Clinical Study Report Synopsis	
Drug Substance	Tezepelumab
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A Phase I, Open Label Study to Evaluate the Pharmacokinetics of Tezepelumab in Children ≥ 5 to 11 Years of Age with Mild, Moderate, or Severe Asthma (TRAILHEAD)

Study dates: First patient enrolled: 23 February 2021
Last patient last visit: 27 September 2022
The analyses presented in this report are based on a clinical data lock date of 23 November 2022.

Phase of development: Clinical pharmacology (I)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Six centres in 3 countries: UK (4 sites), Hungary (1 site), and South Africa (1 site).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Outcome Measures
Primary	
• To describe the PK parameters following a single SC administration of tezepelumab CCI in children with mild, moderate, or severe asthma	• Maximum concentration (C_{max}) • Time to C_{max} (t_{max}) • Area under the concentration-time curve (AUC) • Terminal phase elimination half-life ($t_{½}$) • Apparent clearance (CL/F) • Apparent steady-state volume of distribution (V_{ss}/F)
Secondary	
• To evaluate the immunogenicity of tezepelumab	• Presence of anti-drug antibodies (ADA)
Safety	
• To evaluate the safety and tolerability following a single SC administration of tezepelumab CCI	• Adverse events/serious adverse events • Vital signs • Laboratory parameters • Electrocardiogram (ECG)

PK Pharmacokinetic; SC Subcutaneous.
Exploratory objectives and results are also detailed in the body of the CSR.

Study design

This was a multicentre, open label study designed to evaluate the pharmacokinetic (PK) profile of tezepelumab following a single subcutaneous (SC) CCI dose in children aged ≥ 5 to 11 years with mild, moderate, or severe asthma.

The study consisted of a consent/screening period of up to 14 days, a treatment day (Day 1), and follow-up period of 85 days which included PK, CCI , and safety measurements. A patient was considered to have completed the study if he/she had completed his/her last scheduled contact. The end of study was defined as the date of the last visit of the last patient in the study.

Target population and sample size

The planned enrolment was approximately 24 paediatric patients aged ≥ 5 to 11 years (inclusive) with mild, moderate, or severe asthma. Of these, approximately 14 patients were to receive a single SC CCI dose of tezepelumab in an attempt to have at least 12 paediatric patients complete the study. At least 4 patients were to have a body weight < 25 kg and at least 3 patients were to have a body weight ≥ 25 kg to < 40 kg.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The investigational product was tezepelumab CCI administered as a single SC injection. Two batches of tezepelumab were used in this study: batch numbers 0010431531 and 0010499700.

Duration of treatment

Single dose

Statistical methods

No formal statistical hypothesis tests were performed. Data were provided in data listings sorted by patient number, and tabular summaries were presented. Categorical data were summarised by the number and percentage of patients in each category. Continuous variables were summarised by descriptive statistics, including the number of patients, mean, standard deviation, median, minimum and maximum for non-PK data. Median was presented together with first and third quartile where appropriate. For the summary of PK concentration levels, the geometric mean and coefficient of variation based on log-transformed data were also presented. All summary tables presented descriptive statistics and/or frequency by visit unless otherwise stated.

Study population

Twenty-three patients were enrolled and 18 received treatment (5 screen failures). All 18 patients completed the study and were included in the safety analysis set and the PK analysis set. The median age of patients was 8.0 years (range: 5 to 11 years); the majority were male (11 [61.1%] patients) and listed race as Other (9 patients [50.0%]). Nine patients (50.0%) had a body weight of < 25 kg, 5 patients (27.8%) had a body weight of ≥ 25 kg to < 40 kg, and 4 patients (22.2%) had a body weight ≥ 40 kg. Eight of 18 patients experienced an exacerbation within 6 months prior to Visit 1. Of these, 3/18 (16.7%) experienced 1 exacerbation and 5/18 (27.8%) experienced 2 exacerbations (13 exacerbations in total). All patients were using 1 or more inhaled corticosteroid (ICS) at baseline; the most commonly used ICS was budesonide by 7/18 patients (38.9%).

All patients received the planned dose of investigational product (IP) at the site; no overdoses were reported. The COVID-19 pandemic is judged to have not impacted the overall quality of the study.

Summary of pharmacokinetic results

The maximum serum concentration was observed with a median time to achieve maximum observed serum concentration (t_{max}) of 3.5 days post-dose followed by exponential decline in serum concentration with time. The mean terminal phase elimination half-life ($t_{1/2}$) was 25.7 days, and the mean maximum observed serum concentration (C_{max}) was 27.1 µg/mL with a mean apparent clearance (CL/F) of 0.0802 L/day.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of immunogenicity results

There were 3 anti-drug antibody (ADA) positive patients among 18 patients in the study; none of them were classified as treatment-emergent ADA positive. The ADA prevalence (percentage of ADA-positive patients in the group) was 16.7% and ADA incidence (percentage of treatment-emergent ADA-positive patients in the group) was 0%. Postbaseline ADA titres were low (just above the limit of detection). No patients were neutralising antibody (nAb) positive.

Summary of safety results

Tezepelumab was well tolerated in 5- to 11-year-old patients with mild, moderate, or severe asthma; there were no safety findings of concern. A total of 7/18 patients (38.9%) receiving tezepelumab reported adverse events (AEs). None of the AEs reported were considered causally related to the IP by the Investigator. Two patients (11.1%) reported AEs of moderate intensity; all other AEs were of mild intensity. AEs reported as moderate intensity were asthma and cough, each with one event in one patient. No AEs with outcome of death were reported and no serious AEs were reported during the study. No patient reported AEs leading to discontinuation of the study. Overall, clinical laboratory and other safety assessments were consistent with the reported safety profile of tezepelumab. No safety or tolerability concerns were raised in this study.

Conclusions

- Following a single SC dose of CCI tezepelumab in children aged ≥ 5 to 11 years, the maximum serum concentration was observed with a median t_{max} of 3.5 days post-dose, followed by exponential decline in serum concentration over time. The mean $t_{1/2}$ was 25.7 days, and the mean C_{max} was 27.1 µg/mL with a mean CL/F of 0.0802 L/day.
- There were no treatment-emergent ADA positive or nAb positive patients in the study.

- The single SC dose of [redacted] tezepelumab was well tolerated in ≥ 5- to 11-year-old patients with mild, moderate, or severe asthma and no safety findings or tolerability concerns were raised in this study.