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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/P46/011.1

Note

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

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1. Introduction

On 11-4-2018, the MAH submitted a completed paediatric study for Cinqaero, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended (procedure EMEA/H/C/003912/P46/010).

During this procedure, data for study C38072-AS-30066: *An Open-Label Extension Study of Reslizumab 110-mg Fixed, Subcutaneous Dosing in Patients 12 Years of Age and Older with Severe Eosinophilic Asthma* was submitted, which 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. However, since the extension application did not proceed as planned, this study report was submitted as a standalone study.

The submitted clinical study data with reslizumab sc did not influence the benefit risk evaluation of the registered reslizumab 10 mg/ml IV formulation in adults. No update on the clinical aspects of the SmPC was therefore considered necessary. However, additional clarification was requested on a pharmacokinetic aspect and this follow-up post-authorisation measure EMEA/H/C/003912/P46/011.1 therefore addresses the following question remaining from the above-mentioned procedure:

The applicant should discuss the discrepancy between the SmPC and the presented results, with regard to blood concentrations in the paediatric population. If necessary, the SmPC should be adjusted accordingly.

The MAH applicant provided the requested discussion on the effect of age on the pharmacokinetics of reslizumab. It is agreed that no relevant influence of age is identified and the effect of weight is adequately accounted for in the current SmPC (approved dosing for IV administered reslizumab is weight-based).

2. Scientific discussion

2.1. Clinical aspects

2.1.1. Introduction

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 inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

In this application, results of subcutaneaous (sc) reslizumab in patients from 12 years of age were presented in the clinical study report of Study C38072-AS-30066: An Open-Label Extension Study of Reslizumab 110-mg Fixed, Subcutaneous Dosing in Patients 12 Years of Age and Older with Severe Eosinophilic Asthma. A total of seventeen patients (4%) were 12 to <18 years of age were included in this study.

Study C38072-AS-30066 was initiated in March 2017, and terminated early on 22 February 2018 because the primary endpoint of parent placebo-controlled Study C38072-AS-30025 (the 52-week clinical asthma exacerbation [CAE] study for registration) was not met.

2.1.2. Pharmacokinetics

In Study C38072-AS-30066, reslizumab concentrations were assessed from anti-drug antibody blood samples, which were collected predose at baseline and at weeks 8, 24, and 36 (end of treatment or early withdrawal visit) (Study C38072-AS-30066 CSR).

In the table below, observed pharmacokinetic (PK) data are summarised for each PK sampling timepoint and stratified by age (12 to <18 years and ≥18 years). Data indicate that the lower age group had higher concentrations at weeks 8 and 24. This is similar to parent Study C38072-AS-30025, in which the lower age group (12 to <18 years) had higher concentrations at all visits during the double-blind treatment period than the higher age group (≥18 years) (Article 46 Response for Study C38072-AS-30025). In Study C38072-AS-30066, this trend is not observed on the first visit because roll-over from the parent study was non-seamless for all adolescent patients (age 12 to <18 years), whereas roll-over was mixed (ie, seamless and non-seamless) for the adult population. The timing of PK concentrations taken at early withdrawal and end of treatment varied across the treatment interval due to early termination of the study; therefore, data do not represent concentrations 4 weeks after the last dose, and results should be interpreted carefully.

Because only predose concentration was collected in this study, other PK parameters are not calculated.

Table: Pharmacokinetic Serum Drug Concentration Data (ng/mL) at Each Visit by Age Group (Safety Analysis Set)

Time point Statistic	12 to <18 years (N=17)	≥18 years (N=373)	Total (N=390)
Visit 1 (week 0)			
n	16	258	274
Mean (SD)	295.91 (444.131)	726.08 (2198.687)	700.96 (2138.212)
Visit 3 (week 8)			
n	17	344	361
Mean (SD)	8082.32 (3072.489)	5230.49 (2501.648)	5364.79 (2597.739)

Time point Statistic	12 to <18 years (N=17)	≥18 years (N=373)	Total (N=390)
Visit 7 (week 24)			
n	1	219	220
Mean (SD)	13440.90 (—)	6564.44 (3628.436)	6595.70 (3649.708)
EW/EOT (week 36)			
n	17	365	382
Mean (SD)	9358.12 (4367.755)	6696.03 (3628.880)	6814.50 (3699.253)

Source: Article 46 Summary 4.
EOT=end of treatment; EW=early withdrawal; N=total number of patients; n=number of patients in subgroup; SD=standard deviation.

2.1.3. Remaining request for supplementary information

These presented pharmacokinetic results indicate an effect of age on pharmacokinetics, as the 12 to <18 years age group had higher pre-dose concentrations of reslizumab than the group >18 years. This is in line with findings from Study C38072-AS-30025. However, the higher exposure in the lower age group is not in line with the current information in the SmPC for the product.

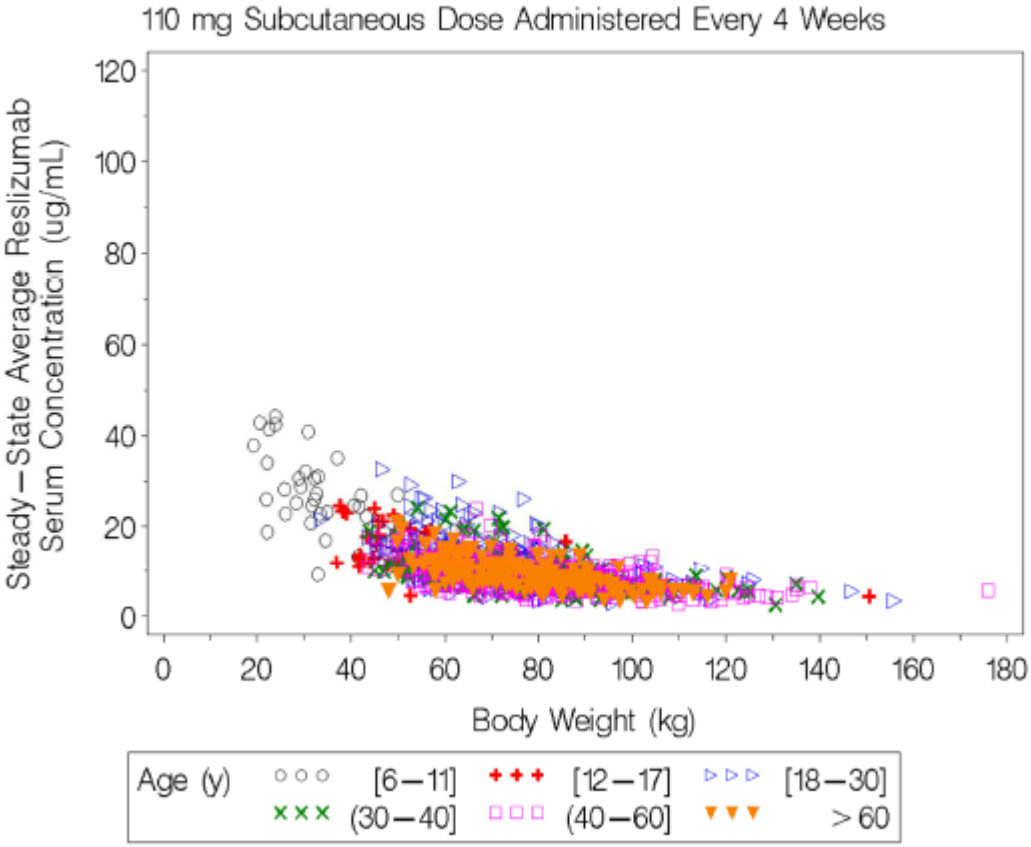
The applicant should discuss the discrepancy between the SmPC and the presented results, with regard to blood concentrations in the paediatric population. If necessary, the SmPC should be adjusted accordingly.

MAH response:

The observed pharmacokinetic (PK) data in Study C38072-AS-30066 and Study C38072-AS-30025 following administration of subcutaneous (sc) fixed-dose 110 mg reslizumab indicate that the lower age group (12 to <18 years) had higher concentrations than the higher age group (≥18 years; refer to Question 1 of document Response to Questions Article 46 Study C38072-AS-30025 CSR, previously submitted in sequence 0055; Question 1 of document Response to Second List of Questions Article 46 Study C38072-AS-30025 CSR, previously submitted in sequence 0062; and Question 1 of document Response to Questions Article 46 Study C38072-AS-30066 CSR, previously submitted in sequence 0059).

Using a population PK model containing concentration-time data collected following either intravenous (iv) or sc reslizumab administration in subjects 6 to 11 years of age, 12 to 17 years of age, and ≥18 years of age, the applicant initially determined that weight and age were influential covariates that explained variability in reslizumab concentration levels (refer to Section 6.1.11 of Report CP-17-15, previously submitted in sequence 0051). Specifically, lower weight and younger age resulted in higher concentrations, as illustrated in Figure 1. To assess how influential the age and weight covariates were on the prediction of the average concentration at steady-state values, the final model including the age and weight covariates was evaluated in comparison to the model with only the weight covariate from the prior model refinement step. This model illustrated the limited influence of age as a covariate and demonstrated that weight is clearly the major contributor to the differences between exposures in paediatric patients and adults (refer to Question 1 of document Response to Questions Article 46 Study C38072-AS-30025 CSR, previously submitted in sequence 0055).

Figure 1: Scatterplot of Model-Predicted Steady-State Average Reslizumab Serum Concentrations Versus Body Weight, Stratified by Age Group, Following Hypothetical 110 mg Subcutaneous Dosing Every 4 Weeks

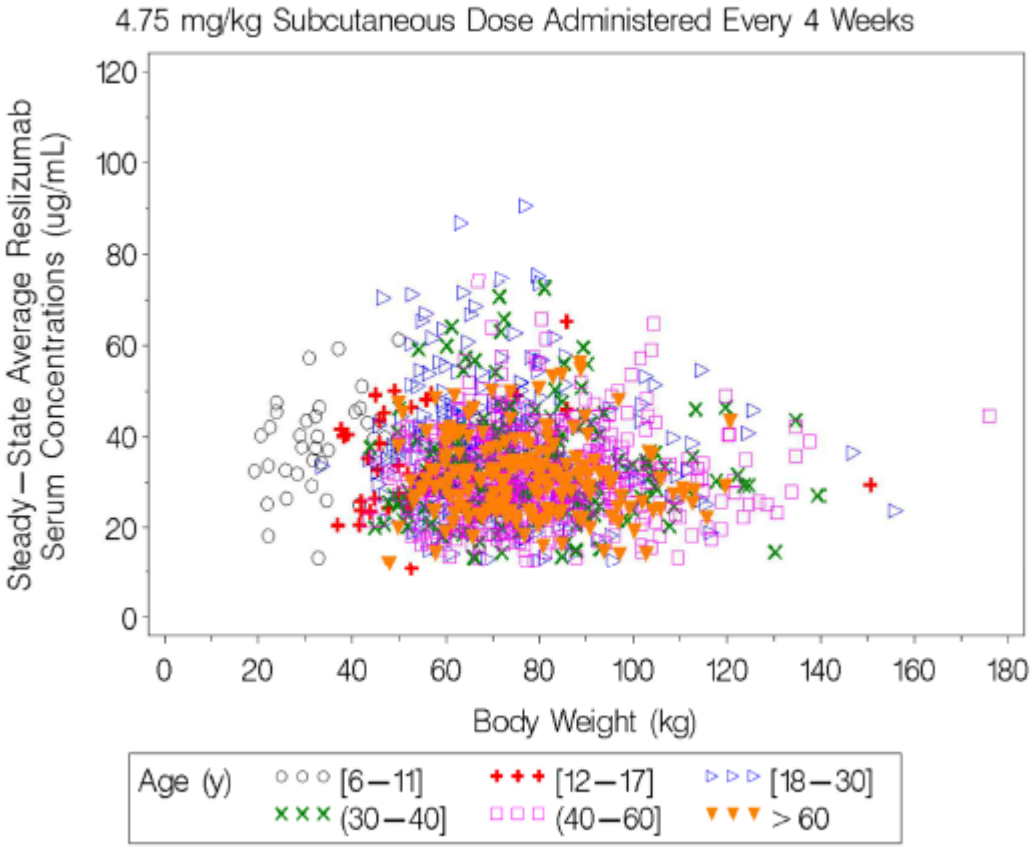


Source: Figure 38 of Report CP-17-15, previously submitted in sequence 0051.
Abbreviation: y=years.

A simulation utilising a hypothetical 4.75 mg/kg sc dose of reslizumab and the model described in Report CP-17-15 suggested that lower variability in exposures is expected across body weights with weight-based dosing (Figure 2) and that normalisation of the predicted concentrations occurred when the weight effect was minimalised through this approach. In this simulation, the exposures in patients 6 to <12 years of age and 12 to <18 years of age were shown to be similar to those of older and higher-weight patients, eliminating the differences in observed concentrations between younger and older patients. It should be noted that weight-based dosing for reslizumab sc at any dose level would result in consistent exposures across weights as predicted for 4.75 mg/kg.

This simulation suggested that lower variability in exposures is expected across body weights with weight-based dosing by minimising the weight effect. These results suggest that fixed dosing (as utilised in the sc reslizumab programme) will result in higher variability in exposures and that weight-based dosing (as utilised in the iv reslizumab programme) would reduce variability in exposures.

Figure 2: Scatterplot of Model-Predicted Steady-State Average Reslizumab Serum Concentrations Versus Body Weight, Stratified by Age Group, Following Hypothetical 4.75 mg/kg Subcutaneous Dosing Every 4 Weeks



Source: Figure 38 of Report CP-17-15, previously submitted in sequence 0051.
Abbreviation: y=years.

The information provided in the Summary of Product Characteristics (SmPC) for the PK properties of iv reslizumab is relevant to the weight-based dosing regimen of the approved iv CINQAERO® product. The PK results from Study C38072-AS-30025 and the long-term extension Study C38072-AS-30066 were determined within the sc fixed-dose reslizumab programme, utilising the investigational subcutaneously administered product. These studies were terminated as the potential registration study, Study C38072-AS-30025, utilising sc reslizumab 110 mg, did not meet the primary end point of clinical asthma exacerbation risk reduction. Patient weight is a significant covariate affecting reslizumab exposure (as described above). Weight influence on exposure is more pronounced in the sc fixed-dose regimen, which is not adjusted to weight, compared to a weight-based dosing. The differences noted between the reslizumab blood concentrations from the studies from the sc fixed-dose reslizumab programme and the reslizumab blood concentration in the SmPC from the iv weight-based dosing programme for exposures in adolescents (12 to <18 years of age) in comparison to adults (≥18 years of age) are explained by the effect of body weight on the fixed dosing of the investigational product, which is corrected for by weight-based dosing of the approved iv product.

Based on the above-mentioned data, the applicant believes that the findings from the sc programme utilising the investigational formulation and fixed-dose regimen are not relevant to the approved iv weight-based product and are consistent with the current information in the SmPC for iv reslizumab product.

CHMP assessment

The MAH provided a discussion on the effect of age on the pharmacokinetics of reslizumab. The MAH believes that the findings from the SC programme are not relevant for the approved IV weight-based dosing and are consistent with the current information in the SmPC. This is agreed.

Both weight and age were originally identified in the population pharmacokinetic modeling as significant covariates explaining pharmacokinetic variability of reslizumab. However, based on the presented argumentation and results, it can be agreed that the influence of age as a covariate on reslizumab exposure is only limited, while the influence of weight on reslizumab exposure is much more pronounced. The applicant performed a simulation study with the original model (weight and age included) and a summary of the results (scatterplot) was presented; indeed, no additional effect of age on the pharmacokinetics can be discerned.

As no influence of age is identified and the effect of weight is adequately accounted for in the current SmPC (approved dosing for IV administered reslizumab is weight-based), no action is further required.

Issue resolved

3. CHMP's overall conclusion and recommendation

The MAH applicant provided the requested discussion on the effect of age on the pharmacokinetics of reslizumab. It is agreed that no relevant influence of age is identified and the effect of weight is adequately accounted for in the current SmPC (approved dosing for IV administered reslizumab is weight-based). The issue is considered resolved and no action is further required.

☒ **Fulfilled:**

☐ **Not fulfilled:**

Please refer to the second list of questions as part of this procedure

4. Additional clarification requested

None