



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 Positive, Chronic Hepatitis B Virus (HBV) Infection

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2014-004751-31 |
| Trial protocol | DE |
| Global end of trial date | 15 December 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 03 December 2017 |
| First version publication date | 03 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | Heparc-2003 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02604212 |
| 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 | 15 December 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 15 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 placebo in subjects 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 took entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) throughout the study. Subjects were pretreated with an oral antihistamine. The antihistamine was in general 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 | 04 November 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Hong Kong: 9 |
| Country: Number of subjects enrolled | Korea, Republic of: 22 |
| Worldwide total number of subjects | 32 |
| EEA total number of subjects | 1 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 31 |
| From 65 to 84 years | 1 |
| 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, Carer, Assessor |

Blinding implementation details:

Blinding to treatment assignment was maintained throughout the study period. However, treatment unblinding may have occurred as required by the investigator or Sponsor to ensure the safety of a study subject.

Arms

| | |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo Low Dose Comparator |

Arm description:

Placebo (low dose comparator) once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day)

| | |
|--|----------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | sterile normal saline 0.9% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Two hours (± 0.5 hours) prior to placebo IV administration, subjects were pretreated with antihistamine. Placebo was administered concomitantly, intravenously 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 | Placebo High Dose Comparator |
|------------------|------------------------------|

Arm description:

Placebo (high dose comparator) once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day)

| | |
|--|----------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | sterile normal saline 0.9% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Two hours (± 0.5 hours) prior to placebo IV administration, subjects were pretreated with antihistamine. Placebo was administered concomitantly, intravenously 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 1.0 mg/kg |
|------------------|-------------------|

Arm description:

Low dose (1.0 mg/kg) ARC-520 once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or

tenofovir (300 mg/day)

| | |
|--|------------------------|
| 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:

Two hours (± 0.5 hours) prior to ARC-520 IV administration, subjects were pretreated with antihistamine. ARC-520 was administered concomitantly, intravenously 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 2.0 mg/kg |
|------------------|-------------------|

Arm description:

High dose (2.0 mg/kg) ARC-520 once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day)

| | |
|--|------------------------|
| 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:

Two hours (± 0.5 hours) prior to ARC-520 IV administration, subjects were pretreated with antihistamine. ARC-520 was administered concomitantly, intravenously 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 | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg |
|---------------------------------------|-----------------------------|------------------------------|-------------------|
| Started | 6 | 5 | 10 |
| Completed | 4 | 4 | 6 |
| Not completed | 2 | 1 | 4 |
| Consent withdrawn by subject | - | - | 1 |
| Study Terminated by Sponsor | 2 | 1 | 3 |

| Number of subjects in period 1 | ARC-520 2.0 mg/kg |
|---------------------------------------|-------------------|
| Started | 11 |
| Completed | 8 |
| Not completed | 3 |
| Consent withdrawn by subject | - |
| Study Terminated by Sponsor | 3 |

Baseline characteristics

Reporting groups

| | |
|---|------------------------------|
| Reporting group title | Placebo Low Dose Comparator |
| Reporting group description: Placebo (low dose comparator) once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) | |
| Reporting group title | Placebo High Dose Comparator |
| Reporting group description: Placebo (high dose comparator) once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) | |
| Reporting group title | ARC-520 1.0 mg/kg |
| Reporting group description: Low dose (1.0 mg/kg) ARC-520 once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) | |
| Reporting group title | ARC-520 2.0 mg/kg |
| Reporting group description: High dose (2.0 mg/kg) ARC-520 once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) | |

| Reporting group values | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg |
|------------------------|-----------------------------|------------------------------|-------------------|
| Number of subjects | 6 | 5 | 10 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--------------------|--------|---------|---------|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 39.8 | 45.0 | 42.1 |
| standard deviation | ± 9.54 | ± 10.68 | ± 12.57 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 1 | 0 |
| Male | 3 | 4 | 10 |

| Reporting group values | ARC-520 2.0 mg/kg | Total | |
|------------------------|-------------------|-------|--|
| Number of subjects | 11 | 32 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--------------------|---------|----|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 41.6 | | |
| standard deviation | ± 12.05 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 6 | 10 | |
| Male | 5 | 22 | |

End points

End points reporting groups

| | |
|---|------------------------------|
| Reporting group title | Placebo Low Dose Comparator |
| Reporting group description: Placebo (low dose comparator) once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) | |
| Reporting group title | Placebo High Dose Comparator |
| Reporting group description: Placebo (high dose comparator) once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) | |
| Reporting group title | ARC-520 1.0 mg/kg |
| Reporting group description: Low dose (1.0 mg/kg) ARC-520 once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) | |
| Reporting group title | ARC-520 2.0 mg/kg |
| Reporting group description: High dose (2.0 mg/kg) ARC-520 once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day) | |

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

| | |
|--|---|
| End point title | Change From Baseline at Day 113 in Quantitative Hepatitis B Surface Antigen (Log qHBsAg) ^[1] |
| End point description: Change From Baseline in log qHBsAg up to Day 113 in response to multiple doses of ARC-520 versus placebo as a measure of efficacy. | |
| 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: Statistical analyses were not performed due to early study termination.

| End point values | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 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 IU/mL | | | | |
| number (not applicable) | | | | |

Notes:

[2] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

[3] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

[4] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

[5] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Log qHBsAg

| | |
|--|--|
| End point title | Change From Baseline Over Time in Log qHBsAg |
| End point description: Change From Baseline in quantitative log qHBsAg up to Day 99 in response to multiple doses of ARC-520 versus placebo as a measure of efficacy. | |
| End point type | Secondary |
| End point timeframe: Baseline, Days 1, 2, 15, 29, 30, 43, 57, 58, 71, 85, 86, 99 | |

| End point values | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 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: log IU/mL | | | | |
| number (not applicable) | | | | |

Notes:

[6] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

[7] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

[8] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

[9] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Log qHBsAg, by Category

| | |
|---|---|
| End point title | Change From Baseline Over Time in Log qHBsAg, by Category |
| End point description: Change in log qHBsAg from baseline up to Day 113, categorized into the following groups: 0 to < 0.5 log IU/mL; 0.5 to 1.0 log IU/mL; > 1.0 log IU/mL, tabulated by dose and treatment for each visit. | |
| End point type | Secondary |
| End point timeframe: Baseline, Days 1, 2, 15, 29, 30, 43, 57, 58, 71, 85, 86, 99, 113 | |

| End point values | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 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: subjects | | | | |
| number (not applicable) | | | | |

Notes:

[10] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

[11] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

[12] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

[13] - Due to the early suspension and termination of the study, efficacy analyses were not analyzed.

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Number of Participants 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 to have a causal relationship with this treatment. A treatment emergent AE (TEAE) was defined as an AE that was not present prior to the first study drug administration and started at/after the time of initiation of administration of study drug, or an AE which was present prior to initiation of study drug administration, which increased in severity after study drug administration. An SAE is any untoward medical occurrence that, at any dose: 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; is a medically important event or reaction.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through Day 169 (\pm 3 days)

| End point values | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 mg/kg |
|--|-----------------------------|------------------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 6 | 5 | 10 | 11 |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| ≥ 1 AE | 4 | 0 | 6 | 3 |
| ≥ 1 TEAE | 4 | 0 | 5 | 3 |
| ≥ 1 Serious TEAE | 0 | 0 | 0 | 0 |
| 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 (AUC ₀₋₂₄) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 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] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[15] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[16] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[17] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

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 | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 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: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[18] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[19] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[20] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[21] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

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 | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 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: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[22] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[23] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[24] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[25] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

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 | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 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: ng/mL | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[26] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[27] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[28] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[29] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

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 | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 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: L/h/kg | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[30] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[31] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[32] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[33] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

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 | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 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: liters | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[34] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[35] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[36] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[37] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

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 | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 mg/kg |
|-------------------------------|-----------------------------|------------------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[38] | 0 ^[39] | 0 ^[40] | 0 ^[41] |
| Units: 1/hour | | | | |
| median (full range (min-max)) | (to) | (to) | (to) | (to) |

Notes:

[38] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[39] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[40] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[41] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ARC-520: Terminal Elimination Half-Life (t_{1/2})

| | |
|-----------------|---|
| End point title | Pharmacokinetics of ARC-520: Terminal Elimination Half-Life (t _{1/2}) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg | ARC-520 2.0 mg/kg |
|--------------------------------------|-----------------------------|------------------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[42] | 0 ^[43] | 0 ^[44] | 0 ^[45] |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[42] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[43] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[44] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

[45] - Due to the early suspension and termination of the study, pharmacokinetic analyses were not analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Through Day 169 (\pm 3 days)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | Placebo Low Dose Comparator |
|-----------------------|-----------------------------|

Reporting group description:

Placebo (low dose comparator) once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day)

| | |
|-----------------------|------------------------------|
| Reporting group title | Placebo High Dose Comparator |
|-----------------------|------------------------------|

Reporting group description:

Placebo (high dose comparator) once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day)

| | |
|-----------------------|-------------------|
| Reporting group title | ARC-520 1.0 mg/kg |
|-----------------------|-------------------|

Reporting group description:

Low dose (1.0 mg/kg) ARC-520 once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day)

| | |
|-----------------------|-------------------|
| Reporting group title | ARC-520 2.0 mg/kg |
|-----------------------|-------------------|

Reporting group description:

High dose (2.0 mg/kg) ARC-520 once every 4 weeks for 4 doses, plus entecavir (0.5 or 1.0 mg/day) or tenofovir (300 mg/day)

| Serious adverse events | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg |
|---|-----------------------------|------------------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 10 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

| Serious adverse events | ARC-520 2.0 mg/kg | | |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |

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

| Non-serious adverse events | Placebo Low Dose Comparator | Placebo High Dose Comparator | ARC-520 1.0 mg/kg |
|---|--------------------------------|---------------------------------|----------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 4 / 6 (66.67%) | 0 / 5 (0.00%) | 5 / 10 (50.00%) |
| Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Eosinophil count increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 5 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 10 (0.00%) 0 |
| Chills subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 2 |
| Discomfort subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 2 |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Pyrexia | | | |

| | | | |
|--|--------------------|--------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 10 (10.00%) 1 |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 5 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Urticaria | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 5 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 1 / 10 (10.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 5 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngitis | | | |

| | | | |
|-----------------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 5 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 10 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-------------------|--|--|
| Non-serious adverse events | ARC-520 2.0 mg/kg | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Eosinophil count increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | | |
| occurrences (all) | 1 | | |
| Chills | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Discomfort</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 11 (0.00%)</p> <p>0</p> <p>0 / 11 (0.00%)</p> <p>0</p> <p>0 / 11 (0.00%)</p> <p>0</p> <p>0 / 11 (0.00%)</p> <p>0</p> | | |
| <p>Gastrointestinal disorders</p> <p>Dyspepsia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastrooesophageal reflux disease</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 11 (0.00%)</p> <p>0</p> <p>0 / 11 (0.00%)</p> <p>0</p> <p>0 / 11 (0.00%)</p> <p>0</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 11 (0.00%)</p> <p>0</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Eczema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Urticaria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 11 (0.00%)</p> <p>0</p> <p>0 / 11 (0.00%)</p> <p>0</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 11 (0.00%)</p> <p>0</p> | | |

| | | | |
|--|--|--|--|
| Intervertebral disc protrusion subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 15 May 2015 | <p>The addition of venous lactate level was added to the Schedule of Assessments at Days 1, 2, 29, 30, 57, 58, 85 and 86.</p> <p>The post-dose observation period was changed from 2 hours to 4 hours; patients were to remain at the clinical facility for 4 hours following administration of ARC-520 Injection or placebo. Additionally, on dosing days patients were dosed sequentially, with at least 30 minutes in between dose initiations. Dose administration was not to be initiated simultaneously in multiple patients.</p> <p>The oral antihistamine pre-treatment was updated to specify that the antihistamine used was in general to 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 Authorization.</p> <p>The maximum blood volume collected from each patient was changed to not exceed approximately 830 mL (previously 820 mL)</p> <p>The protocol (Section 16.1.1) was amended to include information regarding the management of AEs (Section 10.11 of the protocol [Section 16.1.1]).</p> <p>The risk of infusion related reactions was updated to include both anaphylactic and nonanaphylactic or cytokine release syndrome. Cytokine Release Syndrome clinical management guidelines were added to the Appendices. Appendix 2 provided clinical guidelines for management of anaphylactic reactions. Appendix 3 provided clinical guidelines for management of cytokine release syndrome.</p> <p>The protocol was updated to include corrections of administrative, grammatical, formatting errors, and inconsistencies.</p> |

| | |
|---------------|--|
| 17 March 2016 | <p>The total number of patients for the Heparc-2003 study was reduced from 90 to 48. Treatment Groups 1 and 2 were reduced from 15 to 8 patients and Treatment Groups 3 & 4 were reduced from 30 to 16 patients. The planning interim analysis was to be performed after 54 patients had completed their day 71 visit. This total was reduced from 54 to 25 patients.</p> <p>The number of pharmacokinetic patients was reduced from 24 to 12 patients to align with the reduction in patients enrolled.</p> <p>The following changes to the inclusion/exclusion criteria were also incorporated: The exclusion criteria were modified to include the following changes:</p> <ul style="list-style-type: none"> • Exclusion Criterion #2 was modified to clarify that "severe" infection should not be evident within the 4 week screening window. This was done to avoid uncertainty around appropriate enrollment of patients that may have experienced mild infections such as upper respiratory infections or viral syndromes within the screening window. • Exclusion Criterion #4 was modified to increase the Liver Elastography score from 8 to 9. In the chronic hepatitis B population, Liver Elastography scores of 8 and 9 were both indicative of mild to moderate (F2-F3) liver fibrosis. It was not anticipated that this would have changed the risk to patients receiving ARC-520 Injection. • Exclusion Criterion #6 was modified to clarify that only drugs listed that were "systemically administered", specifically systemically administered (oral, intravenous or depot) steroids or immunomodulators/immunosuppressants were excluded. This was done so as to not exclude patients using topical or inhaled products which were unlikely to suppress systemic innate or adaptive immune responses against HBV. • Exclusion Criterion #7 was modified from a detailed list of drugs to prescription medications based on principal investigator (PI) discretion within 14 days of administration of study treatment. |
| 17 March 2016 | <p>(continued)</p> <ul style="list-style-type: none"> • Exclusion Criterion #9 was modified from diabetes mellitus to Non-alcoholic steatohepatitis (NASH) or homozygous or heterozygous familial hypercholesterolemia. There had been no indication that well controlled diabetics would have had a less favorable risk profile. However, the presence of NASH concomitantly with chronic hepatitis B adds a variable potentially making interpretation of transaminase changes difficult. Additionally, small interfering ribonucleic acid (siRNA) molecules used in ARC-520 Injection are targeted to hepatocytes using a cholesterol targeting ligand. Patients with familial hypercholesterolemia lack a normal low density lipoprotein (LDL) receptor and thus are not good candidates for ARC-520 Injection. • Exclusion Criterion #10 was updated with the blood cholesterol removed. Patients with elevated cholesterol were unlikely to have an increased risk profile. Additionally, the Sponsor had evaluated serum total cholesterol levels with HBsAg responses and no correlation had been identified. • Exclusion Criterion #11 was modified to clarify that "poorly controlled" autoimmune disease was excluded. • Exclusion Criterion #24 was modified to remove marijuana use as well as the timeframe for use of 3 months prior to screening, and to remove positive urine drug screen. Use of marijuana was not likely to alter the risk of study participation. • Exclusion Criterion #27 was modified to include only inherited or acquired hepatic disease, (eg, alcoholic liver disease, cirrhosis, Wilson's disease, hemochromatosis or alpha-1 antitrypsin deficiency). This was done to exclude patients who have HBV and concomitant hepatic disease which could alter or obscure safety data interpretation. • Exclusion Criterion #29 was modified to clarify that presence of "poorly controlled" diseases was excluded. |

| | |
|-----------------|--|
| 17 March 2016 | <p>(continued)</p> <p>The following criteria were removed as Exclusion for the study:</p> <ul style="list-style-type: none"> • Concurrent use of dietary and/or herbal supplements. It was unlikely this would alter patient risk profile with regard to this study. • Medications known to prolong QTc intervals. No signs of QTc prolongation had been seen in clinical investigations of ARC-520 Injection to date. • Evidence of severe systemic acute inflammation, sepsis or hemolysis. The Sponsor believed patients with severe systemic inflammation, sepsis or hemolysis would be excluded by other criteria making this criterion redundant. • Positive reaction to bee venom allergy test (immunoglobulin E [IgE]). The Sponsor believed Exclusion Criterion #number 25 was sufficient to exclude patients at risk for hypersensitivity reactions to ARC-520. • History of fever within 2 weeks of screening. Presence of fever within 2 weeks of screening was unlikely to change patient risk profile. • Immunization with a live attenuated vaccine within 7 days of dosing. This was removed as immunization with a live attenuated vaccine within 7 days of dosing was unlikely to change patient risk profile. • Participation in excessive/physical activity within 7 days of screening or enrolment. This was removed as it was unlikely to change patient risk profile. The restrictions and concomitant medications section was updated to align with the modifications made to the exclusion criteria. <p>The sample size considerations were updated to support the reduction in the number of patients in the study as well as the number of patients required for the interim analysis.</p> <p>Additionally typographical and administrative errors were corrected for clarification.</p> |
| 19 October 2016 | <p>A further amendment was made to the global and Hong Kong specific protocols (Version 4.0; 19 Oct 2016); however these protocols were not fully approved in any country prior to study termination.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported