25 May 2023
EMA/273154/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

TEZSPIRE

tezepelumab

Procedure no: EMEA/H/C/005588/P46/008

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 Mar 2023	27 Mar 2023	☐
☐	CHMP Rapporteur Assessment Report	02 May 2023	25 Apr 2023	☐
☐	CHMP members comments	15 May 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	17 May 2023	n/a	☐
☒	CHMP adoption of conclusions:	25 May 2023	25 May 2023	☐

Table of contents

1. Introduction

On 9th March 2023, the MAH submitted a completed paediatric study for tezepelumab, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study D5180C00025 (TRAILHEAD) is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation used in the study was tezepelumab solution for injection - 110 mg/mL.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study D5180C00025 (TRAILHEAD), 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.

2.3.2. Clinical study

Study D5180C00025 (TRAILHEAD)

Description

This was a multicentre, open label study designed to evaluate the pharmacokinetic (PK) profile of tezepelumab following a single subcutaneous (SC) 70 mg dose in children aged ≥ 5 to 11 years with mild, moderate, or severe asthma. The study was conducted globally across 6 study sites in 3 countries: UK (4 sites), Hungary (1 site), and South Africa (1 site).

Methods

Study participants

Children aged ≥ 5 to 11 years with mild, moderate, or severe asthma requiring daily controller medications.

Treatments

Single SC 70 mg dose of tezepelumab.

Objectives and endpoints

The study objectives and endpoints are shown in ***Table 1***.

Table 1 - Objectives and endpoints

Objectives	Outcome Measures
Primary	
• To describe the PK parameters following a single SC administration of tezepelumab 70 mg in children with mild, moderate, or severe asthma	• C_{max} • t_{max} • AUC • $t_{½}$ • CL/F • V_{ss}/F
Secondary	
• To evaluate the immunogenicity of tezepelumab	• Presence of ADAs
Safety	
• To evaluate the safety and tolerability following a single SC administration of tezepelumab 70 mg	• Adverse events/serious adverse events • Vital signs • Laboratory parameters • ECG
Exploratory	
• To evaluate the PD following a single SC administration of tezepelumab 70 mg	• Pulmonary function (FEV_1, FVC) • Blood eosinophil levels • FENO • PQoL

ADA anti-drug antibodies; AUC area under the concentration-time curve; CL/F apparent clearance; C_{max} maximum concentration; ECG electrocardiogram; FENO fractional exhaled nitric oxide; FEV_1 forced expiratory volume in one second; FVC forced vital capacity; PD pharmacodynamics; PK pharmacokinetic; PQoL paediatric quality of life; SC subcutaneous; T_{max} time to C_{max}; $t_{½}$ terminal phase elimination half-life V_{ss}/F apparent steady-state volume of distribution.

Sample size

23 patients were enrolled, 18 patients were dosed, and 18 patients completed the study.

Statistical Methods

A statistical analysis plan (SAP) was developed and finalised before database lock (DBL), which described the patient populations to be included in the analyses and the procedures to account for missing, unused, and spurious data.

No formal statistical hypothesis tests were performed. 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 CV% based on log-transformed data were also presented. All summary tables presented descriptive statistics and/or frequency by visit unless otherwise stated.

Demographics and patient characteristics were summarised using frequency and percentages (for categorical variables) and n, mean, standard deviation, minimum, median and maximum (for continuous variables) using both the PK and safety analysis set.

The frequency and percentages of patient disposition and reasons for withdrawal from the study were presented. Frequency and percentages of patients in each analysis population were provided. Important protocol deviations were defined at patient level prior to DBL and were summarised and listed.

Pharmacokinetics

Tezepelumab serum concentration data were listed by individual and summarised by nominal time using descriptive statistics, including N, geometric mean, geometric CV%, arithmetic mean, arithmetic SD, median, minimum and maximum. The mean and individual serum tezepelumab concentrations were plotted over time. Based on the serum concentration-time data of tezepelumab, the following PK parameters were estimated using noncompartmental analysis method as appropriate: AUC0-inf, AUC0-last, Cmax, tmax, terminal t½, CL/F, and Vss/F. In addition to the primary PK parameters, Vz/F was also derived. PK parameters were listed by individual and were summarised using descriptive statistics. The PK analysis was performed using WinNonlin version 8.3.

Pharmacodynamics

Observed and change from baseline values in forced expiratory volume in one second (FEV1; observed value and percent of the predicted normal values computed by means of the Global Lung Function Initiative equations), forced vital capacity (FVC), eosinophils and fractional exhaled nitric oxide (FENO) were summarised using descriptive statistics. Mean absolute and mean change from baseline values over time for pre-bronchodilator FEV1, FENO, IgE, and blood eosinophil levels were presented.

Data collected by means of the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) were listed by individual. In addition, each domain score (i.e., symptoms, activity limitation and emotional function) and the overall score were summarised, presenting descriptive statistics of observed values and change from baseline values at each scheduled assessment visit.

Immunogenicity

Anti-drug antibody data were summarised using descriptive statistics by visit. Samples confirmed positive for ADA were tested for nAb and listed by patient.

Safety

Safety data were presented using descriptive statistics except where otherwise specified. The overall number and percentage of patients with adverse events (AEs) and serious adverse events (SAEs) were presented. The occurrence of AEs was also described by system organ class (SOC) and preferred term (PT), and separately by severity and by relationship to the IP (as determined by the Investigator). Where a patient reported the same PT/SOC within multiple severity or relationship categories, the patient's worst occurrence (most severe/most related) was tabulated. Serious AEs, AEs leading to death, AEs leading to withdrawal from study, commonly occurring AEs, and adverse events of special interest (AESIs) were included in key listings.

Laboratory data, including serum chemistry, haematology and urinalysis were summarised by presenting summary statistics of observed values and change from baseline values at each scheduled assessment visit. Shift tables were also presented using normal ranges (baseline to most extreme postbaseline value).

The number of patients with elevated liver function tests that met the Hy's Law definition was summarised and evaluated. Vital signs data were summarised by presenting summary statistics of observed values and change from baseline values at each scheduled assessment visit. Abnormal ECGs (as per Investigator's overall interpretation) were summarised using the frequency and percentage of patients.

Description of analysis sets

For this study, the following analysis sets were defined per ***Table 2***:

Table 2 - Populations for Analysis

Population/analysis set	Description
Enrolled	All patients who signed the ICF.
Safety	All patients who received at least one dose of tezepelumab.
PK	Patients in the Safety Analysis set that had at least one detectable tezepelumab serum concentration from a sample collected post-dose that was assumed not to be affected by factors such as important protocol deviations (eg, incorrect dose of study IP received).

| ICF informed consent form; IP investigational product; PK pharmacokinetic.

All PK summaries were based on the PK analysis set. Anti-drug antibodies and PD parameter summaries and safety presentations were based on the safety analysis set.

Determination of sample size

No formal sample size calculation was conducted for this study. The number of patients was based on the desire to obtain adequate PK and safety data while exposing as few paediatric patients as possible to tezepelumab and study procedures. A total of 12 patients was considered sufficient to provide adequate data to characterise the PK of tezepelumab in children aged ≥ 5 to 11 years. At least 4 patients were to have a body weight of < 25 kg and at least 3 patients were to have a body weight of ≥ 25 kg and < 40 kg. To reach the goal of having at least 12 patients complete the study, enrolment aimed for approximately 14 patients to receive tezepelumab.

Patients who were eligible to participate but did not go on to receive tezepelumab, or patients who did not complete the required evaluations through to Day 85 could have been replaced to maintain the stipulated number of evaluable patients, at the discretion of the Sponsor.

Handling of missing data

In the case of a missing value at a scheduled visit, which was then followed by a non-missing value at an unscheduled or repeat assessment within the same visit window, the non-missing value at the unscheduled/repeat assessment was to be used.

If a patient had more than one non-missing value within the same visit window, the following rules applied:

- The non-missing value closest to the target day was selected for analysis at that visit,
- If 2 non-missing values are the same distance from the target day, the earlier of the 2 values was selected for analysis at that visit,
- If 2 non-missing values were recorded on the same day and have a different assessment time associated with both of them, the value with the earliest assessment time was selected for analysis at that visit,
- If 2 non-missing values (for continuous variables) were recorded on the same day and have no assessment time associated with at least one of them, or the same assessment time associated with both of them, the average of the 2 values was selected for analysis at that visit. For categorical variables in this situation, the worst case was used.

If a patient had no value within a particular visit window, then the patient had a missing value on that scheduled study day in summaries and analysis. Where a PK sample was missing for a patient, the pharmacokineticist and Sponsor evaluated the PK samples collected (collection times only, not

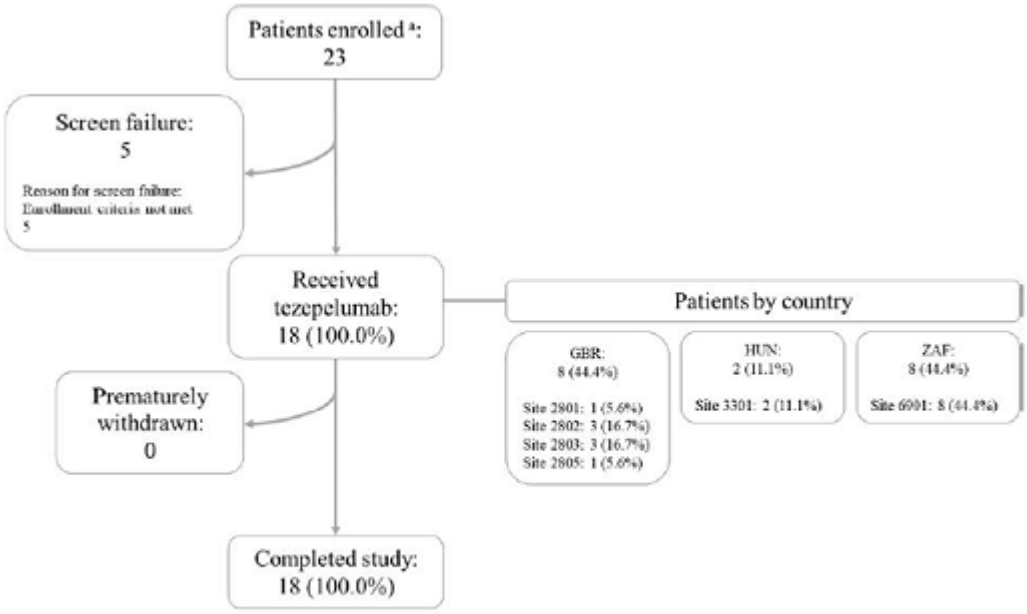
concentrations) for the patient and determined if enough samples were collected to report some or all of the protocol defined PK parameters. Data from patients that had missing PK sample(s) were included in concentration-time listings, individual PK profile plots and associated summary statistics. Available PK parameters were included in the PK parameter listing and associated summary statistics.

Results

Participant flow

The disposition of the patients in this study is summarised in ***Figure 1***.

Figure 1 - Number and disposition of patients recruited



[a] Informed consent received.
GBR UK; HUN Hungary; ZAF South Africa.

Study patients analysed

The analysis sets and the number of patients in each analysis set are summarised in Table 3.

Table 3 - Analysis Sets

Patients in analysis set	Number of patients	
	Tezepelumab 70 mg SC	Total
Patients included in enrolled analysis set	-	23
Patients dosed	18	18
Screen failures	-	5
Patients included in safety analysis set	18	18
Patients excluded from safety analysis set [a]	0	0
Patients included in pharmacokinetic analysis set	18	18
Patients excluded from pharmacokinetic analysis set [a]	0	0

[a] An individual patient could have been excluded for more than one reason.
SC subcutaneous.

Baseline data

The demographic and key baseline characteristics of study patients are summarised in ***Table 4***.

Table 4 - Demographic and patient characteristics (Safety analysis set)

Characteristics	Statistics	Tezepelumab 70 mg SC (N = 18)
Age (years)	n	18
	Mean (SD)	7.9 (1.78)
	Min, Max	5, 11
	Median	8.0
Sex (n [%])	Male	11 (61.1)
	Female	7 (38.9)
Race (n [%])	Asian	2 (11.1)
	Black or African American	1 (5.6)
	White	6 (33.3)
	Other	9 (50.0)
Ethnic Group (n [%])	Not Hispanic or Latino	18 (100.0)
Height (cm)	n	18
	Mean (SD)	130.12 (15.185)
	Min, Max	108.6, 158.6
	Median	128.35
Weight (kg)	n	18
	Mean (SD)	30.575 (13.8746)
	Min, Max	17.10, 67.00
	Median	24.700
Body weight group, n (%)	n	18
	< 25 kg	9 (50.0)
	≥ 25 kg to < 40 kg	5 (27.8)
	≥ 40 kg	4 (22.2)
Body Mass Index (kg/m^2)	n	18
	Mean (SD)	17.296 (4.3414)
	Min, Max	14.20, 29.80
	Median	15.950
Eosinophils (cells/µL)	n	18
	Mean (SD)	437.8 (389.16)
	Min, Max	60, 1660
	Median	330.0
Eosinophils group (cells/µL), n (%)	n	18
	< 150	5 (27.8)
	150 to < 300	3 (16.7)
	300 to < 450	3 (16.7)
	≥ 450	7 (38.9)
FENO (ppb)	n	13 [a]
	Mean (SD)	32.6 (26.13)
	Min, Max	5, 81
	Median	20.0
FENO group (ppb), n (%)	n	13 [a]
	< 25	7 (53.8)
	25 to < 50	1 (7.7)
	≥ 50	5 (38.5)
Total IgE (IU/mL)	n	18
	Mean (SD)	1094.50 (1778.269)
	Min, Max	37.7, 6616.0
	Median	514.00

[a] For 5 patients, the FENO values were either not obtainable, or they could not be saved due to device malfunction.

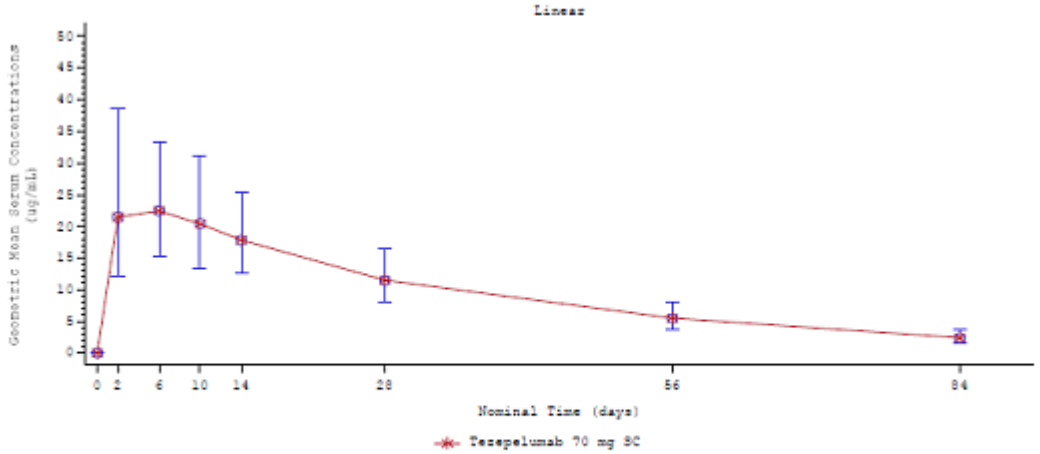
Baseline is defined as the last valid non-missing result obtained on or prior to the date of dosing of tezepelumab.
FENO fractional exhaled nitric oxide; IgE immunoglobulin E; IU international units; Max maximum; Min minimum; N number of patients in treatment group; n number of patients included in analysis; SC subcutaneous; SD standard deviation.

Pharmacokinetic results

Serum samples for PK analysis were collected before dose administration on Study Day 1 (Baseline) and on Study Days 3, 7, 11, 15, 29, 57, and 85/end of study. Blood samples for determination of tezepelumab concentrations in serum were analysed using a validated assay.

Geometric mean (*/ gSD) serum tezepelumab concentrations versus time are presented in ***Figure 2***. Mean PK parameters of serum tezepelumab are presented in ***Table 5***.

Figure 2 - Geometric mean (/gSD) serum concentration (µg/mL) of tezepelumab versus time (Linear scale) (PK Analysis Set)*



Vertical lines represent the geometric mean / gSD and geometric mean * gSD.
Geometric mean / gSD: exp(mean[log$_{PK\ concentration}$] / exp(std[log$_{PK\ concentration}$])
Geometric mean * gSD: exp(mean[log$_{PK\ concentration}$] * exp(std[log$_{PK\ concentration}$])
gSD geometric standard deviation; N number of patients; PK pharmacokinetic; SC subcutaneous.

Table 5 - Summary of pharmacokinetic parameters of tezepelumab

Summary Statistic	C_{max} (µg/mL)	$AUC_{0\text{-}last}$ (Day*µg/mL)	$AUC_{0\text{-}\infty}$ (Day*µg/mL)	t_{max} (Day)	$t_{1/2}$ (Day)	CL/F (L/Day)	V_{ss}/F (L)	V_z/F (L)
n	18	18	18	18	18	18	18	18
Geometric Mean	24.6	826	924	NA	25.0	0.0758	2.82	2.73
Geometric CV%	47.7	35.9	35.2	NA	24.6	35.2	44.7	44.5
Geometric Mean / gSD	15.7	583	656	NA	19.6	0.0538	1.84	1.79
Geometric Mean * gSD	38.8	1170	1300	NA	31.9	0.107	4.33	4.18
Arithmetic Mean	27.1	872	974	NA	25.7	0.0802	3.08	2.98
Arithmetic SD	11.9	285	320	NA	5.94	0.0295	1.32	1.26
Median	26.9	869	969	3.47	25.0	0.0723	2.51	2.48
Mininum	10.9	417	461	1.92	15.1	0.0388	1.40	1.33
Maximum	54.3	1510	1800	9.96	36.2	0.152	5.60	5.35

Geometric mean / gSD: exp(mean[logPK concentration] / exp(std[logPK concentration])
Geometric mean * gSD: exp(mean[logPK concentration] * exp(std[logPK concentration])
C_{max} maximum concentration; CV% coefficient of variation; EOS end of study; gSD geometric standard deviation; LLOQ lower limit of quantification (0.010 ug/mL); N number of patients in the pharmacokinetic analysis set; n number of observations; NA not applicable; PK pharmacokinetic(s); SD standard deviation; t_{max} time to C_{max}; $t_{½}$ terminal phase elimination half-life; V_{ss}/F apparent steady-state volume of distribution; V_z/F: apparent volume of distribution (based on terminal phase), estimated as CL/F*1/ λ_Z.

Pharmacodynamic results

Pulmonary function

The change in pulmonary function variables over time are shown in ***Table 6***. No substantial change was noted in the percent predicted FEV1 or predicted FVC during the study. Similarly, the FEV1/FVC ratio did not demonstrate any substantial change following a single dose of 70 mg SC tezepelumab. No notable changes were observed in pulmonary function parameters following a single dose of tezepelumab.

Table 6 - Pulmonary function variables over time (Safety analysis set)

Pulmonary function variable	Time point	Result						Change from baseline				
		n	Mean	SD	Min	Median	Max	Mean	SD	Min	Median	Max
FEV_1 (L)	Baseline	18	1.528	0.508	0.90	1.440	2.63	-	-	-	-	-
	Day 14	18	1.518	0.492	0.83	1.360	2.74	-0.011	0.109	-0.21	0.010	0.17
	Day 28	18	1.555	0.539	0.90	1.400	2.75	0.027	0.116	-0.14	0.000	0.27
	Day 84/EOS	18	1.556	0.568	0.86	1.470	2.90	0.027	0.127	-0.20	0.030	0.27
Percent predicted FEV_1 (%)	Baseline	18	95.34	11.72	70.0	95.85	119.0	-	-	-	-	-
	Day 14	18	94.67	12.31	76.0	92.00	125.0	-0.67	4.85	-9.0	-0.25	6.0
	Day 28	18	95.72	11.58	76.0	93.50	122.0	0.38	5.22	-8.0	0.00	12.0
	Day 84/EOS	18	93.89	13.69	74.0	90.00	128.0	-1.44	7.59	-16.0	1.00	9.0
Forced vital capacity (L)	Baseline	18	1.931	0.663	1.13	1.865	3.18	-	-	-	-	-
	Day 14	18	1.875	0.640	1.02	1.680	3.14	-0.056	0.145	-0.54	-0.030	0.15
	Day 28	18	1.902	0.672	1.10	1.695	3.18	-0.029	0.177	-0.59	0.010	0.18
	Day 84/EOS	18	1.937	0.703	1.05	1.750	3.36	0.006	0.182	-0.65	0.055	0.20
Percent predicted forced vital capacity (%)	Baseline	18	105.78	11.26	90.0	103.00	139.0	-	-	-	-	-
	Day 14	18	102.46	9.43	88.0	101.50	126.0	-3.33	9.94	-39.0	-2.85	10.0
	Day 28	18	103.27	10.07	86.0	102.00	124.0	-2.52	9.85	-35.0	-1.45	10.0
	Day 84/EOS	18	103.13	9.32	88.1	102.00	129.0	-2.66	10.90	-43.0	1.00	5.0
Ratio of FEV_1/FVC	Baseline	18	0.801	0.084	0.62	0.800	0.96	-	-	-	-	-
	Day 14	18	0.816	0.056	0.69	0.815	0.92	0.016	0.056	-0.13	0.015	0.16
	Day 28	18	0.822	0.051	0.71	0.820	0.92	0.021	0.065	-0.14	0.020	0.17
	Day 84/EOS	18	0.805	0.062	0.72	0.790	0.93	0.004	0.058	-0.10	0.005	0.16

Baseline (nominal Day 0) is defined as the last valid non-missing result obtained on or prior to the date of dosing of tezepelumab.
Time point is given in nominal days (Study Day – 1); see Section 11.7.1.
EOS end of study; FEV_1 forced expiratory volume in 1 second; FVC forced vital capacity; Min minimum; Max maximum; n Number of patients included in analysis; SD standard deviation.

Biomarkers

Changes in biomarkers in this study were reflective of the expected PD effects of tezepelumab. The change in biomarkers over time (blood eosinophils, serum immunoglobulin E, and FENO) following a single dose of tezepelumab are shown in ***Table 7***.

Table 7 - Biomarkers over time (Safety analysis set)

Biomarker variable	Time point	Result						Change from baseline					
		n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Eosinophils, particle conc. (cells/uL)	Baseline	18	437.8	389.2	60	330	1660	-	-	-	-	-	-
	Day 14	18	271.1	250.0	40	180	1130	18	-166.7	178.0	-530	-120	60
	Day 28	16	187.5	112.3	20	185	440	16	-247.5	351.9	-1350	-115	10
	Day 84/EOS	15	391.3	423.9	30	190	1660	15	-48.7	139.8	-320	-30	280
Immunoglobulin E (IU/mL)	Baseline	18	1094.50	1778.27	37.7	514.0	6616.0	-	-	-	-	-	-
	Day 28	18	1054.55	1768.83	46.3	518.0	7346.0	18	-39.95	409.93	-1500.0	-10.5	730.0
	Day 84/EOS	18	938.42	1345.59	38.9	490.5	5420.0	18	-156.08	551.88	-1986.0	-24.6	323.0
Fractional exhaled nitric oxide (ppb)	Baseline	13	32.6	26.1	5	20	81	-	-	-	-	-	-
	Day 14	15	13.7	10.6	5	9	40	12	-17.4	20.6	-53	-7	4
	Day 28	16	17.4	15.9	5	12	69	12	-14.7	24.6	-59	-9	18
	Day 84/EOS	17	27.1	34.6	5	13	113	13	-0.7	31.1	-44	-1	79

Baseline (nominal Day 0) is defined as the last valid non-missing result obtained on or prior to the date of dosing of tezepelumab.
Time point is given in nominal days (Study Day – 1); see Section 11.7.1.
EOS end of study; Min minimum; Max maximum; n number of patients included in analysis; SD standard deviation.

The mean change from baseline over time in blood eosinophils, serum IgE and FENO values are displayed in ***Figure 3***, ***Figure 4*** and ***Figure 5***, respectively. For eosinophils and FENO, the data suggest a trend to an initial reduction at 4 weeks followed by a gradual return to baseline levels. For IgE, the data suggest no notable changes in values over the course of the study.

Figure 3 - Eosinophil data by visit, mean (SD) of change from baseline (Safety analysis set)

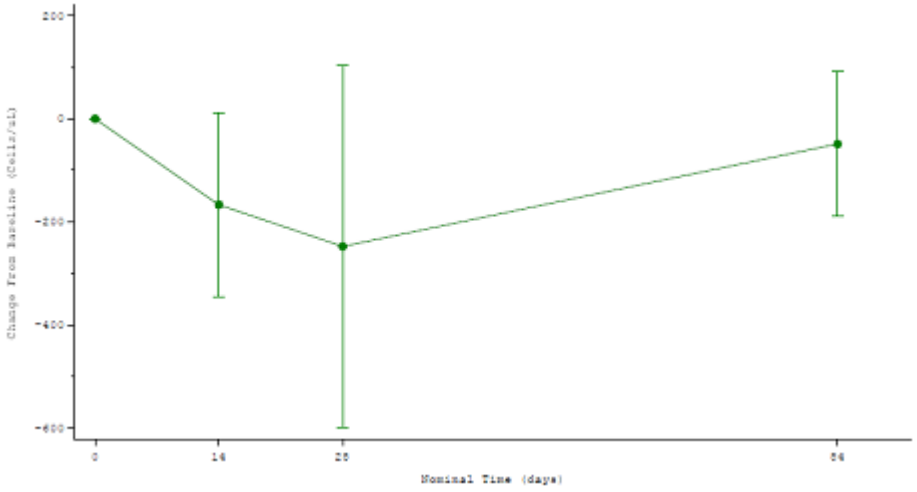


Figure 4 - IgE data by visit, mean (SD) of change from baseline (Safety analysis set)

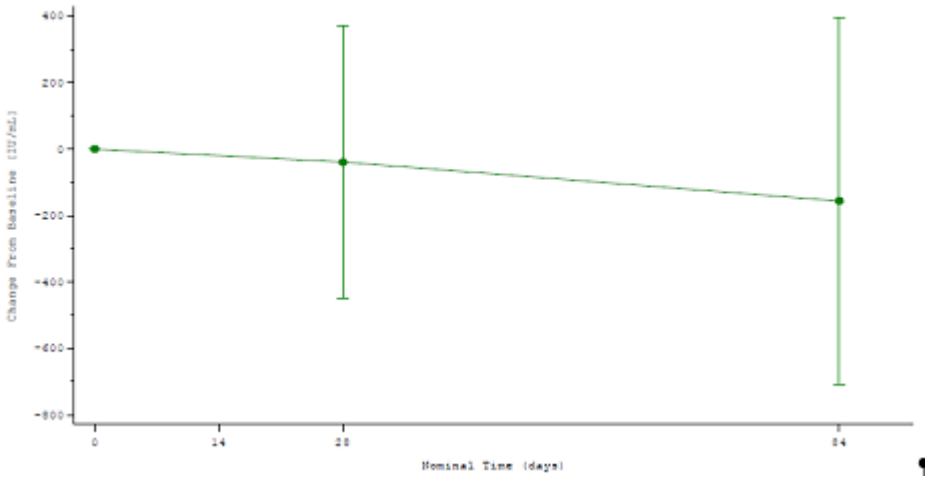
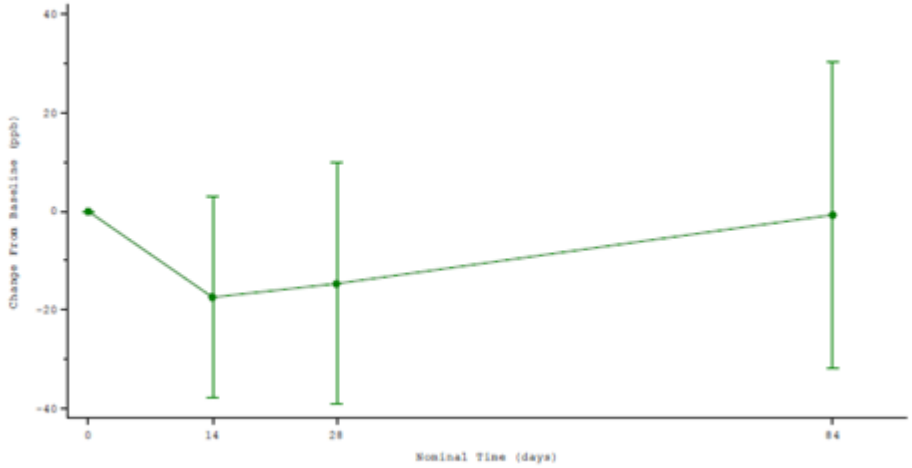


Figure 5 - FENO data by visit, mean (SD) of change from baseline (Safety analysis set)



Paediatric quality of life

There was a trend towards an improvement in the total score as well as all 3 PAQLQ domain scores (activity limitations, symptoms, and emotional function) from baseline to Study Day 29 with gradual return to baseline by Study Day 85/end of study.

Immunogenicity results

Anti-drug antibody prevalence (ADA positive at baseline and/or post-baseline) was 16.7% (3/18 patients) (***Table 8***). One of these patients was ADA positive at both baseline and post-baseline, but the baseline ADA titre did not increase over time. Post-baseline ADA titres were low, being just above the limit of detection. No patient was classified as treatment-emergent ADA positive. No patients were nAb positive.

Table 8 - Summary of anti-drug antibody responses during the study (Safety analysis set)

ADA Category	Tezepelumab 70 mg SC (N = 18)			
	ADA positive n/N (%)	Maximum ADA Titre		
		Min	Median	Max
ADA positive at baseline and/or post-baseline (ADA prevalence)	3/18 [a] (16.7)	67.2	67.20	537.6
Only baseline ADA positive	2/18 [b] (11.1)	67.2	67.20	67.2
Both baseline and at least one post-baseline ADA positive	1/18 [c] (5.6)	537.6	537.60	537.6
ADA positive at baseline regardless of post-baseline result	3/18 [b] (16.7)	67.2	67.20	537.6
Any post-baseline ADA-positive	1/18 [d] (5.6)	537.6	537.60	537.6
Treatment-induced ADA-positive [e]	0	-	-	-
Treatment-boosted ADA positive [f]	0	-	-	-
TE-ADA positive (ADA incidence) [g]	0	-	-	-

[a] Number of patients with any ADA result at baseline and/or post-baseline.
[b] Number of patients with an ADA result at baseline.
[c] Number of patients with an ADA result at baseline and at least one post-baseline assessment.
[d] Number of patients with at least one post-baseline ADA assessment.
[e] Treatment-induced ADA positive is defined as ADA negative at baseline and post-baseline ADA positive.
[f] Treatment-boosted ADA positive is defined as baseline positive ADA titre that was boosted to a 4-fold or higher level following IP administration.
[g] TE-ADA positive is defined as either treatment-induced ADA positive or treatment-boosted ADA positive. ADA incidence is the proportion of TE-ADA positive patients in a population.

Of the 3 ADA positive patients in the study, 1 patient (ADA positive at baseline only) experienced an AE of lower respiratory tract infection; this AE occurred during screening, was assessed as mild, and resolved prior to IP administration.

Safety results

Across the study, 7/18 patients (38.9%) reported AEs, with a total of 17 AEs being reported for these patients (***Table 9***).

Table 9 - Number of patients with adverse events in any category (safety analysis set)

AE Category	Number (%) of patients[a] (N = 18)
Any AE	7 (38.9)
Any AE with outcome of death	0
Any SAE	0
Any AE leading to withdrawal from study	0

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

Includes adverse events that occurred during the on-study period. On-study is any day between the date of IP administration and study completion or withdrawal date. Percentages are based on the total numbers of patients in the treatment group (N).

AE adverse event; IP investigational product; N number of patients in treatment group; SAE serious AE.

Adverse events by SOC and PT are presented in ***Table 10***. No AEs were reported in > 2 patients; AEs reported in 2 patients were COVID-19, nasopharyngitis, and headache; none were considered serious.

Table 10 - Patients with adverse events reported during the on-study period by system organ class and preferred term (safety analysis set)

System organ class / Preferred term	Number (%) of patients[a] (N = 18)
Patients with any AE	7 (38.9)
Infections and Infestations	5 (27.8)
COVID-19	2 (11.1)
Nasopharyngitis	2 (11.1)
Viral Upper Respiratory Tract Infection	1 (5.6)
Nervous System Disorders	2 (11.1)
Headache	2 (11.1)
Respiratory, Thoracic and Mediastinal Disorders	2 (11.1)
Asthma	1 (5.6)
Cough	1 (5.6)
Gastrointestinal Disorders	1 (5.6)
Vomiting	1 (5.6)
General Disorders and Administration Site Conditions	1 (5.6)
Pyrexia	1 (5.6)
Immune System Disorders	1 (5.6)
Seasonal Allergy	1 (5.6)
Injury, Poisoning and Procedural Complications	1 (5.6)
Contusion	1 (5.6)
Fall	1 (5.6)
Musculoskeletal and Connective Tissue Disorders	1 (5.6)
Pain in Extremity	1 (5.6)

[a] Number (%) of patients with AEs, sorted by decreasing frequency for system organ class and preferred term.

Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than one preferred term are counted once in each of those preferred terms. Includes adverse events that occurred during the on-study period. On-study is any day between the date of IP administration and study completion or withdrawal date. Percentages are based on the total numbers of patients in the treatment group (N).

AE adverse event; N number of patients in treatment group.

Out of 7/18 patients (38.9%) with reported AEs, 2/18 patients (11.1%) reported moderate AEs and 5/18 patients (27.8%) reported mild AEs. No patients reported severe AEs. Adverse events reported as moderate were asthma and cough, each reported in one patient.

No AEs were assessed as causally related to the IP by the Investigator. No AEs with fatal outcome, no SAEs and no AEs of special interest were reported in this study. No adverse events were classified as other significant adverse events.

Clinical laboratory evaluation

Aside from the expected effect of tezepelumab on lowering blood eosinophil counts, no trends were noted for haematology results. No AEs related to haematology were reported. No AEs related to clinical chemistry were reported and no clinically meaningful trends were noted. There were no individual clinically important abnormalities in clinical chemistry reported. No patients had ALT $\geq 3 \times$ ULN or AST $\geq 3 \times$ ULN and TBL $\geq 2 \times$ ULN. No patients were found to have a clinically meaningful change in urinalysis results during the study.

Vital signs, electrocardiograms, physical findings and other observations related to safety

There were no clinically meaningful trends in either vital signs or ECG parameters over the course of the study. There were no individual clinically meaningful changes in vital signs or ECG parameters. There were no clinically relevant abnormal medical findings in physical examination observations as compared with the baseline assessment.

2.3.3. Discussion on clinical aspects

The primary aim of this study was to evaluate the PK of tezepelumab following a single 70 mg SC dose in children aged ≥ 5 to 11 years with mild, moderate, or severe asthma. Additional aims were to evaluate the PD, immunogenicity, safety and tolerability. The design and methodology of this study are acceptable.

The PK of tezepelumab in 18 paediatric patients included in this study was well characterised. The mean t1/2 was 25.7 days, which is similar to that previously observed in the adult and adolescent populations.

An exploratory efficacy objective of this study was to evaluate the effect of a single 70 mg SC dose of tezepelumab on pulmonary function in a paediatric population. No notable changes were observed in FEV1, FVC or FEV1/FVC ratio. However, this study was not powered to detect this effect. Further, only a single dose of tezepelumab was administered.

ADA prevalence and ADA incidence were 16.7% and 0%, respectively. There were no treatment-emergent ADA positive patients in the study. Therefore, the potential impact of ADA on PK could not be assessed. One patient, who was ADA positive at baseline only, experienced an AE during screening, which was assessed as mild. No patients were nAb positive.

There were no safety findings of concern or tolerability concerns reported in the study. A total of 7/18 patients (38.9%) reported AEs, none of which were considered causally related to tezepelumab by the Investigator. Two patients reported moderate intensity AEs (asthma and cough, 1 event in each patient); all other AEs were of mild intensity, and there were no SAEs or AEs resulting in death or study discontinuation.

No clinically meaningful laboratory findings for haematology, serum chemistry, or urinalysis parameters were identified. There were also no clinically relevant findings in vital signs, ECGs, physical findings or other safety-related observations. Overall, the data suggest an acceptable safety profile.

3. CHMP's overall conclusion and recommendation

Overall, the results of this study support the further development of tezepelumab in paediatric patients aged ≥ 5 to 11 years with mild, moderate, or severe asthma. However, it is not possible to draw definitive conclusions given the limited number of patients included in this study (n=18). No issues of concern were identified, and no further actions are required.

☒ Fulfilled:

No regulatory action required.