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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Tamiflu

oseltamivir

Procedure no: EMEA/H/C/000402/P46/106

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Abbreviations

AE	Adverse event
ALL	Acute lymphoid leukaemia
AML	Acute myeloid leukaemia
BID	Bis in die (twice a day)
CHMP	Committee for Medicinal Products for Human Use
CrCl	Creatinine clearance
HSCT	haematopoietic stem cell transplant
ICU	Intensive care unit
ITT	Intention to treat patient population
ITTi	Intention to treat influenza-infected patient population
MAH	Marketing authorisation holder
OC	Oseltamivir carboxylate
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDCo	Paediatric Committee
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PKEP	Pharmacokinetic evaluable patient population
popPK	Population pharmacokinetics
RIDT	Rapid influenza diagnostic test
SAE	Serious adverse event
SD	Standard deviation
SEP	Safety evaluable patient population
TTR	Time to resolution
TTRAS	Time to resolution of all symptoms

1. Introduction

On 06 February 2019, the MAH submitted a completed paediatric study for Tamiflu, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study NV25719, *An open-label, randomized, adaptive, two-arm, multicenter trial to evaluate pharmacokinetics and pharmacodynamics of two doses of Oseltamivir (Tamiflu®) in the treatment of influenza in immunocompromised children less than 13 years of age, with confirmed influenza infection* is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Oseltamivir was provided in two forms:

- Capsules in 30 mg, 45 mg or 75 mg strengths
- Oral suspension: 6 or 12 mg/mL powder for oral suspension

The 6 mg/mL oral suspension was used in countries with regulatory approval. In countries that did not have regulatory approval for this formulation, the 12 mg/mL formulation was used instead.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study NV25719 (719) An open-label, randomized, adaptive, two-arm, multicenter trial to evaluate pharmacokinetics and pharmacodynamics of two doses of Oseltamivir (Tamiflu®) in the treatment of influenza in immunocompromised children less than 13 years of age, with confirmed influenza infection. Report No. 1084847 January, 2019.

2.3.2. Clinical study NV25719

2.3.2.1. Description

Study NV25719 was a phase IB, randomized, open-label, multicentre, parallel-group design study with two experimental treatment arms to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of two doses of oseltamivir in the treatment of influenza in IC paediatric patients less than 13 years of age.

Rational for study design: For 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. Although this introduced

potential bias in terms of safety assessments (particularly AE reporting), because the primary aim of the study was to evaluate PK/PD, which are objective assessments, it was deemed that blinding was not practical and the impact of not blinding on the study results was considered minimal.

2.3.2.2. Methods

Objective(s)

- 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.

Study design

Immunocompromised children below 13 years of age, with confirmed influenza infection, were randomized (1:1) into one of two experimental treatment groups: conventional oseltamivir dose or 3x conventional oseltamivir dose (Table 1). Treatment assignment was randomized through an interactive voice/Web response system (IxRS), with the exception of children <1 year of age who would be assigned to the conventional dose group (partial forced randomization).

Table 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).

Oseltamivir was orally administered at a dose of 30 to 225 mg BID for 5 to 20 days, depending on age, weight cohort, and illness duration (duration of viral shedding). The first dose (on Day 1) and the dose around the sparse PK sampling were required to be taken in the clinic. All remaining doses were administered at home if the patient was not hospitalized. Dosing continued until the absence of viral shedding, demonstrated by a negative polymerase chain reaction (PCR) result, up to a maximum duration of 20 days.

If viral shedding persisted after Day 20, patients discontinued study treatment and received standard of care treatment for that region.

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 /Sample size

The study population was 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 [RIDT]) 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 calculations were 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.

It was anticipated that the majority of patients would be inpatients during the study, given their IC status and significant associated comorbidities. However, some patients may have been treated as outpatients (e.g., patients several months after HSCT) entirely or could have been discharged during the study if they were well enough.

For outpatients, the study procedures (e.g., nasal swabs, dosing, AE check) were carried out by the appropriately trained person (e.g., study nurse, parent, or patient) and these data were recorded in a study diary provided.

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 2). Infants less than one year of age would receive an oseltamivir dose of 3 mg/kg (equivalent to conventional dose). All available Tamiflu formulations (tablets and oral solution, see Section 2.2 of this AR) could be used.

Table 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).

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_{0-12}, 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.
- ***Safety:*** Adverse events (AEs), Serious AEs (SAEs), influenza-associated complications (length of hospital stay, length of stay in intensive care unit (ICU), need for ventilator support and length of time on ventilator, frequency and duration of oxygen use, frequency of secondary bacterial infection, mortality) and laboratory evaluations for creatinine clearance (CrCl).

Statistical Methods

No formal hypothesis testing calculations were performed. The main purpose of this study was 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.

2.3.2.3. Results

Recruitment/ Number analysed

Patients were enrolled over 5 northern hemisphere influenza seasons and 5 southern hemisphere influenza seasons (years 2014 – 2018). The study was based in the United States, Canada, Mexico, the

European Union (Northern hemisphere), and South America and South Africa (Southern hemisphere) at approximately 50 sites.

Baseline data

A total of 66 patients were screened, of which 30 patients were enrolled into the study and 36 patients failed screening (35 'flu negative' on RIDT and 1 failed due to withdrawn consent). 15 were randomized into the conventional dose group and 15 to the 3x conventional dose group.

In the ITT population, the majority of patients were white (73.3%); 86.7% in the 3x conventional vs. 60% in the conventional group. The proportion of males (70.0%) was higher than females (30.0%), similarly in both treatment groups. All 30 patients received at least one dose of oseltamivir and 27/30 patients (14 in the conventional dose group and 13 in the 3x conventional dose group) completed the study. Three (3) patients discontinued the study and 4 patients discontinued study treatment (no patient withdrew from the study due to an AE).

In the ITT population, 20 (71.4%) of subjects had acute lymphoid leukaemia (ALL); 4 had Non-Hodgkin's lymphoma; 4 had acute myeloid leukaemia (AML), 2 (13.3%) in the 3x conventional dose group had solid tumour malignancies, which did not meet the study inclusion criteria. Two patients (13.3%) in the conventional dose group and none in the 3xconventional dose group had an HSCT.

The mean age of the patients was 5.6 years (range: 1 to 12 years) and the vast majority of the patients had haematological malignancies and were receiving induction chemotherapy. No infants below age of 1 were recruited. The patients were older in the conventional dose group (mean 6.9 vs. 4.3 years).). There were protocol deviations in 43.3% of patients, mostly due to a procedure or assessment not done or performed on wrong day.

In the ITT population, 59% of patients were infected with influenza type A (4 and 9 patients in the conventional and 3x conventional dose groups, respectively) and 41% were infected with influenza type B (7 and 2 patients in the conventional and 3x conventional dose groups, respectively). Of the patients infected with influenza type A, 7 were infected with the H3N2 subtype (2 and 5 in the conventional and 3x conventional dose groups, respectively) and 6 were infected with the H1N1 subtype (2 and 4 in the conventional and 3x conventional dose groups, respectively, Table 12). There were 8 patients (4 each in the conventional and 3x conventional dose group) that were not infected with influenza. The ITTi population included 20 patients who were central laboratory RT-PCR positive for influenza infection (11 in the conventional dose group and 9 in the 3x conventional dose group), while the PKEP population included 26 patients (14 in the conventional dose group and 12 in the 3x conventional dose group).

Close to all subjects also received concomitant medications (analgesics, non-steroidal anti-inflammatories, sulphonamides, cephalosporins, steroids, 5-HT3 antagonists, antimetabolites and antifungal agents). Three subjects in both study groups received concomitant treatment for malignancy.

Pharmacokinetics

A total of 26 patients (14 in the conventional dose group and 12 in the 3x conventional dose group) with PK samples were available for the analysis. PK samples were collected (at steady-state) at pre-dose, 1.5 hours, 4 hours, and 8 hours post-dose time points.

Concentrations of oseltamivir were approximately 2 to 4 times higher in the 3x conventional dose group than the conventional dose group (Figure 1). Concentrations of OC were approximately 2 times higher in the 3x conventional dose group than the conventional dose group (Figure 2).

Steady-state mean exposure metrics (C_{max} and AUC_{0-12h}) for oseltamivir were 2 to 2.5 times higher in the 3x conventional dose group than those in the conventional dose group; steady-state mean exposure metrics (C_{max} and AUC_{0-12h}) for OC were approximately 2 times higher in the 3x conventional dose group than the conventional dose group.

Figure 1 Mean (SD) Concentration-Time Profiles of Oseltamivir Concentrations Following Multiple Oral Dose Administration of Oseltamivir by Treatment Group (Linear scale)

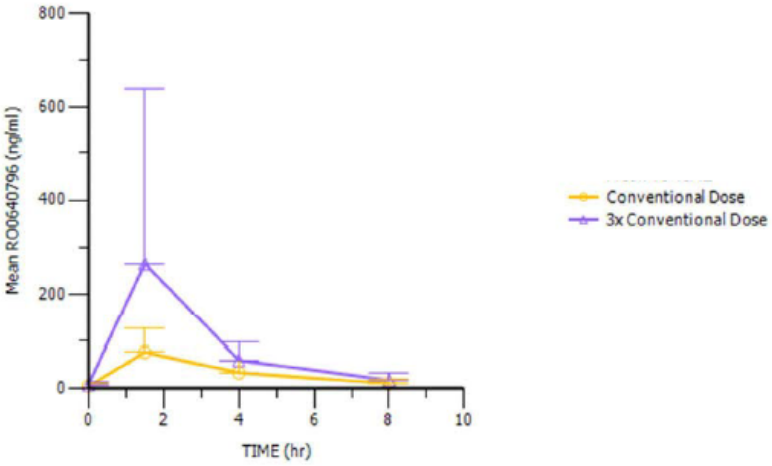
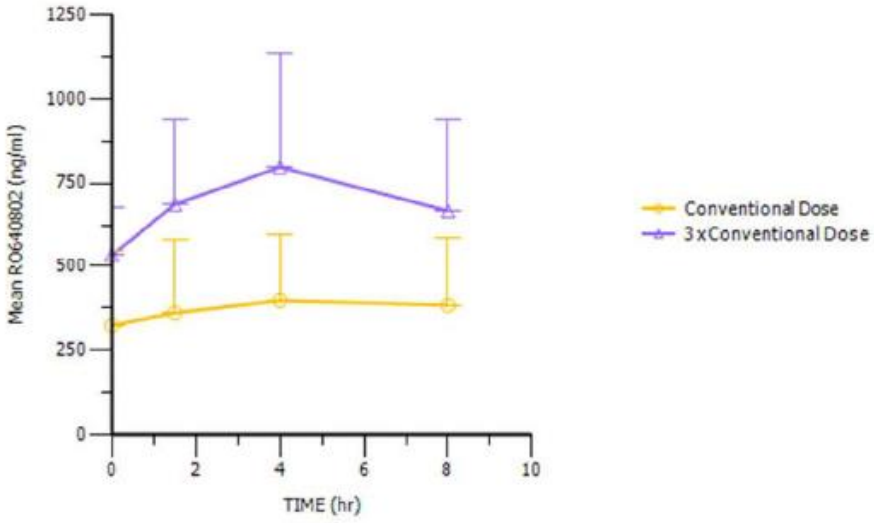


Figure 2 Mean (SD) Concentration-Time Profiles of OC Concentrations Following Multiple Oral Dose Administration of Oseltamivir by Treatment Group (Linear scale)



PopPK analysis, based on a multi-compartment model, showed that the steady-state mean exposure metrics for oseltamivir were 2 to 2.5 times higher in the 3x conventional group than those in the conventional dose group (C_{max} [61.9 ng/mL] conventional vs [153 ng/mL] 3x conventional] and $_{AUC0-12h}$ [265 ng/mL*hr] conventional vs [568 ng/mL*hr] 3x conventional). Similarly, the steady-state mean exposure for OC was approximately 2 times higher in the 3x conventional group than in the conventional group (C_{max} [434 ng/mL] conventional vs [852 ng/mL] 3x conventional], C_{min} [276

ng/mL] conventional vs [486 ng/mL] 3x conventional] and $AUC_{0\text{-}12h}$ [4350 ng/mL*hr] conventional vs [8210 ng/mL*hr] 3x conventional). As none of the established oseltamivir PK models indicated non-linearity, the apparent non-linearity of exposure observed in this study is likely to be related to an imbalance of covariates (age/weight and CrCl) in the two dosing groups. Study effect on CL/F was estimated at 0.901 (95% CI: 0.783, 1.02) while study effect on CLM/F was estimated at 0.887 (95% CI: 0.805, 0.968).

Note: The validity of the PopPK analysis could not be assessed in the current Article 46 Assessment Report, as no modelling report is included in the submission. A modelling report is however not requested, as a dedicated population PK report, supplemented with additional data from IC patients <18 years of age enrolled in a prior study (NV20234), will be prepared by the MAH and included in the subsequent type II variation.

Pharmacodynamics

Viral resistance to oseltamivir

None of the patients in the study had baseline oseltamivir viral resistance. There were 3 patients with post-baseline oseltamivir viral resistance: 1 in the conventional dose group and 2 in the 3xconventional dose group. Overall, given the descriptive statistical summaries and graphical presentations, there was no relationship between increased dose of oseltamivir and a decrease in incidence of patients with oseltamivir resistant virus.

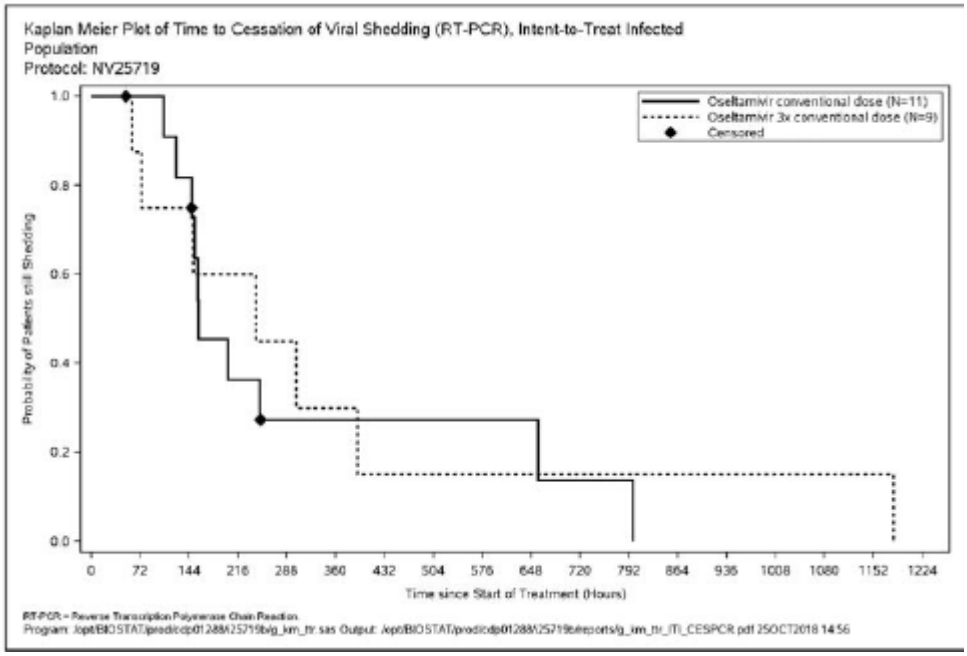
All influenza resistant viruses were detected in patients with influenza A (2 with the H1N1 subtype and one with the H3N2 subtype) and showed both genotypic and phenotypic resistance. One patient with post-baseline resistance in the 3x conventional dose group had persistent viral shedding1 and shed virus until Day 51, measured by RTPCR.

PD

The observed range of peak viral titer by culture and peak viral load by RT-PCR was similar between the dose groups.

The median time to cessation of viral shedding by culture was longer in the conventional group than the 3x conventional group (109.2 vs. 75.9 hours); conversely, the median time to cessation of viral shedding by RT-PCR was shorter in the conventional dose group compared to the 3x conventional dose group (157.2 vs. 242.3 hours) (Figure 3).

Figure 3 Kaplan-Meier Plot of Time to Cessation of Viral Shedding (RTPCR, ITTi population)



PK/PD

The time to cessation of viral shedding, as measured by culture and PCR, was similar between the exposures groups for the first part of the study duration; as the study progressed, the time to cessation of viral shedding was shorter in the low exposure group, driven by patients with post-baseline oseltamivir viral resistance and the intervals between assessments.

There was no observed relationship between area under the viral titre/load curve or peak viral titre/load and exposure.

There was no observed relationship between exposure and treatment-emergent resistance.

Time-to-event analyses

Kaplan-Meier curves showed that the time to cessation of viral shedding, determined by culture and RT-PCR, were similar for the first part of the curve between the low and high exposure groups for C_{min} of OC (Figures 4 and 5). For the second part of the curve, the time to cessation of viral shedding was shorter in the low exposure than the high exposure group. However, this part of the curve is mostly driven by patients with treatment-emergent resistance (1 patient in the low exposure group and 2 patients in the high exposure group) and the intervals between assessments. The exclusion of patients with post-baseline oseltamivir viral resistance from the analysis removed the differences between the treatment groups with a median of 157.1 hours (95% CI: 106.2, 248.1) in the conventional dose group and 150.7 hours (95% CI: 60.4, 302.2) in the 3x conventional dose group.

Figure 4 Kaplan-Meier Plot of Time to Cessation of Viral Shedding by Culture by Exposure Groups, defined by the Median of the Predicted Oseltamivir Carboxylate Steady-State C_{min}

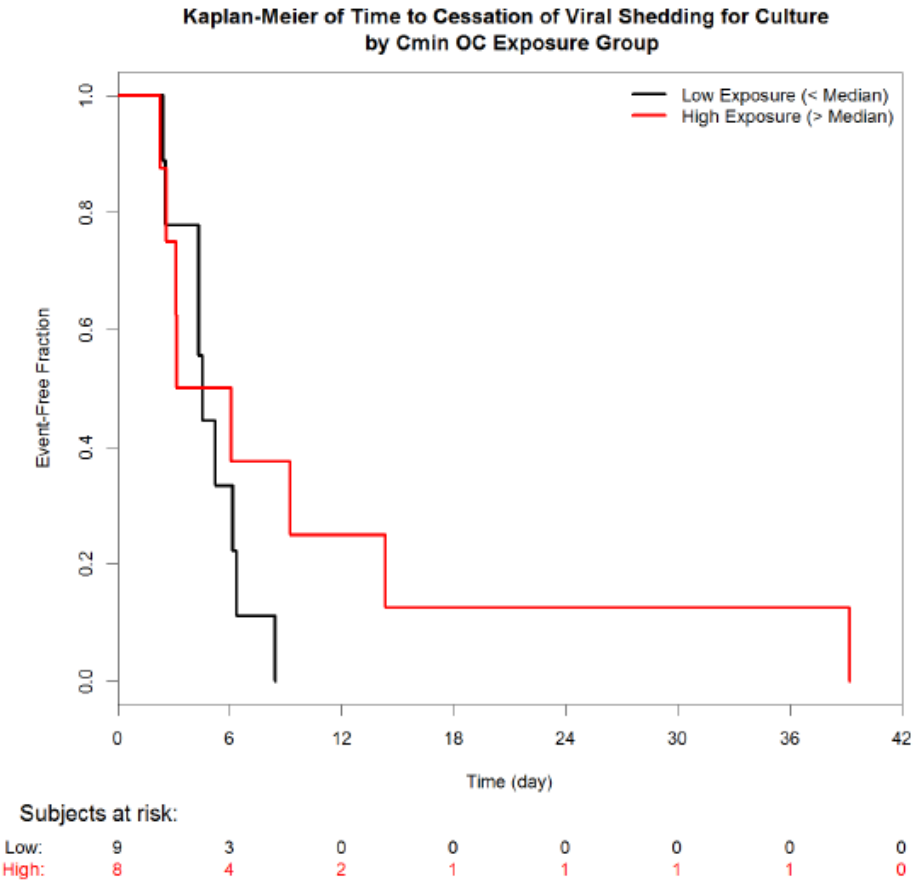
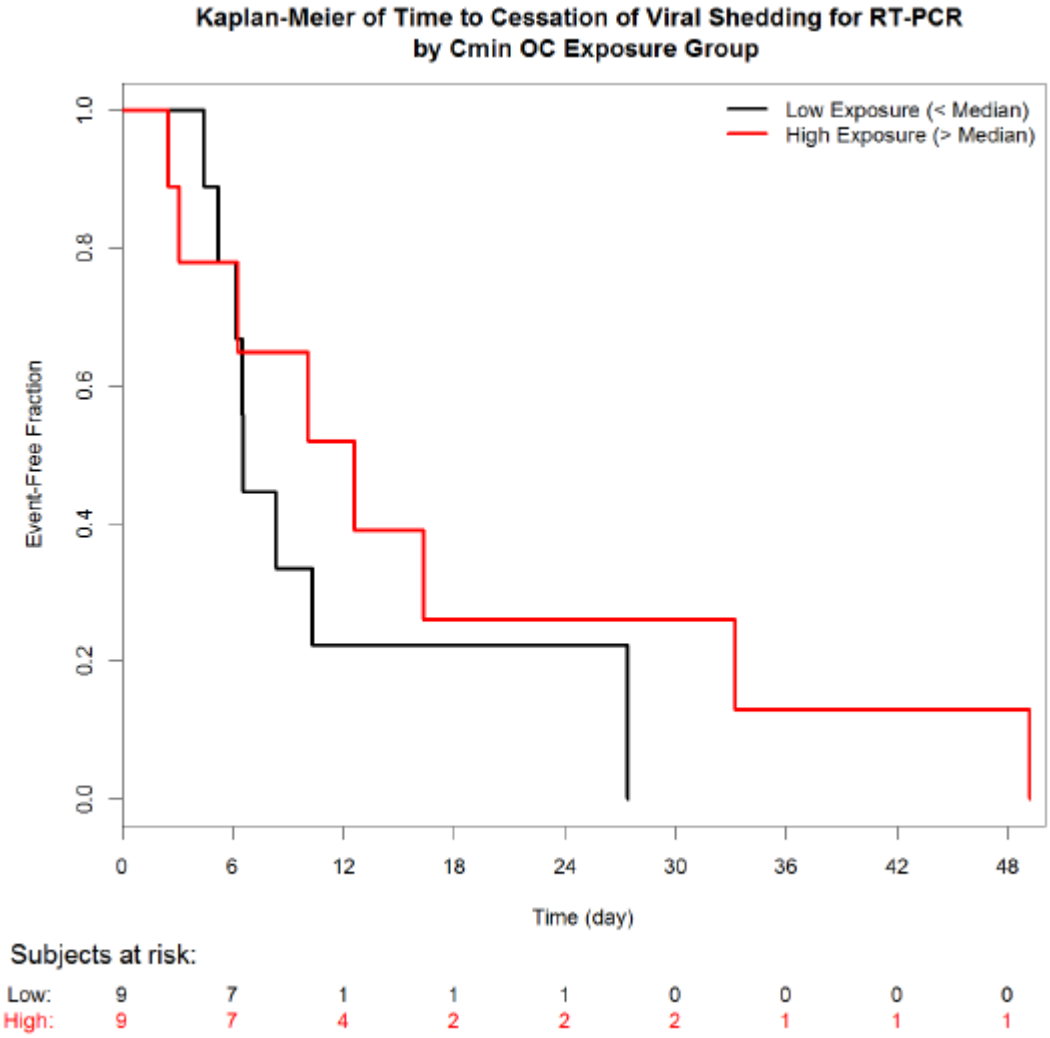

Kaplan-Meier of Time to Cessation of Viral Shedding for Culture
by Cmin OC Exposure Group
Low Exposure (< Median)
High Exposure (> Median)
Event-Free Fraction
0.0
0.2
0.4
0.6
0.8
1.0
0
6
12
18
24
30
36
42
Time (day)
Subjects at risk:
Low: 9 3 0 0 0 0 0 0
High: 8 4 2 1 1 1 1 0

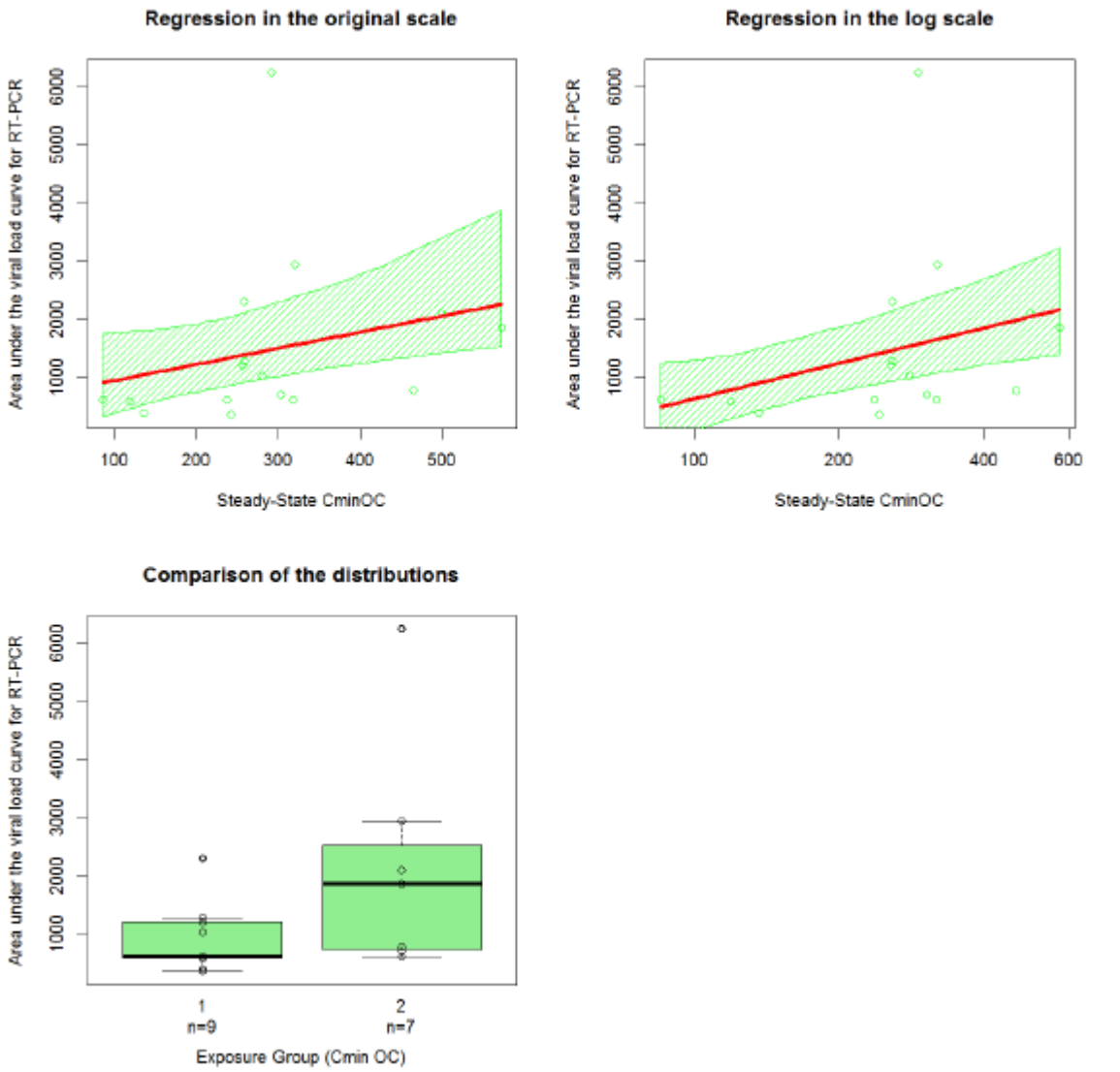
Figure 5. Kaplan-Meier Plot of Time to Cessation of Viral Shedding for RTPCR by Exposure Groups, defined by the Median of the Predicted Oseltamivir Carboxylate Steady-State Cmin



Viral titre/Load measures

A decrease was observed in the exposure-area under the viral load curve in the low exposure group compared to the high exposure group by RT-PCR (Figure 4). However, this is likely due to the variability of the data and the limited sample size. Overall, based on graphical evaluation and regression analyses, there were no relationships observed between the independent variable of exposure (C_{min} of OC) and dependent variables, including the continuous endpoints of area under the viral titre/load curve and peak viral titre/load for culture and RT-PCR.

Figure 4 Area under the Viral Load Curve by RT-PCR vs. Predicted Oseltamivir Carboxylate Steady-State C_{min}



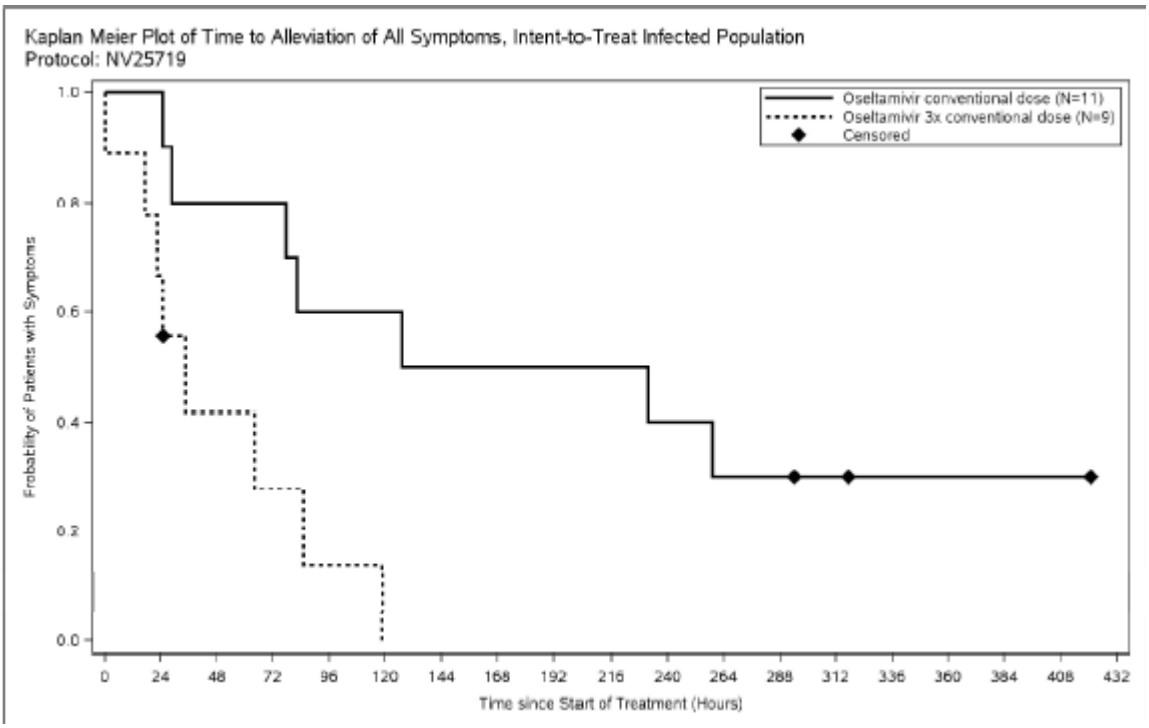
Source: CSR_Res_vs_CminOC_PCRAUCVT.png

1 = low exposure group; 2 = high exposure group

Efficacy results

An overview of these findings for time to resolution of all symptoms (TTRAS, figure 5), time to resolutions (TTR) of fever and the duration of treatment (in the ITTi population, 11 patients in the conventional and 9 patients in the 3x conventional dose groups) is presented below. The overall interpretation of these data is limited by the small sample size. The severity of baseline influenza symptom scores in both treatment groups was similar.

Figure 5 Kaplan-Meier Plot of the Time to Resolution of All Symptoms (ITTi population)



- The median TTRAS was longer in the conventional dose group than the 3x conventional dose group (179.4 hours vs. 34.5 hours).
    - After excluding patients with post-baseline oseltamivir viral resistance from this analysis, the median TTRAS decreased in the conventional dose group (127.2 vs. 179.4 hours) and remained the same in the 3x conventional dose group (34.5 hours).
- The median TTR of fever in patients with baseline fever was 17.1 hours longer in the conventional dose group than the 3x conventional dose group (28.4 vs. 11.3 hours), but only 8 patients (4 patients in each group) had fever at baseline.
- The median duration of treatment was shorter in the conventional dose group than the 3x conventional dose group (251.9 hours vs. 360.5 hours).
- There were 12 patients (6 patients in each group) who initiated treatment less than 48 hours from symptom onset and the median time from symptom onset to initiation of treatment was similar between the groups (44.5 and 44.0 hours in the conventional and 3x conventional dose groups, respectively).

Safety results

Safety analyses were based on the safety population that included all 30 patients randomized to the study who received at least one dose of oseltamivir, regardless of whether they had any follow-up assessments, and were classified according to the treatment actually received. An overview of safety in patients in the safety population is summarized below:

- Overall, the number of patients who experienced at least one AE was similar between the two groups (12 patients [80.0%] in the conventional dose group and 13 patients [86.7%] in the 3x conventional dose group, Table 33).

- The three most frequently reported AEs by SOC were Gastrointestinal Disorders, Infections and Infestations and Blood and Lymphatic System Disorders; the three most common AEs were vomiting, diarrhoea and pyrexia.
- There were 11 patients (73.3%) in the conventional dose group and 13 patients (86.7%) in the 3x conventional dose group who experienced on-treatment AEs. The three most common on-treatment AEs were vomiting, anaemia and diarrhoea.
- The majority of AEs were mild in intensity; more patients reported AEs as severe in the conventional dose group than the 3x conventional dose group (4/12 [33.3%] vs.1/13 [7.7%]).
- One on-treatment AE in the conventional dose group and four on-treatment AEs in the 3x conventional dose group were considered related to oseltamivir.
- There were no deaths during the study and no AEs leading to withdrawal from treatment or the study.
- Overall, 7 patients in the conventional dose group and 5 patients in the 3xconventional dose group experienced at least 1 SAE and none of the SAEs were considered related to oseltamivir. Three of the seven SAEs were on treatment: two in the conventional dose group and one in the 3x conventional dose group.
- Overall, there were no clinically significant changes in CrCl from baseline to postbaseline.
- Two hospitalizations occurred in the conventional dose group before baseline. During the study, there were 8 hospitalizations in the conventional dose group, with a median duration of 8.5 days (range: 6 to 14 days) and 7 hospitalizations in the 3x conventional dose group with a median duration of 5.0 days (range: 2 to 8 days).
- None of the patients were admitted to the ICU or required the use of a ventilator.
- There were 2 cases of supplementary O2 use in patients hospitalized after start of study treatment, 1 in the conventional dose group (duration of 8 hours) and 1 in the 3x conventional dose group (duration of 1 hour). There was one additional case of supplementary O2 use for a duration of 48 hours in a patient in the conventional dose group who was hospitalized before the start of study treatment.
- Two patients in the 3x conventional dose group reported secondary bacterial infections.
- Safety analyses by exposure did not reveal any new safety concerns.

There were no new safety signals associated with oseltamivir treatment for influenza in these severely IC patients receiving chemotherapy for haematological malignancies. Safety was in line with the known profile and both doses were well tolerated.

2.3.3. Discussion on clinical aspects

The exposure to oseltamivir was 2 to 2.5 times higher when a triple dose of oseltamivir, as opposed to the conventional dose, was administered for at least 5 days, followed by a 15-day adaptive dosing period. OC exposure metrics (C_{max} and AUC_{0-12h}) were approximately 2 times higher in the 3x conventional dose group compared to the conventional dose group. However, based on the linear and dose-proportional PK properties of oseltamivir, 3 times higher exposure metrics in the 3x conventional dose group compared to the conventional dose group were expected. The MAH proposes that the lower exposure found in the 3x conventional dose group is likely due to unbalanced baseline demographics

and characteristics between the dose groups. In the conventional dose group patients were older and there was one patient with impaired renal function CrCl [62 mL/min/1.73m2] which could have resulted in a higher exposure than expected in this group, and thus deriving into the less than 3 times exposure in the 3x conventional group. At this stage, a detailed PK analysis of the results is not performed, as the MAH intends to submit a dedicated population PK report, supplemented with additional data from IC patients <18 years of age enrolled in a prior study (NV20234), for the subsequent type II variation.

No notable exposure-response relationships were observed in the PK/PD analyses. No relationship between exposure and area under the viral titre/load curve and peak viral titre/load were seen. Neither any relationship was seen between treatment-emergent resistance and exposure: increased exposure of OC was not associated with a decrease in virological parameters or incidence of patients with oseltamivir resistant virus. The incidence of post-baseline oseltamivir viral-resistance was similar in both dose groups; a total of 3 patients with influenza A were found with oseltamivir viral resistance post-baseline, 1 patient in the conventional dose group and 2 patients in the 3x conventional dose group.

As in earlier studies with oseltamivir, patients with post-baseline viral resistance also had prolonged viral shedding. The median time to cessation of viral shedding by RT-PCR was 157.2 hours (95% CI: 125.3, 658.0) in the conventional dose group and 242.3 hours (95% CI: 60.4, 392.1) in the 3x conventional dose group. However, this part of the curve was driven by patients with treatment-emergent resistance (1 patient in the low exposure group and 2 patients in the high exposure group) and the intervals between assessments). The median time to cessation of viral shedding measured by RT-PCR was similar between the two dose groups following exclusion of patients with post-baseline oseltamivir viral resistance (150 and 157 hours, respectively). The median time to resolution of all symptoms was longer in the conventional dose group than the 3x conventional dose group (127 vs. 35 hours). Some of the symptoms reported in this study as associated with influenza may have been confounded with side effects from other concomitant treatments and the malignancies suffered by these patients.

Historical data do not support a crucial role of the duration of viral shedding on clinical or epidemiological outcomes. In immunocompromised adults (in study NV20234) a double dose vs. conventional dose, both administered over 10 days, was associated with shorter duration of viral shedding. However, shorter duration of viral shedding did not result in better clinical outcome in that study. As the double daily dose was somewhat less well tolerated than the conventional dose in adults, the recommended posology includes conventional daily dose, but the recommended duration of therapy is 10 days (as there are no data on the conventional 5-day course of oseltamivir in immunocompromised adults).

It is noteworthy that extended duration of viral shedding was shown to be inversely associated with age in the Influenza Resistance Information Study (IRIS, NV20237; a prospective, multicentre, information-gathering study, comprising virological surveillance and assessment of clinical outcomes, which enrolled patients over a 7-year period. Overall, 4553 patients were enrolled, of whom 2578 treated with oseltamivir.). Delayed viral clearance was highly significantly associated with treatment-emergent resistance. On the other hand, previous data from IRIS also indicate that treatment-emergent resistance didn’t impact the clinical course of influenza. In IRIS, both naturally-occurring and treatment-emergent viral strains with the H275Y mutation were detected overall at a low level. There is no confirmation that circulating resistant strains (that were detected in IRIS at baseline in some patients) would have originated from treatment-emergent resistance as opposed to spontaneous mutations.

Immunocompromised patients are known to more often have delayed viral clearance of influenza than non-immunocompromised patients. The paediatric immunocompromised patients in study NV25719 are therefore expected to have more frequently extended duration of viral shedding if compared with adults and/or non-immunocompromised patients in general. However, based on former studies, viral shedding of treatment-emergent viral strains does not seem to be crucial either for the course of influenza in an individual patient nor for transmission further of the oseltamivir-resistant viruses. There were no new safety signals and the nature and severity of AEs showed no remarkable findings and were consistent with the drug's established safety profile, the typical complications of influenza infection, or the associated hematologic malignancies and chemotherapy received by this patient population. Safety analyses by exposure did not reveal any new safety concerns.

The results may indicate that a higher dose would be more efficacious for IC children, with increased efficacy and similar safety profile compared with the conventional dose. More profound assessment on the appropriate dose for this patient group will be performed during the assessment of the upcoming variation procedure.

3. CHMP's overall conclusion and recommendation

The currently submitted final CSR for the study NV25719 is considered acceptable. The applicant is reminded that the compliance check is to be performed by the PDCO. No new safety signals were seen in study NV25719. The triple dose of oseltamivir as compared with conventional dose seemed to be more efficacious.

However, as no new safety signals were obvious in this CSR, which would require immediate changes to the SmPC or RMP, the detailed assessment of this CSR will not be done here in the context of Article 46 submission.

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a variation prior any conclusion on product information amendments is made.

4. Additional clarification requested

N/A