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)	EMEA-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: µM*hr				
geometric mean (geometric coefficient of variation)	134.7 (± 19.8)	153.2 (± 9999)	219.4 (± 39.2)	139.4 (± 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: µM*hr				
geometric mean (geometric coefficient of variation)	140 (± 9999)	156 (± 18.9)	163 (± 31.2)	95.4 (± 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: µM*hr				
geometric mean (geometric coefficient of variation)	219.2 (± 39.6)	152.5 (± 14.1)	271.3 (± 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 (Cmax) of IMI 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 pharmacokinetic (PK) data point available for IMI 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:

[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

No statistical analyses for this end point

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: µM*hr				
geometric mean (geometric coefficient of variation)	126.6 (± 53.7)	91.8 (± 18.3)	220.7 (± 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 (± 23.0)	86.52 (± 9999)	60.32 (± 30.7)	57.44 (± 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 (± 9999)	59.05 (± 9.08)	48.59 (± 22.9)	32.74 (± 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 (± 17.1)	34.22 (± 17.3)	61.04 (± 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 (± 20.7)	6.10 (± 9999)	3.96 (± 28.9)	8.03 (± 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 (± 9999)	4.20 (± 40.8)	3.65 (± 54.1)	2.56 (± 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 (± 62.9)	0.74 (± 27.0)	0.35 (± 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 (± 17.2)	6.76 (± 9999)	4.95 (± 1.6)	9.81 (± 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 (± 41.0)	122 (± 9999)	111 (± 51)	80.5 (± 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 (± 9999)	102 (± 32)	80.9 (± 62)	37.0 (± 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 (± 42.0)	63.6 (± 28.0)	107.0 (± 20.0)	

Statistical analyses

No statistical analyses for this end point

Primary: CIL Terminal Half-Life (t1/2)

End point title	CIL Terminal Half-Life (t1/2)[24]

End point description:

Terminal half-life (t1/2) 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 to12 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 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[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.

[59] - 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	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thrombocytoses			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Miliaria			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	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	0 / 2 (0.00%)	0 / 4 (0.00%)	
occurrences (all)	0	0	
Alanine aminotransferase increased			

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