An open-label, multicenter, extension study to evaluate the long-term safety and tolerability of LOU064 in eligible subjects with CSU who have participated in preceding studies with LOU064

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To assess the long-term safety and tolerability of LOU064 in patients with CSU who have participated in preceding studies with LOU064.

Ethical review	Not approved
Status	Will not start
Health condition type	Angioedema and urticaria
Study type	Interventional

Summary

ID

NL-OMON49297

Source
ToetsingOnline

Brief title
CLOU064A2201E1

Condition

- Angioedema and urticaria

Synonym
hives, wheals

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: CSU, LOU064, urticaria

Outcome measures

Primary outcome

To assess the long-term safety and tolerability of LOU064 in patients with CSU who have participated in preceding studies with LOU064.

Secondary outcome

To evaluate the long-term efficacy of LOU064 in patients with CSU who have participated in previous studies with LOU064 with respect to maintaining or achieving controlled disease (defined by a UAS7*6) over time.

To evaluate the long-term efficacy of LOU064 in patients with CSU who have participated in preceding studies with LOU064 with respect to change from baseline in UAS7 over time

To evaluate the efficacy of LOU064 when given without H1-antihistamines in patients with CSU with respect to change from baseline in UAS7, achieving controlled disease (defined by a UAS7*6), and achieving complete response (defined by a UAS7=0) at Week 4 of treatment

Study description

Background summary

Chronic Spontaneous Urticaria (CSU) is defined as the spontaneous occurrence of itchy wheals (hives), angioedema or both lasting for at least 6 weeks. CSU can be debilitating and is associated with intense itching and has a major impact on patient*s well-being.

Second generation H1-antihistamines are recommended as first line treatment for subjects with CSU but less than 40% of these subjects respond adequately. While uptitration of second generation antihistamines is recommended by most CSU treatment guidelines as second line therapy (Zuberbier et al 2018), the efficacy of uptitrated H1-antihistamines in CSU has not been studied in larger clinical studies and hence uptitration is considered off-label. Omalizumab is a highly effective third line therapy for CSU subjects. However, less than 50% of subjects treated with Omalizumab reach a complete control of signs and symptoms of CSU (Kaplan et al 2016). Therefore, there is a high medical need for new treatment options for CSU subjects.

Bruton*s tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase and member of the TEC kinase family. BTK is expressed in selected cells of the adaptive and innate immune system including B cells, macrophages, mast cells/basophils and thrombocytes.

Recently, it has been demonstrated that inhibition of BTK leads to inhibition of mast cell and basophil activation/degranulation in vitro and to reduced wheal sizes in skin prick tests with patients suffering from IgE-mediated allergies (Smiljkovic et al 2017; Regan et al 2017; Dispenza et al 2018). Thus, BTK inhibition is a promising therapeutic concept for the treatment of chronic urticaria.

Study objective

To assess the long-term safety and tolerability of LOU064 in patients with CSU who have participated in preceding studies with LOU064.

Study design

This study is an open-label, single arm, multicenter, extension study for CSU patients rolling-over from CLOU064A2201. It consists of three periods:
* Observational period: Subjects rolling over from CLOU064A2201 with UAS7<16 after the follow-up period at Week 16 will be further followed up without receiving LOU064 for up to 12 weeks. After relapse (UAS7*16 at least once), the observational period can be terminated immediately at any time during these 12

weeks and subjects may enter the treatment period. Subjects who have never relapsed within 12 weeks will discontinue the study after the observational period.
* Treatment period: Subjects will be treated with 100 mg LOU064 bid for 52 weeks. Until Week 4 of treatment, no background medication with H1-antihistamines is permitted. After Week 4, subjects may start a background therapy with H1-antihistamines if deemed necessary by the investigator.
* Follow-up period: Treatment-free follow-up period following the treatment period. The minimum duration of treatment-free follow-up is 4 weeks for all subjects who stop treatment with LOU064 (either after completing the treatment period or after an early discontinuation of study treatment). Subjects who have a UAS7*6 at Week 52 of the treatment period will extend their follow-up period until relapse (UAS7*16) for up to a total of 16 weeks.

Intervention

LOU064 capsules 50 mg

Study burden and risks

Based on a thorough review of safety information currently available in the literature together with an assessment of safety data obtained from both clinical and preclinical experience with LOU064, the following safety topics are considered as potential risks for LOU064 and require close monitoring in the proposed study: infections, impaired platelet function, myomodulation, risk of cardiovascular origin, drug-drug interactions and reproductive toxicity. For details see section 4.3 of the protocol.

Patients should visit the hospital more frequently, visits take longer than usual.Additional procedures are blood draws, completion of diary, ECG, completoin of questionnaires, urinalysis, PK sampling. See for details protocol table 8.1 (assesment schedule).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Written informed consent must be obtained before any assessment is performed.
- Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules.
- Subjects rolling over from CLOU064A2201 must have completed the Week 12 visit (end of treatment period) or the Week 16 visit (end of the follow-up period) and will be allocated to the treatment period or the observational period of CLOU064A2201E1 based on the UAS7 score (of the 7 days prior to the respective visit) as follows:
a) Subjects rolling over at Week 12 of CLOU064A2201 with a UAS7*16 will be allocated to the Treatment period (note: subjects with UAS7<16 at Week 12 are not eligible to rollover into CLOU064A2201E1 but need to enter the follow-up period of CLOU064A2201).
b) Subjects rolling over at Week 16 of CLOU064A2201 with a UAS7*16 will be allocated to the Treatment period.
c) Subjects rolling over at Week 16 of CLOU064A2201 with a UAS7<16 will be allocated to the Observational period.
- Rollover criteria for subjects with CSU from other, not-yet specified studies with LOU064 will be detailed in the protocols of these studies.

Exclusion criteria

- Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days (for small molecules) prior to enrollment or until the expected

pharmacodynamic (PD) effect has returned to baseline (for biologics), whichever is longer; or longer if required by local regulations.
- History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
- Subjects having a clearly defined, predominant or sole trigger of their chronic urticaria (chronic inducible urticaria) including urticaria factitia (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact urticaria
- Other diseases with symptoms of urticaria or angioedema, including but not limited to urticaria vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary urticaria, or acquired/drug-induced urticaria
- Any other skin disease associated with chronic itching that might influence in the investigators opinion the study evaluations and results, eg atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis
- History or current diagnosis of ECG abnormalities indicating significant risk of safety for subjects participating in the study
- Patients/subjects taking medications prohibited by the protocol
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Pregnant or nursing (lactating) women
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days after stopping study medication.
- Sexually active males must use a condom during intercourse while taking drug and for 7 days after stopping study medication and should not father a child in this period. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.
- Major surgery within 8 weeks prior to enrollment or surgery planned prior to end of the treatment period.
- History of live attenuated vaccine within 6 weeks prior to enrollment or requirement to receive these vaccinations at any time during study drug treatment
- Evidence of clinically significant cardiac, neurologic, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic, hematological disorders or gastrointestinal disease that, in the investigator's opinion, would compromise the safety of the participant, interfere with the interpretation of the study results or otherwise preclude participant participation.
- Uncontrolled disease states, such as asthma, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids.
- Hematology parameters at last visit before Day 1 of the Treatment period (either last available value from CLOU064A2201 or most recent value taken during observational period): 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, eg in association with use of Nonsteroidal Anti-Inflammatory Drug (NSAID)
- Requirement for anti-platelet or anticoagulant medication (for example, 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
- History or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or Aspartate Aminotransferase (AST)/Alanine Aminotransferase (ALT) levels of more than 1.5 x upper limit of normal (ULN) at last visit before Day 1 of the Treatment period (either last available value from CLOU064A2201 or most recent value taken during observational period)
- History of renal disease or creatinine level above 1.5x ULN at last visit before Day 1 of the Treatment period (either last available value from CLOU064A2201 or most recent value taken during observational period)
- Known or suspected history of an ongoing, chronic or recurrent infectious disease including but not limited to opportunistic infections (eg tuberculosis, atypical mycobacterioses, listeriosis or aspergillosis), HIV, Hepatitis B/C

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	12
Type:	Anticipated

Ethics review

Approved WMO Date:	05-11-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	31-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Not approved Date:	04-09-2020
Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-001074-29-NL
ClinicalTrials.gov	NCT04109313
CCMO	NL71234.041.19