Clinical trial results:
A randomized, subject- and investigator-blinded, placebo-controlled study to assess the efficacy and safety of LOU064 in patients with inadequately controlled asthma

Summary

EudraCT number	2018-003609-24
Trial protocol	PL
Global end of trial date	27 April 2020

Results information

Result version number	v1 (current)
This version publication date	15 April 2021
First version publication date	15 April 2021

Trial information

Trial identification

Sponsor protocol code	CLOU064D12201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03944707
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	27 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This proof-of-concept study investigated the efficacy and safety of LOU064 in patients with inadequately controlled asthma who were on a standardized background therapy of inhaled corticosteroid plus long acting beta-2 agonist (ICS/LABA). The primary objective of the study was to determine the efficacy of LOU064 compared to placebo with respect to change from baseline in pre-dose FEV1 (forced expiratory volume in one second) at Week 12.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

As a rescue medication, all subjects were supplied with an inhaled short-acting beta2-agonist (SABA): 100 µg/puff salbutamol or other SABA at matching dose strength, corresponding to albuterol 90 µg/puff.

Background therapy:

All participants received a standardized background therapy of budesonide 80 µg/formoterol 4.5 µg two inhalations twice a day (b.i.d) beginning at the run-in visit through the end of study visit.

Evidence for comparator: -

Actual start date of recruitment	18 July 2019
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	Argentina: 8
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	76
EEA total number of subjects	27

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	68
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 19 investigative sites in 5 countries.

Pre-assignment

Screening details:

After the screening, participants went through a Run-in period of 3-5 weeks where they discontinued their current asthma therapy and were placed on budesonide 80 µg/formoterol 4.5 µg delivered by dry powder inhaler. Afterwards, patients were randomized in 3:2 ratio to receive LOU064 or placebo and continued to use the budesonide/formoterol inhaler.

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	LOU064

Arm description:

LOU064 100 mg once daily orally

Arm type	Experimental
Investigational medicinal product name	LOU064
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

LOU064 100 mg once daily orally administered as two 50 mg capsules.

Arm title	Placebo

Arm description:

Placebo once daily orally

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo once daily administered orally as capsules

Number of subjects in period 1	LOU064	Placebo
Started	47	29
PK analysis set	33 [1]	0 [2]
PD analysis set	47	29
Completed	35	19
Not completed	12	10
Adverse event, non-fatal	-	2
Subject decision	-	1
Study terminated by sponsor	12	7

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The intermediate milestones refer to the analysis sets

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The intermediate milestones refer to the analysis sets.

Baseline characteristics

Reporting groups

Reporting group title	LOU064
Reporting group description:	
LOU064 100 mg once daily orally	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily orally	

Reporting group values	LOU064	Placebo	Total
Number of subjects	47	29	76
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	41	27	68
From 65-84 years	6	2	8
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	49.2	53.2	
standard deviation	± 10.96	± 10.40	-
Sex: Female, Male			
Units: participants			
Female	28	22	50
Male	19	7	26
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	42	27	69
Black	4	2	6
Asian	1	0	1

End points

End points reporting groups

Reporting group title	LOU064
Reporting group description:	
LOU064 100 mg once daily orally	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily orally	

Primary: Change from baseline in pre-dose FEV1 at Week 12

End point title	Change from baseline in pre-dose FEV1 at Week 12

End point description:

FEV1 (forced expiratory volume in one second) is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. Pre-dose FEV1 is defined as average of the two FEV1 measurements taken 45 min and 15 min pre-dose.
The baseline pre-dose FEV1 is defined as the average of the FEV1 measurements performed 45 min and 15 min prior to dosing on Day 1.
A positive change from baseline in pre-dose FEV1 is considered a favorable outcome.
Change from baseline in pre-dose FEV1 was analyzed using a Bayesian model for repeated measures, adjusting for effects of treatment*visit interaction and baseline pre-dose FEV1. A weakly informative prior was considered for the placebo response.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	LOU064	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	20		
Units: liters				
arithmetic mean (standard deviation)	0.105 (± 0.0494)	0.075 (± 0.0497)		

Statistical analyses

Statistical analysis title	LOU064 vs Placebo
Comparison groups	LOU064 v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6643 [1]
Method	Bayesian model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.03

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.06
upper limit	0.119
Variability estimate	Standard deviation
Dispersion value	0.0698

Notes:

[1] - Probability LOU064 better than placebo

Secondary: Maximum observed blood concentrations (Cmax) of LOU064 at steady state

End point title	Maximum observed blood concentrations (Cmax) of LOU064 at steady state
End point description:	

Pharmacokinetic (PK) parameters were calculated based on LOU064 blood concentrations determined by a validated liquid chromatography and tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification of 1 ng/mL. Cmax was determined using non-compartmental methods.

