Clinical trial results:
A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group Study of JNJ-38518168 in Symptomatic Adult Subjects with Uncontrolled, Persistent Asthma

Summary

EudraCT number	2012-004920-39
Trial protocol	GB DE IT
Global end of trial date	23 July 2015

Results information

Result version number	v1 (current)
This version publication date	21 July 2016
First version publication date	21 July 2016

Trial information

Trial identification

Sponsor protocol code	38518168ASH2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01823016
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	Archimedesweg 29-2333CM, Leiden, Netherlands, 2333CM
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	23 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to assess the efficacy (as measured by the change from baseline in prebronchodilator [preBD] percent-predicted forced expiratory volume in 1 second [FEV1]) of JNJ 38518168 compared with placebo in subjects with eosinophilic persistent asthma that is inadequately controlled despite current treatment (inhaled corticosteroids [ICS] with or without long-acting beta-2-agonist [LABA], montelukast).

Protection of trial subjects:

The safety assessments included clinical laboratory tests (hematology, serum chemistry and urinalysis), spirometry, electrocardiogram (ECG), vital signs and physical examinations. Adverse events were assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 September 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	Canada: 15
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	United States: 61
Worldwide total number of subjects	165
EEA total number of subjects	67

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)	146
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 82 of the 83 subjects randomized to the placebo group were treated with placebo and 82 of the 82 subjects randomized to the JNJ-38518168 30 mg group were treated with JNJ38518168 30 mg.

Period 1

Period 1 title	Overall Study (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
Arm title	Placebo

Arm description:

Subjects received matching Placebo film coated tablet orally once daily for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received matching placebo film coated tablet orally once daily for 24 Weeks.

Arm title	JNJ-38518168, 30 milligram (mg)

Arm description:

Subjects received JNJ-38518168 30 milligram film coated tablet orally once daily for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	JNJ-38518168
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received JNJ-38518168 30 mg film coated tablet orally once daily for 24 Weeks.

Number of subjects in period 1	Placebo	JNJ-38518168, 30 milligram (mg)
Started	83	82
Completed	65	68
Not completed	18	14
Consent withdrawn by subject	4	5

Adverse event, non-fatal	4	2
Other	9	6
Lost to follow-up	-	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching Placebo film coated tablet orally once daily for 24 weeks.	
Reporting group title	JNJ-38518168, 30 milligram (mg)
Reporting group description:	
Subjects received JNJ-38518168 30 milligram film coated tablet orally once daily for 24 weeks.	

Reporting group values	Placebo	JNJ-38518168, 30 milligram (mg)	Total
Number of subjects	83	82	165
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	75	71	146
From 65 to 84 years	8	11	19
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	48.5	48.8	
standard deviation	± 12.63	± 13.25	-
Title for Gender Units: subjects			
Female	46	40	86
Male	37	42	79

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received matching Placebo film coated tablet orally once daily for 24 weeks.	
Reporting group title	JNJ-38518168, 30 milligram (mg)
Reporting group description:	
Subjects received JNJ-38518168 30 milligram film coated tablet orally once daily for 24 weeks.	

Primary: Change From Baseline in Prebronchodilator (preBD) Percent Predicted Forced Expiratory Volume in one Second (FEV1) at Week 16

End point title	Change From Baseline in Prebronchodilator (preBD) Percent Predicted Forced Expiratory Volume in one Second (FEV1) at Week 16
End point description:	
FEV1 is the amount of air that can be exhaled in one second. FEV1 will be measured by spirometry. A positive change from baseline in FEV1 indicates improvement in lung function. The modified intent-to-treat (mITT) analysis set included all randomized subjects who received at least one dose (partial or complete) 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 and Week 16	

End point values	Placebo	JNJ-38518168, 30 milligram (mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: percent change				
arithmetic mean (standard deviation)				
Baseline (n= 82, 82)	62.84 (± 9.773)	62.77 (± 10.528)		
Change at Week 16 (n= 81, 82)	3.72 (± 8.976)	3.53 (± 9.203)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-38518168, 30 milligram (mg)

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.896
Method	ANCOVA
Parameter estimate	Least Square (LS) means difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.01
upper limit	2.64
Variability estimate	Standard error of the mean
Dispersion value	1.431

Secondary: Change From Baseline in Asthma Control Questionnaire (ACQ) at Week 16

End point title	Change From Baseline in Asthma Control Questionnaire (ACQ) at Week 16

End point description:

ACQ is used to evaluate asthma control, the full range of clinical impairment (well controlled to life threatening) for the participant with asthma. There are 7 questions (5 for symptoms [night-time awakenings, morning symptoms, limitation of activities, shortness of breath, and wheezing], use of daily rescue bronchodilator, and percent predicted forced expiratory volume value). All 7 items are scored on a 7-point scale (0 = good control, 6 = poor control), with the mean score as an overall summary score. The recall period is 7 days. Higher scores indicate worsening. The mITT analysis set included all randomized subjects who received at least one dose (partial or complete) 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 and Week 16

End point values	Placebo	JNJ-38518168, 30 milligram (mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 82, 82)	2.54 (± 0.628)	2.43 (± 0.512)		
Change at Week 16 (n= 81, 82)	-0.77 (± 0.734)	-0.65 (± 0.743)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	JNJ-38518168, 30 milligram (mg) v Placebo
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.512
Method	ANCOVA
Parameter estimate	LS means difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.113

Secondary: Change From Baseline in Postbronchodilator (postBD) Percent-Predicted FEV1 at Week 16

End point title	Change From Baseline in Postbronchodilator (postBD) Percent-Predicted FEV1 at Week 16

End point description:

FEV1 is the amount of air that can be exhaled in one second. FEV1 will be measured by spirometry. A positive change from baseline in FEV1 indicates improvement in lung function. The modified intent-to-treat (mITT) analysis set included all randomized subjects who received at least one dose (partial or complete) 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 and Week 16

End point values	Placebo	JNJ-38518168, 30 milligram (mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: percent change				
arithmetic mean (standard deviation)				
Baseline (n= 82, 82)	76.6 (± 12.702)	75.5 (± 13.243)		
Change at Week 16 (n= 80, 82)	-1.15 (± 6.121)	-0.62 (± 6.827)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-38518168, 30 milligram (mg)
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	ANCOVA
Parameter estimate	LS means difference
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	2.55
Variability estimate	Standard error of the mean
Dispersion value	1.021

Secondary: Change From Baseline in Weekly Average of Daytime Asthma Diary Symptom Score at Week 16

End point title	Change From Baseline in Weekly Average of Daytime Asthma Diary Symptom Score at Week 16

End point description:

Asthma symptom diary score is an index to access the severity of asthma related symptoms. The symptoms are wheezing, coughing, chest tightness and trouble breathing. The severity of each symptom is assessed by a 5-point ranking scale (0 = no symptom, 1 = mild, 2 = moderate, 3 = severe, 4 = extremely severe). Subjects are instructed to score and document their symptoms through e-diary every morning and evening. Daytime asthma symptom score is defined as the average of the four symptom scores collected in evening diaries. The modified intent-to-treat (mITT) analysis set included all randomized subjects who received at least one dose (partial or complete) 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 and Week 16

End point values	Placebo	JNJ-38518168, 30 milligram (mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 82, 82)	0.54 (± 0.472)	0.42 (± 0.35)		
Change at Week 16 (n= 81, 81)	-0.25 (± 0.406)	-0.2 (± 0.349)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-38518168, 30 milligram (mg)
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.794
Method	Rank Analysis of Covariance
Parameter estimate	Median difference (net)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.14

Secondary: Change From Baseline in Weekly Average of Nighttime Asthma Diary Symptom Score at Week 16

End point title	Change From Baseline in Weekly Average of Nighttime Asthma Diary Symptom Score at Week 16

End point description:

Asthma symptom diary score is an index to access the severity of asthma related symptoms. The symptoms are wheezing, coughing, chest tightness and trouble breathing. The severity of each symptom is assessed by a 5-point ranking scale (0 = no symptom, 1 = mild, 2 = moderate, 3 = severe, 4 = extremely severe). Subjects are instructed to score and document their symptoms through e-diary every morning and evening. Nighttime asthma symptom score is defined as the average of the four symptom scores collected in morning diaries. The modified intent-to-treat (mITT) analysis set included all randomized subjects who received at least one dose (partial or complete) 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 and Week 16

End point values	Placebo	JNJ-38518168, 30 milligram (mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 82, 82)	0.39 (± 0.449)	0.19 (± 0.246)		
Change at Week 16 (n= 81, 81)	-0.2 (± 0.359)	-0.11 (± 0.228)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-38518168, 30 milligram (mg)
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.295
Method	Rank Analysis of Covariance
Parameter estimate	Median difference (net)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.09

Secondary: Change From Baseline in Weekly Average of Number of Puffs in a day That Rescue Medication was Used at Week 16

End point title	Change From Baseline in Weekly Average of Number of Puffs in a day That Rescue Medication was Used at Week 16

End point description:

The weekly average of number of puffs in daytime (nighttime) that rescue medication is used for a particular visit (excluding Baseline visit) is calculated as sum of the weekly average of number of puffs in daytime and nighttime the week (7-day period) prior to the visit. The 7-day period does not include the day of visit. If less than 4 data points are available for daytime (nighttime) rescue medication use, the daytime (nighttime) assessment was considered missing. The modified intent-to-treat (mITT) analysis set included all randomized subjects who received at least one dose (partial or complete) 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 and Week 16

End point values	Placebo	JNJ-38518168, 30 milligram (mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: number of puffs				
arithmetic mean (standard deviation)				
Baseline (n= 82, 82)	2.46 (± 2.2)	2.03 (± 2.169)		
Change at Week 16 (n= 81, 81)	-0.86 (± 1.595)	-0.82 (± 1.856)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v JNJ-38518168, 30 milligram (mg)

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Rank Analysis of Covariance
Parameter estimate	Median difference (net)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.67

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
First study agent administration up to follow up (Week 28)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0
Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching Placebo tablet orally once daily for 24 weeks.	
Reporting group title	JNJ-38518168, 30 mg
Reporting group description:	
Subjects received JNJ-38518168 30 mg tablet orally once daily for 24 Weeks.	

Serious adverse events	Placebo	JNJ-38518168, 30 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 82 (0.00%)	0 / 82 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	JNJ-38518168, 30 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 82 (58.54%)	50 / 82 (60.98%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 82 (1.22%)	8 / 82 (9.76%)	
occurrences (all)	1	11	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 82 (0.00%)	2 / 82 (2.44%)	
occurrences (all)	0	2	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 82 (1.22%)	2 / 82 (2.44%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	1 / 82 (1.22%)	2 / 82 (2.44%)	
occurrences (all)	1	2	
Eye disorders			
Conjunctivitis Allergic			
subjects affected / exposed	1 / 82 (1.22%)	2 / 82 (2.44%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	4 / 82 (4.88%)	4 / 82 (4.88%)	
occurrences (all)	4	6	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	20 / 82 (24.39%)	24 / 82 (29.27%)	
occurrences (all)	29	37	
Cough			
subjects affected / exposed	3 / 82 (3.66%)	3 / 82 (3.66%)	
occurrences (all)	3	3	
Dyspnoea			
subjects affected / exposed	3 / 82 (3.66%)	2 / 82 (2.44%)	
occurrences (all)	3	2	
Epistaxis			
subjects affected / exposed	0 / 82 (0.00%)	2 / 82 (2.44%)	
occurrences (all)	0	2	
Nasal Congestion			
subjects affected / exposed	1 / 82 (1.22%)	2 / 82 (2.44%)	
occurrences (all)	1	2	
Oropharyngeal Pain			
subjects affected / exposed	2 / 82 (2.44%)	3 / 82 (3.66%)	
occurrences (all)	2	3	

Rhinitis Allergic			
subjects affected / exposed	1 / 82 (1.22%)	3 / 82 (3.66%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences (all)	2	0	
Back Pain			
subjects affected / exposed	2 / 82 (2.44%)	2 / 82 (2.44%)	
occurrences (all)	2	3	
Muscle Spasms			
subjects affected / exposed	1 / 82 (1.22%)	2 / 82 (2.44%)	
occurrences (all)	1	2	
Infections and infestations			
Acute Sinusitis			
subjects affected / exposed	3 / 82 (3.66%)	1 / 82 (1.22%)	
occurrences (all)	3	1	
Bronchitis			
subjects affected / exposed	8 / 82 (9.76%)	1 / 82 (1.22%)	
occurrences (all)	10	1	
Cystitis			
subjects affected / exposed	1 / 82 (1.22%)	2 / 82 (2.44%)	
occurrences (all)	1	2	
Influenza			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	11 / 82 (13.41%)	10 / 82 (12.20%)	
occurrences (all)	14	12	
Oral Candidiasis			
subjects affected / exposed	2 / 82 (2.44%)	0 / 82 (0.00%)	
occurrences (all)	2	0	

Rhinitis			
subjects affected / exposed	3 / 82 (3.66%)	3 / 82 (3.66%)	
occurrences (all)	3	3	
Sinusitis			
subjects affected / exposed	6 / 82 (7.32%)	3 / 82 (3.66%)	
occurrences (all)	6	4	
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 82 (7.32%)	9 / 82 (10.98%)	
occurrences (all)	10	9	
Urinary Tract Infection			
subjects affected / exposed	3 / 82 (3.66%)	2 / 82 (2.44%)	
occurrences (all)	3	2	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 82 (3.66%)	2 / 82 (2.44%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2013	The amendment includes the following substantial changes: Based upon preliminary pharmacokinetic (PK) results from the 38518168ARA1003 drug-drug interaction (DDI) study with ketoconazole (a potent CYP3A4/Pgp inhibitor), information regarding DDIs, criteria for subject enrollment, and the list of prohibited medications were updated, allowing greater flexibility in subject enrollment and choice of concomitant medications; Total Nasal and Ocular Symptom Score (TNOSS) assessment was removed from Screening Visit 2 as this assessment was not required at this time point; clarification of wording for primary endpoint and hypothesis; clarification of statistical sections; clarification of repeat testing for induced sputum; clarification added regarding dosing of study agent with water; text regarding epigenetic testing was added; clarification added on ferritin unit values and text on retesting to inclusion criterion #10; clarification added on background inhaled corticosteroids (ICS), long-acting beta-2-agonist (LABA), and montelukast use for stratification; added clarifying text on electrocardiogram (ECG) that if the repeat QTcF continues to be above 480 msec based on the central cardiologist's overread, the study medication should be discontinued; list of substrates of CYP2C8 was revised to include montelukast, which was recently identified as a CYP2C8 substrate in clinical studies; added clarifying text for definition of asthma exacerbations as an emergency room visit because of asthma requiring treatment with systemic corticosteroids for at least 3 consecutive days; a criterion was added excluding women from donating eggs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported