



## 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 |
|-----------------------|-------------|

##### 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.,<br>Immunocore Ltd., +1 484 5345263,<br>chris.coughlin@immunocore.com |
| Scientific contact           | Head of Development, Christina M. Coughlin, MD, PhD.,<br>Immunocore Ltd., +1 484 5345263,<br>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                           |
| <b>Arm title</b>             | 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.

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | Arm 2 (daily dose): IMCgp100 |
|------------------|------------------------------|

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.

| <b>Number of subjects in period 1</b> | 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 |
|-----------------------|-------------------------------|

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 |
|-----------------------|------------------------------|

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<br>Units: Subjects                                        |                               |                              |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>full range (min-max) | 58.2<br>25 to 78              | 60.4<br>31 to 75             | -     |
| Gender categorical<br>Units: Subjects                                     |                               |                              |       |
| Female                                                                    | 25                            | 5                            | 30    |
| Male                                                                      | 41                            | 13                           | 54    |
| Race<br>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<br>Units: cm<br>arithmetic mean<br>full range (min-max)            | 172.1<br>151 to 190           | 174.4<br>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 |
|-----------------------|-------------------------------|

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 |
|-----------------------|------------------------------|

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 |
|----------------------------|-------------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

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 |
|----------------------------|--------------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

PK population

|                            |                                                  |
|----------------------------|--------------------------------------------------|
| Subject analysis set title | Arm 1 (by-weight dose weekly): IMCgp100 45 ng/kg |
|----------------------------|--------------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

PK population

|                            |                                                   |
|----------------------------|---------------------------------------------------|
| Subject analysis set title | Arm 1 (by-weight dose weekly): IMCgp100 135 ng/kg |
|----------------------------|---------------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

PK population

|                            |                                                   |
|----------------------------|---------------------------------------------------|
| Subject analysis set title | Arm 1 (by-weight dose weekly): IMCgp100 270 ng/kg |
|----------------------------|---------------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

PK population

|                            |                                                   |
|----------------------------|---------------------------------------------------|
| Subject analysis set title | Arm 1 (by-weight dose weekly): IMCgp100 405 ng/kg |
|----------------------------|---------------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

PK population

|                            |                                                   |
|----------------------------|---------------------------------------------------|
| Subject analysis set title | Arm 1 (by-weight dose weekly): IMCgp100 600 ng/kg |
|----------------------------|---------------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

PK population

|                            |                                                   |
|----------------------------|---------------------------------------------------|
| Subject analysis set title | Arm 1 (by-weight dose weekly): IMCgp100 900 ng/kg |
|----------------------------|---------------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

Subject analysis set description:

PK population

|                            |                                           |
|----------------------------|-------------------------------------------|
| Subject analysis set title | Arm 1 (flat dose weekly): IMCgp100 20 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 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) <sup>[1][2]</sup> |
|-----------------|-----------------------------------------------------------------------|

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  $\geq 3$  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  $\geq 3$  nausea, diarrhea, or vomiting that persisted beyond 72 hours despite optimal medical therapy
- Grade  $\geq 3$  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  $\leq 2$  within a week despite optimal medical therapy

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

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.

|                             |                               |  |  |  |
|-----------------------------|-------------------------------|--|--|--|
| <b>End point values</b>     | 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) <sup>[3][4]</sup> |
|-----------------|----------------------------------------------------------------------|

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  $\geq 3$  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  $\geq 3$  nausea, diarrhea, or vomiting that persisted beyond 72 hours despite optimal medical therapy
- Grade  $\geq 3$  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  $\leq 2$  within a week despite optimal medical therapy

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

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.

|                             |                                 |  |  |  |
|-----------------------------|---------------------------------|--|--|--|
| <b>End point values</b>     | Arm 2 (daily dose):<br>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 <sup>[5]</sup> |
|-----------------|---------------------------------------------------------------------------------|

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 |
|----------------|---------|

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.

|                             |                                                    |                                                     |                                                     |                                                      |
|-----------------------------|----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|------------------------------------------------------|
| <b>End point values</b>     | Arm 1 (by-weight dose weekly):<br>IMCgp100 5 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 15 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 45 ng/kg | Arm 1 (by-weight dose weekly):<br>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                                                    |

|                             |                                                      |                                                      |                                                      |                                                      |
|-----------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| <b>End point values</b>     | Arm 1 (by-weight dose weekly):<br>IMCgp100 270 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 405 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 600 ng/kg | Arm 1 (by-weight dose weekly):<br>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

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

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Safety — Number of subjects with Adverse Events (AEs) <sup>[6]</sup> |
|-----------------|----------------------------------------------------------------------|

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.

| <b>End point values</b>                                  | Arm 1 (weekly dose):<br>IMCgp100 | Arm 2 (daily dose):<br>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 $\geq 3$                   | 36                               | 12                              |  |  |
| Treatment-related Adverse Events of CTCAE Grade $\geq 3$ | 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 (C<sub>max</sub>) of IMCgp100

|                 |                                                              |
|-----------------|--------------------------------------------------------------|
| End point title | Maximum plasma concentration (C <sub>max</sub> ) of IMCgp100 |
|-----------------|--------------------------------------------------------------|

End point description:

PK population

C<sub>max</sub> 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):<br>IMCgp100 15 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 45 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 135 ng/kg | Arm 1 (by-weight dose weekly):<br>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):<br>IMCgp100 405 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 600 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 900 ng/kg | Arm 1 (flat dose weekly):<br>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):<br>IMCgp100 40 mcg | Arm 1 (flat dose weekly):<br>IMCgp100 50 mcg | Arm 2 (flat dose daily):<br>IMCgp100 10 mcg | Arm 2 (flat dose daily):<br>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):<br>IMCgp100 30 mcg | Arm 2 (flat dose daily):<br>IMCgp100 40 mcg | Arm 2 (flat dose daily):<br>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 ( $\pm$ 28383.108)                 | 6350.00 ( $\pm$ 1789.655)                   | 8340.00 ( $\pm$ 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):<br>IMCgp100 15 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 45 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 135 ng/kg | Arm 1 (by-weight dose weekly):<br>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 ( $\pm$ 22469.040)                         | 3187.64 ( $\pm$ 1487.001)                           | 3586.50 ( $\pm$ 2719.970)                            | 11183.44 ( $\pm$ 4080.507)                           |

| End point values                     | Arm 1 (by-weight dose weekly):<br>IMCgp100 405 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 600 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 900 ng/kg | Arm 1 (flat dose weekly):<br>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 ( $\pm$ 19301.380)                          | 68446.83 ( $\pm$ 25833.848)                          | 100589.81 ( $\pm$ 25817.365)                         | 26108.03 ( $\pm$ 8118.542)                   |

| End point values                     | Arm 1 (flat dose weekly):<br>IMCgp100 40 mcg | Arm 1 (flat dose weekly):<br>IMCgp100 50 mcg | Arm 2 (flat dose daily):<br>IMCgp100 10 mcg | Arm 2 (flat dose daily):<br>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 ( $\pm$ 12859.333)                  | 81431.74 ( $\pm$ 36505.518)                  | 5126.71 ( $\pm$ 2036.085)                   | 18229.73 ( $\pm$ 3593.221)                  |

| End point values                     | Arm 2 (flat dose daily):<br>IMCgp100 30 mcg | Arm 2 (flat dose daily):<br>IMCgp100 40 mcg | Arm 2 (flat dose daily):<br>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 ( $\pm$ 14030.039)                 | 30107.22 ( $\pm$ 7086.383)                  | 40120.03 ( $\pm$ 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):<br>IMCgp100 405 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 600 ng/kg | Arm 1 (by-weight dose weekly):<br>IMCgp100 900 ng/kg | Arm 1 (flat dose weekly):<br>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 ( $\pm$ 1.503)                                  | 8.09 ( $\pm$ 8.703)                                  | 6.51 ( $\pm$ 1.155)                                  | 6.35 ( $\pm$ 2.192)                          |

| End point values | Arm 1 (flat | Arm 1 (flat | Arm 2 (flat | Arm 2 (flat |
|------------------|-------------|-------------|-------------|-------------|
|------------------|-------------|-------------|-------------|-------------|

|                                      | dose weekly):<br>IMCgp100 40<br>mcg | dose weekly):<br>IMCgp100 50<br>mcg | dose daily):<br>IMCgp100 10<br>mcg | dose daily):<br>IMCgp100 20<br>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<br>dose daily):<br>IMCgp100 30<br>mcg | Arm 2 (flat<br>dose daily):<br>IMCgp100 40<br>mcg | Arm 2 (flat<br>dose daily):<br>IMCgp100 50<br>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<br>dose):<br>IMCgp100 | Arm 2 (daily<br>dose):<br>IMCgp100 |  |  |
|---------------------------------------------|-------------------------------------|------------------------------------|--|--|
| Subject group type                          | Reporting group                     | Reporting group                    |  |  |
| Number of subjects analysed                 | 66                                  | 18                                 |  |  |
| Units: Number of incidence                  |                                     |                                    |  |  |
| Anti-drug Antibody prevalence -<br>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 |
|-----------------|-----------------------------------------|

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  $\geq 270$ ng/kg (a median absolute dose of  $\geq 16$  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 |
|----------------|-----------|

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):<br>IMCgp100 | Arm 2 (daily dose):<br>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 |
|-----------------|-----------------------|

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 |
|----------------|-----------|

End point timeframe:

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

| <b>End point values</b>           | Arm 1 (weekly dose):<br>IMCgp100 | Arm 2 (daily dose):<br>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 |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description: -

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

Reporting group description: -

| <b>Serious adverse events</b>                                       | Adverse Events :<br>Arm 1 (weekly dosing) | Adverse Events :<br>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 %

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



|                                                                                                            |                        |                       |  |
|------------------------------------------------------------------------------------------------------------|------------------------|-----------------------|--|
| Cough<br>subjects affected / exposed<br>occurrences (all)                                                  | 15 / 66 (22.73%)<br>22 | 2 / 18 (11.11%)<br>2  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                               | 6 / 66 (9.09%)<br>9    | 2 / 18 (11.11%)<br>3  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 66 (6.06%)<br>5    | 1 / 18 (5.56%)<br>1   |  |
| Investigations<br>Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 3 / 66 (4.55%)<br>4    | 2 / 18 (11.11%)<br>2  |  |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)                       | 7 / 66 (10.61%)<br>8   | 4 / 18 (22.22%)<br>5  |  |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)                                      | 5 / 66 (7.58%)<br>14   | 1 / 18 (5.56%)<br>1   |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                   | 16 / 66 (24.24%)<br>30 | 6 / 18 (33.33%)<br>10 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                           | 10 / 66 (15.15%)<br>14 | 1 / 18 (5.56%)<br>2   |  |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)                                               | 5 / 66 (7.58%)<br>8    | 0 / 18 (0.00%)<br>0   |  |
| Blood and lymphatic system disorders<br>Lymphopenia<br>subjects affected / exposed<br>occurrences (all)    | 13 / 66 (19.70%)<br>19 | 4 / 18 (22.22%)<br>5  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                                                | 4 / 66 (6.06%)<br>9    | 5 / 18 (27.78%)<br>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                     | 17 / 66 (25.76%) | 6 / 18 (33.33%) |  |
| occurrences (all)                               | 32               | 15              |  |
| Dry skin                                        |                  |                 |  |
| subjects affected / exposed                     | 18 / 66 (27.27%) | 5 / 18 (27.78%) |  |
| occurrences (all)                               | 23               | 6               |  |
| Erythema                                        |                  |                 |  |
| subjects affected / exposed                     | 17 / 66 (25.76%) | 2 / 18 (11.11%) |  |
| occurrences (all)                               | 27               | 4               |  |
| Rash erythematous                               |                  |                 |  |
| subjects affected / exposed                     | 9 / 66 (13.64%)  | 5 / 18 (27.78%) |  |
| occurrences (all)                               | 17               | 13              |  |
| Vitiligo                                        |                  |                 |  |
| subjects affected / exposed                     | 9 / 66 (13.64%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 9                | 1               |  |
| Hair colour changes                             |                  |                 |  |
| subjects affected / exposed                     | 7 / 66 (10.61%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 7                | 1               |  |
| Musculoskeletal and connective tissue disorders |                  |                 |  |
| Back pain                                       |                  |                 |  |
| subjects affected / exposed                     | 14 / 66 (21.21%) | 2 / 18 (11.11%) |  |
| occurrences (all)                               | 27               | 3               |  |
| Arthralgia                                      |                  |                 |  |
| subjects affected / exposed                     | 7 / 66 (10.61%)  | 3 / 18 (16.67%) |  |
| occurrences (all)                               | 13               | 4               |  |
| Pain in extremity                               |                  |                 |  |
| subjects affected / exposed                     | 9 / 66 (13.64%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 13               | 1               |  |
| Myalgia                                         |                  |                 |  |
| subjects affected / exposed                     | 6 / 66 (9.09%)   | 1 / 18 (5.56%)  |  |
| occurrences (all)                               | 11               | 1               |  |
| Infections and infestations                     |                  |                 |  |
| Lower respiratory tract infection               |                  |                 |  |
| subjects affected / exposed                     | 4 / 66 (6.06%)   | 2 / 18 (11.11%) |  |
| occurrences (all)                               | 5                | 4               |  |
| Conjunctivitis                                  |                  |                 |  |

|                                                  |                        |                      |  |
|--------------------------------------------------|------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 6 / 66 (9.09%)<br>7    | 0 / 18 (0.00%)<br>0  |  |
| Rhinitis                                         |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 6 / 66 (9.09%)<br>7    | 0 / 18 (0.00%)<br>0  |  |
| Upper respiratory tract infection                |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 66 (6.06%)<br>5    | 1 / 18 (5.56%)<br>1  |  |
| Urinary tract infection                          |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 4 / 66 (6.06%)<br>4    | 1 / 18 (5.56%)<br>1  |  |
| Metabolism and nutrition disorders               |                        |                      |  |
| Decreased appetite                               |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 10 / 66 (15.15%)<br>13 | 0 / 18 (0.00%)<br>0  |  |
| Hypophosphataemia                                |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 5 / 66 (7.58%)<br>12   | 3 / 18 (16.67%)<br>4 |  |
| Hypoalbuminaemia                                 |                        |                      |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 66 (4.55%)<br>11   | 2 / 18 (11.11%)<br>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 <sub>max</sub> modelled so that it could be ensured that the dose selected for the next cohort had a predicted C <sub>max</sub> that did not exceed 1 nM. Dose-escalation was to be stopped if C <sub>max</sub> 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 $\geq 3$ 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