

Application of model informed drug development to pediatric program for ligelizumab in Chronic Spontaneous Urticaria

P11-05

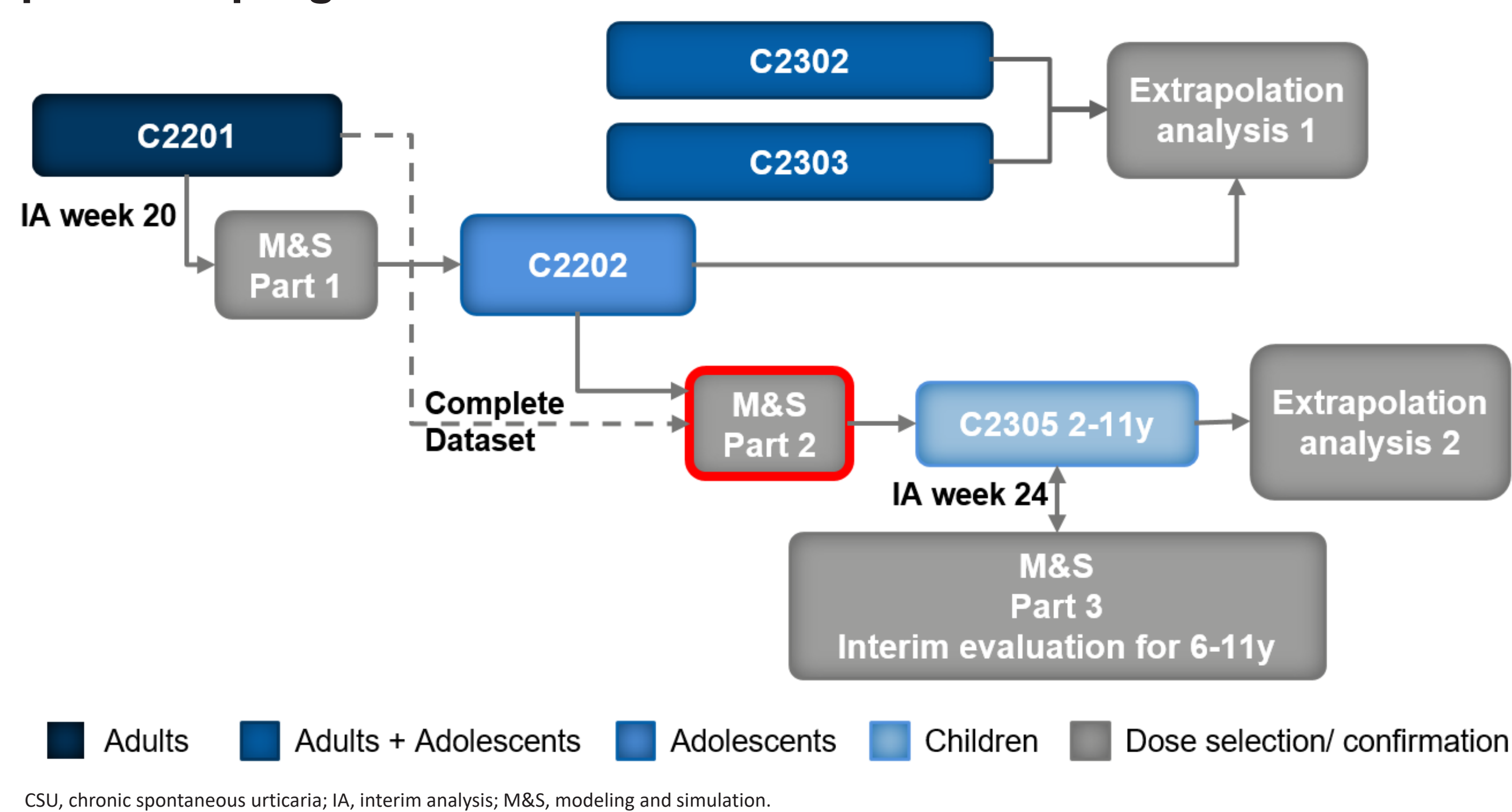
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Introduction

- Chronic spontaneous urticaria (CSU), a disease characterized by spontaneous occurrence of itchy wheals (hives), angioedema, or both for at least 6 consecutive weeks, is prevalent in all age groups [1]. The clinical need of full control of urticaria symptoms remains unmet in a large proportion of patients [2,3], with particularly limited treatment options in children.
- Ligelizumab is a next-generation high-affinity humanized monoclonal anti-IgE antibody that was shown to provide rapid, strong and sustained symptom control of CSU in adult patients [2,4]
- The pediatric development program for ligelizumab in CSU is an example of how model informed drug development (MIDD) can be utilized to inform design and dose selection at various stages of pediatric drug development. The program itself consists of three M&S simulation activities and two extrapolation analyses staggered around the availability of interim and final results from the Phase 2 and 3 studies in adults, adolescents and children (Figure 1). The first M&S activity in this program guided the design of adolescent dose finding study [5]. Here, we will discuss results of the recently completed second of the planned M&S activities (M&S Part 2).

Figure 1 Flow of clinical studies and M&S activities in the ligelizumab pediatric program in CSU



CSU, chronic spontaneous urticaria; IA, interim analysis; M&S, modeling and simulation.

Objectives

- Describe the pharmacokinetics (PK) and exposure-response (ER) relationship to ligelizumab in the adolescent CSU patients from Phase 2b study C2202 [6] and compare to adult CSU patients from Phase 2b study C2201 [7].
- Propose dosing algorithm to be tested in children.

Methods

- Adult population PK (PopPK) and ER models were developed in Monolix 2019R2 using data from the adult study C2201 [7].

PK model

- Ligelizumab PK in adults was described using a 2-compartmental PopPK model [8].

Exposure-response model

- Disease activity in CSU was assessed with weekly urticaria activity scores (UAS7) on scale 0 (no disease activity) to 42 (maximal disease activity). Longitudinal changes in UAS7 (modelled on transformed logit scale) in adults were described using an indirect response model for drug effect combined with an exponential decay model for placebo effect. The inhibitory effect of ligelizumab concentrations on the effect onset rate was expressed using a sigmoidal (hyperbolic) function with an EC50 and Hill coefficient [8].

Analysis steps

- Step 1:** adult PopPK and ER models were used to predict data collected in adolescent study C2202 [6]. Each adolescent in study C2202 was simulated 1000 times using individual demographic characteristics and actual dosing history. Trends in predicted and observed data were visually compared.
- Step 2:** models were refitted on pooled adolescent and adult data.
- Step 3:** simulations based on PK matching were conducted to propose doses to be tested in children.

Results

Table 1 Demographic characteristics

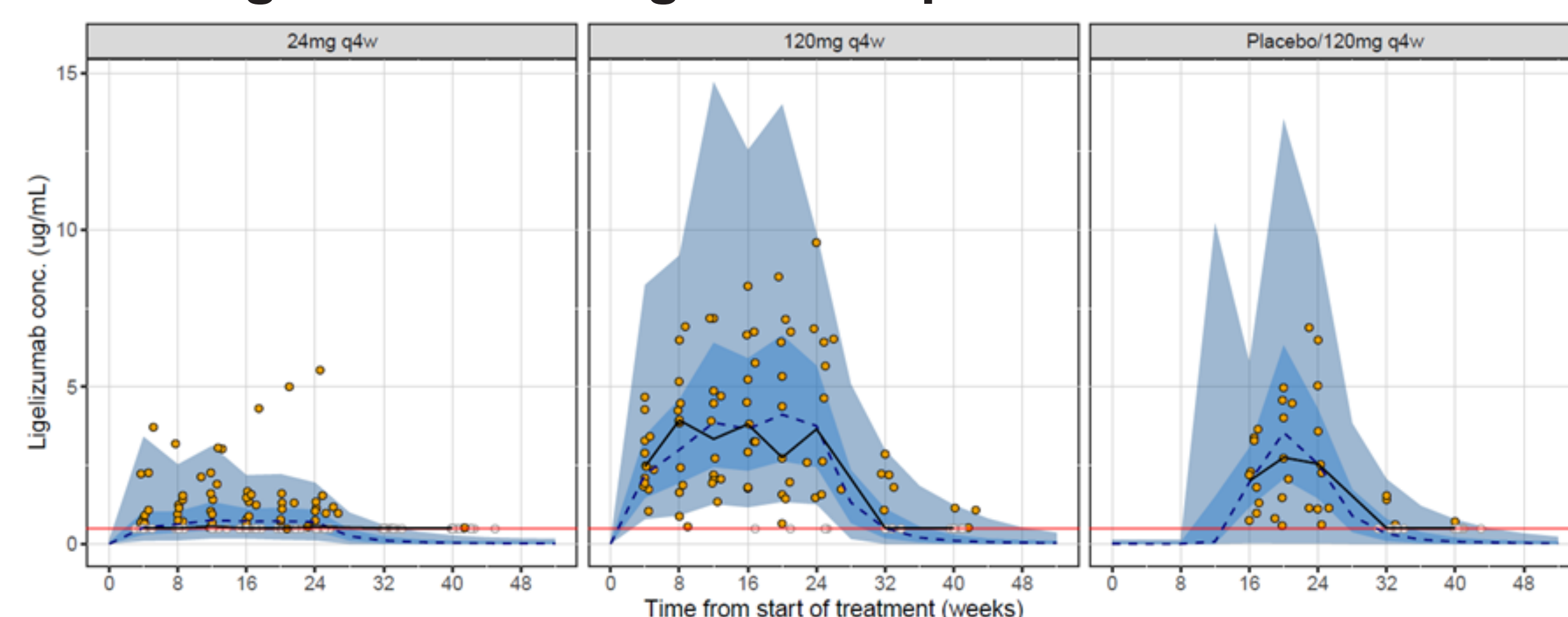
Study	C2201	C2202
Patient number	297 adults	49 adolescents
Age (years) ¹	43.8 (28%, 18-73)	14.8 (11%, 12-17)
Body weight (kg) ¹	76.5 (25%, 40.3-152.5)	63.9 (26%, 31-117)
Baseline total IgE (IU/mL) ²	87.4 (27.2-189.5)	139 (73.6-252)

¹ mean (CV, range), ² median (IQR). CV, coefficient of variation; IgE, immunoglobulin E; IQR, interquartile range.

Is there a difference in PK between adults and adolescents?

- Step 1: adult PopPK model predicted ligelizumab concentrations observed in adolescents in study C2202 (Figure 2).
- Step 2: subsequent model fitting on pooled data showed that ligelizumab PK was correlated with body weight (accounted for by allometric scaling on all volume and clearance parameters) but did not differ with age.

Figure 2 Overlay of observed PK data in study C2202 and predictions generated using adult PopPK model

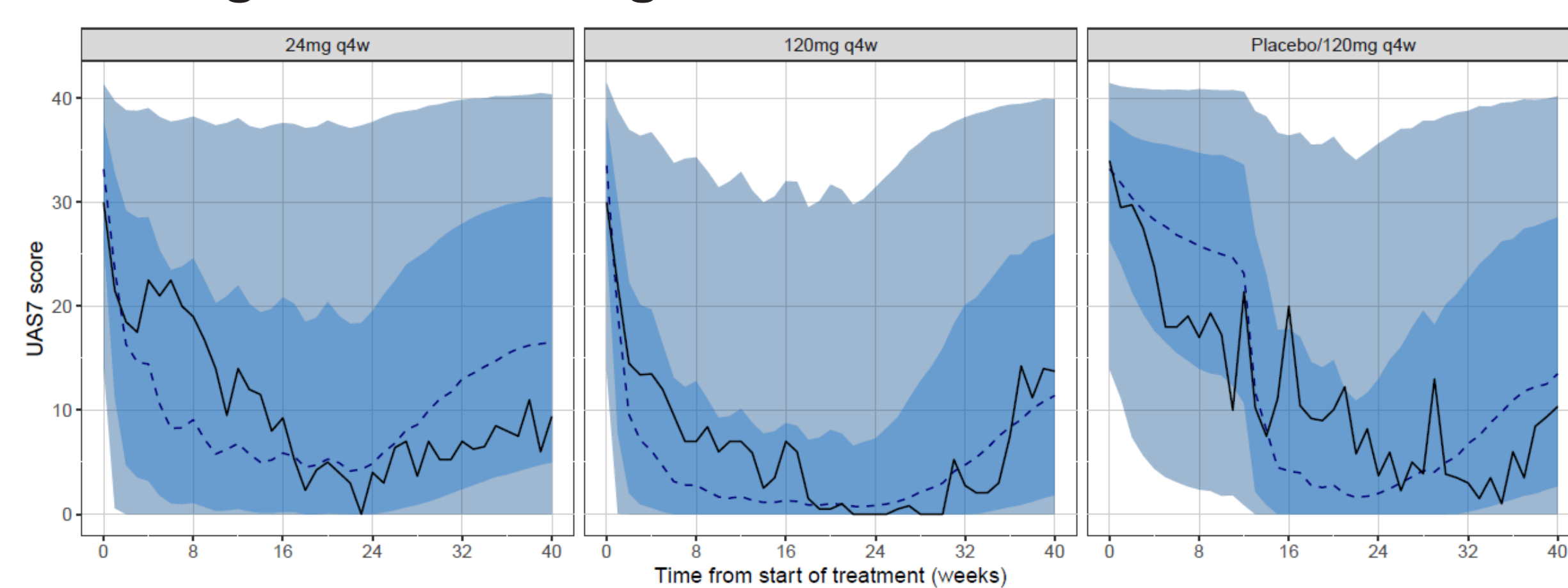


Light shaded area corresponds to 90% PI for PK profiles generated using adult PopPK model, dark shaded area corresponds to 50% PI, yellow points - ligelizumab concentrations > lower limit of quantification (LLOQ), hollow points - ligelizumab concentrations < LLOQ, red horizontal line - LLOQ (0.5 ug/mL), dashed blue line - median of simulated PK, solid black line - median of observed.

Is there a difference in ER between adults and adolescents?

- Step 1: Adult ER model predicted changes in UAS7 scores observed in adolescents in study C2202 (Figure 3).
- Step 2: Subsequent model fitting showed that ligelizumab potency based on EC50 for UAS7 scores was comparable between adults and adolescents.

Figure 3 Overlay of observed UAS7 data in study C2202 and predictions generated using the adult ER model

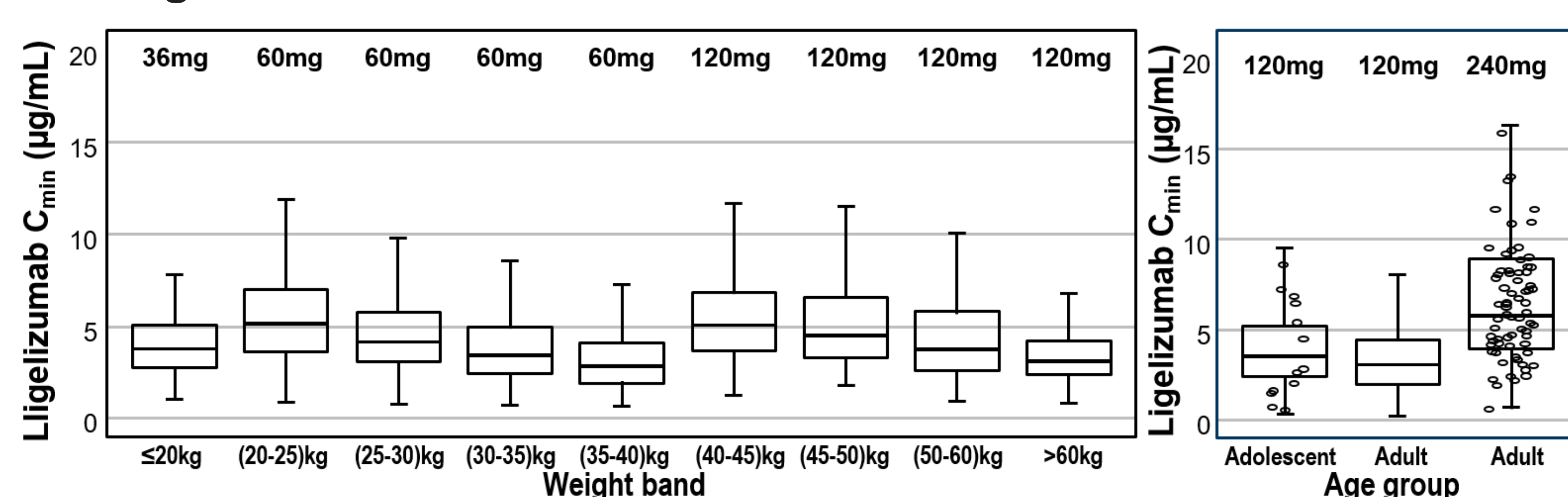


Light shaded area corresponds to 90% PI for UAS7 profiles generated using adult model, dark shaded area corresponds to 50% PI, dashed blue line - median of simulated UAS7, solid black line - median of observed UAS7.

What is the best dose for children? (Step 3)

- Following weight band-based dosing was proposed for children: dose equal to adult dose for > 40 kg, 50% of adult dose for 20 kg to 40 kg, 30% of adult dose for < 20 kg.
- The proposed dosing regimen provides balanced exposures across all weight bands expected in children aged 6 to <12 years (Figure 4), with exposure ranges greatly overlapping with the ones predicted for adolescents and adults.

Figure 4 Predicted steady-state C_{min} by weight bands under proposed dosing scenario in children and adolescents and adults



Boxplots represent distribution of simulated steady-state trough ligelizumab concentrations in presented subgroups, with dose as indicated above each boxplot. The hollow points correspond to observed data in adults in study C2201 and in adolescents in study C2202.

Conclusions

- MIDD can support and accelerate the clinical development in pediatrics.
- In adolescent patients with CSU, ligelizumab exhibited PK and ER consistent with those known in adults. This similarity may permit the use of the same dose for treatment of CSU in both age groups, an approach that is currently being tested in the pivotal studies.
- Confirmation of no significant age-related differences in ligelizumab PK and EC50 between adults and adolescents supported use of partial extrapolation for the paediatric development. Therefore, the dose selection for children was based on the assumption that similar PK exposures should provide similar response across all age groups.

References

[1] Zuberbier T, et al. Allergy. 2018;73(7):1393-1314. [2] Maurer M, et al. Poster presented at: EADV 2018; September 12-16, 2018; Paris, France. [3] Maurer M, et al. Clin Exp Allergy. 2019;49:855-862. [4] Sekerel BE, et al. Presented at: EADV; September 29-October 2, 2021; Virtual Meeting Experience. [5] Lowe P, et al., PAGE 2018 [6] Study to Investigate the Efficacy and Safety of QGE031 in Adolescent Patients with Chronic Spontaneous Urticaria (CSU). <https://clinicaltrials.gov/ct2/show/NCT03437278?term=QGE031C2202&draw=2&rank=2> [7] Maurer M, et al., N Engl J Med 2019; 381:1321-32. [8] Savelieva M, et al., "Pharmacometrics and Integrated Evidence Generation: example of ligelizumab in Chronic Spontaneous Urticaria", PAGE 2022

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