



## Clinical trial results:

### Open-Label, Single-Arm Trial to Evaluate the Pharmacokinetics, Safety and Efficacy of Daclatasvir (DCV) in Combination with Sofosbuvir (SOF) in Children from 3 to less than 18 Years of Age with GT-1 to -6 Chronic Hepatitis C (CHC) Infection

#### Summary

EudraCT number	2017-003338-94
Trial protocol	DE ES PL Outside EU/EEA
Global end of trial date	17 September 2020

#### Results information

Result version number	v1 (current)
This version publication date	28 March 2021
First version publication date	28 March 2021

#### Trial information

##### Trial identification

Sponsor protocol code	AI444-423
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001191-PIP01-11
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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 November 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 September 2020
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To Evaluate the Pharmacokinetics, Safety and Efficacy of Daclatasvir (DCV) in Combination with Sofosbuvir (SOF) in Children from 3 to less than 18 Years of Age with GT-1 to -6 Chronic Hepatitis C (CHC) Infection

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2018
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	Spain: 2
Country: Number of subjects enrolled	Australia: 3
Worldwide total number of subjects	5
EEA total number of subjects	2

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)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

5 participants were enrolled and treated

### Period 1

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

### Arms

<b>Arm title</b>	Daclatasvir (DCV) + Sofosbuvir (SOF)
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Arm description:

DCV 60 mg QD + SOF 400 mg QD for 12 weeks

Arm type	Experimental
Investigational medicinal product name	Sofosbuvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg QD

Investigational medicinal product name	Daclatasvir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg QD

<b>Number of subjects in period 1</b>	Daclatasvir (DCV) + Sofosbuvir (SOF)
Started	5
Completed	4
Not completed	1
Lost to follow-up	1

## Baseline characteristics

### Reporting groups

Reporting group title	Daclatasvir (DCV) + Sofosbuvir (SOF)
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Reporting group description:

DCV 60 mg QD + SOF 400 mg QD for 12 weeks

Reporting group values	Daclatasvir (DCV) + Sofosbuvir (SOF)	Total	
Number of subjects	5	5	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	13.6		
standard deviation	± 1.3	-	
Sex: Female, Male			
Units: Participants			
Female	2	2	
Male	3	3	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	4	4	
More than one race	0	0	
Other	1	1	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	0	0	
Unknown or Not Reported	5	5	

## End points

### End points reporting groups

Reporting group title	Daclatasvir (DCV) + Sofosbuvir (SOF)
Reporting group description: DCV 60 mg QD + SOF 400 mg QD for 12 weeks	

### Primary: Minimum (Trough) Observed Plasma Concentration (Cmin) for Daclatasvir

End point title	Minimum (Trough) Observed Plasma Concentration (Cmin) for Daclatasvir <sup>[1]</sup>
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End point description:

End point type	Primary
End point timeframe: Day 10 after first dose	

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: No statistical analysis was performed for this endpoint.

<b>End point values</b>	Daclatasvir (DCV) + Sofosbuvir (SOF)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	152.94 ( $\pm$ 48.3)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Maximum Observed Plasma Concentration (Cmax) for Daclatasvir

End point title	Maximum Observed Plasma Concentration (Cmax) for Daclatasvir <sup>[2]</sup>
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End point description:

End point type	Primary
End point timeframe: Day 10 after first dose	

Notes:

[2] - 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: No statistical analysis was performed for this endpoint.

<b>End point values</b>	Daclatasvir (DCV) + Sofosbuvir (SOF)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1215.32 ( $\pm$ 37.2)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Time of Maximum Observed Plasma Concentration (Tmax) for Daclatasvir

End point title	Time of Maximum Observed Plasma Concentration (Tmax) for Daclatasvir <sup>[3]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Day 10 after first dose

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: No statistical analysis was performed for this endpoint.

<b>End point values</b>	Daclatasvir (DCV) + Sofosbuvir (SOF)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Hours				
median (full range (min-max))	2.00 (1.0 to 4.0)			

### Statistical analyses

No statistical analyses for this end point

### Primary: Area Under the Concentration-Time Curve (AUC(TAU)) for Daclatasvir

End point title	Area Under the Concentration-Time Curve (AUC(TAU)) for Daclatasvir <sup>[4]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Day 10 after first dose

Notes:

[4] - 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: No statistical analysis was performed for this endpoint.

End point values	Daclatasvir (DCV) + Sofosbuvir (SOF)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	11535.45 ( $\pm$ 26.6)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Apparent Total Body Clearance (CLT/F) for Daclatasvir

End point title	Apparent Total Body Clearance (CLT/F) for Daclatasvir <sup>[5]</sup>
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End point description:

End point type	Primary
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End point timeframe:

Day 10 after first dose

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: No statistical analysis was performed for this endpoint.

End point values	Daclatasvir (DCV) + Sofosbuvir (SOF)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: mL/min				
geometric mean (geometric coefficient of variation)	86.69 ( $\pm$ 22.3)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Experiencing Adverse Events

End point title	Number of Participants Experiencing Adverse Events
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End point description:

This outcome describes the number of participants experiencing different types of any grade adverse events.

End point type	Secondary
End point timeframe:	
From first dose to last dose (12 weeks)	

<b>End point values</b>	Daclatasvir (DCV) + Sofosbuvir (SOF)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Participants				
Adverse Events (AEs)	4			
Serious Adverse Events (SAEs)	0			
AEs leading to discontinuation	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants Experiencing Laboratory Abnormalities - On-treatment analysis

End point title	Number of Participants Experiencing Laboratory Abnormalities - On-treatment analysis
End point description:	
Laboratory tests abnormalities were analyzed in the following categories:	
-Hematology (hemoglobin, platelets, international normalized ratio (INR), white blood cell count (WBC), lymphocytes (absolute), neutrophils + bands (absolute; ANC)).	
-Hepatobiliary enzymes (ALT, AST, alkaline phosphatase, total bilirubin, albumin).	
-Pancreatic enzymes (lipase, creatinine).	
Tests results were reported by worst toxicity grade (0 to 4) based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (2017).	
Only laboratory abnormalities with a worst toxicity grade 3 or higher in any of the above-mentioned tests, experienced during the on-treatment period, are reported here.	
End point type	Secondary
End point timeframe:	
From the day after first dose to last dose (approximately 12 weeks)	

<b>End point values</b>	Daclatasvir (DCV) + Sofosbuvir (SOF)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Participants				
Lipase, Total	1			



## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants Experiencing Laboratory Abnormalities - Follow-up analysis

End point title	Number of Participants Experiencing Laboratory Abnormalities - Follow-up analysis
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End point description:

Laboratory tests abnormalities were analyzed in the following categories:

-Hematology (hemoglobin, platelets, international normalized ratio (INR), white blood cell count (WBC), lymphocytes (absolute), neutrophils + bands (absolute; ANC)).

-Hepatobiliary enzymes (ALT, AST, alkaline phosphatase, total bilirubin, albumin).

-Pancreatic enzymes (lipase, creatinine).

Tests results were reported by worst toxicity grade (0 to 4) based on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (2017).

Only laboratory abnormalities with a worst toxicity grade 3 or higher in any of the above-mentioned tests, experienced during the follow-up period, are reported here.

End point type	Secondary
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End point timeframe:

From the day after last dose to end of follow-up period (up to approximately 96 weeks)

<b>End point values</b>	Daclatasvir (DCV) + Sofosbuvir (SOF)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Participants				
Glomerular Filtration Rate	2			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Hepatitis C Virus (HCV) RNA Levels Below the Lower Limit of Quantitation (LLOQ) at Post-Treatment Follow-Up Week 12

End point title	Percentage of Participants with Hepatitis C Virus (HCV) RNA Levels Below the Lower Limit of Quantitation (LLOQ) at Post-Treatment Follow-Up Week 12
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End point description:

HCV RNA levels were measured by using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0. This assay has limit of detection = 15 IU/mL, LLOQ = 15 IU/mL.

The outcome includes both results where Target was Detected (TD) but below LLOQ and results were

Target was Not Detected (TND)

End point type	Secondary
End point timeframe:	
12 weeks after last dose	

<b>End point values</b>	Daclatasvir (DCV) + Sofosbuvir (SOF)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Percent of Participants				
number (confidence interval 95%)	100 (50 to 100)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose to 30 days following last dose

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	Daclatasvir (DCV) + Sofosbuvir (SOF)
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Reporting group description:

DCV 60 mg QD + SOF 400 mg QD for 12 weeks

Serious adverse events	Daclatasvir (DCV) + Sofosbuvir (SOF)		
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: 5 %

Non-serious adverse events	Daclatasvir (DCV) + Sofosbuvir (SOF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	5		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1  1 / 5 (20.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)  Rhinitis subjects affected / exposed occurrences (all)  Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1  1 / 5 (20.00%) 1  1 / 5 (20.00%) 1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2019	<ul style="list-style-type: none"><li>- Early termination of the study</li><li>- No participants enrolled in Cohorts 2 and 3</li><li>- Reduction of the Long-term follow-up period</li><li>- Removal of analysis for some secondary and exploratory endpoints</li><li>- Removal of interim analysis</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported