NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

LOU064

Trial Indication(s)

Inadequately controlled asthma

Protocol Number

CLOU064D12201

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

Study Start/End Dates

Study Start Date: July 2019 (Actual)
Primary Completion Date: April 2020 (Actual)
Study Completion Date: April 2020 (Actual)

Reason for Termination (If applicable)

Results from the interim analysis did not provide sufficient evidence of efficacy of LOU064 in inadequately controlled asthma and the sponsor decided to terminate early the study in April 2020.

Study Design/Methodology

This was a non-confirmatory, multi-center, randomized, placebo-controlled, subject- and investigator-blinded, parallel-group study to evaluate 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 study included:

- a Screening period of up to 2 weeks to assess eligibility
- a Run-in period of minimum 3 weeks and maximum 5 weeks where patients discontinued their current asthma therapy and were placed on budesonide 80 µg/formoterol 4.5 µg delivered by dry powder inhaler, two inhalations twice a day (b.i.d)
- a Treatment period of 12 weeks. All subjects were randomized 3:2 to receive LOU064 100 mg once daily or placebo for 12 weeks with standard background therapy of budesonide 80 µg/formoterol 4.5 µg, two inhalations b.i.d.
- a Follow-up period of 3 weeks following the last dose of study drug

Centers

19 centers in 5 countries: United States(4), Germany(5), Russia(2), Argentina(4), Poland(4)

Objectives:

The primary objective was to determine the efficacy of LOU064 compared to placebo with respect to change from baseline in pre-dose Forced Expiratory Volume in one second (FEV1) at Week 12.

The secondary objectives were:

- To characterize the pharmacokinetics (PK) profile of LOU064

- To determine the efficacy of LOU064 compared to placebo in terms of:
  - Change from baseline in Asthma Symptom Questionnaire-5 score (ACQ-5) at Week 12
  - Change from baseline in mean morning and mean evening Peak Expiratory Flow (PEF)
  - Change from baseline in number of puffs of short-acting beta2-agonist (SABA) taken per day during the treatment period
  - Change from baseline in daytime and nighttime asthma symptom score
- To evaluate the safety and tolerability of LOU064

Test Product (s), Dose(s), and Mode(s) of Administration

All participants took LOU064 100 mg administered as two 50 mg capsules or matching placebo capsules. The investigational treatment (LOU064 100 mg or placebo) was administered once daily orally. The planned treatment period was 12 weeks (from Day 1 through Day 85). The median duration of exposure (12.0 weeks for LOU064 and 11.7 weeks for placebo) was close to the treatment target, as most of the participants had completed treatment when the study was terminated.

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.

Statistical Methods

The study was powered (80%) to detect a statistically significant effect of LOU064 over placebo in the mean change from baseline in pre-dose FEV1 at Week 12.

Power calculations were performed assuming a true effect of 130 mL with a SD=260 mL. The statistical significance was based on the posterior distribution of the LOU064 effect over placebo and it was defined as a probability > 90% at the end of the study.

Primary endpoint:

The primary endpoint was analyzed using a Bayesian repeated measures model with change from baseline in pre-dose FEV1 as response, adjusting for effects of treatment visit interaction, and baseline pre-dose FEV1.

Based on the fitted Bayesian model for repeated measures, the posterior probabilities of mean LOU064 effect on primary endpoint over placebo were calculated. A weakly informative prior was used for adjusted mean change from baseline at Week 12 under placebo (placebo response).

In addition, the treatment effect at each time point was summarized by presenting posterior mean and 2-sided 80% credible interval based on the fitted model.

Secondary endpoints:

ACQ-5 and all daily collected measurements (morning and evening PEF, morning asthma symptoms score and evening asthma symptoms score) were analyzed using a similar methodology as for the primary endpoint.

Change from baseline in mean daily use of puffs of SABA over 12 weeks were analyzed using a Bayesian regression model. The non-missing data within that interval were used to calculate the mean value.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female adult patients aged ≥ 18 to ≤ 70 years at screening.
- Patients must weigh at least 40 kg to participate in the study, and must have a body mass index (BMI) <35 kg/m2. BMI = Body weight (kg) / [Height (m)]2 at screening
- Patients with a physician-diagnosed history of asthma (according to GINA 2018) for a period of at least 6 months prior to screening.
- Patients who have been treated with:

- Medium or high dose inhaled corticosteroids (ICS), or
- ICS plus long-acting beta agonist (LABA), or
- ICS plus leukotriene receptor antagonist (LTRA), or

- ICS plus long-acting beta agonist (LABA) and long lasting muscarinic antagonist (LAMA)
for at least 1 month prior to screening and on the same doses of the above mentioned medications over at least 2 weeks prior to start of the run-in period.
• Post-bronchodilator reversibility of FEV1 ≥ 12% and ≥ 200 mL at screening. If reversibility is not demonstrated at screening, then two additional attempts are permitted (one at the run-in visit and the last one during the run-in period between the run-in visit and baseline visit if needed)
• Spirometry with pre-bronchodilator FEV1 ≥ 40% of predicted (at screening and baseline) and ≤ 85% of predicted at the baseline visit.
• ACQ-5 score ≥ 1.5 at baseline visit
• ≥ 80% compliance with peak expiratory flow measurement and recording of symptoms in the eDiary during the run-in period.

Exclusion Criteria:
• Patients who have had an asthma exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit within 6 weeks prior to screening or during the screening period.
• Patients who have smoked or inhaled any substance other than asthma medications within the 6 month period prior to screening, or who have a smoking history of greater than 10 pack years (e.g. 10 pack years = 1 pack/day x 10 years or ½ pack/day x 20 years, etc.).
• History of life-threatening asthma event such as significant hypercarbia (pCO_2 > 45 mmHg), endotracheal intubation, non-invasive positive pressure ventilation (NIPPV), respiratory arrest, or seizure as a result of asthma.
• Patients with chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, clinically significant bronchiectasis, sarcoidosis, interstitial lung disease, cystic fibrosis, Churg-Strauss syndrome, allergic broncho-pulmonary aspergillosis, or clinically significant chronic lung diseases related to a history of tuberculosis or asbestosis.
• History or current diagnosis of ECG abnormalities indicating significant risk of safety for subjects participating in the study such as:

- Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
- History of familial long QT syndrome or known family history of Torsades de Pointes
- Resting heart rate (physical exam or 12 lead ECG) < 50 bpm at screening
- Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) at screening or inability to determine the QTcF interval
- Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of study

• At screening and/or run-in period, any severe, progressive or uncontrolled, acute or chronic, medical or psychiatric condition, or other factors such as abnormal vital signs, ECG or physical findings, or clinically relevant abnormal laboratory values, that in the judgment of the investigator may increase the risk associated with study participation/treatment or may interfere with interpretation of study results, and thus would make the patient inappropriate for entry into or continuing the study.

• Major surgery within 8 weeks prior to screening or surgery planned prior to end of study.

• History of live attenuated vaccine within 6 weeks prior to randomization or requirement to receive vaccinations at any time during the study.

• Hematology parameters at screening:

- Hemoglobin: < 10 g/dl
- Platelets: < 100 000/mm3
- White blood cells: < 3 000/mm3
- Neutrophils: < 1 500/mm3

• Significant bleeding risk or coagulation disorders.

• History of gastrointestinal bleeding, e.g. in association with use of Nonsteroidal Anti-Inflammatory Drug (NSAID).

• Requirement for anti-platelet or anticoagulant medication (e.g., warfarin, or clopidogrel or Novel Oral Anti-Coagulant (NOAC)) other than acetylsalicylic acid (up to 100 mg/d).

• History or presence of thrombotic or thromboembolic event, or increased risk for thrombotic or thromboembolic event.

Participant Flow Table

Overall Study

	LOU064	Placebo	Total
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally	
Started	47	29	76
PK analysis set	33	0	33
PD analysis set	47	29	76
Completed	35	19	54
Not Completed	12	10	22
Adverse Event	0	2	2
Study terminated by sponsor	12	7	19
Subject decision	0	1	1

Baseline Characteristics

	LOU064	Placebo	Total
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally	
Number of Participants [units: participants]	47	29	76
Age Continuous (units: years) Mean ± Standard Deviation			
	49.2±10.96	53.2±10.40	50.7±10.85
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)			
Female	28	22	50
Male	19	7	26
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)			
Caucasian	42	27	69
Black	4	2	6
Asian	1	0	1

Primary Outcome Result(s)

Change from baseline in pre-dose FEV1 at Week 12

(Time Frame: Baseline, Week 12)

	LOU064	Placebo
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	32	20
Change from baseline in pre-dose FEV1 at Week 12 (units: liters) Mean ± Standard Deviation		
	0.105 ± 0.0494	0.075 ± 0.0497

Statistical Analysis

Groups	LOU064, Placebo	
P Value	0.6643	Probability LOU064 better than placebo
Method	Other Bayesian model for repeated measures	
Mean Difference (Net)	0.030	Posterior mean difference (LOU064 - placebo) and 80% credible interval are presented.
Standard Deviation	0.0698	
80 % Confidence Interval 2-Sided	-0.060 to 0.119	

Secondary Outcome Result(s)

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

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours after dosing on Days 15 and 85)

	LOU064	Placebo
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	33	0
Maximum observed blood concentrations (Cmax) of LOU064 at steady state (units: ng/mL) Mean ± Standard Deviation		
Day 15 (n=32, 0)	239 ± 152	
Day 85 (n=22, 0)	222 ± 142	

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

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours after dosing on Days 15 and 85)

	LOU064	Placebo
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	33	0
Time to reach maximum blood concentrations (Tmax) of LOU064 at steady state (units: hours (hr)) Median (Full Range)		
Day 15 (n=32, 0)	1.00 (0.483 to 2.00)	

Day 85 (n=22, 0)	1.00 (0.500 to 3.00)

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

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours after dosing on Days 15 and 85)

	LOU064	Placebo
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	33	0
Area under the concentration-time curve from time zero to 24 hours (AUC0-24h) of LOU064 at steady state (units: hr*ng/mL) Mean ± Standard Deviation		
Day 15 (n=21, 0)	471 ± 285	
Day 85 (n=16, 0)	517 ± 342	

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

(Time Frame: Baseline, Week 12)

	LOU064	Placebo
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	33	20
Change from baseline in Asthma Symptom Questionnaire-5 score (ACQ-5) at Week 12 (units: score on scale) Mean ± Standard Deviation		

	-0.95 ± 0.133	-0.86 ± 0.164

Statistical Analysis

Groups	LOU064, Placebo	
P Value	0.6609	Probability LOU064 better than placebo
Method	Other Bayesian model for repeated measures	
Median Difference (Net)	-0.09	Posterior mean difference (LOU064 - placebo) and 80% credible interval are presented.
Standard Deviation	0.210	
80 % Confidence Interval 2-Sided	-0.35 to 0.18	

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

(Time Frame: Baseline, Weeks 9-12)

	LOU064	**Placebo**
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	47	29
Change from baseline in mean morning and mean evening Peak Expiratory Flow (PEF) (units: liters/minute) Mean ± Standard Deviation		

Change from baseline in mean morning PEF (n=29, 18)	-2.4 ± 4.30	-2.6 ± 5.59
Change from baseline in mean evening PEF (n=28, 18)	-9.7 ± 5.58	-6.3 ± 7.23

Statistical Analysis

Groups	LOU064, Placebo	Change from baseline in mean morning PEF
P Value	0.5107	Probability LOU064 better than placebo
Method	Other Bayesian model for repeated measures	
Mean Difference (Net)	0.1	Posterior mean difference (LOU064 - placebo) and 80% credible interval are presented.
Standard Deviation	7.13	
80 % Confidence Interval 2-Sided	-9.0 to 9.1	

Statistical Analysis

Groups	LOU064, Placebo	Change from baseline in mean evening PEF
P Value	0.3611	Probability LOU064 better than placebo
Method	Other Bayesian model for repeated measures	
Mean Difference (Net)	-3.4	Posterior mean difference (LOU064 - placebo) and

		80% credible interval are presented.
Standard Deviation	9.15	
80 % Confidence Interval 2-Sided	-15.2 to 8.1	

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

(Time Frame: Baseline, 12 weeks)

	LOU064	Placebo
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	41	26
Change from baseline in number of puffs of SABA taken per day during the treatment period (units: puffs of SABA) Mean ± Standard Deviation		
	-0.192 ± 0.0946	-0.059 ± 0.1224

Statistical Analysis

Groups	LOU064, Placebo	
P Value	0.8022	Probability LOU064 better than placebo
Method	Other Bayesian model	
Mean Difference (Net)	-0.133	Posterior mean difference (LOU064 - placebo) and 80% credible interval are presented.

Standard Deviation	0.1588
80 % Confidence Interval 2-Sided	-0.336 to 0.071

Change from baseline in daytime and nighttime asthma symptom score

(Time Frame: Baseline, Weeks 9-12)

	LOU064	Placebo
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Number of Participants Analyzed [units: participants]	34	20
Change from baseline in daytime and nighttime asthma symptom score (units: score on scale) Mean ± Standard Deviation		
Change from baseline in daytime asthma symptom score	-0.225 ± 0.0962	-0.175 ± 0.1237
Change from baseline in nighttime asthma symptom score	-0.120 ± 0.0488	-0.195 ± 0.0651

Statistical Analysis

Groups	LOU064, Placebo	Change from baseline in daytime asthma symptom score
P Value	0.6312	Probability LOU064 better than placebo
Method	Other Bayesian model for repeated measures	
Mean Difference (Net)	-0.050	Posterior mean difference (LOU064 - placebo) and

		80% credible interval are presented.
Standard Deviation	0.1573	
80 % Confidence Interval 2-Sided	-0.251 to 0.149	

Statistical Analysis

Groups	LOU064, Placebo	Change from baseline in nighttime asthma symptom score
P Value	0.1752	Probability LOU064 better than placebo
Method	Other Bayesian model for repeated measures	
Mean Difference (Net)	0.075	Posterior mean difference (LOU064 - placebo) and 80% credible interval are presented.
Standard Deviation	0.0819	
80 % Confidence Interval 2-Sided	-0.028 to 0.180	

Safety Results

All-Cause Mortality

	LOU064 N = 47	Placebo N = 29
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

No serious adverse events were reported throughout the study.

Other Adverse Events by System Organ Class

Time Frame	From first dose of study treatment until last dose of study treatment plus 30 days post treatment, up to Day 115.
Additional Description	Any sign or symptom that occurs during the study treatment plus 30 days post treatment.
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LOU064 N = 47	Placebo N = 29
Arm/Group Description	LOU064 100 mg once daily orally	Placebo once daily orally
Total participants affected	8 (17.02%)	10 (34.48%)
Infections and infestations		
Nasopharyngitis	4 (8.51%)	6 (20.69%)
Upper respiratory tract infection	4 (8.51%)	4 (13.79%)
Respiratory, thoracic and mediastinal disorders		
Asthma	0 (0.00%)	2 (6.90%)

Conclusion:

In conclusion, LOU064 was safe and well-tolerated in the asthma population studied.

Whilst numerical trends were seen in the primary endpoint of FEV1 and ACQ-5, no clear evidence of a relevant and robust effect was detected after treatment with LOU064.

Date of Clinical Trial Report

15-Feb-2021