Clinical trial results:
A randomised, double-blind (sponsor-unblind), placebo controlled, cross-over study to investigate the efficacy, effect on cough reflex sensitivity, safety, tolerability and pharmacokinetics of inhaled GSK2339345 in patients with chronic idiopathic cough using an aqueous droplet inhaler

Summary

EudraCT number	2012-004891-20
Trial protocol	GB
Global end of trial date	02 October 2014

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	06 June 2015

Trial information

Trial identification

Sponsor protocol code	PNV117270

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	11 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

EFFICACY: To evaluate the effect of a single dose of GSK2339345, administered on two occasions, four hours apart, versus placebo on objective cough counts in patients with chronic idiopathic cough.

Protection of trial subjects:
Not applicable
Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	20 November 2013
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 Kingdom: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	12
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All eligible participants (par.) received treatment of either GSK2339345 or placebo at each visit in Parts A (Visits 1-3), B (Visits 4 and 5) and Part C (Visits 6 and 7).

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, Monitor

Arms

Arm title	GSK2339345 1000 µg/placebo

Arm description:

Participants received two doses of either GSK2339345 1000 micrograms (µg) or matching placebo as a solution administered via an ADI with a four hour dosing interval at 3 visits (one treatment per visit) in Part A and a single dose at 2 visits (one treatment per visit) in Part B and C. Dose 1 was administered on each treatment day at the same time each morning throughout all of Parts A, B and C. The follow-up of each participant occurred 3-14 days after the last dose. There was a washout of 48 hours to 7 days between visits. Additionally, 5 minutes after the administration of placebo or GSK2339345 at each visit period in Part B and C, participants received an oral inhalation of 10 microliters (µL) of a capsaicin solution at each visit in Part B and 10 µL of a citric acid solution at each visit of Part C. The strength of capsaicin solution ranged from 0.49 to 1000 micromolar (µM) and the citric acid solution strength ranged from 0.03 to 4.0 molar.

Arm type	Experimental
Investigational medicinal product name	GSK2339345
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Solution for oral inhalation - daily dose -1000 µg GSK2339345 administered on two occasions 4 hours apart.

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

Dosage and administration details:

Solution for oral inhalation - dose range 0.49 to 1000 µM.

Investigational medicinal product name	Citric acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Solution for oral inhalation - dose range 0.03 M to 4.0 M.

Number of subjects in period 1	GSK2339345 1000 µg/placebo
Started	16
Completed	11
Not completed	5
Consent withdrawn by subject	2
Adverse event, non-fatal	3

Baseline characteristics

Reporting groups	
Reporting group title	GSK2339345 1000 µg/placebo

Reporting group description:

Participants received two doses of either GSK2339345 1000 micrograms (µg) or matching placebo as a solution administered via an ADI with a four hour dosing interval at 3 visits (one treatment per visit) in Part A and a single dose at 2 visits (one treatment per visit) in Part B and C. Dose 1 was administered on each treatment day at the same time each morning throughout all of Parts A, B and C. The follow-up of each participant occurred 3-14 days after the last dose. There was a washout of 48 hours to 7 days between visits. Additionally, 5 minutes after the administration of placebo or GSK2339345 at each visit period in Part B and C, participants received an oral inhalation of 10 microliters (µL) of a capsaicin solution at each visit in Part B and 10 µL of a citric acid solution at each visit of Part C. The strength of capsaicin solution ranged from 0.49 to 1000 micromolar (µM) and the citric acid solution strength ranged from 0.03 to 4.0 molar.

Reporting group values	GSK2339345 1000 µg/placebo	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 56.7 ± 9.58	 -	
Gender categorical Units: Subjects			
Female Male	13 3	13 3	
Race Units: Subjects			
White - White/Caucasian/European Heritage	16	16	

End points

End points reporting groups

Reporting group title	GSK2339345 1000 µg/placebo

Reporting group description:

Participants received two doses of either GSK2339345 1000 micrograms (µg) or matching placebo as a solution administered via an ADI with a four hour dosing interval at 3 visits (one treatment per visit) in Part A and a single dose at 2 visits (one treatment per visit) in Part B and C. Dose 1 was administered on each treatment day at the same time each morning throughout all of Parts A, B and C. The follow-up of each participant occurred 3-14 days after the last dose. There was a washout of 48 hours to 7 days between visits. Additionally, 5 minutes after the administration of placebo or GSK2339345 at each visit period in Part B and C, participants received an oral inhalation of 10 microliters (µL) of a capsaicin solution at each visit in Part B and 10 µL of a citric acid solution at each visit of Part C. The strength of capsaicin solution ranged from 0.49 to 1000 micromolar (µM) and the citric acid solution strength ranged from 0.03 to 4.0 molar.

Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received two doses of placebo as a solution administered via an ADI with a four hour dosing interval, either at one or two visits in Part A (Visits 1, 2 and 3) and a single dose at one of the 2 visits in Parts B (Visits 4 and 5) and Part C (Visits 6 and 7). Dose 1 was administered on each treatment day at the same time each morning throughout all of Parts A, B and C. The follow-up of each participant occurred 3-14 days after the last dose. There was a washout of 48 hours to 7 days between visits. Additionally, 5 minutes after the administration of placebo at each visit in Part B and C, participants received an oral inhalation of 10 µL of a capsaicin solution at each visit in Part B and 10 µL of a citric acid solution at each visit in Part C. The strength of capsaicin solution ranged from 0.49 to 1000 µM and the citric acid solution strength ranged from 0.03 to 4.0 molar.

Subject analysis set title	GSK2339345 1000 µg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received two doses of GSK2339345 1000 µg via an ADI with a four hour dosing interval, either at one or two visits in Part A (Visits 1, 2 and 3) and a single dose at one of the 2 visits in Parts B (Visits 4 and 5) and Part C (Visits 6 and 7). Dose 1 was administered on each treatment day at the same time each morning throughout all of Parts A, B and C. The follow-up of each participant occurred 3-14 days after the last dose. There was a washout of 48 hours to 7 days between visits. Additionally, 5 minutes after the administration of placebo at each visit in Part B and C, participants received an oral inhalation of 10 µL of a capsaicin solution at each visit in Part B and 10 µL of a citric acid solution at each visit in Part C. The strength of capsaicin solution ranged from 0.49 to 1000 µM and the citric acid solution strength ranged from 0.03 to 4.0 molar.

Primary: Total cough count over 8 hours at Visits 1, 2 and 3 (Part A)

End point title	Total cough count over 8 hours at Visits 1, 2 and 3 (Part A)

End point description:

Total cough count (8 hours [hr] of recording) was conducted at Visits 1, 2 and 3 (4 hours of post-dose recording for each of the two doses administered). Coughs were counted by a cough monitor fitted to the participants for 8 hr post Dose 1. Number of coughs in 8 hr period was loge transformed and used for the analysis. Values were imputed pro-rata if 8 hr epoch was less than 8 hr. All Subjects Population comprised of all participants who receive at least one dose of study medication.

End point type	Primary

End point timeframe:

Up to 8 hours post-dose at Visits 1, 2 and 3 (Part A)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[1]	14[2]		
Units: Cough count				
geometric mean (standard error)	152.7 (± 0.226)	192.5 (± 0.226)		

Notes:

[1] - All Subjects Population. Only participants with at least one 8 hr cough count were analyzed.

[2] - All Subjects Population. Only participants with at least one 8 hr cough count were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK2339345 1000 µg v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.26
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.1
upper limit	1.44

Notes:

[3] - Ratio of adjusted geometric means = GSK2339345/Placebo.

Primary: Total cough count excluding transient coughs over 8 hours at Visits 1, 2 and 3 (Part A)

End point title	Total cough count excluding transient coughs over 8 hours at Visits 1, 2 and 3 (Part A)

End point description:

Total cough count (8 hours [hr] of recording) was conducted at Visits 1, 2 and 3 (4 hours of post-dose recording for each of the two doses administered). Coughs were counted by a cough monitor fitted to the participants for 8 hr post Dose 1. Number of coughs excluding transient cough in 8 hr period was loge transformed and used for the analysis. Values were imputed pro-rata if 8 hr epoch was less than 8 hr. Transient cough was the total number of coughs experienced in the two minutes from the start of the first inhalation of a dose.

End point type	Primary

End point timeframe:

Up to 8 hours post-dose at Visits 1, 2 and 3 (Part A)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[4]	14[5]		
Units: Cough count				
geometric mean (standard error)	151.5 (± 0.237)	153.9 (± 0.237)		

Notes:

[4] - All Subjects Population. Only participants with at least one 8 hr cough count were analyzed.

[5] - All Subjects Population. Only participants with at least one 8 hr cough count were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK2339345 1000 µg v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.87
upper limit	1.19

Notes:

[6] - Ratio of adjusted geometric means = GSK2339345/Placebo.

Secondary: Number of participants with any adverse events (AEs) and any serious adverse events (SAEs)

End point title	Number of participants with any adverse events (AEs) and any serious adverse events (SAEs)

End point description:

An AE is defined as 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. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect, or is an important medical events that jeopardize the participants or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition, or a drug-induced liver injury.

End point type	Secondary

End point timeframe:

From the start of study treatment and until the follow-up contact (up to 8 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[7]	14[8]		
Units: Participants				
Any AE	10	5		
Any SAE	0	0		

Notes:

[7] - All Subjects Population

[8] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean systolic blood pressure and diastolic blood pressure at the indicated time points in Parts A, B and C

End point title	Mean systolic blood pressure and diastolic blood pressure at the indicated time points in Parts A, B and C

End point description:

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were obtained at following time points: pre-dose, 5 minutes (min), 15 min (only in Part A), 30 min, and 1 hr after first administration (FA) and second administration (SA) in Part A and each dose administration of Parts B and C. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Pre-Dose is the average (avg) of the triplicate readings taken at the pre-dose assessment. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose, 5 min, 15 min (only in Part A), 30 min, and 1 hr post each dose administered in Parts A, B and C (up to 8 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[9]	14[10]		
Units: Millimeter of mercury				
arithmetic mean (standard deviation)				
SBP, Part A, FA, Dose 1, avg Pre-dose, n=16, 14	126.1 (± 14.09)	123.3 (± 15.02)		
SBP, Part A, FA, Dose 1, 5 min, n=16, 14	125.5 (± 14.37)	130.2 (± 17.16)		
SBP, Part A, FA, Dose 1, 15 min, n=16, 14	125.3 (± 14.06)	124.1 (± 14.44)		
SBP, Part A, FA, Dose 1, 30 min, n=16, 14	125.6 (± 14.12)	124.1 (± 17.67)		
SBP, Part A, FA, Dose 1, 1 hr, n=16, 14	126.1 (± 15.66)	123.6 (± 13.74)		
SBP, Part A, FA, Dose 2 avg Pre-dose, n=16, 14	117.8 (± 10.95)	119.5 (± 11.42)		
SBP, Part A, FA, Dose 2, 5 min, n=15, 14	120.6 (± 13.21)	128.1 (± 18.58)		
SBP, Part A, FA, Dose 2, 15 min, n=15, 14	120.7 (± 12.96)	123 (± 16.15)		
SBP, Part A, FA, Dose 2, 30 min, n=15, 14	120.8 (± 11.97)	118.2 (± 12.91)		

SBP, Part A, FA, Dose 2, 1hr, n=15, 14	124.5 (± 13.68)	121.5 (± 11.31)		
SBP, Part A, SA, Dose 1, avg Pre-dose, n=7, 7	130.8 (± 15.43)	121.2 (± 8.25)		
SBP, Part A, SA, Dose 1, 5 min, n=7, 7	127.7 (± 16.23)	124.1 (± 11.17)		
SBP, Part A, SA, Dose 1, 15 min, n=7, 7	125.1 (± 22.35)	117.9 (± 9.74)		
SBP, Part A, SA, Dose 1, 30 min, n=7, 7	128 (± 18.83)	119.3 (± 10.21)		
SBP, Part A, SA, Dose 1, 1 hr, n=7, 7	134.4 (± 17.82)	122.4 (± 13.13)		
SBP, Part A, SA, Dose 2 avg Pre-dose, n=7, 7	125 (± 11.95)	112.4 (± 8.54)		
SBP, Part A, SA, Dose 2, 5 min, n=7, 7	125.4 (± 16.29)	118.1 (± 9.32)		
SBP, Part A, SA, Dose 2, 15 min, n=7, 7	118.9 (± 12.4)	112.4 (± 9.71)		
SBP, Part A, SA, Dose 2, 30 min, n=7, 7	119 (± 11.72)	116.3 (± 10.37)		
SBP, Part A, SA, Dose 2, 1hr, n=7, 7	129.9 (± 19.27)	121.4 (± 15.09)		
SBP, Part B, avg Pre-dose, n=10, 11	119.2 (± 11.69)	124 (± 10.42)		
SBP, Part B, 5 min, n=10, 11	119.6 (± 11.24)	123.9 (± 13.88)		
SBP, Part B, 15 min, n=10, 11	121.5 (± 15.23)	118.7 (± 10.86)		
SBP, Part B, 1 hr, n=10, 11	124.2 (± 17)	125.5 (± 12.89)		
SBP, Part C, avg Pre-dose, n=9, 9	125.2 (± 11.37)	123 (± 12.28)		
SBP, Part C, 5 min, n=9, 9	125.6 (± 14.75)	129.3 (± 12.7)		
SBP, Part C, 15 min, n=9, 9	121.6 (± 12.24)	124.1 (± 13.18)		
SBP, Part C, 1hr, n=9, 9	127.1 (± 15.34)	135.9 (± 21.77)		
DBP, Part A, FA, Dose 1, avg Pre-dose, n=16, 14	68.8 (± 7.23)	69.1 (± 4.61)		
DBP, Part A, FA, Dose 1, 5 min, n=16, 14	72.3 (± 6.88)	71.6 (± 5.33)		
DBP, Part A, FA, Dose 1, 15 min, n=16, 14	69.6 (± 7.8)	70.6 (± 6.2)		
DBP, Part A, FA, Dose 1, 30 min, n=16, 14	71.6 (± 10.03)	69.5 (± 7.34)		
DBP, Part A, FA, Dose 1, 1 hr, n=16, 14	70.9 (± 7.53)	69.9 (± 5.14)		
DBP, Part A, FA, Dose 2 avg Pre-dose, n=16, 14	64.6 (± 5.7)	65.2 (± 6.55)		
DBP, Part A, FA, Dose 2, 5 min, n=15, 14	66.3 (± 7.69)	66.4 (± 7.69)		
DBP, Part A, FA, Dose 2, 15 min, n=15, 14	65.5 (± 7.9)	66.1 (± 8.02)		
DBP, Part A, FA, Dose 2, 30 min, n=15, 14	66.7 (± 7.21)	67.1 (± 6.95)		
DBP, Part A, FA, Dose 2, 1hr, n=15, 14	68.4 (± 6.46)	69.6 (± 8.78)		
DBP, Part A, SA, Dose 1, avg Pre-dose, n=7, 7	70.2 (± 5.74)	70.6 (± 7.93)		
DBP, Part A, SA, Dose 1, 5 min, n=7, 7	68.9 (± 6.2)	67.9 (± 4.45)		
DBP, Part A, SA, Dose 1, 15 min, n=7, 7	68.6 (± 4.54)	67.3 (± 6.37)		
DBP, Part A, SA, Dose 1, 30 min, n=7, 7	67 (± 5.72)	68.7 (± 3.3)		
DBP, Part A, SA, Dose 1, 1 hr, n=7, 7	72.4 (± 7)	69.1 (± 6.49)		

DBP, Part A, SA, Dose 2 avg Pre-dose, n=7, 7	67.3 (± 5.95)	63.3 (± 2.89)		
DBP, Part A, SA, Dose 2, 5 min, n=7, 7	65.1 (± 5.98)	67 (± 4.97)		
DBP, Part A, SA, Dose 2, 15 min, n=7, 7	64.4 (± 5.91)	64 (± 4.97)		
DBP, Part A, SA, Dose 2, 30 min, n=7, 7	63.4 (± 6.73)	66.3 (± 5.25)		
DBP, Part A, SA, Dose 2, 1hr, n=7, 7	69.1 (± 7.9)	71.3 (± 5.82)		
DBP, Part B, avg Pre-dose, n=10, 11	63.9 (± 4.74)	67.3 (± 4.29)		
DBP, Part B, 5 min, n=10, 11	63.9 (± 3.31)	66.5 (± 3.67)		
DBP, Part B, 15 min, n=10, 11	64.9 (± 6.51)	66.2 (± 6)		
DBP, Part B, 1 hr, n=10, 11	64.3 (± 6.99)	66.2 (± 2.82)		
DBP, Part C, avg Pre-dose, n=9, 9	64.9 (± 5.5)	68 (± 8.68)		
DBP, Part C, 5 min, n=9, 9	68 (± 7.37)	65.6 (± 5.98)		
DBP, Part C, 15 min, n=9, 9	65.7 (± 4.03)	65.7 (± 7.09)		
DBP, Part C, 1hr, n=9, 9	65.4 (± 6.31)	67.7 (± 6.71)		

Notes:

[9] - All Subjects Population

[10] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean heart rate at the indicated time points in Parts A, B and C

End point title	Mean heart rate at the indicated time points in Parts A, B and C

End point description:

Heart rate measurements were obtained at following time points: pre-dose, 5 min, 15 min (only in Part A), 30 min, and 1 hr after FA and SA in Part A and each dose administration in Parts B and C. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Pre-Dose is the average of the triplicate readings taken at the pre-dose assessment. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose, 5 min, 15 min (only in Part A), 30 min, and 1 hr after each dose administered in Parts A, B and C (up to 8 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[11]	14[12]		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Part A, FA, Dose 1, avg Pre-dose, n=16, 14	68.6 (± 7.44)	66.3 (± 9.9)		
Part A, FA, Dose 1, 5 min, n=16, 14	64.1 (± 7.5)	66.5 (± 10.06)		
Part A, FA, Dose 1, 15 min, n=16, 14	64 (± 6.41)	64.9 (± 9.57)		
Part A, FA, Dose 1, 30 min, n=16, 14	64.1 (± 10.6)	61.8 (± 8.75)		
Part A, FA, Dose 1, 1 hr, n=16, 14	62.6 (± 7.7)	61.6 (± 7.88)		
Part A, FA, Dose 2 avg Pre-dose, n=16, 14	72.6 (± 9.27)	69.4 (± 11.82)		
Part A, FA, Dose 2, 5 min, n=16, 14	69.9 (± 7.29)	69.7 (± 12.02)		

Part A, FA, Dose 2, 15 min, n=16, 14	69 (± 7.8)	68.3 (± 9.52)		
Part A, FA, Dose 2, 30 min, n=16, 14	68.6 (± 9.25)	68.5 (± 13.39)		
Part A, FA, Dose 2, 1hr, n=16, 14	68.5 (± 8.3)	67.6 (± 11.57)		
Part A, SA, Dose 1, avg Pre-dose, n=7, 7	66.8 (± 12.8)	69.6 (± 8.33)		
Part A, SA, Dose 1, 5 min, n=7, 7	61.3 (± 8.9)	65.4 (± 8.08)		
Part A, SA, Dose 1, 15 min, n=7, 7	60.3 (± 9.01)	62.9 (± 6.82)		
Part A, SA, Dose 1, 30 min, n=7, 7	59.1 (± 8.45)	62.4 (± 7.16)		
Part A, SA, Dose 1, 1 hr, n=7, 7	62.6 (± 8.81)	62.4 (± 6.35)		
Part A, SA, Dose 2 avg Pre-dose, n=7, 7	69 (± 7.84)	70.6 (± 6.2)		
Part A, SA, Dose 2, 5 min, n=7, 7	66.7 (± 9.16)	71.1 (± 8.19)		
Part A, SA, Dose 2, 15 min, n=7, 7	66 (± 7.37)	69.6 (± 10.05)		
Part A, SA, Dose 2, 30 min, n=7, 7	65.1 (± 7.78)	65.7 (± 6.99)		
Part A, SA, Dose 2, 1hr, n=7, 7	65.7 (± 7.06)	68.6 (± 8.3)		
Part B, avg Pre-dose, n=10, 11	64.5 (± 6.21)	68.4 (± 8.85)		
Part B, 5 min, n=10, 11	60 (± 6.18)	65.9 (± 8.87)		
Part B, 15 min, n=10, 11	59.4 (± 4.99)	63.5 (± 6.52)		
Part B, 1 hr, n=10, 11	58.6 (± 6.2)	61 (± 6.07)		
Part C, avg Pre-dose, n=9, 9	62.4 (± 4.27)	66.3 (± 7.07)		
Part C, 5 min, n=9, 9	60.3 (± 9.31)	65 (± 9.15)		
Part C, 15 min, n=9, 9	60.8 (± 6.51)	60.7 (± 5.5)		
Part C, 1hr, n=9, 9	59.2 (± 6.5)	61.1 (± 6.47)		

Notes:

[11] - All Subjects Population

[12] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean body temperature at the indicated time points in Parts A, B and C

End point title	Mean body temperature at the indicated time points in Parts A, B and C

End point description:

Body temperature measurements were obtained at1 hr post-dose 2 FA and SA in Part A and each administration in Parts B, and C. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

1 hr post the second dose administered in Part A and 1 hr post each dose administered in Parts B and C (up to 8 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[13]	14[14]		
Units: Degree Celsius				
arithmetic mean (standard deviation)				
Part A, FA, Dose 2, 1 hr, n=15, 12	36.84 (± 0.47)	36.7 (± 0.484)		
Part A, SA, Dose 2, 1 hr, n=7, 7	36.56 (± 0.541)	36.8 (± 0.52)		
Part B, 1 hr, n=10, 10	36.55 (± 0.536)	36.76 (± 0.414)		
Part C, 1 hr, n=9, 9	36.54 (± 0.391)	36.69 (± 0.473)		

Notes:

[13] - All Subjects Population

[14] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal 12-lead electrocardiogram (ECG) findings in Parts A, B and C

End point title	Number of participants with abnormal 12-lead electrocardiogram (ECG) findings in Parts A, B and C

End point description:

A 12-lead ECG was recorded in a seated position after the participant was kept at rest in this position for at least 10 minutes. ECGs were obtained at pre-dose and 5 min, 15 min (only in Part A) 30 min, and 1 hr after FA and SA in Part A and each administration in Parts B, and C. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Data are presented as clinically significant (CS) or not clinically significant (NCS) abnormal findings any time during study. The study investigator determined if the abnormal ECG finding was CS or NCS. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 5min to 1 hr after each dose administered in Parts A, B and C (up to 8 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[15]	14[16]		
Units: Participants				
Part A, FA, Normal, n=16, 14	13	12		
Part A, FA, Abnormal NCS, n=16, 14	2	2		
Part A, FA Abnormal CS, n=16, 14	1	0		
Part A, SA, Normal, n=7, 7	4	7		
Part A, SA, Abnormal NCS, n=7, 7	2	0		
Part A, SA, Abnormal CS, n=7, 7	1	0		
Part B, Normal, n=10, 11	9	10		
Part B, Abnormal NCS, n=10, 11	1	1		
Part B, Abnormal CS, n=10, 11	0	0		

Part C, Normal, n=9, 9	9	8		
Part C, Abnormal NCS, n=9, 9	0	1		
Part C, Abnormal CS, n=9, 9	0	0		

Notes:

[15] - All Subjects Population

[16] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean basophils, eosinophils, lymphocytes, monocytes, total neutrophils, platelet count, and white blood cells (WBC) count values at the indicated time points in Part A

End point title	Mean basophils, eosinophils, lymphocytes, monocytes, total neutrophils, platelet count, and white blood cells (WBC) count values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement of basophils, eosinophils, lymphocytes, monocytes, total neutrophils (ANC - absolute neutrophil count), platelet count, and white blood cells count at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[17]	14[18]		
Units: 10^9 cells/Liter (GI/L)				
arithmetic mean (standard deviation)				
Basophils, FA, Pre-dose, n=16, 14	0.026 (± 0.0126)	0.023 (± 0.0159)		
Basophils, FA, 1 hr Post-dose, n=14, 13	0.031 (± 0.0192)	0.032 (± 0.0242)		
Basophils, SA, Pre-dose, n=6, 7	0.04 (± 0.0329)	0.026 (± 0.0162)		
Basophils, SA, 1 hr Post-dose, n=7, 7	0.019 (± 0.0107)	0.036 (± 0.0299)		
Eosinophils, FA, Pre-dose, n=16, 14	0.091 (± 0.0604)	0.063 (± 0.0365)		
Eosinophils, FA, 1 hr Post-dose, n=14, 13	0.106 (± 0.0776)	0.093 (± 0.0471)		
Eosinophils, SA, Pre-dose, n=6, 7	0.08 (± 0.051)	0.064 (± 0.0299)		
Eosinophils, SA, 1 hr Post-dose, n=7, 7	0.113 (± 0.0502)	0.08 (± 0.0191)		
Lymphocytes, FA, Pre-dose, n=16, 14	1.801 (± 0.4214)	1.673 (± 0.3348)		
Lymphocytes, FA, 1 hr Post-dose, n=14, 13	2.095 (± 0.4572)	1.977 (± 0.5392)		

Lymphocytes, SA, Pre-dose, n=6, 7	1.922 (± 0.4492)	1.536 (± 0.3406)		
Lymphocytes, SA, 1 hr Post-dose, n=7, 7	2.2 (± 0.6387)	1.926 (± 0.2486)		
Monocytes, FA, Pre-dose, n=16, 14	0.363 (± 0.1373)	0.369 (± 0.1957)		
Monocytes, FA, 1 hr Post-dose, n=14, 13	0.414 (± 0.1249)	0.434 (± 0.1601)		
Monocytes, SA, Pre-dose, n=6, 7	0.39 (± 0.1517)	0.297 (± 0.0525)		
Monocytes, SA, 1 hr Post-dose, n=7, 7	0.38 (± 0.1319)	0.364 (± 0.0479)		
Total Neutrophils, FA, Pre-dose, n=16, 14	4.256 (± 1.3244)	4.206 (± 1.123)		
Total Neutrophils, FA, 1 hr Post-dose, n=14, 13	4.73 (± 1.3512)	4.8 (± 1.1399)		
Total Neutrophils, SA, Pre-dose, n=6, 7	4.238 (± 1.4993)	3.993 (± 0.9757)		
Total Neutrophils, SA, 1 hr Post-dose, n=7, 7	4.847 (± 1.4473)	4.25 (± 0.6064)		
Platelet count, FA, Pre-dose, n=16, 13	225.8 (± 51.14)	233.4 (± 56.53)		
Platelet count, FA, 1 hr Post-dose, n=14, 13	209.1 (± 49.01)	215.7 (± 30.69)		
Platelet count, SA, Pre-dose, n=6, 7	259.8 (± 36.98)	238.6 (± 47.9)		
Platelet count, SA, 1 hr Post-dose, n=7, 7	238.4 (± 53.37)	232.3 (± 49.45)		
WBC count, FA, Pre-dose, n=16, 14	6.54 (± 1.565)	6.33 (± 1.315)		
WBC count, FA, 1 hr Post-dose, n=14, 13	7.36 (± 1.663)	7.33 (± 1.596)		
WBC count, SA, Pre-dose, n=6, 7	6.67 (± 1.56)	5.91 (± 1.263)		
WBC count, SA, 1 hr Post-dose, n=7, 7	7.53 (± 1.798)	6.66 (± 0.81)		

Notes:

[17] - All Subjects Population

[18] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean hemoglobin, mean corpuscle hemoglobin concentration (MCHC), albumin and total protein values at the indicated time points in Part A

End point title	Mean hemoglobin, mean corpuscle hemoglobin concentration (MCHC), albumin and total protein values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement of hemoglobin, MCHC, albumin and total protein at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[19]	14[20]		
Units: Grams per liter (G/L)				
arithmetic mean (standard deviation)				
Hemoglobin, FA, Pre-dose, n=16, 14	134.1 (± 11.16)	134.2 (± 11.82)		
Hemoglobin, FA, 1 hr Post-dose, n=14, 13	130.1 (± 11.35)	130.5 (± 11.17)		
Hemoglobin, SA, Pre-dose, n=6, 7	127.5 (± 8.69)	133.4 (± 10.34)		
Hemoglobin, SA, 1 hr Post-dose, n=7, 7	125.4 (± 9.64)	129.6 (± 9.78)		
MCHC, FA, Pre-dose, n=16, 14	325.6 (± 5.76)	326.3 (± 6.14)		
MCHC, FA, 1 hr Post-dose, n=14, 13	327 (± 4.91)	329.2 (± 5.36)		
MCHC, SA, Pre-dose, n=6, 7	327.5 (± 7.2)	324 (± 6.51)		
MCHC, SA, 1 hr Post-dose, n=7, 7	327.7 (± 5.09)	323.3 (± 10.24)		
Albumin, FA, Pre-dose, n=16, 14	43.4 (± 3.1)	43.1 (± 2.11)		
Albumin, FA, 1 hr Post-dose, n=14, 14	41.7 (± 2.23)	41.6 (± 1.82)		
Albumin, SA, Pre-dose, n=6, 7	43.3 (± 3.27)	43.6 (± 2.15)		
Albumin, SA, 1 hr Post-dose, n=7, 7	41.4 (± 2.3)	41.6 (± 1.99)		
Total protein, FA, Pre-dose, n=16, 14	69.3 (± 4.32)	68.5 (± 2.41)		
Total protein, FA, 1 hr Post-dose, n=14, 14	66.1 (± 3.35)	66.6 (± 2.41)		
Total protein, SA, Pre-dose, n=6, 7	69 (± 4.69)	69.1 (± 3.34)		
Total protein, SA, 1 hr Post-dose, n=7, 7	65.4 (± 4.16)	66 (± 3.61)		

Notes:

[19] - All Subjects Population

[20] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean hematocrit values at the indicated time points in Part A

End point title	Mean hematocrit values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement of hematocrit at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[21]	14[22]		
Units: Proportion of one				
arithmetic mean (standard deviation)				
FA, Pre-dose, n=16, 14	0.4126 (± 0.03824)	0.4119 (± 0.04143)		
FA, 1 hr Post-dose, n=14, 13	0.3979 (± 0.03595)	0.3973 (± 0.03701)		
SA, Pre-dose, n=6, 7	0.3895 (± 0.02894)	0.412 (± 0.0395)		
SA, 1 hr Post-dose, n=7, 7	0.3826 (± 0.03321)	0.401 (± 0.03316)		

Notes:

[21] - All Subjects Population

[22] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean corpuscle hemoglobin values at the indicated time points in Part A

End point title	Mean corpuscle hemoglobin values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement of mean corpuscle hemoglobin at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[23]	14[24]		
Units: picograms per cell (pg)				
arithmetic mean (standard deviation)				
FA, Pre-dose, n=16, 14	29.87 (± 1.709)	29.75 (± 1.787)		
FA, 1 hr Post-dose, n=14, 13	29.75 (± 1.874)	29.85 (± 1.859)		
SA, Pre-dose, n=6, 7	29.48 (± 1.958)	29.67 (± 1.627)		

SA, 1 hr Post-dose, n=7, 7	29.67 (± 1.864)	29.4 (± 1.672)		

Notes:

[23] - All Subjects Population

[24] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean corpuscle volume values at the indicated time points in Part A

End point title	Mean corpuscle volume values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement of mean corpuscle volume at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[25]	14[26]		
Units: femtoliters per cell (fL)				
arithmetic mean (standard deviation)				
FA, Pre-dose, n=16, 14	91.8 (± 5.03)	91.3 (± 5.21)		
FA, 1 hr Post-dose, n=14, 13	91 (± 5.04)	90.8 (± 5.63)		
SA, Pre-dose, n=6, 7	90 (± 6.19)	91.6 (± 5.49)		
SA, 1 hr Post-dose, n=7, 7	90.4 (± 5.72)	91.2 (± 5.66)		

Notes:

[25] - All Subjects Population

[26] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean red blood cell count values at the indicated time points in Part A

End point title	Mean red blood cell count values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement of red blood cell count at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants

may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[27]	14[28]		
Units: 10^12 cells per liter (TI/L)				
arithmetic mean (standard deviation)				
FA, Pre-dose, n=16, 14	4.52 (± 0.452)	4.54 (± 0.553)		
FA, 1 hr Post-dose, n=14, 13	4.4 (± 0.47)	4.39 (± 0.46)		
SA, Pre-dose, n=6, 7	4.34 (± 0.296)	4.51 (± 0.522)		
SA, 1 hr Post-dose, n=7, 7	4.24 (± 0.436)	4.42 (± 0.406)		

Notes:

[27] - All Subjects Population

[28] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) values at the indicated time points in Part A

End point title	Mean alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement of ALP, ALT, AST and GGT at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[29]	14[30]		
Units: International Units/Liter (IU/L)				
arithmetic mean (standard deviation)				
ALP, FA, Pre-dose, n=16, 14	67.9 (± 19.33)	64.1 (± 15.01)		
ALP, FA, 1 hr Post-dose, n=14, 14	63.7 (± 16.7)	60.6 (± 13.67)		

ALP, SA, Pre-dose, n=6, 7	69.7 (± 15.11)	57.4 (± 13.36)		
ALP, SA, 1 hr Post-dose, n=7, 7	69 (± 17.45)	55.9 (± 13.59)		
ALT, FA, Pre-dose, n=16, 14	15.8 (± 5.36)	13.9 (± 4.62)		
ALT, FA, 1 hr Post-dose, n=14, 14	15.2 (± 5.83)	14.1 (± 5.77)		
ALT, SA, Pre-dose, n=6, 7	16.5 (± 2.07)	13.6 (± 5.74)		
ALT, SA, 1 hr Post-dose, n=7, 7	15.3 (± 2.75)	12.9 (± 6.54)		
AST, FA, Pre-dose, n=16, 14	23.1 (± 10.37)	19.6 (± 3.98)		
AST, FA, 1 hr Post-dose, n=14, 13	21.4 (± 9.87)	20.7 (± 7.51)		
AST, SA, Pre-dose, n=6, 7	18.5 (± 4.28)	21.6 (± 6.45)		
AST, SA, 1 hr Post-dose, n=6, 7	16.5 (± 3.51)	19.7 (± 7.11)		
GGT, FA, Pre-dose, n=16, 14	24.6 (± 12.93)	22.8 (± 9.95)		
GGT, FA, 1 hr Post-dose, n=14, 14	24.6 (± 13.89)	22.4 (± 9.85)		
GGT, SA, Pre-dose, n=6, 7	20.7 (± 9.18)	22.9 (± 12.82)		
GGT, SA, 1 hr Post-dose, n=7, 7	25 (± 15.58)	22 (± 13.17)		

Notes:

[29] - All Subjects Population

[30] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean direct bilirubin, total bilirubin, creatinine and uric acid values at the indicated time points in Part A

End point title	Mean direct bilirubin, total bilirubin, creatinine and uric acid values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement ofdirect bilirubin, total bilirubin, creatinine and uric acid at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[31]	14[32]		
Units: Micromoles per liter (µmol/L)				
arithmetic mean (standard deviation)				
Direct bilirubin, FA, Pre-dose, n=13, 11	1.77 (± 0.832)	1.64 (± 0.809)		
Direct bilirubin, FA, 1 hr Post-dose, n=10, 11	1.8 (± 0.919)	1.45 (± 0.522)		
Direct bilirubin, SA, Pre-dose, n=4, 6	1.75 (± 0.957)	1.83 (± 0.753)		
Direct bilirubin, SA, 1 hr Post-dose, n=5, 6	1.2 (± 0.447)	1.5 (± 0.548)		
Total bilirubin, FA, Pre-dose, n=16, 14	8.07 (± 3.999)	8.04 (± 3.709)		

Total bilirubin, FA, 1 hr Post-dose, n=14, 14	7.04 (± 4.185)	6.34 (± 2.453)		
Total bilirubin, SA, Pre-dose, n=6, 7	7.35 (± 3.075)	7.71 (± 2.928)		
Total bilirubin, SA, 1 hr Post-dose, n=7, 7	6.59 (± 3.204)	5.87 (± 1.928)		
Creatinine, FA, Pre-dose, n=16, 14	65.1 (± 12.99)	64 (± 11.21)		
Creatinine, FA, 1 hr Post-dose, n=14, 14	65 (± 12.29)	60.5 (± 8.49)		
Creatinine, SA, Pre-dose, n=6, 7	61.1 (± 11.82)	66.5 (± 11.72)		
Creatinine, SA, 1 hr Post-dose, n=7, 7	63 (± 10.92)	65.1 (± 7.83)		
Uric acid, FA, Pre-dose, n=16, 14	283.1 (± 66.3)	272.8 (± 59.36)		
Uric acid, FA, 1 hr Post-dose, n=14, 14	269.3 (± 68.09)	259.2 (± 57.65)		
Uric acid, SA, Pre-dose, n=6, 7	270 (± 30.61)	273.7 (± 74.4)		
Uric acid, SA, 1 hr Post-dose, n=7, 7	275.4 (± 43.08)	257.7 (± 65.8)		

Notes:

[31] - All Subjects Population

[32] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean calcium, chloride, glucose, potassium, sodium, and urea/blood urea nitrogen (BUN) values at the indicated time points in Part A

End point title	Mean calcium, chloride, glucose, potassium, sodium, and urea/blood urea nitrogen (BUN) values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement of calcium, chloride, glucose, potassium, sodium, and urea/blood urea nitrogen (BUN) at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[33]	14[34]		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Calcium, FA, Pre-dose, n=16, 14	2.37 (± 0.085)	2.39 (± 0.107)		
Calcium, FA, 1 hr Post-dose, n=14, 13	2.34 (± 0.099)	2.34 (± 0.091)		
Calcium, SA, Pre-dose, n=6, 7	2.41 (± 0.102)	2.37 (± 0.095)		
Calcium, SA, 1 hr Post-dose, n=6, 7	2.34 (± 0.061)	2.32 (± 0.11)		
Chloride, FA, Pre-dose, n=16, 14	103.6 (± 2.31)	103.4 (± 2.13)		
Chloride, FA, 1 hr Post-dose, n=14, 14	103.6 (± 2.06)	104.3 (± 2.2)		

Chloride, SA, Pre-dose, n=6, 7	103.5 (± 3.02)	103 (± 1.73)		
Chloride, SA, 1 hr Post-dose, n=7, 7	104.9 (± 4.26)	103.6 (± 1.4)		
Glucose, FA, Pre-dose, n=16, 14	5.28 (± 0.884)	5.19 (± 0.791)		
Glucose, FA, 1 hr Post-dose, n=14, 14	5.59 (± 1.124)	5.69 (± 1.279)		
Glucose, SA, Pre-dose, n=6, 7	5.03 (± 1.108)	5.06 (± 0.629)		
Glucose, SA, 1 hr Post-dose, n=7, 7	5.46 (± 1.165)	5.24 (± 0.873)		
Potassium, FA, Pre-dose, n=16, 14	4.18 (± 0.246)	4.18 (± 0.229)		
Potassium, FA, 1 hr Post-dose, n=14, 13	3.94 (± 0.318)	4.55 (± 1.028)		
Potassium, SA, Pre-dose, n=6, 7	4.22 (± 0.24)	4.11 (± 0.241)		
Potassium, SA, 1 hr Post-dose, n=6, 7	4.12 (± 0.736)	3.93 (± 0.206)		
Sodium, FA, Pre-dose, n=16, 14	138.6 (± 1.59)	138.9 (± 1.51)		
Sodium, FA, 1 hr Post-dose, n=14, 14	138.8 (± 1.93)	138.1 (± 1.99)		
Sodium, SA, Pre-dose, n=6, 7	139 (± 1.26)	138.4 (± 0.98)		
Sodium, SA, 1 hr Post-dose, n=7, 7	140 (± 4.58)	138.7 (± 1.6)		
Urea/BUN, FA, Pre-dose, n=16, 14	4.91 (± 1.909)	4.86 (± 1.934)		
Urea/BUN, FA, 1 hr Post-dose, n=14, 14	5.04 (± 2.008)	5.21 (± 2.104)		
Urea/BUN, SA, Pre-dose, n=6, 7	4.03 (± 1.791)	4.81 (± 1.732)		
Urea/BUN, SA, 1 hr Post-dose, n=7, 7	5 (± 2.309)	5.24 (± 1.706)		

Notes:

[33] - All Subjects Population

[34] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean troponin I values at the indicated time points in Part A

End point title	Mean troponin I values at the indicated time points in Part A

End point description:

Blood samples were collected for the measurement of troponin I at pre-dose and 1 hr after each dose of FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population. Cardiac troponin values that were below the quantification limit [0.02 or 0.04 µg/L)] were imputed as 0.01 (µg/L).

End point type	Secondary

End point timeframe:

Pre-dose and 1 hr post each dose administered in Part A (up to 3 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[35]	14[36]		
Units: Micrograms per liter (µg/L)				
arithmetic mean (standard deviation)				
FA, Pre-dose, n=16, 14	0.011 (± 0.0034)	0.01 (± 0)		
FA, 1 hr Post-dose, n=15, 13	0.01 (± 0)	0.01 (± 0)		
SA, Pre-dose, n=7, 7	0.01 (± 0)	0.01 (± 0)		

SA, 1 hr Post-dose, n=7, 7	0.01 (± 0)	0.01 (± 0)		

Notes:

[35] - All Subjects Population

[36] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean forced expiratory volume in one second (FEV1) values at the indicated time points in Parts A, B and C

End point title	Mean forced expiratory volume in one second (FEV1) values at the indicated time points in Parts A, B and C

End point description:

Pulmonary function was measured by FEV1, defined as the maximal amount of air that can be forcefully exhaled in one second. FEV1 was measured by spirometry at pre-dose and 30 min after FA and SA in Part A and each administration in Parts B, and C. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Pre-dose and 30 min post each dose administered in Parts A, B and C (up to 8 Weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[37]	14[38]		
Units: Liters				
arithmetic mean (standard deviation)				
Part A, FA, Dose 1, Pre-dose, n=16, 14	2.55 (± 2.18)	2.43 (± 2.17)		
Part A, FA, Dose 1, 30 min Post-dose, n=16, 14	2.49 (± 2.12)	2.39 (± 2.1)		
Part A, FA, Dose 2, Pre-dose, n=16, 14	2.55 (± 2.22)	2.37 (± 2.1)		
Part A, FA, Dose 2, 30 min Post-dose, n=15, 13	2.44 (± 2.06)	2.29 (± 2.02)		
Part A, SA, Dose 1, Pre-dose, n=7, 7	2.54 (± 2.16)	2.44 (± 1.97)		
Part A, SA, Dose 1, 30 min Post-dose, n=7, 7	2.42 (± 2)	2.31 (± 1.76)		
Part A, SA, Dose 2, Pre-dose, n=7, 7	2.41 (± 1.99)	2.36 (± 1.83)		
Part A, SA, Dose 2, 30 min Post-dose, n=7, 7	2.42 (± 1.97)	2.32 (± 1.8)		
Part B, Pre-dose, n=10, 11	2.26 (± 2.07)	2.31 (± 2.05)		
Part B, 30 min Post-dose, n=10, 11	2.17 (± 2.01)	2.3 (± 2.05)		
Part C, Pre-dose, n=9, 9	2.23 (± 2.08)	2.24 (± 1.98)		
Part C, 30 min Post-dose, n=9, 9	2.13 (± 1.96)	2.22 (± 1.98)		

Notes:

[37] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with perception of change in oropharyngeal sensation at the indicated time points in Part A

End point title	Number of participants with perception of change in oropharyngeal sensation at the indicated time points in Part A

End point description:

The perception of change in oropharyngeal sensation was assessed by a 4 point scale where participants were asked to describe sensitivity and perception of numbness and the responses were recorded. The following information was collected: 0 = no anaesthesia (A), 1 = mild anaesthesia, 2 = moderate anaesthesia and 3 = severe anaesthesia. Oropharyngeal examination was performed at 2 min, 5 min, 15 min, 30 min, 1 hr and 2 hr after FA and SA in Part A. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

From 2 min -2 hr post each dose administered at Visits 1, 2 and 3 in Part A (up to 8 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[39]	14[40]		
Units: Participants				
No A, FA, Dose 1, 2 min Post-dose, n=16, 14	16	14		
No A, FA, Dose 1, 5 min Post-dose, n=16, 14	16	14		
No A, FA, Dose 1, 15 min Post-dose, n=16, 14	16	14		
No A, FA, Dose 1, 30 min Post-dose, n=16, 14	16	14		
No A, FA, Dose 1, 1 hr Post-dose, n=16, 14	16	14		
No A, FA, Dose 2, 2 min Post-dose, n=15, 14	15	14		
No A, FA, Dose 2, 5 min Post-dose, n=15, 14	15	14		
No A, FA, Dose 2, 15 min Post-dose, n=15, 14	15	14		
No A, FA, Dose 2, 30 min Post-dose, n=15, 14	15	14		
No A, FA, Dose 2, 1 hr Post-dose, n=15, 14	15	14		

No A, SA, Dose 1, 2 min Post-dose, n=7, 7	7	7		
No A, SA, Dose 1, 5 min Post-dose, n=7, 7	7	7		
No A, SA, Dose 1, 15 min Post-dose, n=7, 7	7	7		
No A, SA, Dose 1, 30 min Post-dose, n=7, 7	7	7		
No A, SA, Dose 1, 1 hr Post-dose, n=	7	7		
No A, SA, Dose 2, 2 min Post-dose, n=7, 7	7	7		
No A, SA, Dose 2, 5 min Post-dose, n=7, 7	7	7		
No A, SA, Dose 2, 15 min Post-dose, n=7, 7	7	7		
No A, SA, Dose 2, 30 min Post-dose, n=7, 7	7	7		
No A, SA, Dose 2, 1 hr Post-dose, n=7, 7	7	7		
Mild A, FA, Dose 1, 2 min Post-dose, n=16, 14	0	0		
Mild A, FA, Dose 1, 5 min Post-dose, n=16, 14	0	0		
Mild A, FA, Dose 1, 15 min Post-dose, n=16, 14	0	0		
Mild A, FA, Dose 1, 30 min Post-dose, n=16, 14	0	0		
Mild A, FA, Dose 1, 1 hr Post-dose, n=16, 14	0	0		
Mild A, FA, Dose 2, 2 min Post-dose, n=15, 14	0	0		
Mild A, FA, Dose 2, 5 min Post-dose, n=15, 14	0	0		
Mild A, FA, Dose 2, 15 min Post-dose, n=15, 14	0	0		
Mild A, FA, Dose 2, 30 min Post-dose, n=15, 14	0	0		
Mild A, FA, Dose 2, 1 hr Post-dose, n=15, 14	0	0		
Mild A, SA, Dose 1, 2 min Post-dose, n=7, 7	0	0		
Mild A, SA, Dose 1, 5 min Post-dose, n=7, 7	0	0		
Mild A, SA, Dose 1, 15 min Post-dose, n=7, 7	0	0		
Mild A, SA, Dose 1, 30 min Post-dose, n=7, 7	0	0		
Mild A, SA, Dose 1, 1 hr Post-dose, n=	0	0		
Mild A, SA, Dose 2, 2 min Post-dose, n=7, 7	0	0		
Mild A, SA, Dose 2, 5 min Post-dose, n=7, 7	0	0		
Mild A, SA, Dose 2, 15 min Post-dose, n=7, 7	0	0		
Mild A, SA, Dose 2, 30 min Post-dose, n=7, 7	0	0		
Mild A, SA, Dose 2, 1 hr Post-dose, n=7, 7	0	0		
Moderate A, FA, Dose 1, 2 min Post-dose, n=16, 14	0	0		
Moderate A, FA, Dose 1, 5 min Post-dose, n=16, 14	0	0		

Moderate A, FA, Dose 1, 15 min Post-dose, n=16, 14	0	0		
Moderate A, FA, Dose 1, 30 min Post-dose, n=16, 14	0	0		
Moderate A, FA, Dose 1, 1 hr Post-dose, n=16, 14	0	0		
Moderate A, FA, Dose 2, 2 min Post-dose, n=15, 14	0	0		
Moderate A, FA, Dose 2, 5 min Post-dose, n=15, 14	0	0		
Moderate A, FA, Dose 2, 15 min Post-dose, n=15, 14	0	0		
Moderate A, FA, Dose 2, 30 min Post-dose, n=15, 14	0	0		
Moderate A, FA, Dose 2, 1 hr Post-dose, n=15, 14	0	0		
Moderate A, SA, Dose 1, 2 min Post-dose, n=7, 7	0	0		
Moderate A, SA, Dose 1, 5 min Post-dose, n=7, 7	0	0		
Moderate A, SA, Dose 1, 15 min Post-dose, n=7, 7	0	0		
Moderate A, SA, Dose 1, 30 min Post-dose, n=7, 7	0	0		
Moderate A, SA, Dose 1, 1 hr Post-dose, n=	0	0		
Moderate A, SA, Dose 2, 2 min Post-dose, n=7, 7	0	0		
Moderate A, SA, Dose 2, 5 min Post-dose, n=7, 7	0	0		
Moderate A, SA, Dose 2, 15 min Post-dose, n=7, 7	0	0		
Moderate A, SA, Dose 2, 30 min Post-dose, n=7, 7	0	0		
Moderate A, SA, Dose 2, 1 hr Post-dose, n=7, 7	0	0		
Severe A, FA, Dose 1, 2 min Post-dose, n=16, 14	0	0		
Severe A, FA, Dose 1, 5 min Post-dose, n=16, 14	0	0		
Severe A, FA, Dose 1, 15 min Post-dose, n=16, 14	0	0		
Severe A, FA, Dose 1, 30 min Post-dose, n=16, 14	0	0		
Severe A, FA, Dose 1, 1 hr Post-dose, n=16, 14	0	0		
Severe A, FA, Dose 2, 2 min Post-dose, n=15, 14	0	0		
Severe A, FA, Dose 2, 5 min Post-dose, n=15, 14	0	0		
Severe A, FA, Dose 2, 15 min Post-dose, n=15, 14	0	0		
Severe A, FA, Dose 2, 30 min Post-dose, n=15, 14	0	0		
Severe A, FA, Dose 2, 1 hr Post-dose, n=15, 14	0	0		
Severe A, SA, Dose 1, 2 min Post-dose, n=7, 7	0	0		
Severe A, SA, Dose 1, 5 min Post-dose, n=7, 7	0	0		
Severe A, SA, Dose 1, 15 min Post-dose, n=7, 7	0	0		

Severe A, SA, Dose 1, 30 min Post-dose, n=7, 7	0	0		
Severe A, SA, Dose 1, 1 hr Post-dose, n=7, 7	0	0		
Severe A, SA, Dose 2, 2 min Post-dose, n=7, 7	0	0		
Severe A, SA, Dose 2, 5 min Post-dose, n=7, 7	0	0		
Severe A, SA, Dose 2, 15 min Post-dose, n=7, 7	0	0		
Severe A, SA, Dose 2, 30 min Post-dose, n=7, 7	0	0		
Severe A, SA, Dose 2, 1 hr Post-dose, n=7, 7	0	0		

Notes:

[39] - All Subjects Population

[40] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean transient cough counts at the indicated time points in Part A

End point title	Mean transient cough counts at the indicated time points in Part A

End point description:

Cough counts (8 hours of recording) was conducted at Visits 1, 2 and 3 (4 hours of post-dose recording for each of the two doses administered). Coughs was counted by a cough monitor fitted to the participants for 8 hours post Dose 1. Transient coughing was calculated as the total number of coughs experienced in the two minutes from the start of the first inhalation of a dose. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles). Different participants may have been analyzed for different time points, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

0-4 hr, 4-8 hr, 0-8 hr post each dose at Visits 1, 2 and 3 in Part A (up to 8 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[41]	14[42]		
Units: Cough count				
arithmetic mean (standard deviation)				
FA, 0-4 hr, n=14, 14	1.7 (± 3.41)	17.8 (± 16.27)		
FA, 4-8 hr, n=14, 14	0.9 (± 1.88)	19 (± 10.91)		
FA, 0-8 hr, n=14, 14	2.6 (± 4.11)	36.8 (± 25.41)		
SA, 0-4 hr, n=7, 7	0 (± 0)	18.3 (± 13.51)		
SA, 4-8 hr, n=7, 7	2 (± 3.42)	15.9 (± 12.02)		
SA, 0-8 hr, n=7, 7	2 (± 3.42)	34.1 (± 24.83)		

Notes:

[41] - All Subjects Population

[42] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations of GSK2339345at the indicated time points at Visits 1, 2 and 3 (Part A)

End point title	Plasma concentrations of GSK2339345at the indicated time points at Visits 1, 2 and 3 (Part A)

End point description:

Plasma concentrations of GSK2339345following the first dose and second dose at each visit in Part A was measured. Samples were collected at the following time points: pre-dose, 2 min, 5 min, 10 min, 30 min, 1 hr and 2 hr (only after Dose 1) after each dose administration at Visits 1, 2 and 3. All non-quantifiable (NQ) values after the pre-first dose value imputed to half lower limit of quantification (LLQ) (LLQ=0.2 nanogram per milliliter [ng/mL]). The Pharmacokinetic (PK) Population comprised of participants in the All Subjects Population for whom a pharmacokinetic sample was obtained and analysed. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the PK Population.

End point type	Secondary

End point timeframe:

From 0-4 hr post each dose administered at Visits 1, 2 and 3 in Part A (up to 3 weeks)

End point values	GSK2339345 1000 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	14[43]			
Units: nanogram per milliliter (mg/mL)				
arithmetic mean (standard deviation)				
FA, Dose 1, Pre-dose, n=14	0 (± 99999)			
FA, Dose 1, 2 min Post-dose, n=14	1.6426 (± 1.4881)			
FA, Dose 1, 5 min Post-dose, n=14	1.255 (± 0.9955)			
FA, Dose 1, 10 min Post-dose, n=14	0.6627 (± 0.5075)			
FA, Dose 1, 30 min Post-dose, n=14	0.2974 (± 99999)			
FA, Dose 1, 1 hr Post-dose, n=13	0.2781 (± 99999)			
FA, Dose 1, 2 hr Post-dose, n=13	0.2144 (± 99999)			
FA, Dose 2, Pre-dose, n=14	0.1723 (± 99999)			
FA, Dose 2, 2 min Post-dose, n=14	2.8846 (± 3.4305)			
FA, Dose 2, 5 min Post-dose, n=14	2.0515 (± 2.3894)			
FA, Dose 2, 10 min Post-dose, n=14	1.2129 (± 0.9082)			

FA, Dose 2, 30 min Post-dose, n=13	0.6505 (± 0.4645)			
FA, Dose 2, 1 hr Post-dose, n=14	0.5295 (± 0.2788)			
SA, Dose 1, Pre-dose, n=7	0.063 (± 99999)			
SA, Dose 1, 2 min Post-dose, n=7	1.8444 (± 1.6036)			
SA, Dose 1, 5 min Post-dose, n=7	1.3909 (± 1.0466)			
SA, Dose 1, 10 min Post-dose, n=7	0.7493 (± 0.5366)			
SA, Dose 1, 30 min Post-dose, n=7	1.4379 (± 3.1688)			
SA, Dose 1, 1 hr Post-dose, n=7	0.2519 (± 0.1135)			
SA, Dose 1, 2 hr Post-dose, n=7	0.3157 (± 99999)			
SA, Dose 2, Pre-dose, n=7	0.1954 (± 99999)			
SA, Dose 2, 2 min Post-dose, n=7	2.399 (± 3.0811)			
SA, Dose 2, 5 min Post-dose, n=7	1.6199 (± 1.7052)			
SA, Dose 2, 10 min Post-dose, n=7	0.9834 (± 0.8469)			
SA, Dose 2, 30 min Post-dose, n=7	0.415 (± 99999)			
SA, Dose 2, 1 hr Post-dose, n=7	0.5256 (± 0.464)			

Notes:

[43] - PK Population. “Not available (NA)” data is presented as “99999".

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-1) and AUC(0-t) of GSK2339345 following two repeated doses

End point title	AUC(0-1) and AUC(0-t) of GSK2339345 following two repeated doses

End point description:

Area under the concentration-time (AUC) curve from time zero (pre-dose) to 1 hours AUC(0-1) and from time zero to the last time AUC(0-t) of quantifiable concentration of GSK2339345following the first dose and second dose at each visit in Part A was measured. Samples were collected at the following time points: pre-dose; 2 min, 5 min, 10 min, 30 min, 1 hr and 2hr (only after Dose 1) post every dose administration at Visits 1, 2 and 3. For , AUC(0-1) and AUC(0-t), non calculable (NC) were imputed prior to derivation of summary statistics and NCs were imputed as 0.1093 and 0.0855 respectively (=half the lowest observed value). Only those participants available at the specified time points were analyzed (represented by n=X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the PK Population.

End point type	Secondary

End point timeframe:

From 0-4 hr post each dose administered at Visits 1, 2 and 3 in Part A (up to 3 weeks)

End point values	GSK2339345 1000 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	14[44]			
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
AUC(0-1), FA, Dose 1, n=11	0.3968 (± 109.1924)			
AUC(0-1), FA, Dose 2, n=10	0.8168 (± 76.8324)			
AUC(0-1), SA, Dose 1, n=7	0.4509 (± 174.9418)			
AUC(0-1), SA, Dose 2, n=6	99999 (± 99999)			
AUC(0-t), FA, n=14	2.0076 (± 174.1325)			
AUC(0-t), SA, n=7	1.2425 (± 559.182)			

Notes:

[44] - PK Population. “Not available (NA)” data is presented as “99999".

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of GSK2339345 following two repeated doses

End point title	Cmax of GSK2339345 following two repeated doses

End point description:

Cmax is defined as the maximum observed concentration of GSK2339345 following two repeated doses at each visit in Part A. Samples were collected at the following time points: pre-dose; 2 min, 5 min, 10 min, 30 min, 1 hr and 2hr (only after Dose 1) post every dose administration at Visits 1, 2 and 3. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. For Cmax, NCs were imputed prior to derivation of summary statistics and NCs were imputed with 0.5*LLQ (LLQ=0.20 ng/mL). Only those participants available at the specified time points were analyzed (represented by n=X in the category titles). Different participants may have been analyzed for different time points, so the overall number of participants analyzed reflects everyone in the PK Population.

End point type	Secondary

End point timeframe:

From 0-4 hr post each dose administered at Visits 1, 2 and 3 in Part A (up to 3 weeks)

End point values	GSK2339345 1000 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	14[45]			
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
FA, Dose 1, n=14	0.9485 (± 224.0451)			
FA, Dose 2, n=14	1.9212 (± 138.2018)			

SA, Dose 1, n=7	1.0835 (± 474.4072)			
SA, Dose 2, n=7	1.0448 (± 416.3398)			

Notes:

[45] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of GSK2339345 following two repeated doses

End point title	Tmax of GSK2339345 following two repeated doses

End point description:

Tmax is defined as the time to reach the observed maximum GSK2339345concentration following two repeated doses at each visit in Part A. Samples were collected at the following time points: pre-dose; 2 min, 5 min, 10 min, 30 min, 1 hr and 2hr (only after Dose 1) post every dose administered at Visits 1, 2 and 3. FA is the first of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. SA is the second of the two doses of GSK2339345 or placebo administered at any of the three visits in Part A. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles). Different participants may have been analyzed for different time points, so the overall number of participants analyzed reflects everyone in the PK Population.

End point type	Secondary

End point timeframe:

From 0-4 hr post each dose administered at Visits 1, 2 and 3 in Part A (up to 3 weeks)

End point values	GSK2339345 1000 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	14[46]			
Units: Hours				
median (full range (min-max))				
FA, Dose 1, n=11	0.03333 (0.0167 to 0.1)			
FA, Dose 2, n=14	0.03333 (0.0167 to 0.516)			
SA, Dose 1, n=5	0.06667 (0.0333 to 0.416)			
SA, Dose 2, n=5	0.03333 (0.0167 to 1.05)			

Notes:

[46] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean cough count over 4 hours at Visits 1, 2 and 3 (Part A)

End point title	Mean cough count over 4 hours at Visits 1, 2 and 3 (Part A)

End point description:

Total cough count (8 hr of recording) was conducted at Visits 1, 2 and 3 (4 hours of post-dose recording for each of the two doses administered). Coughs were counted by a cough monitor fitted to the participants for 8 hr post Dose 1. Number of coughs in 0-4 hr and 4-8 hr period was log-e transformed and used for the analysis. Values were imputed pro-rata if 4 hr epoch was less than 4 hr.

End point type	Secondary

End point timeframe:

Up to 8 hours post-dose at Visits 1, 2 and 3 (Part A)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[47]	14[48]		
Units: Cough count				
geometric mean (standard error)				
0-4 hr	70.5 (± 0.257)	86.7 (± 0.257)		
4-8 hr	65.1 (± 0.234)	88.4 (± 0.234)		

Notes:

[47] - All Subjects Population. Only participants with at least one 4 hr cough count were analyzed.

[48] - All Subjects Population. Only participants with at least one 4 hr cough count were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK2339345 1000 µg v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[49]
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.86
upper limit	1.75

Notes:

[49] - Ratio of adjusted geometric means = GSK2339345/Placebo. Estimated value and CI are presented for the mean cough count over 0-4 hr.

Statistical analysis title	Analysis 2
Comparison groups	GSK2339345 1000 µg v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[50]
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.07
upper limit	1.72

Notes:

[50] - Ratio of adjusted geometric means = GSK2339345/Placebo. Estimated value and CI are presented for the mean cough count over 4-8 hr.

Secondary: Total cough count excluding transient coughs over 4 hours at Visits 1, 2 and 3 (Part A)

End point title	Total cough count excluding transient coughs over 4 hours at Visits 1, 2 and 3 (Part A)

End point description:

Total cough count (8 hr of recording) was conducted at Visits 1, 2 and 3 (4 hours of post-dose recording for each of the two doses administered). Coughs were counted by a cough monitor fitted to the participants for 8 hr post Dose 1. Number of coughs excluding transient cough in 0-4 hr and 4-8 hr period was log-e transformed and used for the analysis. Values were imputed pro-rata if 4 hr epoch was less than 4 hr. Transient cough was the total number of coughs experienced in the two minutes from the start of the first inhalation of a dose.

End point type	Secondary

End point timeframe:

Up to 8 hours post-dose at Visits 1, 2 and 3 (Part A)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[51]	14[52]		
Units: Cough count				
geometric mean (standard error)				
0-4 Hr	70.2 (± 0.27)	68.3 (± 0.27)		
4-8 Hr	64.6 (± 0.25)	67 (± 0.25)		

Notes:

[51] - All Subjects Population. Only participants with at least one 4 hr cough count were analyzed.

[52] - All Subjects Population. Only participants with at least one 4 hr cough count were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK2339345 1000 µg v Placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[53]
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	0.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.67
upper limit	1.4

Notes:

[53] - Ratio of adjusted geometric means = GSK2339345/Placebo. Estimated value and CI are presented for the mean cough count over 0-4 hr.

Statistical analysis title	Analysis 2
Comparison groups	GSK2339345 1000 µg v Placebo

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[54]
Parameter estimate	Ratio of adjusted geometric mean
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.79
upper limit	1.36

Notes:

[54] - Ratio of adjusted geometric means = GSK2339345/Placebo. Estimated value and CI are presented for the mean cough count over 4-8 hr.

Secondary: Mean cough counts by 1hr epoch at Visits 1, 2 and 3 (Part A)

End point title	Mean cough counts by 1hr epoch at Visits 1, 2 and 3 (Part A)

End point description:

Cough counts (8 hr of recording) were conducted at Visits 1, 2 and 3 (4 hr of post-dose recording for each of the two doses administered). Coughs were counted by a cough monitor fitted to the participant for 8 hr post Dose 1. Mean cough count was calculated per participant if the same treatment was taken during different periods. Values were imputed pro-rata if 1hr epoch is less than 60 min. Only those participants with a 1 hr cough count value were analyzed.

End point type	Secondary

End point timeframe:

Up to 8 hours post-dose at Visits 1, 2 and 3 in Part A (up to 3 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[55]	14[56]		
Units: Cough count				
arithmetic mean (standard deviation)				
0 to 1 hr	41.5 (± 30.25)	46.8 (± 35.58)		
1 to 2 hr	13.9 (± 9.86)	15.7 (± 11.2)		
2 to 3 hr	11 (± 11.68)	17 (± 11.75)		
3 to 4 hr	38.4 (± 35.63)	36.6 (± 26.4)		
4 to 5 hr	20.4 (± 14.78)	54.7 (± 61.49)		
5 to 6 hr	25.3 (± 43.09)	28.9 (± 51.83)		
6 to 7 hr	28.7 (± 44.03)	18.7 (± 22.79)		
7 to 8 hr	32.5 (± 54.26)	28.2 (± 42.78)		

Notes:

[55] - All Subjects Population

[56] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean cough counts by 30 min epoch at Visits 1, 2 and 3 (Part A)

End point title	Mean cough counts by 30 min epoch at Visits 1, 2 and 3 (Part A)

End point description:

Cough counts (8 hr of recording) were conducted at Visits 1, 2 and 3 (4 hr of post-dose recording for each of the two doses administered). Coughs were counted by a cough monitor fitted to the participant for 8 hr post Dose 1. Mean cough count was calculated per participant if the same treatment was taken during different periods. Only those participants with a 30 min cough count value were analyzed.

End point type	Secondary

End point timeframe:

Up to 8 hours post-dose in Visits 1, 2 and 3 in Part A (up to 3 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[57]	14[58]		
Units: Cough count				
arithmetic mean (standard deviation)				
0 to 0.5 hr	15.3 (± 17.93)	25.7 (± 21.17)		
0.5 to 1 hr	26.2 (± 22.58)	21.1 (± 22.18)		
1 to 1.5 hr	7.1 (± 7.8)	9.1 (± 8.29)		
1.5 to 2 hr	6.7 (± 4.86)	6.6 (± 6.1)		
2 to 2.5 hr	5.9 (± 8.35)	10.4 (± 10.29)		
2.5 to 3 hr	5.1 (± 7.41)	6.6 (± 8.67)		
3 to 3.5 hr	19.2 (± 21.84)	16.5 (± 15.6)		
3.5 to 4 hr	19.2 (± 28.72)	20.1 (± 23.39)		
4 to 4.5 hr	5.4 (± 6.24)	35.5 (± 44.15)		
4.5 to 5 hr	15 (± 12.17)	19.2 (± 21.38)		
5 to 5.5 hr	19.1 (± 31.94)	21.1 (± 49.66)		
5.5 to 6 hr	6.2 (± 11.75)	7.8 (± 10.6)		
6 to 6.5 hr	12 (± 17.57)	7.4 (± 8.26)		
6.5 to 7 hr	16.7 (± 29.71)	11.3 (± 16.92)		
7 to 7.5 hr	16.5 (± 18.71)	11.4 (± 15.1)		
7.5 to 8 hr	16 (± 37.36)	16.6 (± 33.54)		

Notes:

[57] - All Subjects Population

[58] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean cough counts by 15 min epoch in Part A

End point title	Mean cough counts by 15 min epoch in Part A

End point description:

Cough counts (8 hr of recording) were conducted at Visits 1, 2 and 3 (4 hr of post-dose recording for each of the two doses administered). Coughs were counted by a cough monitor fitted to the participant for 8 hr post Dose 1. Mean cough count was calculated per participant if the same treatment was taken during different periods. Only those participants with a 15 min cough count value were analyzed.

End point type	Secondary

End point timeframe:

Up to 8 hours post-dose at Visits 1, 2 and 3 in Part A (up to 3 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14[59]	14[60]		
Units: Cough count				
arithmetic mean (standard deviation)				
0 to 0.25 hr	4.6 (± 7.84)	21.1 (± 18.23)		
0.25 to 0.5 hr	10.7 (± 14.99)	4.6 (± 9.21)		
0.5 to 0.75 hr	22.5 (± 21.1)	18.7 (± 19.54)		
0.75 to 1 hr	3.7 (± 6.11)	2.4 (± 3.91)		
1 to 1.25 hr	4.9 (± 7.53)	5.7 (± 6.91)		
1.25 to 1.5 hr	2.3 (± 4.13)	3.5 (± 4.19)		
1.5 to 1.75 hr	3.5 (± 3.08)	3.4 (± 3.67)		
1.75 to 2 hr	3.3 (± 2.96)	3.1 (± 3.61)		
2 to 2.25 hr	4 (± 7.26)	6.9 (± 9.04)		
2.25 to 2.5 hr	1.9 (± 3.04)	3.5 (± 4.77)		
2.5 to 2.75 hr	0.4 (± 0.94)	1.5 (± 4.39)		
2.75 to 3 hr	4.6 (± 7.26)	5.1 (± 6.34)		
3 to 3.25 hr	8.4 (± 14.45)	8.8 (± 13.61)		
3.25 to 3.5 hr	10.9 (± 13.44)	7.7 (± 11.34)		
3.5 to 3.75 hr	7.7 (± 11.21)	5.5 (± 8.6)		
3.75 to 4 hr	11.5 (± 20.13)	14.6 (± 21.35)		
4 to 4.25 hr	1.6 (± 2.88)	23 (± 17.97)		
4.25 to 4.5 hr	3.8 (± 5.97)	12.5 (± 28.66)		
4.5 to 4.75 hr	12.4 (± 13.16)	15.6 (± 19.11)		
4.75 to 5 hr	2.6 (± 4.79)	3.5 (± 5.51)		
5 to 5.25 hr	9.6 (± 17.34)	12 (± 28.61)		
5.25 to 5.5 hr	9.5 (± 16.54)	9.1 (± 21.65)		
5.5 to 5.75 hr	2.1 (± 3.35)	3.9 (± 6.34)		
5.75 to 6 hr	4.1 (± 8.91)	3.9 (± 6.24)		
6 to 6.25 hr	6.8 (± 13.83)	3.2 (± 4.39)		
6.25 to 6.5 hr	5.2 (± 6.6)	4.3 (± 6.01)		
6.5 to 6.75 hr	7.2 (± 14.53)	2.8 (± 4.67)		
6.75 to 7 hr	9.5 (± 16.17)	8.5 (± 12.8)		
7 to 7.25 hr	6.9 (± 7.63)	7.1 (± 11.2)		
7.25 to 7.5 hr	9.6 (± 15.81)	4.3 (± 5.51)		
7.5 to 7.75 hr	6.9 (± 18.06)	4.9 (± 6.24)		
7.75 to 8 hr	9.1 (± 19.35)	11.7 (± 33.1)		

Notes:

[59] - All Subjects Population

[60] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean visual analogue scale (VAS) score of cough severity and urge to cough at the indicated time points at Visits 1, 2 and 3 (Part A)

End point title	Mean visual analogue scale (VAS) score of cough severity and

	urge to cough at the indicated time points at Visits 1, 2 and 3 (Part A)

End point description:

VAS for urge to cough and severity of cough were recorded prior to first dose and 1 hour following the second dose of GSK2339345 or placebo at Visits 1, 2 and 3.VAS is a 100-mm linear scales on which participants indicated the severity of their cough (0 mm represents no severity and 100 mm maximum severity ever experienced) and urge to cough (0 represents no urge to cough, 100 represents maximum urge to cough ever experienced). Mean of replicate values per participants used where the same treatment taken during different periods. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Prior to first dose and 1hr post second dose at Visits 1, 2 and 3 in Part A (up to 3 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[61]	14[62]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Urge to cough, Dose 1, Pre-dose, n=16, 14	42.9 (± 20.51)	42.2 (± 25.94)		
Urge to cough, Dose 2, 1 hr Post-dose, n=15, 14	25.1 (± 15.4)	41.5 (± 22.6)		
Cough severity, Dose 1, Pre-dose, n=16, 14	42.8 (± 16.71)	37.3 (± 23.03)		
Cough severity, Dose 2, 1 hr Post-dose, n=15, 14	26.7 (± 15.03)	39.3 (± 21.7)		

Notes:

[61] - All Subjects Population

[62] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of cough counts at each dose of the challenge agent for the capsaicin challenge at Visits 4 and 5 (Part B)

End point title	Mean number of cough counts at each dose of the challenge agent for the capsaicin challenge at Visits 4 and 5 (Part B)

End point description:

Capsaicin was administered using a dosimeter through a nebulizer pot with flow-limitation. Inhalation of increased concentrations (Conc.) was continued until the maximum dose was tolerated by the par. or highest available Conc. was used. The dose-response relationship between dose of capsaicin and cough response was investigated using non-linear mixed effect modeling using Poisson and Negative Binomial distributions. When using a Poisson distribution, there was some evidence for a reduction in capsaicin Emax with GSK2339345 of 17.6%, however, this was not confirmed when using a Negative Binomial distribution. The Negative Binomial distribution described the data marginally better, but the dataset was too small to make definitive conclusions. There was no treatment difference in capsaicin ED50. CC Population comprised of par. in the All Subjects Population for whom any CC data were available for one or both Part B study visits.

End point type	Secondary

End point timeframe:

After the administration of GSK2339345 or placebo (first and second 15 seconds following each dose) at

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[63]	11[64]		
Units: Cough count				
arithmetic mean (standard deviation)				
0 to 15 sec, CC Conc.0.49 µmol/L, n=10, 11	0 (± 0)	0.3 (± 0.9)		
0 to 15 sec, CC Conc.0.97 µmol/L, n=10, 11	0 (± 0)	0.2 (± 0.6)		
0 to 15 sec, CC Conc.1.95 µmol/L, n=10, 11	2 (± 4.64)	1.8 (± 3.19)		
0 to 15 sec, CC Conc.3.9 µmol/L, n=10, 11	4.7 (± 5.79)	3.3 (± 6.2)		
0 to 15 sec, CC Conc. 7.81 µmol/L, n=10, 11	5.1 (± 6.45)	5.3 (± 6.08)		
0 to 15 sec, CC Conc. 15.62 µmol/L, n=10, 11	8.3 (± 5.96)	6.9 (± 4.66)		
0 to 15 sec, CC Conc. 31.25 µmol/L, n=10, 11	8.7 (± 6.63)	6 (± 4.36)		
0 to 15 sec, CC Conc. 62.5 µmol/L, n=6, 10	8.3 (± 6.15)	6.8 (± 3.55)		
0 to 15 sec, CC Conc. 125 µmol/L, n=5, 9	6 (± 1.22)	7.1 (± 3.02)		
0 to 15 sec, CC Conc. 250 µmol/L, n=3, 6	6.3 (± 0.58)	5.7 (± 1.21)		
0 to 15 sec, CC Conc. 500 µmol/L, n=3, 4	7.3 (± 2.52)	7.3 (± 2.22)		
0 to 15 sec, CC Conc. 1000 µmol/L, n=1, 1	6 (± 99999)	7 (± 99999)		
0 to 30 sec, CC Conc.0.49 µmol/L, n=10, 11	0 (± 0)	0.5 (± 1.81)		
0 to 30 sec, CC Conc.0.97 µmol/L, n=10, 11	0 (± 0)	0.2 (± 0.6)		
0 to 30 sec, CC Conc.1.95 µmol/L, n=10, 11	2 (± 4.64)	1.9 (± 3.36)		
0 to 30 sec, CC Conc.3.9 µmol/L, n=10, 11	5.4 (± 6.59)	4.3 (± 6.83)		
0 to 30 sec, CC Conc. 7.81 µmol/L, n=10, 11	6.7 (± 9.57)	5.5 (± 6.42)		
0 to 30 sec, CC Conc. 15.62 µmol/L, n=10, 11	12.2 (± 9.47)	7.5 (± 5.47)		
0 to 30 sec, CC Conc. 31.25 µmol/L, n=10, 11	11 (± 9.87)	6.5 (± 5.01)		
0 to 30 sec, CC Conc. 62.5 µmol/L, n=6, 10	9.2 (± 7.19)	7.4 (± 4.12)		
0 to 30 sec, CC Conc. 125 µmol/L, n=5, 9	6 (± 1.22)	8.2 (± 4.24)		
0 to 30 sec, CC Conc. 250 µmol/L, n=3, 6	6.3 (± 0.58)	6.7 (± 1.37)		
0 to 30 sec, CC Conc. 500 µmol/L, n=3, 4	8.7 (± 4.73)	8.5 (± 3.51)		
0 to 30 sec, CC Conc. 1000 µmol/L, n=1, 1	6 (± 99999)	7 (± 99999)		

Notes:

[63] - CC Population. “Not available (NA)” data is presented as “99999".

[64] - CC Population. “Not available (NA)” data is presented as “99999".

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of cough counts at each dose of the challenge agent for the citric acid challenge at Visits 6 and 7 (Part C)

End point title	Mean number of cough counts at each dose of the challenge agent for the citric acid challenge at Visits 6 and 7 (Part C)

End point description:

CA was administered using a dosimeter through a nebulizer pot with flow-limitation. Inhalation of increased Conc. was continued until the maximum dose was tolerated by the par. or the highest available Conc. was used. The dose-response relationship between the dose of citric acid and cough response was investigated using non-linear mixed effect modelling using Poisson and Negative Binomial distributions. When using a Poisson distribution, there was some evidence for an increase in citric acid ED50 with GSK2339345 of 41.6%, however, this was not confirmed when using a Negative Binomial distribution. The Negative Binomial distribution described the data marginally better, but the dataset was too small to make definitive conclusions. There was no treatment difference in citric acid Emax. CAC Population comprised of par.in the All Subjects Population for whom any CAC data were available for one or both Part C study visits.

End point type	Secondary

End point timeframe:

After the administration of GSK2339345 or placebo (first and second 15 seconds following each dose) at Visits 6 and 7 in Part C (up to 2 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[65]	9[66]		
Units: Cough count				
arithmetic mean (standard deviation)				
0 to 15 sec, CAC Conc. 0.03 mol/L, n=9, 9	0.2 (± 0.44)	0.2 (± 0.67)		
0 to 15 sec, CAC Conc. 0.06 mol/L, n=9, 9	0.2 (± 0.67)	0.6 (± 1.33)		
0 to 15 sec, CAC Conc. 0.125 mol/L, n=9, 9	3 (± 4.66)	1.8 (± 1.92)		
0 to 15 sec, CAC Conc. 0.25 mol/L, n=9, 9	3.7 (± 4.09)	2.7 (± 3.43)		
0 to 15 sec, CAC Conc. 0.5 mol/L, n=9, 9	6.1 (± 5.13)	4.3 (± 3.43)		
0 to 15 sec, CAC Conc. 1 mol/L, n=9, 9	6 (± 3.5)	6.6 (± 3.4)		
0 to 15 sec, CAC Conc. 2 mol/L, n=5,7	5.8 (± 4.02)	4.1 (± 3.29)		
0 to 15 sec, CAC Conc. 4 mol/L, n=5, 6	4 (± 3.81)	5.3 (± 4.46)		
0 to 30 sec, CAC Conc. 0.03 mol/L, n=9, 9	0.2 (± 0.44)	0.2 (± 0.67)		
0 to 30 sec, CAC Conc. 0.06 mol/L, n=9, 9	0.2 (± 0.67)	0.6 (± 1.33)		

0 to 30 sec, CAC Conc. 0.125 mol/L, n=9, 9	3.2 (± 4.55)	2 (± 2.06)		
0 to 30 sec, CAC Conc. 0.25 mol/L, n=9, 9	4.6 (± 6)	2.7 (± 3.43)		
0 to 30 sec, CAC Conc. 0.5 mol/L, n=9, 9	7.3 (± 6.34)	5 (± 4.09)		
0 to 30 sec, CAC Conc. 1 mol/L, n=9, 9	7.2 (± 4.55)	9.3 (± 6.32)		
0 to 30 sec, CAC Conc. 2 mol/L, n=5, 7	6.8 (± 4.82)	6.4 (± 5.32)		
0 to 30 sec, CAC Conc. 4 mol/L, n=5, 6	4.8 (± 3.83)	6.2 (± 5.34)		

Notes:

[65] - CAC Population

[66] - CAC Population

Statistical analyses

No statistical analyses for this end point

Secondary: Capsaicin challenge agent dose concentration required to achieve C2, C5 and C6 at Visits 4 and 5 (Part B)

End point title	Capsaicin challenge agent dose concentration required to achieve C2, C5 and C6 at Visits 4 and 5 (Part B)

End point description:

Capsaicin challenge (CC) was performed following the administration of GSK2339345 or placebo at Visits 4 and 5. Capsaicin was administered using a dosimeter through a nebulizer. The number of coughs in the first and second 15 sec following each dose of CC agent were recorded. Inhalation of increased conc. was continued until the maximum dose was tolerated by the participant or the highest available conc. was used. CC agent dose concentration required to achieve C2 (2 coughs were first observed [FO]), C5 (5 coughs were FO) and C6 (6 coughs were FO) are presented. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the CC Population. All instances of missing values occurred where a participant did not achieved the required number of coughs for a parameter.

End point type	Secondary

End point timeframe:

After the administration of GSK2339345 or placebo at Visits 4 and 5 in Part B (up to 2 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[67]	11[68]		
Units: µmol/L				
geometric mean (geometric coefficient of variation)				
C2, 0-15 sec, n=10, 11	4.181 (± 88.924)	5.697 (± 207.575)		
C2, 0-30 sec, n=10, 11	4.181 (± 88.924)	5.022 (± 194.425)		
C5, 0-15 sec, n=10, 11	8.967 (± 124.989)	11.394 (± 378.087)		
C5, 0-30 sec, n=10, 11	8.367 (± 110.36)	10.05 (± 535.013)		
C6, 0-15 sec, n=10, 9	11.834 (± 229.845)	12.391 (± 438.063)		
C6, 0-30 sec, n=10, 10	10.3 (± 229.859)	14.575 (± 908.133)		

Notes:

[67] - CC Population

[68] - CC Population

Statistical analyses

No statistical analyses for this end point

Secondary: Citric acid (CA) challenge agent dose concentration required to achieve C2, C5 and C6 at Visits 6 and 7 (Part C)

End point title	Citric acid (CA) challenge agent dose concentration required to achieve C2, C5 and C6 at Visits 6 and 7 (Part C)

End point description:

Citric acid challenge (CAC) was performed following the administration of GSK2339345 or placebo at Visits 6 and 7. CA was administered using a dosimeter through a nebulizer pot with flow-limitation. Number of coughs in the first and second 15 sec following each dose of CAC agent were recorded. Inhalation of increased conc. was continued until the maximum dose was tolerated by the participants or the highest available Conc. was used. CAC agent dose concentration required to achieve C2 (2 coughs were first observed [FO]), C5 (5 coughs were FO) and C6 (6 coughs were FO) are presented. Only those participants available at the specified time points were analyzed (represented by n=X,X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the CAC Population. All instances of missing values occurred where a participant did not achieved the required number of coughs for a parameter.

End point type	Secondary

End point timeframe:

After the administration of GSK2339345 or placebo at Visits 6 and 7 in Part C (up to 2 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[69]	9[70]		
Units: mol/L				
geometric mean (geometric coefficient of variation)				
C2, 0-15 sec, n=8, 9	0.209 (± 111.073)	0.156 (± 142.342)		
C2, 0-30 sec, n=8, 9	0.192 (± 113.563)	0.156 (± 142.342)		
C5, 0-15 sec, n=7, 7	0.305 (± 138.956)	0.61 (± 90.153)		
C5, 0-30 sec, n=7, 8	0.276 (± 101.609)	0.707 (± 127.046)		
C6, 0-15 sec, n=7, 7	0.371 (± 158.73)	0.743 (± 76.173)		
C6, 0-30 sec, n= 7, 8	0.336 (± 141.375)	0.771 (± 98.463)		

Notes:

[69] - CAC Population

[70] - CAC Population

Statistical analyses

No statistical analyses for this end point

Secondary: Capsaicin challenge agent imputed dose concentration required to achieve C2, C5 and C6 at Visits 4 and 5 (Part B)

End point title	Capsaicin challenge agent imputed dose concentration required to achieve C2, C5 and C6 at Visits 4 and 5 (Part B)

End point description:

Capsaicin challenge (CC) was performed following the administration of GSK2339345 or placebo at Visits 4 and 5. Capsaicin was administered using a dosimeter through a nebulizer. The number of coughs in the first and second 15 sec following each dose of CC agent were recorded. Inhalation of increased Conc. was continued until the maximum dose was tolerated by the participant or the highest available Conc. was used. CC agent imputed dose concentration required to achieve C2 (at which 2 coughs were first observed [FO]), C5 (at which 5 coughs were FO) and C6 (at which 6 coughs were FO) are presented. For participants who did not complete the challenge and not reached the endpoint, values were imputed to the next dose in the challenge sequence after stopping. For participants who completed the challenge and had not reached the endpoint, values were imputed to 2000 (=twice the highest dose of capsaicin).

End point type	Secondary

End point timeframe:

After the administration of GSK2339345 or placebo at Visits 4 and 5 in Part B (up to 2 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[71]	11[72]		
Units: µmol/L				
geometric mean (geometric coefficient of variation)				
C2, 0-15 sec	4.181 (± 88.924)	5.697 (± 207.575)		
C2, 0-30 sec	4.181 (± 88.924)	5.022 (± 194.425)		
C5, 0-15 sec	8.967 (± 124.989)	11.394 (± 378.087)		
C5, 0-30 sec	8.367 (± 110.36)	10.05 (± 535.013)		
C6, 0-15 sec	11.834 (± 229.845)	25.85 (± 1279.694)		
C6, 0-30 sec	10.3 (± 229.859)	20.1 (± 1288.571)		

Notes:

[71] - CC Population

[72] - CC Population

Statistical analyses

No statistical analyses for this end point

Secondary: Citric acid (CA) challenge agent imputed dose concentration required to achieve C2, C5 and C6 at Visits 6 and 7 (Part C)

End point title	Citric acid (CA) challenge agent imputed dose concentration required to achieve C2, C5 and C6 at Visits 6 and 7 (Part C)

End point description:

Citric acid challenge (CAC) was performed following the administration of GSK2339345 or placebo at Visits 6 and 7. CA was administered using a dosimeter through a nebulizer pot with flow-limitation.

Number of coughs in the first and second 15 sec following each dose of CAC agent were recorded. Inhalation of increased Conc. was continued until the maximum dose was tolerated by the participants or the highest available Conc. was used. CAC agent imputed dose concentration required to achieve C2 (at which 2 coughs were first observed [FO]), C5 (at which 5 coughs were FO) and C6 (at which 6 coughs were FO) are presented. For participants who did not complete the challenge and not reached the endpoint, values were imputed to the next dose in the challenge sequence after stopping. For participants who completed the challenge and had not reached the endpoint, values were imputed to 2000 (=twice the highest dose of CA).

End point type	Secondary

End point timeframe:

After the administration of GSK2339345 or placebo at Visits 6 and 7 in Part C (up to 2 weeks)

End point values	Placebo	GSK2339345 1000 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[73]	9[74]		
Units: mol/L				
geometric mean (geometric coefficient of variation)				
C2, 0-15 sec	0.314 (± 279.912)	0.156 (± 142.342)		
C2, 0-30 sec	0.29 (± 294.833)	0.156 (± 142.342)		
C5, 0-15 sec	0.63 (± 410.643)	1.08 (± 216.073)		
C5, 0-30 sec	0.583 (± 379.787)	0.926 (± 185.962)		
C6, 0-15 sec	0.735 (± 387.993)	1.26 (± 179.623)		
C6, 0-30 sec	0.68 (± 387.993)	1 (± 152.443)		

Notes:

[73] - CAC Population

[74] - CAC Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the start of study treatment until follow-up (up to 8 weeks).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in participants of the All Subjects Population, comprised of all participants who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received two doses of placebo as a solution administered via an ADI with a four hour dosing interval, either at one or two visits in Part A (Visits 1, 2 and 3) and a single dose at one of the 2 visits in Parts B (Visits 4 and 5) and Part C (Visits 6 and 7). Dose 1 was administered on each treatment day at the same time each morning throughout all of Parts A, B and C. The follow-up of each participant occurred 3-14 days after the last dose. There was a washout of 48 hours to 7 days between visits. Additionally, 5 minutes after the administration of placebo at each visit in Part B and C, participants received an oral inhalation of 10 µL of a capsaicin solution at each visit in Part B and 10 µL of a citric acid solution at each visit in Part C. The strength of capsaicin solution ranged from 0.49 to 1000 µM and the citric acid solution strength ranged from 0.03 to 4.0 molar.

Reporting group title	GSK2339345 1000 µg

Reporting group description:

Participants received two doses of GSK2339345 1000 µg via an ADI with a four hour dosing interval, either at one or two visits in Part A (Visits 1, 2 and 3) and a single dose at one of the 2 visits in Parts B (Visits 4 and 5) and Part C (Visits 6 and 7). Dose 1 was administered on each treatment day at the same time each morning throughout all of Parts A, B and C. The follow-up of each participant occurred 3-14 days after the last dose. There was a washout of 48 hours to 7 days between visits. Additionally, 5 minutes after the administration of placebo at each visit in Part B and C, participants received an oral inhalation of 10 µL of a capsaicin solution at each visit in Part B and 10 µL of a citric acid solution at each visit in Part C. The strength of capsaicin solution ranged from 0.49 to 1000 µM and the citric acid solution strength ranged from 0.03 to 4.0 molar.

Serious adverse events	Placebo	GSK2339345 1000 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 14 (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	GSK2339345 1000 µg	
Total subjects affected by non-serious adverse events subjects affected / exposed	10 / 16 (62.50%)	5 / 14 (35.71%)	
Investigations Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 14 (0.00%) 0	
QRS axis abnormal subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 14 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2	1 / 14 (7.14%) 3	
Dysgeusia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 14 (7.14%) 2	
Headache subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 14 (7.14%) 2	
Hypoaesthesia oral subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 14 (0.00%) 0	
Paraesthesia oral subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 14 (7.14%) 1	
Gastrointestinal disorders Tongue discolouration subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 14 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 14 (7.14%) 1	
Respiratory, thoracic and mediastinal disorders Cough			

subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Throat irritation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2014	The amendment was made to increase the number of eligible patients and reduce participant burden, while preserving data required to meet the primary objective of the study. The changes were to facilitate the participation of participants who were not able to take part due to study duration and intensity of the visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported