

**Clinical trial results:****A Phase I/II, Open label, Dose Finding Study to Assess the Safety, Tolerability and Efficacy of IMCgp100, a Monoclonal T Cell Receptor anti-CD3 scFv Fusion Protein in Patients With Advanced Malignant Melanoma.****Summary**

EudraCT number	2010-019290-15
Trial protocol	GB
Global end of trial date	16 February 2017

Results information

Result version number	v1 (current)
This version publication date	19 May 2018
First version publication date	19 May 2018

Trial information**Trial identification**

Sponsor protocol code	IMCgp100/01
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Immunocore Ltd.
Sponsor organisation address	101 Park Drive, Milton Park, Abingdon, United Kingdom, OX14 4RY
Public contact	Head of Development, Christina M. Coughlin, MD, PhD., Immunocore Ltd., +1 484 5345263, chris.coughlin@immunocore.com
Scientific contact	Head of Development, Christina M. Coughlin, MD, PhD., Immunocore Ltd., +1 484 5345263, chris.coughlin@immunocore.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	09 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2017
Global end of trial reached?	Yes
Global end of trial date	16 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

ARM 1

- To define the dose of IMCgp100 recommended for further investigation based on dose limiting toxicity (DLT) and pharmacokinetic (PK) data in patients with stage IV or unresectable stage III malignant melanomas. (Completed)
- To evaluate the safety and tolerability of IMCgp100 following multiple weekly IV administrations at doses of 20 mcg-50 mcg.

ARM 2

- To establish the Maximum Tolerated Dose (MTD) of IMCgp100 based on Dose Limiting Toxicity (DLT) or recommended phase II dose (RP2D) when given daily over four days to patients with stage IV or unresectable Stage III malignant melanomas.
- To evaluate the safety and tolerability of IMCgp100 following multiple daily IV administrations at the established RP2D.

Protection of trial subjects:

This study was performed in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2010
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	United Kingdom: 65
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	84
EEA total number of subjects	65

Notes:

Subjects enrolled per age group

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

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	57
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at a total of 9 study sites in United Kingdom and United States of America.

Pre-assignment

Screening details:

Of the 84 patients enrolled into the study, 66 patients were treated with the IMCgp100 weekly-dosing regimen and 18 patients were treated with the daily-dosing regimen.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1 (weekly dose): IMCgp100

Arm description:

IMCgp100 5 ng/kg, 15 ng/kg, 45 ng/kg, 135 ng/kg, 270 ng/kg, 405 ng/kg, 600 ng/kg and 900 ng/kg intravenous weight-based single ascending dose weekly

OR

IMCgp100 20, 40 and 50 mcg were flat dose with intra patients dose escalation only for 20 and 40 mcg.

Arm type	Experimental
Investigational medicinal product name	IMCgp100
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IMCgp100 5 ng/kg, 15 ng/kg, 45 ng/kg, 135 ng/kg, 270 ng/kg, 405 ng/kg, 600 ng/kg and 900 ng/kg intravenous weight-based dose

OR

IMCgp100 20, 40 and 50 mcg were flat dose with intra patients dose escalation only for 20 and 40 mcg.

Arm title	Arm 2 (daily dose): IMCgp100
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Arm description:

IMCgp100 10 mcg, 20 mcg, 30 mcg, 40 mcg, and 50 mcg intravenous dose daily.

Arm type	Active comparator
Investigational medicinal product name	IMCgp100
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IMCgp100 10 mcg, 20 mcg, 30 mcg, 40 mcg, and 50 mcg intravenous dose daily.

Number of subjects in period 1	Arm 1 (weekly dose): IMCgp100	Arm 2 (daily dose): IMCgp100
Started	66	18
Completed	43	8
Not completed	23	10
Other	-	1
Adverse event	4	-
Withdrawal of consent	1	-
Progressive disease	18	9

Baseline characteristics

Reporting groups

Reporting group title	Arm 1 (weekly dose): IMCgp100
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Reporting group description:

IMCgp100 5 ng/kg, 15 ng/kg, 45 ng/kg, 135 ng/kg, 270 ng/kg, 405 ng/kg, 600 ng/kg and 900 ng/kg intravenous weight-based single ascending dose weekly

OR

IMCgp100 20, 40 and 50 mcg were flat dose with intra patients dose escalation only for 20 and 40 mcg.

Reporting group title	Arm 2 (daily dose): IMCgp100
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Reporting group description:

IMCgp100 10 mcg, 20 mcg, 30 mcg, 40 mcg, and 50 mcg intravenous dose daily.

Reporting group values	Arm 1 (weekly dose): IMCgp100	Arm 2 (daily dose): IMCgp100	Total
Number of subjects	66	18	84
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean full range (min-max)	58.2 25 to 78	60.4 31 to 75	-
Gender categorical Units: Subjects			
Female	25	5	30
Male	41	13	54
Race Units: Subjects			
White	62	17	79
Black	1	0	1
Asian	1	0	1
Other	2	1	3
Pre-treatment Tumor Response			
Investigator reported best response to any previous treatment Units: Subjects			
Complete response	23	7	30
Partial response	2	4	6
Stable disease	10	2	12
Progressive disease	12	2	14
Not evaluable	17	3	20
Missing	2	0	2
Height Units: cm arithmetic mean full range (min-max)	172.1 151 to 190	174.4 159 to 195	-
Weight			

Units: kg			
arithmetic mean	84.6	77.8	
full range (min-max)	47.3 to 134.2	53.2 to 106.1	-

End points

End points reporting groups

Reporting group title	Arm 1 (weekly dose): IMCgp100
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Reporting group description:

IMCgp100 5 ng/kg, 15 ng/kg, 45 ng/kg, 135 ng/kg, 270 ng/kg, 405 ng/kg, 600 ng/kg and 900 ng/kg intravenous weight-based single ascending dose weekly

OR

IMCgp100 20, 40 and 50 mcg were flat dose with intra patients dose escalation only for 20 and 40 mcg.

Reporting group title	Arm 2 (daily dose): IMCgp100
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Reporting group description:

IMCgp100 10 mcg, 20 mcg, 30 mcg, 40 mcg, and 50 mcg intravenous dose daily.

Subject analysis set title	Arm 1 (by-weight dose weekly): IMCgp100 5 ng/kg
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Pharmacokinetic (PK) population included all patients who received at least one IMCgp100 dose and had at least 1 measurable PK concentration with the relevant date, time and dosing data for this sample.

Subject analysis set title	Arm 1 (by-weight dose weekly): IMCgp100 15 ng/kg
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

PK population

Subject analysis set title	Arm 1 (by-weight dose weekly): IMCgp100 45 ng/kg
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

PK population

Subject analysis set title	Arm 1 (by-weight dose weekly): IMCgp100 135 ng/kg
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

PK population

Subject analysis set title	Arm 1 (by-weight dose weekly): IMCgp100 270 ng/kg
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

PK population

Subject analysis set title	Arm 1 (by-weight dose weekly): IMCgp100 405 ng/kg
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

PK population

Subject analysis set title	Arm 1 (by-weight dose weekly): IMCgp100 600 ng/kg
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

PK population

Subject analysis set title	Arm 1 (by-weight dose weekly): IMCgp100 900 ng/kg
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

PK population

Subject analysis set title	Arm 1 (flat dose weekly): IMCgp100 20 mcg
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

PK population

Subject analysis set title	Arm 1 (flat dose weekly): IMCgp100 40 mcg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
PK population	
Subject analysis set title	Arm 1 (flat dose weekly): IMCgp100 50 mcg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
PK population	
Subject analysis set title	Arm 2 (flat dose daily): IMCgp100 10 mcg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
PK population	
Subject analysis set title	Arm 2 (flat dose daily): IMCgp100 20 mcg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
PK population	
Subject analysis set title	Arm 2 (flat dose daily): IMCgp100 30 mcg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
PK population	
Subject analysis set title	Arm 2 (flat dose daily): IMCgp100 40 mcg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
PK population	
Subject analysis set title	Arm 2 (flat dose daily): IMCgp100 50 mcg
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
PK population	

Primary: Maximum-tolerated Dose (MTD) of Arm 1 (weekly dose)

End point title	Maximum-tolerated Dose (MTD) of Arm 1 (weekly dose) ^{[1][2]}
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End point description:

Safety population: All patients who received at least one IMCgp100 dose.

MTD was the highest dose level with an observed dose-limiting toxicity (DLT) incidence of fewer than 33% of patients.

DLT was defined as any Grade ≥ 3 hematologic or non-hematologic toxicity with suspected causal relationship to IMCgp100, occurring during Day 1 to 8 of Arm 1. DLT did not include transient lymphopenia, transient Grade 3 non-life-threatening cutaneous toxicity, fatigue, nausea, diarrhea, or vomiting other than:

- Grade 3 fatigue that persisted for >7 days
- Grade 4 cutaneous toxicity
- Grade ≥ 3 nausea, diarrhea, or vomiting that persisted beyond 72 hours despite optimal medical therapy
- Grade ≥ 3 lymphopenia that persisted for more than 14 days or the presence of infection indicating clinically-significant lymphopenia
- Grade 3 cutaneous toxicity that did not begin to resolve with a 48-hour period and/or did not resolve to Grade ≤ 2 within a week despite optimal medical therapy

End point type	Primary
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End point timeframe:

Up to Day 8

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: Due to the non-comparative nature of the study design, no formal comparative analysis was conducted.

[2] - 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: Due to the non-comparative nature of the study design, no formal comparative analysis was conducted.

End point values	Arm 1 (weekly dose): IMCgp100			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: ng/kg				
number (not applicable)				
Maximum-tolerated Dose	600			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum-tolerated Dose (MTD) of Arm 2 (daily dose)

End point title	Maximum-tolerated Dose (MTD) of Arm 2 (daily dose) ^{[3][4]}
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End point description:

Safety population.

MTD was the highest dose level with an observed dose-limiting toxicity (DLT) incidence of fewer than 33% of patients.

DLT was defined as any Grade ≥ 3 hematologic or non-hematologic toxicity with suspected causal relationship to IMCgp100, occurring during Day 1 to 15 of Arm 2. DLT did not include transient lymphopenia, transient Grade 3 non-life-threatening cutaneous toxicity, fatigue, nausea, diarrhea, or vomiting other than:

- Grade 3 fatigue that persisted for >7 days
- Grade 4 cutaneous toxicity
- Grade ≥ 3 nausea, diarrhea, or vomiting that persisted beyond 72 hours despite optimal medical therapy
- Grade ≥ 3 lymphopenia that persisted for more than 14 days or the presence of infection indicating clinically-significant lymphopenia
- Grade 3 cutaneous toxicity that did not begin to resolve with a 48-hour period and/or did not resolve to Grade ≤ 2 within a week despite optimal medical therapy

End point type	Primary
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End point timeframe:

Up to Day 15

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: Due to the non-comparative nature of the study design, no formal comparative analysis was conducted.

[4] - 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: Due to the non-comparative nature of the study design, no formal comparative analysis was conducted.

End point values	Arm 2 (daily dose): IMCgp100			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: mcg				
number (not applicable)				
Maximum-tolerated Dose	50			

Statistical analyses

No statistical analyses for this end point

Primary: Tolerability – Number of Grade ≥ 3 acute infusion reaction events

End point title	Tolerability – Number of Grade ≥ 3 acute infusion reaction events ^[5]
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End point description:

Tolerability of IMCgp100 infusion was defined as no Grade ≥ 3 acute infusion reaction (pyrexia, hypotension, chills, joint and/or muscle aches, hypertension, nausea, vomiting, fatigue, breathing difficulties) occurring during infusion or within 30 minutes of completion of the infusion.

End point type	Primary
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End point timeframe:

Day 1 to 8 (Arm 1) and Day 1 to 15 (Arm 2)

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: Due to the non-comparative nature of the study design, no formal comparative analysis was conducted.

End point values	Arm 1 (by-weight dose weekly): IMCgp100 5 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 15 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 45 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 135 ng/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	3
Units: events	0	0	0	0

End point values	Arm 1 (by-weight dose weekly): IMCgp100 270 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 405 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 600 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 900 ng/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	6	6	4
Units: events	0	1	1	2

Statistical analyses

No statistical analyses for this end point

Primary: Safety — Number of subjects with Adverse Events (AEs)

End point title Safety — Number of subjects with Adverse Events (AEs)^[6]

End point description:

Safety population.

CTCAE - Common Terminology Criteria for Adverse Events

Relationship to Investigational Medicinal Products (IMP)

Not related = No possibility that the AE was caused by the IMP

Possibly related = Reasonable suspicion that the AE was caused by the IMP

Probable related = Most likely that the AE was caused by the IMP

End point type Primary

End point timeframe:

Up to Day 80 (follow-up)

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: Due to the non-comparative nature of the study design, no formal comparative analysis was conducted.

End point values	Arm 1 (weekly dose): IMCgp100	Arm 2 (daily dose): IMCgp100		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	18		
Units: Participants				
Treatment-emergent Adverse Events	66	18		
Treatment-related Adverse Event	65	18		
Adverse Events of CTCAE Grade ≥3	36	12		
Treatment-related Adverse Events of CTCAE Grade ≥3	27	9		
Serious Adverse Events	24	5		
Treatment-related Serious Adverse Events	11	1		
Serious Adverse Events leading to death	1	1		
Discontinuation due to Adverse Events	5	1		
Discontinuation due to treatment-related AEs	2	0		
CTCAE Grade 1	66	18		
CTCAE Grade 2	58	18		
CTCAE Grade 3	35	12		
CTCAE Grade 4	6	2		
CTCAE Grade 5	1	1		
Relationship to study drug - Not related	62	14		
Relationship to study drug - Possibly related	60	17		
Relationship to study drug - Probably related	47	6		
Relationship to study drug - Definitely related	48	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (Cmax) of IMCgp100

End point title Maximum plasma concentration (Cmax) of IMCgp100

End point description:

PK population

Cmax for one patient in Arm 1 (by-weight dose weekly) IMCgp100 5 ng/kg is not calculated.

End point type Secondary

End point timeframe:

At Pre-dose, 0.25,0.5,1,2,4,6,8 hours, Day 2,8,9,15,22,29,36 and 66

End point values	Arm 1 (by-weight dose weekly): IMCgp100 15 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 45 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 135 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 270 ng/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	3
Units: pg/ml				
arithmetic mean (standard deviation)	951.67 (± 1462.398)	275.33 (± 56.128)	404.33 (± 178.399)	898.00 (± 308.564)

End point values	Arm 1 (by-weight dose weekly): IMCgp100 405 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 600 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 900 ng/kg	Arm 1 (flat dose weekly): IMCgp100 20 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	20	4	7
Units: pg/ml				
arithmetic mean (standard deviation)	2480.00 (± 1011.632)	6575.50 (± 2027.800)	9140.00 (± 2761.678)	3298.57 (± 660.137)

End point values	Arm 1 (flat dose weekly): IMCgp100 40 mcg	Arm 1 (flat dose weekly): IMCgp100 50 mcg	Arm 2 (flat dose daily): IMCgp100 10 mcg	Arm 2 (flat dose daily): IMCgp100 20 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	11	3	3
Units: pg/ml				
arithmetic mean (standard deviation)	8846.67 (± 3811.198)	9327.27 (± 3802.326)	1041.00 (± 348.659)	3626.67 (± 531.445)

End point values	Arm 2 (flat dose daily): IMCgp100 30 mcg	Arm 2 (flat dose daily): IMCgp100 40 mcg	Arm 2 (flat dose daily): IMCgp100 50 mcg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	4	5	
Units: pg/ml				
arithmetic mean (standard deviation)	21433.33 (± 28383.108)	6350.00 (± 1789.655)	8340.00 (± 2053.083)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve (AUC) of IMCgp100

End point title	Area under the concentration-time curve (AUC) of IMCgp100
End point description:	
PK population	
Estimated AUC for one patient is not quantifiable of 5 ng/kg.	
End point type	Secondary
End point timeframe:	
At Pre-dose, 0.25,0.5,1,2,4,6,8 hours, Day 2,8,9,15,22,29,36 and 66	

End point values	Arm 1 (by-weight dose weekly): IMCgp100 15 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 45 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 135 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 270 ng/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	3
Units: hr*pg/ml				
arithmetic mean (standard deviation)	15125.67 (± 22469.040)	3187.64 (± 1487.001)	3586.50 (± 2719.970)	11183.44 (± 4080.507)

End point values	Arm 1 (by-weight dose weekly): IMCgp100 405 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 600 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 900 ng/kg	Arm 1 (flat dose weekly): IMCgp100 20 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	20	4	7
Units: hr*pg/ml				
arithmetic mean (standard deviation)	36308.04 (± 19301.380)	68446.83 (± 25833.848)	100589.81 (± 25817.365)	26108.03 (± 8118.542)

End point values	Arm 1 (flat dose weekly): IMCgp100 40 mcg	Arm 1 (flat dose weekly): IMCgp100 50 mcg	Arm 2 (flat dose daily): IMCgp100 10 mcg	Arm 2 (flat dose daily): IMCgp100 20 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	11	3	3
Units: hr*pg/ml				
arithmetic mean (standard deviation)	60232.81 (± 12859.333)	81431.74 (± 36505.518)	5126.71 (± 2036.085)	18229.73 (± 3593.221)

End point values	Arm 2 (flat dose daily): IMCgp100 30 mcg	Arm 2 (flat dose daily): IMCgp100 40 mcg	Arm 2 (flat dose daily): IMCgp100 50 mcg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	4	5	
Units: hr*pg/ml				
arithmetic mean (standard deviation)	29819.88 (± 14030.039)	30107.22 (± 7086.383)	40120.03 (± 11733.251)	

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life time (t1/2) of IMCgp100

End point title	Half-life time (t1/2) of IMCgp100
End point description:	
PK population	
Estimated t1/2 for patients of 5, 15, 45, 135, and 270 ng/kg has no results.	
End point type	Secondary
End point timeframe:	
At Pre-dose, 0.25,0.5,1,2,4,6,8 hours, Day 2,8,9,15,22,29,36 and 66	

End point values	Arm 1 (by-weight dose weekly): IMCgp100 405 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 600 ng/kg	Arm 1 (by-weight dose weekly): IMCgp100 900 ng/kg	Arm 1 (flat dose weekly): IMCgp100 20 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	20	4	7
Units: hours				
arithmetic mean (standard deviation)	7.97 (± 1.503)	8.09 (± 8.703)	6.51 (± 1.155)	6.35 (± 2.192)

End point values	Arm 1 (flat	Arm 1 (flat	Arm 2 (flat	Arm 2 (flat
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	dose weekly): IMCgp100 40 mcg	dose weekly): IMCgp100 50 mcg	dose daily): IMCgp100 10 mcg	dose daily): IMCgp100 20 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	11	3	3
Units: hours				
arithmetic mean (standard deviation)	5.89 (± 0.636)	5.72 (± 1.246)	7.95 (± 1.830)	7.79 (± 1.837)

End point values	Arm 2 (flat dose daily): IMCgp100 30 mcg	Arm 2 (flat dose daily): IMCgp100 40 mcg	Arm 2 (flat dose daily): IMCgp100 50 mcg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	4	5	
Units: hours				
arithmetic mean (standard deviation)	4.69 (± 2.692)	6.70 (± 1.265)	6.16 (± 1.904)	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of anti-IMCgp100 antibody formation

End point title	Incidence of anti-IMCgp100 antibody formation
End point description:	
Safety population	
End point type	Secondary
End point timeframe:	
At Day 1 (pre-dose), 8, 29, 36, 43, 50 and 66	

End point values	Arm 1 (weekly dose): IMCgp100	Arm 2 (daily dose): IMCgp100		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	18		
Units: Number of incidence				
Anti-drug Antibody prevalence - Baseline	0	0		
Treatment-induced incidence	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Tumor Response Based on RECIST 1.1

End point title	Best Tumor Response Based on RECIST 1.1
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End point description:

Efficacy population includes subjects with;

- at least one RECIST 1.1 evaluable target lesion
- treated with at least 1 IMCgp100 dose of ≥ 270 ng/kg (a median absolute dose of ≥ 16 mcg)
- recommended Phase II dose (50 mcg)-(Arm 1 subjects only)
- received at least 1 end-of-cycle scan or discontinued prior to the scheduled scan

Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Best tumour response was evaluated using the Response evaluation criteria in Solid tumors (RECIST) v1.1 guideline and response definitions. Complete response(CR) is the disappearance of all baseline lesions and no new lesions. Partial response(PR) is at least a 30% reduction in Target lesion size compared to baseline with at least stable Non-target lesions and no new lesions. Minor response is a reduction in TL size from baseline between 10 and 29% with at least stable non target lesions and no new lesions. Complete or partial response required confirmation at least 28days following initial response.

End point type	Secondary
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End point timeframe:

Day 22 and 66 [all evaluable tumor assessments up until progression or last evaluable assessment in the absence of progression]

End point values	Arm 1 (weekly dose): IMCgp100	Arm 2 (daily dose): IMCgp100		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	15		
Units: Participants				
Partial response	5	1		
Minor response	4	1		
Stable disease	26	7		
Progressive disease	17	6		
Not evaluable	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate

End point title	Overall response rate
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End point description:

Efficacy population.

Best overall response rate is defined as the percentage of patients with a confirmed best response of CR or PR based on the efficacy analysis set.

Overall Response (OR) = CR + PR.

End point type	Secondary
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End point timeframe:

Day 22 and 66 [assessed until progression or last evaluable assessment in the absence of progression]

End point values	Arm 1 (weekly dose): IMCgp100	Arm 2 (daily dose): IMCgp100		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	15		
Units: Percentage of participants				
number (confidence interval 95%)	9.3 (3.1 to 20.3)	6.7 (0.2 to 31.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 80 (follow-up)

Adverse event reporting additional description:

Safety population: All patients who received at least one IMCgp100 dose.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Adverse Events : Arm 1 (weekly dosing)
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Reporting group description: -

Reporting group title	Adverse Events : Arm 2 (daily dosing)
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Reporting group description: -

Serious adverse events	Adverse Events : Arm 1 (weekly dosing)	Adverse Events : Arm 2 (daily dosing)	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 66 (36.36%)	5 / 18 (27.78%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 66 (6.06%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	2 / 66 (3.03%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malaise			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	2 / 66 (3.03%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Laboratory test abnormal			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	2 / 66 (3.03%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			

subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 66 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 66 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 66 (3.03%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Biliary tract infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Adverse Events : Arm 1 (weekly dosing)	Adverse Events : Arm 2 (daily dosing)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 66 (100.00%)	18 / 18 (100.00%)	
Vascular disorders			
Hypotension			

subjects affected / exposed occurrences (all)	21 / 66 (31.82%) 36	7 / 18 (38.89%) 13	
Flushing subjects affected / exposed occurrences (all)	11 / 66 (16.67%) 13	1 / 18 (5.56%) 3	
Hypertension subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 12	1 / 18 (5.56%) 1	
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	35 / 66 (53.03%) 96	13 / 18 (72.22%) 31	
Fatigue subjects affected / exposed occurrences (all)	35 / 66 (53.03%) 65	10 / 18 (55.56%) 13	
Chills subjects affected / exposed occurrences (all)	17 / 66 (25.76%) 42	9 / 18 (50.00%) 11	
Influenza-like illness subjects affected / exposed occurrences (all)	13 / 66 (19.70%) 27	5 / 18 (27.78%) 8	
Peripheral oedema subjects affected / exposed occurrences (all)	10 / 66 (15.15%) 15	8 / 18 (44.44%) 14	
Face oedema subjects affected / exposed occurrences (all)	13 / 66 (19.70%) 18	3 / 18 (16.67%) 4	
Peripheral swelling subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 8	2 / 18 (11.11%) 2	
Chest pain subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 8	0 / 18 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	15 / 66 (22.73%) 22	2 / 18 (11.11%) 2	
Dyspnoea subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 9	2 / 18 (11.11%) 3	
Oropharyngeal pain subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 5	1 / 18 (5.56%) 1	
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 4	2 / 18 (11.11%) 2	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) Sinus tachycardia subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 8 5 / 66 (7.58%) 14	4 / 18 (22.22%) 5 1 / 18 (5.56%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all)	16 / 66 (24.24%) 30 10 / 66 (15.15%) 14 5 / 66 (7.58%) 8	6 / 18 (33.33%) 10 1 / 18 (5.56%) 2 0 / 18 (0.00%) 0	
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	13 / 66 (19.70%) 19 4 / 66 (6.06%) 9	4 / 18 (22.22%) 5 5 / 18 (27.78%) 9	

Eye disorders			
Periorbital oedema			
subjects affected / exposed	30 / 66 (45.45%)	11 / 18 (61.11%)	
occurrences (all)	52	19	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	34 / 66 (51.52%)	10 / 18 (55.56%)	
occurrences (all)	55	19	
Vomiting			
subjects affected / exposed	24 / 66 (36.36%)	10 / 18 (55.56%)	
occurrences (all)	43	19	
Constipation			
subjects affected / exposed	14 / 66 (21.21%)	3 / 18 (16.67%)	
occurrences (all)	16	3	
Diarrhoea			
subjects affected / exposed	10 / 66 (15.15%)	5 / 18 (27.78%)	
occurrences (all)	15	5	
Abdominal pain			
subjects affected / exposed	9 / 66 (13.64%)	2 / 18 (11.11%)	
occurrences (all)	16	4	
Abdominal pain upper			
subjects affected / exposed	5 / 66 (7.58%)	1 / 18 (5.56%)	
occurrences (all)	19	1	
Dyspepsia			
subjects affected / exposed	4 / 66 (6.06%)	1 / 18 (5.56%)	
occurrences (all)	4	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	43 / 66 (65.15%)	16 / 18 (88.89%)	
occurrences (all)	118	45	
Rash			
subjects affected / exposed	47 / 66 (71.21%)	10 / 18 (55.56%)	
occurrences (all)	159	32	
Skin exfoliation			
subjects affected / exposed	19 / 66 (28.79%)	5 / 18 (27.78%)	
occurrences (all)	30	6	
Rash maculopapular			

subjects affected / exposed occurrences (all)	17 / 66 (25.76%) 32	6 / 18 (33.33%) 15	
Dry skin subjects affected / exposed occurrences (all)	18 / 66 (27.27%) 23	5 / 18 (27.78%) 6	
Erythema subjects affected / exposed occurrences (all)	17 / 66 (25.76%) 27	2 / 18 (11.11%) 4	
Rash erythematous subjects affected / exposed occurrences (all)	9 / 66 (13.64%) 17	5 / 18 (27.78%) 13	
Vitiligo subjects affected / exposed occurrences (all)	9 / 66 (13.64%) 9	1 / 18 (5.56%) 1	
Hair colour changes subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 7	1 / 18 (5.56%) 1	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	14 / 66 (21.21%) 27	2 / 18 (11.11%) 3	
Arthralgia subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 13	3 / 18 (16.67%) 4	
Pain in extremity subjects affected / exposed occurrences (all)	9 / 66 (13.64%) 13	1 / 18 (5.56%) 1	
Myalgia subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 11	1 / 18 (5.56%) 1	
Infections and infestations			
Lower respiratory tract infection subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 5	2 / 18 (11.11%) 4	
Conjunctivitis			

subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 7	0 / 18 (0.00%) 0	
Rhinitis			
subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 7	0 / 18 (0.00%) 0	
Upper respiratory tract infection			
subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 5	1 / 18 (5.56%) 1	
Urinary tract infection			
subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4	1 / 18 (5.56%) 1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed occurrences (all)	10 / 66 (15.15%) 13	0 / 18 (0.00%) 0	
Hypophosphataemia			
subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 12	3 / 18 (16.67%) 4	
Hypoalbuminaemia			
subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 11	2 / 18 (11.11%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2010	a) Patients were to have no standard effective therapeutic options for their melanoma. b) Patients in the dose-escalation phase were to have their C _{max} modelled so that it could be ensured that the dose selected for the next cohort had a predicted C _{max} that did not exceed 1 nM. Dose-escalation was to be stopped if C _{max} reached 1 nM. c) Patients who had completed the dose-escalation phase could continue treatment at a higher dose than originally administered, provided the dose had been shown to be tolerable and effective in subsequent dose cohorts. d) Only 3 study centres were to participate in the dose-expansion phase (Arm 1). e) Patients could potentially experience severe systemic adverse reaction to IMCgp100 administration such as generalised cytokine storm; guidance on management of such events was included. f) Patients were to be closely monitored for the duration of infusion and for 2 hours after.
09 March 2011	a) Patients could be enrolled if they had previous malignancy that, in the opinion of the investigator, was cured. b) Localised radiotherapy could be used to treat a tumour flare. c) The number of study centres that could participate in the dose-escalation phase was increased to 5, as recruitment was slower than anticipated. d) gp100 status was to be collected and reported, if available. e) Pregnancy was to be reported as an AE during the study and abortion, stillbirth or malformation/disease in the baby were to be reported as SAEs.
15 July 2011	a) The phrase 'clinically significant' was added to the DLT definition, to allow the investigator discretion in cases of short-lived changes in clinical chemistry or haematology. In addition, transient lymphopenia (Grade 3 and 4) and transient non-life threatening cutaneous toxicity were excluded from the DLT definition; transient Grade 3/4 lymphopenia was no longer considered a reason for discontinuation of study treatment. b) Patients could be included in the study if their lymphocyte count was $\geq 0.5 \times 10^9/L$; this lowering of the permitted lymphocyte count reflected the results of data collected and assessed by the study team, which indicated that patients with low but stable lymphocyte count tolerated IMCgp100 without apparent consequences. c) Patients receiving anti-coagulant treatment could be included in the study, as there was no reason to suspect that IMCgp100 interferes with anticoagulant treatment or vice versa. d) The SMC could choose to expand a dose cohort to further define toxicity before deciding to dose escalate. e) Biopsies were not to be taken from patients whose medical history indicated a risk of uncontrollable bleeding.
22 November 2011	The number of study centres was increased to 6 for the dose-escalation phase of Arm 1 and 8 for the dose-expansion phase; additional study centres could be set up in the USA and Australia.
06 February 2012	Sites in the USA only: a) The phrase 'clinically significant' was removed from the DLT definition, as stipulated by the FDA. b) Follow-up visual, auditory and neurologic assessments were to be available for consideration by the team before escalation could proceed. c) Study treatment was to be discontinued for patients who experienced DLT during the first 30 days of the dose-escalation phase, and dose reduction was mandated for patients who experience Grade 3/4 toxicity that if observed during the DLT period would have met the definition of a DLT. d) Adverse events of Grade ≥ 3 nausea, diarrhoea, or vomiting that persisted beyond 72 hours despite optimal medical therapy were to be considered DLT events. e) A patient continuing treatment in the dose-escalation phase at a dose subsequently identified as being higher than the MTD was to have study treatment discontinued or could have treatment continued at a lower dose level. f) Patients with a change in LVEF of $\geq 20\%$ from baseline were to be discontinued from the study.

25 June 2012	a) The amount of HSA required as a blocking agent for IMCgp100 in saline infusion bags was increased from 125 mcg/kg to 125 to 250 mcg/kg, as a higher amount is needed for USP than for BP saline bags to ensure complete drug delivery. b) Patients were to have QTc, calculated using Bazett's or a locally-preferred formula, of >500 ms.
26 November 2012	a) Patients were to be included in the study if there was an appropriate window between alternative therapeutic options but excluded if early treatment with vemurafenib was an option. The intention was to include patients who had either slow-growing or stable disease that was asymptomatic, where a window existed between therapeutic options. b) Patients with brain metastases were only to be excluded if they were unstable, required steroid treatment, or had been irradiated within the previous 28 days. In addition, MRI scan of the head was to be conducted at screening (rather than CT scan) to provide a better baseline assessment of brain metastases. c) Removed the exclusion criterion specifying that patients with high disease volume were to be excluded from the study; it was deemed that sufficient patients had been treated in the study to date with no signs or symptoms of tumour lysis syndrome. d) Patients could be enrolled if their alkaline phosphatase level was >2.0 x ULN (the related inclusion criterion was removed). e) Biopsy of normal skin was introduced as an optional procedure, to allow investigation of a rash seen in treated patients; in addition, the timing of tumour biopsy was changed to facilitate investigation of tumour flare. f) Patients who required systemic steroid treatment for any reason other than treatment of IMCgp100 related AEs could be replaced. Steroid treatment abrogates IMCgp100 potency, and patients treated with steroids for prolonged periods were considered non-evaluable for efficacy.
23 September 2013	a)The MTD for the IMCgp100 weekly-dosing regimen was 600 ng/kg; methodology relating to the dose-escalation phase of Arm 1 were removed from the protocol as the MTD had been identified. b)Infusion times should be shortened, as previous IMCgp100 infusions (>120 infusions) were tolerated well. c)The 30-day dosing break between treatment cycles was removed, and weekly treatment cycles were to comprise 8 doses administered over 56 days. Disease assessment was to be conducted every 8 weeks during treatment, to reflect the changed treatment cycle duration. d)Periodic brain scans were implemented for patients with brain metastases. e)The frequency of laboratory safety parameter sampling and ECG, echocardiogram, ophthalmological, auditory and neurological assessments was reduced after Cycle 1, as data from the dose-escalation phase indicated no significant concerns. f)At Cycle 1 a detailed pharmacokinetic profile was to be established for the first dose with peak and trough levels being assessed for subsequent doses. At subsequent cycles, pharmacokinetic parameters were only to be assessed at the Day 50 dosing. g)PBMC and serum samples were to be tested for evidence of "epitope-spreading", to assess the ability of IMCgp100 treatment to initiate an adaptive immune response towards tumour antigens. h)Addition of 2 new study sites to recruit patients into the dose-expansion phase of the study. i)A minimum of 6 patients were to provide tumour and skin biopsy samples, and the timing of biopsies was revised to reflect the time of greatest inflammation and T cell infiltration. j)Overnight hospitalisation was required after the first IMCgp100 dose, with careful consideration being given to whether hospitalisation was required for the first dose administered after a treatment break. k)The remit of the SMC was extended, to ensure continued monitoring into the dose-expansion phase of Arm 1 and allow for modification of dosing regimens if appropriate. l)Allowed patient
20 February 2014	a) A daily IMCgp100 dosing regimen was to be tested in a separate treatment arm. Patients were to receive 4 consecutive daily doses of IMCgp100, starting at 10 mcg and escalating to 20, 30, 40 and possibly 50 mcg per day based on observed tolerability, with a 2-week break between each 4 day dosing period. b) Dosing was to change from a per-kg-body-weight basis to a flat dose. For weekly-dosing patients the dose changed from 600 ng/kg to 50 mcg. c) The number of laboratory safety samples be reduced for Arm 1, Cycle 1 to limit the volume of blood being taken. d) The total number of patients to be enrolled was increased to 80, the number of study centres was increased to 10, and the duration of the study was extended to August 2015 to allow for treatment of patients in Arm 2. e) For patients in the dose-expansion phase of Arm 1, dose administrations were to be at least 3 days apart. f) Treatment allocation to Arm 1 or 2 would not be randomised but would depend on the resource availability at each site.

05 August 2014	a) CT/MRI scans be taken at the end of each treatment cycle (every 6 weeks rather than every 12 weeks as planned previously) for the first 6 months of IMCgp100 dosing in Arm 2. This was to allow closer monitoring of disease status and make efficacy data more comparable to those in Arm 1. b) PFS, OS, and investigation of circulating tumour cells were specified as exploratory endpoints. c) For patients in Arm 2 infusion duration was to start at 30 minutes and could subsequently be reduced to 15 minutes if tolerable. d) The DLT assessment window for Arm 2 was 15 days, for logistical reasons. e) Use of low-dose steroids to compensate for a deficiency in natural levels could be considered on an individual-patient basis on discussion with the sponsor.
13 May 2015	a) At least 5 patients in Arm 2 provide a CSF sample and contemporaneous blood sample at the end of dosing on Day 4 or Day 25, to compare IMCgp100 pharmacokinetic parameters in blood and CSF. b) irRECIST be used to assess tumour burden, in addition to RECIST. c) The stringency of the inclusion criteria for haemoglobin levels and creatinine clearance be reduced to reflect clinical experience. d) The time window between treating the first and additional patients in each cohort of the Arm 2 dose-escalation phase be reduced from 5 days to 4 days (after the last dose). e) Grade 3 laboratory values that were not clinically indicated would not trigger expedited communication and an SMC meeting. f) Prophylactic anti-coagulation therapy could be used by patients with or at risk of pulmonary embolism or deep vein thrombosis. g) The number of patients to be enrolled was increased to 100 and the number of study centres was increased to 15. h) Blood sampling for RNA analysis be implemented for patients in Arm 2. i) Recording of BRAF and NRAS status was implemented.
23 July 2015	a) The number of patients enrolled into each expansion cohort be increased to 40, bringing the total number of patients to 140. b) Central independent review of CT scans would be implemented for patients with disease response.
04 November 2015	a) Newly-treated patients would receive 40 mcg IMCgp100 for the first 2 doses administered in Arm 1 and the first 4 doses administered in Arm 2. Thereafter patients were dosed at the RP2D of 50 mcg. This change was implemented in response to an urgent safety measure. b) Patients receiving chronic corticosteroid treatment (longer than 8 weeks duration) for management of pre-existing AEs or patients with a history of chronic corticosteroid treatment of longer than 8 weeks' duration for AEs within 6 months of screening were to be excluded from the study. This change was implemented in response to an urgent safety measure. c) Patients with a history of adrenal insufficiency, maintained on stable replacement dose corticosteroid were eligible for the study, unless there was a history of adrenal crisis. Patients with a history of adrenal insufficiency receiving replacement dose corticosteroid were to receive prophylactic stress-dose corticosteroid prior to dosing for the first 4 IMCgp100 doses. This change was implemented in response to an urgent safety measure. d) The RP2D for Arms 1 and 2 was 50 mcg IMCgp100.
16 December 2015	a) Procedures would be put into place to minimise the risk of severe hypotension. Patients in Arm 1 were to receive lower initial IMCgp100 doses of 20 mcg on Cycle 1 Day 1 and 30 mcg on Cycle 1 Day 8, followed by 50 mcg at the third weekly dose and thereafter. b) Patients in Arm 1 required overnight hospitalisation beyond Cycle 1 Day 1 for the dose increase on Cycle 1 Day 8 and Cycle 1 Day 15. A requirement for in-patient monitoring at Cycle 1 Day 22 was to be determined based on the occurrence of hypotension requiring medical intervention at previous cycles. c) Patients experiencing a break or delay in treatment of >2 weeks who had previously experienced Grade 3 or Grade 4 hypotension following IMCgp100 dosing were to be hospitalised for their first dose following the break or delay.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported