Clinical trial results:
A Multicenter, Extension Study of the Safety and Efficacy of Multi-dose Intravenous ARC-520 in Combination with Entecavir or Tenofovir in Patients with Chronic Hepatitis B Virus (HBV) Infection

Summary

EudraCT number	2014-004201-33
Trial protocol	DE
Global end of trial date	29 December 2016

Results information

Result version number	v1 (current)
This version publication date	18 January 2018
First version publication date	18 January 2018

Trial information

Trial identification

Sponsor protocol code	Heparc-2007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02738008
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Arrowhead Pharmaceuticals, Inc
Sponsor organisation address	225 S. Lake Avenue, Suite 1050, Pasadena, CA, United States, 91101
Public contact	Susan Boynton, Arrowhead Pharmaceuticals, Inc, 001 626-696-4707, sboynton@arrowheadpharma.com
Scientific contact	Susan Boynton, Arrowhead Pharmaceuticals, Inc, 001 626-696-4707, sboynton@arrowheadpharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the percentage of initial responders to ARC-520 therapy achieving a 1-log reduction in Hepatitis B Surface Antigen (HBsAg) at Week 36 of the extension study compared to baseline. Baseline is defined as the average of the pre-dose values in the primary Heparc-2002 and Heparc-2003 studies.

Protection of trial subjects:

Subjects were advised that they were free to withdraw from the study at any time for any reason or, if necessary, the Principal Investigator, or medically trained designee, may have withdrawn a subject from the study, according to the following protocol specified criteria, to protect the subject's health:
• the need to take medication which may have interfered with study measurements;
• intolerable/unacceptable adverse experiences;
• major violation or deviation of study protocol procedures;
• non-compliance of participant with protocol;
• subject unwilling to proceed and/or consent was withdrawn; or
• withdrawal from the study if, in the Principal Investigator’s judgment, it was in the subject’s best interest.

Background therapy:

All subjects took entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) throughout the study. Subjects were pretreated with an oral antihistamine. The antihistamine was, in general, an H1>H2 receptor blocker and would include diphenhydramine 50 mg, cetirizine 10 mg, chlorpheniramine 8 mg or hydroxyzine 50 mg. The Investigator was free to choose any of these antihistamines available locally and consistent with their country’s Marketing Authorisation.

Evidence for comparator: -

Actual start date of recruitment	28 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Korea, Republic of: 9
Worldwide total number of subjects	12
EEA total number of subjects	1

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)	11
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in subjects who successfully completed the primary studies Heparc-2002 (2014-004145-27) and Heparc-2003 (2014-004751-31) through Day 113 and responded to therapy, except for those who achieved loss of Hepatitis B Surface Antigen (HBsAg) during the primary study.

Pre-assignment

Screening details:

No subjects were enrolled from the Heparc-2002 or Heparc-2003 placebo groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Heparc-2002: ARC-520 1.0 mg/kg

Arm description:

ARC-520 2.0 mg/kg administered by intravenous (IV) infusion to subjects previously enrolled in the Heparc-2002 study and receiving ARC-520 1.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

ARC-520 was administered intravenously concomitantly with 0.9% normal saline using an infusion rate of 0.4 mL/min for ARC-520 and 200 cc/hour for normal saline.

Arm title	Heparc-2002: ARC-520 2.0 mg/kg

Arm description:

ARC-520 2.0 mg/kg administered by IV infusion to subjects previously enrolled in the Heparc-2002 study and receiving ARC-520 2.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

ARC-520 was administered intravenously concomitantly with 0.9% normal saline using an infusion rate of 0.4 mL/min for ARC-520 and 200 cc/hour for normal saline.

Arm title	Heparc-2003: ARC-520 2.0 mg/kg

Arm description:

ARC-520 2.0 mg/kg administered by IV infusion to subjects previously enrolled in the Heparc-2003 study and receiving ARC-520 2.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

ARC-520 was administered intravenously concomitantly with 0.9% normal saline using an infusion rate of 0.4 mL/min for ARC-520 and 200 cc/hour for normal saline.

Number of subjects in period 1	Heparc-2002: ARC-520 1.0 mg/kg	Heparc-2002: ARC-520 2.0 mg/kg	Heparc-2003: ARC-520 2.0 mg/kg
Started	1	6	5
Completed	0	0	0
Not completed	1	6	5
Study terminated by sponsor	1	5	3
Adverse event	-	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Heparc-2002: ARC-520 1.0 mg/kg
Reporting group description:	
ARC-520 2.0 mg/kg administered by intravenous (IV) infusion to subjects previously enrolled in the Heparc-2002 study and receiving ARC-520 1.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).	
Reporting group title	Heparc-2002: ARC-520 2.0 mg/kg
Reporting group description:	
ARC-520 2.0 mg/kg administered by IV infusion to subjects previously enrolled in the Heparc-2002 study and receiving ARC-520 2.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).	
Reporting group title	Heparc-2003: ARC-520 2.0 mg/kg
Reporting group description:	
ARC-520 2.0 mg/kg administered by IV infusion to subjects previously enrolled in the Heparc-2003 study and receiving ARC-520 2.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).	

Reporting group values	Heparc-2002: ARC-520 1.0 mg/kg	Heparc-2002: ARC-520 2.0 mg/kg	Heparc-2003: ARC-520 2.0 mg/kg
Number of subjects	1	6	5
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	1	5	5
>=65 years	0	1	0
Gender categorical Units: Subjects			
Female	0	5	2
Male	1	1	3

Reporting group values	Total		
Number of subjects	12		
Age categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	11		
>=65 years	1		
Gender categorical Units: Subjects			
Female	7		
Male	5		

End points

End points reporting groups

Reporting group title	Heparc-2002: ARC-520 1.0 mg/kg

Reporting group description:

ARC-520 2.0 mg/kg administered by intravenous (IV) infusion to subjects previously enrolled in the Heparc-2002 study and receiving ARC-520 1.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).

Reporting group title	Heparc-2002: ARC-520 2.0 mg/kg

Reporting group description:

ARC-520 2.0 mg/kg administered by IV infusion to subjects previously enrolled in the Heparc-2002 study and receiving ARC-520 2.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).

Reporting group title	Heparc-2003: ARC-520 2.0 mg/kg

Reporting group description:

ARC-520 2.0 mg/kg administered by IV infusion to subjects previously enrolled in the Heparc-2003 study and receiving ARC-520 2.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).

Primary: Percentage of Initial Responders to ARC-520 Therapy Achieving a 1-log Reduction in HBsAg at Week 36 Compared to Baseline

End point title	Percentage of Initial Responders to ARC-520 Therapy Achieving a 1-log Reduction in HBsAg at Week 36 Compared to Baseline[1]

End point description:

Initial responders are defined as subjects who showed a ½ log or greater reduction in their serum HBsAg levels from baseline to day 71 ± 3 days of the primary Heparc-2002 and Heparc-2003 studies, where baseline is defined as the average of pre-dose values.

End point type	Primary

End point timeframe:

Baseline, Week 36

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: Due to the early termination of the study, the planned clinical statistical plan could not be conducted; no efficacy endpoints were analyzed.

End point values	Heparc-2002: ARC-520 1.0 mg/kg	Heparc-2002: ARC-520 2.0 mg/kg	Heparc-2003: ARC-520 2.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[2] - Due to the early termination of the study, no efficacy endpoints were analyzed.

[3] - Due to the early termination of the study, no efficacy endpoints were analyzed.

[4] - Due to the early termination of the study, no efficacy endpoints were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence which does not necessarily have a causal relationship with this treatment. An SAE is any AE that: results in death; is life-threatening; requires inpatient hospitalization or prolongation of an existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is a medically important event or reaction. A TEAE was defined as an AE that was not present prior to the first study medication administration and started at/after the time of initiation of administration of study medication, or an AE which was present prior to initiation of study medication administration, which increased in severity after study medication administration.

End point type	Secondary

End point timeframe:

up to 60 weeks

End point values	Heparc-2002: ARC-520 1.0 mg/kg	Heparc-2002: ARC-520 2.0 mg/kg	Heparc-2003: ARC-520 2.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	6	5	
Units: subjects				
number (not applicable)				
AEs	1	4	4	
SAEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Initial Responders to ARC-520 Therapy With HBsAg Loss (Qualitative) Compared to Baseline Over Time

End point title	Percentage of Initial Responders to ARC-520 Therapy With HBsAg Loss (Qualitative) Compared to Baseline Over Time

End point description:

Baseline is defined as the average of the pre-dose values in the primary Heparc-2002 and Heparc-2003 studies.

End point type	Secondary

End point timeframe:

Baseline, Weeks 36, 48, and 60

End point values	Heparc-2002: ARC-520 1.0 mg/kg	Heparc-2002: ARC-520 2.0 mg/kg	Heparc-2003: ARC-520 2.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: percentage of subjects				
number (not applicable)				

Notes:

[5] - Due to the early termination of the study, no efficacy endpoints were analyzed.

[6] - Due to the early termination of the study, no efficacy endpoints were analyzed.

[7] - Due to the early termination of the study, no efficacy endpoints were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 60 weeks

Adverse event reporting additional description:

TEAEs are presented. TEAE=an AE that was not present prior to the first study medication administration and started at/after the time of initiation of administration of study medication, or an AE which was present prior to initiation of study medication administration, which increased in severity after study medication administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Heparc-2002: ARC-520 1.0 mg/kg

Reporting group description:

ARC-520 2.0 mg/kg administered by IV infusion to subjects previously enrolled in the Heparc-2002 study and receiving ARC-520 1.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).

Reporting group title	Heparc-2002: ARC-520 2.0 mg/kg

Reporting group description:

ARC-520 2.0 mg/kg administered by IV infusion to subjects previously enrolled in the Heparc-2002 study and receiving ARC-520 2.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).

Reporting group title	Heparc-2003: ARC-520 2.0 mg/kg

Reporting group description:

ARC-520 2.0 mg/kg administered by IV infusion to subjects previously enrolled in the Heparc-2003 study and receiving ARC-520 2.0 mg/kg. Subjects continued their ongoing entecavir therapy (0.5 or 1.0 mg/day) or tenofovir therapy (300 mg/day).

Serious adverse events	Heparc-2002: ARC-520 1.0 mg/kg	Heparc-2002: ARC-520 2.0 mg/kg	Heparc-2003: ARC-520 2.0 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Heparc-2002: ARC-520 1.0 mg/kg	Heparc-2002: ARC-520 2.0 mg/kg	Heparc-2003: ARC-520 2.0 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	4 / 6 (66.67%)	4 / 5 (80.00%)
Vascular disorders			

Flushing			
subjects affected / exposed	0 / 1 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	3
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 1 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	3
Chills			
subjects affected / exposed	1 / 1 (100.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			

Eczema			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Hordeolum			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

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.

The decision to discontinue development of ARC-EXI-containing programs was not due to any safety findings in clinical studies.

Notes: