Clinical trial results:
Effects of tregalizumab on allergen-induced airway responses and airway inflammation in asthmatic patients

Summary

EudraCT number	2020-000585-41
Trial protocol	DE
Global end of trial date	09 March 2022

Results information

Result version number	v1 (current)
This version publication date	27 January 2023
First version publication date	27 January 2023

Trial information

Trial identification

Sponsor protocol code	OG-061-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04673591
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	T-Balance Therapeutics GmbH
Sponsor organisation address	Waldfriedstr. 4, Frankfurt am Main, Germany, 60528
Public contact	T-Balance Therapeutics GmbH, Dr. Cathrin Schleussner, T-Balance Therapeutics GmbH, +49 69 666 8381,
Scientific contact	T-Balance Therapeutics GmbH, Prof. Dr. med. Gregor Schulz, T-Balance Therapeutics GmbH, +49 69 661 63745 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2022
Global end of trial reached?	Yes
Global end of trial date	09 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to investigate the effect of 100 mg tregalizumab treatment administered weekly (via subcutaneous injection) over 12 weeks to patients with mild controlled allergic asthma and HDM (House Dust Mite) allergy, who were exposed to allergen induced bronchoconstriction under controlled conditions in this challenge study. The primary endpoint supporting this objective was the change from baseline in the Late Asthmatic Response (LAR) after Bronchial Allergen Provocation (BAP).

Protection of trial subjects:

Before undergoing screening procedures for possible participation in the study, the subjects were informed in an understandable form about the nature, scope and possible consequences of the study. This information was given to the subjects orally by a physician who was well informed about the nature, scope, and possible consequences of the study. Written information about the study was also provided in a subject information sheet. Subjects were given ample time and opportunity to inquire about details of the study and to consider their participation in the study. A revision of the subject information sheet and the Informed Consent Form (ICF) was made whenever important new information became available that might be relevant to the subject's consent. Subjects already participating in the study were informed of these changes by the investigator. These changes included the safety measures that were introduced due to the COVID-19 vaccinations taking place throughout Germany.
After enrolment in the study, each subject was issued with a subject identification card that contained information about their participation in the study. Subjects were instructed to carry this card with them throughout the entire duration of the study so that the investigator could be contacted in case of emergency.
Subjects were followed-up until 4 weeks after the last administration of treatment.

Background therapy:

1. Rescue medication
The administration of inhaled ß2-agonist rescue medication (e.g., salbutamol) was allowed at any time during the study. However, if treatment with rescue medication occured within the time period of 8 hours prior to BAP until 7 hours after BAP at Visit V4 and/or at Visit V17, this was considered as an important protocol deviation. Moreover, when any washout periods given in the protocol were violated, the implications were discussed on a case-by-case basis.

2. Provokit®
Provokit® 0.33% powder and solvent to prepare a solution for inhalation via nebulizer.
Substance: Methacholine chloride
Concentration: 0.33%
Dose per Administration: up to 242.9 µg (dose steps planned: 15.2 µg, 30.4 µg, 60.7 µg, 121.4 µg and 242.9 µg)
Mode of Administration: inhalation via nebulizer
Final Release: ARISTO Pharma GmbH, Germany
Batch No. / Expiry date 26709520 / JUN-2022

Evidence for comparator:

n.a.

Actual start date of recruitment	09 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	42
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Screening for the monocentric study with an active site in Germany started on 09-Dec-2020 and ended on 23-Aug-2021 (9 months). The screening period was up to 11 weeks for each subject. The study site was a site management organisation.
A total of 42 patients were included in the study and received randomised treatment.

Pre-assignment

Screening details:

Main inclusion criteria:
- Male or female adult patients (aged 18 to 65)
- Established diagnosis of mild controlled allergic asthma (GINA 2019) and history of allergic bronchial asthma for at least 1 year.
- Non-smoker (all substances)
- who signed ICF

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Treatments were administered under double-blind conditions, meaning that all formulations were externally identical and identification by staff/subjects was not possible. The study data remained blinded until the database was locked. The investigator received a sealed envelope containing the treatment assignment for each subject. The sealed envelope was kept in a secure area by the investigator to decide whether the blinding needed to be lifted in case of emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm I Placebo

Arm description:

In Arm I, the placebo product was used. The placebo product was a sterile solution for subcutaneous injection containing the same excipients as the tregalizumab drug, as the placebo product was the tregalizumab formulation buffer.
Each of the 21 subjects in this group was treated with the placebo product (Tregalizumab formulation buffer) once a week for 12 weeks. The injection was administered into the upper abdomen. At each administration, 1 ml of the solution was injected. The first administration was on day 1 (visit V5). During the treatment phase, defined procedures with a certain number of tests/measurements were performed at each visit (visit V5 – visit V16). A defined number of tests/measurements were also performed during the follow-up phase (visit V17 – visit V19).

Arm type	Placebo
Investigational medicinal product name	Reference product (Placebo)
Investigational medicinal product code	
Other name	Placebo solution (tregalizumab formulation buffer)
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo: Tregalizumab formulation buffer
Concentration: not applicable
Dose per administration: not applicable
Mode of administration: subcutaneous injection
Amount of injection solution: 1 ml

Arm title	Arm II Verum

Arm description:

In arm II, the verum product was used. The verum product was a sterile solution for subcutaneous injection containing 100 mg/ml of tregalizumab plus the excipients of the formulation buffer. The excipients of the formulation buffer were exactly the same as in the placebo product.
Each of the 21 subjects in this group was treated with the verum product once a week for 12 weeks. The injection was administered into the upper abdomen. At each administration, 1 ml of the solution was injected. The first administration was on day 1 (visit V5). During the treatment phase, defined procedures with a specific number of tests/measurements were performed at each visit (visit V5 - visit V16). A defined number of tests/measurements were also performed during the follow-up phase (visit V17- visit V19).

Arm type	Active comparator
Investigational medicinal product name	Test product (Verum)
Investigational medicinal product code	
Other name	Tregalizumab (BT061)
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Verum: Tregalizumab solution
Concentration: 100 mg/mL
Dose per administration: 100 mg
Mode of administration: subcutaneous injection
Amount of injection solution: 1 ml

Number of subjects in period 1	Arm I Placebo	Arm II Verum
Started	21	21
Completed	21	20
Not completed	0	1
One subject moved to another city	-	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	42	42	
Age categorical			
Male and female subjects were enrolled into this study. At the time of the present study, there was no reason (i.e., safety issues) to exclude women from these investigations. As expressed in ICH guidelines, it is an underlying principle of drug development that "patients entering clinical trials should be reasonably representative of the population that will later be treated".			
Units: Subjects			
Adults (18-64 years)	42	42	
Gender categorical Units: Subjects			
Female	27	27	
Male	15	15	

End points

End points reporting groups

Reporting group title	Arm I Placebo

Reporting group description:

In Arm I, the placebo product was used. The placebo product was a sterile solution for subcutaneous injection containing the same excipients as the tregalizumab drug, as the placebo product was the tregalizumab formulation buffer.
Each of the 21 subjects in this group was treated with the placebo product (Tregalizumab formulation buffer) once a week for 12 weeks. The injection was administered into the upper abdomen. At each administration, 1 ml of the solution was injected. The first administration was on day 1 (visit V5). During the treatment phase, defined procedures with a certain number of tests/measurements were performed at each visit (visit V5 – visit V16). A defined number of tests/measurements were also performed during the follow-up phase (visit V17 – visit V19).

Reporting group title	Arm II Verum

Reporting group description:

In arm II, the verum product was used. The verum product was a sterile solution for subcutaneous injection containing 100 mg/ml of tregalizumab plus the excipients of the formulation buffer. The excipients of the formulation buffer were exactly the same as in the placebo product.
Each of the 21 subjects in this group was treated with the verum product once a week for 12 weeks. The injection was administered into the upper abdomen. At each administration, 1 ml of the solution was injected. The first administration was on day 1 (visit V5). During the treatment phase, defined procedures with a specific number of tests/measurements were performed at each visit (visit V5 - visit V16). A defined number of tests/measurements were also performed during the follow-up phase (visit V17- visit V19).

Primary: The primary endpoint was the baseline-corrected LAR measured by the area under the curve (AUC) for FEV1 at 4 to 7 hours after BAP (AUC 4-7 FEV1) on Day 84 in mITT set of patients.

End point title	The primary endpoint was the baseline-corrected LAR measured by the area under the curve (AUC) for FEV1 at 4 to 7 hours after BAP (AUC 4-7 FEV1) on Day 84 in mITT set of patients.

End point description:

As 0 was included in the 95% CI, it was concluded that the results for the two treatment groups were not statistically significantly different (p = 0.0526) when considering the mITT set.

End point type	Primary

End point timeframe:

V 4: 10, 15, 30 and 60 minutes after the last allergen challenge. Afterwards hourly for 9 hours in total.
V 16: 10, 15, 30 and 60 minutes after the last allergen challenge. Afterwards hourly for 9 hours in total.

End point values	Arm I Placebo	Arm II Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: AUC4 7FEV1 [%FEV1*h]				
least squares mean (confidence interval 95%)	-36.764 (-47.408 to -26.120)	-21.610 (-32.520 to -10.701)		

Statistical analyses

Statistical analysis title	ANCOVA Change from Baseline AUC4-7FEV1
Comparison groups	Arm I Placebo v Arm II Verum
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0526
Method	ANCOVA

Secondary: The secondary endpoint was the baseline-corrected LAR measured by the area under the curve (AUC) for FEV1 at 4 to 7 hours after BAP (AUC 4-7 FEV1) on Day 84 in PP set of patients.

End point title	The secondary endpoint was the baseline-corrected LAR measured by the area under the curve (AUC) for FEV1 at 4 to 7 hours after BAP (AUC 4-7 FEV1) on Day 84 in PP set of patients.

End point description:

No obvious change from baseline to Day 84 became apparent for FEV1 max,0 3 and AUC0 3FEV1 in both treatment groups.

End point type	Secondary

End point timeframe:

V 4: 10, 15, 30 and 60 minutes after the last allergen challenge. Afterwards hourly for 9 hours in total.
V 16: 10, 15, 30 and 60 minutes after the last allergen challenge. Afterwards hourly for 9 hours in total.

End point values	Arm I Placebo	Arm II Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: AUC4 7FEV1 [%FEV1*h]				
least squares mean (confidence interval 95%)	-15.044 (-19.531 to -10.557)	-7.493 (-12.090 to -2.895)		

Statistical analyses

Statistical analysis title	ANCOVA Change from Baseline AUC4 7FEV1 - mITT
Comparison groups	Arm I Placebo v Arm II Verum
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0526
Method	ANCOVA
Parameter estimate	Difference of LS means

Secondary: ANCOVA Change from Baseline FEV1 max,4 7 – mITT Set

End point title	ANCOVA Change from Baseline FEV1 max,4 7 – mITT Set

End point description:

End point type	Secondary

End point timeframe:

ANCOVA Change from Baseline FEV1 max,4-7 compared to Day 84.

End point values	Arm I Placebo	Arm II Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: FEV1 max, 4-7 [%]				
least squares mean (confidence interval 95%)	-15.044 (-19.531 to -10.557)	-7.493 (-12.090 to -2.895)		

Statistical analyses

No statistical analyses for this end point

Secondary: ANCOVA Change from Baseline FEV1 max,4 7 – PP Set

End point title	ANCOVA Change from Baseline FEV1 max,4 7 – PP Set

End point description:

End point type	Secondary

End point timeframe:

ANCOVA Change from Baseline till Day 84

End point values	Arm I Placebo	Arm II Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: FEV1 max,4-7 [%]				
least squares mean (confidence interval 95%)	-15.307 (-19.956 to -10.657)	-7.523 (-12.173 to -2.873)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting began with the first treatment of the first subject and ended with the last treatment of the last subject. Each subject received weekly single doses of 100 mg of Tregalizumab or placebo for 12 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Verum
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Verum	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Verum	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 21 (33.33%)	5 / 21 (23.81%)	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Injection site reaction			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Eye disorders			
Corneal oedema			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Dermatitis atopic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			

subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	0 / 21 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2021	Substantial Amendment SA-01 a) A modification of inclusion criterion No. 6 was necessary, due to a typing error that was overlooked during the initial protocol development and has been corrected. A RAST class equal or higher than 2 is a standard criterion in most allergy studies. The specific house dust mite species to be evaluated was also added for clarity. b) Text addition to clarify that screening assessments could be repeated for rescreened subjects. A description that screening assessments could be repeated during rescreening was added for clarity. c) Text adaptation to clarify how a demonstration of a significant EAR and LAR without rescue medication use was defined. A subject who demonstrated EAR and LAR with rescue medication use at Visit V2 was acceptable. However, if the subject took rescue medication within the first 7 hours after the single step BAP at Visit V4, the profile of FEV1 measurements could not be accepted as a baseline profile. In this latter case, Visit V4 could be repeated once. d) Text modification to allow that the individual provocation dose, which causes a decrease in FEV1 of at least 20%, could be selected by the investigator, if deemed clinically adequate. In addition, further clarifications were added which specify in which cases an adaptation of the initial allergen dose (or extrapolated dose) was required. e) Text addition to describe that if a subject was considered a screening failure at Visit V2, a final safety evaluation during Visit V3 could be conducted. Also, a description of the procedures and measurements to be performed at this final safety visit was added.
16 July 2021	Urgent Safety Measure In the summer 2021, the German federal government had made gains in the management of the COVID-19 pandemic by increasing the availability of COVID-19 vaccines to a larger portion of the population.As a result, T-Balance considered the potential impact of COVID-19 vaccination on the management of the ongoing allergic asthma trial and conducted a risk assessment to better understand how this potential impact could be mitigated. The risk assessment was guided by: 1) Historical program data 2) Regulatory and official guidance, 3) Current scientific literature, and 4) Expert medical opinion. The main outcome of the risk assessment was the need to mitigate the possibility that tregalizumab - which works by acting on immune system cells (namely, activation of T regulatory cells) - could affect the efficacy of COVID-19 vaccines (both mRNA and vector-based). Therefore, T-Balance devised an urgent safety measure to protect trial participants against a potential tregalizumab-induced reduction in COVID-19 vaccine efficacy. The premise of the urgent safety measure, which aimed to introduce appropriate intervals between dosing of the Investigational Medicinal Product (IMP) and COVID-19 vaccination, was mainly guided by Pfaar et al., 2021, MHRA Guidance (“Management of COVID-19 vaccination for subjects participating in ongoing non-COVID-19 clinical trials”), STIKO recommendations, and expert opinions.
10 December 2021	Substantial Amendment SA-02 Based on the Urgent Safety Measure regarding the safety measures for COVID-19 vaccination, a second substantial amendment was required to include the relevant measures in the documentation. Along with the USM amendment, a substantial CMC amendment was announced that included an extension of the specification limit for the colour of the placebo. In addition, other non-substantial changes (e.g., CMC relevant) that had occurred since the study was approved were

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported