Clinical trial results:
A 16-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Proof-of-Concept Study to Evaluate the Efficacy and Safety of TEV-48574 in Adults with T2-Low/Non-T2 Severe Uncontrolled Asthma

Summary

EudraCT number	2020-001927-15
Trial protocol	DE BG CZ
Global end of trial date	17 January 2022

Results information

Result version number	v1 (current)
This version publication date	20 January 2023
First version publication date	20 January 2023

Trial information

Trial identification

Sponsor protocol code	TV48574-AS-20031

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04545385
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc.
Sponsor organisation address	145 Brandywine Parkway, West Chester, United States, 19380
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., MedInfo@tevaeu.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products R&D, Inc., MedInfo@tevaeu.com

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	17 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 January 2022
Global end of trial reached?	Yes
Global end of trial date	17 January 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of TEV-48574 compared with placebo on loss of asthma control (LoAC) in adult participants with T2-low and non-T2 severe asthma uncontrolled on inhaled corticosteroids plus long-acting beta-agonists (ICS+LABA).

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (for example, Code of Federal Regulations [CFR] Title 21, Parts 50, 54, 56, 312, and 314 and European Union (EU) Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical studies on medicinal products for human use).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 October 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Czechia: 17
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	65
EEA total number of subjects	37

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)	40
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 65 participants were randomly assigned to treatment (33 participants in the TEV-48574 group and 32 participants in the placebo group). Of these, 64 participants received at least 1 dose of study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matched to TEV-48574 subcutaneously (SC) every 2 weeks for a total of 8 doses.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matched to TEV-48574 was administered per schedule specified in the arm.

Arm title	TEV-48574

Arm description:

Participants received TEV-48574 loading dose SC on the day of randomization and the subsequent corresponding TEV-48574 maintenance doses SC every 2 weeks for a total of 8 doses (1 loading dose and 7 maintenance doses).

Arm type	Experimental
Investigational medicinal product name	TEV-48574
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

TEV-48574 was administered per schedule specified in the arm.

Number of subjects in period 1	Placebo	TEV-48574
Started	32	33
Received at least 1 dose of study drug	31	33
Completed	17	20
Not completed	15	13
Consent withdrawn by subject	2	-
Study termination	10	10
Other than specified	1	-
Sponsor decision	2	2
Loss of asthma control (LoAC)	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to TEV-48574 subcutaneously (SC) every 2 weeks for a total of 8 doses.	
Reporting group title	TEV-48574
Reporting group description:	
Participants received TEV-48574 loading dose SC on the day of randomization and the subsequent corresponding TEV-48574 maintenance doses SC every 2 weeks for a total of 8 doses (1 loading dose and 7 maintenance doses).	

Reporting group values	Placebo	TEV-48574	Total
Number of subjects	32	33	65
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	56.3	58.8	
standard deviation	± 14.14	± 12.38	-
Sex: Female, Male			
Units: participants			
Female	19	22	41
Male	13	11	24
Race/Ethnicity, Customized			
Units: Subjects			
White	28	26	54
Black or African American	4	6	10
Other	0	1	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	5	6	11
Not Hispanic or Latino	27	27	54
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to TEV-48574 subcutaneously (SC) every 2 weeks for a total of 8 doses.	
Reporting group title	TEV-48574
Reporting group description:	
Participants received TEV-48574 loading dose SC on the day of randomization and the subsequent corresponding TEV-48574 maintenance doses SC every 2 weeks for a total of 8 doses (1 loading dose and 7 maintenance doses).	

Primary: Number of Participants who Experienced LoAC during the Treatment Period

End point title	Number of Participants who Experienced LoAC during the Treatment Period
End point description:	
The LoAC was defined as any 1 of the following during the treatment period: - morning peak expiratory flow (PEF) decrease ≥30% from baseline on 2 consecutive days or morning handheld forced expiratory volume in the first second of exhalation (FEV1) decrease ≥20% from baseline on 2 consecutive days; - increase in short-acting beta-agonist (SABA)/quick-relief medication ≥6 puffs over baseline use in 24 hours on 2 consecutive days; increase in inhaled corticosteroids (ICS) dose ≥4 × most recent dose; - systemic corticosteroid use; - asthma emergency room (ER) visit or hospitalization. The intent-to-treat (ITT) analysis set included all randomized participants.	
End point type	Primary
End point timeframe:	
From randomization (Week 0) until Week 16	

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: participants	13	17		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using logistic regression with fixed effects for treatment, baseline FEV1, weight, age group, and gender.	
Comparison groups	Placebo v TEV-48574

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7817
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.545
upper limit	4.071

Secondary: Time From Randomization to LoAC During the Treatment Period

End point title	Time From Randomization to LoAC During the Treatment Period

End point description:

Time (in days) from randomization to LoAC during the treatment period is the interval from randomization to the occurrence of the LoAC. The LoAC was defined as any 1 of the following during the treatment period: - morning PEF decrease ≥30% from baseline on 2 consecutive days or morning handheld FEV1 decrease ≥20% from baseline on 2 consecutive days; - increase in SABA/quick-relief medication ≥6 puffs over baseline use in 24 hours on 2 consecutive days; increase in ICS dose ≥4 × most recent dose; - systemic corticosteroid use; - asthma ER visit or hospitalization. The ITT analysis set included all randomized participants. '99999' signifies 'median and upper limit of 95% confidence interval (CI) could not be calculated due to smaller number of participants with an event'.

End point type	Secondary

End point timeframe:

From randomization (Week 0) until Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: days				
median (confidence interval 95%)	99999 (60.0 to 99999)	109.0 (45.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Asthma Control Questionnaire 6-Question Version (ACQ-6) Score at Week 16

End point title	Change From Baseline in Asthma Control Questionnaire 6-Question Version (ACQ-6) Score at Week 16

End point description:

The ACQ-6 is a 6-item validated asthma assessment tool that has been widely used. Six questions are self-assessments (completed by the participant), 5 questions assessing asthma symptoms: night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and 1 question for

short-acting bronchodilator use. Each item on the ACQ-6 has a possible score ranges from 0 to 6, and the total score is the mean of all responses. The total score ranging from 0-6 (0=totally controlled and 6=severely uncontrolled). A higher score indicated poorer asthma control. The ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	16		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.560 (± 0.4546)	-0.833 (± 0.7250)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Expiratory Volume in the First Second (FEV1) at Week 16

End point title	Change From Baseline in Forced Expiratory Volume in the First Second (FEV1) at Week 16

End point description:

FEV1 (measured by handheld spirometer) is the volume of air that can be forcibly exhaled from the lungs in the first second. The ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	16		
Units: %predicted FEV1				
arithmetic mean (standard deviation)	0.121 (± 8.3126)	4.844 (± 12.4343)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Daily Average Use of Short-acting Beta-agonist (SABA) Quick Relief Medication at Week 16

End point title	Change From Baseline in Daily Average Use of Short-acting Beta-agonist (SABA) Quick Relief Medication at Week 16

End point description:

Number of inhalations/puffs of SABA/quick relief inhaler used was recorded in the e-diary daily. The ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	16		
Units: puffs of SABA/day				
arithmetic mean (standard deviation)	-0.235 (± 1.2641)	-0.305 (± 1.6501)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who had a Clinical Asthma Exacerbation (CAE) During the Treatment Period

End point title	Number of Participants who had a Clinical Asthma Exacerbation (CAE) During the Treatment Period

End point description:

The CAEs during the study were defined as a worsening of asthma symptoms resulting in any 1 of the following: - the use of systemic corticosteroids (oral or injectable); - an emergency department visit due to asthma treated with systemic corticosteroids; - an inpatient hospitalization due to asthma. Worsening asthma included new or increased symptoms or signs that either worried the participant or were related to an asthma-specific alert (if available through the e-diary/handheld spirometer). The ITT analysis set included all randomized participants.

End point type	Secondary

End point timeframe:

From randomization (Week 0) until Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: participants	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Randomization to First CAE During the Treatment Period for Participants With CAE

End point title	Time From Randomization to First CAE During the Treatment Period for Participants With CAE

End point description:

The CAEs during the study were defined as a worsening of asthma symptoms resulting in any 1 of the following: - the use of systemic corticosteroids (oral or injectable); - an emergency department visit due to asthma treated with systemic corticosteroids; - an inpatient hospitalization due to asthma. Worsening asthma included new or increased symptoms or signs that either worried the participant or were related to an asthma-specific alert (if available through the e-diary/handheld spirometer). The ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From randomization (Week 0) until Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	3		
Units: days				
median (full range (min-max))	46.5 (38 to 55)	37.0 (30 to 54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Number of Nighttime Awakenings Due to Asthma at Week 16

End point title	Change From Baseline in Number of Nighttime Awakenings Due to Asthma at Week 16

End point description:

Participants recorded the number of nighttime awakenings due to asthma in the e-diary daily, in the morning. The ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	16		
Units: nighttime awakenings				
arithmetic mean (standard deviation)	-1.224 (± 2.0182)	-0.208 (± 2.7274)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in ICS Dose During the Treatment Period

End point title	Percent Change in ICS Dose During the Treatment Period

End point description:

The ICS use were recorded as one of asthma medications in the prior and concomitant medication data on the case record form. Due to change in planned analysis, this outcome measure was not evaluated.

End point type	Secondary

End point timeframe:

From randomization (Week 0) until Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: percent change				
arithmetic mean (standard deviation)	()	()		

Notes:

[1] - Due to change in planned analysis, this outcome measure was not evaluated.

[2] - Due to change in planned analysis, this outcome measure was not evaluated.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Vital Capacity (FVC) at Week 16

End point title	Change From Baseline in Forced Vital Capacity (FVC) at Week 16

End point description:

FVC (measured by handheld spirometer) is the volume of air that can be forcibly and completely blown out after full inspiration, measured in liters. The ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	16		
Units: liters				
arithmetic mean (standard deviation)	0.014 (± 0.3052)	0.155 (± 0.3964)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Forced Expiratory Flow at 25-75% of Pulmonary Volume (FEF25%-75%) at Week 16

End point title	Change From Baseline in Forced Expiratory Flow at 25-75% of Pulmonary Volume (FEF25%-75%) at Week 16

End point description:

The FEF25%-75% (measured by handheld spirometer) is the forced expiratory flow from 25% to 75% of FVC. The ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	16		
Units: liters/second				
arithmetic mean (standard deviation)	-0.026 (± 0.2451)	0.166 (± 0.4342)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fractional Exhaled Nitric Oxide (FeNO) at Week 16

End point title	Change From Baseline in Fractional Exhaled Nitric Oxide (FeNO) at Week 16

End point description:

FeNO was performed prior to the on-site spirometry. The ITT analysis set included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	16		
Units: parts per billion (ppb)				
arithmetic mean (standard deviation)	5.364 (± 6.9609)	10.375 (± 12.5850)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point description:

An AE was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Serious adverse events (SAEs) included death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event that jeopardized the participant and required medical intervention to prevent 1 of the outcomes listed in this definition. AEs were considered treatment emergent (TEAEs) if onset occurred on or after the first dose date. A summary of serious and non-serious AEs regardless of causality is located in 'Reported Adverse Events module'. Safety analysis set included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From randomization (Week 0) until Week 24

End point values	Placebo	TEV-48574		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: participants	14	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From randomization (Week 0) until Week 24	
Adverse event reporting additional description:	
Safety analysis set included all randomized participants who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	TEV-48574
Reporting group description:	
Participants received TEV-48574 loading dose SC on the day of randomization and the subsequent corresponding TEV-48574 maintenance doses SC every 2 weeks for a total of 8 doses (1 loading dose and 7 maintenance doses).	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to TEV-48574 SC every 2 weeks for a total of 8 doses.	

Serious adverse events	TEV-48574	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)	1 / 31 (3.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal prolapse			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TEV-48574	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 33 (18.18%)	4 / 31 (12.90%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 33 (9.09%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 33 (9.09%)	3 / 31 (9.68%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2020	The following major procedural changes (not all-inclusive) were made to the protocol: - addition of a Joint Data Monitoring Committee to monitor safety of the participants; addition of a futility analysis at the interim analysis; - clarification that the window for the screening and run-in period could also be 4 weeks; - clarification regarding timing of FeNO assessment; additional procedures to confirm TB diagnosis; - clarification that handheld spirometers should not be used for FEV1 testing at screening; - addition of reslizumab to the list of examples of systemic immunosuppressive or immunomodulatory agents.
28 April 2021	The following major procedural changes (not all-inclusive) were made to the protocol: - changes to the inclusion and exclusion criteria to increase enrollment to the study related to participants with prior COVID-19 infection, COVID-19 vaccination, and positive urine test for tetrahydrocannabinol (THC); - addition of malignancies to immunosuppression risk and immunosuppression risk to align with the informed consent form (ICF); - removal of sputum collection; - addition of defining criteria of a participant having T2-low/non-T2 asthma (possessing eosinophil count of <250 cells/microliter [µL] of blood); - addition of text ensuring participants who tested positive for COVID-19 infection were discontinued from investigational medicinal product (IMP); - additional details for primary and secondary efficacy analysis and interim futility analysis; - clarification of specific examples of the types of respiratory conditions that would meet exclusion criterion "a" to provide further context for the investigators.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported