Clinical trial results:
A multi-centre, randomised, double-blind, placebo-controlled, crossover study to investigate the efficacy, safety, and tolerability of repeat doses of inhaled GSK2269557 in adults with persistent, uncontrolled asthma

Summary

EudraCT number	2014-003808-77
Trial protocol	DE
Global end of trial date	28 September 2016

Results information

Result version number	v1
This version publication date	04 June 2017
First version publication date	04 June 2017

Trial information

Trial identification

Sponsor protocol code	201543

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	12 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2016
Global end of trial reached?	Yes
Global end of trial date	28 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of inhaledGSK2269557 administered once daily for 28 days in subjects with persistent uncontrolled asthma, compared with placebo.

Protection of trial subjects:

The study protocol has included the following stopping criteria:

- Liver Chemistry Stopping Criteria
- QTc Stopping Criteria
- Other Safety stopping criteria like

Unacceptable adverse events related to study drug or study procedures.
Clinically significant and relevant changes in laboratory parameters or ECG recordings.
Paradoxical bronchospasm
Pregnancy (female subjects)

- Efficacy stopping criteria
- A subjects may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 October 2015
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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	47
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible participants entered the 2 week Run-in phase and participants who met the randomization eligibility criteria entered into the 4 week Double-blind treatment period (DBTP) 1 followed by a 4-week wash-out period, 4 weeks DBTP 2 and a 2 week follow-up phase. The total duration of participation in the study was 16 weeks.

Pre-assignment

Screening details:

A total of 108 participants with persistent uncontrolled asthma, currently not treated with an inhaled corticosteroid (ICS) or long acting beta2 agonist (LABA) were screened, of these, 58 were screen failures and 50 entered the Run-in phase. All 50 par. were randomized into the study and received study treatments.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo, then GSK2269557

Arm description:

Participants received placebo drug once daily via dry powder inhaler for 28 days during Treatment Period 1. After a washout period of 4 weeks, participants received GSK2269557 1000 micrograms (µg) drug once daily via dry powder inhaler for 28 days during Treatment Period 2. In addition, salbutamol was provided to participants to use on an as-needed basis for relief of asthma symptoms.

Arm type	Experimental
Investigational medicinal product name	GSK2269557
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations of GSK269557 were administered every day before breakfast by using DISKUS dry powder inhaler (DPI). Inhalations were taken approximately 30 seconds apart.

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

Dosage and administration details:

2 inhalations of lactose were administered every day before breakfast by using DISKUS DPI. Inhalations were taken approximately 30 seconds apart.

Arm title	GSK2269557, then Placebo

Arm description:

Participants received GSK2269557 1000 µg drug once daily via dry powder inhaler for the 28 days during Treatment Period 1. After a washout period of 4 weeks, participants received placebo drug once daily via dry powder inhaler for 28 days during Treatment Period 2. In addition, salbutamol was provided to participants to use on an as-needed basis for relief of asthma symptoms.

Arm type	Experimental

Investigational medicinal product name	GSK2269557
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations of GSK269557 were administered every day before breakfast by using DISKUS dry powder inhaler (DPI). Inhalations were taken approximately 30 seconds apart.

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

Dosage and administration details:

2 inhalations of lactose were administered every day before breakfast by using DISKUS DPI. Inhalations were taken approximately 30 seconds apart.

Number of subjects in period 1	Placebo, then GSK2269557	GSK2269557, then Placebo
Started	24	26
Completed	22	23
Not completed	2	3
Other: Reached stopping criteria	2	-
Adverse event, non-fatal	-	2
Protocol deviation	-	1

Period 2

Period 2 title	Washout period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo, then GSK2269557

Arm description:

The two treatment periods were separated by a four-week wash-out period in which all participants did not receive study medication, but were provided a salbutamol inhaler for symptomatic relief of asthma symptoms.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	GSK2269557, then Placebo

Arm description:

The two treatment periods were separated by a four-week wash-out period in which all participants did

not receive study medication, but were provided a salbutamol inhaler for symptomatic relief of asthma symptoms.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Placebo, then GSK2269557	GSK2269557, then Placebo
Started	22	23
Completed	22	23

Period 3

Period 3 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo, then GSK2269557

Arm description:

Participants received placebo drug once daily via dry powder inhaler for 28 days during Treatment Period 1. After a washout period of 4 weeks, participants received GSK2269557 1000 micrograms (µg) drug once daily via dry powder inhaler for 28 days during Treatment Period 2. In addition, salbutamol was provided to participants to use on an as-needed basis for relief of asthma symptoms.

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

Dosage and administration details:

2 inhalations of lactose were administered every day before breakfast by using DISKUS DPI. Inhalations were taken approximately 30 seconds apart.

Investigational medicinal product name	GSK2269557
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations of GSK269557 were administered every day before breakfast by using DISKUS dry powder inhaler (DPI). Inhalations were taken approximately 30 seconds apart.

Arm title	GSK2269557, then Placebo

Arm description:

Participants received GSK2269557 1000 µg drug once daily via dry powder inhaler for the 28 days during Treatment Period 1. After a washout period of 4 weeks, participants received placebo drug once daily via dry powder inhaler for 28 days during Treatment Period 2. In addition, salbutamol was provided to participants to use on an as-needed basis for relief of asthma symptoms.

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

Dosage and administration details:

2 inhalations of lactose were administered every day before breakfast by using DISKUS DPI. Inhalations were taken approximately 30 seconds apart.

Investigational medicinal product name	GSK2269557
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations of GSK269557 were administered every day before breakfast by using DISKUS dry powder inhaler (DPI). Inhalations were taken approximately 30 seconds apart.

Number of subjects in period 3	Placebo, then GSK2269557	GSK2269557, then Placebo
Started	22	23
Completed	22	20
Not completed	0	3
Other: Reached stopping criteria	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period 1
Reporting group description:	
Treatment Period 1	

Reporting group values	Treatment Period 1	Total	
Number of subjects	50	50	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	44.5		
standard deviation	± 13.86	-	
Gender categorical			
Units: Subjects			
Female	28	28	
Male	22	22	
Race/Ethnicity, Customized			
Units: Subjects			
White - White/Caucasian/European Heritage	50	50	

End points

End points reporting groups

Reporting group title	Placebo, then GSK2269557

Reporting group description:

Participants received placebo drug once daily via dry powder inhaler for 28 days during Treatment Period 1. After a washout period of 4 weeks, participants received GSK2269557 1000 micrograms (µg) drug once daily via dry powder inhaler for 28 days during Treatment Period 2. In addition, salbutamol was provided to participants to use on an as-needed basis for relief of asthma symptoms.

Reporting group title	GSK2269557, then Placebo

Reporting group description:

Participants received GSK2269557 1000 µg drug once daily via dry powder inhaler for the 28 days during Treatment Period 1. After a washout period of 4 weeks, participants received placebo drug once daily via dry powder inhaler for 28 days during Treatment Period 2. In addition, salbutamol was provided to participants to use on an as-needed basis for relief of asthma symptoms.

Reporting group title	Placebo, then GSK2269557

Reporting group description:

The two treatment periods were separated by a four-week wash-out period in which all participants did not receive study medication, but were provided a salbutamol inhaler for symptomatic relief of asthma symptoms.

Reporting group title	GSK2269557, then Placebo

Reporting group description:

The two treatment periods were separated by a four-week wash-out period in which all participants did not receive study medication, but were provided a salbutamol inhaler for symptomatic relief of asthma symptoms.

Reporting group title	Placebo, then GSK2269557

Reporting group description:

Participants received placebo drug once daily via dry powder inhaler for 28 days during Treatment Period 1. After a washout period of 4 weeks, participants received GSK2269557 1000 micrograms (µg) drug once daily via dry powder inhaler for 28 days during Treatment Period 2. In addition, salbutamol was provided to participants to use on an as-needed basis for relief of asthma symptoms.

Reporting group title	GSK2269557, then Placebo

Reporting group description:

Participants received GSK2269557 1000 µg drug once daily via dry powder inhaler for the 28 days during Treatment Period 1. After a washout period of 4 weeks, participants received placebo drug once daily via dry powder inhaler for 28 days during Treatment Period 2. In addition, salbutamol was provided to participants to use on an as-needed basis for relief of asthma symptoms.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who received matching placebo once daily via dry powder inhaler for 28 days in either treatment period 1 or 2.

Subject analysis set title	GSK2269557 1000 µg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who received GSK2269557 1000 µg once daily via dry powder inhaler for 28 days in either treatment period 1 or 2.

Primary: Change from Baseline in trough forced expiratory volume in one second (FEV1) at Day 28 in Intent-To-Treat (ITT) Population

End point title	Change from Baseline in trough forced expiratory volume in one second (FEV1) at Day 28 in Intent-To-Treat (ITT) Population

End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 is the maximum volume of air that can be forced out in one second after taking a deep breath approximately 24 hours after the last administration of study drug. FEV1 was

measured using a spirometer. Data was collected pre-dose in the clinic at Baseline, Day 7, Day 14 and Day 28. Change from Baseline is calculated as post-Baseline value minus Baseline value where Baseline is defined as Day 1 (pre-dose). The analysis was performed on the ITT Population which comprised of all participants who received at least one dose of trial medication and have at least one post-dose efficacy assessment. Six participants had entered the study without spirometric evidence of disease, and were excluded from the ITT population prior to unblinding.

End point type	Primary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37[1]	39		
Units: Liters				
median (confidence interval 95%)				
Liters	0.027 (-0.066 to 0.117)	0.035 (-0.061 to 0.124)		

Notes:

[1] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo. The total number of participants included in the analysis is 84; however, the value calculated by the system (76) is incorrect.

Comparison groups	Placebo v GSK2269557 1000 µg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.57 [3]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference.
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.083
upper limit	0.102
Variability estimate	Standard deviation
Dispersion value	0.0468

Notes:

[2] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[3] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Primary: Change from Baseline in trough forced expiratory volume in one second (FEV1) at Day 28 in Per Protocol (PP) Population

End point title	Change from Baseline in trough forced expiratory volume in one second (FEV1) at Day 28 in Per Protocol (PP) Population

End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 is the maximum volume of air that can be forced out in one second after taking a deep breath approximately 24 hours after the last administration of study drug. FEV1 was measured using a spirometer. Data was collected pre-dose in the clinic at Baseline, Day 7, Day 14 and Day 28. Change from Baseline is calculated as post-Baseline value minus Baseline value where Baseline is defined as Day 1 (pre-dose). The analysis was performed on the PP Population which comprised of all participants in the ITT Population not identified as major protocol violators.

End point type	Primary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35[4]	37		
Units: Liters				
median (confidence interval 95%)				
Liters	0.029 (-0.073 to 0.119)	0.042 (-0.058 to 0.132)		

Notes:

[4] - PP Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo. The total number of participants included in the analysis is 78; however, the value calculated by the system (72) is incorrect.

Comparison groups	Placebo v GSK2269557 1000 µg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.61 [6]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference.
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	0.113
Variability estimate	Standard deviation
Dispersion value	0.0501

Notes:

[5] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[6] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Secondary: Weighted mean (0-4 hours) FEV1 at Day 28

End point title	Weighted mean (0-4 hours) FEV1 at Day 28

End point description:

The weighted mean FEV1 on Day 28 was calculated using data collected pre-dose and at 1 hour, 2 hours, 3 hours, and 4 hours post-dose. The weighted mean FEV1 was derived by calculating the average area under the curve using the trapezoidal rule, and then dividing by the relevant time interval.

End point type	Secondary

End point timeframe:

Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[7]	40		
Units: Liters				
median (confidence interval 95%)				
Liters	2.672 (2.556 to 2.783)	2.722 (2.607 to 2.836)		

Notes:

[7] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo. The total number of participants included in the analysis is 84; however, the value calculated by the system (78) is incorrect.

Comparison groups	GSK2269557 1000 µg v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.731 [9]
Method	Bayesian model
Parameter estimate	Posterior median difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.111
upper limit	0.21
Variability estimate	Standard deviation
Dispersion value	0.0818

Notes:

[8] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[9] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Secondary: Change from Baseline in trough FEV1 at Day 7 and Day 14

End point title	Change from Baseline in trough FEV1 at Day 7 and Day 14

End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. The trough FEV1 is the maximum volume of air that can be forced out in one

second after taking a deep breath approximately 24 hrs after the last administration of study drug. Change from Baseline values were calculated as post-Baseline values minus Baseline value where Baseline was defined as Day 1 (pre-dose). The number of participants with data available at the specified time points are represented by n=X in the category titles.

End point type	Secondary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42[10]	42		
Units: Liters				
median (confidence interval 95%)				
Day 7; n= 39, 40	0.012 (-0.102 to 0.131)	0.003 (-0.113 to 0.119)		
Day 14; n= 38,41	0.016 (-0.086 to 0.116)	0.04 (-0.061 to 0.137)		

Notes:

[10] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Day 7. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo.

Comparison groups	Placebo v GSK2269557 1000 µg
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.44 [12]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.151
upper limit	0.131
Variability estimate	Standard deviation
Dispersion value	0.0712

Notes:

[11] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[12] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Day 14. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo.

Comparison groups	Placebo v GSK2269557 1000 µg

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.66 [14]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.087
upper limit	0.137
Variability estimate	Standard deviation
Dispersion value	0.057

Notes:

[13] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[14] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Secondary: Change from Baseline in Forced Vital Capacity (FVC) at Day 7, Day 14 and Day 28

End point title	Change from Baseline in Forced Vital Capacity (FVC) at Day 7, Day 14 and Day 28

End point description:

FVC is defined as the total amount of air exhaled during the FEV test. Data was collected pre-dose at Baseline (Day 1), Day 7, Day 14 and Day 28. Change from Baseline was calculated as the post-Baseline value minus the Baseline value where Baseline was defined as Day 1 (pre-dose). The number of participants with data available at the specified time points are represented by n=X in the category titles.

End point type	Secondary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42[15]	42		
Units: Liter				
median (confidence interval 95%)				
Day 7; n= 39,40	0.036 (-0.075 to 0.146)	0.015 (-0.097 to 0.126)		
Day 14; n= 38,41	-0.002 (-0.11 to 0.107)	0.038 (-0.069 to 0.146)		
Day 28; n= 37,39	0.017 (-0.092 to 0.124)	0.054 (-0.052 to 0.159)		

Notes:

[15] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Day 7. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo.

Comparison groups	GSK2269557 1000 µg v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.35 [17]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference
Point estimate	-0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.099
Variability estimate	Standard deviation
Dispersion value	0.0609

Notes:

[16] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[17] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Day 14. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo.

Comparison groups	GSK2269557 1000 µg v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.76 [19]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.071
upper limit	0.156
Variability estimate	Standard deviation
Dispersion value	0.0578

Notes:

[18] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[19] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Day 28. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo.

Comparison groups	GSK2269557 1000 µg v Placebo

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.76 [21]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.073
upper limit	0.148
Variability estimate	Standard deviation
Dispersion value	0.0559

Notes:

[20] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[21] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Secondary: Change from Baseline in FEV1/FVC at Day 7, Day 14 and Day 28

End point title	Change from Baseline in FEV1/FVC at Day 7, Day 14 and Day 28

End point description:

FEV1 and FVC are measures of lung function. FEV1 is defined as the maximal amount of air that can be forcefully exhaled in one second. FVC is defined as the total amount of air exhaled during the FEV test. Change from Baseline in FEV1/FVC at Day 7, Day 14 and Day 28 was calculated as post-Baseline value minus Baseline value where Baseline was defined as Day 1 (pre-dose). The number of participants with data available at the specified time points are represented by n=X in the category titles.

End point type	Secondary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42[22]	42		
Units: Percentage				
median (confidence interval 95%)				
Day 7; n= 39,40	-0.956 (-2.337 to 0.495)	-0.855 (-2.285 to 0.517)		
Day 14; n= 38,41	-0.456 (-1.944 to 0.986)	-0.444 (-1.899 to 0.992)		
Day 28; n= 37,39	-0.691 (-2.05 to 0.638)	-0.791 (-2.163 to 0.516)		

Notes:

[22] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Day 7. The data entered as the 95% confidence interval represents the 95% equi-tailed credible

interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo.

Comparison groups	Placebo v GSK2269557 1000 µg
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.56 [24]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.102
upper limit	1.346
Variability estimate	Standard deviation
Dispersion value	0.6175

Notes:

[23] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[24] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Day 14. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo.

Comparison groups	Placebo v GSK2269557 1000 µg
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.51 [26]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.271
upper limit	1.341
Variability estimate	Standard deviation
Dispersion value	0.6672

Notes:

[25] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[26] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Day 28. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo.

Comparison groups	Placebo v GSK2269557 1000 µg

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.41 [28]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median difference
Point estimate	-0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.125
upper limit	0.908
Variability estimate	Standard deviation
Dispersion value	0.5148

Notes:

[27] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[28] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Secondary: Change from Baseline in Asthma Control Test (ACT) score at Day 28

End point title	Change from Baseline in Asthma Control Test (ACT) score at Day 28

End point description:

The total ACT score is the sum of five-item questionnaires developed as a measurement of asthma control. Total score can range from five (worse control) to 25 (full control), with higher scores reflecting greater asthma control. Total ACT score at Day 1 (Baseline) and Day 28 in both Treatment Periods was used for this analysis. Change from Baseline in ACT was calculated as post-Baseline value minus Baseline value where Baseline was defined as Day 1 (pre-dose).

End point type	Secondary

End point timeframe:

Baseline and Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[29]	40		
Units: Score on a scale				
median (confidence interval 95%)				
Score on a scale	1.4 (0.5 to 2.2)	1.9 (1 to 2.7)		

Notes:

[29] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median difference is calculated as GSK2269557 1000 µg minus Placebo. The total number of participants included in the analysis is 84; however, the value calculated by the system (78) is incorrect.

Comparison groups	GSK2269557 1000 µg v Placebo

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.81 [31]
Method	Bayesian model
Parameter estimate	Posterior median difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.7
Variability estimate	Standard deviation
Dispersion value	0.59

Notes:

[30] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[31] - The data entered for the p-value represents the posterior probability that the true treatment difference is greater than zero.

Secondary: Change from Baseline in daily FEV1 averaged over the treatment period

End point title	Change from Baseline in daily FEV1 averaged over the treatment period

End point description:

Triplicate measurements of FEV1 were collected in an eDiary pre-dose before breakfast [ante meridiem (AM)], and approximately 12 hours later at evening [post-meridiem (PM)]. The average change from Baseline was calculated by summing the total value of the endpoint (i.e. change from Baseline) within the time period of interest and dividing by the number of days with non-missing data for that endpoint to obtain an average for each subject. The AM Baseline is the Day 1 AM value, the PM Baseline is the last PM reading prior to taking the first dose of blinded study medication within that Treatment Period.

End point type	Secondary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42[32]	42		
Units: Liter				
arithmetic mean (standard deviation)				
AM; n= 38, 40	0 (± 0.2019)	0.065 (± 0.2974)		
PM; n= 34, 39	0.013 (± 0.2634)	0.115 (± 0.3802)		

Notes:

[32] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in daily Peak Expiratory Flow (PEF) averaged over the treatment period

End point title	Change from Baseline in daily Peak Expiratory Flow (PEF) averaged over the treatment period

End point description:

Triplicate measurements of PEF were collected in an eDiary pre-dose before breakfast (AM), and approximately 12 hours later at evening (PM). The average change from Baseline was calculated by summing the total value of the endpoint (i.e. change from Baseline) within the time period of interest and dividing by the number of days with non-missing data for that endpoint to obtain an average for each subject. The AM Baseline is the Day 1 AM value, the PM Baseline is the last PM reading prior to taking the first dose of blinded study medication within that Treatment Period.

End point type	Secondary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42[33]	42		
Units: Liter/minute				
arithmetic mean (standard deviation)				
AM; n= 38,40	-4.8 (± 32.44)	14.2 (± 46.11)		
PM; n= 34, 39	9.8 (± 36.05)	29.8 (± 64.28)		

Notes:

[33] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in trough Fractional exhaled Nitric Oxide (FeNO) at Day 7, Day 14 and Day 28

End point title	Change from Baseline in trough Fractional exhaled Nitric Oxide (FeNO) at Day 7, Day 14 and Day 28

End point description:

Participants with asthma have high levels of NO in their exhaled breath. Evaluation of FeNO is a quantitative, noninvasive method of measuring airway inflammation to assess airway diseases including asthma. FeNO was measured in the clinic using a handheld electronic device. Change from Baseline for Day 7, Day 14 and Day 28 was calculated as the post-Baseline value minus the Baseline value where Baseline was defined as Day 1 (pre-dose). The number of participants with data available at the specified time points are represented by n=X in the category titles.

End point type	Secondary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42[34]	42		
Units: Part per billion (PPB)				
median (confidence interval 95%)				

Day 7; n= 38,34	1.03 (0.93 to 1.13)	0.91 (0.82 to 1.01)		
Day 14; n= 34,35	0.99 (0.89 to 1.11)	0.95 (0.85 to 1.05)		
Day 28; n= 34,34	1.03 (0.91 to 1.17)	1.03 (0.91 to 1.17)		

Notes:

[34] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Day 7. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median ratio is calculated as GSK2269557 1000 µg/ Placebo.

Comparison groups	GSK2269557 1000 µg v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.97 [36]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1
Variability estimate	Standard deviation
Dispersion value	0.063

Notes:

[35] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[36] - The data entered for the p-value represents the posterior probability that the true treatment ratio is less than 1.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Day 14. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median ratio is calculated as GSK2269557 1000 µg/ Placebo.

Comparison groups	GSK2269557 1000 µg v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.76 [38]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.09
Variability estimate	Standard deviation
Dispersion value	0.071

Notes:

[37] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[38] - The data entered for the p-value represents the posterior probability that the true treatment ratio is less than 1.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Day 28. The data entered as the 95% confidence interval represents the 95% equi-tailed credible interval. The posterior median ratio is calculated as GSK2269557 1000 µg/ Placebo.

Comparison groups	GSK2269557 1000 µg v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.51 [40]
Method	Bayesian repeated measures model
Parameter estimate	Posterior median ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.18
Variability estimate	Standard deviation
Dispersion value	0.085

Notes:

[39] - Non-informative priors used for all modelling parameters. Unstructured covariance matrix fitted.

[40] - The data entered for the p-value represents the posterior probability that the true treatment ratio is less than one.

Secondary: Mean number of inhalations per day of rescue medication (salbutamol) over the treatment period

End point title	Mean number of inhalations per day of rescue medication (salbutamol) over the treatment period

End point description:

Daily recordings of rescue medication use were collected in an eDiary by participants. The mean number of inhalations per day of rescue medication was calculated for each participant as number of inhalations over the time period of interest divided by number of days when rescue medication was taken over the time period of interest.

End point type	Secondary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[41]	39		
Units: Number				
arithmetic mean (standard deviation)				
Number	3 (± 1.86)	2.7 (± 1.53)		

Notes:
[41] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of rescue free days over the treatment period

End point title	Percentage of rescue free days over the treatment period

End point description:

Daily recordings of rescue medication use were collected in an eDiary by participants. Percentage of rescue free days was calculated as the number of rescue free days divided by length of treatment period.

End point type	Secondary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42[42]	42		
Units: Percentage				
arithmetic mean (standard deviation)				
Percentage	49.5 (± 35.04)	47.3 (± 34.79)		

Notes:
[42] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse Events (AEs)

End point title	Number of participants with Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The analysis was performed on Safety Population which comprised of all participants who were randomized into the study.

End point type	Secondary

End point timeframe:

From the Start of IP to Follow-Up (Week 16)

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47[43]	48		
Units: Participants				
Participants	18	28		

Notes:

[43] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal values of clinical chemistry parameters

End point title	Number of participants with abnormal values of clinical chemistry parameters

End point description:

Blood samples were collected from participants for evaluation of clinical chemistry parameters by Potential Clinical Importance Criteria. The clinical chemistry parameters included albumin, calcium, creatinine, glucose, potassium and sodium. Participants were counted in the category that their value changes to (low, normal or high), unless there is no change in their category. The number of participants with data available at the specified data points are represented by n=X in the category titles.

End point type	Secondary

End point timeframe:

From start of IP up to Week 14

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47[44]	48		
Units: Participants				
Albumin; Day 1; Change to low; n= 47, 48	0	0		
Albumin; Day 14; Change to low; n= 42, 48	0	0		
Albumin; Day 28; Change to low; n= 41, 45	0	0		
Calcium; Day 1; Change to low; n= 47, 48	0	0		
Calcium; Day 1; Change to high; n= 47, 48	0	0		
Calcium; Day 14; Change to low; n= 42, 48	0	0		
Calcium; Day 14; Change to high; n= 42, 48	0	0		
Calcium; Day 28; Change to high; n= 40, 45	0	0		
Calcium; Day 28; Change to low; n= 40, 45	0	0		
Glucose; Day 1; Change to low; n= 47, 48	0	0		

Glucose; Day 1; change to high; n= 47, 48	0	0		
Glucose; Day 14; Change to low; n= 42, 48	1	0		
Glucose; Day 14; change to high; n= 42, 48	0	0		
Glucose; Day 28; Change to low; n= 41, 45	0	0		
Glucose; Day 28; Change to high; n= 41, 45	0	0		
Potassium; Day 1; Change to low; n= 47, 48	0	0		
Potassium; Day 1; Change to high; n= 47, 48	0	0		
Potassium; Day 14; Change to low; n= 42, 48	0	0		
Potassium; Day 14; Change to high; n= 42, 48	0	0		
Potassium; Day 28; Change to low; n= 40, 45	0	0		
Potassium; Day 28; Change to high; n= 40, 45	0	0		
Sodium; Day 1; Change to low; n= 47, 48	0	0		
Sodium; Day 1; Change to high; n= 47, 48	0	0		
Sodium; Day 14; Change to low; n= 42, 48	0	0		
Sodium; Day 14; Change to high; n= 42, 48	0	0		
Sodium; Day 28; Change to low; n= 41, 45	0	0		
Sodium; Day 28; Change to high; n= 41, 45	0	0		
Hematocrit; Day 1; Change to high; n= 46, 47	0	0		
Hematocrit; Day 14; Change to high; n= 43, 47	0	0		
Hematocrit; Day 28; Change to high; n= 42, 44	0	0		
Hemoglobin; Day 1; Change to high; n= 46, 47	0	0		
Hemoglobin; Day 14; Change to high; n= 43, 47	0	0		
Hemoglobin; Day 28; Change to high; n= 42, 44	0	0		
Lymphocytes; Day 1; Change to low; n= 46, 47	0	0		
Lymphocytes; Day 14; Change to low; n= 43, 47	0	0		
Lymphocytes; Day 28; Change to low; n= 42, 44	0	0		
Platelet count; Day 1; Change to low; n= 46, 47	0	0		
Platelet count; Day 1; Change to high; n= 46, 47	0	0		
Platelet count; Day 14; Change to low; n= 43, 47	0	0		
Platelet count; Day 14; Change to high; n= 43, 47	0	0		
Platelet count; Day 28; Change to low; n= 42, 43	0	0		

Platelet count; Day 28; Change to high; n= 42, 43	0	0		
Total neutrophils; Day 1; Change to low; n= 46, 47	0	0		
Total neutrophils;Day 14; Change to low; n= 43, 47	0	1		
Total neutrophils; Day 28; Change to low; n= 42,44	0	0		
WBC; Day 1; Change to low; n= 46, 47	0	0		
WBC; Day 1; Change to high; n= 46, 47	0	0		
WBC; Day 14; Change to low; n= 43, 47	0	0		
WBC; Day 14; Change to high; n= 43, 47	0	0		
WBC; Day 28; Change to low; n= 42, 44	0	0		
WBC; Day 28; Change to high; n= 42, 44	0	0		

Notes:

[44] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal values of hematology parameters

End point title	Number of participants with abnormal values of hematology parameters

End point description:

Blood samples were collected from participants for evaluation of hematology parameters by Potential Clinical Importance Criteria. The hematology parameters included hematocrit, hemoglobin, lymphocytes, total neutrophils, platelets and white blood cells (WBC). Participants were counted in the category that their value changes to (low, normal or high), unless there is no change in their category. The number of participants with data available at the specified data points are represented by n=X in the category titles.

End point type	Secondary

End point timeframe:

From start of IP up to Week 14

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47[45]	48		
Units: Participants				
Hematocrit; Day 1; Change to high; n= 46, 47	0	0		
Hematocrit; Day 14; Change to high; n= 43, 47	0	0		
Hematocrit; Day 28; Change to high; n= 42, 44	0	0		
Hemoglobin; Day 1; Change to high; n= 46, 47	0	0		
Hemoglobin; Day 14; Change to high; n= 43, 47	0	0		

Hemoglobin; Day 28; Change to high; n= 42, 44	0	0		
Lymphocytes; Day 1; Change to low; n= 46, 47	0	0		
Lymphocytes; Day 14; Change to low; n= 43, 47	0	0		
Lymphocytes; Day 28; Change to low; n= 42, 44	0	0		
Platelet count; Day 1; Change to low; n= 46, 47	0	0		
Platelet count; Day 1; Change to high; n= 46, 47	0	0		
Platelet count; Day 14; Change to low; n= 43, 47	0	0		
Platelet count; Day 14; Change to high; n= 43, 47	0	0		
Platelet count; Day 28; Change to low; n= 42, 43	0	0		
Platelet count; Day 28; Change to high; n= 42, 43	0	0		
Total neutrophils; Day 1; Change to low; n= 46, 47	0	0		
Total neutrophils;Day 14; Change to low; n= 43, 47	0	1		
Total neutrophils; Day 28; Change to low; n= 42,44	0	0		
WBC; Day 1; Change to low; n= 46, 47	0	0		
WBC; Day 1; Change to high; n= 46, 47	0	0		
WBC; Day 14; Change to low; n= 43, 47	0	0		
WBC; Day 14; Change to high; n= 43, 47	0	0		
WBC; Day 28; Change to low; n= 42, 44	0	0		
WBC; Day 28; Change to high; n= 42, 44	0	0		

Notes:

[45] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal vital sign values

End point title	Number of participants with abnormal vital sign values

End point description:

Number of participants with abnormal values of vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were evaluated. Vital signs outside the range of potential clinical importance are presented at the indicated timepoints: Day 7, Day 14, Day 28 and follow-up/Early withdrawal. The number of participants with data available at the specified data points are represented by n=X in the category titles.

End point type	Secondary

End point timeframe:

From start of IP up to Week 14

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47[46]	48		
Units: Participants				
DBP; Day 7; Change to low; n= 46, 46	0	0		
DBP; Day 7; Change to high; n= 46, 46	0	0		
DBP; Day 14; Change to low; n= 43, 48	0	0		
DBP; Day 14; Change to high; n= 43, 48	1	0		
DBP; Day 28; Change to low; n= 42, 45	0	0		
DBP; Day 28; Change to high; n= 42, 45	0	1		
SBP; Day 7; Change to low; n= 46, 46	0	0		
SBP; Day 7; Change to high; n= 46, 46	0	0		
SBP; Day 14; Change to low; n= 43, 48	0	0		
SBP; Day 14; Change to high; n= 43, 48	1	0		
SBP; Day 28; Change to low; n= 42, 45	0	0		
SBP; Day 28; Change to high; n= 42, 45	0	0		
Heart rate; Day 7; Change to low; n= 46, 46	0	0		
Heart rate; Day 7; Change to high; n= 46, 46	0	0		
Heart rate; Day 14; Change to low; n= 43, 48	0	0		
Heart rate; Day 14; Change to high; n= 43, 48	0	0		
Heart rate; Day 28; Change to low; n= 42, 45	0	0		
Heart rate; Day 28; Change to high; n= 42, 45	0	0		

Notes:

[46] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal electrocardiogram (ECG) findings

End point title	Number of participants with abnormal electrocardiogram (ECG) findings

End point description:

Single measurements of 12-lead ECGs were obtained after 5 minutes rest in a semi-supine position at Baseline (Day 1 pre dose) , Day 7, Day 28 pre-dose in each treatment period using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc). ECG values were recorded as abnormal not clinically significant (NCS) and abnormal clinically significant (CS). The number of participants with data available at the specified data points are represented by n= X in the category titles.

End point type	Secondary

End point timeframe:

Baseline to Day 28 for each treatment period

End point values	Placebo	GSK2269557 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47[47]	48		
Units: Participants				
Day 1; abnormal NCS; n= 47,48	2	5		
Day 1; abnormal CS; n= 47,48	0	0		
Day 7; abnormal NCS; n= 46,46	1	4		
Day 7; abnormal CS; n= 46,46	0	0		
Day 28; abnormal NCS; n= 42, 45	0	3		
Day 28; abnormal CS; n= 42,45	0	0		
Any time Post-Baseline; abnormal NCS; n= 47,48	1	6		
Any time Post Baseline; abnormal CS; n= 47,48	0	0		

Notes:

[47] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration of GSK2269557

End point title	Plasma concentration of GSK2269557

End point description:

Blood samples were collected from participants for pharmacokinetic (PK) analysis at Day 7, Day 14 and Day 28 pre dose. On Day 28 samples were also collected between 5-10 minutes post dose and between 2.5-3.5 hours post dose. The analysis was performed on PK Population which comprised of participants in the ITT Population for whom a PK sample was obtained and analyzed. The number of participants with data available at the specified data points are represented by n= X in the category titles.

End point type	Secondary

End point timeframe:

Pre dose at Day 7 and Day 14. At Day 28 pre dose, 5-10 minutes and 2.5-3.5 hours post dose

End point values	GSK2269557 1000 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	42[48]			
Units: pg per Milliliter (Pg/mL)				
geometric mean (confidence interval 95%)				
Day 7; pre dose; n= 40	555.7 (446.2 to 692)			
Day 14; pre dose; n= 40	520.7 (380.3 to 712.9)			
Day 28; pre dose; n= 38	649.2 (519.9 to 810.8)			
Day 28; 5-10 minutes post dose; n= 40	1188.8 (990.5 to 1426.8)			
Day 28; 2.5-3.5 hours post dose; n= 40	1170.8 (976.1 to 1404.4)			

Notes:
[48] - PK Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of the study treatment until the follow up 2 weeks after the last dose (total study duration was 16 weeks)

Adverse event reporting additional description:

AEs and SAEs were collected in Safety Population which comprised of all participants who were randomized.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants who received matching placebo once daily via dry powder inhaler for 28 days in either treatment period 1 or 2.

Reporting group title	GSK2269557 1000 µg

Reporting group description:

Participants who received GSK2269557 1000 µg once daily via dry powder inhaler for 28 days in either treatment period 1 or 2.

Serious adverse events	Placebo	GSK2269557 1000 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	0 / 48 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo	GSK2269557 1000 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 47 (27.66%)	19 / 48 (39.58%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 47 (8.51%)	2 / 48 (4.17%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 4	17 / 48 (35.42%) 18	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 47 (14.89%) 7	2 / 48 (4.17%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2016	Removal of instruction on the need for precautionary measures to protect against potential photosensitive effects of GSK2269557; Addition of 2 secondary efficacy endpoints; Clarification to the requirements surrounding pregnancy testing at screening compared to other time points; Addition of nicotine replacement or containing products to the prohibited medicines list; Alignment of background information to reflect the current status of ongoing clinical investigations pertaining to this investigational medicinal product.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported