Clinical trial results:
A Phase II, Single Arm, Investigative Study of IMM-101 in Combination with Radiation Induced Tumour Necrosis in Patients with Previously Treated Colorectal Cancer.

Summary

EudraCT number	2011-003958-85
Trial protocol	GB
Global end of trial date	09 September 2015

Results information

Result version number	v1 (current)
This version publication date	15 May 2016
First version publication date	15 May 2016

Trial information

Trial identification

Sponsor protocol code	IMM-101-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01539824
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Immodulon Therapeutics Ltd
Sponsor organisation address	6-9 The Square, Stockley Park, Uxbridge, United Kingdom, UB11 1FW
Public contact	Clinical Trials Administrator, Immodulon Therapeutics Ltd, 0044 020 3137 6346 , info@immodulon.com
Scientific contact	Clinical Trials Administrator, Immodulon Therapeutics Ltd, 0044 020 3137 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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2015
Global end of trial reached?	Yes
Global end of trial date	09 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this Simon optimal 2-stage design study was to investigate the efficacy of IMM-101 in combination with radiation induced tumour necrosis (induced by CyberKnife treatment) in patients with colorectal cancer with metastatic disease who had received prior chemotherapy.
Secondary objectives were:
a) to investigate the safety and tolerability of IMM-101 , and
b) to conduct an exploratory investigation of selected markers of tumour burden and immunological status.

No formal hypothesis was tested and no interim analyses were planned or undertaken. The first scheduled CT scan was at Wk 12 and the primary time point was Wk 24.

In similar cohorts of advanced cancer patients with a similar profile of range and number of prior chemotherapies, findings following treatment with Regorafenib, Cetuximab (Grothey et al, 2013), and Panitumumab (van Cutsem, 2007) suggest that ~50% of patients enrolled into this study would have experienced disease progression by Wk 8.

Protection of trial subjects:

This study was conducted in accordance with 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), EU Clinical Trial Directive (2001/20/EC), 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 3 clinicians with relevant general and specialist expertise was established to interpret on an on-going basis the study conduct and results independent of the study conduct. The DMC responsibility was to safeguard the interests of the studies' patients, and potential patients with respect to conduct, safety and tolerability of the study and protect its validity and credibility. The DMC would also adjudicate and confirm any patients who demonstrate stabilisation and/or response to treatment, if applicable.

Background therapy:

Stereotactic body radiotherapy (SBRT) administered by the CyberKnife procedure on a liver lesion targeted by the Principal Investigator.

Evidence for comparator: -

Actual start date of recruitment	30 May 2012
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	United Kingdom: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	5
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 12 patients were recruited across two clinical sites in the United Kingdom between 30 May 2012 and 09 October 2013.

Pre-assignment

Screening details:

A total of 17 patients were screened, between 11 April 2012 and 09 October 2013. Five patients were found to be ineligible and failed screening. These patients were not enrolled into the study, and their data were not included in the results of the study.

Period 1

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

Arms

Arm title	IMM-101 treated

Arm description: -

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

Dosage and administration details:

Patients received single 0.1 mL intradermal injections of IMM-101 (10 mg/mL) every 2 weeks for the first three doses, with the second of these doses being on the same day as the SBRT administered by the CyberKnife procedure then following a rest of 4 weeks after the third dose of IMM-101, patients continued to receive IMM-101 every 2 weeks for the next 3 doses followed by a further 4-week treatment-free period. Thereafter IMM-101 was given at 4-week intervals for up to a further 9 months or until patient withdrawal for any reason.

Number of subjects in period 1	IMM-101 treated
Started	12
Completed	0
Not completed	12
Disease progression	12

Baseline characteristics

Reporting groups

Reporting group title	overall study

Reporting group description:

All patients in the safety population, i.e. all patients receiving at least one dose of IMM-101, the investigational medicinal product (IMP).

Reporting group values	overall study	Total	
Number of subjects	12	12	
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)	5	5	
From 65-84 years	7	7	
85 years and over	0	0	
Age continuous Units: years			
median	65		
full range (min-max)	36 to 77	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	11	11	

Subject analysis sets

Subject analysis set title	IMM-101 treated
Subject analysis set type	Safety analysis

Subject analysis set description:

All analyses were based on the safety population, which comprised all patients who received at least one dose of the investigational medicinal product IMM-101.

Reporting group values	IMM-101 treated		
Number of subjects	12		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	5		
From 65-84 years	7		
85 years and over	0		
Age continuous Units: years			
median	65		
full range (min-max)	36 to 77		
Gender categorical Units: Subjects			
Female	1		
Male	11		

End points

End points reporting groups

Reporting group title	IMM-101 treated
Reporting group description: -	
Subject analysis set title	IMM-101 treated
Subject analysis set type	Safety analysis

Subject analysis set description:

All analyses were based on the safety population, which comprised all patients who received at least one dose of the investigational medicinal product IMM-101.

Primary: Disease stabilisation Rate at Week 24

End point title	Disease stabilisation Rate at Week 24[1]

End point description:

The disease stabilisation rate at 24 weeks defined as the proportion of patients who had complete or partial response or stable disease based on CT scan findings, absence of clinical signs and symptoms of progression, did not withdraw due to disease progression prior to/at the Week 24 assessment and were alive at the Week 24 assessment.

End point type	Primary

End point timeframe:

Week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: None of the 12 Stage 1 patients had disease stabilisation at 24 weeks. Hence the disease stabilisation rate was 0%. Based on the observed disease stabilisation rate of 0% from Stage 1 of the study, the chance of a true disease stabilisation rate of 20% or higher was less than 0.05. Hence, the study did not meet its primary endpoint.

End point values	IMM-101 treated			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: % patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and tolerability

End point title	Safety and tolerability

End point description:

Safety and tolerability criteria defined as no clinically relevant deleterious effect of IMM-101 on safety and tolerability profiles as judged by:
- Local and systemic toxicities.
- Number, type and degree of toxicities as measured by the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) v4.0.

End point type	Secondary

End point timeframe:

Throughout the study

End point values	IMM-101 treated			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Adverse events	156			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease progression rate at Week 12

End point title	Disease progression rate at Week 12

End point description:

Disease progression at Week 12 was defined as progressive disease, based on CT scan findings or based on clinical signs and symptoms of progression, withdrawal due to progression at/prior to the Week 12 assessment or death by Week 12.

End point type	Secondary

End point timeframe:

Week 12

End point values	IMM-101 treated			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: % of patients	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was calculated as the date of death minus the date of Day 0 + 1, and was expressed in months.

End point type	Secondary

End point timeframe:

Overall survival incorporated both on study deaths and deaths post withdrawal.

End point values	IMM-101 treated			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Months				
median (confidence interval 95%)	5.9 (1.4 to 10.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the entire study duration.	
Adverse event reporting additional description:	
Adverse event data were collected from study entry until patient completion, withdrawal or death and for IMP-related AEs, for 30 days after the last study visit. AEs leading to death due to disease progression were reported as AEs, not SAEs. AEs with first onset or worsening after first administration of IMP were summarised descriptively.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17

Reporting groups	
Reporting group title	Safety population
Reporting group description:	
All patients in the safety population, i.e. all patients receiving at least one dose of IMM-101, the investigational medicinal product.	

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Vena cava thrombosis			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	9		
Injection site reaction			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	13		
Oedema peripheral			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	5		
Chest pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
influenza-like illness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Temperature intolerance			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	8		
Dyspnoea			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Haemoptysis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Increased bronchial secretion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Blood bilirubin increased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Blood alkaline phosphatase increased			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Red blood cell sedimentation rate increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Blood creatinine phosphokinase MB Increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
C-reactive protein increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Carcinoembryonic antigen increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Urine ketone body present			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac disorders			

Cardiovascular insufficiency subjects affected / exposed occurrences (all) Sinus tachycardia subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Nervous system disorders Depressed level of consciousness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Sciatica subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all) Abdominal discomfort	 6 / 12 (50.00%) 6 4 / 12 (33.33%) 6 3 / 12 (25.00%) 3 2 / 12 (16.67%) 2		

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Ascites subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Oral pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Proctalgia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Umbilical hernia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Hepatobiliary disorders			
Jaundice subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Hepatic pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Hepatomegaly subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Skin and subcutaneous tissue disorders			
Dry skin			

subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Skin hyperpigmentation subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Osteoarthritis	 2 / 12 (16.67%) 2 2 / 12 (16.67%) 2 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	 3 / 12 (25.00%) 3 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Cachexia subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all)	 5 / 12 (41.67%) 5 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The success criteria for the study, including progression to the second stage, were challenging. A larger sample size facilitating analysis of a less demanding, but still clinically meaningful, treatment effect might have been more appropriate.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23177514

http://www.ncbi.nlm.nih.gov/pubmed/17470858