Clinical trial results:
An Open-Label, Two-Period, Randomized, Crossover Study to Assess the Relative Bioavailability of GSK1120212 Tablet Formulation and the GSK1120212 Pediatric Oral Solution Formulation Following Single-Dose Administration to Adult Subjects with Solid Tumors

Summary

EudraCT number	2011-004901-25
Trial protocol	Outside EU/EEA
Global end of trial date	12 November 2012

Results information

Result version number	v1 (current)
This version publication date	08 March 2016
First version publication date	24 February 2015

Trial information

Trial identification

Sponsor protocol code	MEK115892

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	26 March 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 November 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the relative bioavailability of 2mg GSK1120212 pediatric oral solution formulation to 2mg of the tablet formulation of GSK1120212 in fasted subjects.

Protection of trial subjects:

The safety assessments included monitoring of adverse events (AEs) and SAEs, clinical laboratory tests, vital signs, electrocardiograms (ECGs), MUGA/ECHO, physical examinations, and ophthalmologic examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	16
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)	9
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of 2 treatment periods separated by an incomplete wash-out period of 7 days, and a follow-up period. Sixteen participants were randomized to one of the two treatment sequences in this crossover study.

Period 1

Period 1 title	Period 1- 7 days with incomplete washout
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2

Arm description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 milligrams (mg) tablet formulation with 240 milliliters (ml) of water. Period 1 also consisted of a 7-day pharmacokinetic (PK) sampling/incomplete wash-out period following dosing. In Period 2, after an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric oral solution (OS) formulation administered with a graduated syringe and were required to drink 100 ml of water following dosing. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Arm type	Experimental
Investigational medicinal product name	GSK1120212 (trametinib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single 2 mg tablet oral dose taken with 240 ml of water

Investigational medicinal product name	GSK1120212 (trametinib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Single 2 mg solution oral dose

Arm title	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2

Arm description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric solution formulation administered with a graduated syringe and were required to drink 100 ml of water. Period 1 also consisted of a 7-day PK sampling/incomplete wash-out period following dosing. In Period 2 participants received a single dose of GSK1120212 2 mg tablet formulation with 240 ml of water following an overnight fast of at least 8 hours. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Arm type	Experimental

Investigational medicinal product name	GSK1120212 (trametinib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single 2 mg tablet oral dose taken with 240 ml of water

Investigational medicinal product name	GSK1120212 (trametinib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Single 2 mg solution oral dose

Number of subjects in period 1	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2
Started	8	8
Completed	8	8

Period 2

Period 2 title	Period 2 (7 days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2

Arm description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 milligrams (mg) tablet formulation with 240 milliliters (ml) of water. Period 1 also consisted of a 7-day pharmacokinetic (PK) sampling/incomplete wash-out period following dosing. In Period 2, after an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric oral solution (OS) formulation administered with a graduated syringe and were required to drink 100 ml of water following dosing. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Arm type	Experimental
Investigational medicinal product name	GSK1120212 (trametinib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: Single 2 mg tablet oral dose taken with 240 ml of water	
Investigational medicinal product name	GSK1120212 (trametinib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use
Dosage and administration details: Single 2 mg solution oral dose	
Arm title	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2
Arm description: In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric solution formulation administered with a graduated syringe and were required to drink 100 ml of water. Period 1 also consisted of a 7-day PK sampling/incomplete wash-out period following dosing. In Period 2 participants received a single dose of GSK1120212 2 mg tablet formulation with 240 ml of water following an overnight fast of at least 8 hours. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.	
Arm type	Experimental
Investigational medicinal product name	GSK1120212 (trametinib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Single 2 mg tablet oral dose taken with 240 ml of water	
Investigational medicinal product name	GSK1120212 (trametinib)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use
Dosage and administration details: Single 2 mg solution oral dose	

Number of subjects in period 2	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2
Started	8	8
Completed	8	8

Baseline characteristics

Reporting groups

Reporting group title	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2

Reporting group description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 milligrams (mg) tablet formulation with 240 milliliters (ml) of water. Period 1 also consisted of a 7-day pharmacokinetic (PK) sampling/incomplete wash-out period following dosing. In Period 2, after an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric oral solution (OS) formulation administered with a graduated syringe and were required to drink 100 ml of water following dosing. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Reporting group title	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2

Reporting group description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric solution formulation administered with a graduated syringe and were required to drink 100 ml of water. Period 1 also consisted of a 7-day PK sampling/incomplete wash-out period following dosing. In Period 2 participants received a single dose of GSK1120212 2 mg tablet formulation with 240 ml of water following an overnight fast of at least 8 hours. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Reporting group values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2	Total
Number of subjects	8	8	16
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.1	57.4	
standard deviation	± 13.07	± 16.66	-
Gender categorical Units: Subjects			
Female	4	5	9
Male	4	3	7
Race Units: Subjects			
White - White/Caucasian/European Heritage	8	8	16

End points

End points reporting groups

Reporting group title	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2

Reporting group description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 milligrams (mg) tablet formulation with 240 milliliters (ml) of water. Period 1 also consisted of a 7-day pharmacokinetic (PK) sampling/incomplete wash-out period following dosing. In Period 2, after an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric oral solution (OS) formulation administered with a graduated syringe and were required to drink 100 ml of water following dosing. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Reporting group title	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2

Reporting group description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric solution formulation administered with a graduated syringe and were required to drink 100 ml of water. Period 1 also consisted of a 7-day PK sampling/incomplete wash-out period following dosing. In Period 2 participants received a single dose of GSK1120212 2 mg tablet formulation with 240 ml of water following an overnight fast of at least 8 hours. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Reporting group title	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2

Reporting group description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 milligrams (mg) tablet formulation with 240 milliliters (ml) of water. Period 1 also consisted of a 7-day pharmacokinetic (PK) sampling/incomplete wash-out period following dosing. In Period 2, after an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric oral solution (OS) formulation administered with a graduated syringe and were required to drink 100 ml of water following dosing. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Reporting group title	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2

Reporting group description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric solution formulation administered with a graduated syringe and were required to drink 100 ml of water. Period 1 also consisted of a 7-day PK sampling/incomplete wash-out period following dosing. In Period 2 participants received a single dose of GSK1120212 2 mg tablet formulation with 240 ml of water following an overnight fast of at least 8 hours. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Subject analysis set title	GSK1120212 tablet
Subject analysis set type	Full analysis

Subject analysis set description:

Following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 milligrams (mg) tablet formulation with 240 milliliters (ml) of water. Period 1 also consisted of a 7-day pharmacokinetic (PK) sampling/incomplete wash-out period following dosing.

Subject analysis set title	GSK1120212 pediatric oral solution
Subject analysis set type	Full analysis

Subject analysis set description:

Following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric solution formulation administered with a graduated syringe and were required to drink 100 ml of water. Period 1 also consisted of a 7-day PK sampling/incomplete wash-out period following dosing.

Primary: Area under the plasma concentration-time curve from zero to 24 hours AUC(0-24) of plasma GSK1120212 following a single dose administration in Period 1, Period 2 and combined periods

End point title	Area under the plasma concentration-time curve from zero to 24 hours AUC(0-24) of plasma GSK1120212 following a single dose administration in Period 1, Period 2 and combined periods[1]

End point description:

AUC is defined as the area under the drug concentration-time curve and is a measure of drug

concentration. Blood samples were collected at the following time points: pre-dose and 0, 0.25, 0.5, 1, 2, 2.5, 3, 4, 6, 6.5, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours in both Period 1 and Period 2. Pharmacokinetic (PK) Population is defined as all participants who received study medication, for whom a PK blood sample was obtained and analyzed.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

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: The Geometric Mean Ratio and the CI was not calculated for the uncorrected AUC.

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[2]	8[3]		
Units: nanograms*hours/milliliter (ng*hr/mL)				
geometric mean (geometric coefficient of variation)				
AUC(0-24), Period 1	49.542 (± 35.233)	64.7164 (± 67.275)		
AUC(0-24), Period 2	98.8235 (± 63.104)	100.5039 (± 35.545)		
AUC(0-24), Combined	69.9708 (± 63.435)	80.6489 (± 57.01)		

Notes:

[2] - PK Population

[3] - PK Population

Statistical analyses

No statistical analyses for this end point

Primary: Corrected AUC(0-24) (CorrAUC[0-24]) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point title	Corrected AUC(0-24) (CorrAUC[0-24]) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point description:

Corrected area under the plasma concentration-time curve CorrAUC(0-24) for P2 was calculated as corrAUC(0-24) = AUC(0-24)(P2) – extrapAUC(P1) where in extrapAUC(P1) was the extrapolated AUC from P1. ExtrapAUC(P1) was calculated as extrapAUC(P1) = AUC(0-infinity)(P1) - AUC(0-t)(P1), where the last time point was pre-dose from P2. Blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 hours post-dose in Period 1 (P1) and Period 2 (P2).

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[4]	8[5]		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Period 1	49.542 (± 35.233)	64.7164 (± 67.275)		
Period 2	78.5862 (± 68.192)	83.7081 (± 35.882)		
Combined	62.3965 (± 57.954)	73.6022 (± 53.102)		

Notes:

[4] - PK Population

[5] - PK Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK1120212 tablet v GSK1120212 pediatric oral solution
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	Mixed Effects Model
Point estimate	1.1796
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.0493
upper limit	1.3261

Notes:

[6] - Corrected PK parameters were used for the statistical analysis

Primary: AUC extrapolated to infinity (0-infinity) following a single dose administration of GSK1120212 in Period 1, Period 2 and combined periods

End point title	AUC extrapolated to infinity (0-infinity) following a single dose administration of GSK1120212 in Period 1, Period 2 and combined periods[7]

End point description:

AUC(0-infinity) was calculated as the sum of AUC(0-t) and Ct/lambda z, where Ct was the observed concentration obtained from the log-linear regression analysis of the last quantifiable time-point and lambda z was the terminal phase rate constant. Blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both P1 and P2.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

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: The Geometric Mean Ratio and the CI was not calculated for the uncorrected AUC.

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[8]	8[9]		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Period 1	364.3343 (± 34.105)	436.6415 (± 48.187)		
Period 2	597.7219 (± 48.463)	572.8397 (± 30.003)		
Combined	466.659 (± 48.995)	500.1256 (± 41.276)		

Notes:

[8] - PK Population

[9] - PK Population

Statistical analyses

No statistical analyses for this end point

Primary: CorrAUC(0-infinity) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point title	CorrAUC(0-infinity) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point description:

Corrected AUC(0-infinity) for Period 2 was calculated as corrAUC(0-infinity)=AUC(0-infinity), Period 2 - extrap AUC, Period 1 (extrapolated AUC from Period 1) where extrap AUC, Period 1=AUC(0-infinity), Period 1- AUC(0-last), Period 1 where last time point is predose from Period 2. Blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both P1 and P2.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[10]	8[11]		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Period 1	364.3343 (± 34.105)	436.6415 (± 48.187)		
Period 2	394.665 (± 60.935)	409.9326 (± 27.342)		
Combined	379.1965 (± 47.107)	423.0763 (± 37.587)		

Notes:

[10] - PK Population

[11] - PK Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK1120212 tablet v GSK1120212 pediatric oral solution
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[12]
Parameter estimate	Mixed Effects Model
Point estimate	1.1157
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.0043
upper limit	1.2394

Notes:

[12] - Corrected PK parameters were used for the statistical analysis

Primary: AUC to the last quantifiable concentration (0-last) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point title	AUC to the last quantifiable concentration (0-last) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods[13]

End point description:

AUC(0-last) was determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations. Blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both P1 and P2.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

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: The Geometric Mean Ratio and the CI was not calculated for the uncorrected AUC.

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[14]	8[15]		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Period 1	200.7343 (± 33.649)	238.6422 (± 60.676)		
Period 2	389.5295 (± 54.163)	379.9972 (± 33.682)		

Combined	279.6282 (± 57.692)	301.1368 (± 53.792)		

Notes:

[14] - PK Population

[15] - PK Population

Statistical analyses

No statistical analyses for this end point

Primary: CorrAUC(0-last) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point title	CorrAUC(0-last) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point description:

CorrAUC(0-last) for P2 was calculated as corrAUC(0- last) = AUC(0- last)(P2) – extrapAUC(P1) where in extrapAUC(P1) was the extrapolated AUC from P1. ExtrapAUC(P1) was calculated as extrapAUC(P1) = AUC(0-infinity)(P1) - AUC(0-last)(P1), where the last time point is pre-dose from P2. Blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both P1 and P2.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[16]	8[17]		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Period 1	200.7343 (± 33.649)	238.6422 (± 60.676)		
Period 2	288.8255 (± 57.874)	293.8191 (± 33.148)		
Combined	240.7845 (± 49.627)	264.7974 (± 47.889)		

Notes:

[16] - PK Population

[17] - PK Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK1120212 tablet v GSK1120212 pediatric oral solution

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[18]
Parameter estimate	Mixed Effects Model
Point estimate	1.0997
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.0331
upper limit	1.1706

Notes:

[18] - Corrected PK parameters were used for the statistical analysis

Primary: First occurrence of the maximum observed concentration (Cmax) values following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point title	First occurrence of the maximum observed concentration (Cmax) values following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods[19]

End point description:

Cmax was determined directly from the raw concentration-time data. Blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both P1 and P2.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

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: The Geometric Mean Ratio and the CI was not calculated for the uncorrected Cmax.

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[20]	8[21]		
Units: nanograms/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Period 1	6.0255 (± 81.291)	10.7118 (± 72.805)		
Period 2	8.8983 (± 67.572)	13.7994 (± 41.345)		
Combined	7.3224 (± 75.677)	12.158 (± 57.913)		

Notes:

[20] - PK Population

[21] - PK Population

Statistical analyses

No statistical analyses for this end point

Primary: Corrected Cmax (CorrCmax) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point title	Corrected Cmax (CorrCmax) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point description:

CorrCmax for P2 was calculated as, corrCmax = Cmax, observed, P2 - Cpred, tmax where Cpred, tmax (predicted concentration at tmax [P2]) was calculated as Cpred, tmax = C0, P2*exp(-lambda z[P1]*tmax [P2]), where C0 = pre-dose concentrations from P2, lambda z was the elimination rate constant from P1 and tmax was observed time of Cmax from P2. Blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both P1 and P2.

End point type	Primary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[22]	8[23]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Period 1	6.0255 (± 81.291)	10.7118 (± 72.805)		
Period 2	7.9531 (± 71.818)	13.0262 (± 42.625)		
Combined	6.9225 (± 75.531)	11.8124 (± 57.608)		

Notes:

[22] - PK Population

[23] - PK Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK1120212 pediatric oral solution v GSK1120212 tablet
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority[24]
Parameter estimate	Mixed Effects Model
Point estimate	1.7064
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.2278
upper limit	2.3715

Notes:

[24] - Corrected PK parameters were used for the statistical analysis

Secondary: Apparent terminal elimination half-life (t1/2) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point title	Apparent terminal elimination half-life (t1/2) following a single

	dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point description:

t1/2 was obtained as the ratio of log-linear regression analysis of the last quantifiable time-point and the terminal phase rate constant (ln2/lambda z). Blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both P1 and P2.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[25]	8[26]		
Units: hour (hr)				
geometric mean (geometric coefficient of variation)				
Period 1	152.2262 (± 15.906)	150.9817 (± 36.013)		
Period 2	109.7371 (± 21.946)	108.4432 (± 19.551)		
Combined	129.2473 (± 25.328)	127.9568 (± 33.042)		

Notes:

[25] - PK Population

[26] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time at which Cmax is observed (Tmax) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point title	Time at which Cmax is observed (Tmax) following a single dose administration of GSK1120212 2 mg in Period 1, Period 2 and combined treatment periods

End point description:

Tmax was determined directly from the raw concentration-time data. Blood samples were collected at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both P1 and P2.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 96 and 168 hours post-dose in both treatment periods

End point values	GSK1120212 tablet	GSK1120212 pediatric oral solution		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[27]	8[28]		
Units: Hr				
geometric mean (geometric coefficient of variation)				
Period 1	2.3627 (± 112.408)	0.8857 (± 55.566)		
Period 2	1.9805 (± 59.933)	0.8387 (± 30.76)		
Combined	2.1632 (± 83.882)	0.8619 (± 42.848)		

Notes:

[27] - PK Population

[28] - PK Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK1120212 tablet v GSK1120212 pediatric oral solution
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (net)
Point estimate	-1.483325
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.77495
upper limit	-0.5333

Secondary: Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point description:

An AE was defined as 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 was defined as any untoward medical occurrence that, at any dose, resulted in death, was life threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, was a congenital anomaly/birth defect, or was an event of possible drug-induced liver injury. All-Treated Population is defined as all participants who received at least one dose of any study treatment.

End point type	Secondary

End point timeframe:

From the start of study treatment until 30 days after the last dose of study treatment (up to approximately 40 days)

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[29]	8[30]		
Units: Participants				
Any AE	4	6		
Any SAE	0	0		

Notes:

[29] - All-Treated Population

[30] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean basophils, eosinophils, lymphocytes, monocytes, total absolute neutrophil count (ANC) and white blood cell (WBC) count at Screening and Day 1 of each treatment period

End point title	Mean basophils, eosinophils, lymphocytes, monocytes, total absolute neutrophil count (ANC) and white blood cell (WBC) count at Screening and Day 1 of each treatment period

End point description:

Blood samples were collected for the measurement of basophils, eosinophils, lymphocytes, monocytes, Total ANC and WBC at Screening and Day 1 of each treatment period. All-Treated Population: 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[31]	8[32]		
Units: Giga (10^9) cells per liter				
arithmetic mean (standard deviation)				
Basophils, Screening, n=8, 8	0.0393 (± 0.04345)	0.0933 (± 0.09513)		
Basophils, Period 1, n=4,5	0 (± 0)	0.0515 (± 0.05011)		
Basophils, Period 2, n=7,7	0.1005 (± 0.10715)	0.0851 (± 0.0948)		
Eosinophils, Screening, n=8, 8	0.2035 (± 0.03896)	0.2548 (± 0.32471)		
Eosinophils, Period 1, n=4,5	0.175 (± 0.09574)	0.1218 (± 0.16276)		
Eosinophils, Period 2, n=7,7	0.2167 (± 0.07304)	0.2253 (± 0.24651)		

Lymphocytes, Screening, n=8, 8	1.5122 (± 0.68398)	1.3858 (± 0.79946)		
Lymphocytes, Period 1, n=4,5	1.425 (± 0.80571)	1.4825 (± 0.87552)		
Lymphocytes, Period 2, n=7,7	1.4552 (± 0.83932)	1.3457 (± 0.59371)		
Monocytes, Screening, n=8, 8	0.5772 (± 0.18387)	0.6685 (± 0.20024)		
Monocytes, Period 1, n=4,5	0.55 (± 0.1291)	0.845 (± 0.30842)		
Monocytes, Period 2, n=7,7	0.4913 (± 0.19271)	0.542 (± 0.15878)		
Platelet count, Screening, n=8, 8	261.3 (± 88.49)	264.6 (± 80.23)		
Platelet count, Period 1, n=4,5	202 (± 29.64)	320 (± 74.4)		
Platelet count, Period 2, n=7,7	253.9 (± 79.71)	253.9 (± 73.33)		
Total ANC, Screening, n=8, 8	5.0948 (± 2.66263)	5.9603 (± 1.81951)		
Total ANC, Period 1, n=4,5	4 (± 1.95789)	7.2 (± 2.28145)		
Total ANC, Period 2, n=7,7	4.1288 (± 1.58216)	5.8857 (± 2.50171)		
WBC, Screening, n=8, 8	7.43 (± 2.989)	8.36 (± 2.292)		
WBC, Period 1, n=4,5	6.15 (± 2.042)	9.7 (± 2.511)		
WBC, Period 2, n=7,7	6.47 (± 2.26)	8.09 (± 2.822)		

Notes:

[31] - All-Treated Population

[32] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean hemoglobin and mean corpuscular hemoglobin concentration (MCHC) at Screening and Day 1 of each treatment period

End point title	Mean hemoglobin and mean corpuscular hemoglobin concentration (MCHC) at Screening and Day 1 of each treatment period

End point description:

Blood samples were collected for the measurement of hemoglobin and MCHC at Screening and Day 1 of each treatment period. The MCH concentration is the average concentration of hemoglobin in a red blood cell. Hemoglobin is the red pigment in the blood, and it is reponsible for carrying oxygen. 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[33]	8[34]		
Units: Grams per liter (G/L)				
arithmetic mean (standard deviation)				
Hemoglobin, Screening, n=8, 8	128.6 (± 15.98)	113 (± 11.81)		
Hemoglobin, Period 1, n=4,5	131.5 (± 15.93)	108 (± 14.78)		
Hemoglobin, Period 2, n=7,7	120 (± 16.34)	109.9 (± 9.34)		
MCHC, Screening, n=8, 8	329.4 (± 6.93)	328.9 (± 6.36)		
MCHC, Period 1, n=4,5	329 (± 3.56)	330.6 (± 6.69)		
MCHC, Period 2, n=7,7	331 (± 5.66)	327.1 (± 8.09)		

Notes:

[33] - All-Treated Population

[34] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Corpuscle Hemoglobin (MCH) values at Screening and Day 1 of each treatment period

End point title	Mean Corpuscle Hemoglobin (MCH) values at Screening and Day 1 of each treatment period

End point description:

Blood samples were collected for the measurement of MCH values at Screening and Day 1 of each treatment period. MCH is the average mass or amount of hemoglobin per red blood cell in a sample of blood. 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population .

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[35]	8[36]		
Units: Picograms (PG)				
arithmetic mean (standard deviation)				
MCH, Screening, n=8, 8	29.81 (± 2.092)	28.9 (± 2.026)		
MCH, Period 1, n=4,5	31.43 (± 1.179)	28.28 (± 2.413)		
MCH, Period 2, n=7,7	29.69 (± 2.084)	28.84 (± 2.025)		

Notes:

[35] - All-Treated Population

[36] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean corpuscular volume (MCV) value at Screening and Day 1 of each treatment period

End point title	Mean corpuscular volume (MCV) value at Screening and Day 1 of each treatment period

End point description:

Blood samples were collected for the measurement of MCV values at Screening and Day 1 of each treatment period. MCV is a measure of the average red blood cell size that is reported as part of a standard complete blood count. 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[37]	8[38]		
Units: Femtoliters (10^15Liter) (F/L)				
arithmetic mean (standard deviation)				
MCV, Screening, n=8, 8	90.6 (± 6.102)	87.9 (± 5.955)		
MCV, Period 1, n=4,5	95.75 (± 3.775)	85.56 (± 6.178)		
MCV, Period 2, n=7,7	89.77 (± 6.219)	88.16 (± 6.097)		

Notes:

[37] - All-Treated Population

[38] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean hematocrit values at Screening and Day 1 of each treament period

End point title	Mean hematocrit values at Screening and Day 1 of each treament period

End point description:

Blood samples were collected for the measurement of hematocrit values at Screening and Day 1 of each treatment period. The hematocrit is the percentage of the RBCs in the blood. 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[39]	8[40]		
Units: percentage of RBCs				
arithmetic mean (standard deviation)				
Hematocrit, Screening, n=8, 8	0.3895 (± 0.04288)	0.3434 (± 0.03187)		
Hematocrit, Period 1, n=4,5	0.4 (± 0.05105)	0.3258 (± 0.041)		
Hematocrit, Period 2, n=7,7	0.3619 (± 0.04822)	0.3357 (± 0.0258)		

Notes:

[39] - All-Treated Population

[40] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean calcium, chloride, carbon dioxide content (CO2)/bicarbonate, glucose, potassium, magnesium, phosphorus, sodium and urea/blood urea nitrogen (BUN) values at Screening and Day 1 of each treatment period

End point title	Mean calcium, chloride, carbon dioxide content (CO2)/bicarbonate, glucose, potassium, magnesium, phosphorus, sodium and urea/blood urea nitrogen (BUN) values at Screening and Day 1 of each treatment period

End point description:

Samples were collected for the measurement of Calcium, Chloride, CO2/Bicarbonate, Glucose, Potassium, Magnesium, Phosphorus, Sodium and Urea/BUN values at Screening and Day 1 of each treatment period. 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[41]	8[42]		
Units: Millimoles per liter (MMOL/L)				
arithmetic mean (standard deviation)				
Calcium, Screening, n=8, 8	2.3204 (± 0.11703)	2.2112 (± 0.2009)		
Calcium, Period 1, n=4,5	2.1457 (± 0.07345)	2.2006 (± 0.21993)		
Calcium, Period 2, n=7,7	2.2705 (± 0.08399)	2.1885 (± 0.09304)		
CO2/Bicarbonate, Screening, n=8, 8	27.5 (± 1.93)	26.8 (± 4.03)		
CO2/Bicarbonate, Period 1, n=4,5	27.3 (± 2.06)	27.6 (± 2.79)		
CO2/Bicarbonate, Period 2, n=7,7	27.1 (± 3.08)	27.4 (± 2.82)		
Chloride, Screening, n=8, 8	100.4 (± 3.46)	102 (± 4.75)		
Chloride, Period 1, n=4,5	103 (± 2.16)	101 (± 3.87)		
Chloride, Period 2, n=7,7	101.3 (± 3.5)	103.1 (± 4.74)		
Glucose, Screening, n=8, 8	5.5371 (± 1.13636)	6.4392 (± 2.12973)		
Glucose, Period 1, n=4,5	4.9959 (± 0.41292)	5.3845 (± 1.14235)		
Glucose, Period 2, n=7,7	5.0514 (± 0.31072)	6.4074 (± 3.17862)		
Magnesium, Screening, n=8, 8	0.7655 (± 0.06189)	0.7449 (± 0.06381)		
Magnesium, Period 1, n=4,5	0.7295 (± 0.06165)	0.7069 (± 0.11769)		
Magnesium, Period 2, n=7,7	0.7398 (± 0.0411)	0.7398 (± 0.10067)		
Phosphorus, Screening, n=8, 8	1.1947 (± 0.1802)	1.0736 (± 0.21401)		
Phosphorus, Period 1, n=4,5	1.0817 (± 0.24521)	1.072 (± 0.31588)		
Phosphorus, Period 2, n=7,7	1.2685 (± 0.14997)	1.0794 (± 0.23274)		
Potassium, Screening, n=8, 8	4.05 (± 0.689)	4.06 (± 0.58)		
Potassium, Period 1, n=4,5	4 (± 0.374)	3.72 (± 0.665)		
Potassium, Period 2, n=7,7	4.06 (± 0.58)	4.04 (± 0.395)		
Sodium, Screening, n=8, 8	138.8 (± 2.25)	137.4 (± 3.11)		
Sodium, Period 1, n=4,5	140 (± 2)	136.6 (± 1.82)		
Sodium, Period 2, n=7,7	138.3 (± 1.8)	138.6 (± 3.21)		
Urea/BUN, Screening, n=8, 8	6.2029 (± 2.05469)	4.5071 (± 1.8297)		
Urea/BUN, Period 1, n=4,5	6.5153 (± 1.94174)	5.355 (± 1.87212)		
Urea/BUN, Period 2, n=7,7	6.069 (± 1.69966)	4.539 (± 2.04785)		

Notes:

[41] - All-Treated Population

[42] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean total bilirubin, uric acid and creatinine values at Screening and Day 1 of each treatment period

End point title	Mean total bilirubin, uric acid and creatinine values at Screening and Day 1 of each treatment period

End point description:

Blood samples were collected for the measurement of total bilirubin, uric acid, creatinine values at screening and Day 1 of each treatment period. 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[43]	8[44]		
Units: micromoles per liter (UMOL/L)				
arithmetic mean (standard deviation)				
Creatinine, Screening, n=8, 8	92.9305 (± 33.00339)	68.6205 (± 20.65577)		
Creatinine, Period 1, n=4,5	83.98 (± 21.04341)	69.6592 (± 11.08354)		
Creatinine, Period 2, n=7,7	86.1269 (± 26.80264)	64.4057 (± 12.95624)		
Total bilirubin, Screening, n=8, 8	11.756 (± 3.3506)	10.474 (± 3.473)		
Total bilirubin, Period 1, n=4,5	12.398 (± 4.4972)	11.286 (± 3.1064)		
Total bilirubin, Period 2, n=7,7	10.749 (± 3.9137)	8.794 (± 2.3003)		
Uric acid, Screening, n=8, 8	335.3185 (± 110.3161)	300.374 (± 64.92395)		
Uric acid, Period 1, n=4,5	336.062 (± 31.28595)	302.1584 (± 24.30688)		
Uric acid, Period 2, n=7,7	344.1343 (± 111.8808)	329.6891 (± 53.18469)		

Notes:

[43] - All-Treated Population

[44] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean albumin and total protein values at Screening and Day 1 of each treatment period

End point title	Mean albumin and total protein values at Screening and Day 1 of each treatment period

End point description:

Blood samples were collected for the measurement of albumin and total protein values at Screening and Day 1 of each treatment period . 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[45]	8[46]		
Units: Grams per liter (G/L)				
arithmetic mean (standard deviation)				
Albumin, Screening, n=8, 8	40.9 (± 3.04)	36.4 (± 3.29)		
Albumin, Period 1, n=4,5	41.3 (± 1.26)	35.2 (± 3.11)		
Albumin, Period 2, n=7,7	38.9 (± 3.72)	34.4 (± 2.3)		
Total Protein, Screening, n=8, 8	66.3 (± 5.06)	62 (± 6.28)		
Total Protein, Period 1, n=4,5	62 (± 1.15)	59.4 (± 5.59)		
Total Protein, Period 2, n=7,7	64.4 (± 2.7)	59.6 (± 3.64)		

Notes:

[45] - All-Treated Population

[46] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean alkaline phosphatase (ALP), alanine amino transferase (ALT) and aspartate amino transferase (AST) values at Screening and Day 1 of each treatment period

End point title	Mean alkaline phosphatase (ALP), alanine amino transferase (ALT) and aspartate amino transferase (AST) values at Screening and Day 1 of each treatment period

End point description:

Blood samples were collected for the measurement of ALP, ALT and AST values at Screening and Day 1 of each treatment period. 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[47]	8[48]		
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
ALP, Screening, n=8, 8	84.5 (± 18.63)	184.8 (± 161.56)		
ALP, Period 1, n=4,5	66.8 (± 11.5)	108.2 (± 46.5)		
ALP, Period 2, n=7,7	82.7 (± 18.14)	180.9 (± 130.94)		
AST, Screening, n=8, 8	22.9 (± 10.99)	33.6 (± 24.97)		
AST, Period 1, n=4,5	17 (± 2.58)	27 (± 18.53)		
AST, Period 2, n=7,7	26 (± 14.47)	37.7 (± 24.45)		
ALT, Screening, n=8, 8	21.6 (± 7.13)	29 (± 17.82)		
ALT, Period 1, n=4,5	16.3 (± 1.71)	27.6 (± 16.29)		
ALT, Period 2, n=7,7	22.3 (± 8.06)	24.9 (± 16.72)		

Notes:

[47] - All-Treated Population

[48] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean creatinine clearance values estimated using Cockcroft-Gault formula at Screening and Day 1 of each treatment period

End point title	Mean creatinine clearance values estimated using Cockcroft-Gault formula at Screening and Day 1 of each treatment period

End point description:

Creatinine Clearance was estimated using Cockcroft-Gault formula. The Cockcroft-Gault formula estimates creatinine clearance without correction for body surface area (BSA) and is based on predicting the daily urine creatinine excretion using the age, weight and sex of the participant. 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population. A Standard Deviation = 0 is entered because there were were too few participants to provide the SD.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[49]	8[50]		
Units: milliliters/minute (mL/min)				
arithmetic mean (standard deviation)				

Creatinine clearence, Screening, n=8,7	75.715 (± 35.2201)	107.219 (± 46.1563)		
Creatinine clearence, Period 1, n=1,3	43.3 (± 0)	99.947 (± 32.2818)		
Creatinine clearence, Period 2, n=4,5	73.078 (± 36.9831)	67.234 (± 53.0275)		

Notes:

[49] - All-Treated Population

[50] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean systolic and diastolic blood pressure (BP) at Screening and Day 1 of each treatment period

End point title	Mean systolic and diastolic blood pressure (BP) at Screening and Day 1 of each treatment period

End point description:

Vital sign monitoring included systolic and diastolic BP measurements. BP measurements were taken in semi-supine position after 5 minutes (min) of rest. Measurements were taken at Screening and Day 1 of each treatment period.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[51]	8[52]		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Diastolic BP, Screening	75.8 (± 11.87)	71.6 (± 8.53)		
Diastolic BP, Period 1	75.6 (± 8.98)	75.1 (± 9.7)		
Diastolic BP, Period 2	74 (± 9.12)	76.4 (± 10.95)		
Systolic BP, Screening	130.3 (± 13.34)	120.5 (± 14.4)		
Systolic BP, Period 1	129.6 (± 17.26)	123.4 (± 13.07)		
Systolic BP, Period 2	131.5 (± 16.42)	121 (± 12.02)		

Notes:

[51] - All-Treated Population

[52] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean heart rate at screening and Day 1 of each treatment period

End point title	Mean heart rate at screening and Day 1 of each treatment period

End point description:

Vital sign monitoring included heart rate measurements. Heart rate was measured in semi-supine position after 5 min of rest. Measurements were taken at Screening and Day 1 of each treatment period.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[53]	8[54]		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Heart rate,Screening	83.6 (± 13.1)	82.4 (± 6.8)		
Heart rate, Period 1	83.1 (± 18.94)	80 (± 7.25)		
Heart rate, Period 2	79.1 (± 12.54)	78.5 (± 7.78)		

Notes:

[53] - All-Treated Population

[54] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean electrocardiogram (ECG) values at Screening, and Day 1 of each treatment period

End point title	Mean electrocardiogram (ECG) values at Screening, and Day 1 of each treatment period

End point description:

ECG measurements were obtained using single 12-lead ECGs at Screening and Day 1 of each treatment period. The ECG machine automatically calculated heart rate and measured the ECG parameters: PR interval, QT interval, QRS duration, QT duration corrected by Bazett’s formula (QTcB), QT duration corrected by Fridericia's formula (QTcF) and RR intervals. 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 at different time points, so the overall number of participants analyzed reflects everyone in the All-Treated Population .

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[55]	8[56]		
Units: Milliseconds (msec)				
arithmetic mean (standard deviation)				
PR Interval, Screening, n=7,8	157.7 (± 23.73)	154.6 (± 39.01)		
PR Interval, Period 1, n=4,5	165 (± 22.54)	156.8 (± 15.14)		
PR Interval, Period 2, n=7,8	164 (± 20.46)	157 (± 29.8)		
QRS duration, Screening, n=8, 8	83.8 (± 11.18)	85 (± 9.2)		
QRS duration, Period 1, n=5,5	84.8 (± 12.85)	92.8 (± 6.72)		
QRS duration, Period 2, n=8, 8	85.3 (± 9.5)	87.5 (± 10.18)		
QTcB interval, Screening, n=8, 8	422.4008 (± 27.90254)	428.1997 (± 8.68665)		
QTcB interval, Period 1, n=5,5	408.6607 (± 20.91749)	425.338 (± 12.33659)		
QTcB interval, Period 2, n=8, 8	425.481 (± 17.71296)	427.3145 (± 19.58335)		
QTcF interval, Screening, n=8, 8	407.5738 (± 20.02514)	407.5161 (± 9.84641)		
QTcF interval, Period 1, n=5,5	394.745 (± 15.76832)	409.8421 (± 9.66519)		
QTcF interval, Period 2, n=8, 8	415.4359 (± 16.85693)	411.4918 (± 15.47495)		
Uncorrected QT interval, Screening, n=8, 8	380.3 (± 25.44)	369.5 (± 18.69)		
Uncorrected QT interval, Period 1, n=5,5	368 (± 25.06)	380.4 (± 16.15)		
Uncorrected QT interval, Period 2, n=8, 8	397 (± 32.32)	381.5 (± 16.17)		

Notes:

[55] - All-Treated Population

[56] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated electrocardiogram (ECG) findings

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

End point description:

ECG measurements were obtained using single 12-lead ECGs at Screening and Day 1 of each treatment period. The ECG machine automatically calculated heart rate and measured the ECG parameters: PR interval, QT interval, QRS duration, QTcB, QTcF and RR intervals. ECG findings were categorized as: normal, abnormal - clinically significant (CS) and abnormal - not clinically significant (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 at different time points, so the overall number of participants analyzed reflects everyone in the All Treated Population.

End point type	Secondary

End point timeframe:

Screening and Day 1 of each treatment period

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[57]	8[58]		
Units: Participants				
Screening, Normal, n=8, 8	2	3		
Screening, Abnormal, NCS, n=8, 8	6	5		
Screening, Abnormal, CS, n=8, 8	0	0		
Period 1, Normal, n=5,5	1	3		
Period 1, Abnormal, NCS, n=5,5	4	2		
Period 1, Abnormal, CS, n=5,5	0	0		
Period 2, Normal, n=8, 8	1	3		
Period 2, Abnormal, NCS, n=8, 8	7	5		
Period 2, Abnormal, CS, n=8, 8	0	0		
Any time post-baseline, Normal, n=8, 8	1	3		
Any time post-baseline, Abnormal, NCS, n=8, 8	7	5		
Any time post-baseline, Abnormal, CS, n=8, 8	0	0		

Notes:

[57] - All-Treated Population

[58] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated change from Baseline in left ventricular ejection fraction (LVEF)

End point title	Number of participants with the indicated change from Baseline in left ventricular ejection fraction (LVEF)

End point description:

An echocardiography (ECHO) scan was performed to assess cardiac ejection fraction and cardiac valve morphology. Change from Baseline for LVEF was calculated as Baseline value minus Day 8 value. Baseline was defined as the value of last assessment prior to first dose in Period 1. Absolute change from Baseline for LVEF was summarized into the following categories: no change or any increase, any decrease, >0-<10 percent decrease, 10-19 % decrease, >=20% decrease, >=10% decrease and >= lower limit of normal (LLN), >=10 % decrease and below LLN, >=20 % decrease and >= LLN, >=20 decrease and below LLN.

End point type	Secondary

End point timeframe:

Baseline (Screening) and Day 8 of Period 2

End point values	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[59]	8[60]		
Units: Participants				
No change or any increase	5	5		
>0-<10 decrease	3	3		
10-19 decrease	0	0		
>=20 decrease	0	0		
>=10 decrease and >= LLN	0	0		
>=10 decrease and below LLN	0	0		
>=20 decrease and >= LLN	0	0		
>=20 decrease and below LLN	0	0		

Notes:

[59] - All-Treated Population

[60] - All-Treated Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated palatability ranking score of GSK1120212 pediatric oral solution formulation on Day 1 of Period 1 or 2

End point title	Number of participants with the indicated palatability ranking score of GSK1120212 pediatric oral solution formulation on Day 1 of Period 1 or 2

End point description:

Palatability was assessed by ranking bitterness, sweetness, aroma and overall taste on a four-point scale recorded in the electronic case report form. Bitterness and sweetness were ranked by participants on a scale of 1 to 4, with 1= barely detectable, 2= weak, 3= moderate and 4=strong. Overall taste and aroma were ranked by participants on a scale of 1 to 4, 1= bad, 2= neutral, 3= acceptable and 4=good.

End point type	Secondary

End point timeframe:

Day 1 of each treatment Period

End point values	GSK1120212 pediatric oral solution			
Subject group type	Subject analysis set			
Number of subjects analysed	16[61]			
Units: Scores on a scale				
Bitterness ranking, Barely detectable	4			
Bitterness ranking, Weak	3			
Bitterness ranking, Moderate	7			
Bitterness ranking, Strong	2			
Sweetness perceived, Barely detectable	3			
Sweetness perceived, Weak	1			
Sweetness perceived, Moderate	10			
Sweetness perceived, Strong	2			

Aroma perceived, Bad	0			
Aroma perceived, Neutral	5			
Aroma perceived, Acceptable	5			
Aroma perceived, Good	6			
Overall taste ranking, Bad	2			
Overall taste ranking, Neutral	4			
Overall taste ranking, Acceptable	9			
Overall taste ranking, Good	1			

Notes:

[61] - All-Treated 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 adverse events (AEs) were collected from the start of study treatment until 30 days after the last dose of study treatment. (up to approximately 40 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2

Reporting group description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 milligrams (mg) tablet formulation with 240 milliliters (ml) of water. Period 1 also consisted of a 7-day pharmacokinetic (PK) sampling/incomplete wash-out period following dosing. In Period 2, after an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric oral solution (OS) formulation administered with a graduated syringe and were required to drink 100 ml of water following dosing. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Reporting group title	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2

Reporting group description:

In Period 1, following an overnight fast of at least 8 hours, participants received a single dose of GSK1120212 2 mg pediatric solution formulation administered with a graduated syringe and were required to drink 100 ml of water. Period 1 also consisted of a 7-day PK sampling/incomplete wash-out period following dosing. In Period 2 participants received a single dose of GSK1120212 2 mg tablet formulation with 240 ml of water following an overnight fast of at least 8 hours. Participants were required to fast an additional 4 hours after administration of GSK1120212 in either formulation.

Serious adverse events	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	GSK1120212 tablet in Period 1; GSK1120212 OS in Period 2	GSK1120212 OS in Period 1; GSK1120212 tablet in Period 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	6 / 8 (75.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Lymphoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 8 (25.00%)	2 / 8 (25.00%)	
occurrences (all)	2	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nasal discharge discolouration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Sinus congestion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Memory impairment			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

Neuropathy peripheral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	3 / 8 (37.50%)	
occurrences (all)	0	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2012	Section 3.6 Time & Events Table Corrections Section 1.2.3 Rationale for the Study Population; pg 8 Correction to the number of AEs of special interest (6 versus 4)
23 April 2012	Change in subject population from healthy male volunteers only to male and female subjects with solid tumors. Text revised throughout the protocol to incorporate additional safety assessments (including disease assessments and evaluation of ECOG performance status), revised period of PK blood sample collection from 4 weeks to 7 days and indicated availability of the rollover study, MEK114375 for eligible subjects who completed this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported