Clinical trial results:
An Open-label Randomized Phase 1b/2 Study of the Efficacy and Safety of JNJ-64041757, a Live Attenuated Listeria monocytogenes Immunotherapy, in Combination with Nivolumab Versus Nivolumab Monotherapy in Subjects With Advanced Adenocarcinoma of the Lung

Summary

EudraCT number	2016-002543-41
Trial protocol	ES BE
Global end of trial date	09 October 2018

Results information

Result version number	v1 (current)
This version publication date	24 October 2019
First version publication date	24 October 2019

Trial information

Trial identification

Sponsor protocol code	64041757LUC2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03371381
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate whether the efficacy of JNJ-64041757 combined with nivolumab was better than the efficacy of nivolumab monotherapy for the subjects with mesothelin-positive relapsed/refractory Stage IIIB or Stage IV adenocarcinoma of the lung, by PD-L1 level.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations included monitoring of adverse events, clinical laboratory tests, symptom directed physical examinations, electrocardiograms (ECGs), vital signs, and ECOG performance status.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	12
EEA total number of subjects	10

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)	6
From 65 to 84 years	6

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 12 subjects were enrolled and treated in Phase 1b. No subject was enrolled in phase 2 of the study.

Period 1

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

Arms

Arm title	JNJ-64041757+Nivolumab

Arm description:

Subjects received nivolumab 240 milligram (mg) intravenous (IV) infusion followed by JNJ-64041757 (1*10^9 colony-forming units [CFUs]) IV infusion on Day 1 and nivolumab 240 mg IV infusion on Day 15 of each 28-day cycle until disease progression, unacceptable toxicity, protocol violation requiring discontinuation of study treatment, withdrawal of consent, noncompliance with study procedures, or the sponsor terminates the study.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	OPDIVO
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusions of nivolumab 240mg over approximately 60 minutes on Days 1 and 15 of each 28-day cycle until disease progression, unacceptable toxicity, protocol violation requiring discontinuation of study treatment, withdrawal of consent, noncompliance with study procedures, or the sponsor terminates the study.

Investigational medicinal product name	JNJ-64041757
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received intravenous (IV) infusions of JNJ-64041757 (1*10^9 CFUs) over approximately 60 minutes on Day 1 of each 28-day cycle until disease progression, unacceptable toxicity, protocol violation requiring discontinuation of study treatment, withdrawal of consent, noncompliance with study procedures, or the sponsor terminates the study.

Number of subjects in period 1	JNJ-64041757+Nivolumab
Started	12
Completed	0
Not completed	12
Death	5
Study terminated by sponsor	3
Unspecified	4

Baseline characteristics

Reporting groups	
Reporting group title	JNJ-64041757+Nivolumab

Reporting group description:

Subjects received nivolumab 240 milligram (mg) intravenous (IV) infusion followed by JNJ-64041757 (1*10^9 colony-forming units [CFUs]) IV infusion on Day 1 and nivolumab 240 mg IV infusion on Day 15 of each 28-day cycle until disease progression, unacceptable toxicity, protocol violation requiring discontinuation of study treatment, withdrawal of consent, noncompliance with study procedures, or the sponsor terminates the study.

Reporting group values	JNJ-64041757+Nivolumab	Total	
Number of subjects	12	12	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	6	6	
From 65 to 84 years	6	6	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	61.2		
standard deviation	± 12.63	-	
Title for Gender Units: subjects			
Female	4	4	
Male	8	8	

End points

End points reporting groups

Reporting group title	JNJ-64041757+Nivolumab

Reporting group description:

Subjects received nivolumab 240 milligram (mg) intravenous (IV) infusion followed by JNJ-64041757 (1*10^9 colony-forming units [CFUs]) IV infusion on Day 1 and nivolumab 240 mg IV infusion on Day 15 of each 28-day cycle until disease progression, unacceptable toxicity, protocol violation requiring discontinuation of study treatment, withdrawal of consent, noncompliance with study procedures, or the sponsor terminates the study.

Primary: Phase 1b: Percentage of Subjects with Objective Response

End point title	Phase 1b: Percentage of Subjects with Objective Response[1]

End point description:

Objective response rate is defined as the percentage of subjects who achieved a complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST). RECIST for CR - the disappearance of all lesions, all lymph nodes were non-pathological in size and normalization of tumor marker level; PR - greater than or equal to (>=) 30 percent (%) decrease in the sum of the diameters of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of nontarget lesions. The all treated analysis population consisted of subjects who received at least 1 dose of study agent.

End point type	Primary

End point timeframe:

Up to 6.8 Months

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	JNJ-64041757+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Percentage of Subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Duration of Objective Response (DOR)

End point title	Phase 1b: Duration of Objective Response (DOR)

End point description:

DOR- the time from initial documentation of a response (CR or PR) to first documented date of disease progression (PD) or death from any cause. RECIST for PD - sum of diameters had increased by >= 20% and >=5 mm from nadir (including baseline if it was smallest sum). Subjects with measurable disease: for "unequivocal progression" based on non-target disease, there was an overall level of substantial worsening that merits discontinuation of therapy (if target disease is stable disease [SD]/PR). Subjects without measurable disease: for "unequivocal progression" of non-target disease, increase in overall tumor burden must be comparable to increase required for PD of measurable disease. Furthermore,

appearance of 1 or more new lesions or unequivocal progression of a non-target lesion. The all treated analysis population consisted of subjects who received at least 1 dose of study agent.

End point type	Secondary

End point timeframe:

Up to 6.8 months

End point values	JNJ-64041757+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Hours				
number (not applicable)				

Notes:

[2] - Overall number of subjects analyzed is zero, since none of the subjects had objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Number of Subjects with Progression-free Survival (PFS)

End point title	Phase 1b: Number of Subjects with Progression-free Survival (PFS)

End point description:

PFS - time from date of randomization until date of first documented evidence of PD (or relapse for subjects who experience CR during study) or death from any cause, whichever comes first. RECIST for PD - sum of diameters had increased by >= 20% and >=5 mm from nadir (including baseline if it was smallest sum). Subjects with measurable disease: for "unequivocal progression" based on non-target disease, there was an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Subjects without measurable disease: for "unequivocal progression" of non-target disease, increase in overall tumor burden must be comparable to increase required for PD of measurable disease. Furthermore, appearance of 1 or more new lesions or unequivocal progression of a non-target lesion. The all treated analysis population consisted of subjects who received at least 1 dose of study agent. Number of subjects with PFS event were reported.

End point type	Secondary

End point timeframe:

Up to 6.8 months

End point values	JNJ-64041757+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
number (not applicable)	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Number of Subjects with Overall Survival (OS)

End point title	Phase 1b: Number of Subjects with Overall Survival (OS)

End point description:

Overall Survival was defined as the duration from the date of randomization to the date of subject's death due to subjects with OS event (died) were reported.

End point type	Secondary

End point timeframe:

Up to 6.8 months

End point values	JNJ-64041757+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
number (not applicable)	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Number of Subjects with Treatment Emergent Adverse Events (TEAEs)

End point title	Phase 1b: Number of Subjects with Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event is any untoward medical event that occurs in a subject administered an investigational product and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. TEAEs are defined as adverse events with onset or worsening on or after date of first dose of study treatment. Safety analysis set included subjects who received at least 1 administration of any study medication.

End point type	Secondary

End point timeframe:

Up to 6.8 months

End point values	JNJ-64041757+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Number of Subjects With Positive Blood Culture

End point title	Phase 1b: Number of Subjects With Positive Blood Culture

End point description:

Number of subjects with surveillance cultures positive for listeriosis were reported. The all treated analysis population consisted of subjects who received at least 1 dose of study agent.

End point type	Secondary

End point timeframe:

Up to 6.8 months

End point values	JNJ-64041757+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Number of Subjects with Bacterial Shedding

End point title	Phase 1b: Number of Subjects with Bacterial Shedding

End point description:

Number of subjects with bacterial shedding were reported. The shedding of JNJ-64041757 was studied in feces by stool or rectal swab, urine, and saliva. The all treated analysis population consisted of subjects who received at least 1 dose of study agent.

End point type	Secondary

End point timeframe:

Up to 6.8 months

End point values	JNJ-64041757+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Serum Concentrations of Nivolumab

End point title	Phase 1b: Serum Concentrations of Nivolumab

End point description:

Nivolumab serum concentrations were reported. Pharmacokinetic (PK) population consisted of all subjects who received at least 1 dose of study agent and had one PK blood sample available. Early termination of study limited the evaluation of planned PK analysis.

End point type	Secondary

End point timeframe:

Up to 6.8 months

End point values	JNJ-64041757+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: Microgram per milliliter (mcg/mL)				
arithmetic mean (standard deviation)	()			

Notes:

[3] - Early termination of study limited the evaluation of planned PK analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Number of Subjects With Anti-nivolumab Antibodies

End point title	Phase 1b: Number of Subjects With Anti-nivolumab Antibodies

End point description:

Number of subjects with antibodies to nivolumab were reported. The all treated analysis population consisted of subjects who received at least 1 dose of study agent.

End point type	Secondary

End point timeframe:

Up to 6.8 months

End point values	JNJ-64041757+Nivolumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 6.8 months

Adverse event reporting additional description:

Safety analysis set included subjects who received at least 1 administration of any study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	JNJ-64041757+Nivolumab

Reporting group description:

Subjects received nivolumab 240 milligram (mg) intravenous (IV) infusion followed by JNJ-64041757 (1*10^9 colony-forming units [CFUs]) IV infusion on Day 1 and nivolumab 240 mg IV infusion on Day 15 of each 28-day cycle until disease progression, unacceptable toxicity, protocol violation requiring discontinuation of study treatment, withdrawal of consent, noncompliance with study procedures, or the sponsor terminates the study.

Serious adverse events	JNJ-64041757+Nivolumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema Peripheral			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Intestinal Obstruction			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	2 / 2		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Back Pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal Pain			
subjects affected / exposed	1 / 12 (8.33%)		
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 %

Non-serious adverse events	JNJ-64041757+Nivolumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Inferior Vena Caval Occlusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	11		
Chills			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	8 / 12 (66.67%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Dyspnoea			

subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	6		
Haemoptysis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Investigations			
Body Temperature Increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood Creatinine Increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Weight Decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac disorders			
Sinus Tachycardia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dizziness			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Tremor subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 6		
Leukocytosis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Gastrointestinal disorders			
Abdominal Pain subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3		
Constipation subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Dry Mouth subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Nausea subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 6		
Vomiting subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 4		
Hepatobiliary disorders			
Hepatic Failure subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Skin and subcutaneous tissue disorders			

Dry Skin			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Back Pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Joint Swelling			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Limb Discomfort			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Musculoskeletal Pain			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	5		
Pain in Extremity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Myalgia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) Respiratory Tract Infection subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 2 / 12 (16.67%) 2		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all)	 4 / 12 (33.33%) 7 1 / 12 (8.33%) 1 3 / 12 (25.00%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2017	Protocol Amendment-1 included following changes: Added a phase 1b Run-in phase to assess the safety of the combination of JNJ-64041757 (JNJ-757) with nivolumab, clarified that the phase 2 randomization was limited to subjects with mesothelin-positive status at Screening, changed the stratification for randomization to 3 levels of programmed death receptor ligand-1, modified the assessment schedules for biomarkers, disease evaluation, blood cultures, nivolumab pharmacokinetics, and nivolumab immunogenicity, added measurements of patient-reported outcomes and updated the nivolumab dosing schedule and safety evaluations based on revisions to product labeling for nivolumab.
04 January 2018	Protocol Amendment-2 included following changes: Added mesothelin-positive status as an inclusion criterion for all subjects enrolled (phase 1b and phase 2) at Screening and modifications were made to the assessment schedules for biomarkers, core needle biopsy and to add biomarker measurements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
21 September 2018	The sponsor decided that based on no objective responses in all the 12 treated subjects in the study, along with the new safety concern of increased risk of pneumonitis, that the further development of JNJ-757 in combination with nivolumab would not be pursued. Because of this decision, the sponsor did not proceed to the Randomized phase 2 of the study or enroll any additional subjects in phase 1b, and the study was stopped early.	-

Notes:

Limitations and caveats

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

Sponsor did not proceed to Randomized phase 2 of study or enroll additional subjects in phase 1b as study was stopped early that resulted in limited evaluation of planned patient-related outcomes, PK, immunogenicity and biomarker analyses.

Notes: