

Population Pharmacokinetic and Exposure-Response Analyses of Tezepelumab in the Phase 3 Study (DIRECTION) Supports No Dose Adjustment in Chinese Adults and Adolescents with Asthma



Authors: Caterina Paparsenos Fernandez¹, Jose-Maria Cendros¹, Diansong Zhou², Anna Lundahl³, Lubna Abuqayyas⁴, Carlos Traynor¹, Jacqueline P. Ernest¹, Yanyan Zhang⁵, Yun Chon⁵, Chloe Wu⁵, Wei Jiang⁵, Gillian Hunter⁶, Harbans Lal³, David W Boulton⁷, Peiming Ma⁵, Yuwen Jin⁵

Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Barcelona, Spain¹; Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Boston, Massachusetts, US²; Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Gothenburg, Sweden³; Clinical Pharmacology Modeling and Simulation, Amgen, Cambridge, MA, USA⁴ Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Shanghai, China⁵; Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Cambridge, UK⁶; Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Gaithersburg, Maryland, US⁷

III-071

Abstract

Tezepelumab is a human anti-thymic stromal lymphopoietin, immunoglobulin G2λ human monoclonal antibody. It has demonstrated efficacy in severe asthma and is approved in multiple countries and regions for the treatment of patients over 12 years of age with asthma. This study aims to validate the fixed dosing regimen of 210 mg every 4 weeks (Q4W) administered subcutaneously (SC) for Chinese asthma patients (> 12 years) by examining pharmacokinetic (PK) and exposure-response (ER) relationships in a Phase 3 DIRECTION study, including Chinese asthmatic patients. Results demonstrated no significant difference in PK between Chinese and non-Chinese patients, supporting no need for dose adjustment.

Introduction

- Tezepelumab is a human monoclonal antibody (IgG2λ) that selectively targets thymic stromal lymphopoietin. It was approved in US, EU and Japan and other countries for the treatment of severe asthma in adults and adolescents.
- Tezepelumab demonstrated clinically meaningful efficacy and acceptable safety in a previous pivotal asthma phase 3 study (NAVIGATOR) conducted in non-Chinese patients with severe asthma.
- This study focuses on the population pharmacokinetics (popPK) and exposure-response relationships of tezepelumab in Chinese patients with asthma.

Methods

- The popPK of tezepelumab was characterized using pooled PK data from eight clinical studies involving both Chinese and non-Chinese asthma patients, as well as healthy subjects.
- The ER analysis was conducted using exclusively data from the Asia regional Phase 3 study (DIRECTION).

Summary of popPK Analysis

The previously established population PK model was used as an initial model: 2-compartment model incorporating body weight and race (Asian versus non-Asian) as covariates. PK simulations of final model enabled the prediction of drug exposure in virtual Chinese adolescents, based on Chinese demographic characteristics. Primary and derived PK parameters were calculated following 210 mg Q4W SC administration. Modeling and simulations were conducted in NONMEM 7 using the First Order Conditional Estimation method with Interaction and R software.

Summary of ER Analysis

The annualized asthma exacerbation rate (AAER) (primary endpoint) and the change from baseline in pre-bronchodilator (BD) forced expiratory volume in one second (FEV1) (secondary endpoint) were analyzed in relation to tezepelumab exposure. Efficacy endpoints were evaluated by dividing the results into exposure quartiles according to the through concentration in steady state ($C_{trough,ss}$).

A negative binomial regression model assessed the treatment effect of tezepelumab on AAER during the 52-week planned treatment period. For pre-BD FEV1, a mixed model with repeated measures (MMRM) was utilized. SAS and R software were used for this analysis

Results

Summary of PopPK Analysis

- The analysis included **1,602 subjects**, comprising 1,414 non-Chinese and **188 Chinese participants**, with minimal exclusions of 0.54% due to values below LLOQ.
- The updated China popPK model used a two-compartmental distribution model with first-order absorption and elimination, with typical values of 0.186 L/day for clearance, 4.13 L for central volume and a half-life of 25.3 days, all within 10% of the initial model values.
- In the China updated popPK model, Body weight (BWT), ICS dose level (no/low versus medium/high dose), and race (Asian versus non-Asian) were statistically significant covariates on CL. BWT, ICS and age had a statistically significant impact on central volume of distribution (V_c). BWT was also a significant covariate on distribution clearance (Q) and peripheral volume (V_p).
- No significant PK differences were found between a non-Chinese and Chinese adult populations (figure 1 and 2), suggesting Chinese ethnicity does not impact tezepelumab exposure.

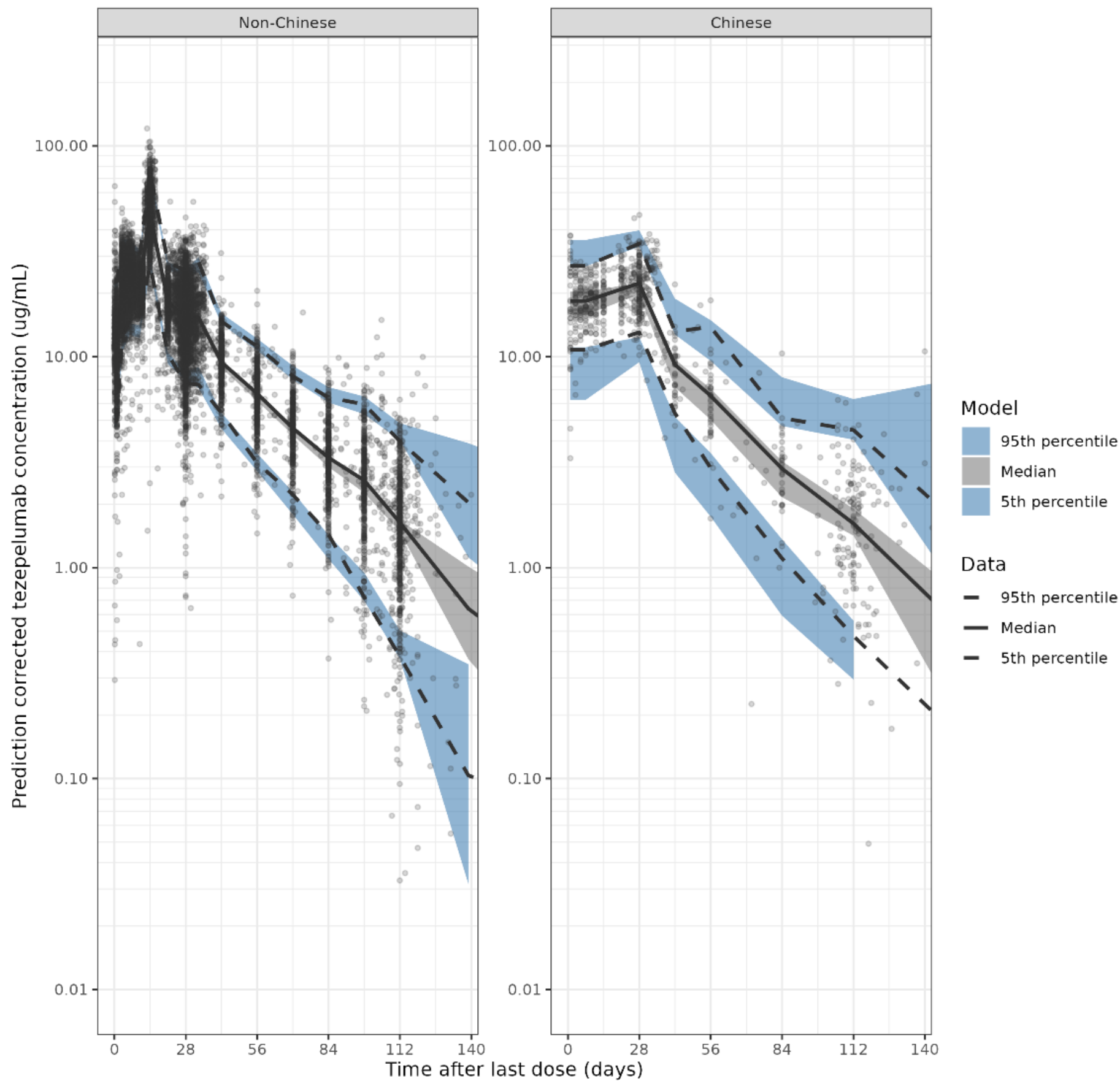


Figure 1: pcVPC of China Updated popPK Model vs Time After Last Dose – Stratified by Chinese Ethnicity Group (Chinese vs non-Chinese adults). Solid and dashed lines = the median, 5th, and 95th percentiles of the observations; shaded grey and blue areas = the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.

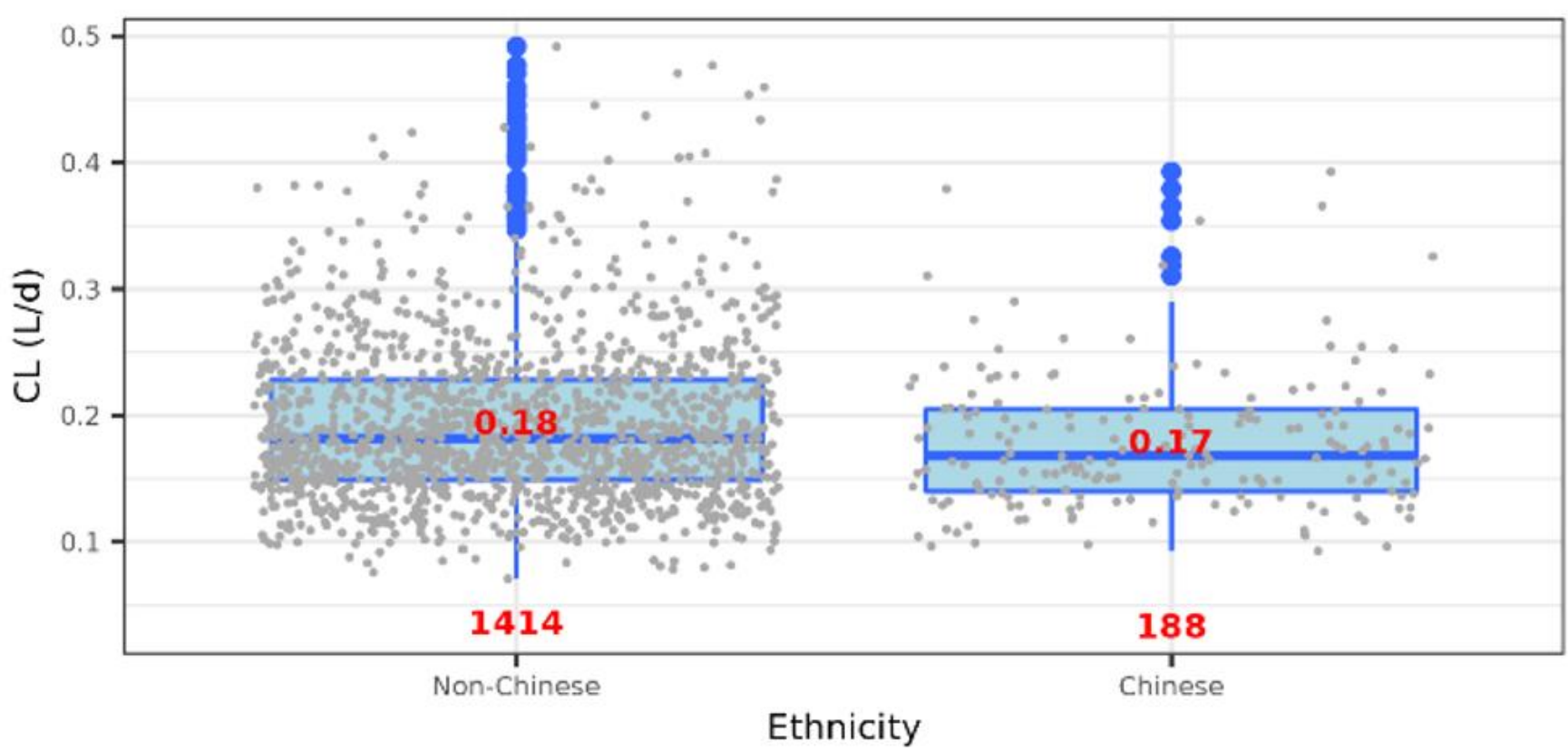


Figure 2 : Tezepelumab CL (L/day) Stratified on Chinese Ethnicity.

Summary of ER Analysis

- The dataset analysis included **190 subjects in the tezepelumab group** and **199 subjects in the placebo group**.
- The reductions in AAER (figure 3) and in pre-BD FEV1 (figure 4) from baseline over 52 weeks was larger in the tezepelumab groups than in the placebo group and consistent across the exposure quartiles for the subjects treated with tezepelumab 210 mg SC Q4W.

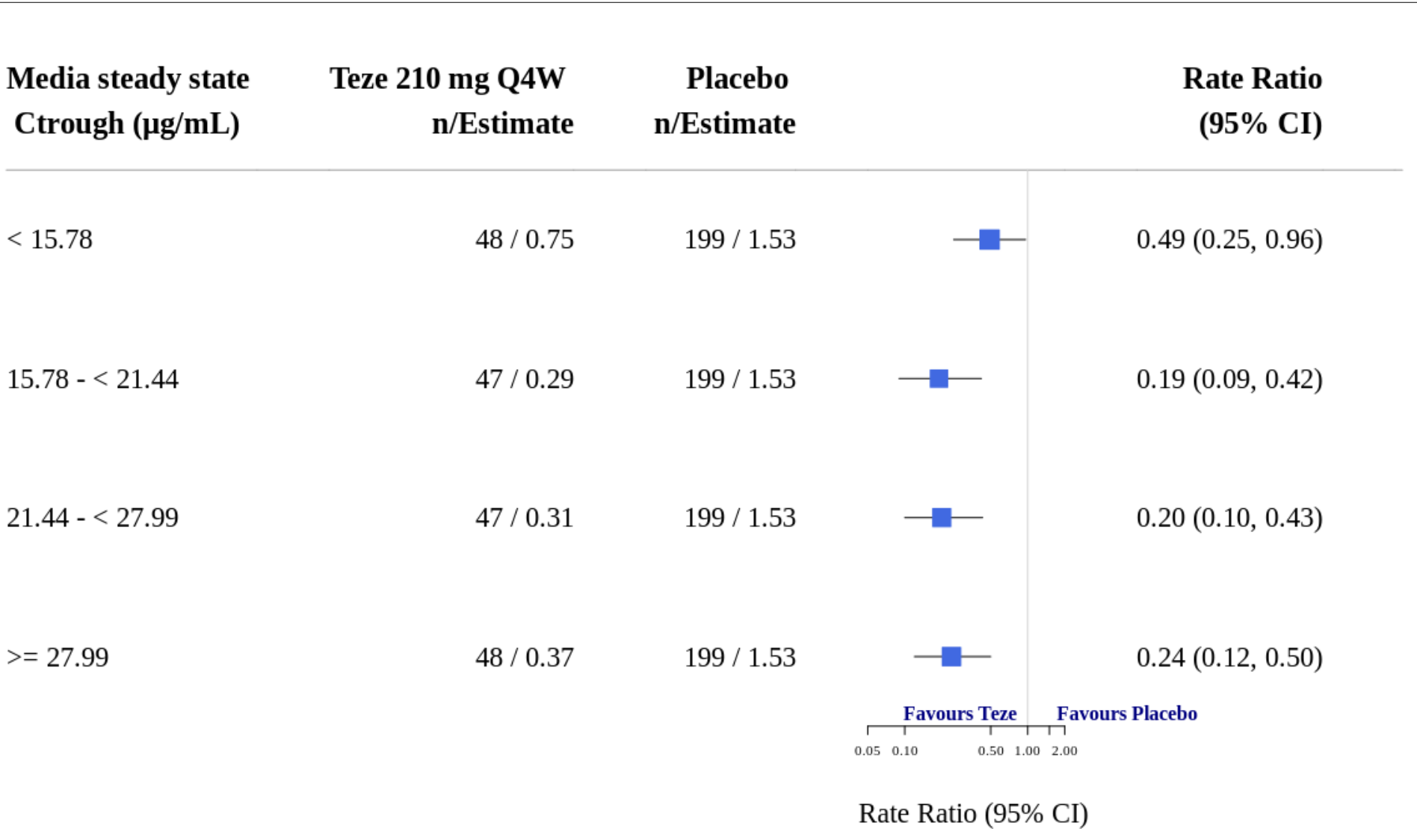


Figure 3: AAER Over 52 Weeks by Observed Median Steady State Through Concentration Quartiles, Negative Binomial Model, Planned Treatment: The overdispersion parameter had an estimation of 2.7226. Model: a negative binomial regression analysis with concentration quartiles (5 groups: Q1, Q2, Q3, Q4, and placebo), region and history of exacerbations as covariates. The logarithm of the time at risk was used as an offset variable. The marginal ratio is presented. The rate ratio is displayed on the log scale. The grey line represents no treatment difference.

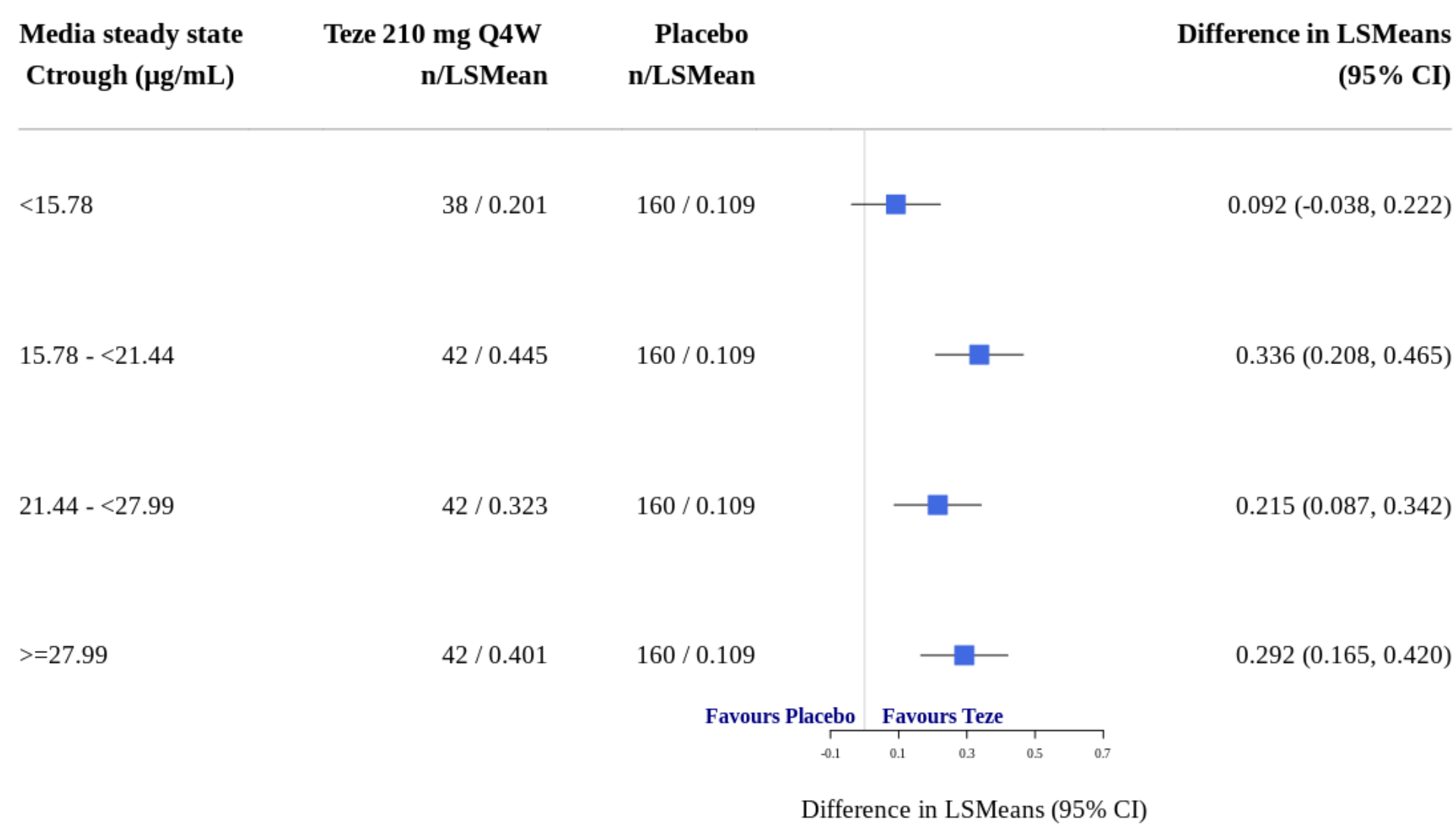


Figure 4: FEV1 (L) Pre-Bronchodilator Change from Baseline at Week 52 by Median Steady State Trough Concentration Quartiles, Mixed Model for Repeated Measures, Planned Treatment The grey line represents no treatment difference. The model is: Change from baseline in FEV1 = concentration quartiles (5 groups: Q1, Q2, Q3, Q4, and placebo) + region + baseline FEV1 + visit + concentration quartiles * visit. The Least Square Means (LSM) and their difference are presented in the plot.

Conclusions

- No statistically significant PK differences were found between non-Chinese and Chinese populations, indicating that tezepelumab exposure is unlikely to be impacted by Chinese ethnicity.
- Although virtual Chinese adolescents showed slightly higher drug exposure, it was not clinically significant, thus not requiring dose adjustments.
- The efficacy results consistently showed a reduction in AAER and pre-BD FEV1 across the exposure range with a 210 mg SC Q4W dose.

These PK and efficacy results support the established fixed dosing regimen of 210 mg SC Q4W for Chinese adults and adolescents with severe asthma.