Sponsor

Novartis Pharmaceuticals

Generic Drug Name

LOU064

Trial Indication(s)

Healthy Volunteers (Part 1 – 5) and Atopic dermatitis (Part 6)

Protocol Number

CLOU064X2101

Protocol Title

A 6-part first-in-human study of LOU064 consisting of a 4-part randomized, double-blind, placebo-controlled SAD and MAD study to investigate the safety and tolerability in healthy volunteers, subjects with atopic diathesis and subjects with atopic dermatitis, an open-label food effect study and a double-blind formulation effect study in healthy volunteers.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

Study initiation date: 18-Aug-2016
Primary completion date: 27-Jan-2020
Study completion date: 27-Jan-2020

Study Design/Methodology

This was a non-confirmatory 6-part first-in-human study in healthy volunteers (Parts 1-5) and patients with atopic dermatitis (AD) (Part 6).

- Part 1 was a double-blind, placebo-controlled single ascending dose (SAD) escalation study of 10 cohorts.
- Part 2 was a double-blind, placebo-controlled multiple ascending dose (MAD) (13 doses over 12 days) escalation study, employing once daily dosing in 6 cohorts in healthy volunteers with asymptomatic atopic diathesis.
- Part 3 was a single dose open-label crossover food effect study in HVs.
- Part 4 was a double-blind, placebo-controlled multiple dose (25 doses over 12 days) study employing twice daily dosing in 2 cohorts of healthy volunteers with asymptomatic atopic diathesis.
- Part 5 was a double-blind single dose, crossover formulation effect study in HVs.
- Part 6 was a double-blind, randomized, placebo-controlled 4-week multiple dose study employing a dose of 100mg LOU064 twice daily in subjects with AD.

The SAD part (Part 1) had ten dose levels and the MAD parts (Parts 2 & 4) consisted of eight dose levels (6 cohorts using single daily dosing in Part 2 and 2 cohorts using twice daily dosing in Part 4). Subjects were randomized into each cohort to receive either LOU064 or matching placebo in a 6:2 (active: placebo) ratio in the SAD and MAD parts. Within the SAD part, doses up to approximately 4 times the estimated pharmacologically active dose (PAD) were to be evaluated before the MAD part of the study was started, providing there was no safety signal emerging from the SAD part until then. The total daily dose of LOU064 used in Part 2 (MAD qd regimen) and Part 4 (Multiple dose bid regimen) did not exceed the highest SAD dose level explored. Moreover, the total daily dose of Part 4 did not exceed the total daily dose of Part 2. In Part 1 (SAD) sentinel dosing was to take place for the first administration at each dose level as follows. The first two subjects were dosed on the first day (one with active drug, one with placebo). After a 48-hour observation period the remaining subjects of the cohort were dosed. Standard safety monitoring was used throughout all study parts. All adverse events, and laboratory safety parameters (blood chemistry, hematology and urinalysis) up to 96 hours post last dose as well as PK data from the previous dose group (if available) up to 48 hours post last dose were to be reviewed in a blinded fashion for each cohort before dose escalation.

In Parts 1, 2 and 4, each subject participated in a 28-day Screening period (Days -29 to -2), a Baseline period, a Treatment period and a Follow-up period that included an End-of-Study evaluation. In Part 1, subjects were admitted to the study site on Day -2 or -1 for baseline safety assessments and to confirm eligibility. Eligible subjects received a single dose of LOU064 or placebo under fasting conditions on Day 1. They were domiciled from Day -1 to the morning of Day 5 (96 hours post last drug administration). In Parts 2 and 4, subjects were

admitted on Day -2 or -1 for baseline safety assessments and to confirm eligibility. Eligible subjects received the first dose of LOU064 under fasting conditions on Day 1, and continued to take study medication under fasting conditions up to and including Day 12. Subjects were domiciled from Day -2 or -1 until the morning of Day 16, which equals 96 hours after the last dose of LOU064 was received. In Parts 2 and 4, the study medication was given once daily and twice daily respectively (details are found in the schedule of assessments).

Part 3 was an open-label, randomized, two-way cross-over, single dose study to assess food effects. In Part 3, each subject participated in a 28 day screening period (Day -29 to -2), 2 baseline (Day -1) and 2 treatment periods, each consisting of a single dose administration on Day 1 followed by safety and PK assessment up to Day 5. Treatment period 2 consisted of a follow-up visit and an end of study evaluation on Day 22 and 40, respectively.

In Part 5 each subject participated in a (maximum) 28 day screening period (Day -29 to -2), two baseline visits and two treatment periods, each consisting of a single dose administration of an either wet-media milled or micronized drug substance formulation in a cross-over design followed by safety, PK and PD follow up assessments up to 1 week after dosing.

In Part 6 subjects participated in a 6-week screening period (Days -43 to -1), a baseline visit, a 4-week treatment period and a 3-week follow-up period which included an end of study evaluation. Subjects were admitted on Day -1 for Baseline assessments and to confirm eligibility. Eligible subjects received the first dose of LOU064 under fasting conditions in the clinic in the morning of Day 1, followed by a second dose in the evening of Day 1 and were discharged from the clinic on Day 2 after receiving the 3rd dose and with sufficient study medication to be taken at home twice daily until the next clinic visit. Subjects returned to the clinic at weekly intervals on an outpatient basis for assessments on study days 8, 15 and 22. Subjects were domiciled prior to the morning dose on Day 29, which was the last dose of the treatment schedule (i.e. no evening dose on Day 29) for a second 24-h PK assessment.

Centers

2 centers in 2 countries: Germany (1) for Parts 1-5, Netherlands (1) for Part 6

Objectives:

Primary objective(s)

To assess the safety and tolerability of single and multiple ascending oral doses of LOU064 (all parts).

Secondary objective(s)

- Parts 1, 2 & 4: To assess the blood PK of single and multiple doses of LOU064 in healthy volunteers and atopic subjects.
- Part 3: To assess the blood PK of a single dose of LOU064 under fed and fasted conditions in healthy volunteers.
- Part 5: To compare the single dose blood PK of LOU064 after oral dosing of the CSF capsule containing either wet-media milled or micronized drug substance in healthy volunteers.
- Part 6: To assess the blood PK of single and multiple doses of LOU064 in subjects with atopic dermatitis (AD).

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

LOU064 or matching placebo was administered orally as a single dose in Part 1, multiple oral doses in Part 2 (13 doses over 12 days) and Part 4 (25 doses over 12 days). Single oral dose was administered in each period of Parts 3 and 5. Multiple oral doses of 100 mg LOU064 or matching placebo was administered in Part 6.

Statistical Methods

Part 1 to 5:

All information obtained on AEs was displayed by study purpose (SAD, MAD, food effect, formulation effect), treatment/treatment sequence and subject. The number and percentages of subjects with AEs were tabulated by body system and preferred term with a breakdown by treatment and also by body system, preferred term and maximum severity with a breakdown by treatment for each study purpose. Data from subjects receiving placebo were pooled within each part of the study. A subject with multiple AEs within a body system was only counted once towards the total of the body system and treatment.

Pharmacokinetic parameters were listed by study purpose, treatment and subject

Part 6:

All information obtained on AEs was displayed by study treatment and subject. The number and percentages of subjects with AEs were tabulated by body system and preferred term with a breakdown by treatment and by body system, preferred term and maximum severity with a breakdown by treatment. A subject with multiple AEs within a body system was only counted once towards the total of the body system and treatment.

LOU064 concentration data were listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics were provided for blood PK parameters.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria (All parts)

- Male and female healthy subjects with an age range between 18 and 65 years (inclusive), and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
- Healthy subjects participated in Part 2 or Part 4 with atopic diathesis with a positive skin prick test to a known allergen at screening (atopic diathesis) but were clinically asymptomatic and did not require any systemic medication for these specific study portions.

Additional key inclusion criteria (Part 6 only)

- Male and female healthy subjects with an age range between 18 and 65 years (inclusive) with AD according to the American Academy of Dermatology Consensus Criteria, that had been present for at least 1 year before the baseline visit and defined as:
    - Eczema Area and Severity Index (EASI) ≥ 12 at screening and baseline
    - IGA (Investigator's Global Assessment) ≥2 on a 5-point scale at screening and baseline
    - BSA (Body Surface Area) involvement ≥ 8% at screening and baseline
    - Subjects have applied a stable dose of bland topical emollient at least twice daily for at least 7 consecutive days immediately before the baseline visit

- Subjects were required to weigh at least 50 kg with a body mass index (BMI) within the range of 18-35 kg/m2 (inclusive).

Key exclusion criteria

- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
- History of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening and/or pre-treatment:
    - PR > 200 msec
    - QRS complex > 120 msec
    - QTcF > 450 msec (males)
    - QTcF > 460 msec (females)

- Hemoglobin levels below 12.0 g/dL at screening or first baseline.
- Platelet count outside of the normal range (below 150 x 109/L or above 450 x 109) at screening or first baseline.
- Any clinically significant abnormalities in any of the standard coagulation tests including the prothrombin time (PT), partial thromboplastin time (PTT), or International Normalized Ratio (INR) at screening and/or baseline.
- History or presence of thrombotic or thromboembolic event, or increased risk for thrombotic or thromboembolic event.
- Sexually active males unwilling to use a condom from the time of consent until 7 days after stopping study medication. A condom is required for all sexually active male participants even vasectomized men to prevent them from fathering a child and to prevent delivery of the drug via seminal fluid to their partner.
- For topical treatments in Part 6, the following rules were considered:
    - Topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) were to be stopped 1 week prior to randomization to allow an adequate washout-period.
    - Other topical treatments for AD such as crisaborole, tar etc. and prescription moisturizers or moisturizers containing ingredients such as ceramides, lactic acid, urea, α-hydroxy- or fruit acids, vitamins A, D or E were to be discontinued during the 4-week treatment period.
    - Phototherapy or tanning booth treatment was stopped 4 weeks prior to baseline.

Participant Flow Table

Part 1 (Safety analysis set) SAD - Subject disposition - n (percent) of subjects

Epoch: Treatment	LOU064												
	0.5 mg N=6 n (%)	1.5 mg N=6 n (%)	5 mg N=6 n (%)	15 mg N=6 n (%)	30 mg N=6 n (%)	60 mg N=6 n (%)	100 mg N=6 n (%)	200 mg N=6 n (%)	400 mg N=6 n (%)	600 mg N=6 n (%)	All N=60 n (%)	Placebo (SAD) N=20 n (%)	Total N=80 n (%)
Subjects													
Completed	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	60 (100.0)	20 (100.0)	80 (100.0)

Parts 2 and 4 (Safety analysis set) MAD - Subject disposition - n (percent) of subjects

Epoch: Treatment	LOU064										
	10 mg qd N=6 n (%)	25 mg qd N=6 n (%)	50 mg qd N=6 n (%)	100 mg qd N=6 n (%)	400 mg qd N=6 n (%)	100 mg bid N=6 n (%)	200 mg bid N=6 n (%)	600 mg qd N=6 n (%)	All N=48 n (%)	Placebo (MAD) N=16 n (%)	Total N=64 n (%)
Subjects											
Completed	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	48 (100.0)	16 (100.0)	64 (100.0)

Part 3 (Safety analysis set) Food effect - Subject disposition - n (percent) of subjects

Epoch: Treatment	LOU064 60 mg		
	fed / fasted N=6 n (%)	fasted / fed N=6 n (%)	Total N=12 n (%)
Subjects			
Completed	6 (100.0)	6 (100.0)	12 (100.0)

Part 5 (Safety analysis set) Formulation effect - Subject disposition - n (percent) of subjects

Epoch: Treatment	LOU064 50 mg		
	Wet-media milled / Micronized N=6 n (%)	Micronized / Wet-media milled N=7 n (%)	Total N=13 n (%)
Subjects			
Completed	6 (100.0)	6 (85.7)	12 (92.3)
Discontinued	0 (0.0)	1 (14.3)	1 (7.7)
Main cause of discontinuation			
Subject/Guardian Decision	0 (0.0)	1 (14.3)	1 (7.7)

Part 6 (All subjects) 4-week treatment cohort - Subject disposition – n (percent) of subjects

	LOU064 100 mg bid N=13 n (%)	Placebo N=4 n (%)	Total N=17 n (%)
Epoch: Baseline			
Subjects			
Randomized	13 (100.0)	4 (100.0)	17 (100.0)
Exposed	12 (92.3)	4 (100.0)	16 (94.1)
Completed	12 (92.3)	4 (100.0)	16 (94.1)
Discontinued	1 (7.7)	0 (0.0)	1 (5.9)
Main cause of discontinuation			
Subject/Guardian Decision	1 (7.7)	0 (0.0)	1 (5.9)

	LOU064 100 mg bid N=12 n (%)	Placebo N=4 n (%)	Total N=16 n (%)
Epoch: Treatment			
Subjects			
Randomized	12 (100.0)	4 (100.0)	16 (100.0)
Exposed	12 (100.0)	4 (100.0)	16 (100.0)
Completed	9 (75.0)	4 (100.0)	13 (81.3)
Discontinued	3 (25.0)	0 (0.0)	3 (18.8)
Main cause of discontinuation			
Physician Decision	3 (25.0)	0 (0.0)	3 (18.8)

Baseline Characteristics

Part 1 (Safety analysis set) SAD - Subject demographics by treatment group

		LOU064					
		0.5 mg N=6	1.5 mg N=6	5 mg N=6	15 mg N=6	30 mg N=6	60 mg N=6
Age (years)	Mean (SD)	44.2 (12.80)	47.0 (11.66)	51.7 (12.21)	52.0 (7.92)	50.5 (11.41)	50.3 (10.98)
	Median	46.0	48.0	56.5	53.0	54.5	52.5
	Range	[29,58]	[26,59]	[34,64]	[39,62]	[31,61]	[29,61]
Sex - n (%)	Male	5 (83.3)	5 (83.3)	3 (50.0)	5 (83.3)	4 (66.7)	4 (66.7)
	Female	1 (16.7)	1 (16.7)	3 (50.0)	1 (16.7)	2 (33.3)	2 (33.3)
Race - n (%)	White	6 (100.0)	5 (83.3)	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)
	Asian	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)

		LOU064						
		100 mg N=6	200 mg N=6	400 mg N=6	600 mg N=6	All N=60	Placebo (SAD) N=20	Total N=80
Age (years)	Mean (SD)	45.7 (10.73)	47.7 (11.86)	47.2 (10.03)	44.7 (15.82)	48.1 (11.12)	45.7 (12.74)	47.5 (11.51)
	Median	48.0	50.5	48.5	47.5	51.0	46.0	50.5
	Range	[25,56]	[28,61]	[32,57]	[18,61]	[18,64]	[22,63]	[18,64]
Sex - n (%)	Male	5 (83.3)	4 (66.7)	4 (66.7)	5 (83.3)	44 (73.3)	15 (75.0)	59 (73.8)
	Female	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	16 (26.7)	5 (25.0)	21 (26.3)
Race - n (%)	White	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	58 (96.7)	20 (100.0)	78 (97.5)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	2 (2.5)

Parts 2 and 4 (Safety analysis set) MAD - Subject demographics by treatment group

		LOU064				
		10 mg qd N=6	25 mg qd N=6	50 mg qd N=6	100 mg qd N=6	400 mg qd N=6
Age (years)	Mean (SD)	39.5 (17.42)	40.5 (14.94)	30.2 (4.92)	30.7 (5.89)	42.7 (10.65)
	Median	31.5	35.0	30.5	29.5	41.0
	Range	[23,63]	[25,60]	[24,38]	[25,40]	[30,57]
Sex - n (%)	Male	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)
	Female	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Race - n (%)	White	6 (100.0)	6 (100.0)	5 (83.3)	6 (100.0)	6 (100.0)
	Asian	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)

		LOU064					
		100 mg bid N=6	200 mg bid N=6	600 mg qd N=6	All N=48	Placebo (MAD) N=16	Total N=64
Age (years)	Mean (SD)	51.5 (8.76)	42.5 (9.83)	47.0 (11.58)	40.6 (12.45)	43.3 (13.82)	41.3 (12.75)
	Median	53.0	42.0	48.0	37.0	46.5	38.0
	Range	[35,59]	[30,57]	[28,62]	[23,63]	[23,59]	[23,63]
Sex - n (%)	Male	6 (100.0)	6 (100.0)	6 (100.0)	47 (97.9)	12 (75.0)	59 (92.2)
	Female	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	4 (25.0)	5 (7.8)
Race - n (%)	White	6 (100.0)	6 (100.0)	6 (100.0)	47 (97.9)	16 (100.0)	63 (98.4)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)

Part 3 (Safety analysis set) Food effect - Subject demographics by treatment sequence

		LOU064 60 mg		
		fed / fasted N=6	fasted / fed N=6	Total N=12
Age (years)	Mean (SD)	41.2 (11.34)	41.7 (19.36)	41.4 (15.13)
	Median	39.0	39.0	39.0
	Range	[30,62]	[22,65]	[22,65]
Sex - n (%)	Male	5 (83.3)	4 (66.7)	9 (75.0)
	Female	1 (16.7)	2 (33.3)	3 (25.0)
Race - n (%)	White	5 (83.3)	5 (83.3)	10 (83.3)
	Black or African American	1 (16.7)	0 (0.0)	1 (8.3)
	Asian	0 (0.0)	1 (16.7)	1 (8.3)

Part 5 (Safety analysis set) Formulation effect - Subject demographics by treatment sequence

		LOU064 50 mg		
		Wet-media milled / Micronized N=6	Micronized / Wet-media milled N=7	Total N=13
Age (years)	Mean (SD)	46.3 (16.17)	44.1 (15.04)	45.2 (14.94)
	Median	48.0	44.0	44.0
	Range	[22,62]	[20,60]	[20,62]
Sex - n (%)	Male	5 (83.3)	5 (71.4)	10 (76.9)
	Female	1 (16.7)	2 (28.6)	3 (23.1)
Race - n (%)	White	6 (100.0)	7 (100.0)	13 (100.0)

Part 6 (Safety analysis set) 4-week treatment cohort - Subject demographics by treatment group

		LOU064 100 mg bid N=12	Placebo N=4	Total N=16
Age (years)	Mean (SD)	25.2 (6.53)	23.5 (2.65)	24.8 (5.77)
	Median	24.0	23.0	23.0
	Range	[19,42]	[21,27]	[19,42]
Sex - n (%)	Male	5 (41.7)	3 (75.0)	8 (50.0)
	Female	7 (58.3)	1 (25.0)	8 (50.0)
Race - n (%)	White	11 (91.7)	2 (50.0)	13 (81.3)
	Asian	1 (8.3)	0 (0.0)	1 (6.3)
	Other	0 (0.0)	2 (50.0)	2 (12.5)

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Part 1 (PK analysis set) SAD - Summary statistics of PK parameter values

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood					
	LOU064				
PK parameter (unit)	0.5 mg N=6	1.5 mg N=6	5 mg N=6	15 mg N=6	30 mg N=6
Cmax (ng/mL)	0 ± 0 (NA)	1.26 ± 1.12 (89.0)	5.86 ± 3.37 (57.5)	24.8 ± 14.6 (59.1)	64.8 ± 34.3 (52.9)
	0 (0-0) [6]	1.33 (0-2.80) [6]	5.99 (1.19-9.92) [6]	26.6 (6.39-39.6) [6]	55.1 (19.9-112) [6]
Tmax (h)		0.500 (0.500-0.500) [4]	0.525 (0.500-1.02) [6]	0.500 (0.483-1.02) [6]	0.500 (0.483-3.00) [6]
AUClast (h*ng/mL)	0 ± 0 (NA)	0.315 ± 0.280 (89.0)	2.77 ± 1.89 (68.5)	25.1 ± 25.7 (102.0)	75.1 ± 45.9 (61.1)
	0 (0-0) [6]	0.333 (0-0.700) [6]	2.28 (0.882-5.87) [6]	17.5 (4.01-74.7) [6]	71.4 (31.0-153) [6]
AUCinf (h*ng/mL)				41.3 ± 30.8 (74.7)	77.5 ± 45.9 (59.3)
				29.3 (18.2-76.3) [3]	75.0 (32.1-154) [6]
T1/2 (h)				0.557 (0.367-0.915) [3]	0.908 (0.415-1.40) [6]
Vz/F (L)				397 ± 229 (57.5)	617 ± 276 (44.8)
				271 (260-661) [3]	606 (234-1070) [6]
CL/F (L/h)				511 ± 313 (61.3)	523 ± 303 (57.9)
				513 (197-823) [3]	423 (195-934) [6]
MRT (h)		0.500 ± 0 (0.0)	0.618 ± 0.0935 (15.1)	0.981 ± 0.460 (46.9)	1.46 ± 0.825 (56.6)
		0.500 (0.500-0.500) [4]	0.636 (0.500-0.738) [6]	0.827 (0.598-1.88) [6]	1.27 (0.691-3.07) [6]

Statistics are Mean ± SD (CV%)
Median (Min-Max) [n]
CV% = Coefficient of variation (%) = SD/Mean*100
For Tmax and T1/2, only Median (Min-Max) [n] are presented

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood					
	LOU064				
PK parameter (unit)	60 mg N=6	100 mg N=6	200 mg N=6	400 mg N=6	600 mg N=6
Cmax (ng/mL)	138 ± 65.3 (47.2)	141 ± 85.7 (60.6)	245 ± 147 (60.1)	432 ± 334 (77.3)	511 ± 225 (44.2)
	150 (22.8-215) [6]	133 (44.7-298) [6]	201 (97.1-449) [6]	331 (193-1070) [6]	500 (240-763) [6]
Tmax (h)	1.01 (1.00-1.50) [6]	1.03 (1.00-1.50) [6]	1.25 (0.983-3.00) [6]	1.24 (0.950-2.00) [6]	1.02 (1.00-1.52) [6]
AUClast (h*ng/mL)	206 ± 118 (57.1)	269 ± 124 (46.1)	624 ± 302 (48.4)	1060 ± 937 (88.4)	1160 ± 356 (30.8)
	229 (26.0-355) [6]	254 (115-491) [6]	471 (401-1100) [6]	739 (438-2910) [6]	1250 (724-1610) [6]
AUCinf (h*ng/mL)	245 ± 87.6 (35.8)	333 ± 143 (42.8)	693 ± 330 (47.6)	1080 ± 935 (86.4)	1180 ± 403 (34.3)
	245 (120-358) [5]	285 (221-494) [3]	544 (407-1100) [5]	769 (443-2930) [6]	1250 (754-1700) [5]
T1/2 (h)	1.03 (0.891-1.28) [5]	0.905 (0.722-1.33) [3]	3.22 (1.34-28.4) [5]	11.4 (2.47-17.1) [6]	14.1 (12.3-34.4) [5]
Vz/F (L)	430 ± 183 (42.6)	469 ± 204 (43.5)	3710 ± 3620 (97.6)	8260 ± 6300 (76.2)	14800 ± 6310 (42.7)
	356 (303-743) [5]	471 (264-672) [3]	2280 (433-8260) [5]	6490 (2070-18500) [6]	14100 (8760-24100) [5]
CL/F (L/h)	280 ± 130 (46.2)	335 ± 126 (37.5)	343 ± 147 (42.7)	543 ± 279 (51.3)	564 ± 200 (35.5)
	245 (167-501) [5]	351 (203-452) [3]	368 (181-492) [5]	544 (136-902) [6]	479 (353-796) [5]
MRT (h)	1.76 ± 0.295 (16.8)	2.84 ± 0.974 (34.3)	3.62 ± 1.42 (39.2)	3.76 ± 0.828 (22.0)	5.80 ± 1.39 (23.9)
	1.72 (1.47-2.30) [6]	2.87 (1.79-3.91) [6]	3.61 (1.80-5.84) [6]	4.04 (2.17-4.40) [6]	6.14 (3.89-7.09) [6]

Statistics are Mean ± SD (CV%)
Median (Min-Max) [n]
CV% = Coefficient of variation (%) = SD/Mean*100
For Tmax and T1/2, only Median (Min-Max) [n] are presented

Part 2 (PK analysis set) MAD qd - Summary statistics of PK parameter values – Day 1

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood and Urine
Profile: Day 1

PK parameter (unit)	LOU064 10 mg qd N=6	25 mg qd N=6	50 mg qd N=6	100 mg qd N=6	400 mg qd N=6	600 mg qd N=6
Cmax (ng/mL)	8.40 ± 2.02 (24.1)	40.9 ± 21.6 (52.9)	76.5 ± 22.0 (28.8)	187 ± 85.0 (45.4)	518 ± 89.1 (17.2)	550 ± 87.6 (15.9)
	8.03 (6.36-11.4) [6]	37.3 (14.1-80.4) [6]	70.1 (47.3-107) [6]	189 (75.6-285) [6]	513 (383-622) [6]	545 (461-691) [6]
Tmax (h)	0.517 (0.500-1.00) [6]	0.875 (0.283-1.50) [6]	0.500 (0.483-2.00) [6]	0.742 (0.500-1.95) [6]	0.750 (0.500-1.50) [6]	0.750 (0.500-3.00) [6]
AUClast (h*ng/mL)	4.17 ± 1.38 (33.0)	43.9 ± 24.6 (56.2)	113 ± 34.2 (30.3)	311 ± 89.1 (28.6)	973 ± 379 (39.0)	1080 ± 377 (35.1)
	4.40 (1.79-5.62) [6]	45.5 (15.3-78.5) [6]	103 (81.9-154) [6]	333 (168-416) [6]	826 (694-1720) [6]	931 (699-1700) [6]
AUC0-24 (h*ng/mL)	4.94 ± 1.35 (27.2)	44.9 ± 25.2 (56.0)	116 ± 32.9 (28.4)	315 ± 91.5 (29.0)	977 ± 378 (38.7)	1080 ± 377 (35.0)
	4.94 (3.99-5.89) [2]	46.6 (15.6-79.7) [6]	107 (84.0-155) [6]	338 (168-419) [6]	826 (702-1720) [6]	932 (700-1700) [6]
MRT (h)	0.761 ± 0.151 (19.8)	1.18 ± 0.490 (41.6)	2.53 ± 1.17 (46.4)	2.79 ± 1.28 (45.7)	3.02 ± 1.11 (36.8)	3.14 ± 0.580 (18.5)
	0.766 (0.548-0.956) [6]	1.17 (0.460-1.87) [6]	2.44 (1.17-4.65) [6]	2.16 (1.65-4.62) [6]	2.94 (1.64-4.98) [6]	3.22 (2.31-3.96) [6]

Statistics are Mean ± SD (CV%)
Median (Min-Max) [n]
CV% = Coefficient of variation (%) = SD/Mean*100
For Tmax and T1/2, only Median (Min-Max) [n] are presented

Part 2 (PK analysis set) MAD qd - Summary statistics of PK parameter values – Day 2

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood and Urine
Profile: Day 2

PK parameter (unit)	LOU064 10 mg qd N=6	25 mg qd N=6	50 mg qd N=6	100 mg qd N=6	400 mg qd N=6	600 mg qd N=6
Amount recovered (mg)	0.0110 ± 0.0105 (95.8)	0.0539 ± 0.0412 (76.4)	0.122 ± 0.0270 (22.2)	0.335 ± 0.161 (48.0)	0.903 ± 0.486 (53.8)	1.27 ± 0.881 (69.3)
	0.00738 (0-0.0289) [6]	0.0393 (0.0177-0.132) [6]	0.112 (0.0945-0.165) [5]	0.310 (0.161-0.593) [6]	0.734 (0.335-1.51) [6]	1.08 (0.277-2.73) [6]
Percent recovered (%)	0.110 ± 0.105 (95.8)	0.216 ± 0.165 (76.4)	0.244 ± 0.0540 (22.2)	0.335 ± 0.161 (48.0)	0.226 ± 0.121 (53.8)	0.212 ± 0.147 (69.3)
	0.0738 (0-0.289) [6]	0.157 (0.0709-0.528) [6]	0.224 (0.189-0.329) [5]	0.310 (0.161-0.593) [6]	0.184 (0.0837-0.378) [6]	0.179 (0.0461-0.456) [6]

Statistics are Mean ± SD (CV%)
Median (Min-Max) [n]
CV% = Coefficient of variation (%) = SD/Mean*100
For Tmax and T1/2, only Median (Min-Max) [n] are presented

Part 2 (PK analysis set) MAD qd - Summary statistics of PK parameter values – Day 12

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood and Urine
Profile: Day 12

PK parameter (unit)	LOU064 10 mg qd N=6	25 mg qd N=6	50 mg qd N=6	100 mg qd N=6	400 mg qd N=6	600 mg qd N=6
Cmax (ng/mL)	18.2 ± 5.90 (32.4)	85.9 ± 31.5 (36.6)	102 ± 22.0 (21.6)	233 ± 84.1 (36.1)	551 ± 263 (47.7)	563 ± 229 (40.6)
	17.2 (11.8-26.4) [6]	78.4 (43.9-126) [6]	100 (73.3-131) [6]	205 (167-386) [6]	476 (260-928) [6]	475 (377-985) [6]
Tmax (h)	0.625 (0.500-1.00) [6]	0.750 (0.500-1.00) [6]	1.00 (0.533-1.50) [6]	0.867 (0.733-1.50) [6]	0.758 (0.700-1.50) [6]	0.883 (0.500-3.00) [6]
AUClast (h*ng/mL)	22.9 ± 3.50 (15.3)	114 ± 59.7 (52.3)	207 ± 80.4 (38.9)	488 ± 172 (35.3)	1300 ± 602 (46.3)	1240 ± 341 (27.5)
	22.4 (18.3-28.2) [6]	98.2 (30.1-190) [6]	179 (126-323) [6]	444 (336-770) [6]	1180 (650-2310) [6]	1070 (953-1740) [6]
AUCinf (h*ng/mL)	24.7 ± 3.65 (14.8)	117 ± 60.4 (51.5)	209 ± 80.0 (38.2)	577 ± 207 (35.9)	1330 ± 608 (45.8)	1260 ± 338 (26.8)
	24.3 (19.6-29.9) [6]	102 (31.7-194) [6]	181 (127-325) [6]	595 (361-774) [3]	1210 (665-2330) [6]	1090 (994-1760) [6]
	24.0 ± 3.60 (15.0)	117 ± 60.9 (52.2)	209 ± 80.2 (38.4)	485 ± 179 (36.9)	1280 ± 577 (45.3)	1230 ± 356 (29.0)

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood and Urine
Profile: Day 12

PK parameter (unit)	LOU064 10 mg qd N=6	25 mg qd N=6	50 mg qd N=6	100 mg qd N=6	400 mg qd N=6	600 mg qd N=6
AUC0-24 (h*ng/mL)	23.6 (18.9-29.3) [6]	101 (30.9-194) [6]	181 (127-325) [6]	429 (336-774) [6]	1140 (677-2270) [6]	1060 (908-1740) [6]
T1/2 (h)	0.961 (0.667-1.21) [6]	1.15 (0.680-1.33) [6]	1.15 (0.813-1.55) [6]	1.41 (1.41-11.9) [3]	8.51 (1.22-22.3) [6]	8.29 (4.69-17.3) [6]
Vss/F (L)	554 ± 90.4 (16.3)	407 ± 208 (51.1)	431 ± 172 (40.0)	1910 ± 2780 (145.9)	4400 ± 3340 (75.8)	7130 ± 5120 (71.9)
	562 (407-657) [6]	334 (247-793) [6]	346 (313-751) [6]	338 (264-5120) [3]	3440 (624-8820) [6]	7070 (2340-16500) [6]
CLss/F (L/h)	425 ± 64.8 (15.3)	307 ± 253 (82.5)	268 ± 92.8 (34.6)	198 ± 88.7 (44.8)	366 ± 150 (41.0)	521 ± 131 (25.1)
	423 (341-529) [6]	248 (129-809) [6]	276 (154-395) [6]	166 (129-298) [3]	351 (177-591) [6]	569 (345-661) [6]

Part 4 (PK analysis set) MAD bid - Summary statistics of PK parameter values – Day 1

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood and Urine
Profile: Day 1

PK parameter (unit)	LOU064 100 mg bid N=6	200 mg bid N=6
Cmax (ng/mL)	180 ± 83.4 (46.3)	236 ± 134 (56.8)
	187 (54.8-267) [6]	255 (62.9-371) [6]
Tmax (h)	1.50 (0.467-2.97) [6]	0.875 (0.500-1.52) [6]
AUClast (h*ng/mL)	334 ± 146 (43.8)	464 ± 211 (45.5)
	343 (77.4-511) [6]	502 (187-696) [6]
AUC0-12 (h*ng/mL)	337 ± 147 (43.6)	464 ± 211 (45.4)
	345 (79.8-517) [6]	503 (187-696) [6]

Part 4 (PK analysis set) MAD bid - Summary statistics of PK parameter values – Day 12

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood and Urine
Profile: Day 12

	LOU064	
PK parameter (unit)	100 mg bid N=6	200 mg bid N=6
Cmax (ng/mL)	306 ± 202 (66.2)	347 ± 112 (32.3)
	268 (109-600) [6]	332 (231-500) [6]
Tmax (h)	0.775 (0.500-2.00) [6]	0.992 (0.517-2.50) [6]
AUClast (h*ng/mL)	518 ± 334 (64.4)	963 ± 439 (45.6)
	441 (214-1130) [6]	889 (398-1710) [6]
AUCinf (h*ng/mL)	570 ± 368 (64.6)	989 ± 442 (44.7)
	563 (219-1160) [5]	929 (412-1730) [6]
AUC0-12 (h*ng/mL)	496 ± 306 (61.7)	890 ± 416 (46.7)
	430 (214-1040) [6]	810 (398-1660) [6]
T1/2 (h)	2.84 (2.15-18.9) [5]	12.4 (2.26-26.3) [6]
Vss/F (L)	2040 ± 1610 (79.0)	4590 ± 3520 (76.8)
	1920 (531-4460) [5]	4740 (866-9140) [6]
CLss/F (L/h)	255 ± 153 (60.1)	267 ± 126 (47.4)

Part 3 (PK analysis set) Food effect - Summary statistics of PK parameter values

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood

	LOU064 60 mg	
PK parameter (unit)	Fed N=12	Fasted N=12
Cmax (ng/mL)	83.4 ± 21.4 (25.7)	115 ± 58.0 (50.5)
	87.4 (52.1-126) [12]	118 (33.9-252) [12]
Tmax (h)	2.78 (1.98-6.02) [12]	0.767 (0.733-2.00) [12]
AUClast (h*ng/mL)	236 ± 78.0 (33.0)	192 ± 89.1 (46.5)
	244 (126-371) [12]	184 (67.2-389) [12]
AUCinf (h*ng/mL)	214 ± 72.7 (34.0)	201 ± 92.2 (45.9)
	222 (129-327) [7]	192 (68.6-395) [12]
T1/2 (h)	0.928 (0.781-2.08) [7]	2.72 (0.809-18.9) [12]
MRT (h)	4.17 ± 1.20 (28.8)	2.29 ± 0.717 (31.3)
	3.89 (2.50-6.68) [12]	2.15 (1.30-3.95) [12]

Statistics are Mean ± SD (CV%)
Median (Min-Max) [n]
CV% = Coefficient of variation (%) = SD/Mean*100
For Tmax and T1/2, only Median (Min-Max) [n] are presented

Part 5 (PK analysis set) Formulation effect - Summary statistics of PK parameter values

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood		
	LOU064 50 mg	
PK parameter (unit)	Wet-media milled N=12	Micronized N=13
Cmax (ng/mL)	95.6 ± 66.3 (69.3)	40.6 ± 31.1 (76.6)
	94.4 (9.54-239) [12]	34.1 (4.19-96.2) [13]
Tmax (h)	0.750 (0.733-2.00) [12]	1.00 (0.733-2.50) [13]
AUClast (h*ng/mL)	136 ± 80.2 (59.0)	66.2 ± 51.1 (77.2)
	127 (15.7-289) [12]	62.3 (4.61-131) [13]
AUCinf (h*ng/mL)	140 ± 79.9 (57.3)	90.7 ± 39.3 (43.4)
	135 (18.2-290) [12]	101 (30.3-131) [6]
T1/2 (h)	0.962 (0.867-7.36) [12]	0.824 (0.649-8.62) [6]
MRT (h)	1.89 ± 0.339 (17.9)	2.20 ± 1.21 (54.8)
	1.80 (1.48-2.64) [12]	2.17 (0.839-4.85) [13]

Part 6 (PK analysis set) 4-week treatment cohort Summary statistics of PK parameter values

Compound: LOU064 , Analyte: LOU064 , Matrix: Blood		
	LOU064 100 mg bid N=12	
PK parameter (unit)	Profile: Day 1	Profile: Day 29
Cmax (ng/mL) Mean ± SD (CV%)	249 ± 152 (61.1)	396 ± 196 (49.5)
Median (Min-Max) [n]	209 (85.2-564) [12]	395 (119-675) [9]
Tmax (h)	0.750 (0.750-4.23) [12]	1.00 (0.500-2.65) [9]
AUClast (h*ng/mL)	552 ± 372 (67.4)	877 ± 316 (36.0)
	359 (167-1270) [12]	913 (373-1260) [9]
AUC0-12h (h*ng/mL)	552 ± 372 (67.3)	880 ± 313 (35.5)
	359 (167-1270) [12]	913 (373-1260) [9]
T1/2 (h)	1.87 (1.13-5.70) [10]	2.89 (1.69-20.4) [6]

Statistics are Mean ± SD (CV%)
Median (Min-Max) [n]
CV% = Coefficient of variation (%) = SD/Mean*100
For Tmax and T1/2, only Median (Min-Max) [n] are presented. The calculated T1/2 corresponds to the initial elimination half-life not the terminal half-life

Safety Results

No deaths and SAEs were reported in this study

Part 1 (Safety analysis set) SAD - Incidence of AEs by primary system organ class - n (percent) of subjects

	LOU064					
	0.5 mg N=6 n (%)	1.5 mg N=6 n (%)	5 mg N=6 n (%)	15 mg N=6 n (%)	30 mg N=6 n (%)	60 mg N=6 n (%)
Subjects with at least one AE	2 (33.3)	3 (50.0)	3 (50.0)	2 (33.3)	1 (16.7)	1 (16.7)
System organ class						
Nervous system disorders	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)
Infections and infestations	1 (16.7)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)
Gastrointestinal disorders	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	LOU064						
	100 mg N=6 n (%)	200 mg N=6 n (%)	400 mg N=6 n (%)	600 mg N=6 n (%)	All N=60 n (%)	Placebo (SAD) N=20 n (%)	Total N=80 n (%)
Subjects with at least one AE	0 (0.0)	0 (0.0)	1 (16.7)	4 (66.7)	17 (28.3)	3 (15.0)	20 (25.0)
System organ class							
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.0)	1 (5.0)	7 (8.8)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.7)	1 (5.0)	5 (6.3)

	LOU064						
	100 mg N=6 n (%)	200 mg N=6 n (%)	400 mg N=6 n (%)	600 mg N=6 n (%)	All N=60 n (%)	Placebo (SAD) N=20 n (%)	Total N=80 n (%)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	3 (5.0)	0 (0.0)	3 (3.8)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	3 (5.0)	0 (0.0)	3 (3.8)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (3.3)	0 (0.0)	2 (2.5)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	2 (2.5)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (1.7)	0 (0.0)	1 (1.3)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.3)

Part 1 (Safety analysis set) SAD - Incidence of AEs by preferred term - n (percent) of subjects

	LOU064					
	0.5 mg N=6 n (%)	1.5 mg N=6 n (%)	5 mg N=6 n (%)	15 mg N=6 n (%)	30 mg N=6 n (%)	60 mg N=6 n (%)
Subjects with at least one AE	2 (33.3)	3 (50.0)	3 (50.0)	2 (33.3)	1 (16.7)	1 (16.7)
Preferred term						
Headache	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)
Nasopharyngitis	1 (16.7)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	LOU064					
	0.5 mg N=6 n (%)	1.5 mg N=6 n (%)	5 mg N=6 n (%)	15 mg N=6 n (%)	30 mg N=6 n (%)	60 mg N=6 n (%)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling hot	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ligament sprain	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Medical device site irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pollakiuria	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Skin irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sunburn	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	LOU064						
	100 mg N=6 n (%)	200 mg N=6 n (%)	400 mg N=6 n (%)	600 mg N=6 n (%)	All N=60 n (%)	Placebo (SAD) N=20 n (%)	Total N=80 n (%)
Subjects with at least one AE	0 (0.0)	0 (0.0)	1 (16.7)	4 (66.7)	17 (28.3)	3 (15.0)	20 (25.0)
Preferred term							
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.0)	1 (5.0)	7 (8.8)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.7)	1 (5.0)	5 (6.3)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	2 (3.3)	0 (0.0)	2 (2.5)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	2 (3.3)	0 (0.0)	2 (2.5)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (1.7)	0 (0.0)	1 (1.3)
Diarrhoea	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Feeling hot	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Ligament sprain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)

	LOU064						
	100 mg N=6 n (%)	200 mg N=6 n (%)	400 mg N=6 n (%)	600 mg N=6 n (%)	All N=60 n (%)	Placebo (SAD) N=20 n (%)	Total N=80 n (%)
Medical device site irritation	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (1.7)	0 (0.0)	1 (1.3)
Pollakiuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Skin irritation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (1.3)
Sunburn	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.3)

Parts 2 and 4 (Safety analysis set) MAD - Incidence of AEs by primary system organ class - n (percent) of subjects

	LOU064					
	10 mg qd N=6 n (%)	25 mg qd N=6 n (%)	50 mg qd N=6 n (%)	100 mg qd N=6 n (%)	400 mg qd N=6 n (%)	600 mg qd N=6 n (%)
Subjects with at least one AE	5 (83.3)	4 (66.7)	1 (16.7)	5 (83.3)	2 (33.3)	4 (66.7)
System organ class						
Infections and infestations	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0.0)	1 (16.7)
Nervous system disorders	0 (0.0)	3 (50.0)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)
Skin and subcutaneous tissue disorders	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)
Gastrointestinal disorders	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)
General disorders and administration site conditions	0 (0.0)	1 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)	1 (16.7)
Respiratory, thoracic and mediastinal disorders	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Cardiac disorders	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)

	LOU064				
	100 mg bid N=6 n (%)	200 mg bid N=6 n (%)	All N=48 n (%)	Placebo (MAD) N=16 n (%)	Total N=64 n (%)
Subjects with at least one AE	2 (33.3)	1 (16.7)	24 (50.0)	8 (50.0)	32 (50.0)
System organ class					
Infections and infestations	2 (33.3)	1 (16.7)	8 (16.7)	2 (12.5)	10 (15.6)
Nervous system disorders	0 (0.0)	0 (0.0)	6 (12.5)	2 (12.5)	8 (12.5)
Skin and subcutaneous tissue disorders	1 (16.7)	0 (0.0)	5 (10.4)	1 (6.3)	6 (9.4)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	3 (6.3)	2 (12.5)	5 (7.8)
General disorders and administration site conditions	1 (16.7)	0 (0.0)	5 (10.4)	0 (0.0)	5 (7.8)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	2 (4.2)	1 (6.3)	3 (4.7)
Psychiatric disorders	1 (16.7)	0 (0.0)	1 (2.1)	1 (6.3)	2 (3.1)
Vascular disorders	0 (0.0)	0 (0.0)	1 (2.1)	1 (6.3)	2 (3.1)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Eye disorders	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)

Parts 2 and 4 (Safety analysis set) MAD - Incidence of AEs by preferred term - n (percent) of subjects

	LOU064					
	10 mg qd N=6 n (%)	25 mg qd N=6 n (%)	50 mg qd N=6 n (%)	100 mg qd N=6 n (%)	400 mg qd N=6 n (%)	600 mg qd N=6 n (%)
Subjects with at least one AE	5 (83.3)	4 (66.7)	1 (16.7)	5 (83.3)	2 (33.3)	4 (66.7)
Preferred term						
Headache	0 (0.0)	2 (33.3)	1 (16.7)	0 (0.0)	1 (16.7)	1 (16.7)
Nasopharyngitis	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toothache	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Diarrhoea	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Dysphonia	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Oral herpes	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin irritation	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sleep disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vessel puncture site haematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Agitation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Blister	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Catheter site pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Catheter site phlebitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Catheter site related reaction	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Conjunctivitis	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dry skin	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)

	LOU064					
	10 mg qd N=6 n (%)	25 mg qd N=6 n (%)	50 mg qd N=6 n (%)	100 mg qd N=6 n (%)	400 mg qd N=6 n (%)	600 mg qd N=6 n (%)
Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Hordeolum	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Hot flush	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Iritis	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oropharyngeal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Palpitations	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash maculo-papular	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhoea	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin abrasion	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	LOU064				
	100 mg bid N=6 n (%)	200 mg bid N=6 n (%)	All N=48 n (%)	Placebo (MAD) N=16 n (%)	Total N=64 n (%)
Subjects with at least one AE	2 (33.3)	1 (16.7)	24 (50.0)	8 (50.0)	32 (50.0)
Preferred term					
Headache	0 (0.0)	0 (0.0)	5 (10.4)	1 (6.3)	6 (9.4)
Nasopharyngitis	2 (33.3)	0 (0.0)	3 (6.3)	1 (6.3)	4 (6.3)
Toothache	0 (0.0)	0 (0.0)	1 (2.1)	2 (12.5)	3 (4.7)
Diarrhoea	0 (0.0)	0 (0.0)	2 (4.2)	0 (0.0)	2 (3.1)
Dysphonia	0 (0.0)	0 (0.0)	1 (2.1)	1 (6.3)	2 (3.1)
Nausea	0 (0.0)	0 (0.0)	2 (4.2)	0 (0.0)	2 (3.1)

	LOU064				
	100 mg bid N=6 n (%)	200 mg bid N=6 n (%)	All N=48 n (%)	Placebo (MAD) N=16 n (%)	Total N=64 n (%)
Oral herpes	0 (0.0)	0 (0.0)	1 (2.1)	1 (6.3)	2 (3.1)
Skin irritation	1 (16.7)	0 (0.0)	2 (4.2)	0 (0.0)	2 (3.1)
Sleep disorder	1 (16.7)	0 (0.0)	1 (2.1)	1 (6.3)	2 (3.1)
Vessel puncture site haematoma	1 (16.7)	0 (0.0)	2 (4.2)	0 (0.0)	2 (3.1)
Vomiting	0 (0.0)	0 (0.0)	2 (4.2)	0 (0.0)	2 (3.1)
Agitation	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.6)
Back pain	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Blister	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Catheter site pain	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Catheter site phlebitis	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Catheter site related reaction	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Conjunctivitis	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Decreased appetite	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.6)
Dry skin	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Eczema	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Gastroenteritis	0 (0.0)	1 (16.7)	1 (2.1)	0 (0.0)	1 (1.6)
Gastrointestinal infection	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Haematoma	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Hordeolum	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Hot flush	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.6)
Iritis	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Oropharyngeal pain	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Palpitations	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.6)
Rash maculo-papular	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (1.6)

	LOU064				
	100 mg bid N=6 n (%)	200 mg bid N=6 n (%)	All N=48 n (%)	Placebo (MAD) N=16 n (%)	Total N=64 n (%)
Rhinorrhoea	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Skin abrasion	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Syncope	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)

Part 3 (Safety analysis set) Food effect - Incidence of AEs by primary system organ class - n (percent) of subjects

	LOU064 60 mg		
	Fed N=12 n (%)	Fasted N=12 n (%)	Total N=12 n (%)
Subjects with at least one AE	6 (50.0)	2 (16.7)	7 (58.3)
System organ class			
Vascular disorders	2 (16.7)	1 (8.3)	3 (25.0)
Musculoskeletal and connective tissue disorders	2 (16.7)	0 (0.0)	2 (16.7)
Nervous system disorders	2 (16.7)	0 (0.0)	2 (16.7)
Cardiac disorders	1 (8.3)	0 (0.0)	1 (8.3)
Infections and infestations	1 (8.3)	0 (0.0)	1 (8.3)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (8.3)	1 (8.3)

Part 3 (Safety analysis set) Food effect - Incidence of AEs by preferred term - n (percent) of subjects

	LOU064 60 mg		
	Fed N=12 n (%)	Fasted N=12 n (%)	Total N=12 n (%)
Subjects with at least one AE	6 (50.0)	2 (16.7)	7 (58.3)
Preferred term			
Headache	2 (16.7)	0 (0.0)	2 (16.7)
Alopecia areata	0 (0.0)	1 (8.3)	1 (8.3)
Haematoma	1 (8.3)	0 (0.0)	1 (8.3)
Myalgia	1 (8.3)	0 (0.0)	1 (8.3)
Nasopharyngitis	1 (8.3)	0 (0.0)	1 (8.3)
Orthostatic hypotension	1 (8.3)	0 (0.0)	1 (8.3)
Pain in extremity	1 (8.3)	0 (0.0)	1 (8.3)
Palpitations	1 (8.3)	0 (0.0)	1 (8.3)
Phlebitis	0 (0.0)	1 (8.3)	1 (8.3)

Part 5 (Safety analysis set) Formulation effect - Incidence of AEs by primary system organ class - n (percent) of subjects

	LOU064 50 mg		
	Wet-media milled N=12 n (%)	Micronized N=13 n (%)	Total N=13 n (%)
Subjects with at least one AE	5 (41.7)	2 (15.4)	6 (46.2)
System organ class			
Infections and infestations	3 (25.0)	1 (7.7)	4 (30.8)
Renal and urinary disorders	1 (8.3)	1 (7.7)	1 (7.7)
Respiratory, thoracic and mediastinal disorders	1 (8.3)	0 (0.0)	1 (7.7)

Part 5 (Safety analysis set) Formulation effect - Incidence of AEs by preferred term - n (percent) of subjects

	LOU064 50 mg		
	Wet-media milled N=12 n (%)	Micronized N=13 n (%)	Total N=13 n (%)
Subjects with at least one AE	5 (41.7)	2 (15.4)	6 (46.2)
Preferred term			
Nasopharyngitis	3 (25.0)	1 (7.7)	4 (30.8)
Epistaxis	1 (8.3)	0 (0.0)	1 (7.7)
Pollakiuria	1 (8.3)	1 (7.7)	1 (7.7)

Part 6 (Safety analysis set) 4-week treatment cohort - Incidence of AEs by primary system organ class - n (percent) of subjects

	LOU064 100 mg bid N=12 n (%)	Placebo N=4 n (%)	Total N=16 n (%)
Subjects with at least one AE	11 (91.7)	4 (100.0)	15 (93.8)
System organ class			
Nervous system disorders	7 (58.3)	2 (50.0)	9 (56.3)
Infections and infestations	5 (41.7)	3 (75.0)	8 (50.0)
Gastrointestinal disorders	4 (33.3)	3 (75.0)	7 (43.8)
Vascular disorders	4 (33.3)	1 (25.0)	5 (31.3)
General disorders and administration site conditions	4 (33.3)	0 (0.0)	4 (25.0)
Skin and subcutaneous tissue disorders	3 (25.0)	1 (25.0)	4 (25.0)
Eye disorders	3 (25.0)	0 (0.0)	3 (18.8)
Injury, poisoning and procedural complications	2 (16.7)	1 (25.0)	3 (18.8)
Musculoskeletal and connective tissue disorders	2 (16.7)	0 (0.0)	2 (12.5)
Respiratory, thoracic and mediastinal disorders	2 (16.7)	0 (0.0)	2 (12.5)
Blood and lymphatic system disorders	1 (8.3)	0 (0.0)	1 (6.3)
Immune system disorders	0 (0.0)	1 (25.0)	1 (6.3)
Psychiatric disorders	1 (8.3)	0 (0.0)	1 (6.3)

Part 6 (Safety analysis set) 4-week treatment cohort - Incidence of AEs by preferred term - n (percent) of subjects

	LOU064 100 mg bid N=12 n (%)	Placebo N=4 n (%)	Total N=16 n (%)
Subjects with at least one AE	11 (91.7)	4 (100.0)	15 (93.8)
Preferred term			
Headache	5 (41.7)	0 (0.0)	5 (31.3)
Viral upper respiratory tract infection	3 (25.0)	2 (50.0)	5 (31.3)
Haematoma	3 (25.0)	1 (25.0)	4 (25.0)
Fatigue	3 (25.0)	0 (0.0)	3 (18.8)
Gingival bleeding	2 (16.7)	1 (25.0)	3 (18.8)
Somnolence	2 (16.7)	1 (25.0)	3 (18.8)
Influenza like illness	2 (16.7)	0 (0.0)	2 (12.5)
Abdominal pain upper	0 (0.0)	1 (25.0)	1 (6.3)
Aphthous ulcer	0 (0.0)	1 (25.0)	1 (6.3)
Arthralgia	1 (8.3)	0 (0.0)	1 (6.3)
Back pain	1 (8.3)	0 (0.0)	1 (6.3)
Chest wall haematoma	1 (8.3)	0 (0.0)	1 (6.3)

	LOU064 100 mg bid N=12 n (%)	Placebo N=4 n (%)	Total N=16 n (%)
Conjunctival haemorrhage	1 (8.3)	0 (0.0)	1 (6.3)
Conjunctivitis	1 (8.3)	0 (0.0)	1 (6.3)
Contusion	1 (8.3)	0 (0.0)	1 (6.3)
Dermatitis	0 (0.0)	1 (25.0)	1 (6.3)
Dermatitis allergic	1 (8.3)	0 (0.0)	1 (6.3)
Dermatitis atopic	1 (8.3)	0 (0.0)	1 (6.3)
Dizziness	1 (8.3)	0 (0.0)	1 (6.3)
Drug eruption	1 (8.3)	0 (0.0)	1 (6.3)
Epistaxis	1 (8.3)	0 (0.0)	1 (6.3)
Eye haemorrhage	1 (8.3)	0 (0.0)	1 (6.3)
Eye irritation	1 (8.3)	0 (0.0)	1 (6.3)
Flatulence	1 (8.3)	0 (0.0)	1 (6.3)
Food poisoning	1 (8.3)	0 (0.0)	1 (6.3)
Gastroenteritis	1 (8.3)	0 (0.0)	1 (6.3)
Insomnia	1 (8.3)	0 (0.0)	1 (6.3)
Ligament rupture	0 (0.0)	1 (25.0)	1 (6.3)
Ligament sprain	1 (8.3)	0 (0.0)	1 (6.3)
Lymphadenopathy	1 (8.3)	0 (0.0)	1 (6.3)
Medial tibial stress syndrome	1 (8.3)	0 (0.0)	1 (6.3)
Migraine	1 (8.3)	0 (0.0)	1 (6.3)
Muscle contractions involuntary	0 (0.0)	1 (25.0)	1 (6.3)
Nausea	0 (0.0)	1 (25.0)	1 (6.3)
Non-cardiac chest pain	1 (8.3)	0 (0.0)	1 (6.3)
Oral herpes	0 (0.0)	1 (25.0)	1 (6.3)
Oropharyngeal pain	1 (8.3)	0 (0.0)	1 (6.3)
Paraesthesia	1 (8.3)	0 (0.0)	1 (6.3)
Phlebitis	1 (8.3)	0 (0.0)	1 (6.3)
Scratch	1 (8.3)	0 (0.0)	1 (6.3)
Seasonal allergy	0 (0.0)	1 (25.0)	1 (6.3)
Skin fragility	1 (8.3)	0 (0.0)	1 (6.3)
Viral rash	1 (8.3)	0 (0.0)	1 (6.3)

Part 1 (Safety analysis set) SAD - Overall incidence of AEs - number of events and number of subjects

	LOU064					
	0.5 mg N=6 nE, nS (%)	1.5 mg N=6 nE, nS (%)	5 mg N=6 nE, nS (%)	15 mg N=6 nE, nS (%)	30 mg N=6 nE, nS (%)	60 mg N=6 nE, nS (%)
AEs, Subjects with AEs	3, 2 (33.3)	6, 3 (50.0)	3, 3 (50.0)	2, 2 (33.3)	2, 1 (16.7)	1, 1 (16.7)
AEs of Mild intensity	3, 2 (33.3)	5, 2 (33.3)	3, 3 (50.0)	2, 2 (33.3)	2, 1 (16.7)	1, 1 (16.7)
AEs of Moderate intensity	0, 0 (0.0)	1, 1 (16.7)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs of Severe intensity	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study drug-related AEs	0, 0 (0.0)	3, 1 (16.7)	2, 2 (33.3)	1, 1 (16.7)	0, 0 (0.0)	0, 0 (0.0)
Serious AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study-drug related AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

	LOU064						
	100 mg N=6 nE, nS (%)	200 mg N=6 nE, nS (%)	400 mg N=6 nE, nS (%)	600 mg N=6 nE, nS (%)	All N=60 nE, nS (%)	Placebo (SAD) N=20 nE, nS (%)	Total N=80 nE, nS (%)
AEs, Subjects with AEs	0, 0 (0.0)	0, 0 (0.0)	1, 1 (16.7)	6, 4 (66.7)	24, 17 (28.3)	3, 3 (15.0)	27, 20 (25.0)
AEs of Mild intensity	0, 0 (0.0)	0, 0 (0.0)	1, 1 (16.7)	6, 4 (66.7)	23, 16 (26.7)	2, 2 (10.0)	25, 18 (22.5)
AEs of Moderate intensity	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	1, 1 (1.7)	1, 1 (5.0)	2, 2 (2.5)
AEs of Severe intensity	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study drug-related AEs	0, 0 (0.0)	0, 0 (0.0)	1, 1 (16.7)	3, 2 (33.3)	10, 7 (11.7)	0, 0 (0.0)	10, 7 (8.8)
Serious AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

	LOU064						
	100 mg N=6 nE, nS (%)	200 mg N=6 nE, nS (%)	400 mg N=6 nE, nS (%)	600 mg N=6 nE, nS (%)	All N=60 nE, nS (%)	Placebo (SAD) N=20 nE, nS (%)	Total N=80 nE, nS (%)
AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study-drug related AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

Parts 2 and 4 (Safety analysis set) MAD - Overall incidence of AEs - number of events and number of subjects

	LOU064					
	10 mg qd N=6 nE, nS (%)	25 mg qd N=6 nE, nS (%)	50 mg qd N=6 nE, nS (%)	100 mg qd N=6 nE, nS (%)	400 mg qd N=6 nE, nS (%)	600 mg qd N=6 nE, nS (%)
AEs, Subjects with AEs	8, 5 (83.3)	11, 4 (66.7)	2, 1 (16.7)	13, 5 (83.3)	3, 2 (33.3)	7, 4 (66.7)
AEs of Mild intensity	8, 5 (83.3)	8, 3 (50.0)	2, 1 (16.7)	12, 5 (83.3)	1, 1 (16.7)	6, 4 (66.7)
AEs of Moderate intensity	0, 0 (0.0)	2, 1 (16.7)	0, 0 (0.0)	1, 1 (16.7)	2, 2 (33.3)	1, 1 (16.7)
AEs of Severe intensity	0, 0 (0.0)	1, 1 (16.7)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study drug-related AEs	0, 0 (0.0)	3, 2 (33.3)	0, 0 (0.0)	4, 1 (16.7)	1, 1 (16.7)	0, 0 (0.0)
Serious AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study-drug related AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

	LOU064				
	100 mg bid N=6 nE, nS (%)	200 mg bid N=6 nE, nS (%)	All N=48 nE, nS (%)	Placebo (MAD) N=16 nE, nS (%)	Total N=64 nE, nS (%)
AEs, Subjects with AEs	6, 2 (33.3)	1, 1 (16.7)	51, 24 (50.0)	12, 8 (50.0)	63, 32 (50.0)
AEs of Mild intensity	6, 2 (33.3)	1, 1 (16.7)	44, 22 (45.8)	9, 6 (37.5)	53, 28 (43.8)
AEs of Moderate intensity	0, 0 (0.0)	0, 0 (0.0)	6, 5 (10.4)	3, 3 (18.8)	9, 8 (12.5)
AEs of Severe intensity	0, 0 (0.0)	0, 0 (0.0)	1, 1 (2.1)	0, 0 (0.0)	1, 1 (1.6)
Study drug-related AEs	1, 1 (16.7)	0, 0 (0.0)	9, 5 (10.4)	4, 3 (18.8)	13, 8 (12.5)
Serious AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

	LOU064				
	100 mg bid N=6 nE, nS (%)	200 mg bid N=6 nE, nS (%)	All N=48 nE, nS (%)	Placebo (MAD) N=16 nE, nS (%)	Total N=64 nE, nS (%)
Study-drug related AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

Part 3 (Safety analysis set) Food effect - Overall incidence of AEs - number of events and number of subjects

	LOU064 60 mg		
	Fed N=12 nE, nS (%)	Fasted N=12 nE, nS (%)	Total N=12 nE, nS (%)
AEs, Subjects with AEs	8, 6 (50.0)	2, 2 (16.7)	10, 7 (58.3)
AEs of Mild intensity	7, 6 (50.0)	2, 2 (16.7)	9, 7 (58.3)
AEs of Moderate intensity	1, 1 (8.3)	0, 0 (0.0)	1, 1 (8.3)
AEs of Severe intensity	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study drug-related AEs	3, 3 (25.0)	0, 0 (0.0)	3, 3 (25.0)
Serious AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study-drug related AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

Part 5 (Safety analysis set) Formulation effect -Overall incidence of AEs - number of events and number of subjects

	LOU064 50 mg		
	Wet-media milled N=12 nE, nS (%)	Micronized N=13 nE, nS (%)	Total N=13 nE, nS (%)
AEs, Subjects with AEs	5, 5 (41.7)	3, 2 (15.4)	8, 6 (46.2)
AEs of Mild intensity	5, 5 (41.7)	1, 1 (7.7)	6, 5 (38.5)
AEs of Moderate intensity	0, 0 (0.0)	2, 1 (7.7)	2, 1 (7.7)
AEs of Severe intensity	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study drug-related AEs	2, 2 (16.7)	1, 1 (7.7)	3, 2 (15.4)
Serious AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study-drug related AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

Part 6 (Safety analysis set) 4-week treatment cohort - Overall incidence of AEs – number of events and number of subjects

	LOU064 50 mg		
	Wet-media milled N=12 nE, nS (%)	Micronized N=13 nE, nS (%)	Total N=13 nE, nS (%)
AEs, Subjects with AEs	5, 5 (41.7)	3, 2 (15.4)	8, 6 (46.2)
AEs of Mild intensity	5, 5 (41.7)	1, 1 (7.7)	6, 5 (38.5)
AEs of Moderate intensity	0, 0 (0.0)	2, 1 (7.7)	2, 1 (7.7)
AEs of Severe intensity	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study drug-related AEs	2, 2 (16.7)	1, 1 (7.7)	3, 2 (15.4)
Serious AEs	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)
Study-drug related AEs leading to discontinuation of study treatment	0, 0 (0.0)	0, 0 (0.0)	0, 0 (0.0)

N = number of subjects studied
nE = number of AE events in the category
nS = number of subjects with at least one AE in the category
% is based on the number of subjects

Other Relevant Findings

None

Conclusion:

Part 1 to 5

- Results of this first-in-human study indicated favorable safety, tolerability, PK and PD profile of LOU064 and also provided evidence of pharmacological activity of the compound in the skin.

Part 6

- On average, a slightly higher drug exposure is noted in the AD cohort compared to the previous cohorts in healthy volunteers. However, given the small subject number and the inherent variability of exposure, this is not considered clinically relevant
- No relevant safety signals and no major infections were reported.

Date of Clinical Study Report

Interim CSR for Parts 1 to 5: Jun 07, 2019

Final CSR including Part 6: Sep 16, 2020