Clinical trial results:
A Phase 1 Relative Bioavailability and Food Effect Study of a Pediatric Granules Formulation of Ledipasvir/Sofosbuvir in Healthy Adult Subjects

Summary

EudraCT number	2015-003570-32
Trial protocol	Outside EU/EEA
Global end of trial date	30 June 2015

Results information

Result version number	v1 (current)
This version publication date	15 July 2016
First version publication date	15 July 2016

Trial information

Trial identification

Sponsor protocol code	GS-US-337-1115

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, United States,
Public contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001411-PIP01-12
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	30 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was to evaluate the relative bioavailability of a pediatric granules formulation of ledipasvir/sofosbuvir (LDV/SOF) relative to tablet formulation in healthy participants and to evaluate the effect of concomitant food intake on the pharmacokinetics of a pediatric granules formulation of LDV/SOF.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	42
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)	42
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States. The first participant was screened on 13 May 2015. The last study visit occurred on 30 June 2015.

Pre-assignment

Screening details:

63 participants were screened.

Period 1

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

Arms

Arm title	Overall Participants

Arm description:

Participants were randomized to 1 of 6 treatment sequences and received each of the following treatments with a 9-day washout interval between each treatment:

- Treatment A: Single dose of LDV/SOF tablet administered under fasted conditions
- Treatment B: Single dose of LDV/SOF oral granules administered under fasted conditions
- Treatment C: Single dose of LDV/SOF oral granules administered under fed conditions

Arm type	Experimental
Investigational medicinal product name	Ledipasvir/sofosbuvir
Investigational medicinal product code	Harvoni®; LDV/SOF
Other name	
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 90/400 mg tablet or 90/400 mg (8 x 11.25/50 mg units) granules administered orally under fasted or fed conditions

Number of subjects in period 1	Overall Participants
Started	42
Completed	42

Baseline characteristics

Reporting groups

Reporting group title	Overall Participants

Reporting group description:

Participants were randomized to 1 of 6 treatment sequences and received each of the following treatments with a 9-day washout interval between each treatment:

- Treatment A: Single dose of LDV/SOF tablet administered under fasted conditions
- Treatment B: Single dose of LDV/SOF oral granules administered under fasted conditions
- Treatment C: Single dose of LDV/SOF oral granules administered under fed conditions

Reporting group values	Overall Participants	Total	
Number of subjects	42	42	
Age categorical Units: Subjects			
Adults (18-64 years)	42	42	
Gender categorical Units: Subjects			
Female	21	21	
Male	21	21	
Race Units: Subjects			
Asian	1	1	
Black or African American	2	2	
White	39	39	
Ethnicity Units: Subjects			
Hispanic or Latino	41	41	
Not Hispanic or Latino	1	1	

End points

End points reporting groups

Reporting group title	Overall Participants

Reporting group description:

Participants were randomized to 1 of 6 treatment sequences and received each of the following treatments with a 9-day washout interval between each treatment:

- Treatment A: Single dose of LDV/SOF tablet administered under fasted conditions
- Treatment B: Single dose of LDV/SOF oral granules administered under fasted conditions
- Treatment C: Single dose of LDV/SOF oral granules administered under fed conditions

Subject analysis set title	Treatment A
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Ledipasvir/sofosbuvir 90/400 mg (1 x 90/400 mg tablet) administered orally under fasted conditions

Subject analysis set title	Treatment B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Ledipasvir/sofosbuvir 90/400 mg (8 x 11.25/50 mg units, LDV/SOF oral granules) administered orally under fasted conditions

Subject analysis set title	Treatment C
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Ledipasvir/sofosbuvir 90/400 mg (8 x 11.25/50 mg units, LDV/SOF oral granules) administered orally under fed conditions

Primary: PK Parameter of LDV as measured by Cmax

End point title	PK Parameter of LDV as measured by Cmax

End point description:

Cmax was defined as maximum observed plasma concentration of drug. PK Analysis Set: participants who received at least 1 dose of study drug and had at least 1 non-missing PK concentration data reported by PK lab for each respective analyte.

End point type	Primary

End point timeframe:

Predose (≤ 5 minutes), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12,16, 20, 24, 48, 72, 96, 120, and 144 hours postdose on Days 1, 11, and 21

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	42	
Units: Participants				
geometric mean (confidence interval 95%)	274.41 (234.5 to 321.1)	163.9 (145.5 to 184.5)	216 (200.8 to 232.3)	

Statistical analyses

Statistical analysis title	LDV: Treatment B/Treatment A for Cmax

Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric least-squares mean (GLSM) ratio (Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. Bioequivalence was concluded if the 90% CIs fell within the prespecified boundaries of 80% to 125%. "Subjects in this analysis" states 82; however, participants analyzed in PK analysis set were 40 for Treatment B and 42 for Treatment A.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	59.53
Confidence interval	
level	90 %
sides	2-sided
lower limit	52.71
upper limit	67.24

Primary: PK Parameter of GS-331007 (SOF metabolite) as measured by Cmax

End point title	PK Parameter of GS-331007 (SOF metabolite) as measured by Cmax

End point description:

End point type	Primary

End point timeframe:

Predose (≤ 5 minutes), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12,16, 20, 24, 48, 72, 96, 120, and 144 hours postdose on Days 1, 11, and 21

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	42	
Units: Participants				
geometric mean (confidence interval 95%)	826.8 (771.6 to 886.1)	959.8 (890.6 to 1034.5)	537.6 (507.6 to 569.4)	

Statistical analyses

Statistical analysis title	GS-331007: Treatment B/Treatment A for Cmax

Statistical analysis description:

A parametric mixed effect ANOVA model was used to estimate the GLSM ratio (Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. Bioequivalence was concluded if the 90% CIs fell within the prespecified boundaries of 80% to 125%. "Subjects in this analysis" states 82; however participants in analyzed in PK analysis were 40 for Treatment B and 42 for Treatment A.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	115.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	109.31
upper limit	121.64

Primary: PK Parameter of LDV as measured by AUClast and AUCinf

End point title	PK Parameter of LDV as measured by AUClast and AUCinf

End point description:

- AUClast was defined as area under the plasma concentration-time curve from time 0 to the last measurable concentration.
- AUCinf was defined as area under the plasma concentration-time curve from time zero to infinity.

End point type	Primary

End point timeframe:

Predose (≤ 5 minutes), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12,16, 20, 24, 48, 72, 96, 120, and 144 hours postdose on Days 1, 11, and 21

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	42	
Units: Participants				
geometric mean (confidence interval 95%)				
AUClast	7939.8 (6762.3 to 9322.3)	4863.9 (4299.4 to 5502.5)	6451.6 (5956.7 to 69857.5)	
AUCinf	9257 (7824.5 to 10951.9)	5763.9 (5044.3 to 6586.1)	7553.4 (6860.5 to 8316.4)	

Statistical analyses

Statistical analysis title	LDV: Treatment B/Treatment A for AUClast

Statistical analysis description:

A parametric mixed effect ANOVA model was used to estimate the GLSM ratio (Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. Bioequivalence was concluded if the 90% CIs fell within the prespecified boundaries of 80% to 125%. "Subjects in this analysis" states 82; however, participants analyzed in PK analysis set were 40 for Treatment B and 42 for Treatment A.

Comparison groups	Treatment B v Treatment A

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	60.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	54.72
upper limit	67.91

Statistical analysis title	LDV: Treatment C/Treatment B for AUClast

Statistical analysis description:

A parametric mixed effect ANOVA model was used to estimate the GLSM ratio (Treatment C/Treatment B) of the PK parameter and the corresponding 90% CI. PK equivalence was concluded if the 90% CIs fell within the prespecified boundaries of 70% to 143%. "Subjects in this analysis" states 82; however, participants analyzed in PK analysis set were 42 for Treatment C and 40 for Treatment B.

Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	134.79
Confidence interval	
level	90 %
sides	2-sided
lower limit	123.55
upper limit	147.05

Statistical analysis title	LDV: Treatment B/Treatment A for AUCinf

Statistical analysis description:

A parametric mixed effect ANOVA model was used to estimate the GLSM ratio (Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. Bioequivalence was concluded if the 90%
CIs fell within the prespecified boundaries of 80% to 125%. "Subjects in this analysis" states 82; however,
participants analyzed in PK analysis set were 40 for Treatment B and 42 for Treatment A.

Comparison groups	Treatment B v Treatment A
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	61.86
Confidence interval	
level	90 %
sides	2-sided
lower limit	55.38
upper limit	69.1

Statistical analysis title	LDV: Treatment C/Treatment B for AUCinf

Statistical analysis description:

A parametric mixed effect ANOVA model was used to estimate the GLSM ratio (Treatment C/Treatment B) of the PK parameter and the corresponding 90% CI. PK equivalence was concluded if the 90% CIs fell within the prespecified boundaries of 70% to 143%. "Subjects in this analysis" states 82; however, participants analyzed in PK analysis set were 40 for Treatment C and 42 for Treatment B.

Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	133.51
Confidence interval	
level	90 %
sides	2-sided
lower limit	122.31
upper limit	145.75

Primary: PK Parameter of GS-331007 (SOF metabolite) as measured by AUClast and AUCinf

End point title	PK Parameter of GS-331007 (SOF metabolite) as measured by AUClast and AUCinf

End point description:

End point type	Primary

End point timeframe:

Predose (≤ 5 minutes), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12,16, 20, 24, 48, 72, 96, 120, and 144 hours postdose on Days 1, 11, and 21

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	42	40	42	
Units: Participants				
geometric mean (confidence interval 95%)				
AUClast	10418.5 (9727.2 to 11158.9)	10897.8 (10121.2 to 11734)	11999.5 (11330.9 to 12707.5)	
AUCinf	10958.4 (10257.8 to 11706.8)	11438.5 (10640 to 12296.9)	12640.5 (11972.5 to 13345.7)	

Statistical analyses

Statistical analysis title	GS-331007: Treatment B/Treatment A for AUClast

Statistical analysis description:

A parametric mixed effect ANOVA model was used to estimate the GLSM ratio (Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. Bioequivalence was concluded if the 90% CIs fell within the prespecified boundaries of 80% to 125%. "Subjects in this analysis" states 82; however, participants analyzed in PK analysis set were 40 for Treatment B and 42 for Treatment A.

Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	103.38
Confidence interval	
level	90 %
sides	2-sided
lower limit	99.63
upper limit	107.27

Statistical analysis title	GS-331007: Treatment C/Treatment B for AUClast

Statistical analysis description:

A parametric mixed effect ANOVA model was used to estimate the GLSM ratio (Treatment C/Treatment B) of the PK parameter and the corresponding 90% CI. PK equivalence was concluded if the 90% CIs fell within the prespecified boundaries of 80% to 125%. "Subjects in this analysis" states 82; however, participants analyzed in PK analysis set were 42 for Treatment C and 40 for Treatment B.

Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	111.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	106.44
upper limit	115.83

Statistical analysis title	GS-331007: Treatment B/Treatment A for AUCinf

Statistical analysis description:

A parametric mixed effect ANOVA model was used to estimate the GLSM ratio (Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. Bioequivalence was concluded if the 90%
CIs fell within the prespecified boundaries of 80% to 125%. "Subjects in this analysis" states 82; however,
participants analyzed in PK analysis set were 40 for Treatment B and 42 for Treatment A.

Comparison groups	Treatment B v Treatment A

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	103.13
Confidence interval	
level	90 %
sides	2-sided
lower limit	99.5
upper limit	106.9

Statistical analysis title	GS-331007: Treatment C/Treatment B for AUCinf

Statistical analysis description:

A parametric mixed effect ANOVA model was used to estimate the GLSM ratio (Treatment C/Treatment B) of the PK parameter and the corresponding 90% CI. PK equivalence was concluded if the 90% CIs fell within the prespecified boundaries of 80% to 125%. "Subjects in this analysis" states 82; however, participants analyzed in PK analysis set were 42 for Treatment C and 40 for Treatment B.

Comparison groups	Treatment B v Treatment C
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric least-squares mean ratio
Point estimate	111.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	106.89
upper limit	116.21

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Up to 21 days plus 30 days

Adverse event reporting additional description:

Safety Analysis Set included all randomized subjects who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Treatment A

Reporting group description:

Ledipasvir/sofosbuvir 90/400 mg (1 x 90/400 mg tablet) administered orally under fasted conditions

Reporting group title	Treatment B

Reporting group description:

Ledipasvir/sofosbuvir 90/400 mg (8 x 11.25/50 mg units, LDV/SOF oral granules) administered orally under fasted conditions

Reporting group title	Treatment C

Reporting group description:

Ledipasvir/sofosbuvir 90/400 mg (8 x 11.25/50 mg units, LDV/SOF oral granules) administered orally under fed conditions

Serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 42 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 42 (0.00%)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: None of the non-serious AE preferred terms occurred to at least 5% of subjects in any of the treatment groups.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There were no limitations affecting the analysis or results.

Notes: