



## Clinical trial results:

### A Phase 2, Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of Inhaled JNJ-49095397 (RV568) in Subjects With Moderate to Severe Chronic Obstructive Pulmonary Disease

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

#### Summary

EudraCT number	2012-005184-27
Trial protocol	BE GB DE HU CZ NL PL RO
Global end of trial date	01 September 2014

#### Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	22 April 2016

#### Trial information

##### Trial identification

Sponsor protocol code	49095397OPD2001
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01867762
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Archimedesweg 29-2333CM, Leiden, Netherlands, 2333CM
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, 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	01 September 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 September 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to assess the efficacy (as measured by change from baseline in prebronchodilator [preBD] percent predicted forced expiratory volume in 1 second [FEV1]) of JNJ-49095397 compared with placebo in subjects with symptomatic moderate (global initiative for chronic obstructive lung disease [GOLD] Grade II) to severe (GOLD Grade III) chronic obstructive pulmonary disease (COPD).

Protection of trial subjects:

The safety assessments included the incidence and severity of adverse events (AEs), clinical laboratory tests (hematology, serum chemistry and urinalysis), electrocardiogram (ECG), vital signs and physical examinations which were assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 August 2013
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	Belgium: 6
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Czech Republic: 18
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Russian Federation: 25
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	211
EEA total number of subjects	134

Notes:

<b>Subjects enrolled per age group</b>	
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)	108
From 65 to 84 years	103
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 211 subjects were randomized in the study out of these 106 subjects were randomized to the placebo group and 105 subjects were randomized to the JNJ-49095397 400 microgram (µg) group.

### Period 1

Period 1 title	Overall Study Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Subjects received Placebo capsule oral inhalation once daily using dry powder inhaler for 12 Weeks.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received Placebo once daily by using a dry powder inhaler for 12 weeks.

<b>Arm title</b>	JNJ-49095397
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Arm description:

Subjects received JNJ-49095397 400 µg capsule oral inhalation once daily using dry powder inhaler for 12 Weeks.

Arm type	Experimental
Investigational medicinal product name	JNJ-49095397
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received JNJ-49095397 400 µg once daily by using a dry powder inhaler for 12 weeks.

<b>Number of subjects in period 1</b>	Placebo	JNJ-49095397
Started	106	105
Completed	85	92
Not completed	21	13
Consent withdrawn by subject	3	2
Adverse event, non-fatal	11	6
Other	6	4
Adverse event, serious non-fatal	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received Placebo capsule oral inhalation once daily using dry powder inhaler for 12 Weeks.	
Reporting group title	JNJ-49095397
Reporting group description: Subjects received JNJ-49095397 400 µg capsule oral inhalation once daily using dry powder inhaler for 12 Weeks.	

Reporting group values	Placebo	JNJ-49095397	Total
Number of subjects	106	105	211
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	52	56	108
From 65 to 84 years	54	49	103
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	64.5	63.7	
standard deviation	± 7.08	± 7.69	-
Title for Gender Units: subjects			
Female	41	42	83
Male	65	63	128

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received Placebo capsule oral inhalation once daily using dry powder inhaler for 12 Weeks.	
Reporting group title	JNJ-49095397
Reporting group description:	
Subjects received JNJ-49095397 400 µg capsule oral inhalation once daily using dry powder inhaler for 12 Weeks.	

### Primary: Change From Baseline in preBD (before taking an inhaled bronchodilator) Percent-predicted Forced Expiratory Volume in one Second (FEV1) at Week 12

End point title	Change From Baseline in preBD (before taking an inhaled bronchodilator) Percent-predicted Forced Expiratory Volume in one Second (FEV1) at Week 12
End point description:	
FEV1 is the amount of air that can be forcibly exhaled in one second after a maximal inhalation. FEV1 will be measured by spirometry. A positive change from baseline in FEV1 indicates improvement in lung function. The data are shown in two ways in the 'end point values' table below. The first display is 'per cent predicted' where the absolute value of FEV1 (in Liters) is compared to a normal population of the same age, height and gender. The second value displayed is change from baseline at week 12 in per cent predicted which is the primary endpoint. The modified intent-to-treat (mITT) analysis set included all randomized subjects who received at least one dose of study agent and had at least 1 post treatment efficacy measurement. Here, 'n' signifies number of subjects analyzed for this endpoint at given timepoint.	
End point type	Primary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo	JNJ-49095397		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: percent change				
arithmetic mean (standard deviation)				
Baseline (n= 106, 105)	49.33 (± 9.649)	48.8 (± 9.525)		
Change in percent predicted at Week 12(n= 106,104)	-1.94 (± 5.748)	-1.75 (± 6.037)		

### Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-49095397

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.838
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	0.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.18
upper limit	1.51
Variability estimate	Standard error of the mean
Dispersion value	0.815

### Secondary: Change From Baseline in Postbronchodilator (postBD, after taking an inhaled bronchodilator) Percent-Predicted FEV1 at Week 12

End point title	Change From Baseline in Postbronchodilator (postBD, after taking an inhaled bronchodilator) Percent-Predicted FEV1 at Week 12
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#### End point description:

FEV1 is the amount of air that can be forcibly exhaled in one second after a maximal inhalation. FEV1 will be measured by spirometry. A positive change from baseline in FEV1 indicates improvement in lung function. The data are shown in two ways in the 'end point values' table below. The first display is 'per cent predicted' where the absolute value of FEV1 (in Liters) is compared to a normal population of the same age, height and gender. The second value displayed is change from baseline at week 12 in per cent predicted which is the primary endpoint. The mITT analysis set included all randomized subjects who received at least one dose of study agent and had at least 1 post treatment efficacy measurement. Here, 'n' signifies number of subjects analyzed for this endpoint at given timepoint.

End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo	JNJ-49095397		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: percent change				
arithmetic mean (standard deviation)				
Baseline (n= 106, 105)	53.91 (± 9.05)	53.59 (± 8.929)		
Change in percent predicted at Week 12(n= 104,104)	-1.87 (± 5.79)	-1.78 (± 4.996)		

### Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-49095397



Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.894
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.14
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.754

### Secondary: Change From Baseline in Weekly Average Number of Occasions in a day That Rescue Medication is Used at Week 12

End point title	Change From Baseline in Weekly Average Number of Occasions in a day That Rescue Medication is Used at Week 12
End point description:	Use of inhaled rescue medication (expressed as the number of occasions) taken on a schedule and/or for control of symptoms will be recorded twice daily. The mITT analysis set included all randomized subjects who received at least one dose of study agent and had at least 1 post treatment efficacy measurement. Here, 'n' signifies number of subjects analyzed for this endpoint at given timepoint.
End point type	Secondary
End point timeframe:	
Baseline to Week 12	

End point values	Placebo	JNJ-49095397		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: number				
arithmetic mean (standard deviation)				
Baseline (n= 106, 105)	2.57 (± 1.985)	2.43 (± 2.373)		
Change at Week 12 (n= 105, 104)	0.07 (± 1.552)	-0.08 (± 1.641)		

### Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-49095397

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.407
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.53
upper limit	0.18
Variability estimate	Standard error of the mean
Dispersion value	0.213

### Secondary: Change From Baseline in Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (E-RS) Total Score at Week 12

End point title	Change From Baseline in Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (E-RS) Total Score at Week 12
End point description:	E-RS is an 11-items respiratory system scoring algorithm to assess the severity of respiratory symptoms in participants with COPD. Each item has either 5 or 6 response options. Higher score indicates more severe COPD. The mITT analysis set included all randomized subjects who received at least 1 dose of study agent and had at least 1 post treatment efficacy measurement. Here, 'n' signifies number of subjects analyzed for this endpoint at given timepoint.
End point type	Secondary
End point timeframe:	Baseline to Week 12

End point values	Placebo	JNJ-49095397		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 106, 105)	13.09 (± 6.35)	11.97 (± 6.1)		
Change at Week 12 (n= 105, 104)	-0.01 (± 4.446)	-0.38 (± 3.57)		

### Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-49095397

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.363
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.51
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.43
upper limit	0.41
Variability estimate	Standard error of the mean
Dispersion value	0.557

### Secondary: Change From Baseline in the Total Score of the St. George's Respiratory Questionnaire for COPD Subjects (SGRQ-C) at Week 12

End point title	Change From Baseline in the Total Score of the St. George's Respiratory Questionnaire for COPD Subjects (SGRQ-C) at Week 12
End point description:	SGRQ-C is a 40-item questionnaire designed to measure health impairment in participants with COPD. SGRQ-C is divided into two components: 1) symptoms, 2) activity & impacts. Total SGRQ-C score ranges from 0 (best) and 100 (worst). Higher scores indicate greater health impairment. The mITT analysis set included all randomized subjects who received at least 1 dose of study agent and had at least one post treatment efficacy measurement. Here, 'n' signifies number of subjects analyzed for this endpoint at given timepoint.
End point type	Secondary
End point timeframe:	
Baseline to week 12	

End point values	Placebo	JNJ-49095397		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 106, 105)	49.67 (± 15.584)	47.96 (± 18.889)		
Change at Week 12 (n= 104, 104)	-1.88 (± 11.454)	0.88 (± 11.25)		

### Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-49095397

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.47
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.08
upper limit	5.02
Variability estimate	Standard error of the mean
Dispersion value	1.544

### Secondary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events
End point description: An adverse event is any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product.	
End point type	Secondary
End point timeframe: Up to Week 16	

<b>End point values</b>	Placebo	JNJ-49095397		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: subjects	57	54		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to follow up (up to Week 16)

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	JNJ-49095397 400µg
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Reporting group description:

Daily inhalation of JNJ-49095397 400 µg for 12 weeks

Reporting group title	PLACEBO
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Reporting group description:

Daily inhalation of Placebo for 12 weeks

Serious adverse events	JNJ-49095397 400µg	PLACEBO	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 105 (2.86%)	5 / 106 (4.72%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Myocardial Infarction			
subjects affected / exposed	0 / 105 (0.00%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial Ischaemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 105 (0.95%)	2 / 106 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Spondylolisthesis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	JNJ-49095397 400µg	PLACEBO	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 105 (20.95%)	22 / 106 (20.75%)	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 105 (0.95%)	6 / 106 (5.66%)	
occurrences (all)	1	7	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	13 / 105 (12.38%)	14 / 106 (13.21%)	
occurrences (all)	15	21	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 105 (8.57%)	6 / 106 (5.66%)	
occurrences (all)	10	7	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2013	The amendment includes the following substantial changes: The reference was removed to RVH008 (internal study designation) as alternate name of study to avoid confusion. Text was clarified indicating that the assessments at Study Visit 7 should be performed in the event of early withdrawal from the study. The safety follow-up electrocardiogram (ECG) was moved from Study Visit 8 to Study Visit 7. It updated and clarified text on nonclinical safety pharmacology, and nonclinical genotoxicity, updated text to reflect completed clinical studies and data, and update the dose rationale. Clarified text on summary of safety from clinical studies, removed unnecessary assessment for inventory of study agent at Study Visit 8. Clarification of text on inclusion criterion and reporting for subjects with laboratory values outside normal reference ranges during screening and clarification of inclusion criterion text on use of contraception. The text was clarified on changes to background medications and for storage conditions.
10 October 2013	In a subset of consenting subjects in selected countries and sites, additional PK blood samples were added to the study procedures at the week 8 study visit. Prior scheduled PK assessments were adjusted in this subset. The text was clarified on exclusion criteria regarding previous episodes of COPD exacerbations.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported