unit	Mean (CV%)	90% CI
Influenza parameters				
β	Target cell infection rate	$(vp/mL)^{-1}.day^{-1}$	4.59×10^{-5}	2.37×10^{-5}, 7.97×10^{-5}
c	Viral clearance rate	day^{-1}	1.89	1.57, 2.31
δ	Infected cell clearance rate	day^{-1}	1.07	0.966, 1.20
pNT	Viral production rate	$(vp/mL).day^{-1}$	0.0507	0.0332, 0.0743
Drug parameters				
AUC_{50}	Exposure at half-maximal effect	ng.h/mL	146	65.8, 270
Covariate				
f_δ	Pediatric covariate on δ		0.781	0.627, 0.956
Random effect parameters				
σ_{error}	Residual error variance		1.05	0.975, 1.15
BSV_β	Between-subject variability of β		0.922 (66.8)	0.279, 2.10
BSV_c	Between-subject variability of c		0.467 (23.8)	0.309, 0.662
BSV_δ	Between-subject variability of δ		0.141 (33.4)	0.0881, 0.217
BSV_{pNT}	Between-subject variability of pNT		1.16 (53.4)	0.362, 2.29
BSV_{AUC50}	Between-subject variability of AUC_{50}		1.46 (141)	0.266, 4.69

BSV = between-subject variability; CV = coefficient of variation; CI = credibility interval

Figure 5.2.15 shows population- and individual-predicted viral load versus observed viral load for IC adult and IC paediatric patients. Observations BLQ appear as red dots and rebound viral load observations as light blue dots. In both population and individual predictions, discrepancies at high viral loads are due to the limit on the number of target cells. The population-predicted viral load versus observed panels show a systematic under-prediction in the lower-left tail of the observed data. As seen by the concentration of red and blue points in this region, the population under-prediction is largely due to a combination of observations at or approaching BLQ and observations from a relatively small number of subjects that exhibited viral rebound. The rebounding viral load profiles from these subjects represent a departure from the majority of the populations' viral load profiles and is thereby difficult to capture in population-predicted viral loads. In contrast, however, rebound viral load observations are sufficiently captured at the individual-prediction level.

Figure 5.2.15. Population and individual observed versus final model predicted log transformed viral load values, stratified by patient population



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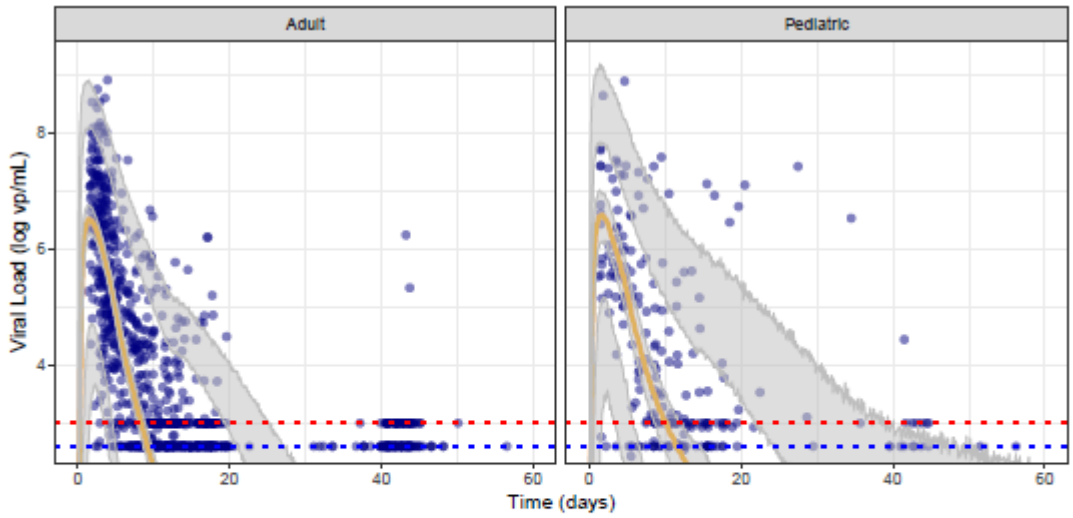
Population and individual log viral load values are shown on the left and right panel, respectively. IC adult and IC pediatric patient data are trellised in top and bottom panel, respectively. Solid black lines are the lines of identity, dashed blue lines indicate trends via LOESS regression. A conservative selection of rebound viral load observations were identified and appear as light blue dots to distinguish those observations from black likely non-rebound observations, while red dots indicate actual or estimated BLQ values

Figure 5.2.16 shows the model predicted 10th, 50th and 90th percentile viral load trajectories versus observed data. In general, the model recapitulates the time course of the observed viral dynamics and accurately represents the point at which large fractions of the observed data reach the limit of quantification. The slight discrepancy between model predicted peak viral loads and observed peak viral loads is likely due to a limit on the number of target cells in the model. The change in slope in the predicted viral load shortly after 10 days is likely an artefact of aggregating several different scenarios near this time period, such as the variability in the timing of withdrawal of treatment and the occurrence of rebounding viral loads. Individual predictions (presented in Appendix of the modelling report), however, clearly highlight the model's ability to represent subject-level variability in such timings and rebounding of viral load.

Figure 5.2.16. Visual predictive check of observed versus final model predicted log transformed viral loads, stratified by IC adult and IC paediatric patients

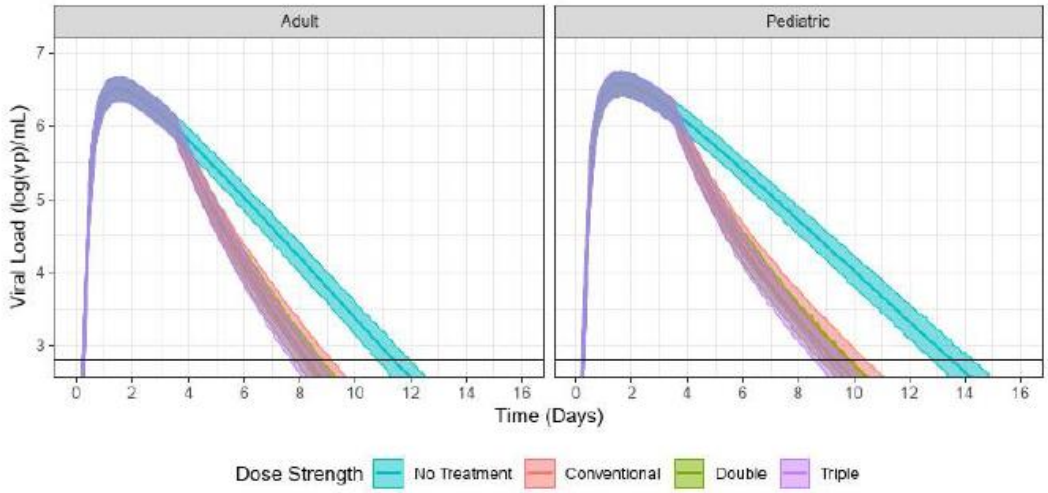


Source code: reportFigs.R
Source graphic: ./deliv/figure/reportFigs_VPC4_Zoomed.pdf

Navy points are log viral load (DV) observations while dotted blue and red lines indicate the limit of quantification for Influenza Type A and B, respectively. The metrics for summarizing the visual predictive check are the 10th, 50th (median) and 90th percentile of the log10 viral load, calculated in 0.1 day increments. Summaries are shown for N=500 posterior replicates. The solid orange line shows the simulated median viral load. The grey shaded areas illustrate 90% credible intervals around the simulated metrics.

Model Simulations: Clinical trial simulations, using the final model parameters, were performed to investigate the impact of dose, time of initiation of oseltamivir therapy and treatment duration. Figure 5.2.17 illustrates how the dose-response relationship translates to effect on the viral load curve with simulations of the time course of influenza viral load without treatment and with oseltamivir study doses (conventional, 2x and 3x conventional dose administered BID for 10 days; treatment started 2 days after onset of symptoms). A conventional dose produces similar viral kinetics to a 2x or 3x conventional dosing regimen and suggests a similar treatment effect of oseltamivir for the IC paediatric and the IC adult population.

Figure 5.2.17. Predicted Treatment Effect and Effect of Dose on Viral Load Profiles

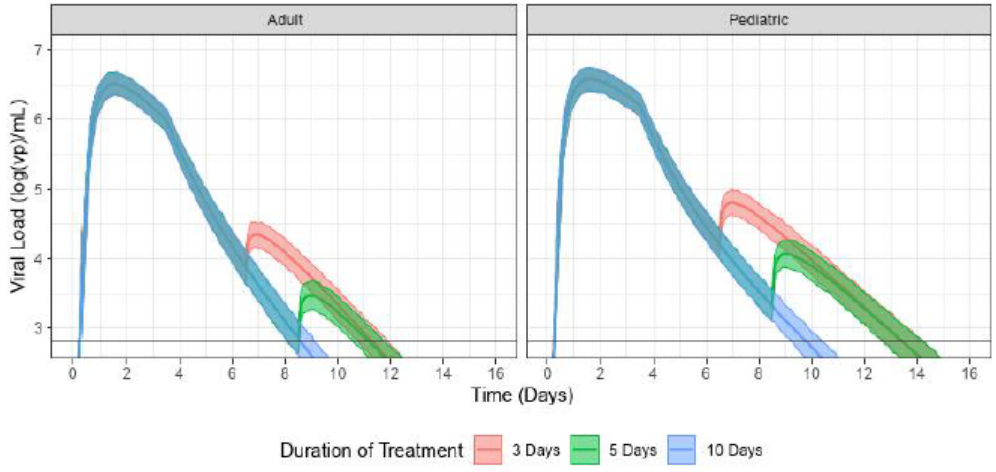


Simulated Median (90% PI) Influenza Viral Load versus Time Following no Treatment, Oral Administration of Conventional, Double and Triple Dose Oseltamivir Treatment BID for 10 Days in Immunocompromised Pediatric (< 18 Years) and Adult Patients

PI = Prediction Interval. Infection was assumed 36 hours before onset of symptoms. Oseltamivir treatment is assumed to be administered 2 days after onset of symptoms.

Figure 5.2.18 illustrates the simulated effect of oseltamivir treatment duration over 3, 5 and 10 days of conventional oseltamivir dose BID. The simulated viral load versus time curve suggests that treatment duration of 10 days limits potential occurrences of viral rebound, which occurs with shorter treatment duration of 3 or 5 days. Finally, model-based simulations indicated that early start of treatment after onset of symptoms is favourable to show maximum impact on viral load, which accelerates cessation of viral shedding.

Figure 5.2.18. Predicted Effect of Treatment Duration on Viral Load Curve.



Simulated Median (90% PI) Influenza Viral Load versus Time Following Conventional Dose Oral Administration of Oseltamivir BID for 3, 5 and 10 Days in Immunocompromised Pediatric (< 18 Years) and Adult Patients

PI = Prediction Interval. Infection was assumed 36 hours before onset of symptoms.
Oseltamivir treatment is assumed to be administered 2 days after onset of symptoms.

5.3 Discussion

Pharmacokinetics: Pharmacokinetics of the pro-drug oseltamivir and the active metabolite OC in IC paediatric patients with influenza were investigated using population PK modelling. Because the data for this new population were limited, previously developed models were utilised. This approach is appropriate. The selected PK model was based on extensive oseltamivir and OC concentration-time data following oseltamivir oral and intravenous administration in paediatric and young adult subjects and developmental physiological changes are taken into account.

In IC adult patients, approximately 30−35% reduction in the apparent clearances of oseltamivir and OC has been reported. The current PK analyses indicated that in IC paediatric subjects from 10 to 17 years of age the apparent clearances of oseltamivir and OC were decreased by 44% (95% CI: 26.8−62.0%) and 49% (95% CI: 34.5−63.8%), respectively, compared to otherwise healthy (OwH) subjects in the same age range. One IC subject in this age group (a patient with a history of nephrectomy and a decreased creatinine clearance on a PK assessment day, but not at baseline) had very low estimated OC clearance. IC paediatric subjects from one to <10 years old appeared to have similar apparent clearances of oseltamivir and OC compared to otherwise healthy subjects in the same age range. Simulations indicated that the predicted OC exposures in IC subjects <10 years old were comparable (4-9% higher) with otherwise healthy subjects in the same age range, whereas in older paediatric IC subjects the predicted OC exposures were approximately 2.1-2.2 fold higher than in otherwise healthy subjects in the same age range. When the IC subject with nephrectomy was excluded, the point estimates of predicted OC exposures were approximately 1.7−1.8 fold higher than in otherwise healthy subjects in the same age range. These figures were based on data from only 5 IC subjects from 10 to 17 years of age. For comparison, in adult IC patients the average OC exposures were approximately 2 fold higher than in otherwise healthy adults (see EMEA/H/C/000402/II/0136). Approximately half of this difference was attributed to impaired renal function in IC patients, many of whom had a history of renal transplantation, and the other half to unidentified factors. In other words, apparent clearance of OC was decreased by 50% in IC adults compared with OwH adults with similar renal function.

It remains unknown why in the younger children 1 to <10 years of age the PK of OC was similar in IC and otherwise healthy subjects, in contrast to lower OC clearance and higher exposure observed in older children and adults. The underlying reason for IC status (e.g. primary immunodeficiency vs. immunosuppression due to organ transplant) may be one contributing factor. The available data are too limited to explore this aspect. There were no IC patients younger than 1 years of age in the dataset. It can be expected, however, that the population PK model that accounts for developmental physiological changes taking place in the two first years after birth is applicable also for IC patients younger than 1 years of age.

Exposure-Response: No relationships were identified between exposure to OC (predicted steady state C_{min}) and virologic efficacy endpoints time to cessation of viral shedding by culture and by RT-PCR. This was not surprising, because the trough levels achieved with the conventional dose are already near or at the plateau of the previously established exposure-response curve. Furthermore, exposure-response analyses did not indicate that higher than conventional dose would decrease development of viral resistance to oseltamivir in IC children. Time to resolution of symptoms appeared to be shorter in the high exposure group as compared to the low exposure group, which was driven by data observed in study NV25719. Of note, the CARIFS symptom score might not be optimal for IC paediatric population (see section Clinical Efficacy of this AR). For comparison, previously conducted analyses in IC adult patients treated with conventional and double dose did not indicate exposure-response relationships for virologic and symptomatic efficacy endpoints (EMEA/H/C/000402/II/0136).

Viral kinetics model: Influenza disease PK / viral kinetics model in IC paediatric and adult patients was also submitted by the MAH; a similar model for IC adult patients was assessed in procedure EMEA/H/C/000402/II/0136. Although some assumptions were not verified, it can be agreed that the observed data could be described reasonably well by the model. It was estimated that IC paediatric patients

had approximately 22% (90%CI 4.4-37.3) lower infected cell clearance rate than IC adult patients, whereas the free influenza virus clearance rate was similar in IC paediatric and adult patients. Model-based simulations indicated that undetectable virus levels were achieved approximately four days earlier following treatment with oseltamivir compared with no treatment. Conventional, double and triple doses produced essentially the same effect on viral load profiles, which is in agreement with the results of the exposure-response analyses summarized above. Importantly, the simulations suggested that a 5-day treatment (which is recommended for OwH subjects) is associated with a risk of viral rebound in IC paediatric patients, and that a 10-day treatment could decrease this risk. It is known that treatment should be initiated early for best efficacy, which was also observed in the simulations.

See also section 8 of this AR for discussion on extrapolation.

6. Studies providing data on oseltamivir treatment of paediatric IC patients

The paediatric and adolescent data from studies NV20234 and NV25719 are presented in this section. As both clinical study reports have been assessed previously (see section Introduction of this AR), no thorough assessment of the design, methodology etc. of the studies is included in this AR; only data relevant for the current variation are included.

The applicant has in the current submission summarised efficacy results from these two studies separately, instead of pooled, to avoid masking the differences observed between them. However, resistance and safety results have been pooled for the present analysis.

Assessor's comment

Pooling of the resistance and safety results is deemed acceptable. Taking in account the different background conditions and different posology implemented in studies NV20234 and NV25719, it is appropriate that clinical efficacy results have not been pooled.

6.1 Study NV20234

6.1.1 Study design

NV20234 was a phase III, double blind, randomized, multicentre study of conventional and double dose oseltamivir for the treatment of influenza in IC patients. Immunocompromised patients, who developed an influenza-like illness and tested positive with a rapid diagnostic test, reverse transcription–polymerase chain reaction (RT-PCR), or viral culture for influenza, were enrolled during the influenza season. Due to widespread use of oseltamivir for treating IC patients in clinical practice at the time the study was designed, a placebo arm in NV20234 was considered unethical. Therefore, otherwise healthy (OwH) and "at risk" patients (those with chronic respiratory and/or cardiac conditions) from previous studies served as historical controls. This comparison was performed separately for adults (with pivotal adult studies) and for the paediatric patients pooled form studies NV25719 and NV20234 (with pivotal paediatric studies).

In the two comparative arms of the study, oral doses of oseltamivir, conventional dose (as appropriate for age group and weight) or double dose were administered twice daily (BID) for 10 days. Of note, the duration of the treatment course was in both arm double the conventional course of 5 days.

Study NV20234 faced significant recruitment challenges. In order to improve recruitment and ensure the provision of data within a reasonable timeframe, several amendments to the NV20234 study were implemented. These amendments included a change to the study's primary objective from efficacy to safety and resistance and the sample size was reduced from 250 to 166 patients. While efficacy became a

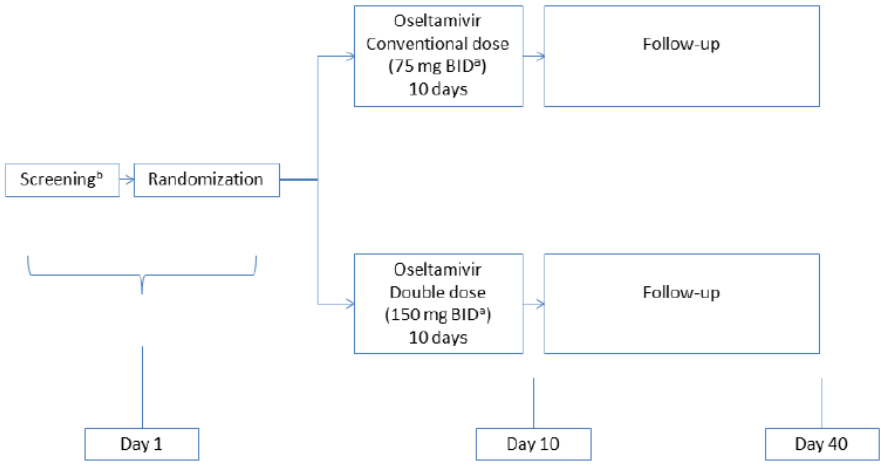
secondary objective, the same efficacy analyses were still planned. The confidence interval approach to compare the treatment groups with matched historical controls was retained.

The MAH opened more study sites and extended the duration of the study to achieve planned patient numbers. Altogether 62 active centres in 19 countries participated in the study. First patient entered the study in 2/2008 and last patient in 5/2017. Inclusion criteria were broadened (see below under "Study population". Additionally, patients could be enrolled beyond the 48 hours symptom onset window, up to 96 hours after symptom onset.

Patients were randomized 1:1 to conventional oseltamivir or double dose oseltamivir, stratified according to four binary stratification factors. Patients randomized under protocol versions A and B were stratified according to transplant (SOT, HSCT); time between onset of influenza symptoms and treatment start (≤ 24 hours, >24 hours); influenza vaccination status for current influenza season (yes, no), and age (≤12 years, >12 years).Patients randomized under Protocol C through Protocol F were stratified according to transplant (yes, no); time between onset of influenza symptoms and treatment start (up to 96 hours, ≤48 hours, >48 hours); influenza vaccination status for current influenza season (yes, no); and by age (≤12 years, >12 years). As only transplant patients were enrolled during protocol A and B, at this time, the randomization was not stratified by transplant status.

Schematic view of the Study NV20234 is shown in Figure 6.1.1.1. Definition of age-related terms is described in Table 6.1.1.1.

Figure 6.1.1.1 Schematic view of the study NV20234



[a]Pediatric patients ≤ 12 years received a weight-based dose

[b]Screening could occur up to 96 hours prior to randomization, providing time between onset of symptoms and first dose of oseltamivir did not exceed 96 hours

Table 6.1.1.1 Definition of age-related terms

Term	Age Range
Adult	≥18 years
Child/Children	<13 years
Adolescent	≥13 to <18 years
Paediatric	<18 years
Infants	<1 year

Study population and sample size

IC adults (patients ≥18 years of age) and children ≥1 and <18 years of age (including adolescents and children <13 years of age) with confirmed influenza infection (<96 hours between symptom onset and first dose of study medication).

IC patients were defined as one who met any of the following:

- Primary immunodeficiency at risk for viral infections or
- Secondary immunodeficiency
    - Solid organ transplant (SOT) with ongoing immunosuppression (severe combined immunodeficiency (SCID), primary T cell deficiency or predominantly antibody deficiency or other well-defined immunodeficiency syndromes) or
    - Allogenic hematopoietic stem cell transplant (HSCT) with ongoing immunosuppression or
    - HIV with a most recent CD4 count <500/mm3 (or < 25% in children ≤5 years old) within the last 6 months and, in the investigator's opinion, considered immunocompromised or
    - Haematologic malignancies (ALL, lymphomas; CLL, small lymphocytic lymphoma; hairy cell leukaemia, myelodysplastic syndromes; peripheral T cell and NK neoplasms, Hodgkin's disease; AML, CML) or
    - Systemic immunosuppressive therapy, irrespective of medical indication, started at least 12 weeks prior to, and ongoing at the time of first dose of study drug

The study was designed to enrol approximately 166 patients (83 patients per treatment group); final enrolment was 228 patients. Only 20 children aged below 18 years were included, 10 to the conventional dose group and 10 to the double dose group. Of these 20 children, 7 completed the study in the conventional daily dose, and 9 in the double dose group.

6.1.2 Objectives

The primary objective of the study was to evaluate prospectively the safety and tolerability of oseltamivir for the treatment of influenza in IC patients and characterize the effects of oseltamivir in IC patients on the development of resistant influenza virus.

The secondary objectives of the study were to evaluate the effects of conventional and double dose oseltamivir in IC patients on:

- The population PK of oseltamivir and OC in IC patients with confirmed influenza infection, through the application of established population PK models to the sparse plasma concentration data generated
- The virologic course of influenza (proportion shedding and viral loads at different timepoints)
- The time to resolution of influenza symptoms

- The clinical course of influenza (fever, symptoms, secondary illnesses as evidenced by otitis media, bronchitis, pneumonia, or sinusitis)
- To explore the relationship of metrics of exposure (e.g., steady-state area under the concentration-time curve [AUC], minimum concentration under steady-state conditions within a dosing interval [C_{min}]) to relevant PD endpoints

Outcomes/endpoints

RESISTANCE:

- Incidence of baseline resistance
- Incidence of post-baseline resistance
- Viral load (in log_{10} vp/mL) in patients with genotypic and phenotypic resistance at baseline
- Incidence of known OC resistance mutations in phenotypic outlier samples compared with phenotypically OC-sensitive samples
- Incidence of post-baseline resistance in patients with detectable viral shedding (in log10 vp/mL) at EOT and during the follow-up period
- Time to resolution (TTR) of all symptoms by post-baseline resistance status
- Incidence of resistance in patients with persistent shedding, defined as < 1 log_{10} vp/mL reduction at EOT, compared with baseline

SAFETY: Adverse events (AEs), clinical laboratory evaluations, physical examination, vital signs, and rejection and/or graft versus host disease (presented in the submission pooled with study NV25719 for paediatric patients).

EFFICACY: TTR of all symptoms, TTR of fever, viral load, viral shedding, persistent viral shedding, secondary illnesses (lower respiratory tract complications), and hospitalizations, and length of stay during hospitalization.

6.2 Study NV25719

Study NV25719 was phase IB, open-label, randomized, multicentre, parallel-group design study with two experimental treatment arms to generate data for the purpose of extrapolation of efficacy from adults with immunodeficiency and to compare and/or integrate exposure and response observations in the paediatric IC population to that seen in other, non-immunocompromised populations.

• To estimate the exposure achieved with each of different dose levels of oseltamivir through the application of an established population PK (popPK) model to the sparse concentration data generated.

• To examine the duration of treatment, of viral shedding, and of fever and to examine the safety, tolerability, incidence of influenza-associated complications and of resistance observed with different doses and duration of treatment and characterize any resistant virus isolate in terms of sequence and phenotype.

6.2.1 Study design

A young (<13 years of age) and highly IC patient population was chosen for this study, considered to be the most at-risk for viral resistance due to their young age and severe IC status. These factors were deemed to increase the chances of prolonged viral shedding and therefore, increase the likelihood of viral resistance. Comparing the conventional and 3x conventional doses of oseltamivir in this patient population was expected to enable estimation of the exposure achieved with two different dose levels of oseltamivir to generate data for extrapolation of efficacy from IC adults and to evaluate the virological outcomes,

resistance, safety and tolerability, in this highly IC patient population. The extrapolation plan has however changed to include extrapolation from OwH children with influenza.

The MAH's rational for the study setting was that this population, where treatment for influenza was both indicated and available, a placebo arm could not be justified. The only potential active comparator, zanamivir, was not indicated in children below 7 years of age. Consequently, offering only one treatment in an open-label fashion represented the most appropriate approach in this patient group. As the primary aim of the study was to evaluate PK/PD, which are objective assessments, the impact of not blinding on the study results was considered minimal by the MAH.

Patients were enrolled at 16 active centres in 8 countries.

Figure 6.2.1 Study NV25719 design

			Study Day		
			1 to 5	6 to 20[a]	35 to 50
Eligible patients (n = 20)	Randomization	Oseltamivir conventional dose (75 mg BID)[b] (n = 10)	Minimum dosing period	Adaptive dosing period	Follow-up period
		Oseltamivir 3x conventional dose (225 mg BID) (n = 10)	Minimum dosing period	Adaptive dosing period	Follow-up period

[a] The adaptive dosing period continued until the cessation of viral shedding (demonstrated by a negative PCR result) or Day 20, whichever came first.

[b] Infants < 1 year of age would be assigned to the conventional dose group (partial forced randomization).

The dosing of oseltamivir was adapted to cessation of viral shedding (Figure 6.2.1). Dosing was stopped when viral shedding ended, or at Day 20, whichever came first.

Originally, three daily dose levels had been planned (conventional, double and triple dose). However, the middle dose cohort was discontinued by amendment with a concomitant increase in the size of the remaining two dose cohorts.

Oseltamivir was administered at a dose of 30 to 225 mg orally BID for a minimum of 5 days (Table 6.2.1). Subsequent adaptive dosing continued until absence of viral shedding, demonstrated by a negative PCR result, up to a maximum duration of 20 days. If viral shedding persisted after Day 20, patients had to discontinue study treatment and receive standard of care treatment for that region. The dosing regimen was adjusted according to age, weight cohort, and illness duration.

Table 6.2.1 Dosing regimen according to age and dose group

Cohort	Infants[a] (< 1 year)	Children (1 to < 13 years)
Conventional dose (BID)		
≤ 15 kg	3 mg/kg	30 mg
> 15 to 23 kg		45 mg
> 23 to 40 kg		60 mg
> 40 kg		75 mg
3x conventional dose (BID)		
≤ 15 kg	Not applicable	90 mg
> 15 to 23 kg		135 mg
> 23 to 40 kg		180 mg
> 40 kg		225 mg

[a] If an infant was born pre-term, the post-menstrual age must be calculated and be ≥ 36 weeks.

Note: Post-menstrual age is the time from the date of last menstrual period to birth (in weeks).

The total study duration ranged from approximately 35 to 50 days, depending on the extent of total treatment duration and the timing of the follow-up visits. This comprised of the following:

- 5 days minimum dosing period
- Up to 15 days of potential additional treatment period
- At least 30 days of follow-up period post last dose

At least 20 patients, including at least 12 patients with <48 hours of influenza symptoms duration at randomization and including at least 10 patients per dose cohort, were to be enrolled.

Study population and sample size

The study population comprised of paediatric IC patients less than 13 years of age with a laboratory-confirmed diagnosis of influenza (e.g., by PCR, culture, or rapid influenza detection test) who were receiving induction, consolidation, or re-intensification chemotherapy for a haematological malignancy or were undergoing a conditioning regimen either prior to haematopoietic stem cell transplant (HSCT) or less than 6 months after HSCT.

The main analysis populations included the intent-to-treat population (ITT), the intent-to-treat influenza-infected population (ITTi), the pharmacokinetic evaluable population (PKEP) and the safety evaluable population (SEP) (the same as the ITT population).

No sample size calculation was performed. The planned sample size of a minimum of 20 influenza-infected enrolled patients was arrived at empirically, taking into account the prevalence of the patient population and primary objective of the study. This included the randomization of at least 12 influenza-infected patients with less than 48 hours of influenza symptom duration and at least 10 patients per dose cohort.

Assessors' comment

The open-label setting may have introduced potential bias in terms of safety assessments (particularly AE reporting). This issue is not considered major, taking in account the relatively good tolerability of oseltamivir in general. The safety results have been presented by the MAH pooled from the two studies (NV20234 and NV25719).

The severe background conditions of the subjects are prone to confound symptoms of influenza, which decreases reliability of the obtained efficacy data based on clinical symptoms.

Treatments

Oseltamivir was administered at a dose of 30 to 225 mg orally BID for a minimum of 5 days. Subsequent adaptive dosing continued until absence of viral shedding, demonstrated by a negative PCR result, up to a maximum duration of 20 days. If viral shedding persisted after Day 20, patients had to discontinue study treatment and receive standard of care treatment for that region. The dosing regimen was adjusted according to age, weight cohort, and illness duration (Table 6.2.2.). Infants less than one year of age would receive an oseltamivir dose of 3 mg/kg (equivalent to conventional dose).

Table 6.2.2 Dosing regimen according to age and dose group

Cohort	Infants[a] (< 1 year)	Children (1 to < 13 years)
Conventional dose (BID)		
≤ 15 kg	3 mg/kg	30 mg
> 15 to 23 kg		45 mg
> 23 to 40 kg		60 mg
> 40 kg		75 mg
3x conventional dose (BID)		
≤ 15 kg	Not applicable	90 mg
> 15 to 23 kg		135 mg
> 23 to 40 kg		180 mg
> 40 kg		225 mg

[a] If an infant was born pre-term, the post-menstrual age must be calculated and be ≥ 36 weeks.

Note: Post-menstrual age is the time from the date of last menstrual period to birth (in weeks).

6.2.2 Objectives

- To generate data for the purpose of extrapolation of efficacy from adults with immunodeficiency and to compare and/or integrate exposure and response observations in the paediatric immunocompromised population to that seen in other, non-immunocompromised populations.
- To estimate the exposure achieved with each of different dose levels of oseltamivir through the application of an established population PK (popPK) model to the sparse concentration data generated.
- To examine the duration of treatment, of viral shedding, and of fever and to examine the safety, tolerability, incidence of influenza-associated complications and of resistance observed with different doses and duration of treatment and characterize any resistant virus isolate in terms of sequence and phenotype.

Outcomes/endpoints

The following endpoints were assessed to address study objectives:

- *Pharmacokinetics:* PK characterization for oseltamivir and OC was based on an established PopPK multi-compartment model and assessed model-predicted PK parameters: steady-state $AUC_{0\text{-}12}$, C_{max}, C_{min}, t_{max}, apparent clearance (CL) and volume of distribution for oseltamivir and OC.
- *Pharmacodynamics:* virologic endpoints (resistance, viral load, viral shedding, persistent viral shedding).
- *PK/PD:* Exposure-response analyses were performed for patients who had PK samples and PD data. Exposure-response relationships were evaluated graphically, using regression (linear and logistic) models and time-to-event by exposure curves, as appropriate.
- *Efficacy:* Time to resolution (TTR) of all symptoms (TTRAS), TTR of fever, and duration of treatment.

Time to resolution of all symptoms (TTRAS) was defined as the time in hours from randomization to the start of the 24-hour period in which all 18 symptoms items (Canadian Acute Respiratory Illness and Flu Scale [CARIFS] 18-symptom scale) had scores of ≤1 (minor problem) and remained ≤1 for at least 21.5 hours. Symptoms of influenza-like illness were captured at baseline and twice daily throughout the study using the CARIFS and were graded on a nominal scale from 0 (absent or no problem) to 3 (severe or major problem). The MAH states in the CSR that CARIFS has been validated for use in otherwise healthy children (*Whitley RJ, Hayden FG, Reisinger KS, et al. Oral Oseltamivir Treatment of Influenza in Children. Pediatr Infect Dis J 2001, 20 (2):127–33*); however, obviously not for children with background conditions or IC children.

The CARIFS questionnaire consists of 18 items covering symptoms, function and parental impact of illness, and includes several measures that are not specific to influenza but to general health: 1) poor appetite, 2) not sleeping well, 3) irritable, cranky, fussy, 4) feels unwell, 5) low energy, tired, 6) not playing well, 7) crying more than usual, 8) needing extra care, 9) clinginess, 10) headache, 11) sore throat, 12) muscle aches or pains,13) fever, 14) cough, 15) nasal congestion, runny nose, 16) vomiting, 17) not interested in what's going on, 18) unable to get out of bed. Some of the symptoms reported as associated with influenza are likely confounded with side effects from other concomitant treatments and illnesses (e.g. leukaemia, chemotherapy).

Assessor's comment

It is noteworthy that the method of recording clinical outcomes was in this study different from the diary used in pivotal clinical studies with oseltamivir in adult and adolescent patients. In the pivotal studies in adults and adolescents, patients recorded their symptoms themselves on a 7-symptom diary. The CARIFS questionnaire is filled out by the guardian of the paediatric patient. However, the same method has been used in paediatric studies on oseltamivir.

The CARIFS questionnaire includes several measures that are not specific to influenza but to general health. Some of the symptoms reported as associated with influenza are likely confounded with symptoms of background conditions and side effects from other concomitant treatments (e.g. poor appetite and sleeping, crankiness, tiredness, clinginess, lack of interest, being not able to get out of bed could be due to leukaemia; muscle aches and vomiting by chemotherapy, etc.). Hence, in a severely ill patient population for which the scale has not been validated, the efficacy results obtained should be interpreted with great caution. Using any symptom diary could be seen more reliable in OwH patients, as the observed symptoms can in OwH patients be addressed to the acute infection.

Influenza infection *per se* is very similar across different patients groups, as respiratory and systemic symptoms are present and there is a risk of secondary bacterial infections and other complications. Nevertheless, there are some issues in comparing symptoms in OwH and IC patients. The immunocompromised state causes attenuation of fever and other inflammatory-derived symptoms of influenza in IC subjects. Even complications of influenza are considered to be related to the inflammatory response. E.g., the damage to lungs during Influenza A infection is thought to be mostly due to cytokine storm (*Yang, Tang. Aberrant coagulation causes a hyper-inflammatory response in severe influenza pneumonia. Cell Mol Immunol. 2016 Jul; 13(4): 432–442, doi: 10.1038/cmi.2016.1*).

Consequently, due to the somewhat different clinical picture of influenza in OwH and IC subjects, the estimation of efficacy of oseltamivir might not have been fully reliable as based solely on comparison between time to resolution of symptoms in OwH and IC subjects even if the studies on IC patients had been powered for efficacy. Even a direct comparison between OwH and IC subjects would not necessarily have been reliable demonstration of efficacy of oseltamivir in IC subjects, as even fever is more often absent already at baseline in IC subjects than in OwH subjects with influenza. Therefore, time to resolution of fever could be shorter in IC patients than in OwH patients even if the infection had not been cured; and on the other hand, the true recovery from any infection is expected to be slower in IC subjects.

Therefore, the disease modelling based on objective viral outcomes is considered more appropriate to define course of influenza in IC patients than relying on the presence or absence of clinical symptoms.

6.3 Results on oseltamivir treatment in paediatric IC subjects

The results are presented here for children and adolescents from studies NV20234 and NV25719. The Clinical Overview and Clinical Summaries included in the current submission contain additional, mostly descriptive, paediatric data from these studies that have not been assessed previously.

6.3.1 Demographic and baseline characteristics

Both studies included an intent-to-treat (ITT) population, an intent-to-treat influenza-infected population (ITTi), a safety-evaluable population (SEP), and a pharmacokinetic-evaluable population (PKEP). Study NV20234 also included a modified ITTi population (mITTi). These populations are described below:

- ITT: All randomized IC patients were included in the ITT population. Patients infected with oseltamivir-resistant influenza strains at baseline were excluded from this population. Patients were summarized under the treatment to which they were randomized.
- ITTi: A subset of ITT patients who had laboratory confirmed influenza infection from any swab sample collected at baseline or during the study (by RT-PCR). Efficacy endpoints were evaluated in this population.
- mITTi (Study NV20234 only): All patients randomized to a particular treatment, regardless of whether they received that treatment or not, who received at least one dose of study drug and with central laboratory confirmation of influenza infection, excluding patients infected with oseltamivir-resistant influenza at baseline. This population was in fact the same as the ITTi.
- SEP: The safety evaluable population included all patients who received at least one dose of study drug and had a safety assessment performed post randomization. Patients were classified according to treatment actually received.
- PKEP: All patients in the ITT population who had at least one post-dose drug concentration measurement at a scheduled visit timepoint (excluding those who violated inclusion/exclusion criteria, had protocol deviations or unavailable or incomplete data). Patients were summarized according to treatment actually received.

Altogether 46 paediatric IC patients were included in studies NV20234 and NV25719 and received at least one dose of study drug (Table 6.3.1.1, SEP). Of these, 36 provided data for efficacy evaluation (Table 6.3.1.2, ITT).

Study NV20234 enrolled 20 paediatric patients, 16 of whom contributed data to the mITTi and safety (SEP) populations (3 were randomized but not dosed and 1 had baseline resistance). All of the 16 paediatric patients who received at least one dose of oseltamivir completed the study (7 in the conventional dose group and 9 in the double dose group; mITTi population). These 16 patients comprised 9 children and 7 adolescents. The PKEP contained only four (4) patients who had PK samples available for analyses.

Study NV25719 enrolled 30 patients. All 30 patients received at least one dose of oseltamivir and 27 patients completed the study (14 in the conventional dose group and 13 in the triple dose group). There were 3 patients who discontinued the study and 4 patients who discontinued study treatment. The safety and ITT populations included all 30 patients enrolled and randomized in the study (15 each in the conventional and 3x conventional dose groups).

The ITTi population included 20 patients who were central laboratory RT-PCR positive for influenza infection. Of the 10 patients excluded from ITTi, 8/10 as there was no evidence of influenza infection confirmed by PCR

at the Central Lab at baseline and 2/10 as the patients' malignancies did not meet the inclusion criteria. As a result, there were more patients in the conventional dose group than the 3x conventional dose groups (11 vs. 9 patients) in ITTi.

The PKEP population included 26 patients (14 in the conventional dose group and 12 in the 3x conventional dose group): two patients were excluded because they did not have any post-dose drug concentration measurements and two patients were excluded because they had malignancies not acceptable for inclusion into the study.

Table 6.3.1.1 Summary of studies contributing to safety evaluation in paediatric IC patients (SEP)

Study No. (Phase)	Study Design	Population	No. of Patients randomized	No. of Patients contributing to this evaluation	Dose, Route, and Regimen [a]
NV25719 (Phase IB)	Open-label, randomized, parallel-group, multicenter	IC children < 13 years with confirmed influenza infection	30[b]	Total 30: 15 to conventional dose; 15 to triple dose	Oral oseltamivir 30 to 225 mg BID for 5 to 20 days (children > 40 kg, 75 mg or 225 mg; children ≤40 kg, weight based dose adjustment)
NV20234 (Phase III)	Double-blind, randomized, stratified, multicenter	IC adults (≥18 years), adolescents (≥13 to< 18 years) and children (≥1 to<13 years) with confirmed influenza infection	228 (207 adults, 20 patients <18 years)[b,c]	Total 16 patients < 18 years: 9 children (4 in conventional dose and 5 in double dose) and 7 adolescents (3 in conventional dose and 4 in triple dose)	Oral oseltamivir 30 to 150 mg BID for 10 days (children >40 kg, 75 mg or 150 mg; children ≤40 kg, weight based dose adjustment)

BID = bis in die (twice a day); IC = immunocompromised.

[a] Formulations used: Adolescents (13 to <18 years) and Adults: oseltamivir 75 mg capsules; Children (1 to <13 years): oseltamivir capsules 75 mg, 45 mg and 30 mg (NV25719 study) and oral suspension (12 mg/mL [NV20234 and NV25719 studies] and 6 mg/mL [NV25719 study]).

[b] Overall Safety population: N=30 in Study NV25719 and N=215 in Study NV20234, which included 16 patients <18 years and 199 adults.

[c] No age information was available for 1 patient (who was randomized but not dosed).

Table 6.3.1.2 Summary of studies contributing to efficacy evaluation in paediatric IC patients (ITT)

Study No. (Phase)	Study Design, Control Type	Population	No. of Patients Randomized	No. of Patients Contributing to This Evaluation	Dose, Route, and Regimen [a]
NV25719 (Phase IB)	Open-label, randomized, parallel-group, multicenter	IC children (< 13 years) with confirmed influenza infection	30	Total 20: 11 in conventional dose group; 9 in triple dose group	Oral oseltamivir 30 to 225 mg BID for 5 to 20 days (children > 40 kg, 75 mg or 225 mg; children ≤40 kg, weight based dose adjustment)
NV20234 (Phase III)	Double-blind, randomized, stratified, multicenter	IC adults (≥18 years), adolescents (≥13 to<18 years) and children (≥1 to<13 years) with confirmed influenza infection	228 (207 adults, 20 patients <18 years)[b]	Total 16 patients <18 years: 9 children ≥1 <13 years (4 to conventional dose and 5 to double dose) and 7 adolescents (3 to conventional dose and 4 to double dose	Oral oseltamivir 30 to 150 mg BID for 10 days (children >40 kg, 75 mg or 150 mg; children ≤40 kg, weight based dose adjustment)

BID = bis in die (twice a day); IC = immunocompromised.

[a] Formulations used: Adolescents (13 to <18 years) and Adults: oseltamivir capsules, 75 mg; Children (1 to <13 years): oseltamivir capsules 75 mg, 45 mg and 30 mg (NV25719 study) and oral suspension (12 mg/mL [NV20234 and NV25719 studies] and 6 mg/mL [NV25719 study]).

[b] No age information was available for 1 patient (who was randomized but not dosed and was only included in the ITT population).

Combined demographic and baseline characteristics of children below 13 years of age in studies NV25719 and NV20234 (ITT population) are shown in Table 6.3.1.3. There were 7 adolescent patients aged from 13 to 17 years in study NV20234 (table 6.3.1.4).

Table 6.3.1.3 Demographic and baseline characteristics of children in studies NV25719 and NV20234 (ITT Population)

Demographic and Baseline Characteristics: NV25719 and NV20234 (<13 years) combined, Safety Evaluable Population
Project: CD012880

	NV25719 and NV20234(< 13 Y.O.) Total (N=39)
Age (years) at baseline	
n	39
Mean (SD)	5.8 (3.3)
Median	5.0
Min - Max	1 - 12
Age group (years)	
n	39
Infants and toddlers (28 days - 23 months)	1 (2.6%)
Children (2 - 12 years)	38 (97.4%)
Sex	
n	39
Male	28 (71.8%)
Female	11 (28.2%)
Race	
n	39
American Indian or Alaska Native	1 (2.6%)
Asian	1 (2.6%)
White	30 (76.9%)
Other	7 (17.9%)
Ethnicity	
n	39
Hispanic or Latino	13 (33.3%)
Not Hispanic or Latino	25 (64.1%)
Not Stated	1 (2.6%)

Table 6.3.1.4 Demographic and baseline characteristics of adolescent patients (<18 Years) in Study NV20234 (safety population)

	Ro 64-0796 Conventional (N=7)	Ro 64-0796 Double (N=9)	All Patients (N=16)
Age (years) at baseline			
N	7	9	16
Mean (SD)	10.0 (5.0)	10.1 (5.0)	10.1 (4.8)
Median	10.0	8.0	9.0
Range	4 - 17	5 - 17	4 - 17
Age group (years)			
n	7	9	16
<= 12	4 (57.1%)	5 (55.6%)	9 (56.3%)
13 - 17	3 (42.9%)	4 (44.4%)	7 (43.8%)
Sex			
n	7	9	16
Male	5 (71.4%)	6 (66.7%)	11 (68.8%)
Female	2 (28.6%)	3 (33.3%)	5 (31.3%)
Race			
n	7	9	16
White	6 (85.7%)	7 (77.8%)	13 (81.3%)
Black or African American	1 (14.3%)	1 (11.1%)	2 (12.5%)
Other	0	1 (11.1%)	1 (6.3%)
Ethnicity			
n	7	9	16
Non-Hispanic	4 (57.1%)	7 (77.8%)	11 (68.8%)
Hispanic	3 (42.9%)	2 (22.2%)	5 (31.3%)
Female Reproductive Status			
n	2	3	5
With Contraceptive Protection	0	1 (33.3%)	1 (20.0%)
Practicing Abstinence	1 (50.0%)	1 (33.3%)	2 (40.0%)
Premenarchal	1 (50.0%)	1 (33.3%)	2 (40.0%)
Influenza Vaccination Status			
n	7	9	16
No	6 (85.7%)	7 (77.8%)	13 (81.3%)
Yes	1 (14.3%)	2 (22.2%)	3 (18.8%)
Transplant Status			
n	7	9	16
No	5 (71.4%)	8 (88.9%)	13 (81.3%)
Yes	2 (28.6%)	1 (11.1%)	3 (18.8%)
Time from Onset of Symptoms to Start of Drug (hours)			
N	7	9	16
Mean (SD)	49.80 (30.13)	47.99 (26.74)	48.78 (27.30)
Median	65.83	53.75	58.67
Range	12.3 - 89.6	8.4 - 82.4	8.4 - 89.6

Children are determined as patients with age less than 18.

The immunosuppressive conditions in the ITT population of studies NV20234 and NV25719 are presented in Tables 6.3.1.5 and 6.3.1.6.

Imbalances were seen between groups in study NV25719. In the ITT population, the majority of patients (71.4%) had acute lymphoid leukaemia (ALL) (8 patients [61.5%] vs. 12 patients [80.0%] in the conventional dose and 3x conventional dose group, respectively); 4 (14.3%) had acute myeloid leukaemia (AML) (all in the conventional dose group) and 2 patients (7.1%) had Non-Hodgkin's Lymphoma (1 patient each in the conventional and in the 3x conventional dose groups). Two patients (13.3%) in the 3x conventional dose group labelled with 'Other' had solid tumour malignancies, which did not meet the study inclusion criteria Two patients (13.3%) in the conventional dose group had an HSCT, while none of the patients in the 3x conventional dose group had a haematopoietic stem cell transplant (HSCT).

In the paediatric ITTi population of Study NV20234, there was an equal number of patients with haematologic malignancies or systemic immunosuppressive therapy (7 patients; 41.2%, in each treatment group). Two patients in the conventional dose groups had undergone an HSCT (22.2%) and 3 (17.6%) patients had HIV.

In the pooled Safety/ITT population of IC children (below 13 years of age) from both studies, there were 33 events of hematologic malignancies and 5 events of systemic immunosuppressive therapy.

Table 6.3.1.5 Immunodeficiency conditions, paediatric patients (<18 years), study NV20234

Summary of Immunodeficiency Conditions, Intent-to-Treat Population, Children
Protocol: NV20234

Category Description	Ro 64-0796 Conventional (N=10)	Ro 64-0796 Double (N=10)	All Patients (N=20)
IMMUNODEFICIENCY CONDITION			
Total number of patients	10 (100.0%)	10 (100.0%)	20 (100.0%)
Total number of events	12	10	22
HEMATOLOGIC MALIGNANCIES	5 (50.0%)	3 (30.0%)	8 (40.0%)
SYSTEMIC IMMUNOSUPPRESSIVE THERAPY	3 (30.0%)	4 (40.0%)	7 (35.0%)
HIV (WITH CD4 COUNT <500/MM3)	2 (20.0%)	2 (20.0%)	4 (20.0%)
TRANSPLANT	2 (20.0%)	1 (10.0%)	3 (15.0%)
TRANSPLANT STATUS			
Total number of patients	2 (20.0%)	1 (10.0%)	3 (15.0%)
Total number of events	2	1	3
HAEMATOPOIETIC STEM CELL TRANSPLANT	2 (20.0%)	0	2 (10.0%)
SOLID ORGAN TRANSPLANT	0	1 (10.0%)	1 (5.0%)
TYPE OF SOLID ORGAN TRANSPLANT			
Total number of patients	0	1 (10.0%)	1 (5.0%)
Total number of events	0	1	1
KIDNEY	0	1 (10.0%)	1 (5.0%)

Immunodeficiency condition HIV with CD4 count <500/MM3 includes conditions of HIV with CD4 count <200/MM3.
Children are determined as patients with age less than 18.

Table 6.3.1.6 Immunodeficiency conditions and other baseline characteristics, study NV20234 (ITT) (all aged <13 years)

	Oseltamivir conventional dose (N=15)	Oseltamivir 3x conventional dose (N=15)	All Patients (N=30)
Age (years) at baseline			
n	15	15	30
Mean (SD)	6.9 (4.2)	4.3 (2.3)	5.6 (3.6)
Median	6.0	3.0	5.0
Range	1 - 12	2 - 8	1 - 12
Age group (years)			
n	15	15	30
>= 1	15 (100.0%)	15 (100.0%)	30 (100.0%)
Sex			
n	15	15	30
Male	10 (66.7%)	11 (73.3%)	21 (70.0%)
Female	5 (33.3%)	4 (26.7%)	9 (30.0%)
Race			
n	15	15	30
American Indian or Alaska Native	1 (6.7%)	0	1 (3.3%)
Asian	0	1 (6.7%)	1 (3.3%)
White	9 (60.0%)	13 (86.7%)	22 (73.3%)
Other	5 (33.3%)	1 (6.7%)	6 (20.0%)
Ethnicity			
n	15	15	30
Hispanic or Latino	5 (33.3%)	3 (20.0%)	8 (26.7%)
Not Hispanic or Latino	10 (66.7%)	11 (73.3%)	21 (70.0%)
Not Stated	0	1 (6.7%)	1 (3.3%)
Haematopoietic Stem Cell Transplant Status			
n	15	15	30
Yes	2 (13.3%)	0	2 (6.7%)
No	13 (86.7%)	15 (100.0%)	28 (93.3%)
Haematological Malignancy History			
n	13	15	28
ACUTE LYMPHOID LEUKAEMIA	8 (61.5%)	12 (80.0%)	20 (71.4%)
ACUTE MYELOID LEUKAEMIA	4 (30.8%)	0	4 (14.3%)
NON-HODGKIN LYMPHOMA	1 (7.7%)	1 (6.7%)	2 (7.1%)
OTHER	0	2 (13.3%)	2 (7.1%)

Assessor's comment

The total number of the IC children and adolescents from studies NV20234 and NV25719 was small consisting of only 50 patients, 46 of whom received at least one dose of study drug (39 children <13 years of age and 7 adolescents aged 13 to 17 years). Efficacy evaluation could only be performed on 20 ITTi patients from study NV25719 and 16 mITTi patients from study NV20234.

The background conditions in the patients varied markedly. Patients in study NV25719 (30 children aged < 13 years) had received induction, consolidation, or re-intensification chemotherapy for a haematological malignancy (most prevalent was ALL, but some patients had AML or non-Hodgkin's lymphoma) or were undergoing a conditioning regimen either prior to hematopoietic stem cell transplant (HSCT) or less than 6 months after HSCT. These patients represent the most severely IC paediatric population investigated. Study NV20234 included 20 paediatric patients, 16 of whom received at least one dose of oseltamivir (9 children aged <13 years and 7 adolescents aged 13 to 17 years). The 22 background conditions causing immunosuppression among the 20 paediatric patients in NV20234 were kidney transplant (1), allogenic HSCT (2), HIV with CD4 count <500/mm^3 (4), hematologic malignancies (8), and systemic immunosuppressive therapy (7).

Due to the small number of subjects and variable background conditions, efficacy data from these patients should be interpreted with caution. Imbalances between groups in study NV25719 increase confounding by background conditions. However, the samples collected from these patients are considered sufficient for evaluation of posology based on population PK analyses, PK/PD evaluation, and disease modelling (see Section 6 Clinical Pharmacology aspects and Section 8 Extrapolation of this AR).

Time to treatment from onset of symptoms

The median time from onset of symptoms to start of treatment was shorter in Study NV25719 than in Study NV20234. In the ITTi population of Study NV25719, the median time from onset of symptoms to start of treatment was 44.25 hours (range: 20.0–94.8 hours) and was similar between the 2 treatment groups. In this study, 6/11 patients in the conventional dose group and 6/9 patients in the higher dose group started treatment less than 48 hours from symptom onset. In Study NV20234 the median time from onset of symptoms to start of drug in paediatric patients in the safety population was 58.67 hours (range: 8.4 – 89.6), with patients in the conventional dose group having a slightly longer time from onset of symptoms than those in the double dose group (median 65.83 [range 12.3 - 89.6] and 53.75 hours [range 8.4 - 82.4], respectively). In this study, 3/7 paediatric patients in the conventional dose group and 4/9 paediatric patients in the double dose group started treatment less than 48 hours from symptom onset.

Assessor's comment

When comparing the data on paediatric IC patients with otherwise healthy (OwH) children, it should be born in mind that in Studies WV15758 and M76001, patients were enrolled if the duration between onset of symptoms and first dose of study drug was ≤48 hours and ≤ 36 hours, respectively. In Studies NV20234 and NV25719, due to the typically delayed presentation of influenza symptoms, because of their IC status, patients were enrolled if the duration between onset of influenza symptoms and first dose of study drug was ≤ 96 hours. There was however the requirement to include in study NV25719 at least 12 patients, for whom oseltamivir was initiated within 48 hours. Hence, the median time to treatment from onset of symptoms was shorter in NV25719 than in NV20234.

It is noteworthy that in adult patients in study NV20234 the efficacy results were (non-significantly) better when treatment was initiated within 48 hours vs. later than 48 from onset of symptoms. Therefore, the PI of oseltamivir contains the recommendation to start treatment in IC patients as soon as possible.

6.3.2 Viral resistance

Resistance was defined as the presence of known mutations conferring resistance to oseltamivir in viruses isolated from nasopharyngeal swab samples, or as phenotypic outliers in culture assays. Viral load was determined from nasal swabs using 2 methodologies: RT-PCR and culture.

Baseline resistance

At baseline, none of the patients in Study NV25719 had oseltamivir-resistant influenza viruses (genotypic and/or phenotypic) detected in their baseline samples. One adolescent patient from Study NV20234 had an oseltamivir-resistant influenza virus at baseline. This patient was infected with an A/H1N1 virus carrying an H274Y mutation (genotypic resistance) and was withdrawn from treatment.

Post-baseline resistance

In Study NV25719, there were 3 children with post-baseline oseltamivir viral resistance: 1/11 patients (9.1%) in the conventional dose group and 2/9 patients (22.2%) in the triple dose group. Both patients in the triple dose group had ALL and the patient in the conventional dose group had undergone HSCT.

Among the children in Study NV20234, three patients developed post-baseline resistance: 2/4 children (50%) in the conventional dose group and 1/5 children (20%) in the double dose group.

None of the 7 adolescent patients in NV20234 had treatment-emergent resistance.

Overall, the majority (5 out of 6) of subjects with post-baseline viral resistance were ≤5 years of age, 4 children had underlying ALL and 2 children had received HSCT. All of the children with post-baseline resistant viruses were infected with influenza type A virus. Three of the children with resistant viruses was patients had received the conventional and three had received higher dose of oseltamivir.

Table 6.3.2.1 presents the characteristics of paediatric IC patients (<13 years of age) with treatment-emergent oseltamivir resistance (as none of the teenaged subjects had post-baseline resistance). The overall treatment-emergent resistance rate in IC children below 13 years of age was 20.7% (95% CI 8.0% to 39.7%).

Table 6.3.2.1. Characteristics of Paediatric IC Patients with Treatment-Emergent Oseltamivir Resistance

Dose	**Conventional**	**Conventional**	**Conventional**	**Triple Dose**	**Triple Dose**	**Double Dose**
Study	NV25719	NV20234	NV20234	NV25719	NV25719	NV20234
Patient ID	10034	61916	65851	10005	10006	65061
Age, years	12	4	4	3	3	5
Condition	HSCT	HSCT	ALL	ALL	ALL	ALL
Flu type/Subtype	A/H1N1	A/H1-pdm09	A/H3N2	A/H1N1	A/H3N2	A/H1-pdm09
Genotypic mutation(s)	H274Y	H275H/Y	E119E/V	H274Y	R292K E119V	H275Y
Phenotypic mutation (reduced susceptibility degree)	Extreme outlier	Extreme outlier	Outlier	Extreme outlier	Outlier	Not done
Treatment Duration (days)	15	10	11	20	20	10
Dose Intensity	100%	100%	100%	100%	86.8%	95%
Time to cessation of viral shedding by RT-PCR (days)	29	10	40	18	51	15
Time to resolution of all symptoms (days)	12	1	1	1	3	21

ALL = acute lymphoid leukaemia; HSCT = haematopoietic stem cell transplant; RT-PCR = reverse transcriptase polymerase chain reaction.

Assessor's comment

Six children had treatment-emergent oseltamivir resistance. Consistent with earlier data, resistance was more frequent in younger children, as none of the teenaged patients (13 to 17 years of age) and only one

patient aged 12 years had post-baseline resistance, and all other subjects with post-baseline resistance were 3 to 5 years of age.

Time to cessation of viral shedding

For study NV20234, time to cessation of viral shedding (TTCVS) has now been presented by the MAH together for children and adolescents (whereas in the previously assessed CSR, results from adults and adolescents had been pooled).

TTCVS by cell culture

Table 6.3.2.2 shows the median TTCVS by viral culture for IC paediatric patients in studies NV25719 and NV20234. In paediatric patients in Study NV20234, the median TTCVS was longer in the conventional dose group compared with the double dose group and with wide CI. The wider CI in the conventional dose group of this study compared to double dose is driven by 2 large values collected during the follow-up period of the study (i.e. weeks apart rather than hours as determined by the study visits schedule). The range of TTCVS was similar between the dose groups when excluding assessments during the follow-up period.

Table 6.3.2.2 Median TTCVS by culture for IC paediatric patients in studies NV25719 and NV20234

Study	**N***	**Median, hours (95% CI)**	
		Conventional Dose[a]	**Higher Dose[b]**
NV25719	11/9	109.2 (95% CI: 60.9, 153.0)	75.9 (95% CI: 54.7, 344.1)
NV20234	8/8	150.3 (95% CI: 34.2, 891.3)	94.9 (95% CI: 8.6, 109.4)

CI = confidence interval.
*N for conventional dose/higher dose, respectively.
[a]75 mg BID, weight adjusted.
[b] Study NV25719: triple dose; Study NV20234: double dose; weight adjusted.
Source: NV25719 CSR Table 18 NV20234 CSR Table 57
TTCVS=time to cessation of viral shedding

To attempt to investigate the effect of oseltamivir resistance on the median TTCVS, the MAH repeated the analysis was for the conventional and higher dose groups, excluding patients who developed post-baseline resistance. In Study NV25719, the median TTCVS excluding patients with post-baseline oseltamivir resistance (1 and 2 patients in the conventional and triple dose groups, respectively), only changed slightly and remained longer in the conventional dose group than in the triple dose group with wide and overlapping CIs (Table 6.3.2.3).

The MAH states that data from a similar analysis for Study NV20234 is not presented in the Summary of Efficacy as the results were mainly driven by the assessments during the follow-up period. The MAH however also states that none of the adolescent patients had post-baseline oseltamivir resistance. The TTCVS for children and adolescent patients from NV20234 (separately from NV25719) are shown in Table 6.3.2.4.; however, this table includes also paediatric patients with post-baseline resistance.

Table 6.3.2.3 Median TTCVS (by culture) excluding patients with post-baseline oseltamivir resistance (ITTi, study NV25719)

Summary of Time to Cessation of Viral Shedding (Culture) Excluding Patients with Post-Baseline Resistance, Intent-to-Treat Infected Population
Protocol: NV25719

Time to Event (a) (hours)	Oseltamivir conventional dose (N=10)	Oseltamivir 3x conventional dose (N=7)
n	10	6
Number Censored	0	1
Median (95% CI) (b)	106.9 (58.2, 148.3)	74.5 (54.7, 146.3)
Range	58.2 - 222.0	54.7 - 146.3
Group Comparison		
- Oseltamivir conventional dose vs. Oseltamivir 3x conventional dose		
Difference of Medians (95% CI) (c)	-	32.4 (-37.1, 78.3)

(a) Time from randomisation date to the time of first negative result from culture with no subsequent positive results.
(b) Median time was estimated from the Kaplan-Meier curve (unstratified).
(c) Obtained with 10000 bootstraps.
NE = Not Estimable(Brookmeyer and Crowley, 1982).

Table 6.3.2.4 Median TTCVS (by culture) for patients below <18 years of age from NV20234 (ITTi; including children with post-baseline resistance)

Summary of Time to Cessation of Viral Shedding (Culture), Intent-to-Treat Infected Population, Children
Protocol: NV20234

Time to Event (a) (Hours)	Ro 64-0796 Conventional (N=9)	Ro 64-0796 Double (N=8)
n	8	8
Number of Censored	1	0
Median (95% CI) (b)	150.3 (34.2, 891.3)	94.9 (8.6, 109.4)
Min-Max	34.2 - 946.4	8.6 - 150.3

(a) Time from start of treatment to the time of first negative result from culture with no subsequent positive results.
(b) Median time was estimated from the Kaplan-Meier curve (unstratified).
Children are determined as patients with age less than 18.

Comparison of viral shedding (by culture) across registration studies and studies on IC subjects

The results on the time course of patients remaining shedding virus are summarised in table 6.3.2.5 from paediatric and adult studies in otherwise healthy subjects and IC subjects.

OwH adults/adolescents in study M766001 had stopped shedding by Day 4, whereas viral shedding continued in OwH children and in IC patients.

At Day 6, the percentages shedding virus were 32% (oseltamivir group) and 33% (placebo group) among OwH children from study WV15758; 15.4% (oseltamivir conventional dose) and 18.3% (oseltamivir double dose) in IC adults from NV20234; and in IC children <13 years of age 4/10 (40%) in the conventional dose group and 3/6 in the triple dose group of NV25719: and finally, in the paediatric (1 to 17 years) age group of NV20234 3/7 (42.9%) in the conventional dose group and 0/7 in the double dose group.

At Day 10/11, 2% of OwH children continued shedding both in the oseltamivir and placebo groups. Among IC adults from study NV20234, 1/65 in the conventional dose group and 3/71 in the double dose group were shedding virus at Day 10/11; whereas from the same study, paediatric patients (from 1 to 17 years old) 1/7

in the conventional dose group and 0/0 in the double dose groups were shedding virus at Day 10/11. In Study NV25719, the corresponding numbers were 0/8 in the conventional dose group and 2/4 in the triple dose group at Day 10/11.

Table 6.3.2.5 Summary of patients with viral shedding by visit (by culture) in registration studies (WV15758 and M76001) and studies in IC patients (Studies NV20234 and NV25719)

	Registration Studies		Studies in IC Patients		
Study	**WV15758[a]**	**M76001[b]**	**NV20234[c]**	**NV25719[d]**	**NV20234[e]**
Population	OwH Children (1 to 12 years)	OwH Adults/ Adolescents (≥13 to 80 years)	IC Adults (≥18 years)	IC Children (<13 years)	IC Pediatrics (≥1 to <18 years)
N	Oseltamivir (conventional[f]): 217 Placebo: 235	Oseltamivir (conventional): 702 Placebo: 361	Conventional: 73 Double Dose: 78	Conventional: 11 Triple Dose: 9	Conventional: 8 Double Dose: 8
Baseline	Oseltamivir: 93/93 (100%) Placebo: 105/105 (100%)	Oseltamivir: 608/697 (87%) Placebo: 309/357 (87%)	Conventional: 64/70 (91.4%) Double Dose: 64/76 (84.2%)	Conventional: 11/11 (100%) Triple Dose: 8/9 (88.9%)	Conventional: 8/8 (100%) Double Dose: 8/8 (100%)
Day 2/3	Oseltamivir: 72/93 (77%) Placebo: 88/105 (84%)	Oseltamivir: 98/647 (15%) Placebo: 75/333 (23%)	Conventional: 45/67 (67.2%) Double Dose: 43/73 (58.9%)	N/A	Conventional: 5/7 (71.4%) Double Dose 6/8 (75.0%)
Day 4	Oseltamivir: 51/93 (55%) Placebo:72/105 (69%)	Oseltamivir: N/A Placebo: N/A	N/A	Conventional: 8/10 (80%) Triple Dose: 3/9 (33.3%)	N/A
Day 6	Oseltamivir: 30/93 (32%) Placebo: 35/105 (33%)	Oseltamivir: N/A Placebo: N/A	Conventional: 10/65 (15.4%) Double Dose: 13/71 (18.3%)	Conventional: 4/10 (40%) Triple Dose: 3/6 (50%)	Conventional: 3/7 (42.9%) Double Dose: 0/7
Day 10/11	Oseltamivir: 2/88 (2%) Placebo:2/100 (2%)	Oseltamivir: N/A Placebo: N/A	Conventional: 1/65 (1.5%) Double Dose: 3/71 (4.2%)	Conventional: 0/8 (0%) Triple Dose: 2/4 (50%)	Conventional: 1/7 (14.3%) Double Dose: 0/7 (0%)

IC = immunocompromised; N/A = not available; OwH = otherwise healthy.

Assessor's comments on results by viral culture

The results obtained by viral culture indicate longer median time to cessation of viral shedding in paediatric IC patients receiving conventional dose of oseltamivir vs. higher dose; and the results do not markedly change by exclusion of patients with post-baseline resistance. The numbers of patients are, however, low, and confidence intervals (CI) are very wide. The exact point of median can be considered coincidental when CIs are extremely wide.

When the time course of cessation of viral shedding is compared between otherwise healthy (OwH) historical subjects from registration studies and studies on IC subjects, it is obvious that adult OwH patients stop shedding virus earlier than OwH children do and earlier than IC adults and IC paediatric subjects. One third of OwH children were shedding virus at Day 6 and 2% at Day 10/11 from onset of treatment. In study NV20234, the proportion of adult IC patients with continued shedding at days 6 and 10/11 were roughly similar at Days 6 and 10/11 regardless of group (conventional vs. double dose). In the small paediatric subset of NV20234, 3/7 subjects in the conventional dose group and 0/7 in the double dose groups were still shedding virus at Day 6, and the respective numbers at Day 10/11 were 1/7 and 0/7. In study NV25719, on the other hand, at Day 6 4/10 in the conventional dose group and376 in the triple dose group continued shedding virus; the corresponding numbers at Day 10/11 were 0/8 in the conventional and 2/4 in the triple dose arm of the study.

It is in line with prior observative data from e.g. the IRIS study (see section 5 Introduction of this AR) that OwH adults stop shedding earlier than OwH children do and earlier than IC patients. The results obtained by viral culture on shedding among paediatric IC patients receiving conventional daily dose of oseltamivir vs. higher (double or triple) dose are not consistent between studies NV20234 and NV25719. It is obvious that

among the small number of subjects with variable background conditions chance findings are to be expected; hence, no robust interpretation of optimal dose in IC children can be deduced based on the results, without help of population PK/PD and disease modelling and extrapolation from other patient groups (see sections 6 and 8 of this AR).

TTCVS by RT-PCR

In Study NV25719, including patients with post-baseline oseltamivir viral resistance, the median TTCVS was shorter in the conventional dose group than in the triple dose group (Table 6.3.2.6, Figure 6.3.2.1) when analysed by RT-PCR; of note, the Kaplan-Meier curves crossed in several places.

In Study NV20234, the median TTCVS in paediatric patients (<18 years of age) was the similar in the 2 treatment groups (Table 6.3.2.6). However, the wider CI in the conventional dose group is driven by the data collected during the follow-up period of this study.

Table 6.3.2.6. Median TTCVS by RT-PCR for IC paediatric patients in NV25719 and NV20234

Study	N*	Median, hours (95% CI)	
		Conventional Dose[a]	Higher Dose[b]
NV25719	11/9	157.2 (95% CI: 125.3, 658.0)	242.3 (95% CI: 60.4, 392.1)
NV20234	8/8	181.0 (95% CI: 106.2, 943.7)	180.5 (95% CI: 8.6, 247.8)

CI = confidence interval.

*N for conventional dose/higher dose, respectively.

[a]75 mg BID, weight adjusted.

[b]NV25719 study: triple dose; NV20234 study: double dose; weight adjusted.

Similar to the cell culture results, the effect of oseltamivir resistance on median TTCVS by RT-PCR was determined by repeating the analysis for the 2 treatment groups excluding patients who developed post-baseline resistance.

In Study NV25719, the median TTCVS excluding patients with post-baseline oseltamivir resistance (1 and 2 patients in the conventional and triple dose groups, respectively), was similar between the dose groups with wide and overlapping CIs (Table 6.3.2.7).

In Study NV20234, exclusion of patients with viral resistance lowered the median TTCVS in the double-dose group only, leading to an apparent small difference among paediatric patients receiving different dose (181.0 hours [95% CI: 106.2, 946.4] in the conventional dose group vs. 155.6 hours [95% CI: 8.6, 226.3] in the double dose group). It should be noted that in the conventional dose group, although 2 patients with treatment-emergent resistance were excluded (1 with prolonged viral shedding and 1 with cessation of viral shedding before EOT), no change was observed, and in the double dose group, although only 1 patient with treatment-emergent resistance was excluded (the patient with the longest viral shedding), a difference was observed. Nevertheless, the CIs were broad and overlapping. (Table 6.3.2.7).

Table 6.3.2.7. Median TTCVS by RT-PCR for IC paediatric patients excluding those with post-baseline resistance in NV25719 and NV20234

Study	N*	Median, hours (95% CI)	
		Conventional Dose[a]	Higher Dose[b]
NV25719	10/7	157.1 (95% CI: 106.2, 248.1)	150.7 (95% CI: 60.4, 302.2)
NV20234	6/7	181.0 (95% CI: 106.2, 946.4)	155.6 (95% CI: 8.6, 226.3)

CI = confidence interval.

*N for conventional dose/higher dose, respectively.

[a]75 mg BID, weight adjusted.

[b]NV25719 triple dose; NV20234 double dose; weight adjusted.

Comparison of TTCVS (RT-PCR) with IC adults

Table 6.3.2.8 demonstrates the results for TTCVS analysed by RT-PCR in all IC patients, adults included. As measured by RT-PCR, the median TTCVS was similar across dose groups when patients with resistance were excluded.

The group with the longest median TTCVS was the conventional dose of the IC paediatric patients in Study NV20234 (181 hours regardless of whether patients with resistance were excluded). The wide CI of this group is driven by patients who were still shedding virus during the follow-up period of the study when the frequency of the assessments was low.

Table 6.3.2.8 TTCVS by RT-PCR in all IC patients in studies NV20234 and NV25719

		Studies in IC Patients		
Study		**NV20234 [a]**	**NV20234 [b]**	**NV25719 [c]**
Population		IC Adults (≥18 years)	IC Paediatric patients (≥1 to <18 years)	IC Children (<13 years)
TTCVS Median, hours (95% CI)	All patients	Conventional (N=72): 178.0 (152.2, 227.0) Double Dose (N=76): 154.1 (128.5, 171.0	Conventional (N=8): 181.0 (106.2, 943.7) Double Dose (N=8): 180.5 (8.6, 247.8)	Conventional (N=11): 157.2 (125.3, 658.0) Triple Dose (N=10): 242.3 (60.4, 392.1)
	Excluding patients with post-baseline resistance	Conventional (N=62): 155.4 [133.8, 220.5] Double Dose (N=74): 154.0 [124.0, 159.3]	Conventional (N=6): 181.0 (106.2, 946.4) Double Dose (N=6): 155.6 (8.6, 226.3)	Conventional (N=10): 157.1 (106.2, 248.1) Triple Dose (N=8): 150.7 (60.4, 302.2)

CI = confidence interval; IC = immunocompromised; RT-PCR = reverse transcriptase polymerase chain reaction

Assessor's comments of TTCVS

Time to cessation of viral shedding (TTCVS) obtained by culture was shorter than that obtained by RT-PCR in both studies. These methods furthermore gave discrepant results (Tables 6.3.2.4 and 6.3.2.6). The observed difference between results from the 2 assays may be partly due to the fact that viral culture assay depends on sufficient amount of viable organisms. On the other hand, RT-PCR recognizes fragments and non-viable viral particles in addition to viable viruses. Taking in account the small number of patients in all paediatric study groups, the marked inter-individual variation in the TTCVS, and the inherent differences between the two methods, no solid conclusion can be made on the contradictory results. The observed difference in the results on median time to viral clearance obtained by viral culture and by PCR is likely due to chance. As can be seen in table 6.3.2.5, the different times to viral clearance were based on very few subjects. This issue is not pursued further.

The subjects with post-baseline resistance had prolonged viral shedding, as expected based on previous studies. In Study NV25719, there were 3 children with post-baseline oseltamivir viral resistance: 1/11 patients (with HSCT) in the conventional dose group and 2/9 patients (with ALL) in the triple dose group.

Among the children in Study NV20234, three patients developed post-baseline resistance: 2/4 children in the conventional dose group (1 with HSCT and 1 with ALL) and 1/5 children in the double dose group (the patient had ALL).

None of the 7 adolescent patients in NV20234 had treatment-emergent resistance.

Overall, the majority (5 out of 6) of subjects with post-baseline viral resistance were ≤5 years of age. All of the children with post-baseline resistant viruses were infected with influenza type A virus. Three of the children with resistant viruses had received the conventional daily dose and three had received higher dose of oseltamivir, one of whom had received double dose and 2 had received triple dose of oseltamivir. TTCVS was 10, 29, and 40 days in the 3 individual children treated with conventional dose, and 15, 18, and 51 days in the 3 patients treated with higher dose of oseltamivir.

As a conclusion, the small numbers and large inter-individual variation do not allow for direct interpretation of the effect of conventional vs. higher dose of oseltamivir on emergence of postbaseline viral resistance or duration to viral clearance. Hence, the extrapolation of recommended dose for IC children based on PK/PD and disease modelling and extrapolation from IC adults and OwH children is deemed necessary, as has been previously accepted.

Literature data on oseltamivir resistance reviewed by the MAH

The MAH has included in the submission a review of publications on the treatment of influenza in children (and adults), including both immunocompetent and immunocompromised (IC) patients (table 6.3.2.9.). The studies are mostly observational and small (with a smaller number of IC patients than in Studies NV25719 and NV20234). However, the results on resistance in published literature is in general similar to studies NV25719 and NV20234. The incidence of post-baseline resistance is higher in IC children than in otherwise healthy (OwH) children. Similar results have been obtained in IC adults compared with OwH adults (*Alonso et al, Tramontana et al*) and on the treatment of influenza in children (*Stephenson et al*) (Table 6.3.2.9).

Table 6.3.2.9 Summary of Reviewed Studies Reporting Resistance

Reference	Number of Patients	Population	Age (years)	Number of Patients With Oseltamivir Resistance (%)	Oseltamivir Dosing (Duration)
Fraaij et al. The ins and outs of universal childhood influenza vaccination. Future Microbiol. (2011) 6(10), 1171–1184.	24	Majority of hospitalized transplant patients (kidney or HSCT)	1-73	4 (17)	75 mg BID (7-16 days)
Van der Vries et al. Prolonged influenza virus shedding and emergence of antiviral resistance in immunocompromised patients and ferrets. PLoS Pathog. (2013); 9:1-11.	16	Hospitalized IC patients with a prolonged shedding (>14 days)[a]	Median age 22.3 (range 0-81)	5 (31)	NS (5-30 days)
Stephenson et al. Neuraminidase Inhibitor Resistance after Oseltamivir Treatment of Acute Influenza A and B in Children. Clinical Infectious Diseases (2009); 48:389–96	64	Non IC attending hospital children's unit with influenza symptoms	1-12	4 (6.3)	Weight based 75 mg BID (5 days)
Alonso et al. Resistance and virulence mutations in patients with persistent infection by pandemic 2009 A/H1N1 influenza. J Clin Virol (2011); 50:114-8.	12	IC patients[b]	> 18	2 (16.7)	75 or 150 mg BID (5-27 days)
	16	non IC patients		0 (0)	
Tramontana et al. Oseltamivir resistance in adult oncology and hematology patients infected with pandemic (H1N1) 2009 virus, Australia. Emerg Infect Dis 2010;16:1068-75.	30	Hospitalized IC patients[c]	> 18	4 (13.3%)	NS (5-43 days)

BID = twice daily, HSCT = hematopoietic stem cell transplant, IC = immunocompromised, NS = not specified.

[a] HIV-infected patients, cancer patients on chemotherapy, patients that had received a solid organ transplant or patients with an auto-immune disease on immunosuppressive therapy.

[b] HIV-infected patients, patients that had received a solid organ transplant, patients with hematological malignancy.

[c] Patients with hematological malignancy or having received an HSCT.

Assessor's comment

The results from the analyses of treatment-emergent resistance in studies NV20234 and NV25719 are in line with the scarce data available from literature. The incidence of oseltamivir resistance in all children treated in Roche sponsored studies is 4.5% (78/1727). This incidence encompasses mainly OwH children (EU SmPC).

The overall incidence of treatment-emergent resistance in IC children was 20.7% (6/29) (95% CI 8.0% to 39.7%) (Section 2.3.2), which was higher than the incidence for OwH children and IC adults, but similar to that seen in OwH infants <1 year (18.3% [13/71]) (EU SmPC).

6.3.3 Clinical efficacy

Time to resolution of symptoms (TTRAS) was defined in children as follows: the time from treatment initiation to the start of the 24-hour period in which all 18 symptoms items of the CARIFS (see section 7.2.2) had scores ≤1 (minor or no problem) and remained ≤1 for at least 21.5 hours. If a score of 4 ("do not know" or "not applicable") occurred at any assessment during the study for any given symptom, the assessment was not be included in the calculation of the resolution of all CARIFS symptoms. Patients with symptom scores ≤1 at baseline, which remained ≤1 for at least 21.5 hours thereafter, would have a TTRAS set to missing. Patients with symptom scores ≤1 at baseline followed immediately by scores ≤1 for at least 21.5 hours would have a TTRAS set to zero.

In adolescents (and adults) in study NV20234, the TTRAS was defined using a 7-symptom score card filled out by the study subjects.

Results on the median TTRAS for the IC children (<13 years of age) from studies NV25719 and NV20234 are presented in Table 6.3.3.1 (ITTi population) and Figures 6.3.3.1 and 6.3.3.2.

Table 6.3.3.1 Median TTRAS in children aged <13 years in Studies NV25719 and NV20234, ITTi

Study	N	Median TTRAS, hours (95% CI)	
		Conventional Dose[a]	Higher Dose[b]
NV25719			
All patients	11/9	179.4 (24.7, NE)	34.5 (0.0, 84.9)
Excluding patients with post-baseline viral resistance	9/7	127.2 (24.7, NE)	34.5 (0.0, 118.3)
NV20234			
All patients	4/5	32.1 (20.2, NE)	115.9 (45.5; 495.0)
Excluding patients with post-baseline viral resistance	2/4	NE	107.7 (45.5; 117.2)

CI = confidence interval; NE = not estimated; TTRAS = time to resolution of all symptoms
N: patient numbers in the conventional dose/higher dose, respectively.
[a] Oseltamivir Conventional Dose =75 mg BID, weight adjusted.
[b] Oseltamivir Higher Dose in NV25719 study: 3× conventional dose; in NV20234 study: 2×conventional dose; weight adjusted.

Figure 6.3.3.1 Kaplan-Meier plot of the TTRAS in study NV20234, patients <13 years of age (ITTi population)

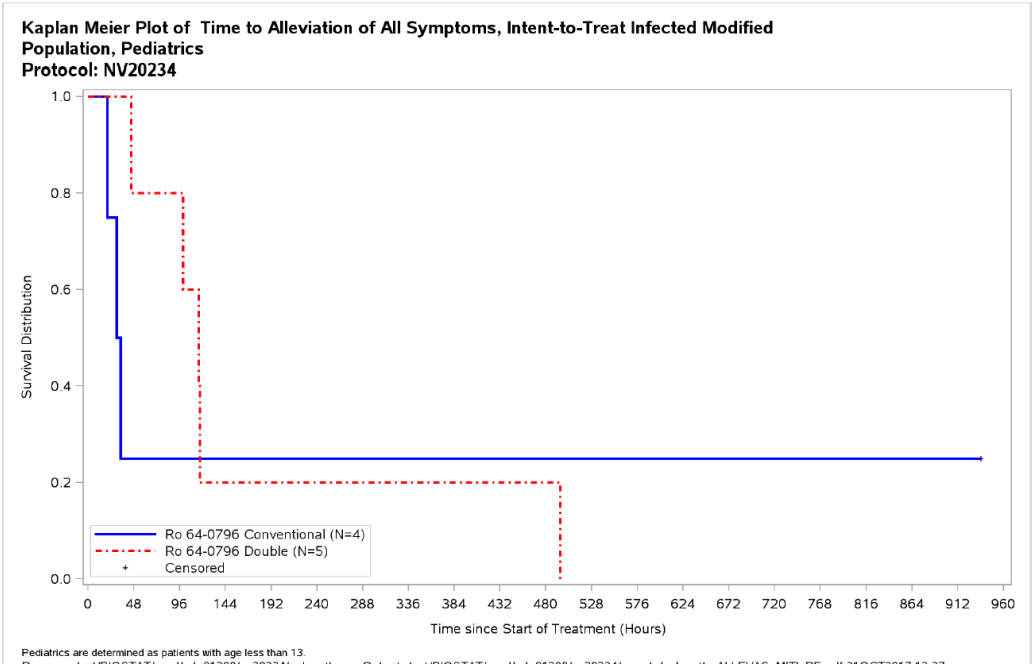
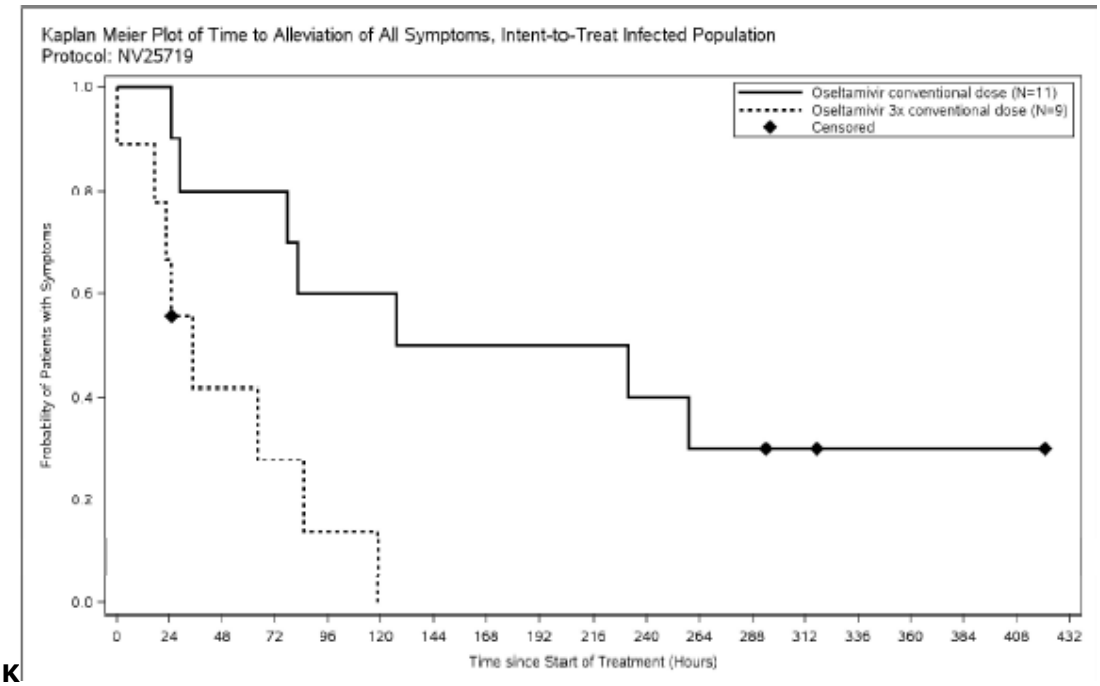


Figure 6.3.3.2. Kaplan-Meier plot of the TTARS in study NV25719 (ITTi population)



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Among the 7 adolescent subjects from NV20234, the TTRAS varied as follows: the individual values were 0, 126, 173 and 304 hours in the conventional treatment arm and 63.2, 111 and 326 hours in the double dose group (the 0 value corresponds to a patient with symptoms at baseline but no further records.)

Time to resolution of fever

For both studies, the small number of patients with fever at baseline limits data interpretation: 8/20 children in Study NV25719 and 3/9 children in Study NV20234 had fever at baseline.

In Study NV25719, 4/11 children in the conventional and 4/9 children in the triple dose groups had fever at baseline. The median TTR of fever in patients with baseline fever was 17.1 hours longer in the conventional dose group than the triple dose group (28.4 vs. 11.3 hours).

In Study NV20234, there were 3 children with fever at any time from baseline onwards. The TTR of fever for the patient in the conventional dose group was censored as defined in the Statistical Analysis Plan. The TTR of fever in the patients in the double dose group was 0 and 51.9 hours.

Assessor's comments

In children below 13 years of age in Study NV20234, the median time to resolution of all symptoms (TTRAS) was 32.1 hours (95% CI: 20.2, not evaluable, NE) in the study group treated with the conventional dose and 115.9 hours (95% CI: 45.5, 495.0) in the group treated with double dose of oseltamivir.

In the study NV25719, on the contrary, the median TTRAS was longer in the conventional dose group than in the higher dose group (179.4 hours (95% CI: 24.7, not estimable) and 34.5 hours (95% CI: 0.0, 84.9), respectively.

It is to be noted that the patient populations in NV20234 and NV25719 were different, the latter being more severely ill. The MAH has also stated that there was imbalance between study arms of NV26719, Furthermore, the CARIFS score includes several items that may be positive due to severe overall condition of study subjects with leukaemia, concomitant chemotherapy etc., which is expected to confound results in such a small study. Nevertheless, the difference in TTRAS between patients in the conventional and triple dose groups is seemingly large in study NV25719.

Analysis excluding patients with post-baseline oseltamivir resistance did not change these trends found among IC children in studies NV 20234 and NV 25719.

The analysis on the time to resolution of fever is based on even less patients than analysis on TTRAS, since only 8/20 children in Study NV25719 and 3/9 children in Study NV20234 had fever at baseline; reflecting obviously the IC condition of the subjects. Therefore, no reliable comparison between different doses can be performed regarding resolution of fever.

Due to the small number of patients and extremely large variation, the efficacy results of these studies are deemed insufficient for determination of efficacy in IC paediatric patients.

See section 6.3. of this AR for discussion on appropriate dosage as assessed based on the PK/PD and disease modelling results.

6.3.4 Safety

Safety data from studies NV25719 and NV20234 are presented by the MAH for the 46 oseltamivir-treated safety-evaluable IC paediatric patients with influenza: 39 children and 7 adolescents. All subjects who received at least one dose of treatment and had a safety assessment performed post randomization were included in the safety evaluation. The summary of the safety population is given Table 6.3.4.1.

Table 6.3.4.1 Summary of studies contributing to safety evaluation

Study No. (Phase)	Study Design	Population	No. of Patients randomized	No. of Patients contributing to this evaluation	Dose, Route, and Regimen [a]
NV25719 (Phase IB)	Open-label, randomized, parallel-group, multicenter	IC children < 13 years with confirmed influenza infection	30[b]	Total 30: 15 to conventional dose; 15 to triple dose	Oral oseltamivir 30 to 225 mg BID for 5 to 20 days (children > 40 kg, 75 mg or 225 mg; children ≤40 kg, weight based dose adjustment)
NV20234 (Phase III)	Double-blind, randomized, stratified, multicenter	IC adults (≥18 years), adolescents (≥13 to< 18 years) and children (≥1 to<13 years) with confirmed influenza infection	228 (207 adults, 20 patients <18 years)[b,c]	Total 16 patients < 18 years: 9 children (4 in conventional dose and 5 in double dose) and 7 adolescents (3 in conventional dose and 4 in triple dose)	Oral oseltamivir 30 to 150 mg BID for 10 days (children >40 kg, 75 mg or 150 mg; children ≤40 kg, weight based dose adjustment)

BID = bis in die (twice a day); IC = immunocompromised.

[a] Formulations used: Adolescents (13 to <18 years) and Adults: oseltamivir 75 mg capsules; Children (1 to <13 years): oseltamivir capsules 75 mg, 45 mg and 30 mg (NV25719 study) and oral suspension (12 mg/mL [NV20234 and NV25719 studies] and 6 mg/mL [NV25719 study]).

[b] Overall Safety population: N=30 in Study NV25719 and N=215 in Study NV20234, which included 16 patients <18 years and 199 adults.

[c] No age information was available for 1 patient (who was randomized but not dosed).

The background conditions of the pooled safety population of children are given in Table 6.3.4.2. Notably, 85% of the children had haematological malignancy.

The background conditions of the 7 adolescents from study NV20234 are not given separately in the Clinical overview or Summary of clinical safety. However, the overall numbers of background conditions among the 16 patients <18 years in the safety population from NV20234 were the following: haematologic malignancies 6, systemic immunosuppressive therapy 6, HIV (WITH CD4 count <500/mm^3) 3, transplant 3 (HSCT 2, SOT 1).

Table 6.3.4.2 Immunodeficiency conditions in the pooled safety population, children < 13 years

Summary of Immunodeficiency Conditions: NV25719, NV20234 (<13 years) and combined, Safety Evaluable Population
Project: CD01288O

Category Description	NV25719 Conventional Dose (N=15)	NV25719 3X Conventional Dose (N=15)	NV25719 Total (N=30)	NV25719 and NV20234(< 13 Y.O.) Total (N=39)
IMMUNODEFICIENCY CONDITION				
Total number of patients	15 (100.0%)	15 (100.0%)	30 (100.0%)	39 (100.0%)
Total number of events	15	15	30	41
HAEMATOLOGICAL MALIGNANCY	13 (86.7%)	15 (100.0%)	28 (93.3%)	33 (84.6%)
HAEMATOPOIETIC STEM CELL TRANSPLANT	2 (13.3%)	0	2 (6.7%)	3 (7.7%)
SYSTEMIC IMMUNOSUPPRESSIVE THERAPY	0	0	0	5 (12.8%)

Immunodeficiency condition HIV with CD4 count <500/MM3 includes conditions of HIV with CD4 count <200/MM3.

Adolescents ≥ 13 to <18 years of age

Of the 7 oseltamivir-treated adolescents aged ≥13 to <18 years (3 in the conventional dose group and 4 in the double dose group) who were evaluated for safety, all 3 patients in the conventional dose group and 1 patient in the double dose group reported at least 1 adverse event (AE) during the study period. There was a higher number of reported AEs in the conventional dose group (6 AEs: one of each of the following: diarrhoea, vomiting, joint effusion, bradycardia, pyrexia, somnolence) compared with the double dose group (2 AEs: nausea 1, juvenile idiopathic arthritis 1). All these events were mild to moderate in intensity. No severe or life-threatening events were reported in this age group.

All AEs reported were considered unrelated to study drug by the investigator, except for 1 event in the double dose group, which was considered probably related (nausea).

Children <13 years of age

Of the 39 IC children exposed to oseltamivir in Studies NV25719 and NV20234, 34 completed treatment (5-20 days in Study NV25719 and 10 days in Study NV20234). The patient disposition of the pooled safety population of children below 13 years of age is presented in Table 6.3.4.3.

In Study NV25719, 15 patients received conventional dose and 15 received triple dose and in Study NV20234, 4 patients received conventional dose and 5 received double dose. Hence, in the pooled safety population, a total of 19 patients received conventional dose and 20 patients received a higher dose (i.e., double or triple dose).

Table 6.3.4.3 Patient disposition (pooled safety population, children)

Patient Disposition (Overall extent of exposure): NV25719, NV20234 (<13 years) and combined, Safety Evaluable Population
Project: CD01288O

Total	NV25719 Conventional Dose (N=15)	NV25719 3X Conventional Dose (N=15)	NV25719 Total (N=30)	NV25719 and NV20234 (< 13 Y.O.) (N=39)
Completed study	14 (93.3%)	13 (86.7%)	27 (90.0%)	36 (92.3%)
Completed treatment	13 (86.7%)	13 (86.7%)	26 (86.7%)	34 (87.2%)
Discontinued study	1 (6.7%)	2 (13.3%)	3 (10.0%)	3 (7.7%)
Non-safety	1 (6.7%)	2 (13.3%)	3 (10.0%)	3 (7.7%)
NON-COMPLIANCE	1 (6.7%)	0	1 (3.3%)	1 (2.6%)
OTHER	0	1 (6.7%)	1 (3.3%)	1 (2.6%)
WITHDRAWAL BY SUBJECT	0	1 (6.7%)	1 (3.3%)	1 (2.6%)
Discontinued treatment	2 (13.3%)	2 (13.3%)	4 (13.3%)	5 (12.8%)
Safety	0	0	0	1 (2.6%)
ADVERSE EVENT	0	0	0	1 (2.6%)
Non-safety	2 (13.3%)	2 (13.3%)	4 (13.3%)	4 (10.3%)
NON-COMPLIANCE	1 (6.7%)	0	1 (3.3%)	1 (2.6%)
OTHER	1 (6.7%)	1 (6.7%)	2 (6.7%)	2 (5.1%)
WITHDRAWAL BY SUBJECT	0	1 (6.7%)	1 (3.3%)	1 (2.6%)

In the pooled safety population of IC children (Study NV25719 and NV20234), 188 on- or off-treatment AEs were reported in 31 patients (79.5%) (Table 6.3.4.4). Fourteen patients (35.9%) experienced on- or off-treatment SAEs.

Table 6.3.4.4 Overall incidence of all AEs (on and off treatment) (pooled safety population, children <13 years)

	NV25719 Conventional Dose (N=15)	NV25719 3X Conventional Dose (N=15)	NV25719 Total (N=30)	NV25719 and NV20234(< 13 Y.O.) Total (N=39)
Total number of patients with at least one adverse event	12 (80.0%)	13 (86.7%)	25 (83.3%)	31 (79.5%)
Total number of events	96	77	173	188
Total number of deaths	0	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0	0
Total number of patients with at least one				
AE with fatal outcome	0	0	0	0
Serious AE	7 (46.7%)	5 (33.3%)	12 (40.0%)	14 (35.9%)
Serious AE leading to withdrawal from treatment	0	0	0	0
Serious AE leading to dose modification/interruption	0	0	0	0
Related Serious AE	0	0	0	0
AE leading to withdrawal from treatment	0	0	0	1 (2.6%)
AE leading to dose modification/interruption	0	0	0	0
Related AE	1 (6.7%)	4 (26.7%)	5 (16.7%)	5 (12.8%)
Related AE leading to withdrawal from treatment	0	0	0	0
Related AE leading to dose modification/interruption	0	0	0	0

Investigator text for AEs encoded using MedDRA version 20.0 for study NV20234 and 21.0 for study NV25719.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" row in which multiple occurrences of the same AE are counted separately.

Common adverse events

On-treatment AEs

The percentage of IC children reporting AEs was lower in patients treated with standard dose (13/19, 77%) compared with those who received double or triple dose (17/20, 85%), however the difference was due to only 4 patients.

The 3 most common system organ classes (SOC) in which AEs were reported in children were Gastrointestinal disorders (37 events in 22 patients [56.4%], Blood and lymphatic system disorders (13 events in 10 patients [25.6%]) and Infections and infestations (10 events in 7 patients [17.9%]).

The most frequently reported individual preferred term (PT) was vomiting (11 patients [28.2%]), followed by anaemia (5 patients [12.8%]), and abdominal pain and diarrhoea (4 patients [10.3%] each); no other individual PT was reported in more than 10% of patients overall in the pooled population.

Most of the on-treatment AEs were mild (n=24) or moderate (n=14) in intensity. No life-threatening events were reported and only 5 events were considered severe (neutropenia in 2 patients and thrombocytopenia, influenza and hallucination in 1 patient each). Four patients experienced 5 on-treatment AEs that were considered as having a possible relationship to study treatment by the investigator: 3 events of vomiting, 1 event of abdominal pain and 1 event of nausea.

When the frequency of AEs was compared to historical pooled population of OwH children, some differences were observed. Frequency of vomiting (included in the SmPC of Tamiflu) was higher (28.2%) in the IC children than in OwH children (15.2%) as expected in a population where 85% have underlying haematological conditions and many were receiving chemotherapy, antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs).

Anaemia is not listed in the AEs in the SmPC of Tamiflu, and was reported for 1/851 (0.1 %) of subjects in the OwH pooled children and 5/39 (12.8%) of the pooled IC children. Anaemia is however an expectable finding in a population where 85% of subjects have leukaemia.

Abdominal pain is a labelled ADR with a frequency of common (≥1% - <10%) which was reported in 10.3% of the pooled population of IC children as compared to 3.3% in OwH children treated with oseltamivir (Table 9). All events were reported as mild or moderate, all but one in the triple dose group (moderate and resolved) were assessed as not related to oseltamivir by the investigator, and in 3 of the 5 cases, abdominal pain occurred in concomitance with diarrhoea, constipation or vomiting. (Table 6.3.4.5)

None of these events were serious. All events resolved without requiring treatment discontinuation, except for one mild event of abdominal pain in the conventional dose group, which was reported as not resolved.

Table 6.3.4.5. Most frequent on-treatment AEs in IC children from studies NV20234 +NV25719 compared with OwH Children in clinical trials in SmPC and IC Adult NV20234 Data

PT	NV25719 (N=30)		Pooled NV20234+NV25719 IC Children (N=39)	SmPC Pooled OwH Children Oseltamivir (N=851)	SmPC Pooled OwH Children Placebo (N=622)	ADR (per Label in Children)	NV20234 IC Adults (N=199)
	Conventional Dose (N=15)	Triple Dose (N=15)					
Any AE	11 (73.3%)	13 (86.7%)	30 (76.9%)	384 (45.1%)	300 (48.23)	NA	85 (42.7 %)
Vomiting	5 (33.3%)	5 (33.3%)	11 (28.2%)	129 (15.2%)	51 (8.2%)	Very common (≥10%)	17 (8.5%)
Anemia	4 (26.7%)	1 (6.7%)	5 (12.8%)	1 (0.1%)	0	NA	3 (1.5 %)
Abdominal pain[a]	2 (13.3%)	2 (13.3%)	4 (10.3%)	28 (3.3%)	21 (3.4%)	Common (>1% - <10%)	2 (1.0%)
Diarrhea	3 (20.0%)	1 (6.7%)	4 (10.3%)	62 (7.3%)	49 (7.9%)	NA	15 (7.5%)

[a] Abdominal pain includes 2 MedDRA PTs: abdominal pain upper and abdominal pain NOS.

The proportion of subjects with AEs was higher (76.9%) in the pooled paediatric subset than in adult IC patients from NV20234 (42.7%) (Table 6.3.4.5).There was a marked difference in reports on vomiting and anaemia, obviously reflecting the high prevalence of haematological malignancies and chemotherapy in the children. Differences in percentages of patients with AEs also reflect chance within the small numbers of paediatric subjects (e.g. in NV25719, anaemia was reported for 4 patients in the conventional dose arm and 1 patient in the triple dose arm of the study.)

Deaths and serious adverse events (SAEs)

No deaths were reported in the IC children recruited in Study NV25719 or Study NV20234.

In the pooled paediatric analyses, 14 patients (35.9%) experienced a total of 20 SAEs. Four events in were in the Infections and infestations SOC, 3 events (in 1 patient) were in the General disorders and administration site conditions SOC, 3 events were in the Blood and lymphatic system disorders, 2 events (in 1 patient) were in the Investigations SOC, and 2 events (in 1 patient) were in the Eye disorders SOC. All other events were single events spread across 5 SOCs. By individual PT, the only SAEs reported more than once were pyrexia (3 patients [7.7%]) and febrile neutropenia (2 patients [5.1%]). All SAEs were considered unrelated to treatment and all had resolved except for one event of febrile neutropenia.

In Study NV25719, 7/15 patients [46.7%] reported 11 SAEs in the conventional dose group and 5/15 patients [33.3%] reported 7 SAEs in the triple dose group). In Study NV20234, 2 children reported SAEs (oral herpes in 1 patient in the conventional dose group and thrombocytopenia [of severe intensity] in 1 patient in the double-dose group).

Adverse reactions of special interest

Graft-vs-host disease (GvHD) was defined in the protocol as an AE of special interest for patients who had undergone transplantation. In Study NV25719, 2 GvHD events were reported (one serious and one non-serious), both events in the same patient. These events were considered by the investigator to be unrelated to oseltamivir. In Study NV20234, none of the transplant patients experienced tissue rejection and/or GvHD during the study.

Adverse reactions leading to discontinuation

In Study NV25719, no patients withdrew treatment due to an AE. In Study NV20234, one 8-year old boy in the double dose group experienced an AE of hallucination that led to withdrawal of study treatment. He received a total of 2 doses of study treatment prior to discontinuation. The investigator considered the event of hallucination to be possibly related to study treatment. The event resolved on the same day.

Analysis of AEs by organ system or syndrome

A detailed analysis was performed of all AEs occurring in Study NV25719 and in children in Study NV20234 reported under the categories of the identified important risks for oseltamivir, as per the approved EU RMP/PBRER, i.e. the following important identified risks: neuropsychiatric events, skin disorders, gastrointestinal bleeding and haemorrhagic colitis, hepatobiliary disorders, development of oseltamivir-induced viral resistance (table 6.3.4.6). No new relevant safety information was identified.

Table 6.3.4.6 Summary of all AEs reported for IC children in Study NV25719 and Study NV20234 presented under the categories of the important identified risks for oseltamivir

Important Identified Risk preferred term [PT]	**Number of Events in NV25719 and NV20234 (Children)**			
	Conventional dose N=19	**Triple dose N=15**	**Double dose N=5**	**All Patients N=39**
Psychiatric Disorders and Nervous System Disorders				
Headache	1	1	0	2
Nervousness	0	1	0	1
Dysgeusia	0	1	0	1
Abnormal behaviour	1	0	0	1
Tremor	1	0	0	1
Sleep disorder	0	0	1	1
Hallucination	0	0	1	1
Skin Disorders				
Rash	3	2	0	5
Rash erythema	0	1	0	1
Skin discolouration	0	1	0	1
Gastrointestinal Bleeding and Hemorrhagic Colitis				
There were no AEs reported in NV25719 and NV20234 (children) studies matching the MedDRA PTs for gastrointestinal bleeding and hemorrhagic colitis.				
Hepatobiliary Disorders				
There were no AEs reported in NV25719 and NV20234 (children) studies matching the MedDRA PTs for hepatobiliary disorders.				
Development of Oseltamivir Induced Viral Resistance				
There were no AEs reported in NV25719 and NV20234 (children) studies matching the MedDRA PTs for viral resistance.				

There were no relevant changes from baseline in vital signs.

Assessor's comment

The AE data do not contain any new findings on safety of oseltamivir treatment that would warrant changing the Product Information.

No relevant difference in the frequency of AEs is seen between conventional and higher (double or triple) daily dose. The overall incidence of AEs was clearly higher in IC children that healthy controls, obviously due to the serious background conditions and concomitant medications in this severely ill population.

Secondary Illnesses/Complications

In Study NV25719, an analysis was performed of the frequency and/or duration of influenza-associated complications: length of hospital stay, length of intensive care unit stay, length of time on ventilator, frequency and duration of oxygen use, frequency of secondary bacterial infections. No patients were admitted to the intensive care unit or required ventilator support. For the other complications analysed, non-remarkable differences were observed between treatment groups.

In Study NV25719, none of the patients in the conventional dose group reported secondary bacterial infections. Two patients (13.3%) in the triple dose group who reported secondary bacterial infections; there was 1 on-treatment event of bronchitis and 1 off-treatment event of sinusitis, which was also an SAE. In Study NV20234, none of the children (n=9) experienced a secondary illness.

Assessor's comment

Somewhat unexpectedly, there were only two secondary bacterial infections (one bronchitis and one sinusitis) in the pooled paediatric dataset, even though the patients were seriously ill IC subjects. This may in part be due to attenuated inflammatory response caused by influenza in IC patients.

Safety analysis by exposure

A safety analysis by exposure (in terms of C_{max} and AUC for both oseltamivir and OC) was also undertaken in Study NV25719. This safety analysis included 26 study patients (14 patients in the conventional and 12 in the triple dose groups) for whom exposure metrics were available. Safety analyses by exposure focused on the incidence and severity of on-treatment AEs and on influenza-associated complications.

Study patients were grouped by exposure, defined by both C_{max} and AUC being either below (low exposure group) or above (high exposure group) the median of the predicted C_{max} and AUC for both oseltamivir and OC.

Nine of 13 patients (69.2%) in the low exposure group and 12 of 13 patients (92.3%) in the high exposure group experienced at least 1 on-treatment AE based on the oseltamivir exposure grouping. The same incidences of on-treatment AEs were observed in the OC exposure groups.

The 3 most common on-treatment AEs by PT were

- Vomiting: 4 patients (30.8%) each based on both oseltamivir and OC exposure;
- Anaemia: 4 patients (30.8%) vs. 1 patient (7.7%) based on oseltamivir exposure; 2 patients (15.4%) vs. 3 patients (23.1%) based on OC exposure.
- Abdominal pain: 2 patients (15.4%) each based on oseltamivir exposure; 1 patient (7.7%) vs. 3 patients (23.1%) based on OC exposure.

Out of a total of 14 post-baseline hospitalizations, 3 hospitalizations occurred in 2 patients in the low OC exposure group and 11 hospitalizations occurred in 6 patients in the high OC exposure group.

These analyses were not conducted in Study NV20234 as they were not part of the Statistical Analysis Plan.

Assessor's comment

The MAH states that no clinically meaningful differences were noted between high and low exposure groups as well as with the corresponding dose groups, as the numerical imbalances between exposure groups were

driven by single AEs shifting from one group to another based on either oseltamivir or OC exposure. This can be agreed upon.

Overall, no new safety concerns based on exposure were identified in the analysis of Study NV25719.

Post-marketing safety experience

The MAH conducted a safety analysis based on the post-marketing experience with oseltamivir in IC patients <13 years of age for the cumulative data reported in the MAH's global safety database with a cut-off date of 20 September 2018. Cases from clinical trials NV20234 and NV25719 were excluded from the database search.

A total of 56 cases reporting 169 AEs (of which 72.8% were serious) in IC patients aged <13 years were retrieved from the company global safety database. The most frequently affected SOCs in these patients < 13 years of age were as follows:

- General disorders and administration site conditions (61 [36.1%] AEs), with the most commonly reported AEs being drug ineffective (27), drug resistance (25) and pyrexia (3).
- Infections and infestations (35 [20.7%] AEs), with the most commonly reported AEs being pathogen resistance (13), pneumonia (3) and sepsis (3)
- Respiratory, thoracic and mediastinal disorders (24 [14.2%] AEs) with the most commonly reported AEs being respiratory failure (5), rhinorrhoea (4) and cough (3).
- Investigations (17 [10.1%] AEs) with the most commonly reported AEs being white blood cell count decreased (4), neutrophil count decreased (3) and platelet count decreased (2).

A total of 15 AEs (8.9%) in 9 cases reported a fatal outcome. The most commonly reported AEs with fatal outcome were drug ineffective (3 AEs), pathogen resistance (3 AEs), and respiratory failure (2 AEs).The remaining seven events were single events of acute respiratory distress, death, encephalitis, gastrointestinal haemorrhage, multiple organ dysfunction syndrome, sepsis and respiratory distress. All events reported were either expected complications of influenza that may result in death or were confounded by the patients' underlying immunocompromised status and were not related to treatment with oseltamivir. The MAH states that the data on viral resistance reviewed periodically did not identify any new safety concern or significant changes to oseltamivir risk management and labelling.

According to the MAH, the post-marketing data retrieved from the company safety database pertaining to IC children patients were consistent with known safety profile of oseltamivir and/or were anticipated in this population.

Assessor's comment

Drug ineffective, drug resistance and pathogen resistance were frequently reported in this population. The relatively scarce postmarketing safety data do not contain signs that would warrant additional PhV measures or changes to the Product Information.

6.4 Discussion

The interventional studies NV20234 and NV25719 have been carried out to establish the oseltamivir dose recommendation for the treatment of immunocompromised (IC) children with influenza. Both studies compared the conventional dose of oseltamivir with higher doses: in study NV20234 the conventional dose was compared with the double dose of oseltamivir and in the study NV25719 with triple dose.

The clinical study reports of these studies have already been assessed in previous procedures (EMA/H/C/402/P46/105, EMA/H/C/402/ P46/106). However, new descriptive and partly pooled data on paediatric subjects have been submitted by the MAH and are therefore included in this AR.

The dose recommendation for IC adults was accepted based on data from IC adults in study NV20234 and PK/PD and disease modelling (EMEA/H/C/000402/II/0136). The recommended posology for IC adults is the conventional daily dose of 75 mg BID for an extended duration of 10 days. In adult subjects in study NV20234, the time to onset of treatment had (non-significant) effect on treatment response, therefore the recommendation for IC adults is to start treatment as soon as feasible.

The total number of the IC children and adolescents from studies NV20234 and NV25719 was small consisting of only 50 patients, 46 of whom received at least one dose of study drug (39 children <13 years of age and 7 adolescents aged 13 to 17 years). Efficacy evaluation could only be performed on 20 ITTi patients from study NV25719 and 16 mITTi patients from study NV20234; safety was assessed for the 46 patients.

There was marked variation in the background conditions in the patients. Patients in study NV25719 (30 children aged < 13 years) had received induction, consolidation, or re-intensification chemotherapy for a haematological malignancy or were undergoing a conditioning regimen either prior to hematopoietic stem cell transplant (HSCT) or less than 6 months after HSCT. Study NV20234 included 20 paediatric patients, 16 of whom received at least one dose of oseltamivir (9 children aged <13 years and 7 adolescents aged 13 to 17 years). The 22 background conditions causing immunosuppression among the 20 paediatric patients in NV20234 were kidney transplant (1), allogenic HSCT (2), HIV with CD4 count <500/mm3 (4), hematologic malignancies (8), and systemic immunosuppressive therapy (7).

Due to the small number of subjects and variable background conditions and concomitant treatments in these severely ill paediatric subjects, efficacy data from these patients should be interpreted with caution. Imbalances between groups in study NV25719 increase confounding by background conditions. Time to resolution of all symptoms varied highly due to large interindividual variation and small number of patients with different underlying IC conditions. No constant pattern favouring a higher dose of oseltamivir for the treatment of IC children with influenza was observed. The MAH submitted more detailed data and discussion on the patient populations in the two studies with IC children and the CARIFS measure used for assessing efficacy of oseltamivir in IC children. Based on the submitted information, it is obvious that the conflicting results in time to resolution of symptoms noted in the small studies cannot be considered reliable due to lack of power of the studies, considerable variability between study subjects in terms of baseline conditions and other characteristics, different influenza strains and unreliability of the CARIFS scale in severely ill subjects.

It is noteworthy that the MAH has not suggested deleting the statement in the current SmPC that efficacy in IC patients has not been firmly confirmed. It is deemed appropriate to keep that sentence in light of the scarcity of the clinical data. However, the samples collected from these patients are considered sufficient for evaluation of posology based on population PK analyses, PK/PD evaluation, and disease modelling (see Section 6 Clinical Pharmacology aspects and Section 8 Extrapolation of this AR).

Overall, based mainly on the PK/PD population kinetic report and disease simulation report it could be concluded that the conventional daily dose of oseltamivir for IC adults can be extended also to IC children (as appropriate for age and weight). Similar to IC adults, a 10-day course is recommended both due to the modelling results and also in concordance with the mean duration of oseltamivir treatment in studies NV20234 and NV25719.

There were no new safety signals associated with oseltamivir treatment for influenza in IC children. The amount of reported adverse events was higher than in OwH children; but the great majority of adverse reactions were not considered by the investigator to be related to oseltamivir. The most frequent adverse

reaction found among IC children was vomiting, which is not unexpected in study population rich with haematological malignancies and chemotherapy.

No need for amending the Product Information of Tamiflu regarding safety was identified. All doses (conventional, double and triple) were relatively well tolerated. The MAH implemented all changes to the Product Information that were requested during the procedure. The finally submitted SmPC, PL and Labelling are considered acceptable.

7. Extrapolation

Extrapolation framework

The presentation of the extrapolation framework is constructed by the Rapporteur considering the EMA guidance (EMA Reflection paper on the use of extrapolation in the development of medicines for paediatrics, EMA/189724/2018).

About the product

Oseltamivir (Tamiflu) is an ethyl ester prodrug that is rapidly absorbed from the gastrointestinal tract after oral administration and metabolized in the liver by high capacity carboxylesterases to form oseltamivir carboxylate (OC), a potent, stable, and selective inhibitor of influenza A and B neuraminidase enzymes. The active form, OC, is excreted unchanged by the kidney via glomerular filtration and active tubular secretion by the organic anion transport system.

Nature of influenza

Influenza is an acute respiratory infection caused by a virus of the orthomyxoviridae family which occurs in three forms, influenza A, B, and C. Influenza virus types A and B cause an acute febrile infection of the respiratory tract characterized by the sudden onset of fever, malaise, headaches, myalgias, and cough. Although difficult to assess, annual influenza epidemics are thought to result in between 3 and 5 million cases of severe illness and between 250,000 and 500,000 deaths every year around the world (*WHO Influenza. Fact Sheet. 2018, Iuliano et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 2018; 391, 1285-1300*). Influenza can cause serious complications resulting in substantial morbidity and mortality, particularly in higher-risk populations such as children, the elderly, and the immunocompromised.

Influenza in immunocompromised populations

Influenza infection is usually a self-limiting condition. However, in immunocompromised and in children population, influenza infection can be associated with substantial morbidity and mortality. The presentation of influenza is slightly different in IC patients. Although the same upper respiratory symptoms (sore throat, nasal symptoms, and/or headache) are usually seen, but also systemic symptoms (fever, myalgia, and fatigue) can be reduced or completely absent. The increased morbidity in IC patients is associated with increased viral load and increased duration of virus shedding compared to that in healthy patients. In otherwise healthy adults, elderly patients, and children, the median duration of viral shedding in untreated patients was 3, 4, and 5 days, respectively. In contrast, in a retrospective HSCT study, influenza virus was shed in nasopharyngeal secretions (evaluated at least weekly) for a median duration of 7 days (range: 2 to 37 days). Therefore, a key objective of anti-viral therapy in this population is to reduce the duration of viral shedding which in turn should reduce influenza-associated morbidity.

Current therapies of influenza for IC children with influenza

Two main classes of therapeutics are licensed for treatment of influenza in both the EU and the US: adamantane derivatives and neuraminidase inhibitors (ECDC 2016, CDC 2016). Influenza B is resistant to adamantane derivatives and these agents are not recommended for influenza treatment (*European Centre for Disease Prevention and Control. Influenza. 2016, Centers for Disease Control and Prevention. Influenza (flu). 2016.*), making neuraminidase inhibitors the preferred option at present. Three neuraminidase inhibitors are currently licensed in the EU: zanamivir, peramivir and oseltamivir. Only a small number of IC patients have been exposed to inhaled zanamivir and data regarding its safety and efficacy are limited to case reports in this population. This paucity of data is reflected in the zanamivir Summary of Product Characteristics (SmPC), which states that efficacy and safety has not been demonstrated in IC patients (*Zanamivir EU SmPC*). Intravenous peramivir has been licenced for uncomplicated influenza in 2018. Intravenous zanamivir has been licenced for complicated and potentially life-threatening influenza in 2019.

Development of oseltamivir treatment in IC-paediatric patients (PIP and PDCO history with extrapolation plan)

The initial PDCO-opinion adopted in 2009 included only the clinical study NV20234 and the modelling study. In 2010 the MAH proposed changes to study NV20234 main design features, based on major recruitment issues. Study NV20234, as per this M01 request, could no longer be a basis for extrapolation to the paediatric population, because it was no longer designed to provide efficacy data in adults, or to achieve an indication in immunocompromised patients (whether adults or children). Thus, PDCO concluded that a controlled study with the paediatric population to establish a paediatric use is still required and it should include subsets with well-defined immune system compromise. A new study proposal was required.

In 2010, the MAH requested a new modification (M02) at PDCO. The content was exactly the same as M01, which had received a negative PDCO-opinion. The MAH requested to change the main design features of trial NV20234 in immunocompromised children (and adults) from efficacy to safety. Because the modification did not include a new proposal to replace study NV20234 as requested by PDCO and the outcome of M01 disregarded, PDCO issued a negative opinion on M02. In 2011, a modification (M03) was submitted at PDCO; however, the changes requested did not impact the IC studies. Changes were for the study in OwH children less than 1 year of age.

In 2011 a paediatric scientific advice was submitted to discuss the new study requested by PDCO in immunocompromised patients: NV25719 - an open label, prospective, single arm, multi-centre trial in 100 paediatric patients with solid organ and non-solid (within 2 years) organ transplantation and with haematological malignancy" (EMEA/H/SA/2208/1/2011/PED/II). PDCO and SAWP were in line and in agreement for the Final Advice Letter.

In 2012, the MAH submitted a new modification (M04) at PDCO to remove study NV20234 and replace it by Study NV25719 discussed with the SAWP. Because there was no proof of efficacy supported by data, PDCO in agreement with SAWP were not in favour of removing the NV20234 study in order to replace it by NV25719. However, study NV25719 was added to the PIP.

In 2013, the MAH submitted a new modification (M05) requesting to remove study NV20234 and to add study NV25719. PDCO did not agree to remove NV20234 from the PIP, because it remained open for children. However, it was agreed to change the required completion date and to reduce the required patient numbers. With regards to study NV25719, this was added to the PIP, with some changes compared to the study originally agreed with SAWP (e.g. a smaller sample size), while the source data for extrapolation and strategy remained unclear. Considering the changes alongside the PIP history, the PDCO discussed that the data from studies NV25719 (now in at least 20 children) and NV20234 (at least 15 children) with immunocompromised would not be sufficient to establish the targeted paediatric use in

immunocompromised children. Therefore, the PDCO required a further study 6 as part of the PIP for the targeted indication in immunocompromised children.

In 2013, the MAH submitted a new modification (M06) at PDCO with regards to NV25719 in order to change Study duration for participants, date of initiation and date of completion. PDCO did not support the request. In April 2014, Variation 107 was submitted and agreed with the CHMP to change the RMP and retrospective changes to have study NV20234 as a safety study.

In 2014, the MAH requested follow-up scientific advice in particular for studies in the current immunocompromised program, NV20234 and NV25719 (EMEA/H/SA/2208/1/FU/1/2014/PED/II); the questions were also referred for discussion to the Infectious Disease Working Party and the PDCO. The SAWP recommended the MAH to complete the two ongoing studies that will provide safety and efficacy data in immunocompromised children and proceed to identify the final dose regimen based on the planned PK/PD analyses, taking into account the efficacy data in adults that will come from NV20234. Once the studies were completed, the need for an additional study such as Measure 6 could be reconsidered.

The MAH´s extrapolation plan as presented to the PDCO in the submission material (Annex 9) during the latest modification procedure -M10 (current Opinion EMEA-000365-PIP01-08-M10, 29 June 2018) consists of data from immunocompetent and immunocompromised adults, immunocompetent and IC paediatric patients, and modelling and simulation." The reduction of evaluable subjects from 20 to 19 in study NV25719 was also discussed, and, while this might have been agreed, the number was kept at 20 as an additional patient was recruited during the procedure.

Development of oseltamivir treatment in IC adults

For the treatment of IC adult patients, the recommended dose is 75 mg oseltamivir, orally, BID for 10 days. The Committee for Medicinal Products for Human Use (CHMP) endorsed this recommendation within variation II/136 (positive opinion dated 15 November 2018). The recommendation for the treatment of IC adult patients with influenza was based on a recently completed double blind, randomized, stratified, multicentre trial in IC patients with influenza (NV20234) that evaluated conventional dose (75 mg BID) and double dose (150 mg BID) of oseltamivir for 10 days**.**

The clinical development program of oseltamivir for IC adults with influenza included Population PK modelling and disease simulation model; in more detail see previous procedure (variation II/136). The purpose of the disease modelling was to characterize the kinetics of naturally occurring influenza infections in immunocompromised adult subjects. Data from previous studies were integrated into the model previously developed to characterize naturally occurring influenza infections and the treatment effect of oseltamivir in immunocompromised adult subjects.

The model and NV20234-study results showed that doubling the dose in IC-adults did not provide any further benefit for the patients; notably the OC-exposure-levels in IC-adults were about 2-fold higher than in otherwise healthy adults.

Extrapolation from adult IC patients to paediatric IC patients

The clinical data from the oseltamivir IC adults with influenza development programme are considered relevant for both adults and paediatrics for the following reasons. Firstly, the nature of the disease (influenza) is quite similar among adult and children population, as well quite similar with the same kind of underlying conditions. In addition, the clinical efficacy and safety endpoint data from the adult and paediatric studies are considered relevant for both adults and the paediatric patients. Similarly to adult IC patients with influenza, emphasis is on early diagnosis and antiviral therapy. In addition the mechanism of action of the oseltamivir is the same in all treatment groups studied, which further supports the rationale for the extrapolation from these adult populations for the target population, that is to say to paediatric IC population

with influenza. Regarding these similarities, an extrapolation approach by using PK/PD-modelling and disease simulation modelling was considered suitable to characterize the clinical profile of oseltamivir treatment from adults to children population.

It is noteworthy, that the overall paediatric development plan of oseltamivir in IC-paediatric patients has largely evolved during the years after the initial MA was granted in 2002 (see above for details related to oseltamivir paediatric development plan). Initially the PIP included the study NV20234 (a study in IC adults and children ≥1 year) in a crucial role to contribute adult efficacy data upon which to base extrapolation via PK to children. Some uncertainties however became apparent on this approach of extrapolating overall efficacy (treatment benefit) from IC-adults to IC-children, as the MAH changed the primary efficacy endpoint of this study (time to resolution of symptoms) into safety/ resistance endpoint due to recruitment problems. Not surprisingly, efficacy in IC-adult patients in study NV20234 was not conclusively confirmed, but only a trend (the CIs of active compared with placebo controls did overlap; historical controls included age and gender matched otherwise healthy adults or "at risk" patients, i.e. those with chronic respiratory or cardiac conditions) for reduction in time to resolution of symptoms compared to controls was seen when either of the doses (conventional or double) were used. There were several reasons for this, including the relatively small sample size (the final sample size being so small that the study was no longer fully powered for efficacy demonstration), furthermore, it was not possible to have placebo-arm in the trial due to ethical reasons, but the comparison had to be performed against historical controls. It was however concluded that it is important to reflect the findings in the SmPC, to inform prescribing physician about the fact that the conventional dose (but for longer duration) provides the best benefit/risk balance in the adult IC population, however with the warning that efficacy has not been firmly established in IC-patients.

Thus, during the years additional clinical measures/ studies (PK/PD, safety as main endpoints) have been added to the PIP and extrapolation plan. **The current PIP/ extrapolation plan (PIP-M10) focuses on determining the correct dosing for IC-children** using mainly PK/PD-modelling approach.

In this context, it is important to note that the currently approved SmPC does not preclude use in IC subjects in any age group, but there is no recommended dose for IC paediatric patients. For IC adults, the recommended posology is 75 mg twice daily for 10 days. The MAH now proposes the posology for IC paediatric patients <18 years of age: 75 mg (weight-adjusted in children < 13 years of age) twice daily for 10 days. The proposed dose is the same as in otherwise healthy paediatric subjects, but duration of treatment is prolonged from 5 to 10 days.

Extrapolation of previous paediatric and adult data in immunocompetent (otherwise healthy) patients, in addition to IC-adult data, to the IC-paediatric population/ proposed posology

Extrapolation of previous paediatric data and the adult data to the paediatric population was carried out by using the PK modelling and the disease simulation modelling, see in more detail section 6 of this AR; the pharmacokinetics (PK) of oseltamivir and oseltamivir carboxylate in adult and paediatric population was investigated using the population PK modelling approach. The extrapolation plan to determine dosing in IC children was endorsed in PIP-M10.

According to this PIP-M10/ extrapolation plan, approved by the PDCO, the specific steps to determine dosing in immunocompromised children were:

1) Using sparse PK data generated primarily from NV25719 together with any paediatric PK data collected from NV20234, if necessary, adapt and validate the existing population PK model in immunocompetent paediatric patients to describe the disposition of oseltamivir and OC in immunocompromised children.

2) Use model-simulated key exposure parameters, e.g. AUC, across the range of exposures studied in NV25719 to confirm the assumption that oseltamivir and OC PK does not differ to a clinically important extent based solely on immune status.

Steps 1 and 2 of the plan have been carried out adequately. The observed PK data in IC paediatric patients 1 to ≤18 years of age were used in population PK modelling and simulations. There was a reasonable number (n=22) of children from one to <10 years of age in the dataset. The previously developed PK model "Healthy Paediatric and Young Adult Subjects" was selected as the structural model. The final model indicated that in IC paediatric subjects ≥10 years of age the apparent clearances of oseltamivir and OC were decreased by 44.4 % (95%CI: 26.8−62.0%) and 49.1% (95%CI: 34.5−63.8%), respectively, compared to OwH subjects in the same age range, whereas in younger children (1 to <10 years) the PK of oseltamivir and OC were comparable in IC and OwH subjects. The conducted PK simulations included comparison of predicted oseltamivir and OC exposures between IC patients of study NV25719 and OwH patients of study WV15758, stratified by age. The results indicated that the predicted OC exposures in paediatric IC subjects ≥10 years of age were approximately 2.1−2.2 fold higher than in OwH subjects in the same age range. One IC patient with nephrectomy was found to be an outlier, having more than 2 times higher AUC compared with all other IC paediatric patients from NV25719 study. When this outlier was excluded, the predicted OC exposures in IC patients were approximately 1.7−1.8 fold higher than in OwH subjects. This increase in exposure is comparable with that observed in IC adults (see procedure EMEA/H/C/000402/II/0136) and it is not expected to be associated with safety problems, taking into account the known safety profile of oseltamivir. In IC subjects <10 years of age, the predicted exposures were similar as in otherwise healthy subjects in the same age range.

3) Examine the relationship between simulated exposure parameters and observed PD measures to determine if any PK/PD relationship exists. This relationship could form the basis of a dose recommendation at least for children up to 13 years and potentially up to 18 years. For adolescents, consideration could also be given to adult data from NV20234.

Step 3 of the plan has been carried out adequately. Relationships between predicted exposure and observed PD parameters (e.g. viral shedding and resolution of symptoms) were explored in 22 subjects with PK and PD data. No relationships between predicted exposure and viral parameters, such as time to cessation of viral shedding and viral titre/load measures were found. Treatment-emergent resistance developed in four patients with PK and PD data. There were no differences in exposures between patients that developed and did not develop resistance, indicating that higher than conventional dose and higher exposure to OC is not expected to decrease the incidence of resistance. Time to resolution of symptoms was the only parameter suggesting a potential benefit of a high exposure. This finding should be interpreted with caution because of limited number of subjects in the dataset. Furthermore, the collected CARIFS symptom score contains several items that are not specific for respiratory tract infections. CARIFS was developed in paediatric population that did not have underlying disease requiring daily medication and it is uncertain whether it is reliable in immunocompromised children (for further discussion on the scale, see Section 7.2.2 of this AR). The results of exposure-response analyses for IC adults of study NV20234 did not suggest any relationships between predicted OC exposure and virologic PD parameters or time to resolution of clinical symptoms. The overall results of exposure-response analyses did not provide robust evidence to support benefit of higher than conventional oseltamivir dose in IC paediatric patients. This is not surprising, because OC trough concentrations achieved with conventional dose are above inhibitory concentrations of tested influenza strains.

There were no new safety signals identified in IC children < 18 years of age, who were treated with conventional, double or triple dose of oseltamivir in the studies NV20234 and NV25119. The nature and severity of AEs were consistent with the established safety profile of oseltamivir. All doses (conventional, double and triple) were relatively well tolerated. Hence, it seems justifiable to use all acquired knowledge on oseltamivir as a basis for safety characterisation of oseltamivir use in IC-children. However, it has to be

noted that in addition to relatively small number of children in the studies NV20234 and NV25119, there were no placebo groups in those studies for ethical reasons.

Finally, the current Product Information for Tamiflu does not preclude the use in paediatric IC subjects in either Section 4.1 Indication or Section 4.3 Contraindications. In Section 4.4, it is however stated "*the efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established. However, the duration of treatment of influenza in immunocompromised adult patients should be 10 days, as there are no studies of a shorter course of oseltamivir in this patient group*". Even though the unambiguously conclusive confirmatory efficacy demonstration in IC paediatric and IC adult patients is still missing, the Rapporteur is of the opinion that it is important to reflect in the SmPC that based on the totality of evidence, there is no benefit in using higher (double or triple) than conventional daily dose in any IC paediatric age groups. Nevertheless, the duration of treatment in these patients should be 10 days (double the standard duration). This opinion is based on all the evidence from multiple sources in IC adults and IC paediatric patients: results from immunocompetent paediatric patients from the original MAA confirming efficacy in paediatric patients in general; the mode of action of oseltamivir is expected to be the same in IC and non-IC adults and paediatric patients; the exposure levels are similar in IC children compared to otherwise healthy children (and in IC adolescents with those of IC adults). Importantly, the trough concentrations are above inhibitory concentrations of tested influenza strains in these patients.

However, related specifically to the extrapolation concept overall, it is important that the SmPC reflects the overall setting correctly. Hence, the warning in the SmPC that efficacy has not been firmly established in IC-patients should remain.

In addition, the MAH-proposed text in the Section 5.1 of the SmPC, namely "*The pharmacokinetic and pharmacodynamic data generated in these studies supported the extrapolation of efficacy data interpretation from immunocompromised adults to immunocompromised paediatric patients (<18 years old)*." is not entirely correct, as the extrapolation exercise has been performed based on the totality of evidence, including also immunocompetent adults and children. As the sentence is not deemed important to be included for guidance of prescribers, it was proposed to be deleted. Some additional amendments were requested in the information in Section 5.2 on exposure in IC patients in comparison with otherwise healthy subjects. During assessment of the amended Product Information, some further need for changes was identified. These are requested to be performed.

Overall conclusion

The MAH´s extrapolation plan concerning the present variation as presented to the PDCO during the latest modification procedure of the PIP (EMEA-000365-PIP01-08-M10, 29 June 2018) has focused on determining the correct dosing for IC children. Based on the review of the data on PK/PD-modelling, disease simulation modelling, safety and efficacy data in IC adults and IC paediatric patients, as well as immunocompetent adult and paediatric patients, the Rapporteur considers that the dosing recommendation for the use of oseltamivir for IC children with influenza is approvable. The recommended daily dose in IC patients of all ages is the same as the corresponding daily dose for otherwise healthy subjects in the respective age groups. However, the recommended duration of treatment of influenza with oseltamivir in IC patients is 10 days instead of the standard duration of 5 days in otherwise healthy subjects.

Notably, related to extrapolation of data from the source populations, it is important that the warning in the SmPC that efficacy has not been firmly established in IC-patients remains; and the MAH does not propose to delete it.

8. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were

the following:

Section in the RMP	Summary of changes
PART I: PRODUCT OVERVIEW	Table 1: Dosage in EEA: Current dosing in the treatment of adult immunocompromised patients and the proposed dosing in the treatment of paediatric immunocompromised patients have been added.
PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)	Baloxavir marboxil was added to the current options for treatment of influenza.
PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE	Clinical exposure data was updated with 'Treatment Indication in Immunocompromised Patients' based on the completed study NV25719 (Tables 2-6)
PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE **SV.1.2** Exposure	Post-marketing exposure updated as per the most recent PBRER (1089368).(Table 9)
PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS **SVII.2** New Safety Concerns and Reclassification with a Submission of an Updated RMP	The text summarizing the reclassification of risks in the previous RMP based on updated GVP Module V (included in RMP V 16 approved on 12 July 2018) was removed. Important identified risk of "Development of oseltamivir-induced viral resistance", important potential risk of "Exposure during pregnancy", and missing information of "Treatment of influenza in immunocompromised patients" are no longer presented in the EU RMP and rationale for the change is provided.(See below)
PART II: MODULE SVII.3 - DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION **SVII3.1**. Presentation of Important Identified Risks and Important Potential Risks	The information on Important identified risk of "Development of Oseltamivir-Induced Viral Resistance" and important potential risk of "Exposure during Pregnancy" were deleted as they were removed from the list of safety concerns.
SVII3.2. Presentation of Missing Information	The information on Missing information of "Treatment of Influenza in Immunocompromised Patients" was deleted as it is removed from the list of safety concerns.
PART II SVIII – SUMMARY OF THE SAFETY CONCERNS	Table 11: Important identified risk of "Development of Oseltamivir-Induced Viral Resistance", important potential risk of "Exposure During Pregnancy", and missing information of "Treatment of influenza in immunocompromised patients" were removed.
PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES) **III.2** Additional Pharmacovigilance Activities	Additional pharmacovigilance activities (now completed) addressing Missing Information was removed. Table 11: Study NV25719 was completed and therefore removed.

Section in the RMP	Summary of changes
III.3 Summary Table of Additional Pharmacovigilance Activities	Table of Ongoing and planned additional pharmacovigilance activities was removed.
PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES) **V.1** Routine Risk Minimization Measures **V.3.** Summary Of Risk Minimisation Measures	Table 14 Description of Routine Risk Minimization Measures by Safety Concern was removed. Table 15 Summary Table of Pharmacovigilance activities and risk minimization activities was removed.
PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN **II.A** List of Important Risks and Missing Information **II.B** Summary of important risks **II.C.2** Other studies in post-authorization development plan	Important identified risk of "Development of oseltamivir-induced viral resistance", important potential risk of "Exposure during pregnancy", and missing information of "Treatment of influenza in immunocompromised patients" were removed. Important identified risk of "Development of oseltamivir-induced viral resistance", important potential risk of "Exposure during pregnancy", and missing information of "Treatment of influenza in immunocompromised patients" were removed. Updated that there are no other studies in the post-authorization plan.
Annex 2: Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Program	Table 1 Planned and on-going studies: Study NV25719 (completed) was moved to Table 2 (Completed studies) and Table 1 was removed
Annex 3: Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan Part C Previously Agreed Protocols For On-Going Studies And Final Protocols Not Reviewed By The Competent Authority	Study NV25719 was removed.
Annex 7: Other Supporting Data (Including Referenced Material)	References updated to include NV25719 final clinical study report and to remove references submitted previously.

The MAH's reasons for changes (reclassification/removal) to the list of safety concerns:

The MAH has removed 'development of oseltamivir -induced viral resistance', 'Exposure during pregnancy' and 'Treatment of influenza in immunocompromised patients' from the list of safety concerns and provided the reasons as follows:

"Development of Oseltamivir-Induced Viral Resistance" -important identified risk

In the MAH's opinion, Development of oseltamivir-induced viral resistance no longer meets the definition of an important safety concern i.e., it does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk. The post-authorization measure (MEA075) that required elucidation of clinical significance of new resistance information in IC patients has been fulfilled following submission of final reports from the Influenza Resistance Information Study (IRIS; NV20237), Study NV22155, and Study NV20234. Moreover, additional

data on resistance in IC paediatric patients has been provided with the submission of the final report of Study NV25719. In summary, treatment-emergent oseltamivir resistance was observed in 6 of 29 IC children that had no notable impact on the clinical outcomes of influenza. This risk of "Development of Oseltamivir-Induced Viral Resistance" for Tamiflu, managed through routine PV activities and risk minimization measures, will continue to be evaluated periodically based on new data collected during the periodic safety update report (PSUR) reporting interval and presented in Section 16.3 "Evaluation of risks and new information" of the PSUR. This is in line with the revised guideline in the GVP Module V (Rev.2), and the Explanatory Note to GVP Module VII that states: "*the definition in GVP module V should generally not be used for the purpose of risk reclassification in the PSUR. As a consequence, the list of safety concerns in the RMP and PSUR might differ*".

"Exposure During Pregnancy" - important potential risk

In the MAH's opinion, Exposure during pregnancy no longer meets the definition of an important safety concern i.e., it does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk. The LEG 087 Assessment Report (dated 9 March 2019) stated that the post-authorization measure was fulfilled. Reviews of pregnancy including clinical and post marketing data with review of epidemiology data and relevant literature shall be submitted in future periodic reports. The risk of "Exposure during pregnancy" for Tamiflu, managed through routine PV activities and risk minimization measures, will continue to be evaluated periodically based on new data collected during the PSUR reporting interval and presented in Section 15.1 "Non-signal related evaluations" of the PSUR. This is in line with the revised guideline in the GVP Module V (Rev.2), and the Explanatory Note to GVP Module VII as described above.

"Treatment of Influenza in Immunocompromised Patients"- missing information:

In the MAH's opinion, 'Treatment of Influenza in immunocompromised patients' no longer meets the definition of an important safety concern i.e., the safety profile of oseltamivir in IC patients does not differ from what was characterized in non-IC patients; moreover, this safety concern does not require additional PV activities or additional risk minimization activities or routine risk minimization activities recommending specific clinical measures to address the risk. Studies NV20234 and NV25719 are now complete and the final reports were submitted on 8 December 2017 (Study NV20234) and on 5 February 2019 (Study NV25719). No new safety concerns were identified in these studies in 199 immunocompromised adults and 46 immunocompromised paediatric patients (aged < 18 years).

Rapporteur's comments:
The updated RMP v 19 was submitted in support of a type II variation on guidance for use in immunocompromised paediatric patients with influenza following the completion of the paediatric studies NV20234 and NV25719 and downstream population PK and PK/PD analysis which are part of the approved Tamiflu Paediatric Investigation plan (PIP). Accordingly, clinical exposure data in the RMP was updated and the treatment of influenza in immunocompromised patients was removed from the missing information. The other major changes were removal of development of oseltamivir induced viral resistance, and exposure during pregnancy from the list of safety concerns.

The PAM (MEA075) to elucidate clinical significance of new resistance information in IC patients has been fulfilled following the completion of the Influenza Resistance Information Study (IRIS; NV20237), Study NV22155, and Study NV20234. Data on resistance in IC paediatric patients has been provided in the final report of Study NV25719 (submitted in February 2019). Since the study NV25719 was completed, there were no ongoing additional Phv studies for Tamiflu. Neither additional risk minimization activities are in place for Tamiflu. Therefore, the MAH's conclusions to remove safety concerns Development of oseltamivir induced viral resistance and Treatment of influenza in immunocompromised patients are endorsed. Regarding pregnancy issue, the LEG 087 was recently fulfilled; however, reviews of pregnancy including

clinical and post marketing data with review of epidemiology data and relevant literature were requested in future PSURs. Accordingly, the MAH's proposal to remove exposure during pregnancy is also endorsed. The risks of 'development of oseltamivir induced viral resistance' and "Exposure during pregnancy" for Tamiflu can be managed through routine PV activities and risk minimization measures, and will continue to be evaluated periodically based on new data collected during the PSUR reporting interval and presented in relevant sections of the future PSURs.

In summary, the removal of development of oseltamivir induced viral resistance, exposure during pregnancy and treatment of influenza in immunocompromised patients from the list of safety concerns of the RMP is endorsed. Development of oseltamivir induced viral resistance and exposure during pregnancy remain in the safety concerns of the PSUR and will be monitored accordingly.

The RMP v 19 is endorsed.

During the procedure the MAH has submitted an updated RMP v 19.1, in which information regarding the 12 mg/ml in powder dosage form, powder for oral suspension and extemporaneous formulation was deleted further to the approval issued on 08 October 2019 for procedure EMEA/H/C/000402/IB/0143. In addition minor changes in the Section SI.1 including deleting information on treatment option with Baloxavir marboxil have been implemented.

The RMP v 19.1 is approvable.

8.1 Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

9. The 1st Request for supplementary information

9.1 Major objections

N/A

9.2 Other concerns

Clinical aspects

1. It has been shown in the IC paediatric development programme that there are no major differences in viral shedding, development of resistance, or adverse events between the high dose and conventional dose groups. However, the Marketing Authorisation of Tamiflu is based on the only clearly established clinical benefit, namely its ability to reduce time to resolution of symptoms. Hence, fully acknowledging the small number of patients, and large variation in efficacy outcomes in the studies on paediatric IC patients without placebo control groups, there seemed to be difference in this parameter between the two studies. In study NV25719 with severely ill IC patients, the time to resolution of symptoms was shorter with triple than conventional dose, with divergent results from the paediatric (≥1 to <13 years) subgroup of study NV20234 with less severely IC-patients, where symptoms resolved faster in the conventional dose group than the double dose group.
Therefore, the MAH should further discuss these findings and confirm their view on the benefit/risk balance of conventional and higher doses. Primary interest is on 1 to 10 (13) year old patients who achieved lower predicted exposure with the conventional dose than IC-adults and IC-adolescents.
The discussion should include the following points (but not limited to these):

- the validity and reliability of the used symptom score scale (CARIFS) in IC paediatric patients;

- reasons why the results on time to resolution of symptoms were discrepant between the two paediatric studies, including the possibility that the major difference in disease severity of patients or the slight difference in time to treatment from onset of symptoms between the two studies played a role;
- if there were differences between study arms of NV25719 that might explain the obtained results (age, background conditions, concomitant medications, etc.);
- the clinical relevance of the lower predicted OC-concentrations in 1 to 10-year old children compared to IC adults/IC adolescents (although slightly higher than in otherwise healthy children) in this context;
- and importance of these "time to resolution of symptoms"-findings in the overall B/R balance.

3. The MAH should also discuss the posology in children aged 0 to 1 years, for whom the OC concentrations in otherwise healthy infants have been higher due to immaturity of kidneys.

2. The data on selection of resistance in immunocompromised patients cause some concern.
The MAH should discuss whether the apparently higher risk of selecting for resistance in the immunocompromised patients should be highlighted in Section 4.4 of the SmPC (with cross-reference to 5.1).

RMP aspects

N/A

10. Assessment of the responses to the 1st request for supplementary information

10.1 Major objections

N/A

10.2 Other concerns

Clinical aspects

Question 1

It has been shown in the IC pediatric development programme that there are no major differences in viral shedding, development of resistance, or adverse events between the high dose and conventional dose groups. However, the Marketing Authorization of Tamiflu is based on the only clearly established clinical benefit, namely its ability to reduce time to resolution of symptoms. Hence, fully acknowledging the small number of patients, and large variation in efficacy outcomes in the studies on pediatric IC patients without placebo control groups, there seemed to be difference in this parameter between the 2 studies. In study NV25719 with severely ill IC patients, the time to resolution of symptoms was shorter with triple than conventional dose, with divergent results from the pediatric (≥1 to <13 years) subgroup of study NV20234 with less severely IC patients, where symptoms resolved faster in the conventional dose group than the double dose group.

Therefore, the MAH should further discuss these findings and confirm their view on the benefit/risk balance of conventional and higher doses. Primary interest is on 1 to 10 (13) year old patients who achieved lower predicted exposure with the conventional dose than IC adults and IC adolescents.

The discussion should include the following points (but not limited to these), **see in more detail Questions 1a-1e:**

MAH's response Q 1

The strategy agreed with CHMP and PDCO to provide data to support guidance for use of oseltamivir in immunocompromised (IC) patients < 18 years, was based on extrapolation from data in adult IC patients. The extrapolation approach leveraged population-pharmacokinetic (PK) and exposure-response analyses (PK/PD) in immunocompromised [IC] pediatric patients, also taking into account safety and resistance data. The extrapolation is based on the more objective measures of PK utilizing blood samples and PD utilizing nasal swabs. It was considered by the MAH, CHMP and PDCO that this was a viable approach (CHMP PDCO Face-to Face Meeting, 27-Jan-2016).

Whilst in fully powered efficacy studies, the endpoint of time to resolution of all symptoms (TTRAS) has been used as the primary efficacy endpoint in pivotal studies as the key efficacy endpoint in influenza trials, as noted in the EMA concept paper (EMA/CHMP/EWP/808940/2016) and supported by the FDA (FDA Guidance Document 2011), pediatric efficacy data by symptoms were collected in Studies NV25719 and NV20234 only to support the extrapolation strategy. There was no intention in these pediatric data sets to power for efficacy endpoints. Symptom data is both subjective and highly variable, and adequately powered, blinded studies are needed to draw reliable conclusions with these endpoints.

Assessment of the MAH response

It is acknowledged that the PDCO and CHMP agreed that appropriate posology of oseltamivir for immunocompromised paediatric patients could be defined based on PK and PK/PD studies since the originally planned efficacy study strategy failed due to recruitment problems. The conducted small studies were not powered to confirm therapeutic efficacy.

The endpoint of time to resolution of all symptoms (TTRAS) is in general acceptable. There is however no validated measure for TTRAS for IC children or IC subjects in general. See assessment of Q2.

This is acceptable. The MAH's justifications for the study strategy are accepted.

The MAH's justifications for the study strategy are accepted.

The issue is resolved.

Question 1a

Discussion of the validity and reliability of the used symptom score scale (CARIFS) in IC pediatric patients.

MAH's response

In Study NV20234, 2 different symptoms scales were used, one for adults (≥ 18 years) and adolescents (13-17 years) using the symptoms score in Figure 1 and one for children (≤ 12 years) using the Canadian Acute Respiratory Infections Scale (CARIFS) scale in Figure 2. Study NV25719 used only the CARIFS scoring system due to the age of the children enrolled.

Figure 1 Symptoms Scoring for Adults and Adolescents

Symptoms of influenza-like illness

Please record the worst you have felt since the last assessment.
Please mark one box only per symptom.
The information you provide is very important and will remain strictly confidential.

	absent 0	mild 1	moderate 2	severe 3
1. Nasal congestion	☐	☐	☐	☐
2. Sore throat	☐	☐	☐	☐
3. Cough	☐	☐	☐	☐
4. Aches and pains	☐	☐	☐	☐
5. Fatigue (tiredness)	☐	☐	☐	☐
6. Headache	☐	☐	☐	☐
7. Chills/sweats (feverish)	☐	☐	☐	☐

Figure 2 Symptoms Scoring for Children (≤12 Years)

Influenza-like Illness Symptom Scale (CARIFS)

	No Problem 0	Minor Problem 1	Moderate Problem 2	Major Problem 3	Don't Know or not Applicable
1. Poor appetite	☐	☐	☐	☐	☐
2. Not sleeping well	☐	☐	☐	☐	☐
3. Irritable, cranky, fussy	☐	☐	☐	☐	☐
4. Feels unwell	☐	☐	☐	☐	☐
5. Low energy, tired	☐	☐	☐	☐	☐
6. Not playing well	☐	☐	☐	☐	☐
7. Crying more than usual	☐	☐	☐	☐	☐
8. Needing extra care	☐	☐	☐	☐	☐
9. Clinginess	☐	☐	☐	☐	☐
10. Headache	☐	☐	☐	☐	☐
11. Sore throat	☐	☐	☐	☐	☐
12. Muscle aches or pains	☐	☐	☐	☐	☐
13. Fever	☐	☐	☐	☐	☐
14. Cough	☐	☐	☐	☐	☐
15. Nasal congestion, runny nose	☐	☐	☐	☐	☐
16. Vomiting	☐	☐	☐	☐	☐
17. Not interested in what's going on	☐	☐	☐	☐	☐
18. Unable to get to get out of bed	☐	☐	☐	☐	☐

CARIFS = Canadian Acute Respiratory Infections Scale, validated for use in children below 13 years of age.

The CARIFS scale (Figure 2) was published in 2000 (Jacobs et al 2000) and was developed because, although acute respiratory infection (ARI) is the most frequent clinical syndrome in childhood, there was no validated measure of its severity. It was comprised of 3 domains: symptoms (e.g. cough), function (e.g. play) and parental impact (e.g. clinginess). It was considered that all 3 domains were critical to assess ARI, as young children may not be able to articulate their complaints clearly, and may manifest illness with functional problems alone. However, with this approach, only 4 out of the 18 symptoms are specific for influenza; the other 14 symptoms are associated with the fatigue and malaise of being ill. Additionally, as the scale is used in younger children, it is scored by the caregiver and not the patient, giving rise to more subjectivity.

The scale was developed and evaluated in Canada, in a study of 220 children with ARI. Construct validity was assessed by comparing the CARIFS score with physician, nurse, and parental assessment of the child's health. Data were available from 206 children (94%). The CARIFS correlated well with measures of the construct (Spearman's correlations between 0.36 and 0.52). The CARIFS score was used for the pivotal oseltamivir study in patients aged 1- 12 year (Study WV15758) and is still in use today, although, as the score is nearly 20 years old, it has not been rigorously validated with current methods.

Whilst CARIFS is generally regarded as a clinically robust scoring system, crucially in the context of IC children, patients with underlying illness for which daily medication was taken were excluded from the work underpinning the CARIFS. Thus when assessing children < 13 years in Studies NV20234 and NV25719, there

were potential limitations. In both studies, patients had a serious underlying illness, which was particularly true of Study NV25719, in which patients were undergoing active treatment for cancer or hematopoietic stem cell transplantation (HSCT). These underlying illnesses are likely to have confounded the CARIFS scale assessment of influenza, with a potentially negative impact on its reliability.

In addition, IC patients often present atypically, due to their IC status. For example, whilst high spiking body temperature is characteristic of influenza infection in OWH patients, it can be absent in IC patients. Study NV20234 also collected patients' body temperature to assess fever as an efficacy measure. In the otherwise healthy (OwH) population, this is an objective measure of symptoms. However, in the IC population, systemic symptoms of influenza can be absent. Indeed, the number of patients under 13 years in Study NV20234 who presented with fever any time during the study in the intent-to-treat infected (ITTi) population was very small (1 out of 4 in the conventional dose group and 2 out of 5 in the double dose group). In Study NV25719, fever was reported as part of the CARIFS scale, but in the ITTi population, only 4 patients out of 11 in the convention dose group and 4 out of 9 in the triple dose group had fever at baseline. So even the more objective measure of symptoms based on fever has limited utility in IC patients.

Whilst the TTRAS symptoms is a very important efficacy endpoint, it is highly subjective and thus prone to high levels of variability, making it most reliable when used in large, powered, blinded efficacy studies that take this variability into account. This was not the case in the studies with pediatric patients in this program, which was based on an extrapolation approach and enrolled modest numbers of patients (Table 1).

Table 1 Numbers of Patients Using Each Scoring System (ITTi)

	Influenza-like Illness Symptoms Scale CARIFS (< 13 Years)		Symptoms of influenza-like-Illness (13-17 Years and Adults)	
	Conventional	Higher	Conventional	Higher
NV25719[a]	11	9	NA	NA
NV20234[b]	4	5	3	4

NA=not applicable

[a]NV25719 higher dose is 3x conventional dose

[b]NV20234 higher dose is 2x conventional dose

In conclusion, with the highly variable and subjective endpoint of symptoms measured by the CARIFS scale, which had not been validated in an IC population, and a modest sample size, there was a risk of unreliable and ambiguous results for TTRAS.

Assessment of the MAH's response

The MAH's discussion on the CARIFS endpoint is agreed with. Even though the CARIFS scale is useful in otherwise healthy paediatric population, it has not been validated in IC population. Since the symptoms recorded in the CARIFS may often have been caused by the background conditions of study subjects instead of influenza, the score is not considered to be reliable in severely ill paediatric patients, such as many of the IC population in studies NV20234 and NV25719. As the studies were furthermore not powered to show efficacy, the efficacy results from the studies are not robust and cannot as such be used for defining correct dosage for paediatric IC patients. Hence, the extrapolation strategy for defining posology in these patients is appropriate, as was already accepted by the PDCO and CHMP. Secondarily, it can be concluded that the

results do not confirm efficacy of oseltamivir in paediatric IC patients, which information is correctly given in the proposed Product Information.

The issue is resolved.

Question 1b

Discussion of reasons why the results on time to resolution of symptoms were discrepant between the two paediatric studies, including the possibility that the major difference in disease severity of patients or the slight difference in time to treatment from onset of symptoms between the two studies played a role.

MAH's response

Differences in study design

Other than the patient population, there were numerous differences in designs of Studies NV25719 and NV20234, which included: disease severity, age, blinding, dose, dose duration and symptom scoring scales (Table 2).

Table 2 Differences in Study Design between NV20234 and NV25719

	Study NV25719	Study NV20234
Disease severity	Severe IC	Broad, mild/moderate/severe IC
Age	Children < 13 years	Adolescents and children (1-17 years)
Blinding	Open label	Double blind
Dose	Conventional vs triple dose	Conventional vs double dose
Dose duration	5-20 days adaptive	10 days fixed duration
Symptoms scoring	CARIFS for all	CARIFS for < 13 years Adult/adolescent scoring ≥ 18 years

Abbreviations: CARIFS=Canadian Acute Respiratory Infections Scale, IC=immunocompromised

Disease severity: The population eligible for Study NV20234 was very broad, and included patients with primary and secondary immunodeficiency, with a wide range of severity. Study NV25719 enrolled a narrow population, including only severely IC children who were undergoing active treatment for hematological malignancy or immediately pre- or post-HSCT. Patients eligible for Study NV25719 would also have been eligible for Study NV20234.

Age: The 7 adolescents included in Study NV20234 used the adult symptoms scoring. This had the effect of reducing the sample size for efficacy as determined by CARIFS in patients < 13 years to 9 for Study NV20234 (Table 1).

Blinding: Study NV20234 was a double-blind, placebo-controlled study, thereby minimizing the potential for bias in the reporting of symptom data. Study NV25719 was open label, which was considered reasonable for a PK/PD study with objective primary endpoints measured from blood and nasal swab samples. However, the open-label design of Study NV25719 could potentially lead to bias in reporting the subjective symptom data.

Dose and dose duration: the dosing regimen was different between the studies, with Study NV20234 having conventional vs double dose given for a fixed duration of 10 days. Study NV25719 compared conventional and triple dose for a variable duration of 5-20 days determined by viral shedding. Whilst the adaptive dosing in Study NV25719 was considered the best treatment approach for patients, this limited the ability to discern between the effects due to dose or treatment duration and made 'time to' analyses like TTRAS challenging to assess reliably.

Symptom scoring: children < 13 years used the CARIFS scoring and the reliability of this in an IC population is discussed in Question 1a.

However, as the program was based around extrapolation of adult data to pediatrics < 18 years using the objective endpoints of PK from blood samples and PD from nasal swabs, it was considered by the MAH, CHMP and PDCO that this development plan was a viable approach (CHMP PDCO Face-to Face Meeting, 27-Jan-2016). However, when considering a highly variable subjective endpoint such as symptoms, the differences in study designs could have contributed considerably to the variability in this endpoint.

Time from symptom onset to start of treatment

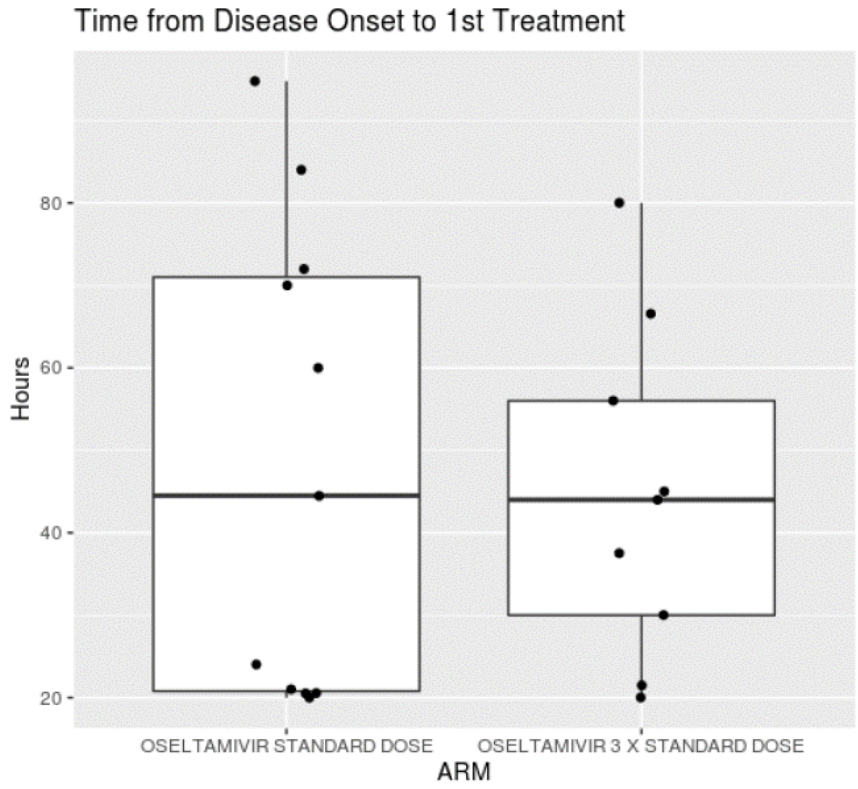
For Studies NV20234 and NV25719 in IC patients, a wide time window of 96 hours between influenza symptom onset and first dose of study drug was chosen. This was considerably longer than the 36 hours allowed in the pivotal studies with OwH patients. This time window was longer for the IC studies as patients typically present later than OwH patients due to their IC status and lack of systemic symptoms, and IC patients typically shed virus for longer than OwH ones. However, this longer time window may have contributed to the variability in the median time between symptom onset and treatment start between the studies (Table 3). The pediatric patients (1-17 years) in Study NV20234 had approximately half a day longer between symptom onset and start of treatment (~ 60 hours or 2.5 days) than the adults in Study NV20234 and the children < 13 years in Study NV25719 (~ 44 to 55 hours or 2 days).

Table 3 Median Time from Onset of Symptoms to Start of Treatment in IC Patients

	NV20234	NV25719	NV20234
	IC Adults (≥18 years)	IC Children (<13 years)	IC Pediatrics (≥1 to <18 years)
Median time from onset of symptoms to start of treatment, hours (range)	Conventional (n=68): 44.42 (15.9 - 94.0) Double Dose (n=66): 54.83 (7.7 - 90.4)	Conventional (n=11): 44.50 (20.0, 94.8) Triple Dose (n=9): 44.00 (20.0, 80.0)	Conventional (n=8): 60.11 (12.3, 89.6) Double Dose (n=8): 58.67 (8.4, 82.4)

Although it is well established that earlier treatment with oseltamivir is beneficial, due to the extrapolation approach using modest patient numbers, there is a lack of precision in determining the median time between onset of symptoms and start of treatment. This is illustrated in Figure 3, where in the conventional dose group of Study NV25719, the distribution of the three values closest to the median for 'time from onset of symptoms to first treatment' is such that the median could vary between approximately 24 hours and 60 hours (Figure 3). Thus the estimate of the median time is likely unreliable.

Figure 3 Box Plot of Time from Onset of Symptoms to Start of Treatment for Patients in Study NV25179



It is of note that observed ranges (from onset of symptoms to start of treatment) were similar between the different dose groups and studies (8.4 to 20 hours for minimum values and 80 to 94.8 hours for maximum ones).

Conclusion

In conclusion, the MAH opinion is that variation of the symptoms data in Study NV20234 and Study NV25719 did not indicate a meaningful difference between the populations due to disease severity or different time between symptoms and treatment start. It is more likely that the difference in TTRAS between the studies and treatment is due to: variability within and between studies, the open label NV25719 study design which potentially lead to bias in symptoms assessment, as well as the small sample size that reduced the precision of the median TTRAS by CARIFS (which was not optimized for use in IC patients).

Assessment of the MAH's response

The MAH discusses the differences between studies NV25719 and NV20234, as requested. The severity of the background IC conditions, age of study subjects, blinding, dose, dose duration and symptom scoring scales were different in the two studies. Furthermore, the studies were not powered to reliably show efficacy of oseltamivir, hence, any differences in the efficacy endpoints can also be due to chance. As shown by the MAH, there was marked variation in the time from onset of symptoms to onset of treatment, which further adds to the variation in efficacy between individual study subjects. It is known from previous studies that oseltamivir should be initiated as soon as possible after onset of symptoms for achieving efficacy. Hence, it

is expectable that patients who started treatment as late as up to 96 hours after onset of symptoms may not have benefitted from treatment, contrary to patients who started treatment sooner.

In conclusion, the MAH has sufficiently discussed the inherent differences in the design and conduct of the two paediatric studies NV20234 and NV25719, reasons for the observed variability and the discrepancy of the results on the main clinical outcome measure TTRAS of the studies NV20234 and NV25719.

The issue is resolved.

Question 1c

Discussion of whether there were differences between study arms of NV25719 that might explain the obtained results (age, background conditions, concomitant medications, etc.).

MAH's response

In the ITTi population, the median TTRAS was 179.4 hours (95% confidence interval [CI]: 24.7, NE) in the conventional dose group and 34.5 hours (95% CI: 0.0, 84.9) in the triple dose group with wide and overlapping CIs (Table 4, Figure 4).

Table 4 NV25719 Summary of Time to Resolution of All Symptoms (ITTi population)

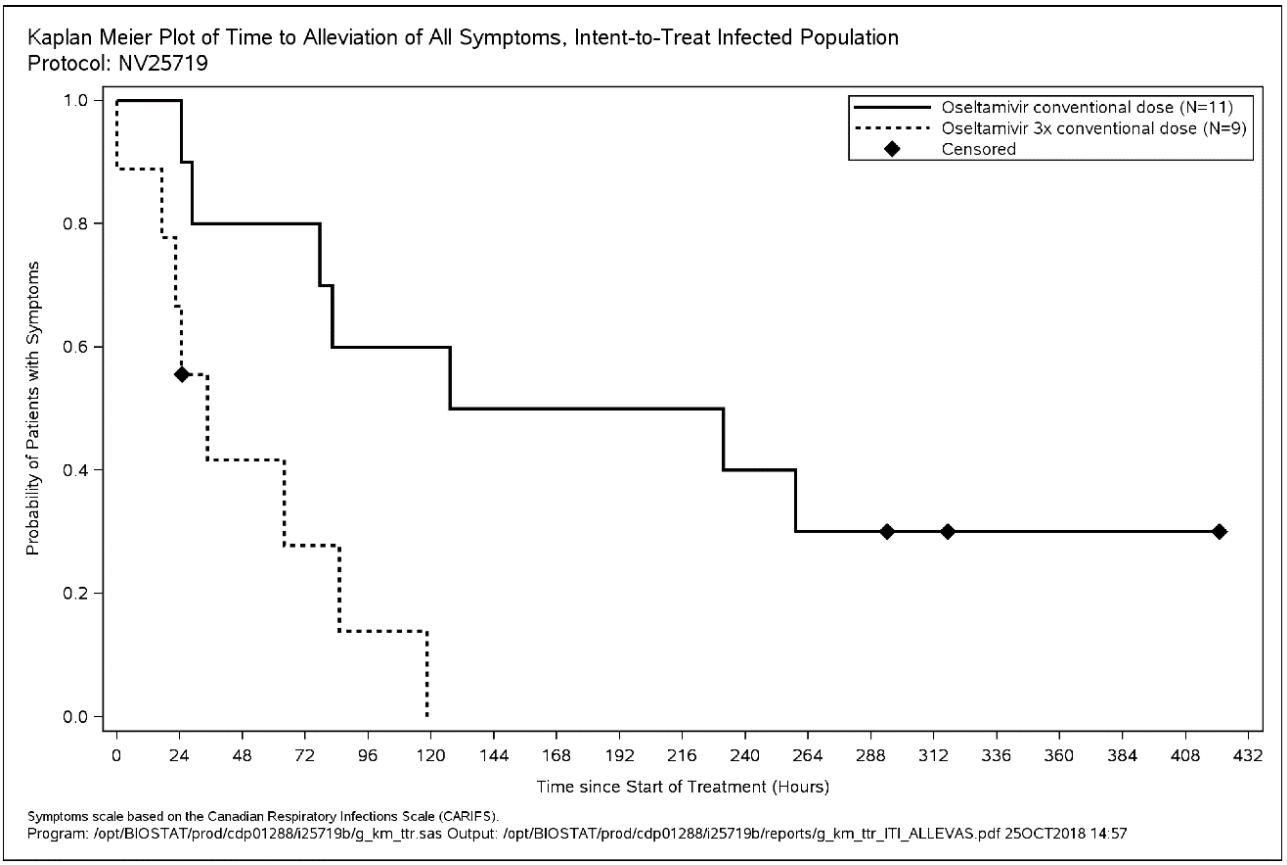
Summary of Time to Alleviation of All Symptoms, Intent-to-Treat Infected Population
Protocol: NV25719

Time to Event (a) (hours)	Oseltamivir conventional dose (N=11)	Oseltamivir 3x conventional dose (N=9)
n	10	9
Number Censored	3	1
Median (95% CI) (b)	179.4 (24.7, NE)	34.5 (0.0, 84.9)
Range	24.7 - 259.0	0.0 - 118.3
Group Comparison - Oseltamivir conventional dose vs. Oseltamivir 3x conventional dose		
Difference of Medians (95% CI) (c)	-	144.8 (-5.1, 234.3)

Symptoms scale based on the Canadian Respiratory Infections Scale (CARIFS).
(a) Time from randomisation date to time of alleviation of all symptoms.
(b) Median time was estimated from the Kaplan-Meier curve (unstratified).
(c) Obtained with 10000 bootstraps.
NE = Not Estimable(Brookmeyer and Crowley, 1982).

Note: One patient in the conventional dose group with all symptoms scores ≤1 at baseline and remaining ≤1 for at least 21.5 hours had TTRAS set to missing as per the SAP

Figure 4 Study NV25719 Kaplan-Meier Plot of the Time to Resolution of All Symptoms (ITTi population)



In order to determine if there were any differences between the study arms that may have contributed to the symptoms data, baseline characteristics were investigated (Table 5, Table 6). Patients in the triple dose group were younger (mean 3.7 years vs 6.7 years) and more homogeneous in terms of race (77.8% white) and underlying malignancy (89.9%) acute lymphoid leukemia. Patients in the conventional dose group were predominantly infected with the type B strain, in contrast to the triple dose group, who were mainly infected with type A strains.

Table 5 Study NV25719 - Demographic Data and Baseline Characteristics (ITTi population)

	Oseltamivir conventional dose (N=11)	Oseltamivir 3x conventional dose (N=9)	All Patients (N=20)
Age (years) at baseline			
n	11	9	20
Mean (SD)	6.7 (4.2)	3.7 (2.0)	5.4 (3.6)
Median	6.0	3.0	4.5
Range	1 - 12	2 - 8	1 - 12
Age group (years)			
n	11	9	20
>= 1	11 (100.0%)	9 (100.0%)	20 (100.0%)
Sex			
n	11	9	20
Male	6 (54.5%)	7 (77.8%)	13 (65.0%)
Female	5 (45.5%)	2 (22.2%)	7 (35.0%)
Race			
n	11	9	20
American Indian or Alaska Native	1 (9.1%)	0	1 (5.0%)
Asian	0	1 (11.1%)	1 (5.0%)
White	5 (45.5%)	7 (77.8%)	12 (60.0%)
Other	5 (45.5%)	1 (11.1%)	6 (30.0%)
Ethnicity			
n	11	9	20
Hispanic or Latino	5 (45.5%)	3 (33.3%)	8 (40.0%)
Not Hispanic or Latino	6 (54.5%)	6 (66.7%)	12 (60.0%)
Haematopoietic Stem Cell Transplant Status			
n	11	9	20
Yes	1 (9.1%)	0	1 (5.0%)
No	10 (90.9%)	9 (100.0%)	19 (95.0%)
Haematological Malignancy History			
n	10	9	19
ACUTE LYMPHOID LEUKAEMIA	6 (60.0%)	8 (88.9%)	14 (73.7%)
ACUTE MYELOID LEUKAEMIA	3 (30.0%)	0	3 (15.8%)
NON-HODGKIN LYMPHOMA	1 (10.0%)	1 (11.1%)	2 (10.5%)

Table 6 Study NV25719 - Summary of Influenza Infection (ITTi population)

	Oseltamivir conventional dose (N=11)	Oseltamivir 3x conventional dose (N=9)	All Patients (N=20)
Yes (a)			
n	11	9	20
A(H3N2)	2 (18.2%)	4 (44.4%)	6 (30.0%)
B	7 (63.6%)	1 (11.1%)	8 (40.0%)
A(H1N1 (2009))	2 (18.2%)	4 (44.4%)	6 (30.0%)

(a) Positive result from culture or RT-PCR at any time during the study.

There were 5 patients in the conventional dose group (Patient 10008, Patient 10021, Patient 10030, Patient 10034 and Patient 10055) driving the longer TTRAS group whose TTRAS were above the median (Figure 5). There were some differences between these 5 patients and those who had TTRAS less than the median (1 patient in the conventional dose group with all symptoms scores $\leq$1 at baseline and remaining $\leq$1 for at least 21.5 hours had TTRAS set to missing as per the SAP) (see l_dm_IT and l_cm_SE_CONCOM of CSR NV25719). Within the Conventional group, patients with the longer TTRAS vs shorter TTRAS:

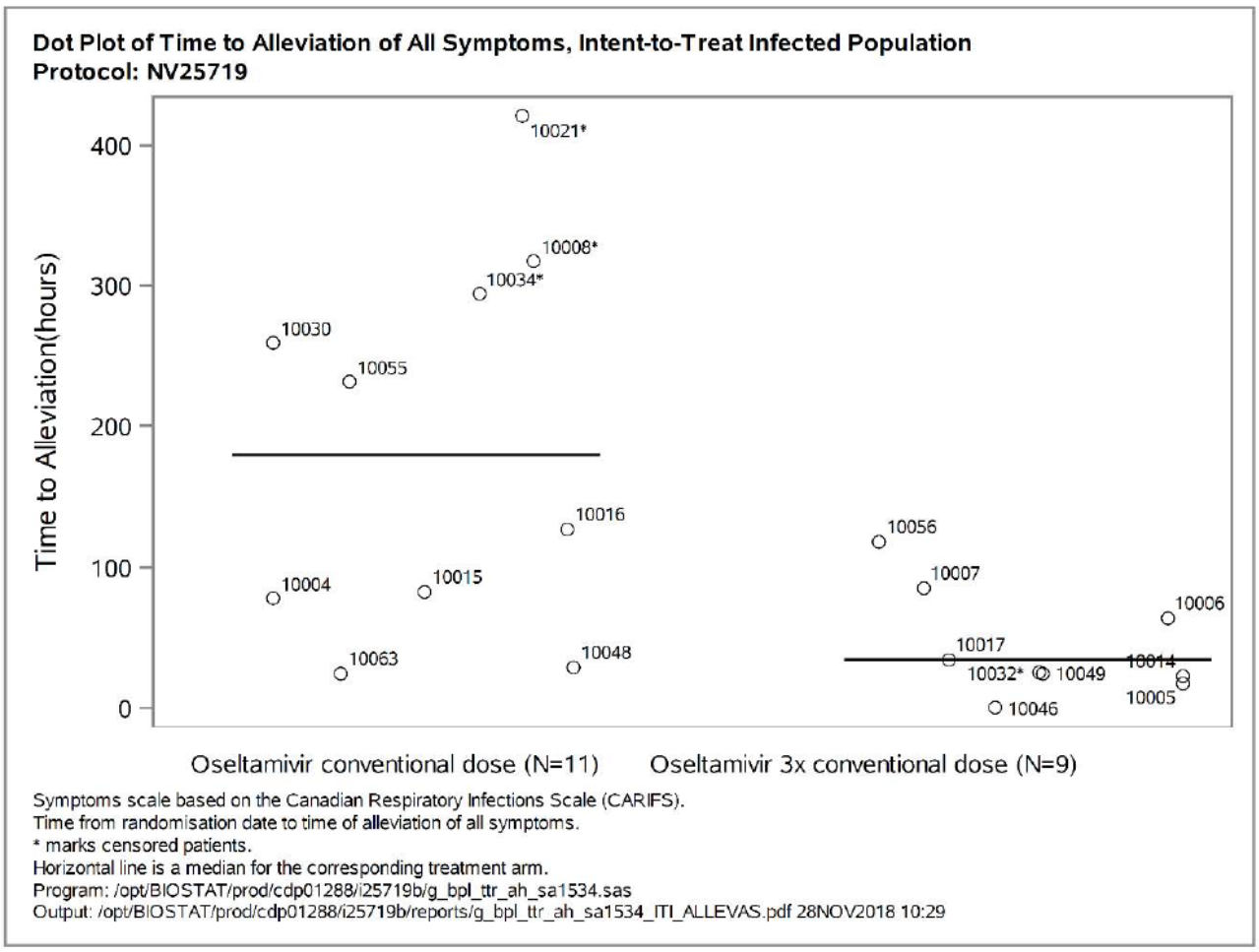
- were older (mean age 9 years vs years)
- had more baseline symptoms that were a 'major problem' (13 symptoms in 2 patients vs 1 symptom in 1 patient)
- were treated with concomitant corticosteroids prior to resolution of all symptoms (4/5

patients vs 1/5 patients)

- had lower number with acute lymphoid leukemia as the underlying hematological condition (2/5 patients vs 4/5 patients)

However, when comparing the conventional and triple dose, there were patients in the triple dose group who did not experience prolonged TTRAS who had similar characteristics to the patients in the conventional group with prolonged TTRAS.

Figure 5 Dot Plot of Time to Resolution of All Symptoms (ITTi population)



Note: One patient in the conventional dose group with all symptoms scores ≤1 at baseline and remaining ≤1 for at least 21.5 hours had TTRAS set to missing as per the SAP.

Conclusion

There was considerable variation between the baseline demographics and concomitant treatments of the conventional and triple dose in Study NV25719. There are no clear factors that could independently explain the difference in TTRAS between the groups. The MAH's opinion is that the ambiguous TTRAS data are driven by the highly variable and subjective endpoint of TTRAS - this may have been exacerbated by the CARIFS score not being optimised for IC patients - as well as the modest sample size for this primarily PK/PD study where symptom data was never intended to be more than supportive.

Assessment of the MAH's response

As expectable, the study arms differed in many aspects that affect therapeutic response. The study was very small, with only 5 and 7 subjects in the compared groups. The mean age of study subjects in the triple dose group was 3.7 years (range 2-8 years) vs 6.7 years (range 1-12 years) in the conventional dose arm. The inclusion criteria comprised a range on different conditions that were unevenly distributed between the study arms: acute lymphatic leukaemia (ALL) in 8/9 subjects in the triple dose group, and ALL in 6/10, acute myeloid leukaemia (AML) in 3/10 and Non-Hodgkin lymphoma in 1/10 subjects in the conventional dose group. Patients in the conventional dose group were predominantly infected with the type B strain, whereas in the triple dose group mainly with type A strains. Hence, the baseline characteristics of the patients in the conventional dose arm and triple dose arm were not comparable, and it is possible that the general condition of the subjects was also variable, even though no information on the overall condition at baseline is available.

It is interesting that the conventional dose group with a higher mean age had less patients with elongated TTRAS and the TTRAS was in general longer in older children. In healthy children, age has not been associated with duration of influenza symptoms, however, viral shedding has been longer in younger subjects in studies conducted on otherwise healthy subjects. On the other hand, interindividual variation was very large, and the difference across study groups was driven by three subjects in the conventional dose group.

Even though no definitive conclusion can be drawn for the obtained differential results on resolution of influenza in the two groups, the submitted data demonstrate fundamental differences between study arms. Therefore, no conclusion is possible on any potential contribution of oseltamivir dose on the observed duration of influenza in either group.

The issue is resolved

Question 1d

Discussion of the clinical relevance of the lower predicted OC concentrations in 1 to 10-year old children compared to IC adults/IC adolescents (although slightly higher than in otherwise healthy children) in this context.

MAH's response

Oseltamivir inhibition of neuraminidase

In adult IC patients in Study NV20234, there were no notable exposure-response relationships for any of the efficacy measures and PD parameters, although the sample size was not large enough to make definitive conclusions. This is not overly surprising, as in Study NV20234, the doses tested were 75 and 150 mg and exposures from both of these doses were considered to be very close to the maximum effect (at the plateau of the exposure-response curve). In adults and pediatric patients, the disease model in IC patients estimated a half-maximal effective area under curve (AUC_{50}) of 160 ng*hr/mL which corresponds to a dose of approximately 2.2 mg. This is consistent with the low estimated half-maximal effective dose (3.2 mg) for oseltamivir in a previously developed disease model in immunocompetent subjects (Kamal et al. 2015).

Whilst there were some differences in patterns of exposure between IC patients < 10 years and older patients, the exposure across all age groups of IC patients investigated (children, adolescents and adults) was at least the same as found in OwH populations. Among all 30 IC pediatric patients, the lowest individual predicted exposure (C_{min} of 84.6 ng/mL for OC) was still above inhibitory concentrations (IC_{95} values) for

a range of influenza virus strains (Preclincial Virology Summary, 2000). This level of exposure is anticipated to lead to full inhibition of the influenza neuraminidase.

Pediatric TTRAS by 'low exposure' and 'high exposure'

To increase the sample size with the aim to make the assessment more robust, an exploratory combined analysis was carried out for pediatric patients < 13 years old, investigating the relationship between TTRAS and exposure in Studies NV25719 and NV20234. Patients were included in the analyses if they received 10 or more doses of oseltamivir. For patients with no PK data collected, population predictions were computed from the final pop PK model using patient dose level and individual covariate values. $C_{min,OC}$ was highly correlated with $AUC_{12h,OC}$ and therefore only one out of the two parameters was investigated further. The 'high exposure' and 'low exposure' groups were based on exposure by C_{min} of OC, the active metabolite of oseltamivir, rather than 'conventional' or 'higher' dose groups. The low and high exposure groups were split at the median value.

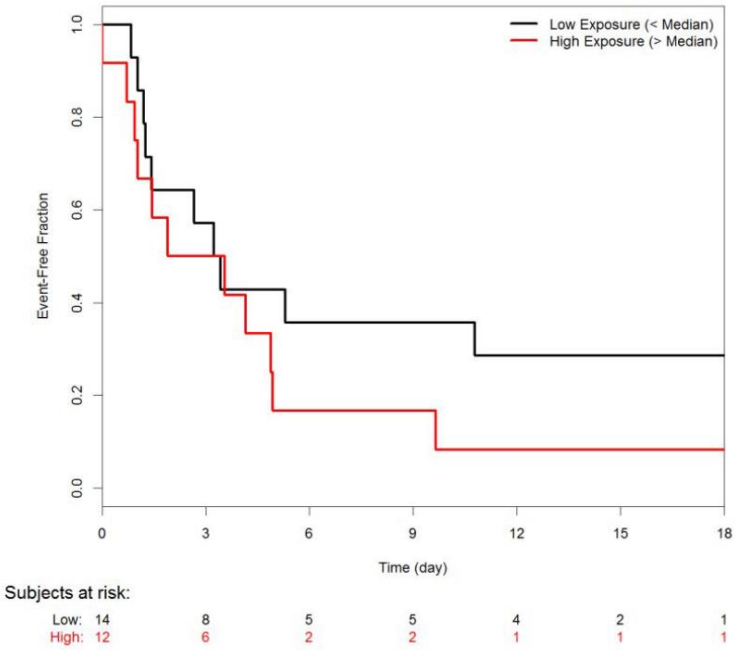
In total, 36 pediatric patients from Studies NV25719 and NV20234 had evaluable PD/efficacy data. As symptoms were recorded differently for adolescents (age ≥ 13) in Study NV20234 compared with younger children, the data for adolescents were not used in the analysis of TTRAS (including fever). Kaplan-Meier plots for time to event endpoints were stratified by patients in low and high exposure categories as well as Cox proportional hazards of these endpoints versus $C_{min,OC}$, $\log(C_{min,OC})$, and $C_{min,OC}$ category (Pop PK report 2019). The analysis was performed for 1-10 year olds and 1-12 year olds.

Kaplan-Meier plots and Cox proportional hazards did not find any notable relationships between exposure and TTRAS. The curves of the Kaplan-Meier plots crossed in several places for children up to 12 years (Figure 6) and 10 years (Figure 7), respectively.

Clearance of oseltamivir and OC for pediatric patients were similar for IC patients as compared with OwH subjects < 10 years. Thus, exposures for IC pediatric patients < 10 years were similar (or slightly higher) as compared with OwH subjects of the same age range. In contrast, clearance is higher in OwH adolescents and adults compared with IC adolescents and adults.

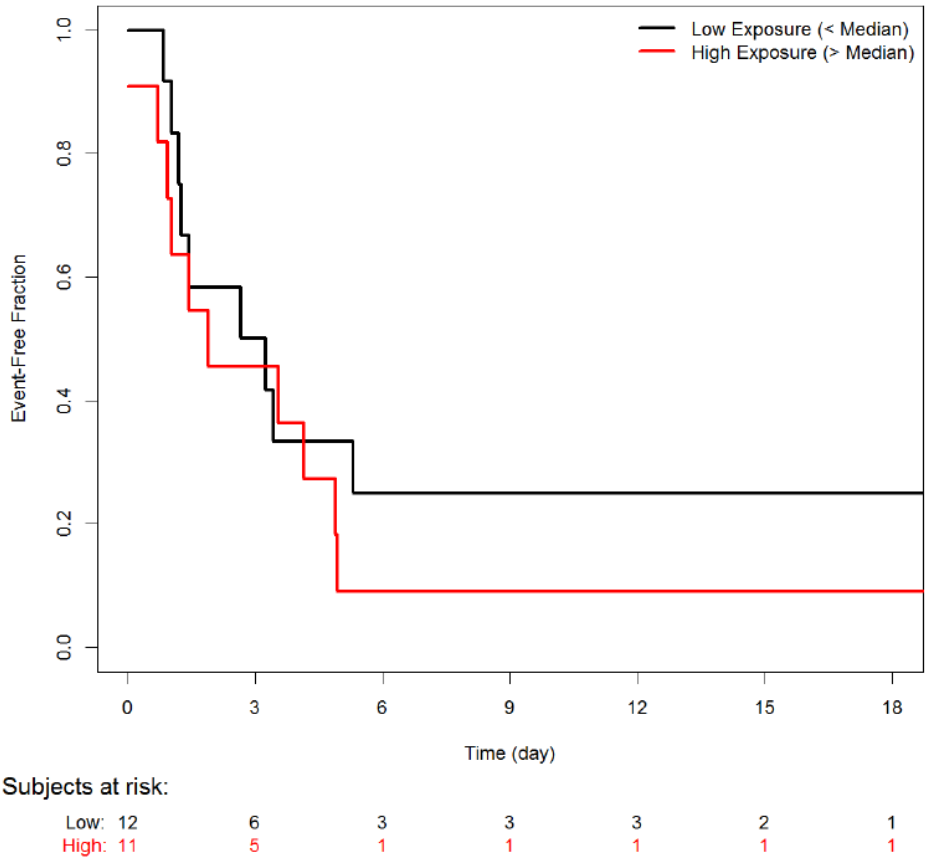
The lack of exposure-response relationship in IC pediatric patients was similar to the observation in IC adults (Figure 8) by applying the same approach as for IC pediatrics. That means inclusion of patients with no PK data collected; population predictions were computed from the final pop PK model using patient dose level and individual covariate values, and OwH patients of all ages (including pediatric patients < 1 year). This was likely due to the fact that all oseltamivir doses tested were considered at or close to the plateau of the exposure-response curve, i.e. already at maximal dose-response level.

Figure 6. Kaplan-Meier of Time to Resolution of Symptoms (Including Fever) by Cmin OC Exposure Group – Children (up to 12 Years) Studies NV25719 and NV20234



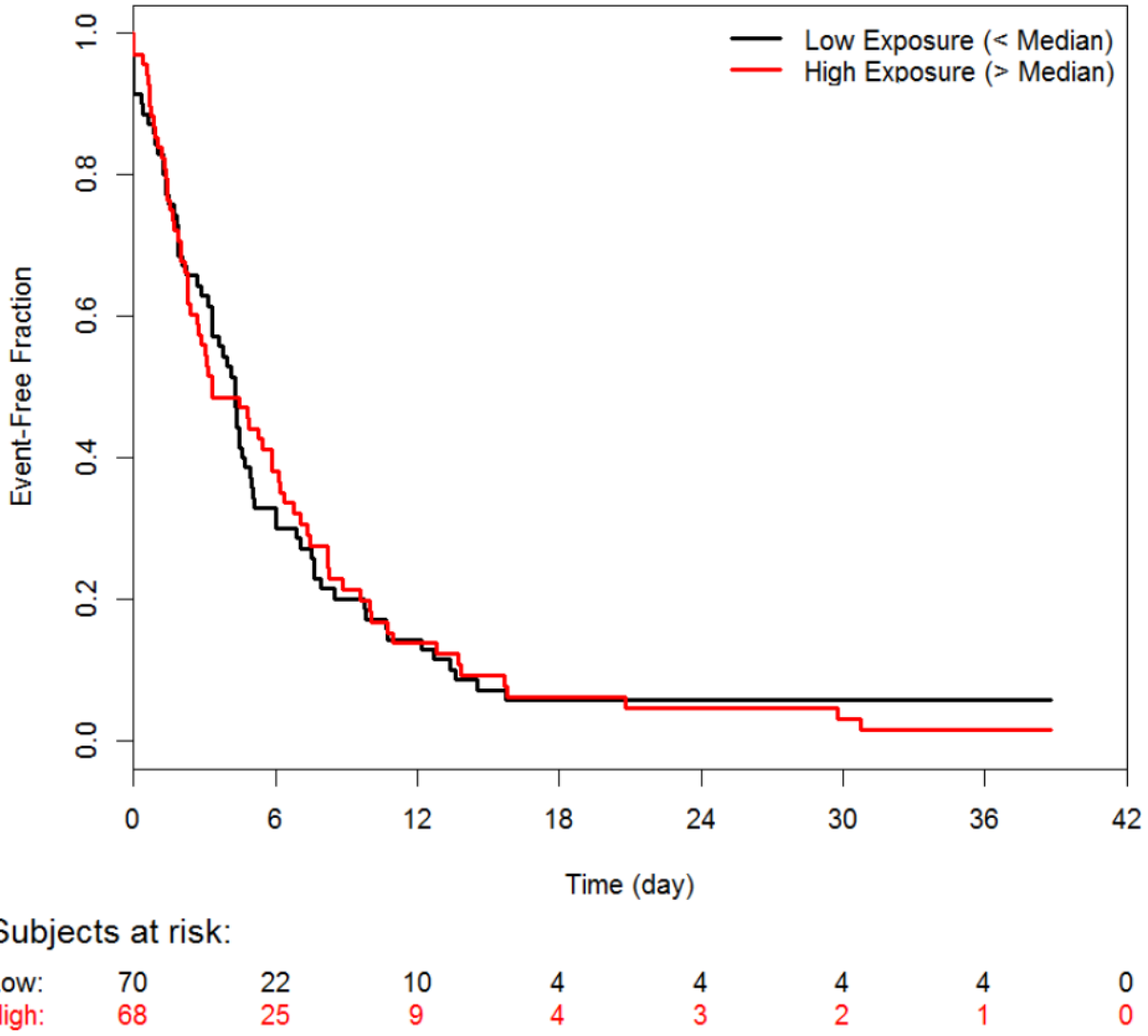
Note: When observed PK values were not available, these were imputed from the population PK model using patient dose level and individual covariate values

Figure 7. Kaplan-Meier of Time to Resolution of Symptoms (Including Fever) by Cmin OC Exposure Group – Pediatrics Up to 10 Years (NV25719 and NV20234)



Note: When observed PK values were not available, these were imputed from the population PK model using patient dose level and individual covariate values

Figure 8. Kaplan-Meier of Time to Resolution of Symptoms (Including Fever) by Cmin OC Exposure Group – Adults (NV20234)



Note: When observed PK values were not available, these were imputed from the population PK model using patient dose level and individual covariate values

Conclusion

The predicted minimum concentrations of OC at steady-state in all IC children, adolescent and adults with conventional dose of oseltamivir were still above inhibitory concentrations of OC and at a therapeutic level for a range of influenza virus strains. Furthermore, an exploratory analysis across all the patients up to 12 years, and also all the patients up to 10 years, in Studies NV25719 and NV20234 showed that no additional benefit for TTRAS was seen in patients with higher exposures compared with lower exposures in pediatric IC population. A similar analysis in IC adults also reflected no benefit for TTRAS with higher exposure. TTRAS data were in agreement with the data for virological endpoints. Thus, it seems that the risk of under-dosing of patients aged 1-10 years is minimal.

The MAH's conclusion is that the conventional dose is adequate for all age groups of IC patients.

Assessment of the MAH's response

Following the dosage that is approved for otherwise healthy children, the observed and predicted serum OC levels in IC paediatric patients > 1 year of age are substantially higher than those required for full inhibition of the influenza neuraminidase. The Kaplan-Meier curves (Figure 6 and Figure 7) suggested no obvious relationships between OC exposure and time to resolution of all symptoms (TTRAS) in IC paediatric patients. It is acknowledged that the number of subjects in each group was small (n=11 to n=14).

It is agreed with the MAH that the risk of under-dosing of paediatric IC patients following the proposed posology is minimal.

The issue is resolved.

Question 1e

Discussion of importance of these "time to resolution of symptoms"-findings in the overall B/R balance.

MAH's response

Benefit risk section to summarize Q1

Pediatric development program and extrapolation approach

As CHMP states, the Tamiflu Marketing Authorization is based on the only clearly established clinical benefit of oseltamivir treatment, namely its ability to reduce time to resolution of symptoms. However, the IC pediatric development program in patients < 18 years, as agreed with PDCO and CHMP SAWP, was based on a PK and PK/PD extrapolation approach from adult efficacy to pediatrics (CHMP PDCO Face-to Face Meeting). There was no attempt by the MAH to power the studies in the PIP to be support standalone efficacy claims for pediatrics, as the larger size required would have made such studies unfeasible.

The CHMP agrees with the MAH position that the IC pediatric development program demonstrated that there are no major differences in viral shedding, development of resistance, or adverse events between the high dose and conventional dose groups.

Efficacy by TTRAS

It is recommended in the EU SmPC that IC adults should receive the conventional 75mg dose of oseltamivir for the extended duration of 10 days. Study NV20234 provided the data to support this claim from ~ 150 patients who received 75 mg or 150 mg BID, where the median TTRAS was similar between the treatment arms.

In the pediatric patients, the symptoms data as measured by TTRAS appear to provide conflicting conclusions in terms of relationship between dose and response between Studies NV25719 and NV20234. In Study NV25719, TTRAS in patients receiving the triple dose of oseltamivir was considerably shorter than those receiving conventional dose, although the open label design lead to potential for bias in symptom assessment. In contrast, in patients < 13 years in the double-blind Study NV20234, TTRAS with conventional dose was shorter than with double dose. There was not a consistent trend showing a shorter TTRAS with increasing dose. This was in line with what was seen in the virology data TTCVS, where there was

no PK/PD response between exposure and viral titers. The MAH considers that the difference in TTRAS between the studies and treatment arms does not represent a true clinically meaningful difference due to underlying disease severity or dose regimen. It is more likely due to the variability within and between the studies, which were not designed to investigate treatment effect on symptoms in patients < 18 years, in conjunction with the highly variable and subjective symptoms assessment by the CARIFS scale which was not optimised in IC patients, and modest patient numbers to support an extrapolation approach.

Exposure in 1-10 year olds

To increase the sample size with the aim to make the assessment more robust, an exploratory combined analysis was carried out for all PD/efficacy evaluable pediatric patients < 13 years old to investigate the relationship between TTRAS by CARIFS and exposure in studies NV25719 and NV20234. A total of 36 patients were evaluable and PK data were imputed from the pop PK model if not available. The analyses of both patients 1- 12 years (Figure 6) and patients 1-10 years (Figure 7) showed that no additional benefit for TTRAS was seen in patients with higher exposures of OC (the active metabolite of oseltamivir) compared with lower exposures of OC in pediatric IC patients. With the caveat of the modest sample size, these results suggest that no additional benefit in TTRAS was seen at exposures higher than those achieved after the administration of the conventional dose. The risk of under dosing in this population appears minimal.

In adults and adolescents, the exposures of OC and oseltamivir were higher in IC patients compared with OwH patients. In patients 1-10 years, the exposures in OwH and IC patients were similar. However, the concentrations of OC achieved with the conventional dose of oseltmivir in IC children aged 1-10, as well as adolescents and adults, are above inhibitory concentrations (IC_{95} values) of viral neuraminidase.

Conclusion

Considering all the evidence submitted in the IC adult and pediatric (< 18 years) filing dossiers, which included: safety, resistance, virology, population PK, PK/PD, disease modeling and the extrapolation of efficacy from adults to pediatrics, the MAH's position is that the conventional dose of oseltamivir for an extended duration of 10 days offers the best balance of benefit and risk for IC pediatrics < 18 years of age, regardless of age and of severity of IC.

Assessment of the MAH's response

Q 1e Discussion of importance of the "time to resolution of symptoms"-findings in the overall B/R balance.

It is agreed with the MAH that the IC paediatric development program for children and adolescents is not sufficient for standalone efficacy claims for these age groups. Hence, the MAH proposes no such claim in the Product Information. The obtained results in the small studies were, as the MAH also agrees, conflicting regarding dose-response relationship. As separately assessed earlier in this AR (in assessment of the MAH's responses to each question), the results on efficacy are not deemed reliable due to considerable variation in background conditions and other baseline characteristics of the paediatric IC subjects, unreliability of the CARIFS scale in severely ill patients, and the small size and lack of power of the studies. Hence, the results are likely biased by chance and by individual differences between study subjects.

As the MAH states, no consistent trend was seen between dose and duration of illness. As a conclusion, the dose recommendation is based on the population PK, PK/PD, disease modelling and extrapolation of efficacy from adult to paediatric subjects. Since no certainty prevails of efficacy of oseltamivir in IC subjects in general, no extrapolation from IC adults to IC paediatric patients is feasible regarding efficacy.

However, the submitted data are considered sufficient for extrapolation of recommended posology from IC adults to IC adolescents and children, i.e. conventional daily dose but extended treatment duration of 10 days.

The issue is resolved.

Question 2

The MAH should also discuss the posology in children aged 0 to 1 years, for whom the OC concentrations in otherwise healthy infants have been higher due to immaturity of kidneys.

MAH's response Q 2

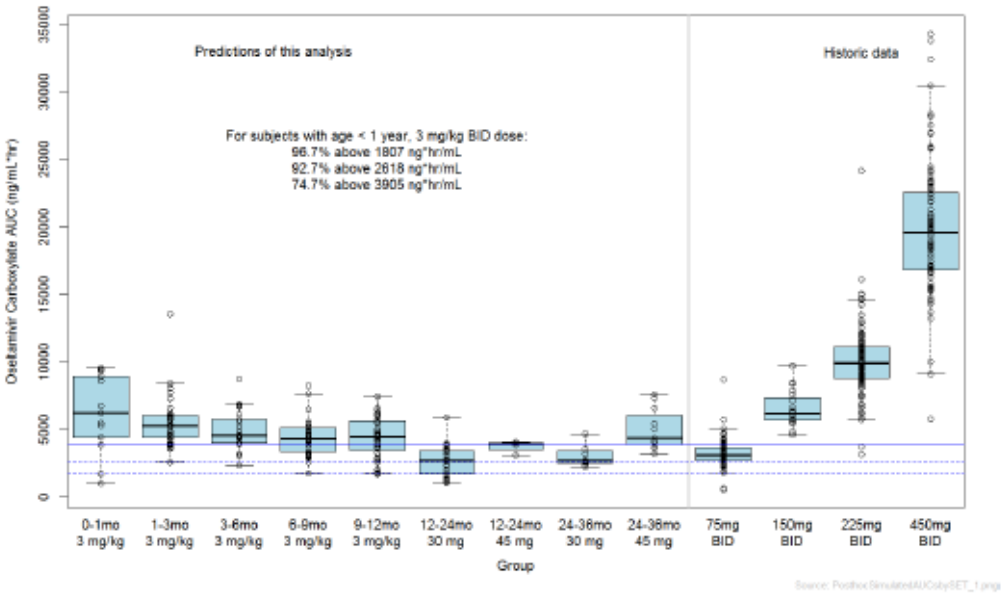
A previously described mechanistic population-pharmacokinetic model was developed to predict oseltamivir and OC exposures down to neonates accounting for physiological changes during the first 2 years of life (pop PK report). The model included data from 13 studies, compromising 436 subjects with normal renal function (317 pediatric and 119 adult subjects < 40 years). Renal maturational changes were implemented by description of OC clearance with the allometric function of weight and Hill function of postmenstrual age.

Clearance of oseltamivir and OC for pediatrics were similar for IC patients from Studies NV25719 and NV20234, as compared with OwH subjects < 10 years in previous studies. Thus, exposures for IC pediatric patients < 10 years were similar (or slightly higher) as compared with OwH subjects of the same age range.

Based on the above, and as the established population PK model accounts for developmental changes, it is predicted that this applies (similar exposures as in OwH subjects) for pediatric patients during their first year of life and that an increase in OC concentrations would not provide additional benefit.

In patients < 1 year, the exposure metrics of OC increased in younger OwH subjects. In the lowest age group 0-1 month, the predicted median exposure (AUC_{0-12h}) of OC at steady-state were approximately 40% higher than in infants aged 9-12 months (Figure 9), which is consistent with renal maturation. However, the OC exposure especially in neonates was very variable. Thus, the slightly higher OC AUCs for younger infants safeguards from underexposure and subsequent risk of treatment failure. The increase in OC exposure at the conventional dose is not considered to alter the safety and tolerability of oseltamivir due to its large safety window. In addition, a 3 mg/kg BID regimen across OwH and IC patient populations and across the < 1 year of age cohort provides less potential medication errors than separate doses for different age cohorts (SCP EU <1 yr submission).

Figure 9 Comparison of Predicted Post-hoc Steady-State Oseltamivir Carboxylate AUCs by Age following 3 mg/kg BID versus AUCs redicted in Other Populations



In the IC program, the lack of exposure-response relationship in IC pediatric patients from Studies NV25719 and NV20234 (Figure 6 and Figure 7) was similar to the observation in IC adults (Figure 8) and OwH patients of all ages (including pediatric patients < 1 year) at similar exposure levels. This was likely due to the fact that all oseltamivir doses tested in IC patients were considered at or close to the plateau of the exposure-response curve i.e. already at maximal dose-response level.

Conclusion

The dose of 3 mg/kg BID in IC infants < 1 year - the same as in OwH infants – is considered to be appropriate based on the above mentioned points. However, in the case of the IC infants < 1 year, the duration of the treatment should also be extended to 10 days to correspond to that recommended in IC adults, adolescents and older children to limit potential viral rebound (Influenza Disease Model Report, 2019).

Assessment of the MAH's response

The available data indicate that OC exposures in IC subjects 1 to <10 years of age are expected to be comparable with OwH subjects in the same age range. There are no observed PK data for oseltamivir in IC infants < 1 year of age, whereas limited data in OwH infants are available.

According to the MAH the dose of 3 mg/kg BID in IC infants < 1 year - the same as in OwH infants - is considered to be appropriate. However, in the case of the IC infants < 1 year, the duration of the treatment should also be extended to 10 days to correspond to that recommended in IC adults, adolescents and older children to limit potential viral rebound (Influenza Disease Model Report, 2019). This justification of the MAH is acceptable. There are no grounds to recommend altered dose in IC infants < 1 year of age and the duration of treatment should be 10 days as in IC older children, adolescents and adults.

The issue is resolved.

Question 3

The data on selection of resistance in immunocompromised patients cause some concern. The MAH should discuss whether the apparently higher risk of selecting for resistance in the immunocompromised patients should be highlighted in Section 4.4 of the SmPC (with cross-reference to 5.1).

MAH's response Q 3

It is documented in the literature that younger children have higher rates of resistance, compared with adolescents and adults, this may reflect higher replications rates and/or relativea immaturity of immune system in particular extent of prior exposure to influenza infection (Roosenhoff et al. 2019). A pooled analysis of clinical trials sponsored by the MAH, with a population mainly comprised of OwH patients, showed the higher incidence of resistance in children and especially infants < 1 year (CDS v 16) (Table 7).

Table 7 Incidence of Oseltamivir Resistance in Clinical Studies from EU SmPC V 16

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping [a]	Geno- and Phenotyping [a]
Adults and adolescents	0.88% (21/2382)	1.13% (27/2396)
Children (1-12 years)	4.11% (71/1726)	4.52% (78/1727)
Infants (<1year)	18.31% (13/71)	18.31% (13/71)

[a] Full genotyping was not performed in all studies.

Additionally, IC patients are known to have higher incidence of resistance than OwH patients, likely due to poorer viral clearance (van der Vries et al. 2013, Alonso et al. 2011, Tramontana et al. 2010, Stephenson et al. 2009). In Studies NV25719 and NV20234 in IC adults and children (there were no adolescents with resistance) this was also the case, although the small numbers of patients with viral resistance is acknowledged. When studies and treatment groups were pooled, IC children had an overall incidence of resistance of 20.7%, which is comparable to the 18.31% incidence seen in OWH infants < 1 year.

Table 8 Incidence of viral resistance in IC patients from Studies NV25719 and NV20234

	NV25719		NV20234	
	Conventional Dose	Triple Dose	Conventional Dose	Double Dose
Adults and adolescents	-	-	13.7% (10/73)	2.6% (2/78)
Children (1-12 yrs)	9.1% (1/11)	22.2% (2/9)	2/4	1/5

Across all age groups in Studies NV20234 and NV25719, patients with virus resistant to oseltamivir tended to have longer viral shedding, but all IC children with resistance cleared the influenza infection with no notable impact on the clinical outcomes of influenza and without influenza-related complications, e.g. secondary bacterial infections.

The MAH proposed to add additional wording regarding post-baseline oseltamivir- resistant virus into Section 5.1 'Pharmacodynamic properties, Clinical studies' of the EU SmPC version 16, which was already submitted with this variation.

The MAH does not propose to add additional information to Section 4.4 'Special warnings and precautions for use' for the following reasons:

- It is understood by the prescribing community that IC status and younger age both contribute to an increased likelihood of oseltamivir viral resistance, but the majority of patients will not develop resistance. In fact, in the small number of adolescent patients in these studies, none had resistance, and resistance was comparable between IC < 13 year olds and OwH < 1 year olds.
- IC patients will likely benefit from oseltamivir treatment as post-baseline oseltmivir resistance typically does not occur until several days after treatment initiation, and these viral species will ultimately be cleared by the immune response including in the vast majority of IC patients .
- Based on EMA's EU SmPC Section 4.4 guidance (SmPC training presentation), Section 4.4 aims to inform Healthcare professionals on specific risks only and should not be overloaded with other information pertaining to common medical practice to avoid diluting important precautions and warnings.

Given that the majority of IC patients did not develop resistance and patients that developed resistance resolved their influenza without complications, the MAH does not believe the potential for higher treatment emergent resistance in IC patients preclude the use of oseltamivir in these patients or offers a critical factor in deciding to treat or not. In fact, IC patients will likely benefit from oseltamivir treatment and additional language in the *Warnings and precautions* section of the label may over-emphasize a potential risk in this population. The MAH considers that this point is adequately addressed with the new text proposed as part of the SmPC in 'Section 5.1 Pharmacodynamic properties, Clinical studies, Oseltamivir resistance' which will, in the opinion of the MAH, better inform, physician prescribing practices.

Assessment of the MAH's response

It is known from published literature that younger children have higher incidence of treatment-emergent resistance and extended viral shedding compared with adolescents and adults. Similarly, IC subjects have already previously been shown to have higher incidence of treatment-emergent resistance than OwH patients, likely due to poorer viral clearance. However, similar to earlier trial data e.g. The Influenza Resistance Information Study (IRIS, NV20237, see Introduction of this AR), prolonged viral shedding and treatment-emergent resistance did not affect the clinical course of influenza compared with subjects without prolonged shedding or emergent resistant strains. Across all age groups in studies NV20234 and NV25719, patients with virus resistant to oseltamivir tended to have longer viral shedding, but all IC children with resistance cleared the influenza infection with no notable impact on the clinical outcomes or complications of infuenza.

The MAH proposes not to add additional information to Section 4.4 'Special warnings and precautions for use" and justified this with three reasons: Firstly, it is likely that among the prescribing community this aspect is understood. This is probably correct. Secondly, the MAH states that IC patients will likely benefit from oseltamivir treatment as post-baseline oseltamivir resistance typically does not occur until several days after treatment initiation, and these viral species will be cleared by the immune response including in the majority of IC patients. This justification is somewhat controversial in absence of robust data on clinical efficacy of oseltamivir in IC patients. Thirdly, the MAH points out that based on EMA's EU SmPC Section 4.4

guidance, Section 4.4 aims to inform Healthcare professionals on specific risks only, and should not be overloaded with other information pertaining to common medical practice to avoid diluting important precautions and warnings. The Rapporteur agrees that, according to the SmPC guideline, information on a specific risk should be given in section 4.4 only when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk. Since there are no precautions that would be known to reduce the risk of treatment-emergent resistance in IC subjects, any warning in section 4.4 on this issue is not regarded warranted.

The Rapporteur agrees with the MAH that this point is adequately addressed with the new text proposed as part of the SmPC in 'Section 5.1 Pharmacodynamic properties, Clinical studies, Oseltamivir resistance' which will better inform the prescribing practitioners.

The issue is resolved.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

RMP aspects

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

11. The 2nd Request for supplementary information

11.1 Major objections

N/A

11.2 Other concerns

Clinical aspects

None remaining.

Product Information

Please see the enclosed PI document with all remaining amendment requests by the Rapporteur.

RMP aspects

N/A

12. Assessment of the responses to the 2nd request for supplementary information

12.1 Major objections

12.2 Other concerns

Clinical aspects

Summary of the MAH's response

The MAH submitted updated Product Information.

Assessment of the MAH's response

All requested changes have been appropriately implemented in the PI. The updated PI is deemed acceptable.

There are no remaining questions.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

RMP aspects

Question

N/A. The RMP v 19.1 was accepted earlier during the procedure.

Summary of the MAH's response

Assessment of the MAH's response

Conclusion

☒ No need to update overall conclusion and impact on benefit-risk balance

Other concerns

Clinical aspects

N/A