

**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
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**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
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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
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Arm description:

ITT Gemcitabine

Arm type	Active comparator
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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
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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:	ITT IMM-101 + Gemcitabine
Reporting group title	ITT GEM
Reporting group description:	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:	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:	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:	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:	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:	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)
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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
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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
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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
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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
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End point timeframe:

From randomisation to death with a data cutoff date of 5 February 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%)	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**

<b>Statistical analysis title</b>	Overall survival
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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
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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
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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14
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### Reporting groups

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

<b>Serious adverse events</b>	IMM-101 + GEM Main study only	GEM Main study only	IMM-101 + GEM Main and Sub 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
<b>General physical health deterioration</b>			
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
<b>Mucosal inflammation</b>			
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
<b>Sudden death</b>			
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
<b>Blood and lymphatic system disorders</b>			
<b>Anaemia</b>			
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
<b>Febrile neutropenia</b>			
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>Splenomegaly</b>			
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
<b>Gastrointestinal disorders</b>			
<b>Abdominal pain</b>			
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
<b>Ascites</b>			

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>			
<b>Bile duct obstruction</b>			
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
<b>Cholangitis</b>			
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
<b>Cholecystitis</b>			
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>			
<b>Dyspnoea</b>			
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
<b>Pleural effusion</b>			
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
<b>Pneumonitis</b>			
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>Pulmonary embolism</b>			
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
<b>Diabetic ketoacidosis</b>			
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>Hypoglycaemia</b>			
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
<b>Hypocalcaemia</b>			
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		
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	10 / 35 (28.57%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	5		
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
<b>Pancreatic carcinoma metastatic</b>			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Injury, poisoning and procedural complications</b>			
<b>Toxicity to various agents</b>			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Incisional hernia</b>			

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

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

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

subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Dyspnoea</b>			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Pleural effusion</b>			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Pneumonitis</b>			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Pulmonary embolism</b>			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Pneumothorax</b>			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
<b>Biliary sepsis</b>			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Infection</b>			
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 Main study only	GEM Main study only	IMM-101 + GEM Main and Sub 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 occurrences (all)	4 / 74 (5.41%) 6	0 / 35 (0.00%) 0	4 / 74 (5.41%) 6
Pain subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	2 / 35 (5.71%) 2	5 / 74 (6.76%) 6
Injection site reaction subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	0 / 35 (0.00%) 0	5 / 74 (6.76%) 8
Oedema subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	0 / 35 (0.00%) 0	4 / 74 (5.41%) 6
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 8	3 / 35 (8.57%) 4	7 / 74 (9.46%) 10
Cough subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 10	1 / 35 (2.86%) 1	7 / 74 (9.46%) 11
Epistaxis subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1	2 / 35 (5.71%) 2	1 / 74 (1.35%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	8 / 74 (10.81%) 8	2 / 35 (5.71%) 4	9 / 74 (12.16%) 9
Insomnia subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 7	3 / 35 (8.57%) 4	9 / 74 (12.16%) 9
Depression subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5	2 / 35 (5.71%) 2	5 / 74 (6.76%) 6
Investigations			
Platelet count decreased subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 24	7 / 35 (20.00%) 14	7 / 74 (9.46%) 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 subjects affected / exposed occurrences (all)	13 / 74 (17.57%) 17	2 / 35 (5.71%) 2	13 / 74 (17.57%) 17
Lethargy subjects affected / exposed occurrences (all)	8 / 74 (10.81%) 11	1 / 35 (2.86%) 2	9 / 74 (12.16%) 15
Dizziness subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 8	1 / 35 (2.86%) 1	8 / 74 (10.81%) 9
Headache subjects affected / exposed occurrences (all)	8 / 74 (10.81%) 9	0 / 35 (0.00%) 0	8 / 74 (10.81%) 9
Paraesthesia subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 3	1 / 35 (2.86%) 1	4 / 74 (5.41%) 4
<b>Blood and lymphatic system disorders</b>			
Anaemia subjects affected / exposed occurrences (all)	23 / 74 (31.08%) 37	9 / 35 (25.71%) 14	23 / 74 (31.08%) 40
Neutropenia subjects affected / exposed occurrences (all)	16 / 74 (21.62%) 37	10 / 35 (28.57%) 24	16 / 74 (21.62%) 48
Thrombocytopenia subjects affected / exposed occurrences (all)	10 / 74 (13.51%) 20	7 / 35 (20.00%) 13	11 / 74 (14.86%) 21
Leukopenia subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 15	3 / 35 (8.57%) 9	4 / 74 (5.41%) 24
<b>Gastrointestinal disorders</b>			
Diarrhoea subjects affected / exposed occurrences (all)	32 / 74 (43.24%) 55	14 / 35 (40.00%) 27	33 / 74 (44.59%) 65
Abdominal pain subjects affected / exposed occurrences (all)	32 / 74 (43.24%) 46	11 / 35 (31.43%) 22	35 / 74 (47.30%) 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 subjects affected / exposed occurrences (all)	8 / 74 (10.81%) 9	1 / 35 (2.86%) 1	9 / 74 (12.16%) 10
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 10	2 / 35 (5.71%) 2	6 / 74 (8.11%) 10
Pruritus subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 7	2 / 35 (5.71%) 3	7 / 74 (9.46%) 8
Dry skin subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 6	3 / 35 (8.57%) 3	5 / 74 (6.76%) 6
Alopecia subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5	2 / 35 (5.71%) 3	5 / 74 (6.76%) 6
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1	2 / 35 (5.71%) 2	1 / 74 (1.35%) 1
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	17 / 74 (22.97%) 22	5 / 35 (14.29%) 6	17 / 74 (22.97%) 24
Arthralgia subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 7	2 / 35 (5.71%) 3	7 / 74 (9.46%) 9
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 8	3 / 35 (8.57%) 4	7 / 74 (9.46%) 10
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 4	1 / 35 (2.86%) 3	5 / 74 (6.76%) 8
Respiratory tract infection			

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

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

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

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

Tachycardia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Lethargy subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 2		
Dizziness subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Headache subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	9 / 35 (25.71%) 14		
Neutropenia subjects affected / exposed occurrences (all)	10 / 35 (28.57%) 24		
Thrombocytopenia subjects affected / exposed occurrences (all)	7 / 35 (20.00%) 13		
Leukopenia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 9		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	14 / 35 (40.00%) 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 occurrences (all)	0 / 35 (0.00%) 0		
Hepatobiliary disorders Jaundice subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)  Pruritus subjects affected / exposed occurrences (all)  Dry skin subjects affected / exposed occurrences (all)  Alopecia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2  2 / 35 (5.71%) 3  3 / 35 (8.57%) 3  2 / 35 (5.71%) 3		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)  Arthralgia subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 6  2 / 35 (5.71%) 3		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)  Nasopharyngitis	3 / 35 (8.57%) 4		

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

Notes:

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## **Online references**

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