



## Clinical trial results:

### A Randomised, Open-Label, Proof-of-Concept, Phase II Trial Comparing Gemcitabine with and without IMM-101 in Advanced Pancreatic Cancer Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2010-022757-42  |
| Trial protocol           | GB ES IT IE     |
| Global end of trial date | 14 January 2016 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 08 February 2019 |
| First version publication date | 08 February 2019 |

#### Trial information

##### Trial identification

|                       |                          |
|-----------------------|--------------------------|
| Sponsor protocol code | IMM-101-002/IMM-101-002A |
|-----------------------|--------------------------|

##### Additional study identifiers

|                                    |                  |
|------------------------------------|------------------|
| ISRCTN number                      | -                |
| ClinicalTrials.gov id (NCT number) | NCT01303172      |
| WHO universal trial number (UTN)   | -                |
| Other trial identifiers            | IMAGE 1: IMAGE 1 |

Notes:

#### Sponsors

|                              |                                                                                                   |
|------------------------------|---------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Immodulon Therapeutics                                                                            |
| Sponsor organisation address | 6-9 The Square, Stockley Park, Uxbridge, United Kingdom, UB11 1FW                                 |
| Public contact               | Clinical Trials Co-ordinator, Immodulon Therapeutics Ltd, 00 44 0203317 6346, info@immodulon.com  |
| Scientific contact           | Clinical Trials Co-ordinator, Immodulon Therapeutics Ltd, 00 44 0203 317 6346, info@immodulon.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:

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## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 27 July 2016    |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 14 January 2016 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 14 January 2016 |
| Was the trial ended prematurely?                     | No              |

Notes:

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## General information about the trial

Main objective of the trial:

To compare, in treatment-naïve patients with advanced pancreatic cancer, the effects of gemcitabine (GEM) in combination with IMM-101 to GEM alone on:

- Safety and tolerability, including Quality of Life (QoL).
- Clinical signs and symptoms of disease.
- Overall survival (OS), progression-free survival (PFS) and overall response rate (ORR).

The objectives of the Sub-Study (for patients who completed the Main Study and who provided informed consent for long-term follow-up) were to:

Describe the long-term safety profile of IMM-101 administered intradermally for extended use in patients completing the Main Study.

Document the clinical course of the patients who previously completed the Main Study and agreed to enter the Sub-Study.

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Protection of trial subjects:

Protection of trial subjects:

The trial was conducted in accordance with the study protocol, the guidelines of the World Medical Association Declaration of Helsinki as amended (Fortaleza, 2013), the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines (CPMP/ICH/135/95), designated standard operating procedures (SOPs), and with local laws and regulations relevant to the use of new therapeutic agents.

A Data Monitoring Committee (DMC) consisting of oncologists and clinicians with relevant expertise, that was established for the purposes of reviewing safety data on an ongoing basis throughout the Main and Sub studies. The DMC responsibility was to safeguard the interests of the studies' patients, with respect to safety and efficacy of IMM-101, study conduct, and compliance with the protocol.

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Background therapy:

In the Main Study (IMM-101-002), all patients received GEM administered intravenously at 1000 mg/m<sup>2</sup> over 30 minutes once weekly for 3 consecutive weeks out of every 4 weeks up to a maximum of 12 cycles. Patients in the IMM-101 treated group began GEM at least 14 days after the first dose of IMM-101.

Upon disease progression or toxicity to GEM, second-line chemotherapy of the investigator's choice was allowed. For the IMM-101 treated group this second-line chemotherapy was alongside continued treatment with IMM-101. Patients in the IMM-101 treated group could also continue on study and receive IMM-101 alone.

All patients entering the Sub-Study (IMM-101-002A) received IMM-101 and were free to receive any other anti-cancer therapy (including GEM) as considered appropriate by the Investigator.

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Evidence for comparator:

Gemcitabine was the standard care for treatment of inoperable advanced pancreatic cancer at the time IMM-101-002 was initiated having been established as such since first approval in 1995. Significant improvement in disease-related symptoms and prolonged survival were demonstrated in a comparative study between GEM and 5-fluorouracil (5-FU) (1-year survival: 18% versus 2%,

respectively, Burris, 1997 ). In that study, median survival was 5.65 months for GEM-treated patients and 4.41 months for 5-FU treated patients.

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 15 July 2011 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 49          |
| Country: Number of subjects enrolled | United Kingdom: 32 |
| Country: Number of subjects enrolled | Ireland: 2         |
| Country: Number of subjects enrolled | Italy: 21          |
| Country: Number of subjects enrolled | Cyprus: 6          |
| Worldwide total number of subjects   | 110                |
| EEA total number of subjects         | 110                |

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)                      | 37 |
| From 65 to 84 years                       | 72 |
| 85 years and over                         | 1  |

## Subject disposition

### Recruitment

Recruitment details:

110 patients were randomised into the study at 20 sites in 5 countries. Patients were randomised to receive either IMM-101 and GEM (75) or GEM (35).

12 patients who completed the Main Study were enrolled into the Sub-Study; 11 of these patients had previously been randomised to the IMM-101 treated group and 1 to the GEM group.

### Pre-assignment

Screening details:

Patients aged  $\geq 18$  years were eligible for the study if they had histologically and/or cytologically confirmed inoperable ductal adenocarcinoma of the pancreas, including the mucinous variant. This included locally advanced and metastatic disease (stage III/IV).

In total 142 patients were screened of whom 32 failed screening.

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Complete study (overall period) |
| Is this the baseline period? | Yes                             |
| Allocation method            | Randomised - controlled         |
| Blinding used                | Not blinded                     |

Blinding implementation details:

Not Applicable

### Arms

|                              |                   |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes               |
| <b>Arm title</b>             | ITT IMM-101 + GEM |

Arm description:

ITT IMM-101 + Gemcitabine

|                                        |                                                       |
|----------------------------------------|-------------------------------------------------------|
| Arm type                               | Experimental                                          |
| Investigational medicinal product name | Heat killed Mycobacterium obuense NCTC13365 (IMM-101) |
| Investigational medicinal product code | UPI EMA/569517 (IMM-101)                              |
| Other name                             | IMM-101                                               |
| Pharmaceutical forms                   | Suspension for injection                              |
| Routes of administration               | Intradermal use                                       |

Dosage and administration details:

During the Main Study, patients received a single 0.1 mL intradermal (i.d.) injection of IMM-101 every 2 weeks for the first 3 doses, followed by a 4-week rest period, then IMM-101 every 2 weeks for the next 3 doses. Thereafter, patients received doses every 4 weeks to a maximum of 15 doses. IMM-101 was given via i.d. injection into the skin overlying the deltoid muscle, with the arm being alternated between each dose. Patients enrolling in the Sub-Study continued to receive IMM-101 every 4 weeks.

GEM was administered intravenously at 1000 mg/m<sup>2</sup> over 30 minutes once weekly for 3 consecutive weeks out of every 4 weeks to a maximum of 12 cycles. The first dose of GEM was given at least 14 days after the first dose of IMM-101.

Patients enrolling in the Sub-Study from the Main study GEM group received IMM-101 every 2 weeks for the first 3 doses, then a rest of 4 weeks, then 1 dose every 2 weeks for the next 3 doses. Thereafter, the treatment regimen was 1 dose every 4 weeks.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | ITT GEM |
|------------------|---------|

Arm description:

ITT Gemcitabine

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Gemcitabine           |
| Investigational medicinal product code |                       |
| Other name                             | GEM                   |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Gemcitabine was administered intravenously at 1000 mg/m<sup>2</sup> over 30 minutes once weekly for 3 consecutive weeks out of every 4 weeks to a maximum of 12 cycles. In the experimental arm (IMM-101 + GEM) the first dose of GEM was given at least 14 days after the first dose of IMM-101. GEM could be continued in the Sub-Study at the Investigator's discretion.

| <b>Number of subjects in period 1</b>              | ITT IMM-101 + GEM | ITT GEM |
|----------------------------------------------------|-------------------|---------|
| Started                                            | 75                | 35      |
| Completion of main study                           | 12                | 1       |
| Completion of sub-study                            | 0                 | 0       |
| Completed                                          | 0                 | 0       |
| Not completed                                      | 75                | 35      |
| Consent withdrawn and patient decision             | 7                 | 2       |
| Adverse event, non-fatal                           | 5                 | -       |
| Toxicity                                           | -                 | 2       |
| Completed main study then lost to follow up        | 1                 | -       |
| Death                                              | 22                | 7       |
| Fracture                                           | 1                 | -       |
| Disease progression/clinical deterioration         | 37                | 23      |
| Change in therapy                                  | 2                 | -       |
| Functional impairment(without disease progression) | -                 | 1       |

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Complete study |
|-----------------------|----------------|

Reporting group description:

All randomised patients

| Reporting group values                             | Complete study | Total |  |
|----------------------------------------------------|----------------|-------|--|
| Number of subjects                                 | 110            | 110   |  |
| Age categorical                                    |                |       |  |
| Units: Subjects                                    |                |       |  |
| In utero                                           | 0              | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0              | 0     |  |
| Newborns (0-27 days)                               | 0              | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0              | 0     |  |
| Children (2-11 years)                              | 0              | 0     |  |
| Adolescents (12-17 years)                          | 0              | 0     |  |
| Adults (18-64 years)                               | 37             | 37    |  |
| From 65-84 years                                   | 72             | 72    |  |
| 85 years and over                                  | 1              | 1     |  |
| Age continuous                                     |                |       |  |
| Units: years                                       |                |       |  |
| median                                             | 67             |       |  |
| full range (min-max)                               | 45 to 88       | -     |  |
| Gender categorical                                 |                |       |  |
| Units: Subjects                                    |                |       |  |
| Female                                             | 51             | 51    |  |
| Male                                               | 59             | 59    |  |

## End points

### End points reporting groups

|                                                                                                                           |                                                    |
|---------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| Reporting group title                                                                                                     | ITT IMM-101 + GEM                                  |
| Reporting group description:<br>ITT IMM-101 + Gemcitabine                                                                 |                                                    |
| Reporting group title                                                                                                     | ITT GEM                                            |
| Reporting group description:<br>ITT Gemcitabine                                                                           |                                                    |
| Subject analysis set title                                                                                                | ITT IMM-101 + GEM patients with metastatic disease |
| Subject analysis set type                                                                                                 | Intention-to-treat                                 |
| Subject analysis set description:<br>All IMM-101 + Gemcitabine treated patients who had metastatic disease at study entry |                                                    |
| Subject analysis set title                                                                                                | ITT GEM patients with metastatic disease           |
| Subject analysis set type                                                                                                 | Intention-to-treat                                 |
| Subject analysis set description:<br>All Gemcitabine treated patients who had metastatic disease at study entry           |                                                    |

### Primary: Overall survival in the ITT IMM-101 + GEM arm compared with that in the ITT GEM arm until completion of the Main Study

|                                                                                                                                                                                                                              |                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                              | Overall survival in the ITT IMM-101 + GEM arm compared with that in the ITT GEM arm until completion of the Main Study |
| End point description:<br>OS was defined as the time in months from randomisation in the Main Study to death due to any cause. Patients without death date were censored at the date the patient was last known to be alive. |                                                                                                                        |
| End point type                                                                                                                                                                                                               | Primary                                                                                                                |
| End point timeframe:<br>From randomisation to death due to any cause with a data cutoff date of 9 September 2014.                                                                                                            |                                                                                                                        |

| End point values                 | ITT IMM-101 + GEM | ITT GEM          | ITT IMM-101 + GEM patients with metastatic disease | ITT GEM patients with metastatic disease |
|----------------------------------|-------------------|------------------|----------------------------------------------------|------------------------------------------|
| Subject group type               | Reporting group   | Reporting group  | Subject analysis set                               | Subject analysis set                     |
| Number of subjects analysed      | 75                | 35               | 64                                                 | 28                                       |
| Units: Months                    |                   |                  |                                                    |                                          |
| median (confidence interval 95%) | 6.7 (5.4 to 7.5)  | 5.6 (3.2 to 7.2) | 7.0 (5.5 to 9.0)                                   | 4.4 (2.8 to 6.5)                         |

### Statistical analyses

|                                                                                                                                                                                                          |                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Statistical analysis title                                                                                                                                                                               | Overall survival            |
| Statistical analysis description:<br>The difference in OS between treatment groups was assessed using Kaplan-Meier methods and a 2-sided logrank test. The HR was estimated using a Cox regression model |                             |
| Comparison groups                                                                                                                                                                                        | ITT IMM-101 + GEM v ITT GEM |

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 110               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.074           |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.68              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.44              |
| upper limit                             | 1.04              |

|                                   |                                                |
|-----------------------------------|------------------------------------------------|
| <b>Statistical analysis title</b> | Overall survival (metastatic disease patients) |
|-----------------------------------|------------------------------------------------|

Statistical analysis description:

The difference in OS between treatment groups was assessed using Kaplan-Meier methods and a 2-sided logrank test for the ITT subgroup of patients with metastatic disease. The HR was estimated using a Cox regression model. Statistical values relate to the treatment effect of IMM-101 + GEM treated patients relative to that of GEM treated patients.

|                                         |                                                                                               |
|-----------------------------------------|-----------------------------------------------------------------------------------------------|
| Comparison groups                       | ITT GEM patients with metastatic disease v ITT IMM-101 + GEM patients with metastatic disease |
| Number of subjects included in analysis | 92                                                                                            |
| Analysis specification                  | Pre-specified                                                                                 |
| Analysis type                           | superiority                                                                                   |
| P-value                                 | = 0.01                                                                                        |
| Method                                  | Logrank                                                                                       |
| Parameter estimate                      | Hazard ratio (HR)                                                                             |
| Point estimate                          | 0.54                                                                                          |
| Confidence interval                     |                                                                                               |
| level                                   | 95 %                                                                                          |
| sides                                   | 2-sided                                                                                       |
| lower limit                             | 0.33                                                                                          |
| upper limit                             | 0.87                                                                                          |

#### **Other pre-specified: Progression-free survival in the ITT IMM-101 + GEM arm compared with that in the ITT GEM arm until completion of the Main Study**

|                 |                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | Progression-free survival in the ITT IMM-101 + GEM arm compared with that in the ITT GEM arm until completion of the Main Study |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|

End point description:

PFS was defined as the time in months from randomisation to objective tumour progression or death (whichever occurred first). Progression included biological progression, clinical progression, withdrawal due to progression, and death due to any cause. Patients with no event were censored at the last contact.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From randomisation to progression or death (whichever occurred first) with a data cutoff of 9 September 2014



| <b>End point values</b>          | ITT IMM-101 + GEM | ITT GEM          | ITT IMM-101 + GEM patients with metastatic disease | ITT GEM patients with metastatic disease |
|----------------------------------|-------------------|------------------|----------------------------------------------------|------------------------------------------|
| Subject group type               | Reporting group   | Reporting group  | Subject analysis set                               | Subject analysis set                     |
| Number of subjects analysed      | 75                | 35               | 64                                                 | 28                                       |
| Units: months                    |                   |                  |                                                    |                                          |
| median (confidence interval 95%) | 4.1 (3.3 to 4.8)  | 2.4 (2.1 to 4.0) | 4.4 (3.3 to 5.1)                                   | 2.3 (1.9 to 2.8)                         |

## Statistical analyses

| <b>Statistical analysis title</b>                                                                                                                                                            | Progression free survival   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Statistical analysis description:                                                                                                                                                            |                             |
| The difference in PFS between treatment groups was assessed using Kaplan-Meier methods and a 2-sided logrank test for the ITT population. The HR was estimated using a Cox regression model. |                             |
| Comparison groups                                                                                                                                                                            | ITT IMM-101 + GEM v ITT GEM |
| Number of subjects included in analysis                                                                                                                                                      | 110                         |
| Analysis specification                                                                                                                                                                       | Pre-specified               |
| Analysis type                                                                                                                                                                                | superiority                 |
| P-value                                                                                                                                                                                      | = 0.016                     |
| Method                                                                                                                                                                                       | Logrank                     |
| Parameter estimate                                                                                                                                                                           | Hazard ratio (HR)           |
| Point estimate                                                                                                                                                                               | 0.58                        |
| Confidence interval                                                                                                                                                                          |                             |
| level                                                                                                                                                                                        | 95 %                        |
| sides                                                                                                                                                                                        | 2-sided                     |
| lower limit                                                                                                                                                                                  | 0.37                        |
| upper limit                                                                                                                                                                                  | 0.91                        |

| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                            | Progression free survival - metastatic disease                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                            |                                                                                               |
| The difference in PFS between treatment groups was assessed using Kaplan-Meier methods and a 2-sided logrank test for the ITT subgroup of patients with metastatic disease. The HR was estimated using a Cox regression model. Statistical values relate to the treatment effect of IMM-101 + GEM treated patients relative to that of GEM treated patients. |                                                                                               |
| Comparison groups                                                                                                                                                                                                                                                                                                                                            | ITT GEM patients with metastatic disease v ITT IMM-101 + GEM patients with metastatic disease |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                      | 92                                                                                            |
| Analysis specification                                                                                                                                                                                                                                                                                                                                       | Pre-specified                                                                                 |
| Analysis type                                                                                                                                                                                                                                                                                                                                                | superiority                                                                                   |
| P-value                                                                                                                                                                                                                                                                                                                                                      | = 0.001                                                                                       |
| Method                                                                                                                                                                                                                                                                                                                                                       | Logrank                                                                                       |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                           | Hazard ratio (HR)                                                                             |
| Point estimate                                                                                                                                                                                                                                                                                                                                               | 0.46                                                                                          |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.28    |
| upper limit         | 0.75    |

### Other pre-specified: Overall Response rate

|                                                                                                                                                                                                                                                                                  |                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                  | Overall Response rate |
| End point description:                                                                                                                                                                                                                                                           |                       |
| ORR was defined as the percentage of patients with a complete response (CR) or partial response (PR) as assessed by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria. A responder was defined as a patient experiencing either a CR or PR by these criteria. |                       |
| End point type                                                                                                                                                                                                                                                                   | Other pre-specified   |
| End point timeframe:                                                                                                                                                                                                                                                             |                       |
| From randomisation to death with a data cut-off date of 9 September 2014                                                                                                                                                                                                         |                       |

| End point values            | ITT IMM-101 + GEM | ITT GEM         | ITT IMM-101 + GEM patients with metastatic disease | ITT GEM patients with metastatic disease |
|-----------------------------|-------------------|-----------------|----------------------------------------------------|------------------------------------------|
| Subject group type          | Reporting group   | Reporting group | Subject analysis set                               | Subject analysis set                     |
| Number of subjects analysed | 75                | 35              | 64                                                 | 28                                       |
| Units: Patients             |                   |                 |                                                    |                                          |
| Complete response           | 0                 | 0               | 0                                                  | 0                                        |
| Partial response            | 8                 | 1               | 7                                                  | 1                                        |

### Statistical analyses

|                                                                                                                                                                                                     |                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Statistical analysis title                                                                                                                                                                          | Overall Response Rate       |
| Statistical analysis description:                                                                                                                                                                   |                             |
| The difference between the percentage of patients with a response (complete response (CR) or partial response (PR) by RECIST 1.1) in the IMM-101 + GEM group to that in the GEM group was assessed. |                             |
| Comparison groups                                                                                                                                                                                   | ITT IMM-101 + GEM v ITT GEM |
| Number of subjects included in analysis                                                                                                                                                             | 110                         |
| Analysis specification                                                                                                                                                                              | Pre-specified               |
| Analysis type                                                                                                                                                                                       | other                       |
| P-value                                                                                                                                                                                             | = 0.164                     |
| Method                                                                                                                                                                                              | Chi-squared                 |

|                                                                                                                                                                                                     |                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Statistical analysis title                                                                                                                                                                          | Overall Response Rate |
| Statistical analysis description:                                                                                                                                                                   |                       |
| The difference between the percentage of patients with a response (complete response (CR) or partial response (PR) by RECIST 1.1) in the IMM-101 + GEM group to that in the GEM group was assessed. |                       |

|                                         |                                                                                               |
|-----------------------------------------|-----------------------------------------------------------------------------------------------|
| Comparison groups                       | ITT IMM-101 + GEM patients with metastatic disease v ITT GEM patients with metastatic disease |
| Number of subjects included in analysis | 92                                                                                            |
| Analysis specification                  | Pre-specified                                                                                 |
| Analysis type                           | other                                                                                         |
| P-value                                 | = 0.249                                                                                       |
| Method                                  | Chi-squared                                                                                   |

### Other pre-specified: Overall survival in the ITT IMM-101 + GEM arm compared to that in the ITT GEM arm including Sub-Study survival

|                        |                                                                                                                                                                                                                                                                                    |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Overall survival in the ITT IMM-101 + GEM arm compared to that in the ITT GEM arm including Sub-Study survival                                                                                                                                                                     |
| End point description: | OS was defined as the time in months from randomisation in the Main study to death due to any cause including extended follow-up from the Sub-Study and post study survival status. Patients without a death date were censored at the date the patient was last known to be alive |
| End point type         | Other pre-specified                                                                                                                                                                                                                                                                |
| End point timeframe:   | From randomisation to death with a data cutoff date of 5 February 2016                                                                                                                                                                                                             |

| End point values                 | ITT IMM-101 + GEM | ITT GEM          | ITT IMM-101 + GEM patients with metastatic disease | ITT GEM patients with metastatic disease |
|----------------------------------|-------------------|------------------|----------------------------------------------------|------------------------------------------|
| Subject group type               | Reporting group   | Reporting group  | Subject analysis set                               | Subject analysis set                     |
| Number of subjects analysed      | 75                | 35               | 64                                                 | 28                                       |
| Units: Months                    |                   |                  |                                                    |                                          |
| median (confidence interval 95%) | 6.7 (5.4 to 7.5)  | 5.6 (3.2 to 7.2) | 7.0 (5.5 to 9.0)                                   | 4.4 (2.8 to 6.5)                         |

### Statistical analyses

|                                         |                                                                                                                                                                     |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title              | Overall survival                                                                                                                                                    |
| Statistical analysis description:       | The difference in OS between treatment groups was assessed using Kaplan-Meier methods and a 2-sided logrank test. The HR was estimated using a Cox regression model |
| Comparison groups                       | ITT IMM-101 + GEM v ITT GEM                                                                                                                                         |
| Number of subjects included in analysis | 110                                                                                                                                                                 |
| Analysis specification                  | Pre-specified                                                                                                                                                       |
| Analysis type                           | superiority                                                                                                                                                         |
| P-value                                 | = 0.0706                                                                                                                                                            |
| Method                                  | Logrank                                                                                                                                                             |
| Parameter estimate                      | Hazard ratio (HR)                                                                                                                                                   |
| Point estimate                          | 0.67                                                                                                                                                                |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.44    |
| upper limit         | 1.04    |

|                                         |                                                                                               |
|-----------------------------------------|-----------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Overall survival (metastatic disease patients)                                                |
| Comparison groups                       | ITT IMM-101 + GEM patients with metastatic disease v ITT GEM patients with metastatic disease |
| Number of subjects included in analysis | 92                                                                                            |
| Analysis specification                  | Pre-specified                                                                                 |
| Analysis type                           | superiority                                                                                   |
| P-value                                 | = 0.0093                                                                                      |
| Method                                  | Logrank                                                                                       |
| Parameter estimate                      | Hazard ratio (HR)                                                                             |
| Point estimate                          | 0.53                                                                                          |
| Confidence interval                     |                                                                                               |
| level                                   | 95 %                                                                                          |
| sides                                   | 2-sided                                                                                       |
| lower limit                             | 0.33                                                                                          |
| upper limit                             | 0.86                                                                                          |

**Other pre-specified: Progression free survival in the ITT IMM-101 + GEM arm compared to that in the ITT GEM arm until completion of the Sub-Study**

|                 |                                                                                                                              |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|
| End point title | Progression free survival in the ITT IMM-101 + GEM arm compared to that in the ITT GEM arm until completion of the Sub-Study |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|

End point description:

PFS was defined as the time in months from randomisation to objective tumour progression or death (whichever occurred first). Progression included biological progression, clinical progression, withdrawal due to progression, and death due to any cause. Patients with no event were censored at the last contact.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From randomisation to progression or death (whichever occurred first) with a data cutoff of 14 Jan 2016

| <b>End point values</b>          | ITT IMM-101 + GEM | ITT GEM          | ITT IMM-101 + GEM patients with metastatic disease | ITT GEM patients with metastatic disease |
|----------------------------------|-------------------|------------------|----------------------------------------------------|------------------------------------------|
| Subject group type               | Reporting group   | Reporting group  | Subject analysis set                               | Subject analysis set                     |
| Number of subjects analysed      | 75                | 35               | 64                                                 | 28                                       |
| Units: months                    |                   |                  |                                                    |                                          |
| median (confidence interval 95%) | 4.1 (3.3 to 4.8)  | 2.4 (2.1 to 4.0) | 4.4 (3.3 to 5.1)                                   | 2.3 (1.9 to 2.8)                         |

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                            |                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                          | Progression free survival   |
| Statistical analysis description:                                                                                                                                                                                                                                                                                          |                             |
| The difference in PFS between treatment groups was assessed using Kaplan-Meier methods and a 2-sided logrank test for the ITT population. The HR was estimated using a Cox regression model. Statistical values relate to the treatment effect of IMM-101 + GEM treated patients relative to that of GEM treated patients. |                             |
| Comparison groups                                                                                                                                                                                                                                                                                                          | ITT GEM v ITT IMM-101 + GEM |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                    | 110                         |
| Analysis specification                                                                                                                                                                                                                                                                                                     | Pre-specified               |
| Analysis type                                                                                                                                                                                                                                                                                                              | other                       |
| P-value                                                                                                                                                                                                                                                                                                                    | = 0.0158                    |
| Method                                                                                                                                                                                                                                                                                                                     | Logrank                     |
| Parameter estimate                                                                                                                                                                                                                                                                                                         | Hazard ratio (HR)           |
| Point estimate                                                                                                                                                                                                                                                                                                             | 0.58                        |
| Confidence interval                                                                                                                                                                                                                                                                                                        |                             |
| level                                                                                                                                                                                                                                                                                                                      | 95 %                        |
| sides                                                                                                                                                                                                                                                                                                                      | 2-sided                     |
| lower limit                                                                                                                                                                                                                                                                                                                | 0.37                        |
| upper limit                                                                                                                                                                                                                                                                                                                | 0.91                        |

|                                                                                                                                                                                              |                                                                                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                            | Progression free survival - metastatic disease                                                |
| Statistical analysis description:                                                                                                                                                            |                                                                                               |
| The difference in PFS between treatment groups was assessed using Kaplan-Meier methods and a 2-sided logrank test for the ITT population. The HR was estimated using a Cox regression model. |                                                                                               |
| Comparison groups                                                                                                                                                                            | ITT IMM-101 + GEM patients with metastatic disease v ITT GEM patients with metastatic disease |
| Number of subjects included in analysis                                                                                                                                                      | 92                                                                                            |
| Analysis specification                                                                                                                                                                       | Pre-specified                                                                                 |
| Analysis type                                                                                                                                                                                | other                                                                                         |
| P-value                                                                                                                                                                                      | = 0.0012                                                                                      |
| Method                                                                                                                                                                                       | Logrank                                                                                       |
| Parameter estimate                                                                                                                                                                           | Hazard ratio (HR)                                                                             |
| Point estimate                                                                                                                                                                               | 0.46                                                                                          |
| Confidence interval                                                                                                                                                                          |                                                                                               |
| level                                                                                                                                                                                        | 95 %                                                                                          |
| sides                                                                                                                                                                                        | 2-sided                                                                                       |
| lower limit                                                                                                                                                                                  | 0.28                                                                                          |
| upper limit                                                                                                                                                                                  | 0.75                                                                                          |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Complete study duration

Adverse event reporting additional description:

AE data were collected from informed consent until patient completion, withdrawal or death and followed until 30 days after end of study/withdrawal visit. AEs leading to hospitalisation/death due to disease progression were reported as AEs, not SAEs, if this was expected as a normal course of the disease and was not more rapid than was expected.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 14 |
|--------------------|----|

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | IMM-101 + GEM Main study only |
|-----------------------|-------------------------------|

Reporting group description:

Treatment-emergent AEs reported for IMM-101 + GEM treated patients during the 12-cycle Main study. Treatment-emergent AEs were those commencing or worsening after first exposure to IMM-101. Only treatment-emergent fatalities are reported. One additional fatality occurred in this group prior to exposure to any study drug. Treatment-related events refer to those with a reported causality to either IMM-101, GEM, or both.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | GEM Main study only |
|-----------------------|---------------------|

Reporting group description:

Treatment-emergent AEs reported for GEM treated patients during the 12-cycle Main study. Treatment-emergent AEs were those commencing or worsening after first exposure to GEM. Only treatment-emergent fatalities are reported. Treatment-related events refer to those with a reported causality to GEM.

|                       |                                             |
|-----------------------|---------------------------------------------|
| Reporting group title | IMM-101 + GEM Main and Sub studies combined |
|-----------------------|---------------------------------------------|

Reporting group description:

Treatment-emergent AEs reported for IMM-101 treated patients combined with additional AE data for the 11 patients who entered the long term follow up Sub-Study. Treatment-emergent AEs were those commencing or worsening after first exposure to IMM-101 in the Main study. Only treatment-emergent fatalities are reported. One additional fatality occurred in this group prior to exposure to any study drug. Treatment-related events refer to those with reported causality to IMM-101, GEM or both in the Main study and to IMM-101 in the Sub-Study.

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | GEM Main and Sub studies combined |
|-----------------------|-----------------------------------|

Reporting group description:

Treatment-emergent AEs reported for GEM treated patients in the main study combined with AE data for the one patient who entered the long-term follow-up Sub-Study. Treatment-emergent AEs were those commencing or worsening after first exposure to GEM in the Main study, but before first exposure to IMM-101 in the Sub-Study. Note any AEs starting or worsening after first exposure to IMM-101 in this GEM patient are treatment emergent to IMM-101. Only treatment-emergent fatalities are reported. Treatment-related events refer to those with a reported causality to GEM in the Main study only. There were no SAEs which were related to IMM-101 after commencing IMM-101 treatment in this reporting group.

| Serious adverse events                            | IMM-101 + GEM<br>Main study only | GEM Main study only | IMM-101 + GEM<br>Main and Sub<br>studies combined |
|---------------------------------------------------|----------------------------------|---------------------|---------------------------------------------------|
| Total subjects affected by serious adverse events |                                  |                     |                                                   |
| subjects affected / exposed                       | 36 / 74 (48.65%)                 | 10 / 35 (28.57%)    | 38 / 74 (51.35%)                                  |
| number of deaths (all causes)                     | 20                               | 7                   | 22                                                |
| number of deaths resulting from                   | 14                               | 5                   | 15                                                |

|                                                                     |                |                |                |
|---------------------------------------------------------------------|----------------|----------------|----------------|
| adverse events                                                      |                |                |                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |                |
| Pancreatic carcinoma metastatic                                     |                |                |                |
| subjects affected / exposed                                         | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 1          | 0 / 0          | 0 / 1          |
| Injury, poisoning and procedural complications                      |                |                |                |
| Toxicity to various agents                                          |                |                |                |
| subjects affected / exposed                                         | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all                     | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Incisional hernia                                                   |                |                |                |
| subjects affected / exposed                                         | 0 / 74 (0.00%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                                                   |                |                |                |
| Arrhythmia                                                          |                |                |                |
| subjects affected / exposed                                         | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac failure congestive                                          |                |                |                |
| subjects affected / exposed                                         | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all                     | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                                            |                |                |                |
| Cerebral infarction                                                 |                |                |                |
| subjects affected / exposed                                         | 1 / 74 (1.35%) | 1 / 35 (2.86%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all                     | 1 / 1          | 0 / 1          | 1 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Cerebellar infarction                                               |                |                |                |
| subjects affected / exposed                                         | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all                     | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Convulsion                                                          |                |                |                |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| IVth nerve paralysis                                 |                |                |                |
| subjects affected / exposed                          | 0 / 74 (0.00%) | 1 / 35 (2.86%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Nerve root compression                               |                |                |                |
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Peroneal nerve palsy                                 |                |                |                |
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Syncope                                              |                |                |                |
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Disease progression                                  |                |                |                |
| subjects affected / exposed                          | 3 / 74 (4.05%) | 2 / 35 (5.71%) | 3 / 74 (4.05%) |
| occurrences causally related to treatment / all      | 0 / 3          | 0 / 2          | 0 / 3          |
| deaths causally related to treatment / all           | 0 / 3          | 0 / 2          | 0 / 3          |
| Pyrexia                                              |                |                |                |
| subjects affected / exposed                          | 4 / 74 (5.41%) | 1 / 35 (2.86%) | 4 / 74 (5.41%) |
| occurrences causally related to treatment / all      | 2 / 4          | 1 / 1          | 2 / 4          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Chest pain                                           |                |                |                |
| subjects affected / exposed                          | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Fatigue                                              |                |                |                |



|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| General physical health deterioration           |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| Mucosal inflammation                            |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sudden death                                    |                |                |                |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 35 (2.86%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| Anaemia                                         |                |                |                |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 0 / 35 (0.00%) | 2 / 74 (2.70%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Febrile neutropenia                             |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Splenomegaly                                    |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 4 / 74 (5.41%) | 0 / 35 (0.00%) | 4 / 74 (5.41%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 0          | 0 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ascites                                         |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 3 / 74 (4.05%) | 0 / 35 (0.00%) | 3 / 74 (4.05%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 0          | 0 / 4          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vomiting                                        |                |                |                |
| subjects affected / exposed                     | 3 / 74 (4.05%) | 0 / 35 (0.00%) | 3 / 74 (4.05%) |
| occurrences causally related to treatment / all | 2 / 3          | 0 / 0          | 2 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Intestinal obstruction                          |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 1 / 35 (2.86%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diarrhoea                                       |                |                |                |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 35 (2.86%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal haemorrhage                    |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| Large intestine perforation                     |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| Small intestine perforation                     |                |                |                |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 35 (2.86%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Upper gastrointestinal haemorrhage              |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| Pancreatic duct stenosis                        |                |                |                |

|                                                        |                |                |                |
|--------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                            | 0 / 74 (0.00%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Hepatobiliary disorders</b>                         |                |                |                |
| Bile duct obstruction                                  |                |                |                |
| subjects affected / exposed                            | 2 / 74 (2.70%) | 0 / 35 (0.00%) | 2 / 74 (2.70%) |
| occurrences causally related to treatment / all        | 0 / 2          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholangitis                                            |                |                |                |
| subjects affected / exposed                            | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Cholecystitis                                          |                |                |                |
| subjects affected / exposed                            | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all        | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                |                |                |
| Dyspnoea                                               |                |                |                |
| subjects affected / exposed                            | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Pleural effusion                                       |                |                |                |
| subjects affected / exposed                            | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 2 / 74 (2.70%) |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonitis                                            |                |                |                |
| subjects affected / exposed                            | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all        | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary embolism                                     |                |                |                |
| subjects affected / exposed                            | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0          | 0 / 0          |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Pneumothorax                                    |                |                |                |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Biliary sepsis                                  |                |                |                |
| subjects affected / exposed                     | 4 / 74 (5.41%) | 0 / 35 (0.00%) | 4 / 74 (5.41%) |
| occurrences causally related to treatment / all | 2 / 6          | 0 / 0          | 2 / 6          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infection                                       |                |                |                |
| subjects affected / exposed                     | 3 / 74 (4.05%) | 0 / 35 (0.00%) | 3 / 74 (4.05%) |
| occurrences causally related to treatment / all | 1 / 3          | 0 / 0          | 1 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 3 / 74 (4.05%) | 0 / 35 (0.00%) | 3 / 74 (4.05%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 3          | 0 / 0          | 0 / 3          |
| Sepsis                                          |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 1 / 35 (2.86%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 2          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lower respiratory tract infection               |                |                |                |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 0 / 35 (0.00%) | 2 / 74 (2.70%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 2 / 74 (2.70%) | 0 / 35 (0.00%) | 2 / 74 (2.70%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Clostridium difficile colitis                   |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Biliary tract infection                         |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Device related infection                        |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Liver abscess                                   |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Lung infection                                  |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Septic shock                                    |                |                |                |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 35 (2.86%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| Urinary tract infection fungal                  |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                |                |                |
| Decreased appetite                              |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Dehydration                                     |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 35 (2.86%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Diabetic ketoacidosis                           |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypoglycaemia                                   |                |                |                |
| subjects affected / exposed                     | 1 / 74 (1.35%) | 0 / 35 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypocalcaemia                                   |                |                |                |
| subjects affected / exposed                     | 0 / 74 (0.00%) | 1 / 35 (2.86%) | 0 / 74 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                                       | GEM Main and Sub studies combined |  |  |
|---------------------------------------------------------------------|-----------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                   |  |  |
| subjects affected / exposed                                         | 10 / 35 (28.57%)                  |  |  |
| number of deaths (all causes)                                       | 7                                 |  |  |
| number of deaths resulting from adverse events                      | 5                                 |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |  |  |
| Pancreatic carcinoma metastatic                                     |                                   |  |  |
| subjects affected / exposed                                         | 0 / 35 (0.00%)                    |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                             |  |  |
| deaths causally related to treatment / all                          | 0 / 0                             |  |  |
| Injury, poisoning and procedural complications                      |                                   |  |  |
| Toxicity to various agents                                          |                                   |  |  |
| subjects affected / exposed                                         | 0 / 35 (0.00%)                    |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                             |  |  |
| deaths causally related to treatment / all                          | 0 / 0                             |  |  |
| Incisional hernia                                                   |                                   |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Arrhythmia                                      |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac failure congestive                      |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Cerebral infarction                             |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cerebellar infarction                           |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Convulsion                                      |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| IVth nerve paralysis                            |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nerve root compression                          |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Peroneal nerve palsy                            |                |  |  |

|                                                      |                |  |  |
|------------------------------------------------------|----------------|--|--|
| subjects affected / exposed                          | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Syncope                                              |                |  |  |
| subjects affected / exposed                          | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Disease progression                                  |                |  |  |
| subjects affected / exposed                          | 2 / 35 (5.71%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 2          |  |  |
| Pyrexia                                              |                |  |  |
| subjects affected / exposed                          | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Chest pain                                           |                |  |  |
| subjects affected / exposed                          | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Fatigue                                              |                |  |  |
| subjects affected / exposed                          | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General physical health deterioration                |                |  |  |
| subjects affected / exposed                          | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Mucosal inflammation                                 |                |  |  |
| subjects affected / exposed                          | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Sudden death                                         |                |  |  |



|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Anaemia                                         |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Febrile neutropenia                             |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Splenomegaly                                    |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ascites                                         |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting                                        |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Intestinal obstruction                          |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diarrhoea                                       |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal haemorrhage                    |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Large intestine perforation                     |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Small intestine perforation                     |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Upper gastrointestinal haemorrhage              |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pancreatic duct stenosis                        |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Bile duct obstruction                           |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholangitis                                     |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cholecystitis                                   |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Dyspnoea                                        |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pleural effusion                                |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonitis                                     |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary embolism                              |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumothorax                                    |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Biliary sepsis                                  |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infection                                       |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|                                                 |                |  |  |  |
|-------------------------------------------------|----------------|--|--|--|
| Pneumonia                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Sepsis                                          |                |  |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lower respiratory tract infection               |                |  |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Urinary tract infection                         |                |  |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Clostridium difficile colitis                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Biliary tract infection                         |                |  |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Device related infection                        |                |  |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Gastroenteritis                                 |                |  |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Liver abscess                                   |                |  |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Lung infection                                  |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Septic shock                                    |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Urinary tract infection fungal                  |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Decreased appetite                              |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dehydration                                     |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diabetic ketoacidosis                           |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypoglycaemia                                   |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypocalcaemia                                   |                |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                                   | IMM-101 + GEM<br>Main study only | GEM Main study only | IMM-101 + GEM<br>Main and Sub<br>studies combined |
|---------------------------------------------------------------------|----------------------------------|---------------------|---------------------------------------------------|
| Total subjects affected by non-serious adverse events               |                                  |                     |                                                   |
| subjects affected / exposed                                         | 72 / 74 (97.30%)                 | 35 / 35 (100.00%)   | 72 / 74 (97.30%)                                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                  |                     |                                                   |
| Tumour pain                                                         |                                  |                     |                                                   |
| subjects affected / exposed                                         | 4 / 74 (5.41%)                   | 3 / 35 (8.57%)      | 4 / 74 (5.41%)                                    |
| occurrences (all)                                                   | 7                                | 6                   | 7                                                 |
| General disorders and administration site conditions                |                                  |                     |                                                   |
| Asthenia                                                            |                                  |                     |                                                   |
| subjects affected / exposed                                         | 32 / 74 (43.24%)                 | 12 / 35 (34.29%)    | 34 / 74 (45.95%)                                  |
| occurrences (all)                                                   | 69                               | 46                  | 77                                                |
| Fatigue                                                             |                                  |                     |                                                   |
| subjects affected / exposed                                         | 19 / 74 (25.68%)                 | 10 / 35 (28.57%)    | 19 / 74 (25.68%)                                  |
| occurrences (all)                                                   | 46                               | 24                  | 50                                                |
| Pyrexia                                                             |                                  |                     |                                                   |
| subjects affected / exposed                                         | 18 / 74 (24.32%)                 | 2 / 35 (5.71%)      | 18 / 74 (24.32%)                                  |
| occurrences (all)                                                   | 28                               | 2                   | 30                                                |
| Oedema peripheral                                                   |                                  |                     |                                                   |
| subjects affected / exposed                                         | 12 / 74 (16.22%)                 | 7 / 35 (20.00%)     | 12 / 74 (16.22%)                                  |
| occurrences (all)                                                   | 19                               | 9                   | 22                                                |
| Mucosal inflammation                                                |                                  |                     |                                                   |
| subjects affected / exposed                                         | 6 / 74 (8.11%)                   | 1 / 35 (2.86%)      | 6 / 74 (8.11%)                                    |
| occurrences (all)                                                   | 8                                | 1                   | 8                                                 |
| Chills                                                              |                                  |                     |                                                   |
| subjects affected / exposed                                         | 6 / 74 (8.11%)                   | 0 / 35 (0.00%)      | 6 / 74 (8.11%)                                    |
| occurrences (all)                                                   | 7                                | 0                   | 7                                                 |
| Injection site pain                                                 |                                  |                     |                                                   |

|                                                                                                                 |                      |                       |                      |
|-----------------------------------------------------------------------------------------------------------------|----------------------|-----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                                                | 4 / 74 (5.41%)<br>6  | 0 / 35 (0.00%)<br>0   | 4 / 74 (5.41%)<br>6  |
| Pain<br>subjects affected / exposed<br>occurrences (all)                                                        | 2 / 74 (2.70%)<br>2  | 2 / 35 (5.71%)<br>2   | 5 / 74 (6.76%)<br>6  |
| Injection site reaction<br>subjects affected / exposed<br>occurrences (all)                                     | 2 / 74 (2.70%)<br>2  | 0 / 35 (0.00%)<br>0   | 5 / 74 (6.76%)<br>8  |
| Oedema<br>subjects affected / exposed<br>occurrences (all)                                                      | 2 / 74 (2.70%)<br>2  | 0 / 35 (0.00%)<br>0   | 4 / 74 (5.41%)<br>6  |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all) | 6 / 74 (8.11%)<br>8  | 3 / 35 (8.57%)<br>4   | 7 / 74 (9.46%)<br>10 |
| Cough<br>subjects affected / exposed<br>occurrences (all)                                                       | 6 / 74 (8.11%)<br>10 | 1 / 35 (2.86%)<br>1   | 7 / 74 (9.46%)<br>11 |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                                                   | 1 / 74 (1.35%)<br>1  | 2 / 35 (5.71%)<br>2   | 1 / 74 (1.35%)<br>1  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                            | 8 / 74 (10.81%)<br>8 | 2 / 35 (5.71%)<br>4   | 9 / 74 (12.16%)<br>9 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                                    | 7 / 74 (9.46%)<br>7  | 3 / 35 (8.57%)<br>4   | 9 / 74 (12.16%)<br>9 |
| Depression<br>subjects affected / exposed<br>occurrences (all)                                                  | 5 / 74 (6.76%)<br>5  | 2 / 35 (5.71%)<br>2   | 5 / 74 (6.76%)<br>6  |
| Investigations<br>Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                  | 7 / 74 (9.46%)<br>24 | 7 / 35 (20.00%)<br>14 | 7 / 74 (9.46%)<br>24 |
| Weight decreased                                                                                                |                      |                       |                      |

|                                      |                  |                 |                  |
|--------------------------------------|------------------|-----------------|------------------|
| subjects affected / exposed          | 12 / 74 (16.22%) | 1 / 35 (2.86%)  | 14 / 74 (18.92%) |
| occurrences (all)                    | 12               | 1               | 17               |
| Alanine aminotransferase increased   |                  |                 |                  |
| subjects affected / exposed          | 6 / 74 (8.11%)   | 2 / 35 (5.71%)  | 6 / 74 (8.11%)   |
| occurrences (all)                    | 15               | 2               | 15               |
| Neutrophil count decreased           |                  |                 |                  |
| subjects affected / exposed          | 5 / 74 (6.76%)   | 2 / 35 (5.71%)  | 5 / 74 (6.76%)   |
| occurrences (all)                    | 8                | 3               | 8                |
| White blood cell count decreased     |                  |                 |                  |
| subjects affected / exposed          | 2 / 74 (2.70%)   | 4 / 35 (11.43%) | 2 / 74 (2.70%)   |
| occurrences (all)                    | 7                | 7               | 7                |
| Blood alkaline phosphatase increased |                  |                 |                  |
| subjects affected / exposed          | 4 / 74 (5.41%)   | 1 / 35 (2.86%)  | 4 / 74 (5.41%)   |
| occurrences (all)                    | 11               | 2               | 11               |
| Aspartate aminotransferase increased |                  |                 |                  |
| subjects affected / exposed          | 4 / 74 (5.41%)   | 1 / 35 (2.86%)  | 4 / 74 (5.41%)   |
| occurrences (all)                    | 11               | 1               | 11               |
| Haemoglobin decreased                |                  |                 |                  |
| subjects affected / exposed          | 3 / 74 (4.05%)   | 2 / 35 (5.71%)  | 3 / 74 (4.05%)   |
| occurrences (all)                    | 8                | 3               | 10               |
| Blood bilirubin increased            |                  |                 |                  |
| subjects affected / exposed          | 4 / 74 (5.41%)   | 1 / 35 (2.86%)  | 5 / 74 (6.76%)   |
| occurrences (all)                    | 5                | 1               | 12               |
| Vitamin D decreased                  |                  |                 |                  |
| subjects affected / exposed          | 5 / 74 (6.76%)   | 0 / 35 (0.00%)  | 5 / 74 (6.76%)   |
| occurrences (all)                    | 6                | 0               | 6                |
| Blood potassium decreased            |                  |                 |                  |
| subjects affected / exposed          | 1 / 74 (1.35%)   | 2 / 35 (5.71%)  | 1 / 74 (1.35%)   |
| occurrences (all)                    | 3                | 4               | 3                |
| Cardiac disorders                    |                  |                 |                  |
| Tachycardia                          |                  |                 |                  |
| subjects affected / exposed          | 4 / 74 (5.41%)   | 0 / 35 (0.00%)  | 4 / 74 (5.41%)   |
| occurrences (all)                    | 4                | 0               | 4                |
| Nervous system disorders             |                  |                 |                  |



|                                                                      |                        |                        |                        |
|----------------------------------------------------------------------|------------------------|------------------------|------------------------|
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)        | 13 / 74 (17.57%)<br>17 | 2 / 35 (5.71%)<br>2    | 13 / 74 (17.57%)<br>17 |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)         | 8 / 74 (10.81%)<br>11  | 1 / 35 (2.86%)<br>2    | 9 / 74 (12.16%)<br>15  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)        | 7 / 74 (9.46%)<br>8    | 1 / 35 (2.86%)<br>1    | 8 / 74 (10.81%)<br>9   |
| Headache<br>subjects affected / exposed<br>occurrences (all)         | 8 / 74 (10.81%)<br>9   | 0 / 35 (0.00%)<br>0    | 8 / 74 (10.81%)<br>9   |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)     | 3 / 74 (4.05%)<br>3    | 1 / 35 (2.86%)<br>1    | 4 / 74 (5.41%)<br>4    |
| Blood and lymphatic system disorders                                 |                        |                        |                        |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)          | 23 / 74 (31.08%)<br>37 | 9 / 35 (25.71%)<br>14  | 23 / 74 (31.08%)<br>40 |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)      | 16 / 74 (21.62%)<br>37 | 10 / 35 (28.57%)<br>24 | 16 / 74 (21.62%)<br>48 |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all) | 10 / 74 (13.51%)<br>20 | 7 / 35 (20.00%)<br>13  | 11 / 74 (14.86%)<br>21 |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)       | 4 / 74 (5.41%)<br>15   | 3 / 35 (8.57%)<br>9    | 4 / 74 (5.41%)<br>24   |
| Gastrointestinal disorders                                           |                        |                        |                        |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)        | 32 / 74 (43.24%)<br>55 | 14 / 35 (40.00%)<br>27 | 33 / 74 (44.59%)<br>65 |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)   | 32 / 74 (43.24%)<br>46 | 11 / 35 (31.43%)<br>22 | 35 / 74 (47.30%)<br>56 |
| Nausea                                                               |                        |                        |                        |

|                                  |                  |                  |                  |
|----------------------------------|------------------|------------------|------------------|
| subjects affected / exposed      | 32 / 74 (43.24%) | 13 / 35 (37.14%) | 33 / 74 (44.59%) |
| occurrences (all)                | 55               | 26               | 59               |
| Constipation                     |                  |                  |                  |
| subjects affected / exposed      | 29 / 74 (39.19%) | 11 / 35 (31.43%) | 31 / 74 (41.89%) |
| occurrences (all)                | 36               | 21               | 42               |
| Vomiting                         |                  |                  |                  |
| subjects affected / exposed      | 21 / 74 (28.38%) | 14 / 35 (40.00%) | 22 / 74 (29.73%) |
| occurrences (all)                | 32               | 19               | 34               |
| Stomatitis                       |                  |                  |                  |
| subjects affected / exposed      | 8 / 74 (10.81%)  | 4 / 35 (11.43%)  | 8 / 74 (10.81%)  |
| occurrences (all)                | 10               | 8                | 11               |
| Ascites                          |                  |                  |                  |
| subjects affected / exposed      | 5 / 74 (6.76%)   | 3 / 35 (8.57%)   | 7 / 74 (9.46%)   |
| occurrences (all)                | 10               | 3                | 13               |
| Abdominal distension             |                  |                  |                  |
| subjects affected / exposed      | 6 / 74 (8.11%)   | 3 / 35 (8.57%)   | 6 / 74 (8.11%)   |
| occurrences (all)                | 6                | 3                | 7                |
| Abdominal pain upper             |                  |                  |                  |
| subjects affected / exposed      | 8 / 74 (10.81%)  | 0 / 35 (0.00%)   | 9 / 74 (12.16%)  |
| occurrences (all)                | 12               | 0                | 15               |
| Dyspepsia                        |                  |                  |                  |
| subjects affected / exposed      | 5 / 74 (6.76%)   | 2 / 35 (5.71%)   | 7 / 74 (9.46%)   |
| occurrences (all)                | 6                | 2                | 9                |
| Abdominal discomfort             |                  |                  |                  |
| subjects affected / exposed      | 6 / 74 (8.11%)   | 0 / 35 (0.00%)   | 6 / 74 (8.11%)   |
| occurrences (all)                | 8                | 0                | 8                |
| Gastrooesophageal reflux disease |                  |                  |                  |
| subjects affected / exposed      | 6 / 74 (8.11%)   | 0 / 35 (0.00%)   | 6 / 74 (8.11%)   |
| occurrences (all)                | 7                | 0                | 8                |
| Malabsorption                    |                  |                  |                  |
| subjects affected / exposed      | 3 / 74 (4.05%)   | 0 / 35 (0.00%)   | 4 / 74 (5.41%)   |
| occurrences (all)                | 4                | 0                | 6                |
| Rectal haemorrhage               |                  |                  |                  |
| subjects affected / exposed      | 2 / 74 (2.70%)   | 0 / 35 (0.00%)   | 4 / 74 (5.41%)   |
| occurrences (all)                | 2                | 0                | 4                |
| Hepatobiliary disorders          |                  |                  |                  |

|                                                                             |                        |                      |                        |
|-----------------------------------------------------------------------------|------------------------|----------------------|------------------------|
| Jaundice<br>subjects affected / exposed<br>occurrences (all)                | 8 / 74 (10.81%)<br>9   | 1 / 35 (2.86%)<br>1  | 9 / 74 (12.16%)<br>10  |
| Skin and subcutaneous tissue disorders                                      |                        |                      |                        |
| Rash<br>subjects affected / exposed<br>occurrences (all)                    | 6 / 74 (8.11%)<br>10   | 2 / 35 (5.71%)<br>2  | 6 / 74 (8.11%)<br>10   |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)                | 6 / 74 (8.11%)<br>7    | 2 / 35 (5.71%)<br>3  | 7 / 74 (9.46%)<br>8    |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)                | 5 / 74 (6.76%)<br>6    | 3 / 35 (8.57%)<br>3  | 5 / 74 (6.76%)<br>6    |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)                | 5 / 74 (6.76%)<br>5    | 2 / 35 (5.71%)<br>3  | 5 / 74 (6.76%)<br>6    |
| Renal and urinary disorders                                                 |                        |                      |                        |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)              | 1 / 74 (1.35%)<br>1    | 2 / 35 (5.71%)<br>2  | 1 / 74 (1.35%)<br>1    |
| Musculoskeletal and connective tissue disorders                             |                        |                      |                        |
| Back pain<br>subjects affected / exposed<br>occurrences (all)               | 17 / 74 (22.97%)<br>22 | 5 / 35 (14.29%)<br>6 | 17 / 74 (22.97%)<br>24 |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)              | 6 / 74 (8.11%)<br>7    | 2 / 35 (5.71%)<br>3  | 7 / 74 (9.46%)<br>9    |
| Infections and infestations                                                 |                        |                      |                        |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 7 / 74 (9.46%)<br>8    | 3 / 35 (8.57%)<br>4  | 7 / 74 (9.46%)<br>10   |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)         | 3 / 74 (4.05%)<br>4    | 1 / 35 (2.86%)<br>3  | 5 / 74 (6.76%)<br>8    |
| Respiratory tract infection                                                 |                        |                      |                        |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 4 / 74 (5.41%)<br>5 | 0 / 35 (0.00%)<br>0 | 4 / 74 (5.41%)<br>6 |
| Metabolism and nutrition disorders               |                     |                     |                     |
| Decreased appetite                               |                     |                     |                     |
| subjects affected / exposed                      | 30 / 74 (40.54%)    | 11 / 35 (31.43%)    | 33 / 74 (44.59%)    |
| occurrences (all)                                | 40                  | 24                  | 45                  |
| Vitamin D deficiency                             |                     |                     |                     |
| subjects affected / exposed                      | 6 / 74 (8.11%)      | 1 / 35 (2.86%)      | 7 / 74 (9.46%)      |
| occurrences (all)                                | 6                   | 1                   | 7                   |
| Hypokalaemia                                     |                     |                     |                     |
| subjects affected / exposed                      | 2 / 74 (2.70%)      | 3 / 35 (8.57%)      | 2 / 74 (2.70%)      |
| occurrences (all)                                | 2                   | 5                   | 3                   |

|                                                                        |                                      |  |  |
|------------------------------------------------------------------------|--------------------------------------|--|--|
| <b>Non-serious adverse events</b>                                      | GEM Main and Sub<br>studies combined |  |  |
| Total subjects affected by non-serious<br>adverse events               |                                      |  |  |
| subjects affected / exposed                                            | 35 / 35 (100.00%)                    |  |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |                                      |  |  |
| Tumour pain                                                            |                                      |  |  |
| subjects affected / exposed                                            | 3 / 35 (8.57%)                       |  |  |
| occurrences (all)                                                      | 6                                    |  |  |
| General disorders and administration<br>site conditions                |                                      |  |  |
| Asthenia                                                               |                                      |  |  |
| subjects affected / exposed                                            | 12 / 35 (34.29%)                     |  |  |
| occurrences (all)                                                      | 46                                   |  |  |
| Fatigue                                                                |                                      |  |  |
| subjects affected / exposed                                            | 10 / 35 (28.57%)                     |  |  |
| occurrences (all)                                                      | 24                                   |  |  |
| Pyrexia                                                                |                                      |  |  |
| subjects affected / exposed                                            | 2 / 35 (5.71%)                       |  |  |
| occurrences (all)                                                      | 2                                    |  |  |
| Oedema peripheral                                                      |                                      |  |  |
| subjects affected / exposed                                            | 7 / 35 (20.00%)                      |  |  |
| occurrences (all)                                                      | 9                                    |  |  |
| Mucosal inflammation                                                   |                                      |  |  |
| subjects affected / exposed                                            | 1 / 35 (2.86%)                       |  |  |
| occurrences (all)                                                      | 1                                    |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Chills                                          |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences (all)                               | 0              |  |  |
| Injection site pain                             |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences (all)                               | 0              |  |  |
| Pain                                            |                |  |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Injection site reaction                         |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences (all)                               | 0              |  |  |
| Oedema                                          |                |  |  |
| subjects affected / exposed                     | 0 / 35 (0.00%) |  |  |
| occurrences (all)                               | 0              |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Dyspnoea                                        |                |  |  |
| subjects affected / exposed                     | 3 / 35 (8.57%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Cough                                           |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Epistaxis                                       |                |  |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Psychiatric disorders                           |                |  |  |
| Anxiety                                         |                |  |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Insomnia                                        |                |  |  |
| subjects affected / exposed                     | 3 / 35 (8.57%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Depression                                      |                |  |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Investigations                                  |                |  |  |

|                                      |                 |  |  |
|--------------------------------------|-----------------|--|--|
| Platelet count decreased             |                 |  |  |
| subjects affected / exposed          | 7 / 35 (20.00%) |  |  |
| occurrences (all)                    | 14              |  |  |
| Weight decreased                     |                 |  |  |
| subjects affected / exposed          | 1 / 35 (2.86%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Alanine aminotransferase increased   |                 |  |  |
| subjects affected / exposed          | 2 / 35 (5.71%)  |  |  |
| occurrences (all)                    | 2               |  |  |
| Neutrophil count decreased           |                 |  |  |
| subjects affected / exposed          | 2 / 35 (5.71%)  |  |  |
| occurrences (all)                    | 3               |  |  |
| White blood cell count decreased     |                 |  |  |
| subjects affected / exposed          | 4 / 35 (11.43%) |  |  |
| occurrences (all)                    | 7               |  |  |
| Blood alkaline phosphatase increased |                 |  |  |
| subjects affected / exposed          | 1 / 35 (2.86%)  |  |  |
| occurrences (all)                    | 2               |  |  |
| Aspartate aminotransferase increased |                 |  |  |
| subjects affected / exposed          | 1 / 35 (2.86%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Haemoglobin decreased                |                 |  |  |
| subjects affected / exposed          | 2 / 35 (5.71%)  |  |  |
| occurrences (all)                    | 3               |  |  |
| Blood bilirubin increased            |                 |  |  |
| subjects affected / exposed          | 1 / 35 (2.86%)  |  |  |
| occurrences (all)                    | 1               |  |  |
| Vitamin D decreased                  |                 |  |  |
| subjects affected / exposed          | 0 / 35 (0.00%)  |  |  |
| occurrences (all)                    | 0               |  |  |
| Blood potassium decreased            |                 |  |  |
| subjects affected / exposed          | 2 / 35 (5.71%)  |  |  |
| occurrences (all)                    | 4               |  |  |
| Cardiac disorders                    |                 |  |  |

|                                                                                                     |                        |  |  |
|-----------------------------------------------------------------------------------------------------|------------------------|--|--|
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 35 (0.00%)<br>0    |  |  |
| Nervous system disorders<br>Dysgeusia<br>subjects affected / exposed<br>occurrences (all)           | 2 / 35 (5.71%)<br>2    |  |  |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)                                        | 1 / 35 (2.86%)<br>2    |  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 35 (2.86%)<br>1    |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 35 (0.00%)<br>0    |  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 35 (2.86%)<br>1    |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 9 / 35 (25.71%)<br>14  |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                                     | 10 / 35 (28.57%)<br>24 |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                                | 7 / 35 (20.00%)<br>13  |  |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 35 (8.57%)<br>9    |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)         | 14 / 35 (40.00%)<br>27 |  |  |
| Abdominal pain                                                                                      |                        |  |  |

|                                  |                  |  |  |
|----------------------------------|------------------|--|--|
| subjects affected / exposed      | 11 / 35 (31.43%) |  |  |
| occurrences (all)                | 22               |  |  |
| Nausea                           |                  |  |  |
| subjects affected / exposed      | 13 / 35 (37.14%) |  |  |
| occurrences (all)                | 26               |  |  |
| Constipation                     |                  |  |  |
| subjects affected / exposed      | 11 / 35 (31.43%) |  |  |
| occurrences (all)                | 21               |  |  |
| Vomiting                         |                  |  |  |
| subjects affected / exposed      | 14 / 35 (40.00%) |  |  |
| occurrences (all)                | 19               |  |  |
| Stomatitis                       |                  |  |  |
| subjects affected / exposed      | 4 / 35 (11.43%)  |  |  |
| occurrences (all)                | 8                |  |  |
| Ascites                          |                  |  |  |
| subjects affected / exposed      | 3 / 35 (8.57%)   |  |  |
| occurrences (all)                | 3                |  |  |
| Abdominal distension             |                  |  |  |
| subjects affected / exposed      | 3 / 35 (8.57%)   |  |  |
| occurrences (all)                | 3                |  |  |
| Abdominal pain upper             |                  |  |  |
| subjects affected / exposed      | 0 / 35 (0.00%)   |  |  |
| occurrences (all)                | 0                |  |  |
| Dyspepsia                        |                  |  |  |
| subjects affected / exposed      | 2 / 35 (5.71%)   |  |  |
| occurrences (all)                | 2                |  |  |
| Abdominal discomfort             |                  |  |  |
| subjects affected / exposed      | 0 / 35 (0.00%)   |  |  |
| occurrences (all)                | 0                |  |  |
| Gastrooesophageal reflux disease |                  |  |  |
| subjects affected / exposed      | 0 / 35 (0.00%)   |  |  |
| occurrences (all)                | 0                |  |  |
| Malabsorption                    |                  |  |  |
| subjects affected / exposed      | 0 / 35 (0.00%)   |  |  |
| occurrences (all)                | 0                |  |  |
| Rectal haemorrhage               |                  |  |  |



|                                                                                                                                                                                                                                                                                                                |                                                                                                      |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                               | 0 / 35 (0.00%)<br>0                                                                                  |  |  |
| Hepatobiliary disorders<br>Jaundice<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                        | 1 / 35 (2.86%)<br>1                                                                                  |  |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Alopecia<br>subjects affected / exposed<br>occurrences (all) | 2 / 35 (5.71%)<br>2<br><br>2 / 35 (5.71%)<br>3<br><br>3 / 35 (8.57%)<br>3<br><br>2 / 35 (5.71%)<br>3 |  |  |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                  | 2 / 35 (5.71%)<br>2                                                                                  |  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)                                                                                                                         | 5 / 35 (14.29%)<br>6<br><br>2 / 35 (5.71%)<br>3                                                      |  |  |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasopharyngitis                                                                                                                                                                              | 3 / 35 (8.57%)<br>4                                                                                  |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| subjects affected / exposed        | 1 / 35 (2.86%)   |  |  |
| occurrences (all)                  | 3                |  |  |
| Respiratory tract infection        |                  |  |  |
| subjects affected / exposed        | 0 / 35 (0.00%)   |  |  |
| occurrences (all)                  | 0                |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Decreased appetite                 |                  |  |  |
| subjects affected / exposed        | 11 / 35 (31.43%) |  |  |
| occurrences (all)                  | 24               |  |  |
| Vitamin D deficiency               |                  |  |  |
| subjects affected / exposed        | 1 / 35 (2.86%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Hypokalaemia                       |                  |  |  |
| subjects affected / exposed        | 3 / 35 (8.57%)   |  |  |
| occurrences (all)                  | 5                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 19 January 2011 | <ol style="list-style-type: none"><li>1. To remove the assessment of circulating tumour cells as an exploratory endpoint and to provide further detail on the immune response analysis.</li><li>2. To add an additional 2 hours of vital signs monitoring (under medical supervision) following the first dose of IMM-101.</li><li>3. To clarify the maximum total blood volume collected from patients who are both in and out of the sub-set of patients recruited from the site(s) participating in the exploratory immune response analysis</li></ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 17 April 2012   | <ol style="list-style-type: none"><li>1. Changes to the manufacturer of IMM-101.</li><li>2. Addition of more sites and countries.</li><li>3. Clarification of inclusion criteria number 6 regarding acceptable baseline WBC.</li><li>4. Clarification of the treatment of local skin reactions and any subsequent dose reduction of IMM-101.</li><li>5. Clarification of the information to be recorded in the case report form following the Investigator's inspection for local reactions.</li><li>6. Clarification of the timing of some procedures:<ul style="list-style-type: none"><li>• Confirmation that some screening procedures can occur on the same day as randomisation.</li><li>• Confirmation that samples (haematology, chemistry, urinalysis) can be taken the day before a scheduled dosing day.</li><li>• Clarification that blood samples for exploratory analysis must be taken prior to administration of IMM-101.</li></ul></li><li>7. Confirmation that influenza vaccination history will be recorded at screening.</li><li>8. Clarification of sample size calculation.</li><li>9. Clarification that patients who change treatment regimen during the study will still be followed up for survival until what would have been the end of the 12 cycles.</li><li>10. Update of personnel details and removal of some personnel details to comply with ICH E6 Section 6.1.</li></ol> |
| 18 May 2012     | <ol style="list-style-type: none"><li>1. Inclusion of a the Sub-Study protocol for a long-term treatment phase to commence once patients have completed the 12 cycle treatment phase in the Main study.</li></ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 07 January 2014 | <ol style="list-style-type: none"><li>1. Changes to allow the Sponsor to follow up all withdrawn and completed patients for survival beyond the time corresponding to the end of 12 cycles, where appropriate including periodic follow-up of patients choosing not to enter the Sub-Study or who withdraw from the Main study early.</li><li>2. Inclusion of a larger volume vial presentation of investigational medicinal product (Note: injection volume and dose remain unchanged and the larger vial size is already approved by all Competent Authorities).</li><li>3. Assessments of CA19.9, CEA CRP and albumin were introduced part-way through the study however, the limited data collected did not allow for meaningful conclusions to be drawn.</li></ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

|                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| This proof of concept study was not formally sized to test a specific pre-defined efficacy hypothesis, however, it has provided important insights into the potential for efficacy improvements with the use of IMM-101 in advanced pancreatic cancer. |
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Notes:

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27599039>