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EMA/333490/2018
Human Medicines Development and Evaluation

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Tamiflu

oseltamivir

Procedure no.: EMA/H/C/402/P46/105

Note

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

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1. Introduction

On 8 Dec 2017, the MAH submitted a completed paediatric study for Tamiflu, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The target population included immunocompromised (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).

These data are also submitted as part of the post-authorisation measures MEA 75 and MEA102.

- MEA75: "To elucidate clinical significance of new resistance information in IC patients, the MAH should provide results and final reports from study NV20234 (final CSR by end of November 2018)".
- MEA102: "Immunocompromised patients - The MAH should review annually the safety of oseltamivir in IC patients up to final submission of the clinical trial NV20234 study report (treatment) as flu and season permits. The MAH should provide the efficacy data after finalization of NV20234 (Due date: Annually in December/ Final CSR by end of November 2018)."

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

NV20234 – A double blind, randomized, stratified, multicenter trial evaluating conventional and double dose oseltamivir in the treatment of immunocompromised patients with influenza is part of a clinical development program.

Information on the pharmaceutical formulation used in the study

The Investigational Medical Product in this study was oseltamivir dry powder (reconstituted to a concentration of 12 mg/mL; it was confirmed that the concentration of 6mg/mL was not used in the study) or 75 mg capsules and matching placebo.

2.2. Clinical aspects

2.2.1. Introduction

The efficacy and safety of oseltamivir in influenza treatment and prevention in influenza-infected otherwise healthy patients and at-risk patients (those with chronic cardiac and/or respiratory diseases) has been established in a series of clinical studies.

Prophylaxis of influenza with oseltamivir in immunocompromised (IC) patients has previously been investigated in study NV20235, 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 (n=475) and children (n=18) of one year of age and older. The study compared the conventional dose of oseltamivir with placebo. The study was assessed within variation II/0069 (Commission decision 15 March 2010). No significant prophylactic effect against

influenza in the investigated IC population with a high vaccination rate was demonstrated in that study; therefore, the benefit/risk of oseltamivir for the prophylaxis of influenza for IC patients remained uncertain. However, the safety profile was similar in IC population as in otherwise healthy patients.

Clinical case reports and small observational patient series reports regarding oseltamivir treatment for IC subjects with influenza are briefly reviewed by the MAH in the Clinical Overview dated 14 Nov 2017. The previous data indicate good tolerability of oseltamivir (by standard dose) in IC adults and children with different background conditions. One concern has been prolonged viral shedding in IC patients treated with oseltamivir, with subsequent emergence of resistance to neuraminidase inhibitors.

The final primary objective of conducting study NV20235 was to evaluate safety and resistance 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. Secondarily, the study aimed to evaluate the efficacy of conventional and double dose of oseltamivir in IC patients.

Including a placebo control arm in the study was considered unethical for the high risk population. The development of resistance following treatment with oseltamivir (one of the primary objectives of the study) was considered an objective assessment (determined by laboratory tests) and unlikely to be impacted by the absence of a placebo arm.

The pivotal registration trials for oseltamivir in healthy adults with influenza had three treatment arms, two active (75 mg and 150 mg) and one placebo. Both treatment arms were found to be significantly better than placebo. No statistical comparisons were made between the two active treatment arms. Evaluation of the results in the two active treatment arms did not reveal any clinically meaningful difference. However, the proportion of subjects shedding virus on day 4 (3 days after the start of treatment), suggested a possible dose response relationship. Because defective immune-mediated virus clearance in IC patients treated with antivirals can result in a higher incidence of selection of drug-resistant viruses, it was decided to use both the conventional and high dose arm for this study. A longer duration of treatment was chosen because a large retrospective study has shown that the median duration of viral shedding of 7 days was greater for HSCT recipients than that seen in the healthy children, adult and elderly population with influenza.

The NV20234 study protocol was amended five times during the course of the study. The primary endpoint was changed during the course of the study. There are two co-primary endpoints for this study – safety/tolerability and resistance to oseltamivir. “Time to resolution of all influenza symptoms” was the primary endpoint in versions A and B of the protocol. However, this endpoint was relegated to a secondary endpoint. The rationale for the change of primary endpoint is stated to be, firstly, that originally response to placebo in pivotal oseltamivir registration trials in the healthy adult population with influenza was chosen as a control in lieu of a placebo arm in the current trial; as a placebo arm was considered unethical. In order to do this, the protocol was designed to be similar to that in the pivotal registration trials, only patients with influenza symptoms for <48 h were to be enrolled. There were several limitations to this original approach, the main being in healthy subjects the influenza virus faster than in IC subjects. The need to enroll patients within 48 hours of the onset of influenza resulted in several patients being ineligible for screening. This required modification of the inclusion criteria to allow patients who had been symptomatic with influenza for more than 48 hours to be enrolled in the study. This imposed an even greater limitation on the ability to compare data between healthy subjects on placebo enrolled within 48 hours from pivotal registration trials with IC subjects who received oseltamivir within 96 hours.

Furthermore, since the original study design, and particularly following the pandemic, there has been increasing evidence for efficacy in the immunocompromised population. National guidelines now recommend the use of anti-virals for the treatment of influenza in the transplant population. In immunocompromised patients, however, there remains the risk for resistance. It was therefore decided to revise the primary objective of this study to the descriptive characterization of safety, tolerability and resistance.

Other amendments included e.g. the following: inclusion criteria were widened to cover more background IC conditions to enhance recruitment; sequencing of the neuraminidase (NAI) and hemagglutinin (HA) genes was extended from original plan; PK assessment reference to oseltamivir was removed as only oseltamivir carboxylate (OC) was evaluated in plasma samples; etc.

The MAH submitted a final report for:

- NV20234 – A double blind, randomized, stratified, multicenter trial evaluating conventional and double dose oseltamivir in the treatment of immunocompromised patients with influenza. Report No. 1078105. December 2017.

2.2.2. Clinical study

NV20234 – A double blind, randomized, stratified, multicenter trial evaluating conventional and double dose oseltamivir in the treatment of immunocompromised patients with influenza.

Description

Methods

Objectives

Primary Objective:

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

Secondary Objectives:

To evaluate the effects of conventional and double dose oseltamivir in IC patients on:

- The population pharmacokinetics 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).
- To explore the relationship of metrics of exposure (e.g., area under the concentration-time curve [AUC], trough plasma concentration [Cmin]) to relevant pharmacodynamic (PD) endpoints.

Study design

NV20234 was a Phase III, double-blind, randomized, stratified, multicenter 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.

The study collected data from 228 patients between 4 February 2008 and 02 May 2017. There were 62 active study centres in 19 countries: USA (16), South Africa (7), Mexico (5), Lithuania (4), Italy (4), Belgium (3), Spain (3), Brazil (3), Argentina (3), Israel (3), Estonia (2), Guatemala (2), Ukraine (1), Latvia (1), Poland (1) Bulgaria (1), Chile (1) Colombia (1), and Hungary (1).

IC patients, who developed an influenza-like illness and tested positive with a rapid diagnostic test, polymerase chain reaction (PCR), or viral culture for influenza, were enrolled during the influenza season. After providing informed consent, eligible patients were randomized to receive oseltamivir twice daily for 10 days at one of two doses: conventional dose or double dose (double the conventional dose).

Enrolled patients were randomized 1:1 to conventional oseltamivir or double dose oseltamivir, stratified according to 4 binary factors: transplant status (SOT, HSCT or yes, no); time between onset of influenza symptoms and treatment start (≤24 hours, >24 hours or up to 96 hours, ≤48 hours, >48 hours); influenza vaccination status for current influenza season (yes, no), and age (≤12 years, >12 years).

Two follow-up visits were scheduled approximately 5 and 30 days after the last dose. Blood samples for the characterization of oseltamivir and OC pharmacokinetics using a sparse sampling strategy were collected (from all patients who opted to participate in the PK assessments) on Day 6, or any day after the 11th dose.

For pharmacodynamic (PD) and virology assessments, two nasopharyngeal swabs and one throat swab were collected from individuals at each visit as specified in the schedule of assessments. All swabs were sent to a central laboratory for RT-PCR (reverse transcription polymerase chain reaction), viral culture testing, assessment of influenza virus shedding, and viral resistance monitoring. At the end of treatment (EOT, Day 11), a rapid diagnostic test was permitted for confirmation of ongoing influenza.

Participation in pharmacokinetic (PK) assessments was not compulsory. Blood samples for the characterization of oseltamivir and OC pharmacokinetics using a sparse sampling strategy were collected from all patients who provided additional consent to participate in the PK assessments.

Enrolled patients recorded influenza signs and symptoms on a diary card which was dispensed on Study Day 1. Adult and adolescent patients (>13 years and older) completed a symptom score card comprising 7 symptoms of influenza. Parents/guardians of children <13 years and younger completed a diary comprising 18 symptoms of influenza based on the Canadian Acute Respiratory Illness Flu Scale (CARIFS).

Study population /Sample size

Immunocompromised 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). Patients with severe hepatic decompensation were excluded.

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

- Primary immunodeficiency at risk for viral infections (see protocol Appendix 6) 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
    - Hematologic malignancies (ALL, lymphomas; CLL, small lymphocytic lymphoma; hairy cell leukemia, myelodysplastic syndromes; peripheral T cell and NK neoplamsms, Hodgkin's disease; AML, CML)) OR
    - Systemic (e.g., enteric, SC, IM, or IV) immunosuppressive therapy, irrespective of medical indication, started at least 12 weeks prior to, and ongoing at the time of first dose of study drug (see protocol Appendix 8)

The study was designed to enrol approximately 166 patients (83 patients per treatment group); final enrolment was 228 patients, with 113 patients randomized to the conventional dose group and 115 patients to the double dose group.

Treatments

Oral doses of oseltamivir, conventional or double dose, administered twice daily (BID) over 10 days.

Outcomes/endpoints

SAFETY: Adverse events (AEs), clinical laboratory evaluations, physical examination, vital signs, and rejection and/or graft versus host disease

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

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

Statistical Methods

The SAP was updated several times together with protocol amendments.

The sample size was chosen to provide an adequate number of patients to estimate the development of resistance (genotypic and/or phenotypic, co-primary endpoint) with reasonable precision. Assuming that 90% of enrolled patients would have laboratory-confirmed influenza, there would be 75 patients in each treatment arm in the population evaluable for the development of resistance. Table 1 shows the 95% Pearson-Clopper CIs that would result with a sample size of 75 patients in a treatment arm if certain rates of resistance are observed in the study.

Table 1.

Observed Rate (%)	95% Confidence Interval
0.0	0.0, 4.8
1.3	0.0, 7.2
2.7	0.3, 9.3
5.3	1.5, 13.1
10.7	4.7, 19.9

A total of 83 patients evaluable for the assessment of safety (co-primary endpoint) were to be enrolled per treatment arm. This number of patients would provide estimates of adverse event rates with similar precision.

Five patient populations were used for the analysis of data from this study:

- *Safety analysis population*: all patients who received at least one dose of study drug and had a safety assessment performed post randomization. All safety variables were summarized and presented in tables.
- *Intent-to-Treat (ITT) Population*: All patients randomized, excluding non-IC patients; used mainly to summarize efficacy endpoints for the purposes of sensitivity analyses.
- *Intent-to-Treat Infected (ITTi) Population*: All patients randomized and with central laboratory confirmation of influenza infection, excluding patients infected with oseltamivir-resistant influenza at baseline and non-IC patients. The ITTi population was the protocol-defined population to summarize all efficacy and resistance endpoints.
- *Modified Intent-to-Treat Infected (mITTi) Population*: 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 and excluding non-IC patients. The mITTi population was used as the primary analysis population for resistance endpoints, and was used to summarize all efficacy endpoints in addition to the ITTi population, as it was expected to render the least biased estimates.

- *Pharmacokinetic evaluable patient (PKEP) population* comprised all patients in the ITT population who had at least one valid post-dose drug concentration measurement at a scheduled visit timepoint. Patients could be excluded from the PKEP population if they significantly violated the inclusion or exclusion criteria, deviated significantly from the protocol, or had unavailable or had incomplete data that could have influenced the PK analysis. Non-IC patients were excluded.

Safety was summarized descriptively for adult patients ≥18 years of age and then separately for children aged <18 years (adolescents and children <13 years) in the Safety population.

The ITTi population was the protocol-defined population to summarize all efficacy and resistance endpoints. The mITTi population was the SAP-defined primary analysis population for resistance endpoints, and was used was to summarize all efficacy endpoints in addition to the ITTi population.

For resistance analyses, the proportion and associated exact Clopper-Pearson 95% CIs of patients with post-baseline genotypic or phenotypic resistance were summarized by treatment group for all patients regardless of age.

As no formal hypothesis testing was performed for any efficacy endpoints, treatment differences presented for any efficacy analyses were supported with associated CIs only. Efficacy summaries and analyses were split by age group: by adults (patients ≥18 years), pooled data for adults and adolescents (patients ≥13 years), and children aged <13 years.

The TTR of all symptoms in adults in the miTTi population was compared with 1:1-matched historical otherwise healthy (OwH) placebo and treated controls from pivotal registration studies, supported by 95% and 90% CIs. Also, as sensitivity analyses, similar comparisons using 1:>1-matched OwH and at-risk (patients with chronic cardiac and/or respiratory diseases) historical placebo and treated controls were performed.

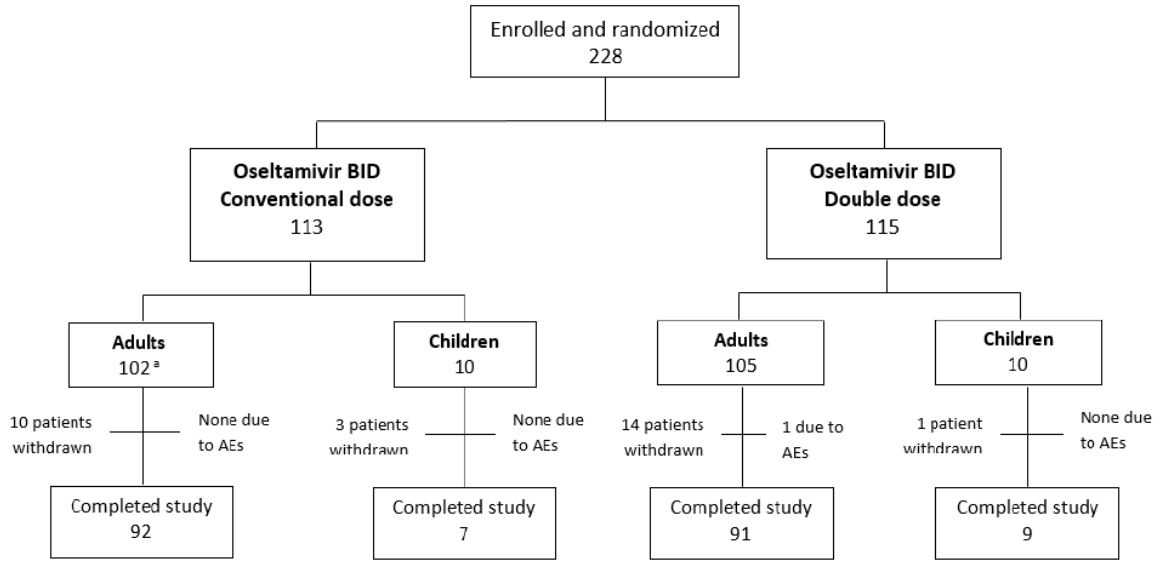
Results

Recruitment/ Number analysed

A total of 843 patients were screened, of which 228 patients were enrolled into the study at 62 active centres in 19 countries. The main reason for screen failure was the inability to meet inclusion criterion 2 (being positive for influenza by rapid diagnostic test, PCR, or viral culture assay at the site). The majority of patients (58.3% [133/228]) were enrolled during the 2012–2013, 2013–2014, and 2014–2015 flu seasons.

Of the 228 enrolled patients, 207 were adults (≥18 years) and 20 were children (patients <18 years). No age information was available for 1 patient (who was randomized but not dosed and was only included in the ITT population). The 228 enrolled patients were randomized: 113 to the conventional dose group and 115 to the double dose group (Figure 1). Of these, 220 patients (109 in the conventional dose group and 111 in the double dose group) received at least 1 dose of oseltamivir, and 199 patients (99 in the conventional dose group and 100 in the double dose group) completed the study.

Figure 1 Patient Disposition (All Enrolled Patients)



AE=adverse event; BID=twice daily.

Notes: Adults were patients aged ≥18 years; children were patients aged <18 years.

[a] Age information was not recorded for 1 adult patient (this patient was randomized but not dosed, and was only included in the intent-to-treat population).

From all enrolled, 24 adults and 4 children were withdrawn mostly due to loss to follow-up and consent withdrawal. One discontinuation occurred due to safety reasons (a fatal AE, recurrent leukemia).

Of the 228 patients enrolled and randomized in the study, 215 patients were included in the Safety population (16 children aged <18 years), 226 patients in the ITT population (20 children), 169 patients in the ITTi population (17 children), 167 patients in the mITTi population (16 children), and 26 patients in the PKEP population (4 children).

Among the adult patients in the Safety population, 22 patients (10 in the conventional and 12 in the double dose group) discontinued treatment. Of these 8 patients (3 in the conventional and 5 in the double dose group) discontinued due to AEs; which included pneumonia, vomiting, nausea, epistaxis, headache, pulmonary tuberculosis, pruritus, renal failure, sepsis, and hallucination. Therefore, 177 adult patients in the Safety population completed the study; and 16 children aged <18 years completed the study.

Baseline data

Demographic data

In the *Safety population*, the majority of adult patients ≥18 years were Caucasian (65.8%), non-Hispanic (84.4%), and the proportion of females (57.3%) was higher than males (42.7%), The mean age of adult patients was 46.2 years. (range: 18–90 years), and the majority of patients (90.5%) were ≤64 years of age. At baseline, 17.6% of adult patients had been vaccinated against seasonal influenza and 42.7% were transplant recipients. The overall mean time from onset of symptoms to the start of drug was 50.2 hours (range: 7.7–94.0 hours). The demographic characteristics were generally balanced between the treatment groups, except for the mean time from symptom onset to treatment

start, which was shorter in the conventional dose group (47.5 hours) compared with the double dose group (53.2 hours).

In children aged <18 years, the majority were Caucasian (81.3%), non-Hispanic (68.8%), and the proportion of males (68.8%) was higher than females (31.3%). The mean age of these patients was 10.1 years (range: 4–17 years), with the majority (56.3%) aged ≤12 years of age. At baseline, 3 children (18.8%) had been vaccinated against seasonal influenza and 3 (18.8%) were transplant recipients. The mean time from onset of symptoms to the start of treatment was 48.8 hours (range: 8.4–89.6 hours). The demographic characteristics were generally balanced between the treatment groups.

In the *mITTi* population, (the primary analysis population for resistance and efficacy endpoints), 19.8% of patients had been vaccinated against seasonal influenza, 51.3% entered the study ≤48 hours after the onset of symptoms, and the majority (70.7%) did not present with fever at baseline.

At baseline, 164 patients (98.2%) had central laboratory-confirmed influenza infection (by RT-PCR). The majority of patients (67.1%) had influenza type A, with the H3N2 strain being the most predominant (45.5%); 18.6% of patients had the A/H1N1 (2009) strain. The proportion of patients who were positive for influenza type B was 30.5%.

Three patients had unknown influenza type at baseline, and were later identified to be positive for influenza type B during the study.

Safety results

In adults (patients aged ≥18 years)

- Treatment exposure in terms of mean dose intensity, defined as the percentage of doses received divided by the expected doses, was high and similar between treatment groups (88.8% in the conventional dose group vs. 90.9% in the double dose group).
- The proportion of patients who experienced at least one adverse events (AE) was higher in the double dose group (59.4%) compared with the conventional dose group (49.0%) (table 2).
- Serious adverse events (SAE) occurred in 7/98 (7.1%) of subjects administered conventional dose and 9/101 (8.9%) of subjects administered double dose of oseltamivir. None of the SAE were considered related to study medication (table 2).
- A higher proportion of adult patients in the double dose group experienced AEs leading to withdrawal from treatment (5.0% vs. 3.1%), related AEs (5.0% vs. 2.0%), and related AEs leading to withdrawal from treatment compared with the conventional dose (2% vs. 1%). Two subjects in the conventional dose group and none in the double dose group experienced AE leading to dose modification/interruption.
- Of all AE, 2 (2.0%) in the conventional dose group and 5 (5.0%) in the double dose group were considered to be related, and altogether 3 subjects withdrew from treatment due to related AE, one in the conventional dose group and two in the double dose group (table 2).

Table 2 Overall Incidence of Adverse Events (All Patients, Safety Population)

Overall Incidence of Adverse Events, Safety-Evaluable Population, Adults
Protocol: NV20234

	Ro 64-0796 Conventional (N=98)	Ro 64-0796 Double (N=101)	All Patients (N=199)
Total number of patients with at least one adverse event	48 (49.0%)	60 (59.4%)	108 (54.3%)
Total number of events	146	215	361
Total number of deaths	0	1 (1.0%)	1 (0.5%)
Total number of patients withdrawn from study due to an AE	0	0	0
Total number of patients with at least one AE with fatal outcome	0	1 (1.0%)	1 (0.5%)
Serious AE	7 (7.1%)	9 (8.9%)	16 (8.0%)
Serious AE leading to withdrawal from treatment	1 (1.0%)	2 (2.0%)	3 (1.5%)
Serious AE leading to dose modification/interruption	0	0	0
Related Serious AE	0	0	0
AE leading to withdrawal from treatment	3 (3.1%)	5 (5.0%)	8 (4.0%)
AE leading to dose modification/interruption	2 (2.0%)	0	2 (1.0%)
Related AE	2 (2.0%)	5 (5.0%)	7 (3.5%)
Related AE leading to withdrawal from treatment	1 (1.0%)	2 (2.0%)	3 (1.5%)
Related AE leading to dose modification/interruption	0	0	0

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.
Percentages are based on N in the column headings.
Related AEs are those which have probable relationship to study medication in CRF.
Includes AEs with onset from first dose of study drug through visit Day 40.
Adults are determined as patients with age greater or equal to 18.

- Incidence of on-treatment AEs was higher in the double dose group (46.5%) compared with the conventional dose group (38.8%). Overall, the most common AEs (≥3% in either treatment arm) were vomiting, diarrhoea, nausea, headache, pneumonia, anaemia, dizziness, and muscle spasms (table 3).
- One adult patient (1.0%) in the double dose group died during the study due to an off-treatment AE with fatal outcome (Grade 5; recurrent leukemia). The event was considered unrelated to oseltamivir by the investigator. No adults died due to AEs with fatal outcome in the conventional dose group.
- There were no new safety signals identified in adult IC patients treated with oseltamivir.

Table 3 Overall Incidence of On-Treatment Adverse Events in Patients ≥18 Years of Age (Safety Population)

Overall Incidence of Adverse Events, on Treatment, Safety-Evaluable Population, Adults
Protocol: NV20234

	Ro 64-0796 Conventional (N=98)	Ro 64-0796 Double (N=101)	All Patients (N=199)
Total number of patients with at least one adverse event	38 (38.8%)	47 (46.5%)	85 (42.7%)
Total number of events	89	106	195
Total number of deaths	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0
Total number of patients with at least one AE with fatal outcome	0	0	0
Serious AE	5 (5.1%)	4 (4.0%)	9 (4.5%)
Serious AE leading to withdrawal from treatment	1 (1.0%)	2 (2.0%)	3 (1.5%)
Serious AE leading to dose modification/interruption	0	0	0
Related Serious AE	0	0	0
AE leading to withdrawal from treatment	3 (3.1%)	5 (5.0%)	8 (4.0%)
AE leading to dose modification/interruption	2 (2.0%)	0	2 (1.0%)
Related AE	2 (2.0%)	5 (5.0%)	7 (3.5%)
Related AE leading to w/d from treatment	1 (1.0%)	2 (2.0%)	3 (1.5%)
Related AE leading to dose modification/interruption	0	0	0

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.
Percentages are based on N in the column headings.
Related AEs are those which have probable relationship to study medication in CRF.
Includes AEs starting during treatment or up to 2 days after the last dose of the study drug.
Adults are determined as patients with age greater or equal to 18.

In children and adolescents (patients aged <18 years)

Safety was evaluated in a total of 16 treated children aged <18 years. Data interpretation is limited by small numbers:

- Treatment exposure in terms of mean dose intensity was higher in the conventional dose group (94.3% vs. 80.6% in the double dose group), indicating more patients who received the conventional dose received the full 10-day course of treatment with fewer treatment discontinuations.
- The proportion of children who experienced at least one AE was higher in the conventional dose group (5 patients [71.4%]) compared with the double dose group (5 patients [55.6%]) (table 4).

There was no indication of clinically significant changes in laboratory parameters or vital signs during the course of treatment.

Table 4 Overall Incidence of All Adverse Events in Patients <18 Years of Age (Safety Population)

Overall Incidence of Adverse Events, Safety-Evaluable Population, Children
Protocol: NV20234

	Ro 64-0796 Conventional (N=7)	Ro 64-0796 Double (N=9)	All Patients (N=16)
Total number of patients with at least one adverse event	5 (71.4%)	5 (55.6%)	10 (62.5%)
Total number of events	12	13	25
Total number of deaths	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0
Total number of patients with at least one AE with fatal outcome	0	0	0
Serious AE	1 (14.3%)	1 (11.1%)	2 (12.5%)
Serious AE leading to withdrawal from treatment	0	0	0
Serious AE leading to dose modification/interruption	0	0	0
Related Serious AE	0	0	0
AE leading to withdrawal from treatment	0	1 (11.1%)	1 (6.3%)
AE leading to dose modification/interruption	0	0	0
Related AE	0	1 (11.1%)	1 (6.3%)
Related AE leading to withdrawal from treatment	0	0	0
Related AE leading to dose modification/interruption	0	0	0

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.
Percentages are based on N in the column headings.
Related AEs are those which have probable relationship to study medication in CRF.
Includes AEs with onset from first dose of study drug through visit Day 40.
Children are determined as patients with age less than 18.

- Incidence of on-treatment AEs was comparable between treatment groups (4 patients [57.1%] vs. 5 patients [55.5%]) (table 5). Except for pyrexia, the individual on-treatment AEs occurred in not more than 1 patient in either treatment group.
- None of the children died due to an AE in either treatment group.

Table 5 Overall Incidence of On-Treatment Adverse Events in Patients <18 Years of Age (Safety Population)

Overall Incidence of Adverse Events, on Treatment, Safety-Evaluable Population, Children
Protocol: NV20234

	Ro 64-0796 Conventional (N=7)	Ro 64-0796 Double (N=9)	All Patients (N=16)
Total number of patients with at least one adverse event	4 (57.1%)	5 (55.6%)	9 (56.3%)
Total number of events	9	11	20
Total number of deaths	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0
Total number of patients with at least one AE with fatal outcome	0	0	0
Serious AE	1 (14.3%)	1 (11.1%)	2 (12.5%)
Serious AE leading to withdrawal from treatment	0	0	0
Serious AE leading to dose modification/interruption	0	0	0
Related Serious AE	0	0	0
AE leading to withdrawal from treatment	0	1 (11.1%)	1 (6.3%)
AE leading to dose modification/interruption	0	0	0
Related AE	0	1 (11.1%)	1 (6.3%)
Related AE leading to withdrawal from treatment	0	0	0
Related AE leading to dose modification/interruption	0	0	0

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.
Percentages are based on N in the column headings.
Related AEs are those which have probable relationship to study medication in CRF.
Includes AEs starting during treatment or up to 2 days after the last dose of the study drug.
Children are determined as patients with age less than 18.

Overall, there were no new safety signals identified in adults and children aged <18 years who were treated with oseltamivir.

Resistance results

Baseline

Of the 226 IC patients in this study (ITT population), influenza virus infection was centrally confirmed by RT-PCR in a total of 175 patients at baseline. Baseline resistance assessment was performed using H274Y mutation-specific RT-PCR, population sequencing, and/or phenotyping assay.

In the ITT population, the overall incidence of baseline resistance (genotypic and/or phenotypic) was low. Six patients (4 in the conventional dose group and 2 in the double dose group) had oseltamivir resistance detected in their baseline sample: two influenza type A/H1N1-infected patients had genotypic resistance, with an H274Y mutation detected by the H274Y mutation-specific RT-PCR; whereas 2 influenza type A/H3N2-infected patients and 2 influenza type B-infected patients had an outlier phenotype with a 2.7- to 4-fold increase in IC50 values from the baseline mean. All 6 patients were aged ≥13 years (5 adults and 1 adolescent).

Due to detection of the H274Y mutation at baseline using RT-PCR methodology performed in real time, the 2 patients (1 in each treatment group) with genotypic resistance were withdrawn from study treatment (at Day 5 for the patient receiving the conventional dose and at Day 4 for the patient

receiving the double dose); the remaining 4 patients with phenotypic baseline resistance completed the full 10-day treatment.

The median baseline viral load (as determined by RT-PCR) for the 6 patients with baseline resistance was 6.23 log10 vp/mL and was comparable to the median baseline viral load obtained for adults and patients aged <18 years.

Cessation of viral shedding, as determined by RT-PCR, occurred before EOT for 2 patients in the conventional dose group, and after EOT for 1 patient in the conventional dose group and for both patients in the double dose group. Viral shedding was still positive for 1 patient in the conventional dose group at the last evaluated timepoint (FU Day 15).

Alleviation of all symptoms (scores ≤1) occurred before EOT for 1 patient in the conventional dose, and for both patients in the double dose group, at EOT for the 1 patient in the conventional dose group, and at Day 18 for 1 patient in the conventional dose group. One patient in the conventional dose group was still experiencing influenza symptoms at the last evaluated timepoint (FU Day 31).

Narratives for these 6 patients, including all virology-associated results, are provided in the CSR.

Post-baseline

Post-baseline resistance assessment was performed using population sequencing and/or phenotyping assay. The incidence of post-baseline resistance was estimated using the mITTi population, which excluded patients with baseline resistance. It should be noted that for some patients in the mITTi population, resistance monitoring was incomplete (i.e., only phenotypic or genotypic resistance assessment was available, mainly due to the limitations of the 2 assays) or not done (especially in the early influenza seasons of the study).

Patients for whom both genotypic and phenotypic resistance were detected were counted only once in the overall resistance rate. A total of 15 patients had oseltamivir (treatment-emergent) resistance detected in one or several of their post-baseline samples: 12 patients in the conventional dose group and 3 patients in the double dose group. All 15 patients had completed the full 10 days of study treatment. Of these, 11 had received a transplant (5 SOT patients and 6 HSCT patients).

Specifically in the conventional dose group, 9 of 40 patients (22.5%; 95% CI: 10.84–38.45) who received a transplant developed resistance compared with 3 of 41 patients (7.3%; 95% CI: 1.54–19.92) who did not received a transplant and developed resistance.

Among adults (patients ≥18 years) in the mITTi population, the overall post-baseline resistance rate was 13.7% (10 patients) in the conventional dose group and 2.6% (2 patients) in the double dose group. The virus type(subtype)s were A(H1N1)(2009) in five patients, A(H1N1) in one patient, A(H3N2) in four patients and B in 2 patients.

Of the 16 children aged <18 years in the mITTi population, 2/8 patients in the conventional dose group and 1/8 patient in the double dose group developed post-baseline resistance; all 3 patients were children aged <12 years old. Two children had influenza A(H1N1)(2009) and one A(H3N2) virus.

As a summary, in the mITTi population:

- Baseline resistance was rare and was detected in 6 patients.
- In adults (patients aged ≥18 years), 13.7% of patients in the conventional dose group and 2.6% of patients in the double dose group developed post-baseline oseltamivir resistance.

- In children aged <18 years, 2 patients (25.0%) in the conventional dose group and 1 patient (12.5%) in the double dose group developed post-baseline oseltamivir resistance; these 3 patients were children <12 years of age.
- Treatment-emergent resistance was observed mostly in influenza type A-infected patients and patients who had prolonged viral shedding.

Clinical outcomes in patients with treatment-emergent resistance

Among the 12 adults with post-baseline treatment-emergent resistance (genotypic and/or phenotypic), the resolution of all symptoms occurred before EOT for 8 patients in the conventional dose group and 1 patient in the double dose group. For the remaining 3 patients, all symptoms resolved after EOT (at Day 12 and Day 16 for 2 patients in the conventional dose group, and at Day 11 for 1 patient in the double dose group).

The median TTR of all symptoms in adult and adolescent patients with treatment-emergent resistance was slightly longer than in patients without treatment-emergent resistance (137.6 hours [95% CI:43.7, 183.6] in the conventional dose group and 149.2 hours [95% CI: not estimable] in the double dose group); however the small number of patients in these two groups (10 patients in the conventional dose group and 2 patients in the double dose group) limits data interpretation.

Among the 3 children (patients <13 years) with treatment-emergent resistance (genotypic and/or phenotypic), resolution of all symptoms occurred before EOT for the 2 patients in the conventional dose group, and after EOT (at Day 22) for 1 patient in the double dose group.

Efficacy results

A summary of key efficacy findings in the mITTi population is presented below. Results of the key efficacy analyses of TTR of all symptoms, TTR of fever, and time to cessation of viral shedding in the ITTi population were identical to the mITTi population (these populations differed by only 2 patients [1 adult and 1 child aged <13 years] who did not have time-to-event data).

In the mITTi population, the TTR of all symptoms was analysed in adults and adolescents (patients aged ≥13 years) with or without treatment-emergent resistance. The median TTR of all symptoms was similar in both treatment groups in patients without treatment-emergent resistance (107.0 hours [95% CI: 53.0, 143.9] in the conventional dose group and 107.2 hours [95% CI: 54.8, 147.7] in the double dose group) and these results are consistent with the overall median TTR of all symptoms observed in this population.

- There was no difference in median TTR of all symptoms in adults aged ≥18 years between the 2 oseltamivir doses (103.3 hours [95% CI: 69.0, 112.7] in the conventional dose group vs. 103.6 hours [95% CI: 57.1, 140.0] in the double dose); the 95% CIs were overlapping.

  – The median TTR of all symptoms between IC oseltamivir-treated adult patients and a 1:1-matched historical OwH placebo control from pivotal registration trials was shorter by 13.5 hours.

  However, the CIs (90% and 95%) overlapped. Of note, the median TTR was comparable between IC patients and the OwH treated controls in the subgroup of patients who were treated ≤48 hours of symptom onset, with overlapping 95% and 90% CIs.
- In the absence of a placebo control in this study, the median TTR of all symptoms in adult IC patients in the mITTi population was compared against a historical control of OwH placebo and

treated adult patients from pivotal registration trials of oseltamivir. As there was little difference between the oseltamivir conventional and double dose groups in the median TTR of all symptoms, these groups were pooled together (combined IC group) and compared with the historical matched OwH placebo controls as well as with the matched OwH treated controls. When compared with 1:1-matched historical at-risk placebo and treated controls, the median TTR of all symptoms was notably shorter (by 54.2 hours and 36 hours, respectively) with little or no overlap in the 95% and 90% CIs; however, the at-risk patients had confounding factors that contributed to a longer median TTR of symptoms.

- The median TTR of all symptoms in adults and adolescents (patients aged ≥13 years, pooled) was comparable between the 2 doses (103.4 hours [95% CI: 75.4, 122.7] in the conventional dose group vs. 107.2 hours [95% CI: 63.9, 140.0] in the double dose group) with overlapping 95% CIs. The median TTR was longer in patients with treatment-emergent resistance compared with that in patients without resistance.
- The median TTR of fever in adults and adolescents (patients aged ≥13 years) was longer by 10.5 hours in the conventional dose group; however, the 95% CIs overlapped.
- There were no differences in the TTR of individual symptoms between the two doses of oseltamivir in adults and adolescents (patients aged ≥13 years); the 95% CIs overlapped for all symptoms. Symptoms of chills/sweats (feverish) and headache resolved the fastest with both doses.
- The time to cessation of viral shedding was 24 hours shorter (by RT-PCR) in adults treated with double dose oseltamivir compared with the conventional dose. This difference may be due to the larger number of patients in the conventional dose that developed treatment-emergent resistance and had corresponding prolonged viral shedding.

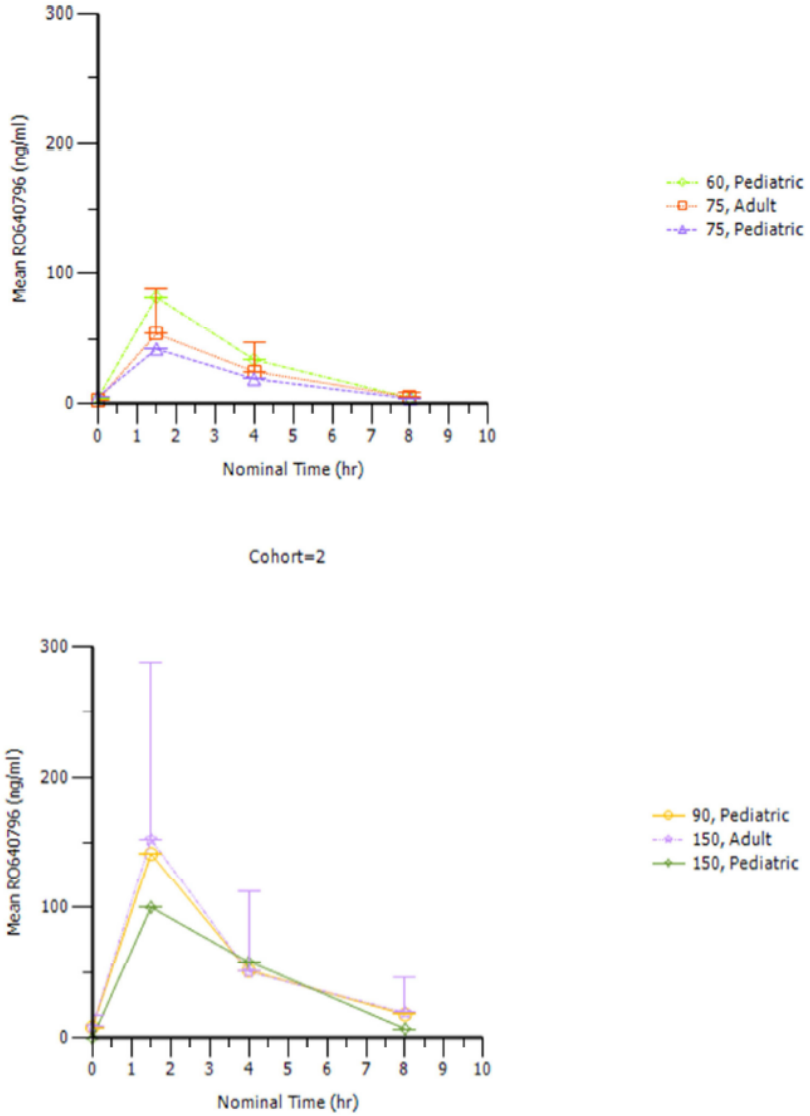
The small number of IC children aged <13 years limits data interpretation of the comparisons of TTR of all symptoms and fever in this age group.

Pharmacokinetic results

A total of 26 patients (11 in the conventional dose group and 15 in the double dose group) with PK samples were available for the analysis. Of these, four were aged below 18 years. These data were used in the modelling described below, but data are only summarized for adults aged ≥18 years given the limited paediatric data.

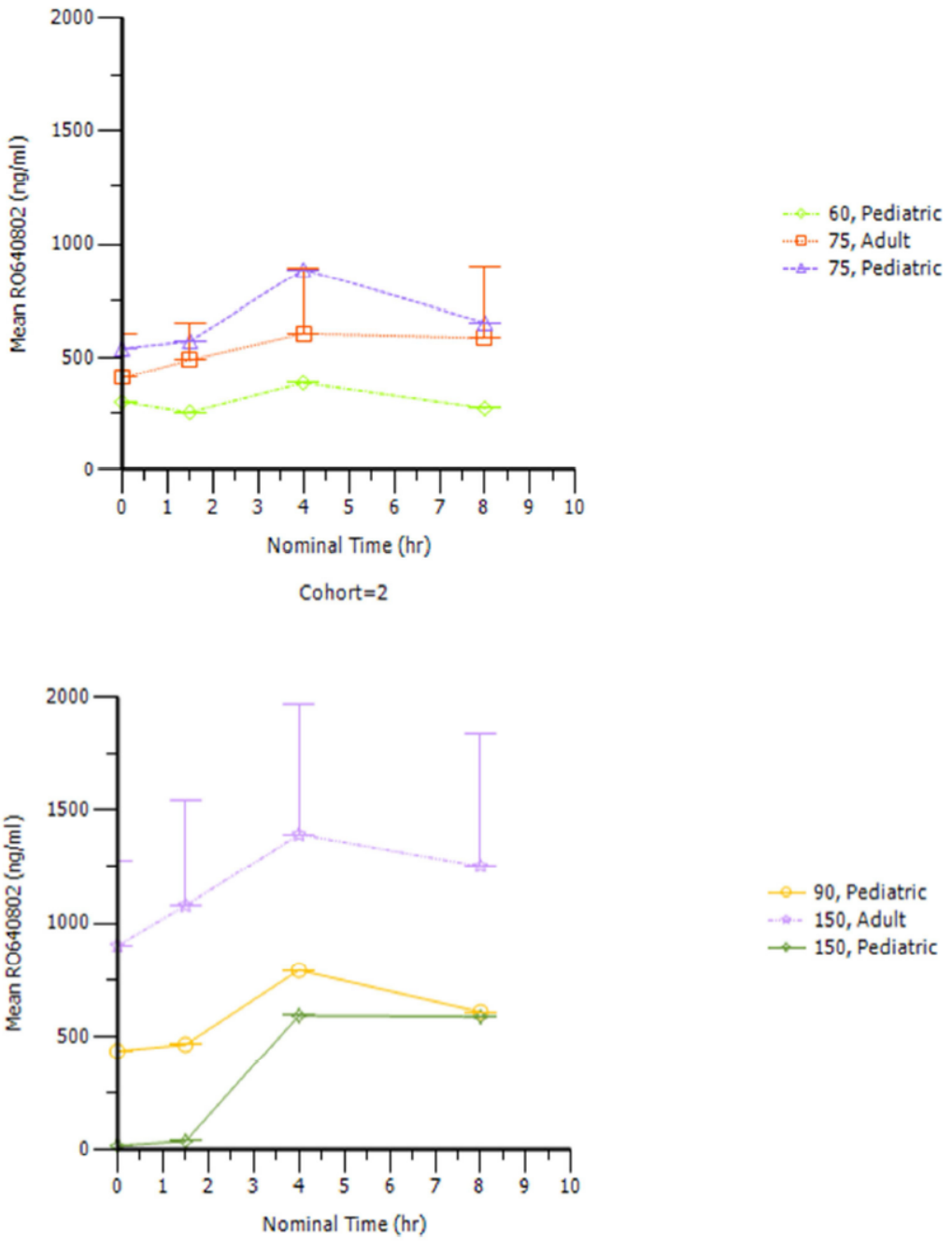
Concentrations of oseltamivir and OC in adults in the double dose group were approximately two times higher than those in the conventional dose group (Figures 2 and 3).

Figure 2 Mean (+SD) Concentration-Time Profiles of Oseltamivir Concentrations Following Multiple Oral Dose Administrations of Oseltamivir by Dose (mg) and Age Group (Linear)



Cohort 1=conventional dose group; Cohort 2=double dose group.
Notes: Adults are patients aged ≥18 years; pediatric patients are children aged <18 years.
Legend presented as Dose (mg), Population.

Figure 3 Mean (+SD) Concentration-Time Profiles of Oseltamivir Carboxylate Concentrations Following Multiple Oral Dose Administrations of Oseltamivir by Dose (mg) and Age Group (Linear)



Cohort 1=conventional dose group; Cohort 2=double dose group.
Notes: Adults are patients aged ≥18 years; pediatric patients are children aged <18 years.
Legend presented as Dose (mg), Population.

Using popPK modelling, the mean and geometric mean of oseltamivir C_{max} were similar to data from historical trials of oseltamivir in generally OwH non-IC patients, whereas C_{trough} and AUC were slightly higher than those observed in the historical trials. The mean and geometric mean of OC C_{trough} and

AUC were approximately two times higher than those observed with historical trials. Approximately 50% of this difference can be attributed to lower OC clearance estimated for patients from this study, and the other half can be attributed by lower than normal estimated creatinine clearance in this study relative to the historic data. Oseltamivir and OC exposure metrics in the double dose group were approximately two times higher than those in the conventional dose group confirming the linear increase of oseltamivir and OC exposure with dose.

The PK modelling methods are not assessed in this AR but will be scrutinised when the results are used later in the Type II variations affecting Product Information.

Pharmacodynamic results

Exposure-response analysis was conducted in 20 adults aged ≥18 years with evaluable efficacy data (resolution of influenza symptoms and virologic course of influenza). The low sample size of children aged <18 years (n=4) precluded a separate ER analysis in these patients. Only C_{trough} for OC was used for the ER analysis. No notable exposure-efficacy relationships were identified, although the sample size was too low to make any definite conclusions.

2.2.3. Discussion on clinical aspects

In summary, the data from study NV20234 of conventional or double dose oseltamivir administered BID over 10 days for the treatment of seasonal influenza in IC patients demonstrate that:

- Both doses of oseltamivir were generally well tolerated in adults and children, with a trend toward better safety with the conventional dose. No new safety signals were observed. The nature and severity of AEs were consistent with the established safety profile of oseltamivir, the typical complications influenza infection, and the associated comorbidities/concomitant medications used in IC patients.
- Treatment-emergent oseltamivir resistance appeared to be higher with the conventional dose compared with the double dose in both adults and children aged <18 years, although the frequency observed for either dose was not unduly high considering the immunocompromised population studied.
- Emergence of resistance seemed to be associated more with patients with influenza-type A and patients with prolonged viral shedding.
- Overall, the TTR of all symptoms was similar between the two doses of oseltamivir.
  – A shorter TTR of all symptoms was seen with oseltamivir treatment in adults when compared with the historical OwH placebo control; however, the 95% CIs were overlapping. The 90% CIs for this comparison were also overlapping but to a lesser extent.
  – When compared with 1:>1-matched historical at-risk placebo and treated controls, the median TTR of all symptoms was notably shorter with little or no overlap in the 95% and 90% CIs; however, the at-risk patients had confounding factors that contributed to a longer median TTR of symptoms.
  – The TTR of all symptoms was also longer in patients with resistance in both treatment groups.
- Virologic data based on RT-PCR indicated that both doses of oseltamivir result in a similar decline in viral load and viral shedding in adults and children aged <18 years. In adults, the time to cessation of viral shedding was shorter with the double dose of oseltamivir, with lower levels of virus shed over time.

- Oseltamivir and OC exposure metrics in the double dose group were approximately two times higher than those in the conventional dose group confirming the linear increase of oseltamivir and OC exposure with dose.
- No notable exposure-response relationships were observed in the PK/PD analyses.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted a completed paediatric study for Tamiflu (*NV20234 – A double blind, randomized, stratified, multicenter trial evaluating conventional and double dose oseltamivir in the treatment of immunocompromised patients with influenza; the study included both adult and paediatric patients*), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The results of study NV20234 do not alter the benefit risk balance of oseltamivir. A double dose of oseltamivir administered over 10 days may be slightly more beneficial than conventional dose regarding evolution of treatment-emergent oseltamivir resistance and duration of viral shedding in immunocompromised (IC) adults. The low number of children in the study limits drawing conclusions on efficacy of both doses. Overall, the described safety findings are in line with the already known profile reflected in the SmPC, even though conventional dose is slightly better tolerated.

The requirement to submit the results of this paediatric study NV20234 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, has been thus fulfilled.

Further, the post-authorisation measures MEA 75 and MEA102 are also considered to be fulfilled now:.

- MEA75: "To elucidate clinical significance of new resistance information in IC patients, the MAH should provide results and final reports from study NV20234 (final CSR by end of November 2018)".
- MEA102: "Immunocompromised patients - The MAH should review annually the safety of oseltamivir in IC patients up to final submission of the clinical trial NV20234 study report (treatment) as flu and season permits. The MAH should provide the efficacy data after finalization of NV20234 (Due date: Annually in December/ Final CSR by end of November 2018)."