Clinical trial results:
A Multicenter, Open-Label Study to Evaluate ARC-520 Administered Alone and in Combination with Other Therapeutics in Patients with Chronic Hepatitis B Virus (HBV) Infection (MONARCH)

Summary

EudraCT number	2015-005499-46
Trial protocol	BG
Global end of trial date	28 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-2008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02577029
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. , +1 626-696-4707, sboynton@arrowheadpharma.com
Scientific contact	Susan Boynton, Arrowhead Pharmaceuticals, Inc. , +1 626-696-4707, 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	28 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the percentage of chronic HBV patients achieving a 1-log reduction in HBsAg compared to baseline (mean of pre-dose values) at Week 60 after completion of 48 weeks of ARC-520

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study at any time for any reason or, if necessary, the Principal Investigator, or medically trained designee, may have withdrawn a subject from the study, according to the following protocol specified criteria, to protect the subject's health: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 subject 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• subject unwilling to proceed and/or consent was withdrawn; or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:

The patients were also required to take concomitant medications (0.5 mg once daily entecavir OR 300 mg once daily tenofovir [Cohorts 2-6]; 180 mcg pegylated interferon-alpha [PEG-IFN α; Cohorts 2-7]). Cohorts 1 and 8 were not required to take any concomitant medication and received ARC-520 Injection as monotherapy. The treatment period for entecavir/tenofovir started concurrently with ARC-520 Injection dosing and was scheduled for 60 weeks. This could be extended if so considered by the assessing investigator however all treatment was to stop once seroconversion was achieved.

The PEG-IFN α start was delayed and started at Day 87 for Cohorts 2-6 or Day 15 for Cohort 7, of treatment. PEG–IFN α treatment was scheduled for 48 weeks. PEG-IFN α was administered weekly as per protocol and any dose reductions were made based on locally approved PEG-IFN α label instructions.

All subjects were pre-treated with an oral antihistamine selected by the investigator from the list of approved antihistamines that is available in that country. Acceptable antihistamines were: diphenhydramine 50 mg p.o., chlorpheniramine 8 mg p.o., hydroxyzine 50 mg p.o., or cetirizine 10 mg p.o.

Evidence for comparator: -

Actual start date of recruitment	09 December 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	Bulgaria: 15
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Moldova, Republic of: 15

Country: Number of subjects enrolled	Thailand: 25
Country: Number of subjects enrolled	Korea, Republic of: 1
Worldwide total number of subjects	79
EEA total number of subjects	15

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)	79
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included up to 60 days of screening period.

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	Cohort 1

Arm description:

Treatment-naïve, hepatitis B "e" antigen (HBeAg)-positive subjects with chronic hepatitis B (CHB) of any genotype administered ARC-520 (2 mg/kg intravenous [IV]) every 4 weeks for 48 weeks (13 doses).

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	ARC-520
Other name	
Pharmaceutical forms	Solution for injection/infusion
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	Cohort 2

Arm description:

Treatment-naïve, HBeAg-positive, Genotype B subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered peginterferon (PEG IFN) alpha 2a for 48 weeks starting Day 87.

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	ARC-520
Other name	
Pharmaceutical forms	Solution for injection/infusion
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	Cohort 3

Arm description:

Treatment-naïve, HBeAg-negative, Genotype B subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.

Arm type	Experimental

Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	ARC-520
Other name	
Pharmaceutical forms	Solution for injection/infusion
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	Cohort 4

Arm description:

Treatment-naïve, HBeAg-positive, Genotype C subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	ARC-520
Other name	
Pharmaceutical forms	Solution for injection/infusion
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	Cohort 5

Arm description:

Treatment-naïve, HBeAg-negative, Genotype C subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	ARC-520
Other name	
Pharmaceutical forms	Solution for injection/infusion
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	Cohort 6

Arm description:

Treatment-naïve, HBeAg-negative, Genotype D subects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	ARC-520
Other name	
Pharmaceutical forms	Solution for injection/infusion
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	Cohort 7

Arm description:

Treatment-naïve, HBeAg-negative or HBeAg-positive subjects with hepatitis delta virus (HDV) administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 15.

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	ARC-520
Other name	
Pharmaceutical forms	Solution for injection/infusion
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	Cohort 8

Arm description:

Treatment-naïve, HBeAg-positive subjects with CHB of any genotype administered ARC-520 (4 mg/kg IV) every 4 weeks for 48 weeks (13 doses).

Arm type	Experimental
Investigational medicinal product name	ARC-520 Injection
Investigational medicinal product code	ARC-520
Other name	
Pharmaceutical forms	Solution for injection/infusion
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	Cohort 1	Cohort 2	Cohort 3
Started	10	2	7
Completed	0	0	0
Not completed	10	2	7
Consent withdrawn by subject	-	-	-
Sponsor termination of the study	9	2	5
Adverse event	1	-	2

Number of subjects in period 1	Cohort 4	Cohort 5	Cohort 6
Started	12	11	13
Completed	0	0	0
Not completed	12	11	13
Consent withdrawn by subject	-	-	1
Sponsor termination of the study	12	10	12
Adverse event	-	1	-

Number of subjects in period 1	Cohort 7	Cohort 8
Started	12	12

Completed	0	0
Not completed	12	12
Consent withdrawn by subject	-	-
Sponsor termination of the study	12	12
Adverse event	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Treatment-naïve, hepatitis B "e" antigen (HBeAg)-positive subjects with chronic hepatitis B (CHB) of any genotype administered ARC-520 (2 mg/kg intravenous [IV]) every 4 weeks for 48 weeks (13 doses).	
Reporting group title	Cohort 2
Reporting group description:	
Treatment-naïve, HBeAg-positive, Genotype B subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered peginterferon (PEG IFN) alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 3
Reporting group description:	
Treatment-naïve, HBeAg-negative, Genotype B subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 4
Reporting group description:	
Treatment-naïve, HBeAg-positive, Genotype C subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 5
Reporting group description:	
Treatment-naïve, HBeAg-negative, Genotype C subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 6
Reporting group description:	
Treatment-naïve, HBeAg-negative, Genotype D subects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 7
Reporting group description:	
Treatment-naïve, HBeAg-negative or HBeAg-positive subjects with hepatitis delta virus (HDV) administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 15.	
Reporting group title	Cohort 8
Reporting group description:	
Treatment-naïve, HBeAg-positive subjects with CHB of any genotype administered ARC-520 (4 mg/kg IV) every 4 weeks for 48 weeks (13 doses).	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	10	2	7
Age categorical Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	32.5	29.5	40.4
standard deviation	± 11.09	± 0.71	± 7.37
Gender categorical			
Units: Subjects			
Female	7	1	4
Male	3	1	3

Reporting group values	Cohort 4	Cohort 5	Cohort 6
Number of subjects	12	11	13
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	36.3	39.6	38.2
standard deviation	± 9.32	± 12.61	± 7.97
Gender categorical			
Units: Subjects			
Female	6	3	2
Male	6	8	11

Reporting group values	Cohort 7	Cohort 8	Total
Number of subjects	12	12	79
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	39.6	36.7	
standard deviation	± 7.73	± 7.32	-
Gender categorical			
Units: Subjects			
Female	6	5	34
Male	6	7	45

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Treatment-naïve, hepatitis B "e" antigen (HBeAg)-positive subjects with chronic hepatitis B (CHB) of any genotype administered ARC-520 (2 mg/kg intravenous [IV]) every 4 weeks for 48 weeks (13 doses).	
Reporting group title	Cohort 2
Reporting group description:	
Treatment-naïve, HBeAg-positive, Genotype B subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered peginterferon (PEG IFN) alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 3
Reporting group description:	
Treatment-naïve, HBeAg-negative, Genotype B subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 4
Reporting group description:	
Treatment-naïve, HBeAg-positive, Genotype C subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 5
Reporting group description:	
Treatment-naïve, HBeAg-negative, Genotype C subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 6
Reporting group description:	
Treatment-naïve, HBeAg-negative, Genotype D subects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.	
Reporting group title	Cohort 7
Reporting group description:	
Treatment-naïve, HBeAg-negative or HBeAg-positive subjects with hepatitis delta virus (HDV) administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 15.	
Reporting group title	Cohort 8
Reporting group description:	
Treatment-naïve, HBeAg-positive subjects with CHB of any genotype administered ARC-520 (4 mg/kg IV) every 4 weeks for 48 weeks (13 doses).	

Primary: Percentage of Subjects Achieving a 1-log Reduction in Hepatitis B Surface Antigen (HBsAg) Compared to Baseline

End point title	Percentage of Subjects Achieving a 1-log Reduction in Hepatitis B Surface Antigen (HBsAg) Compared to Baseline[1]
End point description:	
The percentage of subjects with chronic HBV achieving a 1-log reduction in HBsAg compared to baseline (mean of pre-dose values) at Week 60 after completion of 48 weeks of ARC-520 Injection.	
End point type	Primary

End point timeframe:

Baseline, Week 60

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 final statistical analysis plan was released after the study termination. Planned analysis per protocol for any efficacy variables including virology assessments, immunogenicity, pharmacokinetics and pharmacodynamics were not conducted and not planned for per the SAP.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: percentage of subjects				
number (not applicable)				

Notes:

[2] - Analysis was not planned or conducted per SAP due to study termination.

[3] - Analysis was not planned or conducted per SAP due to study termination.

[4] - Analysis was not planned or conducted per SAP due to study termination.

[5] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	0[7]	0[8]	0[9]
Units: percentage of subjects				
number (not applicable)				

Notes:

[6] - Analysis was not planned or conducted per SAP due to study termination.

[7] - Analysis was not planned or conducted per SAP due to study termination.

[8] - Analysis was not planned or conducted per SAP due to study termination.

[9] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Achieving a 1-log Reduction in HBsAg and Achieving an HBsAg Level < 100 IU/L

End point title	Percentage of Subjects Achieving a 1-log Reduction in HBsAg and Achieving an HBsAg Level < 100 IU/L[10]

End point description:

End point type	Primary

End point timeframe:

Weeks 52, 60, 72 and 96

Notes:

[10] - 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 final statistical analysis plan was released after the study termination. Planned analysis per protocol for any efficacy variables including virology assessments, immunogenicity, pharmacokinetics and pharmacodynamics were not conducted and not planned for per the SAP.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[11]	0[12]	0[13]	0[14]
Units: percentage of subjects				
number (not applicable)				

Notes:

[11] - Analysis was not planned or conducted per SAP due to study termination.

[12] - Analysis was not planned or conducted per SAP due to study termination.

[13] - Analysis was not planned or conducted per SAP due to study termination.

[14] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[15]	0[16]	0[17]	0[18]
Units: percentage of subjects				
number (not applicable)				

Notes:

[15] - Analysis was not planned or conducted per SAP due to study termination.

[16] - Analysis was not planned or conducted per SAP due to study termination.

[17] - Analysis was not planned or conducted per SAP due to study termination.

[18] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs Considered Possibly or Probably Related to Treatment

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs Considered Possibly or Probably Related to Treatment

End point description:

The Principal Investigator (or medically qualified designee) will use clinical judgment to determine the relationship. An adverse event (AE) was considered "possibly related" when there is a reasonable possibility that the incident, experience, or outcome may have been caused by the product under investigation. An AE was considered "probably related" when there are facts, evidence, or arguments to suggest that the event is related to the product under investigation. Only AEs that occurred post-dose were considered treatment-emergent. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs.

End point type	Secondary

End point timeframe:

From first dose of study drug up to Week 96 +/- 3 days

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	2	7	12
Units: subjects				
Related TEAE	1	0	3	2
Related Serious TEAE	0	0	0	0

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	13	12	12
Units: subjects				
Related TEAE	3	4	3	3
Related Serious TEAE	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HBsAg Loss (Based on Qualitative Assay)

End point title	Percentage of Subjects With HBsAg Loss (Based on Qualitative Assay)

End point description:

The qualitative HBsAg assay gives a binary result, positive or negative.

End point type	Secondary

End point timeframe:

Weeks 52, 60, 72 and 96

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[19]	0[20]	0[21]	0[22]
Units: percentage of subjects				
number (not applicable)				

Notes:

[19] - Analysis was not planned or conducted per SAP due to study termination.

[20] - Analysis was not planned or conducted per SAP due to study termination.

[21] - Analysis was not planned or conducted per SAP due to study termination.

[22] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[23]	0[24]	0[25]	0[26]
Units: percentage of subjects				
number (not applicable)				

Notes:

[23] - Analysis was not planned or conducted per SAP due to study termination.

[24] - Analysis was not planned or conducted per SAP due to study termination.

[25] - Analysis was not planned or conducted per SAP due to study termination.

[26] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to HBsAg Loss

End point title	Time to HBsAg Loss

End point description:

End point type	Secondary

End point timeframe:

Baseline through Week 96

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[27]	0[28]	0[29]	0[30]
Units: hours				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[27] - Analysis was not planned or conducted per SAP due to study termination.

[28] - Analysis was not planned or conducted per SAP due to study termination.

[29] - Analysis was not planned or conducted per SAP due to study termination.

[30] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[31]	0[32]	0[33]	0[34]
Units: hours				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[31] - Analysis was not planned or conducted per SAP due to study termination.

[32] - Analysis was not planned or conducted per SAP due to study termination.

[33] - Analysis was not planned or conducted per SAP due to study termination.

[34] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Anti-HBs (Antibody to Hepatitis B Surface Antigen) Seroconversion

End point title	Time to Anti-HBs (Antibody to Hepatitis B Surface Antigen) Seroconversion

End point description:

End point type	Secondary

End point timeframe:

Baseline through Week 96

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[35]	0[36]	0[37]	0[38]
Units: hours				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[35] - Analysis was not planned or conducted per SAP due to study termination.

[36] - Analysis was not planned or conducted per SAP due to study termination.

[37] - Analysis was not planned or conducted per SAP due to study termination.

[38] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[39]	0[40]	0[41]	0[42]
Units: hours				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[39] - Analysis was not planned or conducted per SAP due to study termination.

[40] - Analysis was not planned or conducted per SAP due to study termination.

[41] - Analysis was not planned or conducted per SAP due to study termination.

[42] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Anti-HBs Seroconversion

End point title	Percentage of Subjects With Anti-HBs Seroconversion

End point description:

End point type	Secondary

End point timeframe:

Weeks 52, 60, 72 and 96

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[43]	0[44]	0[45]	0[46]
Units: percentage of subjects				
number (not applicable)				

Notes:

[43] - Analysis was not planned or conducted per SAP due to study termination.

[44] - Analysis was not planned or conducted per SAP due to study termination.

[45] - Analysis was not planned or conducted per SAP due to study termination.

[46] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[47]	0[48]	0[49]	0[50]
Units: percentage of subjects				
number (not applicable)				

Notes:

[47] - Analysis was not planned or conducted per SAP due to study termination.

[48] - Analysis was not planned or conducted per SAP due to study termination.

[49] - Analysis was not planned or conducted per SAP due to study termination.

[50] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HBeAg Loss and Anti-Hepatitis B e Antigen (Anti-HBe) Seroconversion (if HBeAg-Positive at Study Entry)

End point title	Percentage of Subjects With HBeAg Loss and Anti-Hepatitis B e Antigen (Anti-HBe) Seroconversion (if HBeAg-Positive at Study Entry)

End point description:

End point type	Secondary

End point timeframe:

Weeks 52, 60, 72 and 96

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[51]	0[52]	0[53]	0[54]
Units: percentage of subjects				
number (not applicable)				

Notes:

[51] - Analysis was not planned or conducted per SAP due to study termination.

[52] - Analysis was not planned or conducted per SAP due to study termination.

[53] - Analysis was not planned or conducted per SAP due to study termination.

[54] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[55]	0[56]	0[57]	0[58]
Units: percentage of subjects				
number (not applicable)				

Notes:

[55] - Analysis was not planned or conducted per SAP due to study termination.

[56] - Analysis was not planned or conducted per SAP due to study termination.
[57] - Analysis was not planned or conducted per SAP due to study termination.
[58] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Resistance to ARC-520 Injection by Week 52

End point title	Percentage of Subjects With Resistance to ARC-520 Injection by Week 52

End point description:

Resistance is defined as > 1.0 log IU/mL quantitative HBsAg (qHBsAg) increase from nadir, confirmed by repeat test.

End point type	Secondary

End point timeframe:

through Week 52

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[59]	0[60]	0[61]	0[62]
Units: percentage of subjects				
number (not applicable)				

Notes:
[59] - Analysis was not planned or conducted per SAP due to study termination.
[60] - Analysis was not planned or conducted per SAP due to study termination.
[61] - Analysis was not planned or conducted per SAP due to study termination.
[62] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[63]	0[64]	0[65]	0[66]
Units: percentage of subjects				
number (not applicable)				

Notes:
[63] - Analysis was not planned or conducted per SAP due to study termination.
[64] - Analysis was not planned or conducted per SAP due to study termination.
[65] - Analysis was not planned or conducted per SAP due to study termination.
[66] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Resistance to the Combination Therapy From Baseline to Week 60

End point title	Percentage of Subjects With Resistance to the Combination Therapy From Baseline to Week 60

End point description:

Resistance is defined as > 1.0 log IU/mL increase in HBV DNA from nadir, confirmed by repeat test.

End point type	Secondary

End point timeframe:

Baseline, Week 60

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[67]	0[68]	0[69]	0[70]
Units: percentage of subjects				
number (not applicable)				

Notes:

[67] - Analysis was not planned or conducted per SAP due to study termination.

[68] - Analysis was not planned or conducted per SAP due to study termination.

[69] - Analysis was not planned or conducted per SAP due to study termination.

[70] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[71]	0[72]	0[73]	0[74]
Units: percentage of subjects				
number (not applicable)				

Notes:

[71] - Analysis was not planned or conducted per SAP due to study termination.

[72] - Analysis was not planned or conducted per SAP due to study termination.

[73] - Analysis was not planned or conducted per SAP due to study termination.

[74] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With HDV With Undetectable HDV Ribonucleic Acid (RNA) After 48 Weeks of Concomitant ARC-520 Injection and PEG IFN Alpha 2a Therapy (Cohort 7 Only)

End point title	Percentage of Subjects With HDV With Undetectable HDV Ribonucleic Acid (RNA) After 48 Weeks of Concomitant ARC-520 Injection and PEG IFN Alpha 2a Therapy (Cohort 7 Only)

End point description:

End point type	Secondary

End point timeframe:

Weeks 52, 60, 72 and 96

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[75]	0[76]	0[77]	0[78]
Units: percentage of subjects				
number (not applicable)				

Notes:

[75] - Analysis was not planned or conducted per SAP due to study termination.

[76] - Analysis was not planned or conducted per SAP due to study termination.

[77] - Analysis was not planned or conducted per SAP due to study termination.

[78] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[79]	0[80]	0[81]	0[82]
Units: percentage of subjects				
number (not applicable)				

Notes:

[79] - Analysis was not planned or conducted per SAP due to study termination.

[80] - Analysis was not planned or conducted per SAP due to study termination.

[81] - Analysis was not planned or conducted per SAP due to study termination.

[82] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Log Change From Baseline in Quantitative HBV Deoxyribonucleic Acid (DNA) Serum Levels

End point title	Log Change From Baseline in Quantitative HBV Deoxyribonucleic Acid (DNA) Serum Levels

End point description:

End point type	Secondary

End point timeframe:

Baseline, Weeks 52, 60, 72 and 96

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[83]	0[84]	0[85]	0[86]
Units: log change				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[83] - Analysis was not planned or conducted per SAP due to study termination.

[84] - Analysis was not planned or conducted per SAP due to study termination.

[85] - Analysis was not planned or conducted per SAP due to study termination.

[86] - Analysis was not planned or conducted per SAP due to study termination.

End point values	Cohort 5	Cohort 6	Cohort 7	Cohort 8

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[87]	0[88]	0[89]	0[90]
Units: log change				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[87] - Analysis was not planned or conducted per SAP due to study termination.

[88] - Analysis was not planned or conducted per SAP due to study termination.

[89] - Analysis was not planned or conducted per SAP due to study termination.

[90] - Analysis was not planned or conducted per SAP due to study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to Week 96 +/- 3 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Treatment-naïve, HBeAg-positive subjects with CHB of any genotype administered ARC-520 (2 mg/kg IV) every 4 weeks for 48 weeks (13 doses).

Reporting group title	Cohort 2

Reporting group description:

Treatment-naïve, HBeAg-positive, Genotype B subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.

Reporting group title	Cohort 3

Reporting group description:

Treatment-naïve, HBeAg-negative, Genotype B subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.

Reporting group title	Cohort 4

Reporting group description:

Treatment-naïve, HBeAg-positive, Genotype C subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.

Reporting group title	Cohort 5

Reporting group description:

Treatment-naïve, HBeAg-negative, Genotype C subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.

Reporting group title	Cohort 6

Reporting group description:

Treatment-naïve, HBeAg-negative, Genotype D subjects with CHB administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) concomitantly with daily orally administered ETV or TDF for approximately 60 weeks starting Day 1 and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 87.

Reporting group title	Cohort 7

Reporting group description:

Treatment-naïve, HBeAg-negative or HBeAg-positive subjects with HDV administered ARC-520 (2 mg/kg increasing to 4 mg/kg or 4 mg/kg IV) every 4 weeks for 48 weeks (13 doses) and weekly subcutaneously administered PEG IFN alpha 2a for 48 weeks starting Day 15.

Reporting group title	Cohort 8

Reporting group description:

Treatment-naïve, HBeAg-positive subjects with CHB of any genotype administered ARC-520 (4 mg/kg IV) every 4 weeks for 48 weeks (13 doses).

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Vestibular neuronitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4	Cohort 5	Cohort 6
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Vestibular neuronitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 7	Cohort 8	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Vestibular neuronitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	0 / 2 (0.00%)	4 / 7 (57.14%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Peripheral coldness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vasoconstriction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin neoplasm excision			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Administration site bruise			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Chills			

subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Feeling cold			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Injection site erythema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Irritability			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Peripheral coldness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Swelling			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			

Cytokine release syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Hypersensitivity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Euphoric mood			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Infusion related reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 10 (20.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Head discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sedation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Somnolence			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	2
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Flushing			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			

subjects affected / exposed	1 / 10 (10.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4	Cohort 5	Cohort 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)	5 / 11 (45.45%)	8 / 13 (61.54%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Peripheral coldness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vasoconstriction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1

Skin neoplasm excision			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Administration site bruise			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Chills			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	2 / 13 (15.38%)
occurrences (all)	1	1	3
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	3 / 11 (27.27%)	3 / 13 (23.08%)
occurrences (all)	0	3	4
Feeling cold			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	1 / 13 (7.69%)
occurrences (all)	1	1	5
Feeling hot			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 13 (7.69%)
occurrences (all)	0	2	1
Injection site erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Irritability			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Peripheral coldness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	3
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	3
Swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypersensitivity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	1 / 12 (8.33%)	2 / 11 (18.18%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Rhinorrhoea			

subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Euphoric mood			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 13 (7.69%)
occurrences (all)	0	4	1
Infusion related reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Head discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Hypoaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Sedation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	3
Somnolence			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	2 / 13 (15.38%)
occurrences (all)	1	2	2
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	3 / 13 (23.08%)
occurrences (all)	0	0	3
Vomiting			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	6
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Viral infection			
subjects affected / exposed	1 / 12 (8.33%)	2 / 11 (18.18%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Diabetes mellitus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Cohort 7	Cohort 8	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)	6 / 12 (50.00%)	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Peripheral coldness			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Vasoconstriction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Skin neoplasm excision			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Administration site bruise			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Fatigue			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Feeling cold			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Feeling hot			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Injection site erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Irritability			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Peripheral coldness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Swelling			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	

Hypersensitivity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Euphoric mood			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
International normalised ratio increased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Infusion related reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Head discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Sedation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Syncope			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	4 / 12 (33.33%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Lymphopenia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Neutropenia			
subjects affected / exposed	5 / 12 (41.67%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Thrombocytopenia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Dry mouth			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			

Renal colic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Muscle tightness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Tonsillitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Viral infection			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Diabetes mellitus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2015	1. Modify Schedule of Assessments to collect Quantitative and qualitative anti-HBs, qualitative anti-Hbe, and HbsAg epitope mapping Baseline samples at the Day 1 visit for all enrolled patients. 2. Correction of administrative, grammatical, formatting errors, and inconsistencies.
20 November 2015	1. Addition of Cohort 7 (Treatment naïve HBeAg negative or HBeAg positive Hepatitis Delta Virus (HDV) patients administered ARC-520 (2 mg/kg IV) every 4 weeks for 48 weeks concomitantly with PEG IFN alpha 2a and Cohort 8 (Treatment naïve, HBeAg positive, Chronic Hepatitis B (CHB) patients of any genotype administered ARC-520 (4 mg/kg IV) every 4 weeks for 48 weeks). HDV infection requires HBsAg present in chronic HBV infection. Therefore, targeting HBV and specifically HBsAg with ARC-520 may prove therapeutic for HDV. Cohort 8 utilizes a 4 mg/kg dose, which has been extensively studied as a single dose treatment in HBeAg negative and HBeAg positive patients in the Heparc-2001 study. The addition of this cohort is intended to compare monotherapy response between low dose (Cohort 1, 2 mg/kg) and high dose (Cohort 9, 4 mg/kg). 2. Expansion of the study to addition Asia/Pacific and European countries. 3. Correction of administrative, grammatical, formatting errors, and inconsistencies.
22 January 2016	1. Addition of Tenofovir (TDF) as an alternative to Entecavir (ETV) for treatments used in Cohorts 2-6. This addition is intended to provide an appropriate NUC alternative if entecavir is not available. 2. Removal of Cetirizine 10 mg p.o. as an acceptable antihistamine. Sponsor prefers use of antihistamines that are less H1 receptor selective. 3. Changes made to the Exclusion Criteria in protocol version 2.0 (20 November 2015): a. Exclusion criterion #3 modified to allow for enrollment of patients with recent minor infections. b. Exclusion criterion #22 was removed as the exclusion of subjects with these conditions is covered by other exclusion criteria. c. Exclusion criterion #25 modified for clarity. d. Exclusion criterion #29 removed as Sponsor has found no reason why fever alone within 2 weeks of screening should exclude a subject. 4. Cytokines will now be drawn and evaluated for all patients at the pre-dose blood draw regardless of evidence of ALT flares. Sponsor recently presented data at Hepdart in December 2015 showing that 7 of 9 chimps, all being treated with ARC-520 showed signs of cytokine induction. This was seen in the presence of declining HBV viral antigens and ALT flare was not routinely present. Thus, ALT flare may not be necessary to see signs of immune reconstitution in humans. 5. Correction of administrative, grammatical, formatting errors, and inconsistencies.

20 April 2016	1. Changes made to the Inclusion/Exclusion Criteria in protocol version 3.0 (22 January 2016): a. Inclusion criterion #11 was modified for HBeAg positive subjects only: i. ALT at screening ≥ 35 U/L (males) or ≥ 30 U/L (females) ii. Source document verifiable ALT ≥ 35 U/L (males) or ≥ 30 U/L (females) within the last 6 months iii. Tests positive at Screening for presence of basal core promoter mutation For clarity, once any of the above criteria are met in an HBeAg positive subject, this inclusion criteria is to be considered met and the subject can be enrolled. Additionally, there are no corresponding criteria for HBeAg negative subjects. All HBeAg negative subjects can be enrolled assuming they meet all other inclusion and exclusion criteria. b. Exclusion criterion #5 was revised for Liver Elastography (i.e. FibroScan®) score > 10.59 or FibroTest/Fibrosure score > 0.7 at screening. c. Exclusion criterion #8 was removed as Sponsor did not feel the need to exclude patients with poorly controlled diabetes mellitus with a diagnosis of fatty liver disease. d. Exclusion criterion #14 was revised to allow patients with well-controlled blood pressure on hypertensive medication regardless of the time duration. e. Exclusion criterion #17 was removed as it duplicates inclusion criterion #4. f. Exclusion criterion #22 was removed as it duplicates exclusion criteria #27-28. 2. Addition of basal core promoter mutation test for the HBV Genotyping lab sample collected at Screening. 3. Addition of treatment stopping rule that ARC-520 may be discontinued in any subject with treatment emergent platelet count of < 35,000 per microliter. 4. Update to the ARC-520 risk assessment for patients. 5. Additional allowance of Acetaminophen use at the discretion of the PI during pre-treatment or post-treatment or at any other time during the study. 6. Change "Arrowhead Research Corporation" to "Arrowhead Pharmaceuticals, Inc." due to Sponsor name change. 7. Minor corrections.
12 May 2016	1. Correct typo in the protocol secondary objective to determine the percentage of patients achieving a 1-log reduction in achieving a HBsAg level < 100 IU/mL. 2. Change made to the Inclusion/Exclusion Criteria in protocol version 4.0 (20 April 2016): a. Inclusion criterion #8 does not apply to Cohort 7 HDV patients 3. Correction of administrative, grammatical, formatting errors, and inconsistencies.

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: