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Human Medicines Evaluation Division

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

Cinqaero

reslizumab

Procedure no: EMEA/H/C/003912/P46/008

Note

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

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1. Introduction

On 26-3-2018, the MAH submitted the study report of completed paediatric clinical study C38072-AS-10069 for reslizumab (Cinqaero), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This clinical study was part of a clinical development program for a subcutaneous formulation of reslizumab for which an extension application was planned for submission in May 2018. Since the extension application will no longer proceed as planned, this study report is submitted as standalone study.

There are no regulatory consequences identified by the MAH as a result of this study, and no changes to the product information could be recommended based on the submitted clinical study report.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Reslizumab (CEP-38072) is a humanized anti-human interleukin-5 monoclonal antibody (anti-IL-5 mAb). Reslizumab works by binding to IL-5 and preventing its binding to the IL-5 receptor, thereby reducing circulating and tissue eosinophils.

Reslizumab injection for intravenous (iv) administration was first approved via the centralized procedure in the European Union under the tradename CINQAERO® on 16 August 2016, as add-on therapy in adult patients with severe eosinophilic asthma (EA) inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

In this application, results of subcutaneaous (sc) reslizumab in paediatric patients were presented in the clinical study report of **Study C38072-AS-10069**. The MAH stated that Study C38072-AS-10069 is a stand alone study.

Study C38072-AS-10069 is an open-label, randomized, parallel-group study to evaluate the pharmacokinetics, blood eosinophil pharmacodynamics, immunogenicity, safety, and tolerability of reslizumab in paediatric patients with asthma 6 to <12 years of age following administration of a single sc dose. The study was designed to fulfill regulatory commitments under the Paediatric Investigation Plan according to the European Medicines Agency Decision P/0010/2018, dated 30 January 2018 on the acceptance of a modification of an agreed paediatric investigation plan for reslizumab (CINQAERO), (EMEA-001202-PIP02-13-M02).

In paediatric investigation plan EMEA-0012-02-PIP02-13, the development of a subcutaneous formulation in paediatric patients aged 6-<12 was specifically requested. The reslizumab mechanism of action was expected to be relevant in children with EA ages 6 through 11 years, but these patients would be better served by a subcutaneous formulation administered via a thin needle, rather than by an iv infusion. The inconvenience and pain associated with iv infusions of reslizumab generally will not be well accepted by physicians or patients for the treatment of moderate to severe asthma in this age group.

Development of the subcutaneous formulation was deferred until 2019, and a waiver has been granted for development in patients <6 years of age, as the prevalence of severe uncontrolled asthma is extremely low in these patients.

2.2. Information on the pharmaceutical formulation used in the study

Reslizumab solution for subcutaneous (sc) injection (110 mg/mL in a prefilled syringe) is being developed for eosinophilic asthma in adolescent and adult patients. Study C38072/1107 evaluated the bioavailability of reslizumab sc compared to reslizumab iv in healthy subjects. A Phase 1 study in healthy adult subjects (C38072 PK 10071) was conducted to assess dose proportionality of sc reslizumab following single doses of 55, 110, and 220 mg, and to assess for effect of injection site (upper arm, abdomen, thigh) on the pharmacokinetics of sc reslizumab. Two placebo-controlled phase 3 efficacy and safety studies of reslizumab 110 mg sc, administered every 4 weeks (q4w) in patients with eosinophilic asthma ≥12 years of age, have completed clinical conduct and Clinical Study Reports are in preparation (Studies C38072 AS-30025 and C38072-AS-30027). Eligible patients who complete these 2 studies have the opportunity to enter an open label, 36 week extension study (C38072 AS 30066).

The aim of the presented study was to contribute data for determining appropriate doses for further study in paediatric patients.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for the clinical paediatric **Study C38072-AS-10069:** A Single-Dose, Open-Label, Parallel Group Study to Characterize the Pharmacokinetics, Pharmacodynamics, Immunogenicity, Safety, and Tolerability of Reslizumab Following Subcutaneous Administration in Children with Asthma (6 to Less Than 12 Years of Age).

2.3.2. Clinical study

Study C38072-AS-10069

Description

Study C38072-AS-10069 is a single-dose, open-label, parallel group study to characterize the pharmacokinetics, blood eosinophil pharmacodynamics, immunogenicity, safety, and tolerability of reslizumab paediatric patients with asthma (6 to less than 12 years of age), following administration of a single sc dose of reslizumab of 33, 110, or 165 mg.

The study was conducted at 8 centers in the United States, with a study period between 09 August 2016 and 15 Feb 2017.

Methods

Objective(s)

The primary objective was to evaluate the pharmacokinetics and pharmacodynamics of reslizumab in paediatric patients with asthma aged from 6 to <12 years.

The secondary objectives were to evaluate the immunogenicity, safety, and tolerability of reslizumab, and the exploratory objectives were to evaluate the pharmacokinetic/pharmacodynamic relationship between reslizumab serum concentrations and blood eosinophil levels.

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Study design

Study C38072-AS-10069 (PIP Study 3) was an open-label, randomized, parallel-group study to evaluate the pharmacokinetics, blood eosinophil pharmacodynamics, immunogenicity, safety, and tolerability of reslizumab in paediatric patients with asthma aged from 6 to <12 years, following administration of a single sc dose of reslizumab of 33, 110, or 165 mg.

Study population /Sample size

The study planned to enrol 36 patients; 12 in each dose group, with the intent of attaining at least 9 patients per dose group who were evaluable for the primary analysis. Patients had to be taking an inhaled corticosteroid or leukotriene inhibitor (eg, montelukast) for at least 30 days prior to screening, and were allowed to be on additional asthma controllers (eg, long-acting β agonist). Patients were required to have a blood eosinophil level of at least 150 × 106/L at screening.

Treatments

The study consisted of a screening visit within 28 days before the dose of study drug, and a 29-day treatment period which included a baseline visit on the day prior to dosing, treatment on day 1, and 4 outpatient visits (on days 3, 7, 14, and 28). The follow-up period consisted of outpatient visits on days 56 and 84; total study duration was up to 12 weeks after dosing.

On the morning of day 1, patients were randomly assigned (1:1:1) to 1 of 3 dose groups and received a single sc dose in the upper arm as follows:

- 33 mg sc injection of reslizumab;
- 110 mg sc injection of reslizumab;
- 165 mg dose of reslizumab administered as 2 sequential sc injections of 110 and 55 mg, in the same arm, if possible. The injection sites were at least 2.5 cm (1 inch) apart.

Single doses of 33, 110, and 165 mg reslizumab were selected because they represented doses that were expected to produce average steady state concentrations that were similar to those associated with iv reslizumab doses of 0.3, 1, and 2 mg/kg.

PKPD and clinical evaluation

Injection site evaluations were performed at 8 hours after study drug administration. Vital signs were collected 30 minutes prior to reslizumab administration, at 1 hour post-dose and prior to discharge (i.e. 8 hours postdose).

Blood samples for measurement of serum concentrations of reslizumab, blood eosinophil levels, and assessment of incidence of anti-drug antibodies (ADAs) were obtained prior to study drug administration and at pre-specified time points throughout the 12 weeks after study drug administration. Effort was made to also obtain blood samples for pharmacokinetics, pharmacodynamics, and immunogenicity testing in the event of a serious adverse event, adverse event leading to withdrawal, or an asthma exacerbation.

Safety was assessed throughout the study by monitoring the occurrence of adverse events, findings on injection site evaluations, clinical laboratory test results (chemistry, haematology, and urinalysis), vital signs measurements, 12-lead electrocardiogram (ECG) findings, physical examination findings, and use of concomitant medications. Urine pregnancy tests were performed for female patients who were post-menarche or sexually active.

Results

Recruitment / Number analysed

In total 37 patients with asthma were enrolled (12, 12, and 13 patients in the reslizumab 33, 110, and 165 mg sc treatment groups, respectively).

Almost all patients (n=36, 97% received their dose of study drug and were evaluable for safety and pharmacodynamics; 35 patients (95%) were evaluable for pharmacokinetics; and all 36 patients who were dosed completed the study.

One patient in the reslizumab 165 mg group was excluded from the pharmacokinetic analysis set because pharmacokinetic samples were not collected at critical time points (48, 648, 1320, and 1992 hours [days 3, 28, 56, and 84]); therefore, 35 of the 36 dosed patients were included in the pharmacokinetic analysis set.

Baseline data

All patients had a current diagnosis of asthma as required in the inclusion criteria. The 3 treatment groups (33, 110, and 165 mg reslizumab) were well matched with regard to age, race, and gender. All patients were aged between 6 and 11 years, the average age of the patients was 8.7 years. There were more black patients (54%) than white (46%), and more female patients (57%) than male patients (43%). Mean weight was similar for all groups, with individual body weights ranging from 19.2 to 50.1 kg.

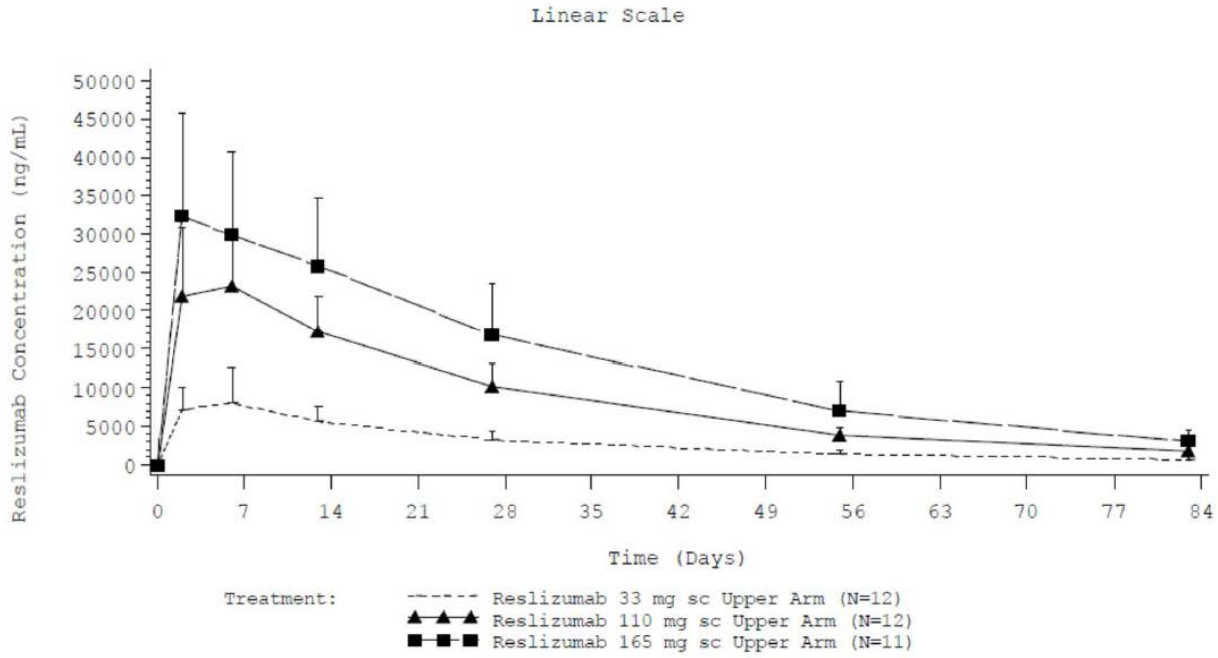
Medical history (excluding asthma) was comparable across the treatment groups. The most frequently reported medical history abnormalities were those related to the Immune system disorders system, reported for 46% of patients, most commonly seasonal allergy (27%).

The treatment groups were comparable in their use of prior medications. All 36 patients who were dosed in the study had received drugs for obstructive airway diseases, most commonly salbutamol (70% of patients), fluticasone propionate (35%), beclomethasone dipropionate (30%), and montelukast sodium (30%). Antihistamines for systemic use were also commonly used as prior medication (59% of patients).

Pharmacokinetics

Following single doses of reslizumab, the overall mean plasma concentration-versus-time profiles of reslizumab were characterized by a slow period of drug absorption followed by a generally monophasic decline from peak levels throughout 83 days after administration (See Figure 1).

Figure 1. Mean (+SD) Serum Concentrations of Reslizumab versus Time Profile by Treatment (Pharmacokinetic Analysis Set Study C38072-AS-10069)



The median time to maximum observed serum drug concentration (tmax) value for reslizumab was approximately 120 hours (i.e. 5 days) post-dose for the 33 and 110 mg doses, and 72 hours for the 165 mg dose. The range of tmax values for the 165 mg dose was consistent with the ranges observed for 33 and 110 mg doses. The difference in median tmax may be an artefact of the number of injections needed to provide the dose (2 injections for 165 mg compared to 1 injection for 33 and 110 mg).

Mean elimination half-life (t½) values were similar across dose levels, ranging from 507 to 526 hours. Mean values of apparent clearance (CL/F) and apparent volume of distribution (Vz/F) were also similar across dose levels, ranging from 6.2 to 6.5 mL/h and from 4.4 to 4.7 L, respectively.

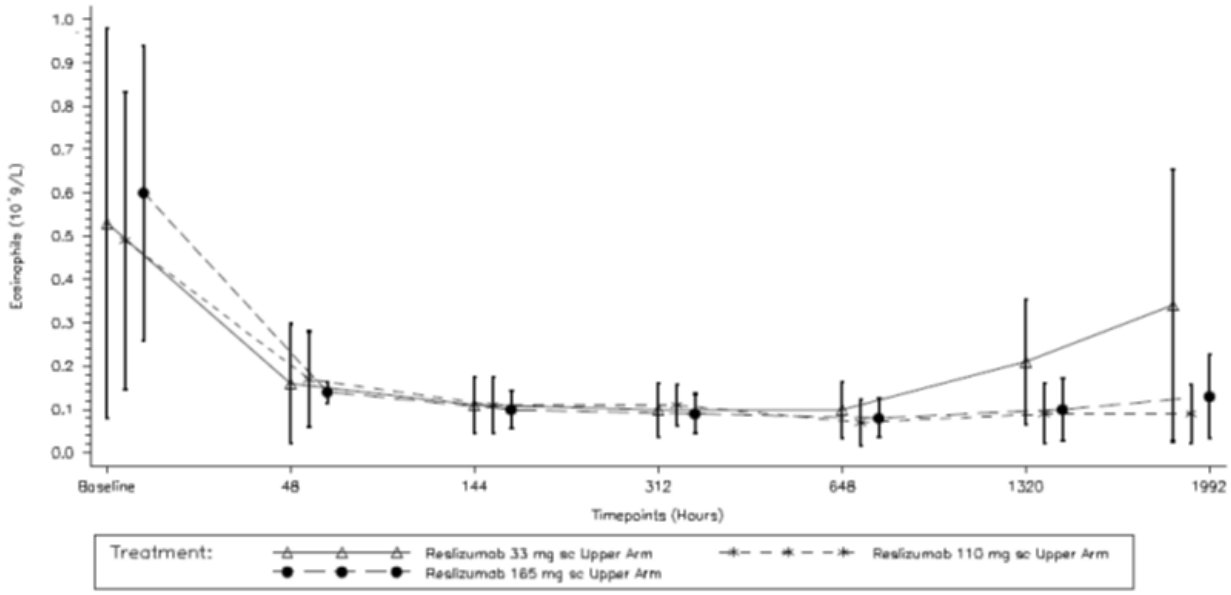
Statistical analyses of the dose-proportionality of reslizumab were performed both without and with weight as a covariate in the model. These analyses did not statistically demonstrate that dose-proportionality was achieved, as the 90% confidence intervals for the slopes of these parameters were not fully within the pre-specified range (0.861, 1.139). However, this was not unexpected since the study was not powered to statistically demonstrate dose-proportionality.

Although proportionality could not be demonstrated statistically, dose-normalized maximum observed serum drug concentration (Cmax), area under the serum drug concentration by time curve from time 0 to the time of the last measurable drug concentration (AUC_{0-t}), and area under the serum drug concentration by time curve from time 0 to infinity ($AUC_{0-\infty}$) were comparable, suggesting that

exposure to reslizumab increases in an approximately dose-proportional manner across the dose range studied.

Pharmacodynamics

Mean baseline eosinophil counts were similar for the 3 treatment groups, ranging from 0.490 to 0.595 × 109/L. Each treatment suppressed eosinophils to a comparable extent with a mean percentage decrease of 57% to 69% (Figure 2) observed as early as the first post baseline time point (48 hours postdose). This suppression was sustained longer in the higher dose groups. At the follow up visits (days 56 and 84), eosinophil suppression was still observed for the 2 higher dose groups (110 and 165 mg), but for the lowest dose group (33 mg dose), eosinophil levels were increasing, although the mean value on day 84 for this dose group (0.335 × 109/L) still represented a mean decrease of approximately 27% compared to baseline.



Source: C38072-AS-10069 CSR Figure 2
sc=subcutaneous; SD=standard deviation

Figure 2. Study C38072-AS-10069: Mean (±SD) Blood Eosinophil Count versus Time Profile by Treatment (Pharmacodynamic Analysis Set)

Immunogenicity

The anti drug antibody (ADA) analysis in human serum employed a validated homogeneous enzyme-linked immunosorbent assay, and it was performed in a 3-tier approach consisting of screening, confirmatory, and titer assays.

A patient was considered ADA positive or having a treatment-emergent ADA response if (1) the patient was tested predose sample negative and postdose sample positive; or (2) the ADA titer of postdose sample increased ≥4 fold compared to the positive titer of predose sample of the patient.

Four patients (11%) had a treatment-emergent ADA positive response: 2 patients in the reslizumab 33 mg sc group, and 1 patient in each of the reslizumab 110 and 165 mg sc groups. In 3 of the patients the ADAs were transient as a positive assay signal was not observed to persist for more than 1 time point. One patient in the reslizumab 33 mg sc group was ADA positive at day 56 and day 84, with day

84 representing the final assessment of ADA status for this patient. All ADA titers for all 4 patients were low, ranging from 3.11 to 7.33.

Efficacy results

There were no assessments of efficacy in Study C38072-AS-10069.

Safety results

Study C38072-AS-10069 provided the first pharmacokinetic and safety data of reslizumab sc in patients aged 6 to <12 years. The safety population consisted of all 36 patients who received a single dose of reslizumab (33, 110, or 165 mg sc).

Adverse Events

The number of patients reporting at least 1 adverse event was 4 (33%), 6 (50%), and 2 (17%) patients in the reslizumab 33, 110, and 165 mg sc treatment groups, respectively (Table 1). There were no deaths or serious adverse events reported in the study, and no patients were withdrawn from the study because of adverse events.

All adverse events were mild or moderate in severity, and, with the exception of injection site reactions, were not considered to be related to treatment.

Table 1. Study C38072-AS-10069: Overview of Adverse Events (Safety Analysis Set)

	Number (%) of patients		
Adverse event category	**Reslizumab 33 mg sc Upper Arm (N=12)**	**Reslizumab 110 mg sc Upper Arm (N=12)**	**Reslizumab 165 mg sc Upper Arm (N=12)**
Any adverse event	4 (33)	6 (50)	2 (17)
Severe adverse events	0	0	0
Treatment-related adverse events	1 (8)	3 (25)	1 (8)
Deaths	0	0	0
Other serious adverse events	0	0	0
Withdrawn from study due to adverse events	0	0	0

Source: Source: C38072-AS-10069 CSR Table 19
sc=subcutaneous
Only adverse events with start date and time occurring after study drug administration (including follow-up) are summarized.

The most frequently occurring adverse events in all treatment groups were injection site reaction (3 patients in the 110 mg sc group) and injection site pain (2 patients; 1 patient in each of the 33 and 165 mg sc groups); all adverse events were mild and resolved without intervention. No other adverse event was reported by more than 1 patient.

Adverse Events of Special Interest

Anaphylactic reactions and non-serious myalgia are adverse drug reactions for reslizumab. In the protocol for this study, the following were considered protocol-defined adverse events for expedited reporting to the sponsor: anaphylaxis, newly-diagnosed malignancy, opportunistic infection, and parasitic helminth infection; there were no cases of these events in this study. There were no muscle

related adverse events, or potentially clinically significant (PCS) elevations in creatinine phosphokinase (CPK).

Clinical Laboratory Assessments

The applicant indicated that based on mean values for clinical laboratory variables by reslizumab treatment group at the assessed time points, no apparent trends in changes from baseline were identified, except that, as expected, decreases in mean eosinophils and eosinophils/leukocytes were observed for all reslizumab treatment groups post baseline.

There were no clinically meaningful trends in mean changes from baseline for any serum chemistry variable or haematology variable (except eosinophils).

2.3.3. Discussion on clinical aspects

Study C38072-AS-10069 is the only completed study of reslizumab sc in paediatric patients. The results from this study were intended to help in determining appropriate doses to take forward into any future study in paediatric patients. However, the applicant no longer pursuits an extension application with a subcutaneous formulation, and no discussion regarding optimal dose of Study C38072-AS-10069 has been provided in the clinical PD, efficacy and safety sections. There is also no discussion for the studied population. In this study a wider range of asthma severity was allowed than authorised for the adults.

The primary objective was to evaluate the pharmacokinetics and pharmacodynamics of reslizumab sc in paediatric patients with asthma aged from 6 to <12 years. Following single doses of reslizumab, the overall mean plasma concentration-versus-time profiles of reslizumab were characterized by a slow period of drug absorption followed by a generally monophasic decline from peak levels throughout 83 days after administration. Cmax and AUC increased in an approximately dose proportional manner over the dose range of 33 to 165 mg, though not supported by the statistical analysis with pre-defined criteria. Each treatment suppressed eosinophils to a comparable extent with a mean percentage decrease of 57to 69% observed as early as the first post- baseline time point (48 hours post-dose). This suppression was more sustained for the higher dose groups.

Evaluation of the immunogenicity of reslizumab was a secondary objective. Four of 36 patients (11%) had a treatment-emergent anti-reslizumab antibody positive status; 2 patients in the reslizumab 33 mg sc group, and 1 patient in each of the reslizumab 110 and 165 mg sc groups. ADA positive status was transient in 3 of the 4 patients and the antibody titers in all 4 patients were low.

There were no assessments of efficacy in Study C38072-AS-10069. The safety profiles of patients in all 3 dose groups were similar for at least up to 84 days after the single sc dose of reslizumab in the upper arm. Most adverse events were mild in intensity. There were no serious adverse events, and no patients were withdrawn from the study due to adverse events. The most frequently occurring adverse events in all treatment groups were injection site reactions, reported in 5 of the 36 patients. These injection site reactions were reported as adverse events of either injection site pain or injection site reaction that were mild in severity and resolved without intervention. All were considered related to study treatment. There was no apparent relationship between dose and the incidence of injection site reactions.

3. Rapporteur's overall conclusion and recommendation

Reslizumab was well tolerated when administered as sc doses of 33, 110, and 165 mg, and the safety profile of the single dose of reslizumab was similar across the dose groups.

The submitted clinical study data with reslizumab sc in paediatric patients did not influence the benefit risk evaluation of the registered reslizumab 10 mg/ml IV formulation in adults. Since the sc formulation is not being developed anymore and sc administration is not included in the current registration dossier for Cinqaero, i.e. Cinqaero is only registered for iv administration, it could be agreed with the applicant that inclusion of the currently provided paediatric sc data in the SmPC is not needed at this stage.

The stop in development of the sc formulation is likely initiated by Study C38072-AS-30025, that was terminated early due to lack of efficacy. Clinical data of this study, investigating 110 mg fixed sc reslizumab dosing in patients aged 12 and older with uncontrolled asthma and elevated blood eosinophils, is currently assessed by the CHMP in LEG procedure EMEA/H/C/003912/LEG. However, in paediatric investigation plan EMEA-0012-02-PIP02-13, the development of a subcutaneous formulation in paediatric patients aged 6-<12 was specifically requested, since the reslizumab mechanism of action was expected to be relevant in children with EA ages 6 through 11 years, and these patients would be better served by a sc formulation administered via a thin needle, rather than by an iv infusion, due to the inconvenience and pain associated with iv infusions. Stopping development of the sc formulation in children aged 6-11 has, therefore, consequences for the existing agreed paediatric investigation plan, and should be discussed within the PDCO.

☒ Not fulfilled:

In paediatric investigation plan EMEA-0012-02-PIP02-13, the development of a subcutaneous formulation in paediatric patients aged 6-<12 was specifically requested. Stopping development of the sc formulation in children aged 6-11 has consequences for the existing agreed paediatric investigation plan and should be discussed within the PDCO.

4. Additional clarification requested

N/A