End point type	Secondary
End point timeframe:	

pre-dose, 0.5, 1, 2, 3 and 4 hours after dosing on Days 15 and 85

End point values	LOU064	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	0[2]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 15 (n = 32, 0)	239 (± 152)	()		
Day 85 (n = 22, 0)	222 (± 142)	()		

Notes:

[2] - Pharmacokinetic parameters were not calculated in the Placebo arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum blood concentrations (Tmax) of LOU064 at steady state

End point title	Time to reach maximum blood concentrations (Tmax) of LOU064 at steady state
End point description:	

PK parameters were calculated based on LOU064 blood concentrations determined by a validated LC-MS/MS method with a lower limit of quantification of 1 ng/mL. Tmax was determined using non-compartmental methods.

End point type	Secondary
End point timeframe:	

pre-dose, 0.5, 1, 2, 3 and 4 hours after dosing on Days 15 and 85

End point values	LOU064	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	0[3]		
Units: hours (hr)				
median (full range (min-max))				
Day 15 (n = 32, 0)	1.00 (0.483 to 2.00)	(to)		
Day 85 (n = 22, 0)	1.00 (0.500 to 3.00)	(to)		

Notes:

[3] - Pharmacokinetic parameters were not calculated in the Placebo arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve from time zero to 24 hours (AUC0-24h) of LOU064 at steady state

End point title	Area under the concentration-time curve from time zero to 24 hours (AUC0-24h) of LOU064 at steady state

End point description:

PK parameters were calculated based on LOU064 blood concentrations determined by a validated LC-MS/MS method with a lower limit of quantification of 1 ng/mL. AUC0-24h was determined using non-compartmental methods. The linear trapezoidal rule was used for AUC0-24h calculation.

End point type	Secondary

End point timeframe:

pre-dose, 0.5, 1, 2, 3 and 4 hours after dosing on Days 15 and 85

End point values	LOU064	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	0[4]		
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Day 15 (n = 21, 0)	471 (± 285)	()		
Day 85 (n = 16, 0)	517 (± 342)	()		

Notes:

[4] - Pharmacokinetic parameters were not calculated in the Placebo arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Asthma Symptom Questionnaire-5 score (ACQ-5) at Week 12

End point title	Change from baseline in Asthma Symptom Questionnaire-5 score (ACQ-5) at Week 12

End point description:

The ACQ-5 is a five-item, self-completed questionnaire, which is used as a measure of asthma control of a participant. Patients were asked to recall how their asthma had been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6=maximum impairment). The questions are equally weighted and the overall ACQ-5 score is the mean of all 5 questions, therefore between 0 (totally controlled) and 6 (severely uncontrolled).
The baseline values of ACQ-5 were collected at the baseline visit.
A negative change from baseline in ACQ-5 is considered a favorable outcome.
Change from baseline in ACQ-5 score was analyzed using a Bayesian model for repeated measures, adjusting for effects of treatment*visit interaction and baseline ACQ-5 score. Non-informative priors were considered.

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

End point values	LOU064	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	20		
Units: score on scale				
arithmetic mean (standard deviation)	-0.95 (± 0.133)	-0.86 (± 0.164)		

Statistical analyses

Statistical analysis title	LOU064 vs Placebo
Comparison groups	LOU064 v Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6609 [5]
Method	Bayesian model for repeated measures
Parameter estimate	Median difference (net)
Point estimate	-0.09
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.35
upper limit	0.18
Variability estimate	Standard deviation
Dispersion value	0.21

Notes:

[5] - Probability LOU064 better than placebo

Secondary: Change from baseline in mean morning and mean evening Peak Expiratory Flow (PEF)

End point title	Change from baseline in mean morning and mean evening Peak Expiratory Flow (PEF)

End point description:

PEF (Peak Expiratory Flow) is a person's maximum speed of expiration. All participants were instructed

to record PEF twice daily before taking any medication using an electronic peak expiratory flow device (ePEF), once in the morning and once approximately 12 h later in the evening at home. At each timepoint, the participant was instructed to perform 3 consecutive manoeuvres within 10 minutes. These PEF values were captured in the e-PEF/diary. For each day the best value in the morning and in the evening were considered and mean values on 4-week intervals were derived.

The baseline values of PEF were the mean values in the run-in period.

A positive change from baseline in PEF is considered a favorable outcome.

Change from baseline in mean morning and mean evening PEF were analyzed using a Bayesian model for repeated measures, adjusting for effects of treatment*weeks interaction and baseline PEF values. Non-informative priors were considered.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 9-12	

End point values	LOU064	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	29		
Units: liters/minute				
arithmetic mean (standard deviation)				
Change in mean morning PEF (n = 29, 18)	-2.4 (± 4.30)	-2.6 (± 5.59)		
Change in mean evening PEF (n = 28, 18)	-9.7 (± 5.58)	-6.3 (± 7.23)		

Statistical analyses

Statistical analysis title	LOU064 vs Placebo
Statistical analysis description:	
Change from baseline in mean morning PEF	
Comparison groups	LOU064 v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5107 [6]
Method	Bayesian model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-9
upper limit	9.1
Variability estimate	Standard deviation
Dispersion value	7.13

Notes:

[6] - Probability LOU064 better than placebo

Statistical analysis title	LOU064 vs Placebo

Statistical analysis description:	
Change from baseline in mean evening PEF	
Comparison groups	LOU064 v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3611 [7]
Method	Bayesian model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-3.4
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-15.2
upper limit	8.1
Variability estimate	Standard deviation
Dispersion value	9.15

Notes:

[7] - Probability LOU064 better than placebo

Secondary: Change from baseline in number of puffs of SABA taken per day during the treatment period

End point title	Change from baseline in number of puffs of SABA taken per day during the treatment period

End point description:

Participants were given a short acting β2-agonist (SABA; salbutamol, known also as albuterol) to use as rescue medication throughout the study along with an electronic diary (eDiary) to record rescue medication use. Participants recorded in the eDiary, once in the morning and once in the evening, the use of rescue medication (number of puffs of SABA taken in the previous 12 hours). The total number of puffs of SABA taken per day was calculated and the mean daily use of puffs of SABA over 12 weeks was derived.

The baseline values of number of puffs of SABA taken per day were defined as the average from all non-missing records taken during the run-in period. A negative change from baseline is considered a favorable outcome.

Change from baseline in number of puffs of SABA taken per day was analyzed using a Bayesian model, adjusting for effects of baseline SABA use, baseline FEV1, baseline asthma daytime symptom score and treatment. Non-informative priors were considered.

End point type	Secondary

End point timeframe:

Baseline, 12 weeks

End point values	LOU064	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	26		
Units: puffs of SABA				
arithmetic mean (standard deviation)	-0.192 (± 0.0946)	-0.059 (± 0.1224)		

Statistical analyses

Statistical analysis title	LOU064 vs Placebo
Comparison groups	LOU064 v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8022 [8]
Method	Bayesian model
Parameter estimate	Mean difference (net)
Point estimate	-0.133
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.336
upper limit	0.071
Variability estimate	Standard deviation
Dispersion value	0.1588

Notes:

[8] - Probability LOU064 better than placebo

Secondary: Change from baseline in daytime and nighttime asthma symptom score

End point title	Change from baseline in daytime and nighttime asthma symptom score

End point description:

Participants recorded asthma symptoms twice daily in the eDiary. Daytime asthma symptoms were assessed before bed and nighttime symptoms on awakening.
Daytime asthma symptom score included 4 questions. Overall score (0 to 6) was calculated as the average of the 4 questions with higher values indicating more asthma symptoms.
Nighttime asthma symptom score included 2 questions. Overall score (0 to 3.5) was calculated as the average of the 2 questions with higher values indicating more asthma symptoms.
Mean values of both scores were calculated over 4-week intervals during the treatment period.
The baseline values of both asthma symptoms scores were defined as the average score during the run-in period. A negative change from baseline is a favorable outcome.
Change from baseline in daytime and nighttime asthma symptom score were analyzed using a Bayesian model for repeated measures, adjusting for effects of treatment*weeks and baseline scores. Non-informative priors were considered.

End point type	Secondary

End point timeframe:

Baseline, Weeks 9-12

End point values	LOU064	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	20		
Units: score on scale				
arithmetic mean (standard deviation)				
Change in daytime asthma symptom score	-0.225 (± 0.0962)	-0.175 (± 0.1237)		
Change in nighttime asthma symptom score	-0.120 (± 0.0488)	-0.195 (± 0.0651)		

Statistical analyses

Statistical analysis title	LOU064 vs Placebo
Statistical analysis description:	
Change from baseline in daytime asthma symptom score	
Comparison groups	LOU064 v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6312 [9]
Method	Bayesian model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.05
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.251
upper limit	0.149
Variability estimate	Standard deviation
Dispersion value	0.1573

Notes:

[9] - Probability LOU064 better than placebo

Statistical analysis title	LOU064 vs Placebo
Statistical analysis description:	
Change from baseline in nighttime asthma symptom score	
Comparison groups	LOU064 v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1752 [10]
Method	Bayesian model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.075
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.028
upper limit	0.18
Variability estimate	Standard deviation
Dispersion value	0.0819

Notes:

[10] - Probability LOU064 better than placebo

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment until last dose of study treatment plus 30 days post treatment, up to Day 115.

Adverse event reporting additional description:

Any sign or symptom that occurs during the study treatment plus 30 days post treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	LOU064

Reporting group description:

LOU064 100 mg once daily orally

Reporting group title	Placebo

Reporting group description:

Placebo once daily orally

Serious adverse events	LOU064	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 47 (0.00%)	0 / 29 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	LOU064	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 47 (17.02%)	10 / 29 (34.48%)	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 47 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 47 (8.51%)	6 / 29 (20.69%)	
occurrences (all)	4	9	

Upper respiratory tract infection subjects affected / exposed	4 / 47 (8.51%)	4 / 29 (13.79%)
occurrences (all)	5	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2019	The purpose of this protocol amendment was to address the recommendation from the US-Health Authority FDA to adjust the dose of standard background medication of inhaled budesonide/formoterol to labeled dose for the therapy of asthma. In addition, the sample size for the study was reduced from 110 to 75 subjects available for analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported