Clinical trial results:
An open-label, single arm study to investigate the safety, pharmacokinetics and pharmacodynamics of repeat doses of inhaled nemiralisib in patients with APDS/PASLI

Summary

EudraCT number	2015-004876-31
Trial protocol	GB
Global end of trial date	04 June 2020

Results information

Result version number	v1 (current)
This version publication date	12 June 2021
First version publication date	12 June 2021

Trial information

Trial identification

Sponsor protocol code	204745

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 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of 84 days repeat dosing of inhaled nemiralisib in patients with activated PI3K delta syndrome (APDS)

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 July 2016
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: 5
Worldwide total number of subjects	5
EEA total number of subjects	0

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)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is an open-label study conducted to investigate safety, pharmacokinetics and pharmacodynamics of repeat doses of inhaled nemiralisib (NEMI) in participants with activated phosphoinositide 3-kinase (PI3K) delta syndrome /p110 delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (APDS/PASLI)

Pre-assignment

Screening details:

Participants received either 1000 mcg NEMI DISKUS or 700 mcg NEMI ELLIPTA or 500 mcg NEMI ELLIPTA. All NEMI DISKUS and NEMI ELLIPTA dose levels were combined as All NEMI treatment group as there was no intent to compare two dose levels or devices. The study had protocol amendments to reflect changes in dose and device administration.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All NEMI

Arm description:

Participants were administered with either NEMI 1000 mcg using DISKUS DPI or NEMI 700 or 500 mcg using ELLIPTA DPI once daily in the morning. NEMI DISKUS and NEMI ELLIPTA were combined as All NEMI treatment group as there was no intent to compare two dose levels or devices.

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

Dosage and administration details:

Participants received either 1000 mcg NEMI DISKUS or 700 mcg NEMI ELLIPTA or 500 mcg NEMI ELLIPTA. All NEMI DISKUS and NEMI ELLIPTA dose levels were combined as All NEMI treatment group. There was no intent to compare two dose levels or devices.

Number of subjects in period 1	All NEMI
Started	5
Completed	4
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	All NEMI

Reporting group description:

Participants were administered with either NEMI 1000 mcg using DISKUS DPI or NEMI 700 or 500 mcg using ELLIPTA DPI once daily in the morning. NEMI DISKUS and NEMI ELLIPTA were combined as All NEMI treatment group as there was no intent to compare two dose levels or devices.

Reporting group values	All NEMI	Total	
Number of subjects	5	5	
Age categorical Units: Subjects			
All participants	5	5	
Age Continuous Units: Years			
arithmetic mean	36.6		
standard deviation	± 12.36	-	
Sex: Female, Male Units: Participants			
Female	3	3	
Male	2	2	
Race/Ethnicity, Customized Units: Subjects			
White-White/Caucasian/European Heritage	5	5	

End points

End points reporting groups

Reporting group title	All NEMI
Reporting group description:	
Participants were administered with either NEMI 1000 mcg using DISKUS DPI or NEMI 700 or 500 mcg using ELLIPTA DPI once daily in the morning. NEMI DISKUS and NEMI ELLIPTA were combined as All NEMI treatment group as there was no intent to compare two dose levels or devices.	
Subject analysis set title	NEMI 1000 mcg Via DISKUS
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants were administered NEMI 1000 mcg using DISKUS DPI once daily in the morning.	
Subject analysis set title	NEMI 700 mcg Via ELLIPTA
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants were administered NEMI 700 mcg using ELLIPTA DPI once daily in the morning.	
Subject analysis set title	NEMI 500 mcg Via ELLIPTA
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants were administered NEMI 500 mcg using ELLIPTA DPI once daily in the morning.	

Primary: Number of participants with any serious adverse events (SAEs) and any non-serious adverse events (Non-SAEs)

End point title	Number of participants with any serious adverse events (SAEs) and any non-serious adverse events (Non-SAEs)[1]
End point description:	
An adverse event is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is defined as any untoward medical occurrence that; results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, other situations as judged by physician. Number of participants with any SAE and non-SAEs are presented. All Subjects Population consisted of all participants who received at least one dose of the study treatment.	
End point type	Primary
End point timeframe:	
Upto 7.5 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[2]			
Units: Participants				
Any non-SAE	5			
Any SAE	0			

Notes:

[2] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP)

End point title	Change From Baseline in Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP)[3]

End point description:

SBP and DBP were measured in participants in a semi-supine position after 5 minutes rest. Baseline value is defined as latest pre-dose (Day 1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. 99999 indicates that standard deviation could not be calculated as a single participant was analyzed. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56, 83 and 84

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[4]			
Units: Millimeters of Mercury (mmHg)				
arithmetic mean (standard deviation)				
DBP, Day 14, n= 5	1.0 (± 6.44)			
DBP, Day 28, n= 4	4.0 (± 6.98)			
DBP, Day 56, n= 4	8.5 (± 5.80)			
DBP, Day 83, n= 4	2.0 (± 4.40)			
DBP, Day 84 n= 1	17.0 (± 99999)			
SBP, Day 14, n= 5	-1.0 (± 3.67)			
SBP, Day 28, n= 4	5.3 (± 8.54)			
SBP, Day 56, n= 4	10.0 (± 9.31)			
SBP, Day 83, n= 4	1.5 (± 3.51)			
SBP, Day 84, n= 1	16.0 (± 99999)			

Notes:

[4] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Pulse Rate

End point title	Change from Baseline in Pulse Rate[5]

End point description:

Pulse rate was measured in participants in a semi-supine position after 5 minutes rest. Baseline value is defined as latest pre-dose (Day 1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. 99999 indicates that standard deviation could not be calculated as a single participant was analyzed. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56, 83 and 84

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[6]			
Units: Beats per minute				
arithmetic mean (standard deviation)				
Day 14, n= 5	3.2 (± 7.73)			
Day 28, n= 4	2.0 (± 10.86)			
Day 56, n= 4	6.8 (± 9.43)			
Day 83, n= 4	4.8 (± 7.76)			
Day 84 n= 1	7.0 (± 99999)			

Notes:

[6] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Respiratory Rate

End point title	Change from Baseline in Respiratory Rate[7]

End point description:

Respiratory rate was measured in participants in a semi-supine position after 5 minutes rest. . Baseline value is defined as latest pre-dose (Day 1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. 99999 indicates that standard deviation could not be calculated as a single participant was analyzed. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56, 83 and 84

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[8]			
Units: Breaths per minute				
arithmetic mean (standard deviation)				
Day 14, n= 5	0.2 (± 2.28)			
Day 28, n= 4	0.8 (± 4.57)			
Day 56, n= 4	1.5 (± 5.26)			
Day 83, n= 4	1.0 (± 2.45)			
Day 84 n= 1	2.0 (± 99999)			

Notes:

[8] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in body temperature

End point title	Change from Baseline in body temperature[9]

End point description:

Temperature was measured in participants in a semi-supine position after 5 minutes rest. Baseline value is defined as latest pre-dose (Day 1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. 99999 indicates that standard deviation could not be calculated as a single participant was analyzed. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56, 83 and 84

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[10]			
Units: Degrees celsius				
arithmetic mean (standard deviation)				
Day 14, n= 5	0.10 (± 0.158)			
Day 28, n= 4	0.17 (± 0.350)			
Day 56, n= 4	0.07 (± 0.171)			
Day 83, n= 4	0.17 (± 0.479)			
Day 84 n= 1	0.50 (± 99999)			

Notes:

[10] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in electrocardiogram (ECG) mean heart rate

End point title	Change from Baseline in electrocardiogram (ECG) mean heart rate[11]

End point description:

Single 12-lead ECGs were recorded at indicated timepoints using an ECG machine that automatically calculated the heart rate. Baseline value is defined as latest pre-dose (Day 1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56 and 83

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[12]			
Units: Beats per minute				
arithmetic mean (standard deviation)				
Day 14, n= 5	-1.0 (± 3.94)			
Day 28, n= 4	-0.8 (± 2.99)			
Day 56, n= 4	5.3 (± 7.54)			
Day 83, n= 4	1.0 (± 2.31)			

Notes:

[12] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in PR interval, QRS duration, uncorrected QT interval, QT corrected interval-Fredericia interval (QTcF) and QTc corrected by Bazett's formula (QTcB)

End point title	Change from Baseline in PR interval, QRS duration, uncorrected QT interval, QT corrected interval-Fredericia interval (QTcF) and QTc corrected by Bazett's formula (QTcB)[13]

End point description:

Twelve lead ECGs were recorded at indicated timepoints. At each time point, ECG machine automatically measured QRS duration, uncorrected QT interval, QTcF interval and QTcB. Baseline value is defined as latest pre-dose (Day 1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56 and 83

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[14]			
Units: Milliseconds				
arithmetic mean (standard deviation)				
PR, Day 14, n= 5	-2.2 (± 9.23)			
PR, Day 28, n= 4	-4.8 (± 4.27)			
PR, Day 56, n= 4	-3.3 (± 11.18)			
PR, Day 83, n= 4	-6.0 (± 11.80)			

QRS Duration, Day 14, n= 5	-5.6 (± 7.33)			
QRS Duration, Day 28, n= 4	-4.5 (± 11.03)			
QRS Duration, Day 56, n= 4	-6.5 (± 8.81)			
QRS Duration, Day 83, n= 4	-6.0 (± 7.79)			
QT Interval, Day 14, n= 5	-7.2 (± 10.66)			
QT Interval, Day 28, n= 4	-2.8 (± 28.89)			
QT Interval, Day 56, n= 4	-22.3 (± 16.01)			
QT Interval, Day 83, n= 4	-16.3 (± 9.74)			
QTcB, Day 14, n= 5	-9.4 (± 4.93)			
QTcB, Day 28, n= 4	-4.5 (± 22.55)			
QTcB, Day 56, n= 4	-8.3 (± 24.55)			
QTcB, Day 83, n= 4	-12.5 (± 8.19)			
QTcF, Day 14, n= 5	-8.2 (± 4.32)			
QTcF, Day 28, n= 4	-3.5 (± 24.09)			
QTcF, Day 56, n= 4	-13.0 (± 19.92)			
QTcF, Day 83, n= 4	-14.0 (± 7.79)			

Notes:

[14] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Clinical Chemistry Parameters: alanine aminotransferase (ALT), alkaline phosphatase (ALP) and aspartate aminotransferase (AST)

End point title	Change From Baseline in Clinical Chemistry Parameters: alanine aminotransferase (ALT), alkaline phosphatase (ALP) and aspartate aminotransferase (AST)[15]

End point description:

Blood samples were collected for the analysis of clinical parameters including ALT, ALP and AST. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day -1) and at Days 14, 28, 56 and 83

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[16]			
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
ALT, Day 14, n= 5	1.0 (± 2.12)			
ALT, Day 28, n= 4	0.8 (± 1.71)			
ALT, Day 56, n= 4	0.0 (± 1.63)			
ALT, Day 83, n= 4	1.3 (± 7.50)			

AST, Day 14, n= 5	-0.8 (± 1.48)			
AST, Day 28, n= 4	0.8 (± 2.22)			
AST, Day 56, n= 4	-0.8 (± 4.79)			
AST, Day 83, n= 4	-1.0 (± 7.70)			
ALP, Day 14, n= 5	2.6 (± 5.77)			
ALP, Day 28, n= 4	3.8 (± 5.68)			
ALP, Day 56, n= 4	7.5 (± 5.00)			
ALP, Day 83, n= 4	6.0 (± 2.94)			

Notes:

[16] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in clinical chemistry parameters : Albumin and Total Protein

End point title	Change from Baseline in clinical chemistry parameters : Albumin and Total Protein[17]

End point description:

Blood samples were collected for the analysis of clinical chemistry parameter-albumin and total protein. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day -1) and at Days 14, 28, 56 and 83

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[18]			
Units: Grams per liter				
arithmetic mean (standard deviation)				
Albumin, Day 14, n= 5	2.6 (± 2.07)			
Albumin, Day 28, n= 4	1.3 (± 3.20)			
Albumin, Day 56, n= 4	2.8 (± 2.36)			
Albumin, Day 83, n= 4	2.0 (± 3.16)			
Total Protein, Day 14, n= 5	4.0 (± 1.58)			
Total Protein, Day 28, n= 4	1.3 (± 3.59)			
Total Protein, Day 56, n= 4	4.0 (± 4.76)			
Total Protein, Day 83, n= 4	4.3 (± 2.50)			

Notes:

[18] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline values in clinical chemistry parameters: sodium, potassium, calcium, glucose and urea

End point title	Change from Baseline values in clinical chemistry parameters: sodium, potassium, calcium, glucose and urea[19]

End point description:

Blood samples were collected for the analysis of clinical parameters including sodium, potassium, calcium, glucose and urea. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day -1) and at Days 14, 28, 56 and 83

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[20]			
Units: Millimoles per liter				
arithmetic mean (standard deviation)				
Sodium, Day 14, n= 5	-0.2 (± 2.68)			
Sodium, Day 28, n= 4	0.5 (± 0.58)			
Sodium, Day 56, n= 4	-0.8 (± 2.06)			
Sodium, Day 83, n= 4	0.0 (± 1.83)			
Potassium, Day 14, n= 5	0.24 (± 0.397)			
Potassium, Day 28, n= 4	0.30 (± 0.346)			
Potassium, Day 56, n= 4	0.35 (± 0.370)			
Potassium, Day 83, n= 4	0.38 (± 0.275)			
Calcium, Day 14, n= 5	0.040 (± 0.0990)			
Calcium, Day 28, n= 4	0.063 (± 0.0704)			
Calcium, Day 56, n= 4	0.133 (± 0.1343)			
Calcium, Day 83, n= 4	0.082 (± 0.1325)			
Glucose, Day 14, n= 5	-0.64 (± 1.557)			
Glucose, Day 28, n= 4	-0.60 (± 1.774)			
Glucose, Day 56, n= 4	-0.48 (± 1.578)			
Glucose, Day 83, n= 4	-0.68 (± 1.333)			
Urea, Day 14, n= 5	4.732 (± 5.8283)			
Urea, Day 28, n= 4	8.330 (± 2.6837)			
Urea, Day 56, n= 4	2.610 (± 5.1954)			
Urea, Day 83, n= 4	2.185 (± 4.1025)			

Notes:

[20] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline values in clinical chemistry parameters: Direct bilirubin, total bilirubin and creatinine

End point title	Change from Baseline values in clinical chemistry parameters: Direct bilirubin, total bilirubin and creatinine[21]

End point description:

Blood samples were collected for the analysis of clinical chemistry parameters: direct bilirubin, total bilirubin and creatinine. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day -1) and at Days 14, 28, 56 and 83

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[22]			
Units: Micromoles per liter				
arithmetic mean (standard deviation)				
Direct bilirubin, Day 14, n= 5	-1.0 (± 0.71)			
Direct bilirubin, Day 28, n= 4	-1.8 (± 0.96)			
Direct bilirubin, Day 56, n= 4	-0.5 (± 1.00)			
Direct bilirubin, Day 83, n= 4	-0.5 (± 1.00)			
Total bilirubin, Day 14, n= 5	-1.8 (± 1.64)			
Total bilirubin, Day 28, n= 4	-3.0 (± 2.45)			
Total bilirubin, Day 56, n= 4	-0.8 (± 1.89)			
Total bilirubin, Day 83, n= 4	-1.5 (± 2.52)			
Creatinine , Day 14, n= 5	-2.0 (± 12.43)			
Creatinine , Day 28, n= 4	-4.3 (± 6.08)			
Creatinine , Day 56, n= 4	5.0 (± 14.07)			
Creatinine , Day 83, n= 4	-2.5 (± 14.93)			

Notes:

[22] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline values in clinical chemistry parameter: C-Reactive Protein

End point title	Change from Baseline values in clinical chemistry parameter: C-Reactive Protein[23]

End point description:

Blood samples were collected for the analysis of clinical chemistry parameter:C-Reactive Protein. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56 and 83

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[24]			
Units: Milligrams per liter				
arithmetic mean (standard deviation)				
Day 14, n= 5	0.56 (± 1.592)			
Day 28, n= 4	0.75 (± 1.085)			
Day 56, n= 4	2.75 (± 6.222)			
Day 83, n= 4	3.90 (± 7.141)			

Notes:

[24] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline for hematology parameters: basophil, eosinophils, White Blood Cells (WBC), lymphocytes, neutrophils, monocytes and platelets

End point title	Change from Baseline for hematology parameters: basophil, eosinophils, White Blood Cells (WBC), lymphocytes, neutrophils, monocytes and platelets[25]

End point description:

Blood samples were collected for the analysis of hematology parameters including basophils, eosinophils, WBC, lymphocytes, neutrophils, monocytes and platelets at indicated timepoints. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day -1) and at Days 14, 28, 56 and 83

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[26]			
Units: 10^9 cells per liters				
arithmetic mean (standard deviation)				
Basophils, Day 14, n= 5	-0.002 (± 0.0045)			
Basophils, Day 28, n= 4	0.008 (± 0.0096)			
Basophils, Day 56, n= 4	0.008 (± 0.0236)			
Basophils, Day 83, n= 4	0.013 (± 0.0222)			
Eosinophils, Day 14, n= 5	0.108 (± 0.1542)			
Eosinophils, Day 28, n= 4	0.088 (± 0.0650)			
Eosinophils, Day 56, n= 4	0.128 (± 0.2241)			
Eosinophils, Day 83, n= 4	0.075 (± 0.0810)			
Lymphocytes, Day 14, n= 5	0.122 (± 0.2411)			
Lymphocytes, Day 28, n= 4	-0.133 (± 0.0918)			
Lymphocytes, Day 56, n= 4	-0.105 (± 0.1115)			
Lymphocytes, Day 83, n= 4	0.037 (± 0.3140)			
Monocytes, Day 14, n= 5	0.096 (± 0.2893)			
Monocytes, Day 28, n= 4	0.030 (± 0.0572)			
Monocytes, Day 56, n= 4	0.115 (± 0.0614)			
Monocytes, Day 83, n= 4	0.065 (± 0.0592)			
Neutrophils , Day 14, n= 5	0.334 (± 1.2388)			
Neutrophils , Day 28, n= 4	0.575 (± 0.6125)			
Neutrophils , Day 56, n= 4	0.553 (± 0.7647)			
Neutrophils , Day 83, n= 4	0.653 (± 0.7857)			
Platelet, Day 14, n= 5	49.4 (± 52.53)			
Platelet, Day 28, n= 4	9.0 (± 25.86)			
Platelet, Day 56, n= 4	17.0 (± 31.79)			
Platelet, Day 83, n= 4	61.8 (± 43.41)			
WBC, Day 14, n= 5	0.656 (± 1.0304)			
WBC, Day 28, n= 4	0.568 (± 0.6004)			
WBC, Day 56, n= 4	0.698 (± 1.0605)			
WBC, Day 83, n= 4	0.845 (± 0.6608)			

Notes:

[26] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline for hematology parameter: hemoglobin

End point title	Change from Baseline for hematology parameter:

End point description:

Blood samples were collected for the analysis of hematology parameter: hemoglobin at indicated timepoints. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56 and 83

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[28]			
Units: Grams per liter				
arithmetic mean (standard deviation)				
Day 14, n= 5	10.0 (± 5.24)			
Day 28, n= 4	8.3 (± 3.77)			
Day 56, n= 4	13.5 (± 8.50)			
Day 83, n= 4	13.3 (± 5.74)			

Notes:

[28] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline for hematology parameter: hematocrit

End point title	Change from Baseline for hematology parameter:

End point description:

Blood samples were collected for the analysis of hematology parameter: hematocrit at indicated timepoints. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56 and 83

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[30]			
Units: Percentage of red blood cells in blood				
arithmetic mean (standard deviation)				
Day 14, n= 5	0.0320 (± 0.01488)			
Day 28, n= 4	0.0333 (± 0.01204)			
Day 56, n= 4	0.0518 (± 0.02337)			
Day 83, n= 4	0.0465 (± 0.01396)			

Notes:

[30] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in hematology parameter: mean corpuscular volume (MCV)

End point title	Change from Baseline in hematology parameter: mean corpuscular volume (MCV)[31]

End point description:

Blood samples were collected for the analysis of hematology parameter: MCV at indicated timepoints. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56 and 83

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[32]			
Units: Femtoliters				
arithmetic mean (standard deviation)				
Day 14, n= 5	1.00 (± 2.187)			
Day 28, n= 4	2.33 (± 2.287)			
Day 56, n= 4	2.02 (± 2.331)			
Day 83, n= 4	1.03 (± 3.407)			

Notes:

[32] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in hematology parameter: mean corpuscular Hemoglobin (MCH)

End point title	Change from Baseline in hematology parameter: mean corpuscular Hemoglobin (MCH)[33]

End point description:

Blood samples were collected for the analysis of hematology parameters including MCH at indicated timepoints. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56 and 83

Notes:

[33] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[34]			
Units: Picograms				
arithmetic mean (standard deviation)				
Day 14, n= 5	0.10 (± 0.485)			
Day 28, n= 4	-0.15 (± 0.676)			
Day 56, n= 4	-0.43 (± 0.763)			
Day 83, n= 4	-0.47 (± 0.525)			

Notes:

[34] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline for hematology parameter: Red Blood Cell Count

End point title	Change from Baseline for hematology parameter: Red Blood Cell Count[35]

End point description:

Blood samples were collected for the analysis of hematology parameter: Blood Cell Count at indicated timepoints. Baseline value is defined as latest pre-dose (Day -1) assessment with a non-missing value, including those from unscheduled visits. Change from Baseline is defined as post-dose visit value minus

Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1 pre-dose) and at Days 14, 28, 56 and 83

Notes:

[35] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[36]			
Units: 10^12 cells per liter				
arithmetic mean (standard deviation)				
Day 14, n= 5	0.304 (± 0.1417)			
Day 28, n= 4	0.280 (± 0.0673)			
Day 56, n= 4	0.488 (± 0.1640)			
Day 83, n= 4	0.485 (± 0.1034)			

Notes:

[36] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in forced expiratory volume in 1 second (FEV1)

End point title	Change From Baseline in forced expiratory volume in 1 second (FEV1)[37]

End point description:

FEV1 is used to assess pulmonary function using a spirometer at indicated timepoints. Baseline value is defined as the maximum measurement of the planned pre-dose measurements on Day 1, predose. Change from Baseline is defined as post-dose visit value minus Baseline value. Spirometry assessments were performed in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.

End point type	Primary

End point timeframe:

Baseline (Day 1: pre-dose) and at Day 1: 1 Hour post-dose; Day 2: 1 Hour post-dose; Day 14: Pre-dose; Day 14: 1 Hour post-dose and Day 83: Pre-dose

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis to report

End point values	All NEMI			
Subject group type	Reporting group			
Number of subjects analysed	5[38]			
Units: Liters				
arithmetic mean (standard deviation)				
Day 1, 1 Hour post-dose	0.226 (± 0.2166)			

Day 2, 1 Hour post-dose	0.290 (± 0.2884)			
Day 14, Pre-dose	-0.165 (± 0.5024)			
Day 14, 1 Hour post-dose	0.016 (± 0.4812)			
Day 83, Pre-dose	-0.002 (± 0.4584)			

Notes:

[38] - All Subjects Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration Following Administration of NEMI

End point title	Plasma Concentration Following Administration of NEMI

End point description:

Blood samples for pharmacokinetic analysis was collected at the indicated time points following administration of NEMI. 99999 indicates that standard deviation could not be calculated as a single participant was analyzed. Only those participants with data available at specified time point were analyzed (represented by n=X in category titles). Pharmacokinetic (PK) Population consisted of all participants in the 'All Subjects' population who had at least 1 non-missing PK assessment.

End point type	Secondary

End point timeframe:

Day 1: Pre-dose, 5 minutes, 3 hours and 24 hours post-dose; Day 14 and 83: pre-dose

End point values	NEMI 1000 mcg Via DISKUS	NEMI 700 mcg Via ELLIPTA	NEMI 500 mcg Via ELLIPTA	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1[39]	1	3	
Units: Picograms per milliliter				
arithmetic mean (standard deviation)				
Day 1: Pre-dose; n=1,1,3	0.00 (± 99999)	0.00 (± 99999)	0.00 (± 0.00)	
Day 1: 5 minutes post-dose; n=1,1,3	467.00 (± 99999)	1524.70 (± 99999)	658.27 (± 394.468)	
Day 1: 3 hours post-dose; n=1,1,3	895.10 (± 99999)	568.60 (± 99999)	397.07 (± 172.226)	
Day 1: 24 hours post-dose; n=1,1,3	444.40 (± 99999)	304.90 (± 99999)	198.17 (± 82.442)	
Day 14: Pre-dose; n=1,1,3	1396.70 (± 99999)	1242.60 (± 99999)	750.83 (± 526.337)	
Day 83: Pre-dose; n=0,1,3	0 (± 0)	1419.60 (± 99999)	1525.83 (± 1181.340)	

Notes:

[39] - PK Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Non-serious and serious adverse events were collected up to 7.5 months	
Adverse event reporting additional description:	
Non-serious and serious adverse events were collected in the All Subjects population. NEMI DISKUS and NEMI ELLIPTA were combined as All NEMI treatment group as there was no intent to compare two dose levels or devices.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	All NEMI
Reporting group description:	
Participants were administered with either NEMI 1000 mcg using DISKUS DPI or NEMI 700 or 500 mcg using ELLIPTA DPI once daily in the morning. NEMI DISKUS and NEMI ELLIPTA were combined as All NEMI treatment group	

Serious adverse events	All NEMI		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All NEMI		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Nervous system disorders			

Headache			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	22		
Migraine			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Feeling hot			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Feeling of body temperature change			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Swelling face			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	4		
Abdominal discomfort			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	3		

Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Abdominal tenderness			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pleuritic pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Rhinorrhoea			

subjects affected / exposed occurrences (all) Wheezing subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2 1 / 5 (20.00%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Fungal skin infection subjects affected / exposed occurrences (all) Skin bacterial infection subjects affected / exposed occurrences (all)	 3 / 5 (60.00%) 7 1 / 5 (20.00%) 2 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1		
Product issues Product taste abnormal subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1		

Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vitamin B complex deficiency			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2016	Minor change to exploratory efficacy endpoint; Reference to randomisation of subjects removed; Mitigation strategy of the APDS exacerbation risk has been updated; Removal of instruction on the need for precautionary measures (following new non-clinical data supporting the discharge of this risk to humans); Inclusion/Exclusion criteria has been modified; Time and Events Table for Screening and Run-in Period updated; Laboratory tests has been amended; Removal of 'severity of infection' as a measurement taken during the screening and critical baseline assessments; Clarification of the period during which details of pregnancies in female subjects will be collected after the start of dosing; Additional text added to clarify which lung lobe will be targeted during BAL procedure; Additional text added to analysis section to clarify the timing of reporting of exploratory biomarker data.
02 November 2016	Replaced administration of GSK2269557 via the DISKUS device (1000µg) by a comparable dose administered via the ELLIPTA device (700µg); Included patients with APDS1 with new disease-associated mutations and APDS2 with mutations in the PIK3R1 regulatory subunit of class IA phosphoinositide 3 kinases; Administrative changes and clarifications.
15 June 2018	Replaced administration of nemiralisib in a blend containing 0.6% MgSt, via a dry powder ELLIPTA inhaler (700 µg) by a comparable dose nemiralisib in a blend containing 0.4% magnesium stearate (MgSt) administered via the ELLIPTA device (500µg); Exploratory Phamacodynamics endpoint Volatile Organic Chemicals (VOCs);analysis in breath removed as capabilities not available at study site; Risk assessment table updated with post inhalation cough; Modified inclusion/exclusion criteria; Dose reduction removed as dose strength is 500µg/blister; Time and Event schedule visit window added to Follow Up Visit; Administrative changes, including change from the compound number GSK2269557 to the INN nemiralisib, corrections, relevant updates

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported