

Ligelizumab Paediatric Investigation Plan: exposure-response analysis in adult chronic spontaneous urticaria with simulation-estimation based design of adolescent dose-finding

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Situation, complication, objective

- Ligelizumab binds immunoglobulin E with higher affinity than omalizumab
- Potentially benefits more patients with chronic spontaneous urticaria (CSU)
- For omalizumab the paediatric investigational plan (PIP) noted significantly reduced potency (higher EC50) in adolescent versus adult population [1]
- Therefore cannot assume that equivalent ligelizumab concentrations would result in equivalent efficacy in these two CSU populations

Objective Design minimal ethical adolescent study to determine whether EC50 for adolescents sufficiently different from adults as to demand different posology

Step 1a, develop adult model

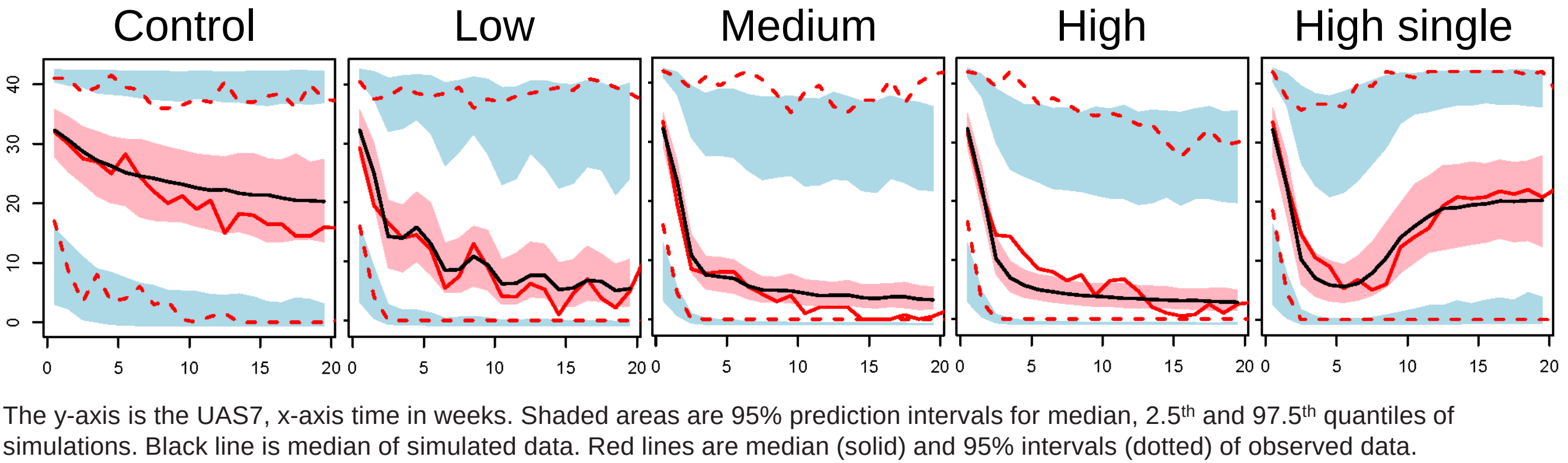
Ligelizumab concentrations and urticaria activity scores (UAS7, 7 day sum of daily itch and hives (0,1,2,3) total score range 0-42) from adult patients treated with placebo, low, medium and high doses every 4 weeks multiple and a high single dose in Phase 2 study [2]. Interim data from 295 patients analysed in longitudinal pharmacokinetic-pharmacodynamic model for continuous UAS7 using NONMEM with importance sampling (**Figure 1**).

Step 1b, check prediction of adults

Two-compartment pharmacokinetics described data well. Clearance 0.85 L/d (residual standard error, RSE, 9.1%) @ 80 kg weight; 49% between subject variation (BSV). Main covariate on clearance weight, power 1.0 (35% RSE).

Continuous UAS7 indirect response model with EC50 1.1 µg/mL (38% RSE) with large BSV (1405%) and steep Hill coefficient 5.72 (0.75% RSE). Visual prediction check deemed sufficient (**Figure 1**) to initiate adolescent study design process over a number of options.

Figure 1 Visual prediction check adult dose range finding



Step 2a, design next study

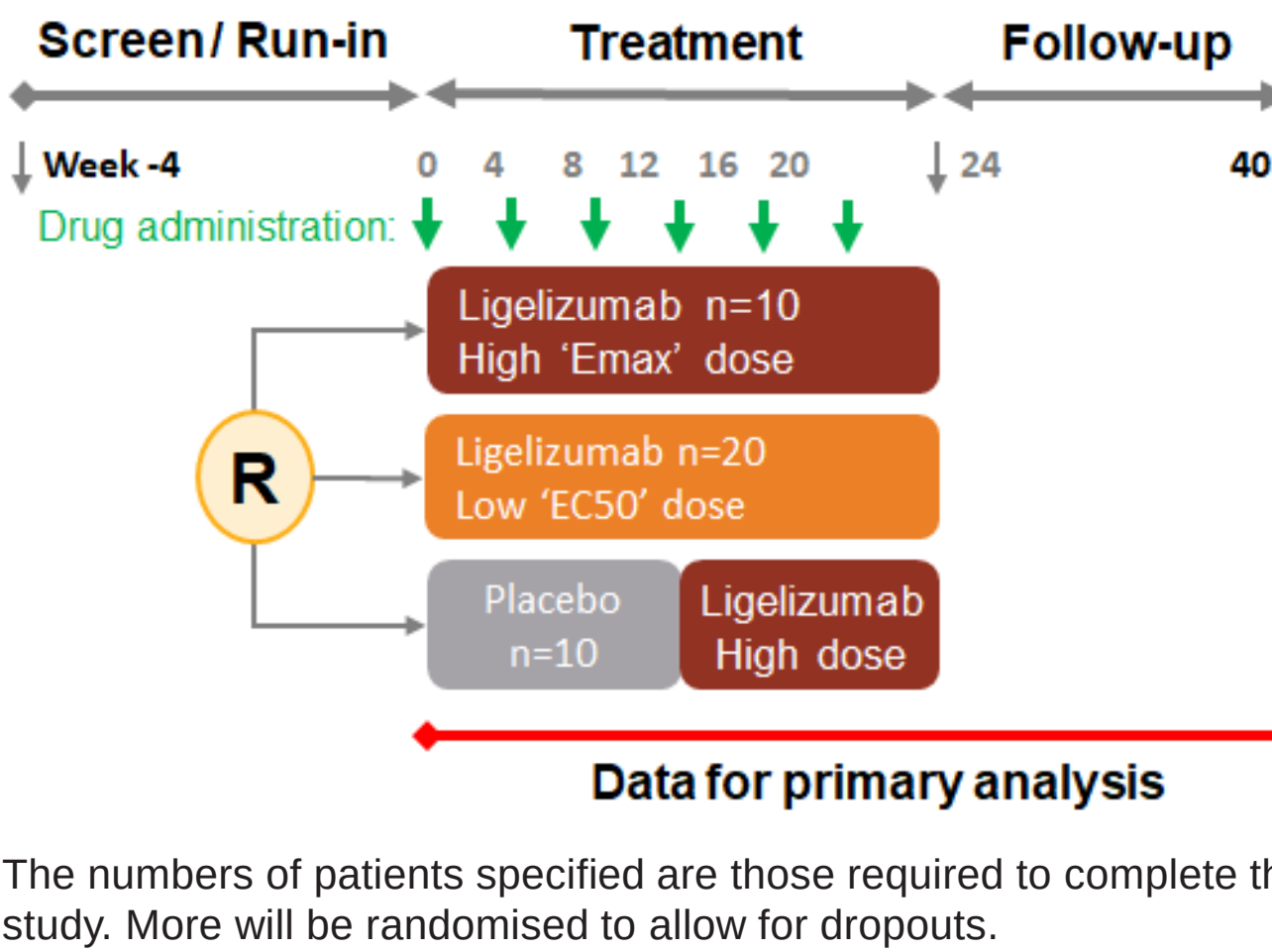
Stochastic simulation-estimation evaluated design options for adolescent CSU patients aged 11-17 years. Per design 100 NONMEM simulations estimated and adolescent EC50 ratioed to known adult value. For numerical stability EC50 BSV was reduced to 300%; sensitivity analysis showed little impact for 0, 100, 200 versus 300%. Software R-3.2.3, NONMEM 7.3.0 [3], PDX-Pop-5.2.

Step 2b, results

Figure 2 Three arm design, high being top dose from adult Phase 3, low to generate concentrations at expected EC50, plus placebo → active control.

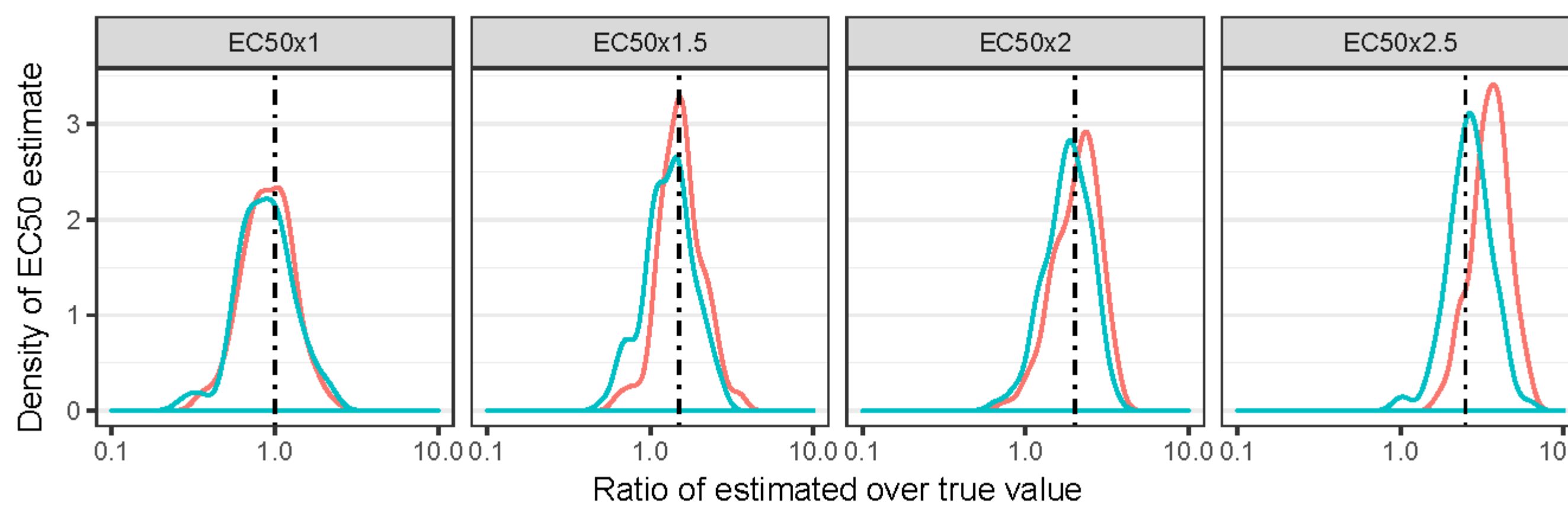
Figure 3 Distribution of 100 estimated ratios adolescent/adult EC50 for different assumptions of true difference. Two low dose options evaluated; chosen was that most accurate and precise for prior omalizumab 1.5 fold difference.

Figure 2 Adolescent design



The numbers of patients specified are those required to complete the study. More will be randomised to allow for dropouts.

Figure 3 Distribution estimates adolescent/adult EC50 ratios



The coloured density curves are two design options. Red has the low dose matching the expected EC50; blue for a dose twice that of the first. The "Emax" dose in both study designs was the same high dose level going forward into the adult Phase 3 program.

Step 2b, design results (continued)

Based on 100 trial simulation-estimations, procedure indicated approximately 80% chance to detect a 2-fold increase in EC50 (**Table 1**) the threshold above which a different posology should be considered for adolescents versus adults

Table 1 – Expected accuracy, precision, confidence intervals and ability to detect adolescent-adult EC50 differences

True difference in EC50	Across 100 trial simulation-estimations			Success rate to detect difference at 90% level
	Precision (CV)	Accuracy (estimate/true)	90% CI for ratio	
None	36%	92%	0.50 – 1.6	21%
1.5 fold	33%	102%	1.0 – 3.2	47%
2 fold	30%	110%	1.1 – 3.2	79%
2.5 fold	26%	145%	2.2 – 5.4	100%

NONMEM stochastic simulation-estimation concatenated \$SIM, each run different seed, then \$EST. Estimation by importance sampling i.e. MET=IMP LAP NUMER SLOW INT NITER=1000 ISAMPLE=300 SEED=540124 SIGL=6 CTYPE=2 MAPITER=1 PRI=1 FNLETA=0

Conclusions

- Exposure-response model described adult placebo and ligelizumab dose-related changes in UAS7 over time reasonably well despite variable data
- Ligelizumab clearance estimates and EC50 potency for reducing urticaria symptoms as expected from previous clinical studies and analyses [4,5,6]
- Stochastic simulation-estimation indicated a design with two parallel active dose levels plus placebo-active crossover control should suffice for prospective adolescent study
- Low dose prioritised to generate concentrations in region of expected EC50, the optimum point of sensitivity for estimating this parameter
- Randomisation therefore uneven, with 20 completing patients on low dose, 10 each on high and placebo. High dose, from both directly treated and crossed-over placebo patients, enables estimation of maximum drug effect
- Pharmacometric analysis will be the subject of a separate pooled modelling and simulation study as per Paediatric Investigational Plan

References

1. EMA 2014. Application II/0048 Assessment report, Section 2.3.4.2 page 10 and Section 2.3.5 page 11. accessed 17th January 2018. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000606/WC500164453.pdf.
2. EudraCT 2014-005559-16. <http://www.clinicaltrialsregister.eu/ctr-search/trial/2014-005559-16/GB> accessed 17th January 2018.
3. Bauer RJ NONMEM Users Guide Introduction to NONMEM 7.3.0. 2013. Icon Development Solutions, Hanover MD 21076, USA.
4. Lowe PJ, Fink M, Milton MN. Two case studies on how study designs can be made more informative using modeling and simulation approaches. Clin Pharmacol Ther 2017; 102(6): 908-911.
5. Gauvreau GM et al. Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. J Allergy Clin Immunol 2016; 138(4): 1051-9.
6. Lowe PJ et al. Integrated quantitation of biotherapeutic drug–target binding, biomarkers, and clinical response to support rational dose regimen selection. In: ADME and Translational Pharmacokinetics/Pharmacodynamics of Therapeutic Proteins: Applications in Drug Discovery and Development, First Edition, Zhou H, Theil FP, editors. Chapter 13. John Wiley & Sons, Inc. 2016.

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Disclosures

PJ Lowe and S Köhne-Voss are employees of and own stock in Novartis Pharma AG. R Mills and C Farrell are employees of ICON plc who were contracted by Novartis Pharma AG to perform these analyses.

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