Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Single-Ascending Dose Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of GWP42003-P in Conjunction with Hypothermia in Neonates with Moderate or Severe Hypoxic Ischemic Encephalopathy

Summary

EudraCT number	2016-000936-17
Trial protocol	GB ES PL
Global end of trial date	01 June 2022

Results information

Result version number	v1 (current)
This version publication date	16 December 2022
First version publication date	16 December 2022

Trial information

Trial identification

Sponsor protocol code	GWEP1560

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GW Research Ltd
Sponsor organisation address	Sovereign House, Vision Park, Histon, Cambridge, United Kingdom, CB24 9BZ
Public contact	Clinical Trial Disclosure & Transparency, GW Research Ltd, +1 215-832-3750, ClinicalTrialDisclosure@JazzPharma.com
Scientific contact	Clinical Trial Disclosure & Transparency, GW Research Ltd, +1 215-832-3750, ClinicalTrialDisclosure@JazzPharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 June 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of a single-ascending intravenous (IV) dose of GWP42003-P compared with placebo in neonates (minimum of 36 weeks plus 0 days gestational age) who are undergoing whole-body hypothermia (standard of care) for the treatment of NHIE.

Protection of trial subjects:

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice, and other applicable laws and regulations. The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents were reviewed and approved by the Institutional Review Board/Independent Ethics Committee prior to study initiation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	13
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	1
Newborns (0-27 days)	12
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 13 patients who met all inclusion criteria and no exclusion criteria were randomized to receive a single dose of GWP42003-P (0.1 mg/kg, 0.3 mg/kg, or 1.0 mg/kg) at 8 clinic centers in Poland, Spain, and United Kingdom.

Pre-assignment

Screening details:

Eligible patients were randomized to receive a single IV dose of GWP42003-P or placebo as soon as possible after the required core temperature for whole-body hypothermia had been achieved and within 18 hours of birth.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GWP42003-P 0.1 mg/kg

Arm description:

Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 0.1 mg/kg.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GWP42003-P was administered as a single 15-minute IV infusion using an infusion pump as soon as possible after the required core temperature for whole-body hypothermia had been achieved and within 18 hours of birth.

Arm title	GWP42003-P 0.3 mg/kg

Arm description:

Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 0.3 mg/kg.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GWP42003-P was administered as a single 15-minute IV infusion using an infusion pump as soon as possible after the required core temperature for whole-body hypothermia had been achieved and within 18 hours of birth.

Arm title	GWP42003-P 1.0 mg/kg

Arm description:

Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 1.0 mg/kg.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GWP42003-P was administered as a single 15-minute IV infusion using an infusion pump as soon as possible after the required core temperature for whole-body hypothermia had been achieved and within 18 hours of birth.

Arm title	Pooled Placebo

Arm description:

All patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of placebo-matched treatment.

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

Dosage and administration details:

Placebo was administered as a single 15-minute IV infusion using an infusion pump as soon as possible after the required core temperature for whole-body hypothermia had been achieved and within 18 hours of birth.

Number of subjects in period 1	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg
Started	3	3	3
Completed	3	2	3
Not completed	0	1	0
Lost to follow-up	-	1	-
Sponsor decision	-	-	-

Number of subjects in period 1	Pooled Placebo
Started	4
Completed	3
Not completed	1
Lost to follow-up	-
Sponsor decision	1

Baseline characteristics

Reporting groups	
Reporting group title	GWP42003-P 0.1 mg/kg
Reporting group description:	
Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 0.1 mg/kg.	
Reporting group title	GWP42003-P 0.3 mg/kg
Reporting group description:	
Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 0.3 mg/kg.	
Reporting group title	GWP42003-P 1.0 mg/kg
Reporting group description:	
Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 1.0 mg/kg.	
Reporting group title	Pooled Placebo
Reporting group description:	
All patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of placebo-matched treatment.	

Reporting group values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg
Number of subjects	3	3	3
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	1	0	0
Newborns (0-27 days)	2	3	3
Infants and toddlers (28 days-23 months)	0	0	0
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
Age continuous			
Age at randomization (hours)			
Units: hours			
arithmetic mean	9.44	8.68	10.23
standard deviation	± 1.11	± 0.91	± 3.98
Gender categorical			
Units: Subjects			
Female	0	1	3
Male	3	2	0

Reporting group values	Pooled Placebo	Total	
Number of subjects	4	13	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	1	
Newborns (0-27 days)	4	12	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age at randomization (hours)			
Units: hours			
arithmetic mean	10.86		
standard deviation	± 0.75	-	
Gender categorical Units: Subjects			
Female	2	6	
Male	2	7	

End points

End points reporting groups

Reporting group title	GWP42003-P 0.1 mg/kg
Reporting group description:	
Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 0.1 mg/kg.	
Reporting group title	GWP42003-P 0.3 mg/kg
Reporting group description:	
Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 0.3 mg/kg.	
Reporting group title	GWP42003-P 1.0 mg/kg
Reporting group description:	
Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 1.0 mg/kg.	
Reporting group title	Pooled Placebo
Reporting group description:	
All patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of placebo-matched treatment.	

Primary: An Overview of Safety Summary in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	An Overview of Safety Summary in Neonatal Patients Who Received GWP42003-P or Matching Placebo[1]
End point description:	
An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Serious AEs are any AE that: results in death, is life threatening, or places the patient at immediate risk of death from the event as it occurred, requires or prolongs hospitalization, causes persistent or significant disability or incapacity, or results in congenital anomalies or birth defects.	
End point type	Primary
End point timeframe:	
Consent (screening) up to and including the post-trial follow-up visit at Day 30	

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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	4
Units: Number of AEs				
number (not applicable)				
Any AE	12	7	9	16
Mild AE	4	6	7	13
Moderate AE	7	0	2	3
Severe AE	1	1	0	0
Study-drug related AE	1	0	1	2

AEs that led to study withdrawal	0	0	0	0
Serious AE	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Mortality Rate in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Mortality Rate in Neonatal Patients Who Received GWP42003-P or Matching Placebo[2]

End point description:

Mortality was defined as death due to any cause.

End point type	Primary

End point timeframe:

Randomization up to Day 30

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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	4
Units: Number of patients				
number (not applicable)				
Death	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Day 10 in Alkaline Phosphatase, Alanine Aminotransferase, and Aspartate Aminotransferase in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Change From Baseline to Day 10 in Alkaline Phosphatase, Alanine Aminotransferase, and Aspartate Aminotransferase in Neonatal Patients Who Received GWP42003-P or Matching Placebo[3]

End point description:

End point type	Primary

End point timeframe:

Baseline up to Day 10

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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[4]	1[5]	1[6]	1[7]
Units: Units/liter				
median (full range (min-max))				
Alkaline phosphatase	31.0 (31.0 to 31.0)	-2.0 (-2.0 to -2.0)	0 (0 to 0)	0 (0 to 0)
Alanine aminotransferase	-15.0 (-21.0 to -9.0)	-103.0 (-103.0 to -103.0)	-65.0 (-65.0 to -65.0)	11.0 (11.0 to 11.0)
Aspartate aminotransferase	-139.0 (-139.0 to -139.0)	0 (0 to 0)	-122.0 (-122.0 to -122.0)	0 (0 to 0)

Notes:

[4] - Alkaline phosphatase n=1; ALT n= 2; AST n=1

[5] - Alkaline phosphatase n=1; ALT n= 1; AST n=0
If 0 (0,0) is reported, it indicates missing values.
[6] - Alkaline phosphatase n=0; ALT n= 1; AST n=1
If 0 (0,0) is reported, it indicates missing values.
[7] - Alk phos n=1; ALT n= 1; AST n=0
0 (0,0) indicates missing values, except Alk phos where 0 is value

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Day 10 in Total Bilirubin and Creatinine in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Change From Baseline to Day 10 in Total Bilirubin and Creatinine in Neonatal Patients Who Received GWP42003-P or Matching Placebo[8]

End point description:

End point type	Primary

End point timeframe:

Baseline up to Day 10

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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[9]	1[10]	0[11]	1
Units: micromole/liter				
median (full range (min-max))				
Total bilirubin	16.0 (8.0 to 24.0)	0 (0 to 0)	(to)	168.0 (168.0 to 168.0)
Creatinine	-27.0 (-27.0 to -27.0)	-31.0 (-31.0 to -31.0)	(to)	-2.0 (-2.0 to -2.0)

Notes:

[9] - Total bilirubin n=2; Creatinine n=1

[10] - Total bilirubin n=0; Creatinine n=1
If 0 (0,0) is reported, it indicates missing values.
[11] - Total bilirubin and creatinine were not assessed in this group.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Day 10 in pH in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Change From Baseline to Day 10 in pH in Neonatal Patients Who Received GWP42003-P or Matching Placebo[12]

End point description:

End point type	Primary

End point timeframe:

Baseline up to Day 10

Notes:

[12] - 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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	0[13]	0[14]	0[15]
Units: logarithmic units				
median (full range (min-max))	0.180 (0.080 to 0.280)	(to)	(to)	(to)

Notes:

[13] - pH was not assessed in this group.

[14] - pH was not assessed in this group.

[15] - pH was not assessed in this group.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Day 10 in Hemoglobin in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Change From Baseline to Day 10 in Hemoglobin in Neonatal Patients Who Received GWP42003-P or Matching Placebo[16]

End point description:

End point type	Primary

End point timeframe:

Baseline up to Day 10

Notes:

[16] - 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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	0[17]	1	1
Units: g/L				
median (full range (min-max))	-77.5 (-130.0 to -25.0)	(to)	-10.0 (-10.0 to -10.0)	-9.0 (-9.0 to -9.0)

Notes:

[17] - Hemoglobin was not assessed in this group.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Day 10 in Platelets and Leukocytes in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Change From Baseline to Day 10 in Platelets and Leukocytes in Neonatal Patients Who Received GWP42003-P or Matching Placebo[18]

End point description:

End point type	Primary

End point timeframe:

Baseline up to Day 10

Notes:

[18] - 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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	0[19]	1	1
Units: 10^9/liter				
median (full range (min-max))				
Platelets	-84.0 (-85.0 to -83.0)	(to)	46.0 (46.0 to 46.0)	24.0 (24.0 to 24.0)
Leukocytes	-8.2 (-16.1 to -0.3)	(to)	-12.6 (-12.6 to -12.6)	-11.8 (-11.8 to -11.8)

Notes:

[19] - Platelets and leukocytes were not assessed in this group.

Statistical analyses

No statistical analyses for this end point

Primary: Median Diastolic and Systolic Blood Pressure Levels in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Median Diastolic and Systolic Blood Pressure Levels in Neonatal Patients Who Received GWP42003-P or Matching Placebo[20]

End point description:

End point type	Primary

End point timeframe:

1 hour after birth up to Visit 7 (discharge from NICU)

Notes:

[20] - 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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[21]	3[22]	3[23]	4[24]
Units: mmHg				
median (full range (min-max))				
Diastolic: 1 hour after birth	29.5 (26 to 33)	32.0 (30 to 50)	0 (0 to 0)	37.5 (32 to 43)
Diastolic: 8 hours after birth	47.0 (40 to 49)	39.0 (35 to 43)	46.0 (46 to 46)	35.0 (33 to 37)
Diastolic: 12 hours after birth	40.0 (36 to 54)	46.0 (40 to 50)	39.0 (31 to 47)	37.5 (36 to 47)
Diastolic: 24 hours after birth	41.0 (30 to 52)	36.5 (25 to 48)	40.0 (34 to 42)	31.0 (20 to 34)
Diastolic: 36 hours after birth	41.0 (30 to 52)	47.0 (44 to 51)	40.0 (36 to 47)	34.0 (32 to 37)
Diastolic: 48 hours after birth	44.0 (36 to 52)	46.0 (43 to 48)	41.0 (35 to 44)	36.5 (30 to 48)
Diastolic:60 hours after birth	42.0 (39 to 48)	41.0 (38 to 64)	37.0 (34 to 41)	45.0 (35 to 54)
Diastolic: 72 hours after birth	46.0 (30 to 48)	49.0 (32 to 66)	43.0 (40 to 46)	36.0 (16 to 56)
Diastolic: 96 hours after birth	42.5 (42 to 43)	42.0 (38 to 46)	28.0 (26 to 42)	33.0 (30 to 41)
Diastolic: 108 hours after birth	47.0 (45 to 49)	51.0 (27 to 53)	40.0 (33 to 51)	40.5 (29 to 48)
Diastolic: 120 hours after birth	44.0 (44 to 44)	46.0 (46 to 46)	56.0 (56 to 56)	59.0 (59 to 59)
Diastolic: Visit 7 (Discharge from NICU)	44.0 (39 to 45)	51.0 (51 to 51)	43.0 (39 to 55)	48.0 (48 to 48)
Systolic: 1 hour after birth	63.0 (56 to 70)	69.0 (62 to 88)	0 (0 to 0)	63.0 (61 to 65)
Systolic: 8 hours after birth	65.0 (61 to 79)	70.0 (62 to 78)	74.0 (74 to 74)	65.0 (59 to 71)
Systolic: 12 hours after birth	53.0 (52 to 79)	70.0 (66 to 70)	68.0 (60 to 76)	66.0 (63 to 75)
Systolic: 24 hours after birth	56.5 (42 to 71)	57.5 (54 to 61)	54.0 (53 to 66)	51.0 (50 to 52)
Systolic: 36 hours after birth	61.0 (50 to 72)	63.0 (60 to 74)	66.0 (61 to 73)	57.0 (45 to 64)
Systolic: 48 hours after birth	60.5 (50 to 71)	62.0 (59 to 71)	70.0 (53 to 73)	61.5 (59 to 62)
Systolic: 60 hours after birth	67.0 (55 to 72)	60.0 (54 to 80)	63.0 (53 to 64)	71.5 (61 to 79)
Systolic: 72 hours after birth	55.0 (46 to 76)	67.0 (55 to 79)	69.5 (66 to 73)	72.5 (62 to 82)
Systolic: 96 hours after birth	63.0 (52 to 74)	74.0 (72 to 75)	71.0 (56 to 74)	64.0 (57 to 70)
Systolic: 108 hours after birth	73.0 (70 to 76)	77.0 (67 to 82)	68.0 (62 to 78)	67.0 (58 to 72)
Systolic: 120 hours after birth	77.0 (77 to 77)	72.0 (72 to 72)	71.0 (71 to 71)	90.0 (90 to 90)
Systolic: Visit 7 (Discharge from NICU)	85.0 (80 to 86)	81.0 (81 to 81)	80.0 (64 to 92)	84.0 (84 to 84)

Notes:

[21] - N's varied by timepoint

[22] - N's varied by timepoint

[23] - N's varied by timepoint
If 0 (0,0) is reported, it indicates missing values.

[24] - N's varied by timepoint

Statistical analyses

No statistical analyses for this end point

Primary: Median Pulse Rate in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Median Pulse Rate in Neonatal Patients Who Received GWP42003-P or Matching Placebo[25]

End point description:

End point type	Primary

End point timeframe:

1 hour after birth up to Visit 7 (discharge from NICU)

Notes:

[25] - 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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[26]	3[27]	3[28]	4[29]
Units: beats/minute				
median (full range (min-max))				
1 hour after birth	139.0 (111 to 140)	142.0 (132 to 152)	130.0 (130 to 130)	100.0 (100 to 136)
8 hours after birth	89.0 (84 to 150)	109.0 (96 to 113)	99.0 (92 to 106)	115.5 (101 to 130)
12 hours after birth	107.0 (93 to 140)	101.0 (98 to 116)	111.0 (80 to 167)	97.0 (89 to 99)
24 hours after birth	109.5 (89 to 130)	101.0 (101 to 101)	107.0 (72 to 141)	101.0 (90 to 111)
36 hours after birth	92.0 (92 to 120)	110.0 (99 to 132)	109.0 (71 to 147)	102.5 (85 to 123)
48 hours after birth	100.0 (94 to 140)	122.0 (99 to 132)	99.0 (80 to 137)	104.0 (101 to 121)
60 hours after birth	100.0 (90 to 107)	108.0 (107 to 116)	88.0 (78 to 111)	97.5 (87 to 125)
72 hours after birth	111.0 (89 to 120)	101.0 (99 to 111)	92.0 (85 to 107)	98.0 (68 to 128)
96 hours after birth	132.0 (128 to 140)	137.0 (128 to 145)	133.0 (119 to 161)	130.0 (122 to 144)
108 hours after birth	128.0 (120 to 140)	124.0 (123 to 143)	126.0 (118 to 138)	135.5 (131 to 138)
120 hours after birth	128.0 (128 to 128)	134.0 (134 to 134)	126.0 (111 to 141)	109.0 (95 to 123)
Visit 7 (Discharge after NICU)	137.0 (118 to 154)	132.0 (126 to 138)	117.0 (107 to 142)	128.0 (128 to 144)

Notes:

[26] - N's varied by timepoint

[27] - N's varied by timepoint

[28] - N's varied by timepoint

[29] - N's varied by timepoint

Statistical analyses

No statistical analyses for this end point

Primary: Median Oxygen Saturation in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Median Oxygen Saturation in Neonatal Patients Who Received GWP42003-P or Matching Placebo[30]

End point description:

End point type	Primary

End point timeframe:

1 hour after birth up to Visit 7 (discharge from NICU)

Notes:

[30] - 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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[31]	3[32]	3[33]	4[34]
Units: percentage of oxygen saturation				
median (full range (min-max))				
1 hour after birth	96.0 (90 to 98)	100.0 (90 to 100)	95.0 (95 to 95)	97.0 (89 to 100)
8 hours after birth	99.0 (94 to 100)	98.0 (95 to 100)	100.0 (100 to 100)	95.5 (95 to 96)
12 hours after birth	97.0 (94 to 100)	97.0 (94 to 98)	97.0 (93 to 98)	98.0 (94 to 100)
24 hours after birth	94.0 (90 to 98)	100.0 (100 to 100)	100.0 (98 to 100)	99.0 (97 to 100)
36 hours after birth	100.0 (100 to 100)	99.0 (93 to 100)	100.0 (95 to 100)	97.5 (95 to 100)
48 hours after birth	100.0 (90 to 100)	100.0 (100 to 100)	99.0 (98 to 100)	98.5 (91 to 99)
60 hours after birth	99.0 (96 to 100)	100.0 (97 to 100)	98.0 (97 to 100)	98.0 (94 to 99)
72 hours after birth	96.0 (96 to 100)	100.0 (96 to 100)	100.0 (99 to 100)	98.5 (95 to 100)
96 hours after birth	99.0 (98 to 100)	100.0 (97 to 100)	97.0 (97 to 100)	95.5 (95 to 100)
108 hours after birth	99.0 (91 to 100)	100.0 (99 to 100)	98.0 (98 to 98)	97.0 (96 to 98)
120 hours after birth	100.0 (100 to 100)	100.0 (100 to 100)	98.0 (97 to 99)	94.5 (93 to 96)
Visit 7 (Discharge from NICU)	100.0 (98 to 100)	0 (0 to 0)	100.0 (99 to 100)	97.0 (95 to 99)

Notes:

[31] - N's varied by timepoint

[32] - N's varied by timepoint
If 0 (0,0) is reported, it indicates missing values.

[33] - N's varied by timepoint

[34] - N's varied by timepoint

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline to Day 10 in Calcium in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Change From Baseline to Day 10 in Calcium in Neonatal Patients Who Received GWP42003-P or Matching Placebo[35]

End point description:

End point type	Primary

End point timeframe:

Baseline up to Day 10

Notes:

[35] - 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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0[36]	0[37]	0[38]
Units: millimole/liter				
median (full range (min-max))				
Calcium	0.86 (0.86 to 0.86)	(to)	(to)	(to)

Notes:

[36] - Calcium was not assessed in the group.

[37] - Calcium was not assessed in this group.

[38] - Calcium was not assessed in this group.

Statistical analyses

No statistical analyses for this end point

Primary: Median Cardiorespiratory Values in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Median Cardiorespiratory Values in Neonatal Patients Who Received GWP42003-P or Matching Placebo[39]

End point description:

End point type	Primary

End point timeframe:

Baseline up to 96–120 hours postnatal

Notes:

[39] - 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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[40]	3[41]	3[42]	4[43]
Units: Age (hours)				
median (full range (min-max))				
Age at initiation of whole-body hypothermia	2.45 (0.70 to 3.63)	2.42 (1.25 to 3.18)	0.50 (0.33 to 4.78)	0.85 (0.08 to 1.17)
Age at hypothermia established	3.28 (1.98 to 4.88)	3.08 (1.58 to 3.68)	3.78 (2.50 to 4.78)	2.90 (0.17 to 5.00)
Age at deviations outside acceptable hypothermia	39.90 (21.42 to 58.38)	19.18 (19.18 to 19.18)	11.53 (11.53 to 11.53)	0 (0 to 0)
Age at reinitiation of rewarming	75.28 (72.92 to 75.63)	75.18 (73.58 to 75.25)	76.53 (74.75 to 76.78)	77.36 (73.57 to 80.67)
Age at normothermia achieved	83.38 (83.28 to 83.92)	85.18 (82.75 to 86.58)	83.53 (82.50 to 86.25)	83.36 (80.07 to 87.67)

Notes:

[40] - N=2 for Age at deviations outside the acceptable hypothermic range start

[41] - N=1 for Age at deviations outside the acceptable hypothermic range start

[42] - N=1 for Age at deviations outside the acceptable hypothermic range start

[43] - N=0; Age at deviations outside acceptable hypothermic range start
0 (0,0) indicates missing values

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients With Whole-Body Hypothermia Deviations in Neonatal Patients Who Received GWP42003-P or Matching Placebo

End point title	Number of Patients With Whole-Body Hypothermia Deviations in Neonatal Patients Who Received GWP42003-P or Matching Placebo[44]

End point description:

End point type	Primary

End point timeframe:

Baseline up to 96–120 hours postnatal

Notes:

[44] - 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: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	4
Units: Number of patients				
number (not applicable)				
Patients with whole-body hypothermia deviations	2	1	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Whole Blood Concentration of Cannibidiol in Neonatal Patients Who Received GWP42300-P

End point title	Mean Whole Blood Concentration of Cannibidiol in Neonatal Patients Who Received GWP42300-P[45]

End point description:

Whole blood concentrations of cannibidiol were assessed from blood samples at end of infusion and at 1, 2, 4, and 8 hours after end of infusion.

End point type	Secondary

End point timeframe:

End of infusion up to 8 hours after end of infusion

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analyses for this endpoint.

End point values	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[46]	3[47]	3[48]	
Units: ng/mL				
arithmetic mean (standard deviation)				
End of infusion	46.77 (± 21.21)	114.67 (± 11.59)	456.00 (± 118.90)	
1 hour after end of infusion	11.07 (± 5.67)	22.75 (± 2.62)	94.95 (± 9.97)	
2 hours after end of infusion	7.50 (± 3.35)	16.65 (± 0.35)	65.67 (± 20.74)	
4 hours after end of infusion	4.74 (± 1.87)	6.44 (± 2.77)	40.55 (± 6.44)	
8 hours after end of infusion	1.80 (± 0.38)	2.47 (± 1.33)	12.65 (± 4.18)	

Notes:

[46] - n=3, except at 4 hours after end of infusion where n=2

[47] - n=3, except at 1, 2, 4, and 8 hours after end of infusion where n=2

[48] - n=3, except at 1 and 4 hours after end of infusion where n=2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment-emergent adverse events were collected from baseline through Day 30.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	GWP42003-P 0.1 mg/kg
Reporting group description:	
Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 0.1 mg/kg.	
Reporting group title	GWP42003-P 0.3 mg/kg
Reporting group description:	
Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 0.3 mg/kg.	
Reporting group title	GWP42003-P 1.0 mg/kg
Reporting group description:	
Patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of GWP42003-P 1.0 mg/kg.	
Reporting group title	Pooled Placebo
Reporting group description:	
All patients with neonatal hypoxic-ischemic encephalopathy (NHIE) who received whole-body hypothermia as standard of care were randomized to receive a single intravenous (IV) dose of placebo-matched treatment.	

Serious adverse events	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Pooled Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GWP42003-P 0.1 mg/kg	GWP42003-P 0.3 mg/kg	GWP42003-P 1.0 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Medical device site reaction			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Atelectasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Coagulation test abnormal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory rate increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Grimacing			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Neonatal oversedation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastric haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Feeding intolerance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Pooled Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Medical device site reaction			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Atelectasis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pulmonary haemorrhage			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Coagulation test abnormal			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory rate increased			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Grimacing			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Neonatal oversedation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

Coagulopathy subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 1 / 4 (25.00%) 1		
Eye disorders Eyelid oedema subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Gastric haemorrhage subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 2 / 4 (50.00%) 2		
Hepatobiliary disorders Jaundice subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Renal and urinary disorders Oliguria subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Sepsis	0 / 4 (0.00%) 0		

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Feeding intolerance			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This trial ended prematurely. Based on the collective data from the first 3 cohorts, the Data Safety Monitoring Committee determined the 3 mg/kg dose for Cohort 4 would not be required.

Notes: