Clinical trial results:
A Multicenter, Randomized, Double-blind, Placebo-controlled, Multi-dose Study to Determine the Depth of Hepatitis B Surface Antigen (HBsAg) Reduction Following Intravenous ARC-520 in Combination with Entecavir or Tenofovir in Patients with HBeAg Negative, Chronic Hepatits B Virus (HBV) Infection

Summary

EudraCT number	2014-004145-27
Trial protocol	DE
Global end of trial date	22 December 2016

Results information

Result version number	v1 (current)
This version publication date	03 January 2018
First version publication date	03 January 2018

Trial information

Trial identification

Sponsor protocol code	Heparc-2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02604199
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	22 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:
• To evaluate the depth of HBsAg decline in response to multiple doses of ARC-520 compared to PBO in patients with chronic HBV infection as a measure of drug activity

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study at any time for any reason or, if necessary, the Principal Investigator, or medically trained designee, may have withdrawn a subject from the study, according to the following protocol specified criteria, to protect the subject's health: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 continued to receiving daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period. Two hours (±30 minutes) prior to PBO or ARC-520 Injection intravenous (IV) administration, patients were pretreated with antihistamine. The antihistamine used should in general be 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	17 November 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	Korea, Republic of: 23
Country: Number of subjects enrolled	Hong Kong: 19
Country: Number of subjects enrolled	Germany: 16
Worldwide total number of subjects	58
EEA total number of subjects	16

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)	56
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Potential subjects underwent Screening within 60 days of first dose administration to confirm eligibility to be enrolled and randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Blinding to treatment assignment will be maintained throughout the study period. Blinding will be achieved by the use of a PBO (matching) product (0.9% normal saline) to be administered intravenously.

Arms

Are arms mutually exclusive?	Yes
Arm title	PBO Low Dose

Arm description:

0.9% normal saline, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.9% normal saline placebo was administered concomitantly, IV with 0.9% normal saline using an infusion rate of 0.4 mL/min for study treatment and 3.6 mL/min for saline.

Arm title	PBO High Dose

Arm description:

0.9% normal saline, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.9% normal saline placebo was administered concomitantly, IV with 0.9% normal saline using an infusion rate of 0.4 mL/min for study treatment and 3.6 mL/min for saline.

Arm title	ARC-520 Injection 1 mg/kg

Arm description:

Intravenous ARC-520 at 1.0 mg/kg, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period

Arm type	Experimental

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

Dosage and administration details:

ARC-520 Injection was administered concomitantly, IV with 0.9% normal saline using an infusion rate of 0.4 mL/min for study treatment and 3.6 mL/min for saline.

Arm title	ARC-520 Injection 2 mg/kg

Arm description:

Intravenous ARC-520 at 2.0 mg/kg, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period

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

Dosage and administration details:

ARC-520 Injection was administered concomitantly, IV with 0.9% normal saline using an infusion rate of 0.4 mL/min for study treatment and 3.6 mL/min for saline.

Number of subjects in period 1	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg
Started	9	11	17
Completed	9	8	17
Not completed	0	3	0
Consent withdrawn by subject	-	1	-
Pregnancy	-	-	-
Study terminated by sponsor	-	2	-

Number of subjects in period 1	ARC-520 Injection 2 mg/kg
Started	21
Completed	18
Not completed	3
Consent withdrawn by subject	-
Pregnancy	1
Study terminated by sponsor	2

Baseline characteristics

Reporting groups	
Reporting group title	PBO Low Dose
Reporting group description:	
0.9% normal saline, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	
Reporting group title	PBO High Dose
Reporting group description:	
0.9% normal saline, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	
Reporting group title	ARC-520 Injection 1 mg/kg
Reporting group description:	
Intravenous ARC-520 at 1.0 mg/kg, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	
Reporting group title	ARC-520 Injection 2 mg/kg
Reporting group description:	
Intravenous ARC-520 at 2.0 mg/kg, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	

Reporting group values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg
Number of subjects	9	11	17
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	46.2	48.7	45.0
standard deviation	± 12.10	± 9.50	± 10.48
Gender categorical			
Units: Subjects			
Female	2	1	7
Male	7	10	10

Reporting group values	ARC-520 Injection 2 mg/kg	Total	
Number of subjects	21	58	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	45.7		
standard deviation	± 10.26	-	
Gender categorical			
Units: Subjects			
Female	9	19	
Male	12	39	

End points

End points reporting groups

Reporting group title	PBO Low Dose
Reporting group description:	
0.9% normal saline, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	
Reporting group title	PBO High Dose
Reporting group description:	
0.9% normal saline, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	
Reporting group title	ARC-520 Injection 1 mg/kg
Reporting group description:	
Intravenous ARC-520 at 1.0 mg/kg, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	
Reporting group title	ARC-520 Injection 2 mg/kg
Reporting group description:	
Intravenous ARC-520 at 2.0 mg/kg, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	

Primary: Change From Baseline in Quantitative Hepatitis B Surface Antigen (Log qHBsAg) at Day 113

End point title	Change From Baseline in Quantitative Hepatitis B Surface Antigen (Log qHBsAg) at Day 113[1]
End point description:	
End point type	Primary
End point timeframe:	
Baseline, Day 113	

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: This analysis was removed from the initial statistical analysis plan due to early study termination.

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: Log qHBsAg				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[2] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[3] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[4] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[5] - Analysis was removed from the initial statistical analysis plan due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs), Serious AEs (SAEs), Deaths and Discontinuations Due to AEs

End point title	Number of Subjects With Adverse Events (AEs), Serious AEs (SAEs), Deaths and Discontinuations Due to AEs

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 treatment emergent AE (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:

Through Day 169

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	11	17	21
Units: subjects				
≥ 1 AE	4	5	6	12
≥ 1 TEAE	4	4	6	12
≥ 1 Serious TEAE	0	0	2	1
Deaths	0	0	0	0
≥ 1 TEAE Leading to Study Discontinuation	0	0	0	0
≥ 1 TEAE Leading to Treatment Discontinuation	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ARC-520: Area Under the Plasma Concentration-Time Curve From Time 0 to 24 Hours (AUC0-24)

End point title	Pharmacokinetics of ARC-520: Area Under the Plasma Concentration-Time Curve From Time 0 to 24 Hours (AUC0-24)

End point description:

End point type	Secondary

End point timeframe:

Through 48 hours post-dosing on Day 1 and Day 85

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	0[7]	0[8]	0[9]
Units: hr*ng/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[6] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[7] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[8] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[9] - Analysis was removed from the initial statistical analysis plan due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ARC-520: Area Under the Plasma Concentration-Time Curve From Time 0 to the Last Quantifiable Plasma Concentration (AUClast)

End point title	Pharmacokinetics of ARC-520: Area Under the Plasma Concentration-Time Curve From Time 0 to the Last Quantifiable Plasma Concentration (AUClast)

End point description:

End point type	Secondary

End point timeframe:

Through 48 hours post-dosing on Day 1 and Day 85

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[10]	0[11]	0[12]	0[13]
Units: hr*ng/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[10] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[11] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[12] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[13] - Analysis was removed from the initial statistical analysis plan due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ARC-520: Area Under the Plasma Concentration-Time Curve From Time 0 Extrapolated to Infinity (AUCinf)

End point title	Pharmacokinetics of ARC-520: Area Under the Plasma Concentration-Time Curve From Time 0 Extrapolated to Infinity (AUCinf)

End point description:

End point type	Secondary

End point timeframe:

Through 48 hours post-dosing on Day 1 and Day 85

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[14]	0[15]	0[16]	0[17]
Units: hr*ng/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[14] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[15] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[16] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[17] - Analysis was removed from the initial statistical analysis plan due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ARC-520: Maximum Observed Plasma Concentration (Cmax)

End point title	Pharmacokinetics of ARC-520: Maximum Observed Plasma Concentration (Cmax)

End point description:

End point type	Secondary

End point timeframe:

Through 48 hours post-dosing on Day 1 and Day 85

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[18]	0[19]	0[20]	0[21]
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[18] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[19] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[20] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[21] - Analysis was removed from the initial statistical analysis plan due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ARC-520: Clearance (CL)

End point title	Pharmacokinetics of ARC-520: Clearance (CL)

End point description:

End point type	Secondary

End point timeframe:

Through 48 hours post-dosing on Day 1 and Day 85

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[22]	0[23]	0[24]	0[25]
Units: mL/min				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[22] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[23] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[24] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[25] - Analysis was removed from the initial statistical analysis plan due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ARC-520: Apparent Volume of Distribution (V)

End point title	Pharmacokinetics of ARC-520: Apparent Volume of Distribution (V)

End point description:

End point type	Secondary

End point timeframe:

Through 48 hours post-dosing on Day 1 and Day 85

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[26]	0[27]	0[28]	0[29]
Units: liters				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[26] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[27] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[28] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[29] - Analysis was removed from the initial statistical analysis plan due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ARC-520: Terminal Elimination Rate Constant (Kel)

End point title	Pharmacokinetics of ARC-520: Terminal Elimination Rate Constant (Kel)

End point description:

End point type	Secondary

End point timeframe:

Through 48 hours post-dosing on Day 1 and Day 85

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[30]	0[31]	0[32]	0[33]
Units: 1/hour				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[30] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[31] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[32] - Analysis was removed from the initial statistical analysis plan due to early study termination.

[33] - Analysis was removed from the initial statistical analysis plan due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ARC-520: Terminal Elimination Half-Life (t1/2)

End point title	Pharmacokinetics of ARC-520: Terminal Elimination Half-Life (t1/2)

End point description:

End point type	Secondary

End point timeframe:

Through 48 hours post-dosing on Day 1 and Day 85

End point values	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg	ARC-520 Injection 2 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[34]	0[35]	0[36]	0[37]
Units: hours				
arithmetic mean (standard deviation)	()	()	()	()

Notes:
[34] - Analysis was removed from the initial statistical analysis plan due to early study termination.
[35] - Analysis was removed from the initial statistical analysis plan due to early study termination.
[36] - Analysis was removed from the initial statistical analysis plan due to early study termination.
[37] - Analysis was removed from the initial statistical analysis plan due to early study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Through Day 169	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	PBO Low Dose
Reporting group description: 0.9% normal saline, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	
Reporting group title	PBO High Dose
Reporting group description: 0.9% normal saline, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	
Reporting group title	ARC-520 Injection 1 mg/kg
Reporting group description: Intravenous ARC-520 at 1.0 mg/kg, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	
Reporting group title	ARC-520 Injection 2 mg/kg
Reporting group description: Intravenous ARC-520 at 2.0 mg/kg, once every 4 weeks for 4 doses plus daily oral entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg) throughout the study period	

Serious adverse events	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	2 / 17 (11.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ARC-520 Injection 2 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PBO Low Dose	PBO High Dose	ARC-520 Injection 1 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)	4 / 11 (36.36%)	4 / 17 (23.53%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	2

Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 17 (0.00%)
occurrences (all)	2	0	0
Toothache			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 11 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 11 (9.09%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 11 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 11 (9.09%)	1 / 17 (5.88%)
occurrences (all)	1	1	1

Non-serious adverse events	ARC-520 Injection 2 mg/kg		

Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 21 (38.10%)		
Investigations			
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Blood cholesterol increased subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Myalgia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Vascular disorders			
Hypotension subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Cardiac disorders			
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Lethargy subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
General disorders and administration site conditions			
Chest discomfort subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 2		
Chills			

subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1 2 / 21 (9.52%) 2 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 2 / 21 (9.52%) 4		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all)	 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	 0 / 21 (0.00%) 0		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 1 / 21 (4.76%) 1 0 / 21 (0.00%) 0 3 / 21 (14.29%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2015	• The addition of venous lactate level to the schedule of assessments. • Changed post-dose observation period from 2 hours to 4 hours. • Clarified there was a risk of infusion-related reactions including both anaphylactic and non-anaphylactic or cytokine release syndrome. Addition of Cytokine Release Syndrome clinical management guidelines. Clinical guidelines for management of anaphylactic reactions were added. • Correction of administrative, grammatical, formatting errors, and inconsistencies.
11 April 2016	• Reduced the number of patients designated as PK patients from 24 to 12 patients. • Altered exclusion criteria 2, 6, 9, 11, 12, 13, 27, 28, 32, 34. • Removed exclusion criteria 7, 8, 20, 26, 30, 36, 37, 39. • Changes to the information presented in the Restrictions and Concomitant Medications section including removal of restriction from strenuous activity and changes to concomitant medications. • "Arrowhead Research Corporation" was changed to "Arrowhead Pharmaceuticals, Inc." due to Sponsor name change.
19 October 2016	• Addition to the Exclusion Criteria and Study Restrictions information regarding planned surgery or non-emergent procedures requiring an induction agent to occur 48 hours before and after ARC-520 Injection administrations.

Notes:

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 ARC-520 Injection development program was terminated early for regulatory and business reasons secondary to findings occurring in a non-clinical toxicology study. Program termination was not due to safety findings in humans.

Notes: