Clinical trial results:
A study to test the combination of tiotropium and olodaterol using the Respimat® inhaler in people with chronic obstructive pulmonary disease (COPD) who have different abilities to inhale

Summary

EudraCT number	2019-001719-21
Trial protocol	DE
Global end of trial date	20 September 2020

Results information

Result version number	v2 (current)
This version publication date	03 November 2021
First version publication date	29 September 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1237-0095

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04223843
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Straße 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.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	06 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2020
Global end of trial reached?	Yes
Global end of trial date	20 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This trial was designed to demonstrate the efficacy of inhaled tiotropium + olodaterol 5 µg/5 µg (referred to as T+O) via Respimat® on lung function in patients with moderate to severe COPD with optimal and sub-optimal peak inspiratory flow rate (PIFR).

Protection of trial subjects:

Prior to the initiation of any trial-related procedure, all patients were informed about the trial verbally and in writing by the investigator. The patient was allowed sufficient time to consider participation in the trial and to ask questions concerning the details of the trial. Each patient signed and dated an ICF according to the local regulatory and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 January 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	United States: 208
Country: Number of subjects enrolled	Germany: 121
Worldwide total number of subjects	329
EEA total number of subjects	121

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)	161
From 65 to 84 years	167
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A randomised, double-blind, placebo-controlled trial to demonstrate the efficacy of 5µg/5µg inhaled tiotropium + olodateral (Tio+Olo) via Respimat® on lung function in patients with moderate to severe chronic obstructive pulmonary disease (COPD) with optimal and sub-obtimal peak inspiratory flow rate (PIFR).

Pre-assignment

Screening details:

Only patients that met all inclusion and none of the exclusion criteria were included in this trial. Prior to the initiation of any trial-related procedure, all patients were informed about the trial verbally and in writing by the investigator. Patients signed and dated an Informed Consent Form according to local regulatory and legal requirements.

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	Subject, Investigator

Blinding implementation details:

Patients, investigators, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial was to remain blinded with regard to the randomised treatment assignments until after database lock. Access to the randomisation code was kept restricted until its release for analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tio+Olo (5µg/5µg) - Sub-optimal PIFR

Arm description:

A fixed dose combination of 5 microgram (µg)/5µg (two times 2.5µg/2.5µg) tiotropium + olodaterol (Tio+Olo) inhalation solution was administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (<60 Liter(L)/minute (min)) over a 4-week treatment period.

Arm type	Experimental
Investigational medicinal product name	Tiotropium + Olodaterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

A fixed dose combination of 5 micorgram (µg)/5µg (two times 2.5µg/2.5µg) tiotropium + olodaterol (Tio+Olo) inhalation solution was administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (<60 Liter(L)/minute (min)) over a 4-week treatment period.

Arm title	Matching Placebo - Sub-optimal PIFR

Arm description:

2 inhalation solutions of matching placebo were administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (<60 L/min) over a 4-week treatment period.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

2 inhalation solutions of matching placebo were administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (<60 L/min) over a 4-week treatment period.

Arm title	Tio+Olo (5µg/5µg) - Optimal PIFR

Arm description:

A fixed dose combination of 5µg/5µg (two times 2.5µg/2.5µg) tiotropium + olodaterol (Tio+Olo) inhalation solution was administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (≥60 L/min) over a 4-week treatment period.

Arm type	Experimental
Investigational medicinal product name	Tiotropium + Olodaterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

A fixed dose combination of 5µg/5µg (two times 2.5µg/2.5µg) tiotropium + olodaterol (Tio+Olo) inhalation solution was administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (≥60 L/min) over a 4-week treatment period.

Arm title	Matching Placebo - Optimal PIFR

Arm description:

2 inhalation solutions of matching placebo were administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with optimal peak inspiratory flow rate (PIFR) (≥60 L/min) over a 4-week treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

2 inhalation solutions of matching placebo were administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with optimal peak inspiratory flow rate (PIFR) (≥60 L/min) over a 4-week treatment period.

Number of subjects in period 1[1]	Tio+Olo (5µg/5µg) - Sub-optimal PIFR	Matching Placebo - Sub-optimal PIFR	Tio+Olo (5µg/5µg) - Optimal PIFR
Started	55	55	51
Completed	55	55	51

Number of subjects in period 1[1]	Matching Placebo - Optimal PIFR
Started	52

Completed	52

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 329 patients were enrolled worldwide, whereof 213 were included in the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Tio+Olo (5µg/5µg) - Sub-optimal PIFR
Reporting group description:	
A fixed dose combination of 5 microgram (µg)/5µg (two times 2.5µg/2.5µg) tiotropium + olodaterol (Tio+Olo) inhalation solution was administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (<60 Liter(L)/minute (min)) over a 4-week treatment period.	
Reporting group title	Matching Placebo - Sub-optimal PIFR
Reporting group description:	
2 inhalation solutions of matching placebo were administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (<60 L/min) over a 4-week treatment period.	
Reporting group title	Tio+Olo (5µg/5µg) - Optimal PIFR
Reporting group description:	
A fixed dose combination of 5µg/5µg (two times 2.5µg/2.5µg) tiotropium + olodaterol (Tio+Olo) inhalation solution was administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (≥60 L/min) over a 4-week treatment period.	
Reporting group title	Matching Placebo - Optimal PIFR
Reporting group description:	
2 inhalation solutions of matching placebo were administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with optimal peak inspiratory flow rate (PIFR) (≥60 L/min) over a 4-week treatment period.	

Reporting group values	Tio+Olo (5µg/5µg) - Sub-optimal PIFR	Matching Placebo - Sub-optimal PIFR	Tio+Olo (5µg/5µg) - Optimal PIFR
Number of subjects	55	55	51
Age categorical			
Treated Set (TS): This patient set included all randomised patients who were dispensed trial medication and were documented to have taken any dose of trial medication. The TS was used for demographics and baseline disease characteristics, concomitant theraphies, treatment exposure, and safety analysis.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	29	23	30
From 65-84 years	25	32	21
85 years and over	1	0	0
Age Continuous			
Treated Set (TS): This patient set included all randomised patients who were dispensed trial medication and were documented to have taken any dose of trial medication. The TS was used for demographics and baseline disease characteristics, concomitant theraphies, treatment exposure, and safety analysis.			
Units: years			
arithmetic mean	64	67.05	62.80
standard deviation	± 9.79	± 7.54	± 7.48

Sex: Female, Male			
Treated Set (TS): This patient set included all randomised patients who were dispensed trial medication and were documented to have taken any dose of trial medication. The TS was used for demographics and baseline disease characteristics, concomitant theraphies, treatment exposure, and safety analysis.			
Units: Participants			
Female	28	37	24
Male	27	18	27
Race (NIH/OMB)			
Treated Set (TS): This patient set included all randomised patients who were dispensed trial medication and were documented to have taken any dose of trial medication. The TS was used for demographics and baseline disease characteristics, concomitant theraphies, treatment exposure, and safety analysis.			
Units: Subjects			
American Indian or Alaska Native	2	1	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	3	1
White	51	51	50
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Forced Expiratory Volume in one second (FEV1) area under the curve from 0 to 3 hours (AUC0-3h)			
FEV1 AUC0-3 at baseline. The baseline FEV1 value will be the measurement made prior to the first dosing at Visit 2. The area under the curve (AUC) is calculated as the area under the curve from 0 to 3 hours at baseline using the trapezoidal rule, divided by 3 hours to report in liters. Full Analysis Set (FAS): This patient set was nested within the TS and included all patients who had a baseline and at least 1 post-baseline measurement for at least 1 efficacy endpoint. Only patients with available data for this endpoint were included.			
Units: Liter (L)			
arithmetic mean	1.224	1.277	1.388
standard deviation	± 0.060	± 0.079	± 0.070

Reporting group values	Matching Placebo - Optimal PIFR	Total	
Number of subjects	52	213	
Age categorical			
Treated Set (TS): This patient set included all randomised patients who were dispensed trial medication and were documented to have taken any dose of trial medication. The TS was used for demographics and baseline disease characteristics, concomitant theraphies, treatment exposure, and safety analysis.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	106	
From 65-84 years	28	106	
85 years and over	0	1	
Age Continuous			
Treated Set (TS): This patient set included all randomised patients who were dispensed trial medication and were documented to have taken any dose of trial medication. The TS was used for demographics and baseline disease characteristics, concomitant theraphies, treatment exposure, and safety analysis.			
Units: years			

arithmetic mean	65.88		
standard deviation	± 7.43	-	

Sex: Female, Male			
Treated Set (TS): This patient set included all randomised patients who were dispensed trial medication and were documented to have taken any dose of trial medication. The TS was used for demographics and baseline disease characteristics, concomitant theraphies, treatment exposure, and safety analysis.			
Units: Participants			
Female	20	109	
Male	32	104	
Race (NIH/OMB)			
Treated Set (TS): This patient set included all randomised patients who were dispensed trial medication and were documented to have taken any dose of trial medication. The TS was used for demographics and baseline disease characteristics, concomitant theraphies, treatment exposure, and safety analysis.			
Units: Subjects			
American Indian or Alaska Native	0	3	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	6	
White	51	203	
More than one race	1	1	
Unknown or Not Reported	0	0	
Forced Expiratory Volume in one second (FEV1) area under the curve from 0 to 3 hours (AUC0-3h)			
FEV1 AUC0-3 at baseline. The baseline FEV1 value will be the measurement made prior to the first dosing at Visit 2. The area under the curve (AUC) is calculated as the area under the curve from 0 to 3 hours at baseline using the trapezoidal rule, divided by 3 hours to report in liters. Full Analysis Set (FAS): This patient set was nested within the TS and included all patients who had a baseline and at least 1 post-baseline measurement for at least 1 efficacy endpoint. Only patients with available data for this endpoint were included.			
Units: Liter (L)			
arithmetic mean	1.523		
standard deviation	± 0.074	-	

End points

End points reporting groups

Reporting group title	Tio+Olo (5µg/5µg) - Sub-optimal PIFR

Reporting group description:

A fixed dose combination of 5 microgram (µg)/5µg (two times 2.5µg/2.5µg) tiotropium + olodaterol (Tio+Olo) inhalation solution was administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (<60 Liter(L)/minute (min)) over a 4-week treatment period.

Reporting group title	Matching Placebo - Sub-optimal PIFR

Reporting group description:

2 inhalation solutions of matching placebo were administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (<60 L/min) over a 4-week treatment period.

Reporting group title	Tio+Olo (5µg/5µg) - Optimal PIFR

Reporting group description:

A fixed dose combination of 5µg/5µg (two times 2.5µg/2.5µg) tiotropium + olodaterol (Tio+Olo) inhalation solution was administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with sub-optimal peak inspiratory flow rate (PIFR) (≥60 L/min) over a 4-week treatment period.

Reporting group title	Matching Placebo - Optimal PIFR

Reporting group description:

2 inhalation solutions of matching placebo were administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) and with optimal peak inspiratory flow rate (PIFR) (≥60 L/min) over a 4-week treatment period.

Primary: Change from baseline in Forced Expiratory Volume in one second (FEV1) area under the curve from 0 to 3 hours (AUC0-3h) after 4 weeks of treatment

End point title	Change from baseline in Forced Expiratory Volume in one second (FEV1) area under the curve from 0 to 3 hours (AUC0-3h) after 4 weeks of treatment

End point description:

FEV1 AUC0-3h was calculated as the area under the FEV1-time curve from 0 to 3h post-dose using the trapezoidal rule, divided by the duration (3h) to report in liters. Mean is adjusted mean.

A hierarchical testing procedure was used to test the primary endpoint. Each of the tests wer considered confirmatory only if all previous tests were successful.
Full Analysis Set (FAS): This patient set was nested within the treated set and included all patients who had a baseline and at least 1 post-baseline measurement for at least 1 efficacy endpoint. Only patients with non-missing endpoint results were included.

End point type	Primary

End point timeframe:

At baseline and at week 4: 10 minutes (min) prior and 5 min, 15 min, 30 min and 1 hour (h), 2h and 3h after drug intake, respectively.

End point values	Tio+Olo (5µg/5µg) - Sub-optimal PIFR	Matching Placebo - Sub-optimal PIFR	Tio+Olo (5µg/5µg) - Optimal PIFR	Matching Placebo - Optimal PIFR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43[1]	47[2]	44[3]	47[4]
Units: Liter (L)				

arithmetic mean (standard error)	0.250 (± 0.033)	-0.086 (± 0.031)	0.333 (± 0.032)	0.012 (± 0.031)

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

[4] - FAS

Statistical analyses

Statistical analysis title	Comparison FEV1 AUC0-3h change from baseline

Statistical analysis description:

H0: There is no difference in the mean FEV1 AUC0-3h change from baseline between Tio+Olo and matching placebo.

Comparison groups	Tio+Olo (5µg/5µg) - Sub-optimal PIFR v Matching Placebo - Sub-optimal PIFR
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference of adjusted means
Point estimate	0.336
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.246
upper limit	0.425
Variability estimate	Standard error of the mean
Dispersion value	0.045

Statistical analysis title	Comparison FEV1 AUC0-3 change from baseline

Statistical analysis description:

H0: There is no difference in the mean FEV1 AUC0-3h change from baseline between Tio+Olo and matching placebo.

Comparison groups	Tio+Olo (5µg/5µg) - Optimal PIFR v Matching Placebo - Optimal PIFR
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Difference of adjusted means
Point estimate	0.321
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.233
upper limit	0.409
Variability estimate	Standard error of the mean
Dispersion value	0.044

Secondary: Change from baseline in trough Forced Expiratory Volume in one second (FEV1) after 4 weeks of treatment

End point title	Change from baseline in trough Forced Expiratory Volume in one second (FEV1) after 4 weeks of treatment

End point description:

Change from baseline in trough Forced Expiratory Volume in one second (FEV1) after 4 weeks of treatment.

FAS: This patient set was nested within the TS and included all patients who had a baseline and at least 1 post-baseline measurement for at least 1 efficacy endpoint. Only patients with non-missing endpoint results were included.

End point type	Secondary

End point timeframe:

At baseline and at week 4.

End point values	Tio+Olo (5µg/5µg) - Sub-optimal PIFR	Matching Placebo - Sub-optimal PIFR	Tio+Olo (5µg/5µg) - Optimal PIFR	Matching Placebo - Optimal PIFR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50[5]	52[6]	47[7]	50[8]
Units: Liter				
arithmetic mean (standard error)	0.095 (± 0.031)	-0.106 (± 0.030)	0.177 (± 0.030)	-0.040 (± 0.029)

Notes:

[5] - FAS

[6] - FAS

[7] - FAS

[8] - FAS

Statistical analyses

Statistical analysis title	Comparison trough FEV1 change from baseline

Statistical analysis description:

H0: There is no difference in the mean trough FEV1 change from baseline between Tio+Olo and matching placebo.

Comparison groups	Tio+Olo (5µg/5µg) - Sub-optimal PIFR v Matching Placebo - Sub-optimal PIFR
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	0.201
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.117

upper limit	0.286
Variability estimate	Standard error of the mean
Dispersion value	0.043

Statistical analysis title	Comparison trough FEV1 change from baseline

Statistical analysis description:

H0: There is no difference in the mean trough FEV1 change from baseline between Tio+Olo and matching placebo.

Comparison groups	Tio+Olo (5µg/5µg) - Optimal PIFR v Matching Placebo - Optimal PIFR
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	0.217
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.135
upper limit	0.299
Variability estimate	Standard error of the mean
Dispersion value	0.041

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From first intake of trial medication until last trial medication intake plus 21 days (residual effect period), up to 50 days.

Adverse event reporting additional description:

Treated Set: This patient set included all randomised patients who were dispensed trial medication and were documented to have taken any dose of trial medication. Adverse events were summarized by treatment group (Tio/Olo vs. Placebo), as defined in the statistical analysis plan.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	5µg/5µg Tio+Olo - Overall

Reporting group description:

A fixed dose combination (FDC) of 5µg/5µg (two times 2.5µg/2.5µg) tiotropium + olodaterol (Tio+Olo) inhalation solution was administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) over a 4-week treatment period. Overall group included patients with both, sub-optimal (<60 L/min) peak inspiratory flow rate (PIFR) and optimal (≥60 L/min) peak inspiratory flow rate (PIFR).

Reporting group title	Matching Placebo - Overall

Reporting group description:

2 inhalation solutions of matching placebo were administered orally once daily via Respimat inhaler in patients with moderate to severe chronic obstructive pulmonary disease (COPD) over a 4-week treatment period. Overall group included patients with both, sub-optimal (<60 L/min) peak inspiratory flow rate (PIFR) and optimal (≥60 L/min) peak inspiratory flow rate (PIFR).

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events were reported.

Serious adverse events	5µg/5µg Tio+Olo - Overall	Matching Placebo - Overall	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 106 (1.89%)	1 / 107 (0.93%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 107 (0.93%)	
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	5µg/5µg Tio+Olo - Overall	Matching Placebo - Overall	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 106 (0.00%)	0 / 107 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2019	In this revision of the trial protocol, the stipulation to perform in-home PIFR measurements at high resistance was removed to reduce the complexity of patient procedures at home; associated text was updated. Text and flow chart footnotes were clarified or corrected to ensure alignment across trial-procedure descriptions within the document.
28 January 2020	In this revision of the trial protocol, exclusion criterion 21 was broadened to exclude patients with eGFR measuring <50 mL/min/1.73 m2; the flowchart was updated in line with this addition. Exclusion criterion 1 was updated to refer to local SmPC/USPI to provide additional guidance regarding exclusions. More precise criteria for discontinuation of trial medication were added, specifically trial medication was to be discontinued if paradoxical bronchospasm, allergic reaction, or 2 or more eye symptoms occurred. Finally, it was clarified that triple combination therapies containing ICS were restricted and that their use was not permitted within 6 months of trial entry, nor at any point during the trial itself.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2020	Due to the current COVID-19 pandemic, the recruitment of new subjects was temporarily discontinued. Ongoing, randomised patients were managed per Trial Protocol.	23 June 2020

Notes:

Limitations and caveats

None reported