17 October 2024
EMA/CHMP/437255/2024
Human Medicines Division

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

RoActemra

Tocilizumab

Procedure no: EMEA/H/C/000955/P46/064

Note

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

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1. Introduction

On 31 July 2024 the MAH submitted completed paediatric study for RoActemra, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study Phase Ib, single-arm, open-label study evaluating the pharmacokinetics, pharmacodynamics, safety of TCZ in paediatric patients hospitalized with COVID-19, WA43811 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

N/A

CHMP comment

The formulation used in the study is authorised in the study population.

2.2.1. Introduction

The MAH submitted a final report(s) for:

- study WA43811 "Phase Ib, single-arm, open-label study evaluating the pharmacokinetics, pharmacodynamics, safety of TCZ in paediatric patients hospitalized with COVID-19".

WA43811 study was a Phase Ib, single-arm, open-label study to assess the PK, PD, safety, and exploratory efficacy of TCZ for the treatment of paediatric participants from birth to less than 18 years old hospitalized with COVID-19 and who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Rationale for an abbreviated clinical study report

Overall, only two patients were recruited at two sites in the United States. (First participant enrolled: 10 June 2022; last participant last visit: 5 December 2022. End of trial: 27 March 2024.) The decline in severe paediatric COVID-19 cases, due to a combination of evolving disease characteristics, increased background immunity, and earlier use of effective treatments, significantly hampered participant recruitment in the study.

Despite efforts, no additional participants were recruited since November 2022 as the clinical sites could no longer identify paediatric COVID-19 participants with severe disease who were receiving systemic corticosteroids and requiring supplemental oxygen or mechanical ventilation further to the use of effective antiviral therapies early in the treatment pathway. In this context of recruitment difficulties and pandemic subsiding, clinical sites started to request withdrawal from the study, further limiting the opportunity to enrol participants.

A Paediatric Investigational Plan (PIP) Modification request (EMEA-000309-PIP07-21-M01) was submitted, where the MAH proposed the replacement of the clinical study by a full modelling and simulation approach. Considering the context and the limitations associated with both the clinical study and the alternative modelling approach, the Paediatric Committee adopted an opinion to grant a PIP waiver for the indication on 15 December 2023.

In alignment with feedback sought and received from different Health Authorities (European Medicines Agency, United States Food and Drug Administration and Medicines and Healthcare Products Regulatory Agency), the MAH made the decision to terminate the trial.

Due to the low recruitment and limited data collected during the study, the interim analysis was not performed and an abbreviated CSR was developed to present the study results.

2.2.2. Clinical study

WA43811 "Phase Ib, single-arm, open-label study evaluating the pharmacokinetics, pharmacodynamics, safety of TCZ in paediatric patients hospitalized with COVID-19

Description

Study WA43811 was designed as a Phase Ib, single-arm, open-label study to assess the PK, PD, safety, and exploratory efficacy of TCZ for the treatment of paediatric participants, from birth to less than 18 years old, hospitalized with COVID-19 and who were receiving systemic corticosteroids and required supplemental oxygen or mechanical ventilation. The main scope of the study was to characterize the PK of the dosing regimens proposed in the paediatric participant population.

CHMP comment

RoActemra is authorised for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. The recommend dose is a single 60-minute intravenous infusion of 8 mg/kg

The paediatric indication for RoActemra are: the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older. RoActemra can be given with MTX or as monotherapy.

For sJIA patients recommended posology in patients above 2 years of age is 8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 30 kg.

For pJIA patients the recommended posology in patients above 2 years of age is 8 mg/kg once every 4 weeks in patients weighing greater than or equal to 30 kg or 10 mg/kg once every 4 weeks in patients weighing less than 30 kg.

Data for children < 2 years of age are not available.

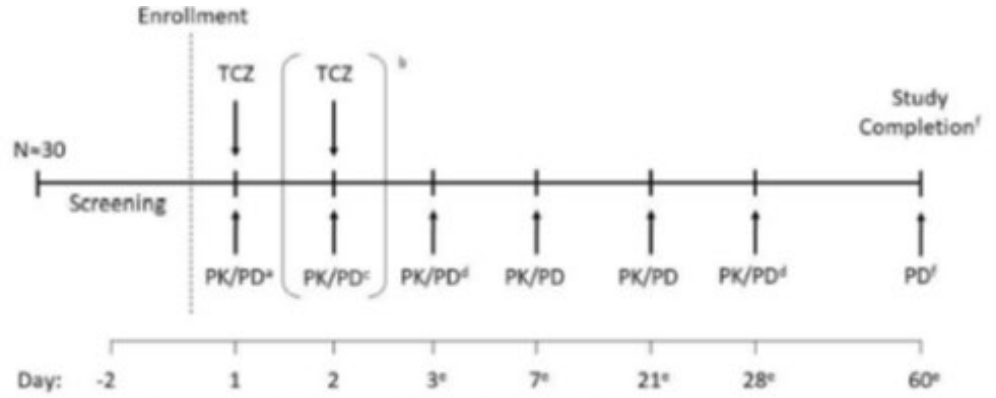
The study planned to enrol at least 30 paediatric participants from birth to less than 18 years old who were hospitalized with COVID-19, confirmed by positive polymerase chain (PCR) reaction and a chest X-ray or computed tomography (CT) scan, and who were receiving systemic corticosteroids and required supplemental oxygen or mechanical ventilation. Overall, at least 10 participants in each body weight category (< 30 kg, ≥ 30 kg) were planned to be enrolled in the study.

Following a screening period of maximum 3 days, participants received a single dose of open-label TCZ on Day 1 (with the option of a second dose 8 - 24 hours later if clinical indicated), and subsequently followed-up for a total of 60 days after first dose of study drug. Participants who were still hospitalized after Day 60 were followed until hospital discharge.

An interim population PK/PD analysis was planned to be conducted once Day 28 data were available from at least 10 PK/PD-evaluable participants (at least 5 participants weighing <30kg and at least 5

participants weighing ≥30kg), in order to confirm the dosing regimens. Following the conclusion of this interim analysis, participants <2 years old would have been enrolled into the study.

Figure 1 Study Design



PD = pharmacodynamic; PK = pharmacokinetic; TCZ = tocilizumab.
N = Number of participants.
[a] Both a predose and a postdose sample (within 15 minutes of completion of the infusion) was collected on Day 1.
[b] Optional second dose within 8–24 hours after the first dose, if clinically indicated.
[c] A postdose sample was collected within 15 minutes of completion of the infusion, if the optional second dose was administered.
[d] Not applicable for participants who weighed < 30 kg.
[e] If a participant received the optional second dose of TCZ on Day 2, subsequent days shifted to Day 4, Day 8, Day 22, and Day 29. The study completion visit was Day 60 (± 3 days).
[f] Upon study completion, a PD sample was collected. In case of early study discontinuation before Day 28, both a PK and PD sample was collected. In case of early study discontinuation after Day 28, only a PD sample was collected.

Methods

Study participants

Paediatric participants from birth to less than 18 years old who were hospitalized with COVID-19, confirmed by positive polymerase chain (PCR) reaction and a chest X-ray or computed tomography (CT) scan, and who were receiving systemic corticosteroids and required supplemental oxygen or mechanical ventilation.

Treatments

Table 1 Tocilizumab Dose Administration and Dilution

Age	Body weight	TCZ dose	IV infusion bag size	Volume (20 mg/mL) per Kilogram of Body Weight	Infusion time	Infusion rate
≥2years	≥30 Kg	8 mg/kg	100 mL	0.4 mL/kg	1 hour	10 mL/hr for first 15 minutes, then 130 mL/hr
≥2 years	<30 Kg	12 mg/kg	50 mL	0.6 mL/kg	1 hour	10 mL/hr for first 15 minutes, then 65 mL/hr
<2 years	<30 Kg	12 mg/kg	25 mL	0.6 mL/kg	2 hours	5 mL/hr for first 30 minutes, then 15 mL/hr

IV = intravenous; TCZ = tocilizumab.

Objective(s)/ Outcomes/endpoints

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
• To characterize the pharmacokinetics of TCZ through Day 28	• Serum concentrations of TCZ at specified timepoints and derived PK parameters (C_{max}, $AUC_{Days\ 0\text{-}28}$, C_{Day28}, CL, and volume of distribution)
Secondary Objective	
• To characterize the pharmacodynamics of TCZ through Day 60	• Duration of 90% saturation of sIL-6R through Day 28 • Concentrations of IL-6, sIL-6R, and CRP at specified timepoints
• To evaluate the safety of TCZ through Day□0	• Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 grading scale • Incidence of serious adverse events • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Objective	
• To explore the efficacy of TCZ through Day 60	• Clinical improvement assessed using a 7-category ordinal scale (see details in Protocol, Section 8.1.1) • Duration of hospitalization (in days) • Duration of PICU or ICU stay (in days) • Mortality • Incidence of mechanical ventilation • Duration of supplemental oxygen
• To assess proof of activity by assessment of pharmacodynamic biomarkers and other disease biomarkers, including, but not limited to, CRP that can increase the knowledge and understanding of disease biology[a]	• Relationship between biomarkers in serum (listed in Protocol, Section 8.7) and efficacy, safety, PK, or other biomarker endpoints

[a] Analyses were not performed as the sample size was too small to draw any robust conclusions.
$AUC_{Day\ 0\text{-}28}$ = area under the concentration–time curve up to Day 28; $C_{Day\ 28}$ = serum concentration on Day 28; CL = total clearance of drug; C_{max} = maximal serum concentration; CRP = C-reactive protein; ICU = intensive care unit; IL-6 = interleukin 6; PICU = pediatric intensive care unit; PK = pharmacokinetic; sIL-6R = soluble interleukin-6 receptor; TCZ = tocilizumab.

Sample size

At least 30 paediatric participants from birth to less than 18 years old.

At least 10 participants in each body weight category (**<** 30 kg, ≥ 30 kg).

Randomisation and blinding (masking)

N/A

Statistical Methods

N/A

Results

Participant flow

Overall, 2 participants were screened and enrolled into the study. There were no screen failures reported during the study.

The first participant was enrolled on 10 June 2022 and the last participant last visit was on 5 December 2022. The end of trial date was 27 March 2024.

Overall, one participant completed the study and one participant discontinued from the study due to withdrawal by the subject.

There were no protocol deviations reported during the study.

Baseline data

One participant was male (weighing <30 kg) and the other was female (weighing <30 kg).

Both participants were aged between 2-11 years. 1 participant was Hispanic or Latino while it was not stated for the other. For both the participants, the baseline ordinal scale for clinical status was 4 (ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen) and the baseline CRP levels for each participant were 89.5 mg/L and 69.1 mg/L, respectively.

There was no COVID-19 vaccination history reported for the 2 participants during the study.

Treatment

Considering their age and body weight, both participants were administered a TCZ IV dose of 12 mg/kg, and only one dose was deemed necessary. No dose modifications were applicable for this study.

Number analysed

The two enrolled participants were included in the safety-evaluable population as well as included in the PK- and PD-evaluable population.

No participant was excluded from the analysis population

Pharmacology

Pharmacokinetics

PK parameters (Cmax, AUCDays 0-28, CDay28, CL, and volume of distribution) for both participants were derived from all observed TCZ serum concentrations following a single dose of TCZ IV 12 mg/kg by performing a Bayesian feedback analysis using an integrated population-PKPD model (PopPK Report Number 1107021 and 1107025) developed for COVID-19.

Table 3 Individual PK Parameter Results

PK Parameter	Participant 1 (weighing <30 kg)	Participant 2 (weighing <30 kg)
Clearance (L/Day)	0.0887	0.133
Volume of Distribution (L)	2.27	2.97
C_{max} (µg/mL)	120	125
$AUC_{(Day\ 0\text{-}28)}$ (µg.Day/mL)	636	703
$C_{(Day28)}$ (µg/mL)	0.171	0.399

$AUC_{Days\ 0\text{-}28}$ = area under the concentration–time curve up to Day 28; C_{Day28} = serum concentration on Day 28; C_{max} = maximal serum concentration; PK = pharmacokinetic.

Source: l_pk_param_19JUN2024_43811

Pharmacodynamics

Serum concentrations for soluble interleukin 6 receptor (sIL-6R) and interleukin 6 (IL-6) both increased following the administration of TCZ, with a maximum observed on Day 21 in the 2 participants.

Serum C-reactive proteins (CRP) levels decreased, with normal values reported on Day 7 in both participants. CRP concentrations were then maintained below the upper limit of normal for the 2 participants until the end of their study participation.

PK/PD

The duration of 90% saturation of the sIL-6R was estimated by performing a Bayesian feedback analysis using an integrated population PK/PD model (PopPK Report Number 1107021 and 1107025). Following a single dose of TCZ IV 12 mg/kg, sIL-6 receptors remained saturated $\geq$ 90% for a duration of 21.5 and 23.5 days, in Participant 1 and Participant 2; respectively.

Efficacy results

Following the administration of tocilizumab, both participants showed improvements in their clinical status markers, including increased oxygen saturation levels and decreased ordinal scale scores.

The ordinal scale for clinical status for both participants on Day 1 of study was 4 (intensive care unit [ICU] or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen). One participant was discharged on Day 7 with the ordinal scale of 1 (discharged or ready for discharge) while the other participant on study Day 3 was scored 2 on the ordinal scale (non-ICU hospital ward or ready for hospital ward not requiring supplemental oxygen) and was discharged on Day 3.

The hospital duration for one participant was 8 days while for the other participant it was 3 days.

The duration of paediatric ICU or ICU stay for one participant was 5 days while for the other participant it was 2 days.

Both the participants received oxygen supplementation, with one requiring 3 days of high-flow oxygen via a mask, followed by 3 days of lower-flow oxygen through nasal cannula, and the second needing 2 days of high-flow oxygen through nasal cannula followed by lower-flow nasal cannula for 2 days.

Safety results

Overall, one participant experienced two AEs of which one AE was Grade 1 (neutropenia) in severity and the other was Grade 3 (device dislocation) in severity. One SAE (device dislocation) was not related to the study drug.

There was no death reported in the study.

There were no AEs that led to withdrawal from study or treatment.

No AESIs were reported.

No clinically meaningful shifts were observed in haematology and chemistry parameters.

On clinically meaningful differences from baseline in vital signs by visit were observed.

The electrocardiogram (ECG) data was done at screening only. ECG interpretation was reported as normal for both the participants.

No pregnancies were reported during the study period.

2.2.3. Discussion on clinical aspects

Two patients were enrolled in the study. TCZ treatment was well tolerated.

Following TCZ treatment the clinical status for both patients improved.

The derived PK parameters following a single dose of TCZ IV 12 mg/kg were comparable between the two participants.

CRP levels decreased and remained within normal ranges from Day 7 until the end of study participation in both participants.

The 90% saturation of the sIL-6 receptors was maintained for at least 3 weeks in the 2 participants.

3. CHMP overall conclusion and recommendation

Only 2 patients were enrolled in the trial before its termination. Therefore only limited data were collected, and the planned analysis were not performed. No conclusion can be drawn from the very small sample size.

☒ Fulfilled:

No regulatory action required.