



Clinical trial results:

A Phase 1b, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of MK-7655A in Pediatric Subjects From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Infections

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2016-004328-43 |
| Trial protocol | NO PL Outside EU/EEA GB BG GR |
| Global end of trial date | 11 August 2020 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 07 May 2022 |
| First version publication date | 22 February 2021 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | MK-7655A-020 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03230916 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001809-PIP01-15 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 11 August 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 July 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 August 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This study aims to obtain plasma pharmacokinetic (PK) data and characterize the PK profile of imipenem (IMI), cilastatin (CIL), and relebactam (REL) following administration of a single intravenous (IV) dose of MK-7655A (a fixed ratio combination of imipenem/cilastatin/relebactam), hereafter referred to as IMI/REL.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 06 November 2017 |
| 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: 2 |
| Country: Number of subjects enrolled | Colombia: 5 |
| Country: Number of subjects enrolled | Greece: 4 |
| Country: Number of subjects enrolled | United States: 8 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Ukraine: 14 |
| Country: Number of subjects enrolled | Norway: 6 |
| Country: Number of subjects enrolled | Poland: 5 |
| Worldwide total number of subjects | 47 |
| EEA total number of subjects | 17 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 12 |

| | |
|--|----|
| Infants and toddlers (28 days-23 months) | 16 |
| Children (2-11 years) | 12 |
| Adolescents (12-17 years) | 7 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study enrolled pediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative infections. Other inclusion criteria applied.

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: IMI/REL 15/7.5 mg/kg |

Arm description:

Adolescents (age 12 to <18 years) administered with a single intravenous (IV) 30-minute infusion dose of imipenem/cilastatin/relebactam (IMI/REL) at 15/7.5 mg/kg, up to maximum dose of 500/250 mg

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Adolescents (age 12 to <18 years) administered with a single intravenous (IV) 30-minute infusion dose of imipenem/cilastatin/relebactam (IMI/REL) at 15/7.5 mg/kg, up to maximum dose of 500/250 mg

| | |
|------------------|--------------------------------|
| Arm title | Cohort 2: IMI/REL 15/7.5 mg/kg |
|------------------|--------------------------------|

Arm description:

Older children (6 to <12 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg, up to a maximum dose of 500/250 mg

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Older children (6 to <12 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg, up to a maximum dose of 500/250 mg

| | |
|------------------|--------------------------------|
| Arm title | Cohort 3: IMI/REL 15/7.5 mg/kg |
|------------------|--------------------------------|

Arm description:

Younger children (2 to <6 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---|
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Younger children (2 to <6 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Arm title | Cohort 4: IMI/REL 10/5 mg/kg |
| Arm description: | |
| Infants (3 months to <1 year) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Arm type | Experimental |
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Infants (3 months to <1 year) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Arm title | Cohort 4: IMI/REL 15/7.5 mg/kg |
| Arm description: | |
| Toddlers (1 to <2 years) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Arm type | Experimental |
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Toddlers (1 to <2 years) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Arm title | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg |
| Arm description: | |
| Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute dose of IMI/REL at 10/5 mg/kg | |
| Arm type | Experimental |
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute dose of IMI/REL at 10/5 mg/kg | |
| Arm title | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg |
| Arm description: | |
| Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Arm type | Experimental |

| | |
|--|---|
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Arm title | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg |
| Arm description: | |
| Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Arm type | Experimental |
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Arm title | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg |
| Arm description: | |
| Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Arm type | Experimental |
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Arm title | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg |
| Arm description: | |
| Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Arm type | Experimental |
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Arm title | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg |
| Arm description: | |
| Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Arm type | Experimental |

| | |
|--|--|
| Investigational medicinal product name | imipenem/cilastatin/relebactam (IMI/REL) |
| Investigational medicinal product code | |
| Other name | MK-7655A |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| Number of subjects in period 1 | Cohort 1: IMI/REL 15/7.5 mg/kg | Cohort 2: IMI/REL 15/7.5 mg/kg | Cohort 3: IMI/REL 15/7.5 mg/kg |
|--------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Started | 7 | 6 | 6 |
| Treated | 7 | 6 | 6 |
| Completed | 7 | 6 | 6 |
| Not completed | 0 | 0 | 0 |
| Consent withdrawn by subject | - | - | - |

| Number of subjects in period 1 | Cohort 4: IMI/REL 10/5 mg/kg | Cohort 4: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg |
|--------------------------------|---------------------------------|-----------------------------------|---|
| Started | 4 | 4 | 6 |
| Treated | 4 | 4 | 5 |
| Completed | 4 | 4 | 5 |
| Not completed | 0 | 0 | 1 |
| Consent withdrawn by subject | - | - | 1 |

| Number of subjects in period 1 | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg |
|--------------------------------|---|---|---|
| Started | 3 | 2 | 2 |
| Treated | 3 | 2 | 2 |
| Completed | 3 | 2 | 2 |
| Not completed | 0 | 0 | 0 |
| Consent withdrawn by subject | - | - | - |

| Number of subjects in period 1 | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg |
|--------------------------------|---|---|
| Started | 3 | 4 |
| Treated | 3 | 4 |
| Completed | 3 | 4 |
| Not completed | 0 | 0 |
| Consent withdrawn by subject | - | - |

Baseline characteristics

Reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Adolescents (age 12 to <18 years) administered with a single intravenous (IV) 30-minute infusion dose of imipenem/cilastatin/relebactam (IMI/REL) at 15/7.5 mg/kg, up to maximum dose of 500/250 mg | |
| Reporting group title | Cohort 2: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Older children (6 to <12 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg, up to a maximum dose of 500/250 mg | |
| Reporting group title | Cohort 3: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Younger children (2 to <6 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Reporting group title | Cohort 4: IMI/REL 10/5 mg/kg |
| Reporting group description: Infants (3 months to <1 year) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Reporting group title | Cohort 4: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Toddlers (1 to <2 years) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg |
| Reporting group description: Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute dose of IMI/REL at 10/5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg |
| Reporting group description: Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg |
| Reporting group description: Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |

| Reporting group values | Cohort 1: IMI/REL 15/7.5 mg/kg | Cohort 2: IMI/REL 15/7.5 mg/kg | Cohort 3: IMI/REL 15/7.5 mg/kg |
|------------------------|--------------------------------|--------------------------------|--------------------------------|
| Number of subjects | 7 | 6 | 6 |

| | | | |
|---|---|---|---|
| Age Categorical Units: Participants | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 6 | 6 |
| Adolescents (12-17 years) | 7 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Sex: Female, Male Units: Participants | | | |
| Female | 5 | 5 | 4 |
| Male | 2 | 1 | 2 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 7 | 6 | 4 |
| More than one race | 0 | 0 | 1 |
| Unknown or Not Reported | 0 | 0 | 1 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 2 |
| Not Hispanic or Latino | 7 | 6 | 4 |
| Unknown or Not Reported | 0 | 0 | 0 |

| Reporting group values | Cohort 4: IMI/REL 10/5 mg/kg | Cohort 4: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg |
|---|---------------------------------|-----------------------------------|---|
| Number of subjects | 4 | 4 | 6 |
| Age Categorical Units: Participants | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 4 | 4 | 6 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Sex: Female, Male Units: Participants | | | |
| Female | 4 | 2 | 2 |
| Male | 0 | 2 | 4 |

| | | | |
|---|---|---|---|
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 1 | 1 |
| White | 3 | 2 | 5 |
| More than one race | 1 | 1 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 2 | 1 |
| Not Hispanic or Latino | 3 | 2 | 5 |
| Unknown or Not Reported | 0 | 0 | 0 |

| Reporting group values | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg |
|--|---|---|---|
| Number of subjects | 3 | 2 | 2 |
| Age Categorical | | | |
| Units: Participants | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 3 | 2 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 2 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 1 | 1 | 2 |
| Male | 2 | 1 | 0 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 2 | 0 | 0 |
| White | 0 | 2 | 2 |
| More than one race | 1 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 0 |
| Not Hispanic or Latino | 1 | 2 | 2 |
| Unknown or Not Reported | 1 | 0 | 0 |

| Reporting group values | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg | Total |
|---|---|---|-------|
| Number of subjects | 3 | 4 | 47 |
| Age Categorical Units: Participants | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 3 | 4 | 12 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 16 |
| Children (2-11 years) | 0 | 0 | 12 |
| Adolescents (12-17 years) | 0 | 0 | 7 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Sex: Female, Male Units: Participants | | | |
| Female | 1 | 1 | 28 |
| Male | 2 | 3 | 19 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 4 |
| White | 3 | 3 | 37 |
| More than one race | 0 | 0 | 4 |
| Unknown or Not Reported | 0 | 0 | 1 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 7 |
| Not Hispanic or Latino | 3 | 4 | 39 |
| Unknown or Not Reported | 0 | 0 | 1 |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Adolescents (age 12 to <18 years) administered with a single intravenous (IV) 30-minute infusion dose of imipenem/cilastatin/relebactam (IMI/REL) at 15/7.5 mg/kg, up to maximum dose of 500/250 mg | |
| Reporting group title | Cohort 2: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Older children (6 to <12 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg, up to a maximum dose of 500/250 mg | |
| Reporting group title | Cohort 3: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Younger children (2 to <6 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Reporting group title | Cohort 4: IMI/REL 10/5 mg/kg |
| Reporting group description: Infants (3 months to <1 year) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Reporting group title | Cohort 4: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Toddlers (1 to <2 years) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg |
| Reporting group description: Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute dose of IMI/REL at 10/5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg |
| Reporting group description: Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg |
| Reporting group description: Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Reporting group title | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg |
| Reporting group description: Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |
| Subject analysis set title | Cohort 1: IMI/REL 500/250 mg 30-minute infusion |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Adolescents (age 12 to <18 years) administered with a single IV 30-minute infusion dose of IMI/REL at 500/250 mg | |
| Subject analysis set title | Cohort 2: IMI/REL 15/7.5 mg/kg 30-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Older children (6 to <12 years) administered with a single IV 30-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|----------------------------|--|
| Subject analysis set title | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Older children (6 to <12 years) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Older children (6 to <12 years) administered with a single IV 30-minute infusion dose of IMI/REL at 500/250 mg

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 2: IMI/REL 500/250 mg 60-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Older children (6 to <12 years) administered with a single IV 60-minute infusion dose of IMI/REL at 500/250 mg

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 3: IMI/REL 15/7.5 mg/kg 30-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Younger children (2 to <6 years) administered with a single IV 30-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 3: IMI/REL 15/7.5 mg/kg 60-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Younger children (2 to <6 years) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 4: IMI/REL 10/5 mg/kg 60-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Infants (3 months to <1 year) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 4: IMI/REL 15/7.5 mg/kg 60-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Toddlers (1 to 2 years) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 5: IMI/REL 10/5 mg/kg 60-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Neonates to infants (birth to <3 months of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg

| | |
|----------------------------|---|
| Subject analysis set title | Cohort 5: IMI/REL 15/7.5 mg/kg 60-minute infusion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Neonates to infants (birth to <3 months of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

Primary: Imipenem (IMI) Area Under the Concentration Time Curve From Time 0 to Infinity (AUC0-∞)

| | |
|-----------------|--|
| End point title | Imipenem (IMI) Area Under the Concentration Time Curve From Time 0 to Infinity (AUC0-∞) ^[1] |
|-----------------|--|

End point description:

Area under the concentration time curve from time 0 to infinity (AUC0-∞) of plasma imipenem (IMI) was calculated. AUC0-∞ is the area under the plasma concentration versus time curve from time zero

(pre-dose) to extrapolated infinite time.

| | |
|--|---------|
| End point type | Primary |
| End point timeframe: | |
| 30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5 | |

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: There were no between-group statistical analyses performed for this endpoint.

| | | | | |
|---|---|---|--|---|
| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: $\mu\text{M}\cdot\text{hr}$ | | | | |
| geometric mean (geometric coefficient of variation) | 134.7 (\pm 19.8) | 153.2 (\pm 9999) | 219.4 (\pm 39.2) | 139.4 (\pm 26.6) |

| | | | | |
|---|---|---|---|---|
| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |
| Units: $\mu\text{M}\cdot\text{hr}$ | | | | |
| geometric mean (geometric coefficient of variation) | 140 (\pm 9999) | 156 (\pm 18.9) | 163 (\pm 31.2) | 95.4 (\pm 39.3) |

| | | | | |
|---|---|---|---|--|
| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 6 | 9 | |
| Units: $\mu\text{M}\cdot\text{hr}$ | | | | |
| geometric mean (geometric coefficient of variation) | 219.2 (\pm 39.6) | 152.5 (\pm 14.1) | 271.3 (\pm 15.4) | |

Statistical analyses

No statistical analyses for this end point

Primary: IMI Maximum Concentration (Cmax)

| | |
|-----------------|---|
| End point title | IMI Maximum Concentration (Cmax) ^[2] |
|-----------------|---|

End point description:

Maximum plasma concentration (C_{max}) of IMI was calculated. C_{max} is the peak plasma concentration of study drug after administration. The analysis population for this endpoint included all allocated participants who were compliant with the protocol and had at least 1 post-dose pharmacokinetic (PK) data point available for IMI C_{max}.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|---|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: µM | | | | |
| geometric mean (geometric coefficient of variation) | 107.6 (± 16.4) | 126.0 (± 9999) | 123.0 (± 20.6) | 114.2 (± 9.2) |

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |
| Units: µM | | | | |
| geometric mean (geometric coefficient of variation) | 110.6 (± 9999) | 150.3 (± 6.7) | 125.1 (± 25.2) | 64.9 (± 29.6) |

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|---|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 6 | 9 | |
| Units: µM | | | | |
| geometric mean (geometric coefficient of variation) | 127.7 (± 36.0) | 79.4 (± 26.4) | 119.8 (± 16.8) | |

Statistical analyses

Primary: IMI Central Volume of Distribution (Vc)

| | |
|-----------------|--|
| End point title | IMI Central Volume of Distribution (Vc) ^[3] |
|-----------------|--|

| |
|------------------------|
| End point description: |
|------------------------|

| |
|---|
| Central volume of distribution (Vc) of plasma IMI was calculated. |
|---|

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

| |
|----------------------|
| End point timeframe: |
|----------------------|

| |
|--|
| 30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5 |
|--|

| |
|--------|
| Notes: |
|--------|

| |
|---|
| [3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. |
|---|

| |
|--|
| Justification: There were no between-group statistical analyses performed for this endpoint. |
|--|

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|---|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | 10.27 (± 16.2) | 8.00 (± 9999) | 4.33 (± 5.2) | 9.60 (± 2.4) |

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | 8.70 (± 9999) | 3.49 (± 19.6) | 2.49 (± 34.6) | 2.39 (± 53.2) |

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|---|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 6 | 9 | |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | 1.52 (± 35.0) | 1.06 (± 29.6) | 0.95 (± 34.2) | |

Statistical analyses

No statistical analyses for this end point

Primary: IMI Clearance (CL)

| | |
|-----------------|-----------------------------------|
| End point title | IMI Clearance (CL) ^[4] |
|-----------------|-----------------------------------|

End point description:

Systemic clearance (CL) of plasma IMI was calculated. The analysis population for this endpoint included all allocated participants who were compliant with the protocol and had at least 1 post-dose PK data point available for IMI CL.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|---|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | 12.58 (± 18.4) | 9.60 (± 9999) | 5.25 (± 9.2) | 11.67 (± 27.6) |

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | 11.74 (± 9999) | 5.31 (± 29.7) | 4.43 (± 45.2) | 3.31 (± 60.1) |

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|---|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 6 | 9 | |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | 1.70 (± 48.1) | 1.10 (± 26.2) | 0.66 (± 20.4) | |

Statistical analyses

No statistical analyses for this end point

Primary: IMI Percentage of Time Above the Minimum Concentration (%TMIC)

| | |
|-----------------|---|
| End point title | IMI Percentage of Time Above the Minimum Concentration (%TMIC) ^[5] |
|-----------------|---|

End point description:

Percentage of time spent above the minimum inhibitory concentration (%TMIC) of plasma IMI was calculated. %TMIC is defined as the percentage of time (in hours) in which the lowest concentration of a study drug, completely inhibits growth of the specific organism being tested. The analysis population for this endpoint included all allocated participants who were compliant with the protocol and had at least 1 post-dose PK data point available for IMI %TMIC.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|---|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: Percentage of time | | | | |
| geometric mean (geometric coefficient of variation) | 56.5 (± 17.1) | 58.3 (± 9999) | 80.3 (± 26.7) | 61.6 (± 25.1) |

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |
| Units: Percentage of time | | | | |
| geometric mean (geometric coefficient of variation) | 56.7 (± 9999) | 50.1 (± 15.7) | 57.7 (± 18.8) | 50.4 (± 30.5) |

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|---|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 6 | 9 | |
| Units: Percentage of time | | | | |
| geometric mean (geometric coefficient of variation) | 73.9 (± 19.7) | 70.2 (± 10.6) | 93.7 (± 9.3) | |

Statistical analyses

No statistical analyses for this end point

Primary: Relebactam (REL) AUC0-∞

| | |
|-----------------|--|
| End point title | Relebactam (REL) AUC0-∞ ^[6] |
|-----------------|--|

End point description:

Area under the concentration time curve from time 0 to infinity (AUC0-∞) of plasma relebactam (REL) was calculated. AUC0-∞ is the area under the plasma concentration versus time curve from time zero (pre-dose) to extrapolated infinite time. The analysis population for this endpoint included all allocated participants who were compliant with the protocol and had at least 1 post-dose PK data point available for REL AUC0-∞.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

Notes:

[6] - 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: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|---|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: µM*hr | | | | |
| geometric mean (geometric coefficient of variation) | 80.1 (± 20.0) | 105.6 (± 9999) | 123.8 (± 59.5) | 90.3 (± 35.1) |

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |
| Units: µM*hr | | | | |
| geometric mean (geometric coefficient of variation) | 80.2 (± 9999) | 85.7 (± 32.4) | 81.7 (± 42.0) | 52.8 (± 33.6) |

| | | | | |
|---|---|---|---|--|
| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 6 | 9 | |
| Units: $\mu\text{M}\cdot\text{hr}$ | | | | |
| geometric mean (geometric coefficient of variation) | 126.6 (\pm 53.7) | 91.8 (\pm 18.3) | 220.7 (\pm 34.1) | |

Statistical analyses

No statistical analyses for this end point

Primary: REL Maximum Concentration (Cmax)

| | |
|--|---|
| End point title | REL Maximum Concentration (Cmax) ^[7] |
| End point description: | |
| Maximum plasma concentration (Cmax) of REL was calculated. Cmax is the peak plasma concentration of study drug after administration. The analysis population for this endpoint included all allocated participants who were compliant with the protocol and had at least 1 post-dose PK data point available for REL Cmax. | |
| End point type | Primary |
| End point timeframe: | |
| 30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5 | |

Notes:

[7] - 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: There were no between-group statistical analyses performed for this endpoint.

| | | | | |
|---|---|---|--|---|
| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: μM | | | | |
| geometric mean (geometric coefficient of variation) | 49.33 (\pm 23.0) | 86.52 (\pm 9999) | 60.32 (\pm 30.7) | 57.44 (\pm 26.1) |

| | | | | |
|-----------------------------|---|---|---|---|
| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |

| | | | | |
|---|---------------------|---------------------|---------------------|---------------------|
| Units: μM | | | | |
| geometric mean (geometric coefficient of variation) | 48.73 (\pm 9999) | 59.05 (\pm 9.08) | 48.59 (\pm 22.9) | 32.74 (\pm 15.0) |

| | | | | |
|---|---|---|---|--|
| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 6 | 9 | |
| Units: μM | | | | |
| geometric mean (geometric coefficient of variation) | 59.55 (\pm 17.1) | 34.22 (\pm 17.3) | 61.04 (\pm 21.9) | |

Statistical analyses

No statistical analyses for this end point

Primary: REL Clearance (CL)

| | |
|-----------------|-----------------------------------|
| End point title | REL Clearance (CL) ^[8] |
|-----------------|-----------------------------------|

End point description:

Systemic clearance (CL) of plasma REL was calculated. The analysis population for this endpoint included all allocated participants who were compliant with the protocol and had at least 1 post-dose PK data point available for REL CL.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

Notes:

[8] - 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: There were no between-group statistical analyses performed for this endpoint.

| | | | | |
|---|---|---|--|---|
| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | 8.98 (\pm 20.7) | 6.10 (\pm 9999) | 3.96 (\pm 28.9) | 8.03 (\pm 35.7) |

| | | | | |
|-------------------------|---|---|---|---|
| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|-------------------------|---|---|---|---|

| | | | | |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | 8.65 (\pm 9999) | 4.20 (\pm 40.8) | 3.65 (\pm 54.1) | 2.56 (\pm 54.5) |

| | | | | |
|---|---|---|---|--|
| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 6 | 9 | |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | 1.27 (\pm 62.9) | 0.74 (\pm 27.0) | 0.35 (\pm 30.7) | |

Statistical analyses

No statistical analyses for this end point

Primary: REL Central Volume of Distribution (Vc)

| | |
|-----------------|--|
| End point title | REL Central Volume of Distribution (Vc) ^[9] |
|-----------------|--|

End point description:

Central volume of distribution (Vc) of plasma REL was calculated. The analysis population for this endpoint included all allocated participants who were compliant with the protocol and had at least 1 post-dose PK data point available for REL Vc.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

Notes:

[9] - 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: There were no between-group statistical analyses performed for this endpoint.

| | | | | |
|---|---|---|--|---|
| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | 10.58 (\pm 17.2) | 6.76 (\pm 9999) | 4.95 (\pm 1.6) | 9.81 (\pm 6.1) |

| | | | | |
|-------------------------|----------------------|-----------------------------|-----------------------------|---------------------------|
| End point values | Cohort 2: IMI/REL | Cohort 3: IMI/REL 15/7.5 | Cohort 3: IMI/REL 15/7.5 | Cohort 4: IMI/REL 10/5 |
|-------------------------|----------------------|-----------------------------|-----------------------------|---------------------------|

| | 500/250 mg 60-minute infusion | mg/kg 30- minute infusion | mg/kg 60- minute infusion | mg/kg 60- minute infusion |
|---|-------------------------------------|------------------------------|------------------------------|------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | 9.38 (± 9999) | 3.83 (± 13.8) | 2.88 (± 27.4) | 2.43 (± 38.8) |

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|---|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 6 | 9 | |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | 1.70 (± 21.1) | 1.21 (± 24.6) | 0.90 (± 36.7) | |

Statistical analyses

No statistical analyses for this end point

Primary: Cilastatin (CIL) AUC0-∞

| | |
|-----------------|---|
| End point title | Cilastatin (CIL) AUC0-∞ ^[10] |
|-----------------|---|

End point description:

Area under the concentration time curve from time 0 to infinity (AUC0-∞) of plasma cilastatin (CIL) was not calculated. AUC0-∞ is the area under the plasma concentration versus time curve from time zero (pre-dose) to extrapolated infinite time.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

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: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|---|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[11] | 0 ^[12] | 0 ^[13] | 0 ^[14] |
| Units: µM*hr | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[11] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[12] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[13] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[14] - Due to sparse PK sampling schedule, per participant data could not be calculated.

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[15] | 0 ^[16] | 0 ^[17] | 0 ^[18] |
| Units: µM*hr | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[15] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[16] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[17] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[18] - Due to sparse PK sampling schedule, per participant data could not be calculated.

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|---|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 0 ^[19] | 0 ^[20] | 0 ^[21] | |
| Units: µM*hr | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | |

Notes:

[19] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[20] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[21] - Due to sparse PK sampling schedule, per participant data could not be calculated.

Statistical analyses

No statistical analyses for this end point

Primary: CIL Time to Maximum Concentration (Tmax)

| | |
|---|--|
| End point title | CIL Time to Maximum Concentration (Tmax) ^[22] |
| End point description: Time to maximum plasma concentration (Tmax) of CIL was determined. Tmax is defined as the time after drug administration at which peak drug concentration in plasma occurs. The analysis population for this endpoint included all allocated participants who were compliant with the protocol and had at least 1 post-dose PK data point available for CIL Tmax. | |
| End point type | Primary |
| End point timeframe: 30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5 | |

Notes:

[22] - 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: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|-------------------------------|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: Hours | | | | |
| median (full range (min-max)) | 0.58 (0.52 to 0.58) | 0.53 (0.53 to 0.53) | 1.1 (1.1 to 1.1) | 0.58 (0.57 to 0.58) |

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|-------------------------------|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 4 |
| Units: Hours | | | | |
| median (full range (min-max)) | 1.1 (1.1 to 1.1) | 0.58 (0.57 to 0.58) | 1.1 (1.1 to 1.1) | 1.1 (1.1 to 1.7) |

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|-------------------------------|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 7 | 9 | |
| Units: Hours | | | | |
| median (full range (min-max)) | 1.2 (1.1 to 1.2) | 1.1 (1.1 to 1.2) | 1.2 (1.1 to 1.3) | |

Statistical analyses

No statistical analyses for this end point

Primary: CIL Concentration at End of Infusion (Ceoi)

| | |
|---|---|
| End point title | CIL Concentration at End of Infusion (Ceoi) ^[23] |
| End point description: Concentration at end of infusion (Ceoi) of plasma CIL was determined. The analysis population for this endpoint included all allocated participants who were compliant with the protocol and had at least 1 post-dose PK data point available for CIL Ceoi. | |
| End point type | Primary |
| End point timeframe: 30 min after the start of infusion for Cohort 1; 60 min after the start of infusion for Cohorts 2-5 | |

Notes:

[23] - 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: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|---|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 1 | 2 | 2 |
| Units: μM | | | | |
| geometric mean (geometric coefficient of variation) | 86.9 (\pm 41.0) | 122 (\pm 9999) | 111 (\pm 51) | 80.5 (\pm 22) |

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1 | 3 | 3 | 3 |
| Units: μM | | | | |
| geometric mean (geometric coefficient of variation) | 74.8 (\pm 9999) | 102 (\pm 32) | 80.9 (\pm 62) | 37.0 (\pm 64.0) |

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|---|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 4 | 7 | 9 | |
| Units: μM | | | | |
| geometric mean (geometric coefficient of variation) | 94.5 (\pm 42.0) | 63.6 (\pm 28.0) | 107.0 (\pm 20.0) | |

Statistical analyses

No statistical analyses for this end point

Primary: CIL Terminal Half-Life ($t_{1/2}$)

| | |
|-----------------|--|
| End point title | CIL Terminal Half-Life ($t_{1/2}$) ^[24] |
|-----------------|--|

End point description:

Terminal half-life ($t_{1/2}$) of plasma CIL was not calculated.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

Notes:

[24] - 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: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|--------------------------------------|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[25] | 0 ^[26] | 0 ^[27] | 0 ^[28] |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[25] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[26] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[27] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[28] - Due to sparse PK sampling schedule, per participant data could not be calculated.

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|--------------------------------------|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[29] | 0 ^[30] | 0 ^[31] | 0 ^[32] |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[29] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[30] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[31] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[32] - Due to sparse PK sampling schedule, per participant data could not be calculated.

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|--------------------------------------|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 0 ^[33] | 0 ^[34] | 0 ^[35] | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | () | () | () | |

Notes:

[33] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[34] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[35] - Due to sparse PK sampling schedule, per participant data could not be calculated.

Statistical analyses

No statistical analyses for this end point

Primary: CIL Clearance (CL)

End point title CIL Clearance (CL)^[36]

End point description:

Systemic clearance (CL) of plasma CIL was not calculated.

End point type Primary

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

Notes:

[36] - 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: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg mg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|---|---|---|--|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[37] | 0 ^[38] | 0 ^[39] | 0 ^[40] |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[37] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[38] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[39] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[40] - Due to sparse PK sampling schedule, per participant data could not be calculated.

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[41] | 0 ^[42] | 0 ^[43] | 0 ^[44] |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[41] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[42] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[43] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[44] - Due to sparse PK sampling schedule, per participant data could not be calculated.

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|---|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 0 ^[45] | 0 ^[46] | 0 ^[47] | |
| Units: L/hr | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | |

Notes:

[45] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[46] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[47] - Due to sparse PK sampling schedule, per participant data could not be calculated.

Statistical analyses

No statistical analyses for this end point

Primary: CIL Volume of Distribution (Vss)

| | |
|-----------------|--|
| End point title | CIL Volume of Distribution (Vss) ^[48] |
|-----------------|--|

End point description:

Volume of distribution (Vss) of plasma CIL was not calculated.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 minutes (min) before start of drug infusion (DI) and 10 min after the end of DI for all cohorts; 1.5 to 2.5 hours (hrs) and 4.5 to 6 hrs after start of DI for Cohorts 1-4; 2 to 5 hrs and 6 to 12 hrs after start of DI for Cohort 5

Notes:

[48] - 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: There were no between-group statistical analyses performed for this endpoint.

| End point values | Cohort 1: IMI/REL 500/250 mg 30-minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 2: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 2: IMI/REL 500/250 mg 30-minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[49] | 0 ^[50] | 0 ^[51] | 0 ^[52] |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[49] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[50] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[51] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[52] - Due to sparse PK sampling schedule, per participant data could not be calculated.

| End point values | Cohort 2: IMI/REL 500/250 mg 60-minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 30- minute infusion | Cohort 3: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 4: IMI/REL 10/5 mg/kg 60- minute infusion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[53] | 0 ^[54] | 0 ^[55] | 0 ^[56] |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | () |

Notes:

[53] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[54] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[55] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[56] - Due to sparse PK sampling schedule, per participant data could not be calculated.

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 10/5 mg/kg 60- minute infusion | Cohort 5: IMI/REL 15/7.5 mg/kg 60- minute infusion | |
|---|---|---|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 0 ^[57] | 0 ^[58] | 0 ^[59] | |
| Units: Liters | | | | |
| geometric mean (geometric coefficient of variation) | () | () | () | |

Notes:

[57] - Due to sparse PK sampling schedule, per participant data could not be calculated.

[58] - Due to sparse PK sampling schedule, per participant data could not be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Adverse Event (AE)

| | |
|---|--|
| End point title | Number of Participants Who Experienced an Adverse Event (AE) |
| End point description: | |
| Number of participants with one or more AEs was calculated. An AE is defined as any untoward medical occurrence in a participant administered study drug and which may or may not have a causal relationship to the study drug. The analysis population for this endpoint included all allocated participants who received an infusion (including partial doses) of study drug. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 17 days | |

| End point values | Cohort 1: IMI/REL 15/7.5 mg/kg | Cohort 2: IMI/REL 15/7.5 mg/kg | Cohort 3: IMI/REL 15/7.5 mg/kg | Cohort 4: IMI/REL 10/5 mg/kg |
|-----------------------------|--------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 6 | 6 | 4 |
| Units: Participants | 1 | 0 | 3 | 1 |

| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg |
|-----------------------------|--------------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 2 |
| Units: Participants | 2 | 1 | 0 | 0 |

| End point values | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 2 | 3 | 4 | |
| Units: Participants | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Drug Due to an AE

| | |
|-----------------|---|
| End point title | Number of Participants Who Discontinued Study Drug Due to an AE |
|-----------------|---|

End point description:

Number of participants who discontinued study drug due to an AE was calculated. An AE is defined as any untoward medical occurrence in a participant administered study drug and which may or may not have a causal relationship to the study drug. The analysis population for this endpoint included all allocated participants who received an infusion (including partial doses) of study drug.

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

End point timeframe:

Day 1

| | | | | |
|-----------------------------|--------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|
| End point values | Cohort 1: IMI/REL 15/7.5 mg/kg | Cohort 2: IMI/REL 15/7.5 mg/kg | Cohort 3: IMI/REL 15/7.5 mg/kg | Cohort 4: IMI/REL 10/5 mg/kg |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 7 | 6 | 6 | 4 |
| Units: Participants | 0 | 0 | 0 | 0 |

| | | | | |
|-----------------------------|--------------------------------------|--|--|--|
| End point values | Cohort 4: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 3 | 2 |
| Units: Participants | 0 | 0 | 0 | 0 |

| | | | | |
|-----------------------------|--|--|--|--|
| End point values | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg | |
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 2 | 3 | 4 | |
| Units: Participants | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 17 days (AE reporting), up to 19 days (all-cause mortality)

Adverse event reporting additional description:

The analysis population included all allocated participants who received infusion (including partial doses) of study drug. Note: Participant information is shown by age cohort and drug dosage, to provide clinically-similar groups for analysis of safety data.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Cohort 1: IMI/REL 15/7.5 mg/kg |
|-----------------------|--------------------------------|

Reporting group description:

Adolescents (age 12 to <18 years) administered with a single IV 30-minute infusion dose of IMI/REL at 15/7.5 mg/kg, up to maximum dose of 500/250 mg

| | |
|-----------------------|--------------------------------|
| Reporting group title | Cohort 2: IMI/REL 15/7.5 mg/kg |
|-----------------------|--------------------------------|

Reporting group description:

Older children (6 to <12 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg, up to a maximum dose of 500/250 mg

| | |
|-----------------------|--------------------------------|
| Reporting group title | Cohort 3: IMI/REL 15/7.5 mg/kg |
|-----------------------|--------------------------------|

Reporting group description:

Younger children (2 to <6 years) administered with a single IV 30-minute or 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|-----------------------|------------------------------|
| Reporting group title | Cohort 4: IMI/REL 10/5 mg/kg |
|-----------------------|------------------------------|

Reporting group description:

Infants (3 months to <1 year) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg

| | |
|-----------------------|--------------------------------|
| Reporting group title | Cohort 4: IMI/REL 15/7.5 mg/kg |
|-----------------------|--------------------------------|

Reporting group description:

Toddlers (1 to <2 years) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|-----------------------|---|
| Reporting group title | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg |
|-----------------------|---|

Reporting group description:

Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute dose of IMI/REL at 10/5 mg/kg

| | |
|-----------------------|---|
| Reporting group title | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg |
|-----------------------|---|

Reporting group description:

Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg

| | |
|-----------------------|---|
| Reporting group title | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg |
|-----------------------|---|

Reporting group description:

Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 10/5 mg/kg

| | |
|-----------------------|---|
| Reporting group title | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg |
|-----------------------|---|

Reporting group description:

Older neonates (1 to <4 weeks of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|-----------------------|---|
| Reporting group title | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg |
|-----------------------|---|

Reporting group description:

Young infants (4 weeks to <3 months of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg

| | |
|--|---|
| Reporting group title | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg |
| Reporting group description: | |
| Younger neonates (<1 week of age) administered with a single IV 60-minute infusion dose of IMI/REL at 15/7.5 mg/kg | |

| Serious adverse events | Cohort 1: IMI/REL 15/7.5 mg/kg | Cohort 2: IMI/REL 15/7.5 mg/kg | Cohort 3: IMI/REL 15/7.5 mg/kg |
|---|--------------------------------|--------------------------------|--------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

| Serious adverse events | Cohort 4: IMI/REL 10/5 mg/kg | Cohort 4: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg |
|---|------------------------------|--------------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

| Serious adverse events | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

| Serious adverse events | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg | |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

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

| Non-serious adverse events | Cohort 1: IMI/REL 15/7.5 mg/kg | Cohort 2: IMI/REL 15/7.5 mg/kg | Cohort 3: IMI/REL 15/7.5 mg/kg |
|--|-----------------------------------|-----------------------------------|-----------------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 1 / 7 (14.29%) | 0 / 6 (0.00%) | 3 / 6 (50.00%) |
| Investigations | | | |
| Aspartate aminotransferase increased subjects affected / exposed | 1 / 7 (14.29%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alanine aminotransferase increased subjects affected / exposed | 1 / 7 (14.29%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neutrophil count decreased subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed | 1 / 7 (14.29%) | 0 / 6 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Thrombocytoses subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Miliaria subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed | 0 / 7 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Cohort 4: IMI/REL 10/5 mg/kg | Cohort 4: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 1: IMI/REL 10/5 mg/kg |
|--|---------------------------------|-----------------------------------|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 1 / 4 (25.00%) | 2 / 4 (50.00%) | 1 / 5 (20.00%) |

| | | | |
|--|----------------|----------------|----------------|
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombocytoses | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Miliaria | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Non-serious adverse events | Cohort 5: Subcohort 3: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 2: IMI/REL 10/5 mg/kg | Cohort 5: Subcohort 2: IMI/REL 15/7.5 mg/kg |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 0 / 3 (0.00%) | 0 / 3 (0.00%) |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |

| | | | |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Thrombocytoses subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Miliaria subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 |

| Non-serious adverse events | Cohort 5: Subcohort 1: IMI/REL 15/7.5 mg/kg | Cohort 5: Subcohort 3: IMI/REL 15/7.5 mg/kg | |
|---|---|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 0 / 2 (0.00%) | 0 / 4 (0.00%) | |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Alanine aminotransferase increased | | | |

| | | | |
|--|--------------------|--------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Thrombocytoses subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders Miliaria subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 2 (0.00%) 0 | 0 / 4 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 30 January 2019 | Amendment 1: To allow enrollment of participants who may have neonatal hyperbilirubinemia within 24 hours of birth that is part of a normal physiologic process and to remove weight-based exclusion criterion for Cohorts 4 and 5. |
| 12 September 2019 | Amendment 2: To allow enrollment into Cohort 5 of participants who are at least 37 weeks postmenstrual age at the time of screening, regardless of their actual gestational age at birth. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported