Dose-finding Phase 2 study to evaluate the efficacy and safety of the novel BTK inhibitor LOU064 in patients with CSU inadequately controlled by H1-antihistamines

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Disclosures

Introduction

- LOU064 is a novel highly selective and potent covalent oral Bruton’s Tyrosine Kinase (BTK) inhibitor that showed a favourable safety profile in a first-in-human study with healthy volunteers and asymptomatic atopic subjects (clinicaltrial.gov number: NCT03918980)\(^1\)
- The covalent binding of LOU064 to BTK resulted in potent and lasting inhibition of BTK-dependent pharmacodynamic biomarkers even with very low and transient systemic drug exposures\(^2\)
- LOU064 has good pharmacodynamic efficacy, including reduction of wheal size in skin prick tests with a fast onset of action. This makes it a strong candidate for oral treatment of basophil- and mast-cell driven skin diseases like chronic spontaneous urticaria (CSU)\(^3\)
- The primary objective of this study is to characterize the dose-response relationship of LOU064 administered once or twice daily in subjects with CSU with respect to change from baseline in the Urticaria Activity Score (UAS7) at Week 4
- The aim of this poster is to describe the design of the ongoing Phase 2b study that is based on the findings of the first-in-human study

BTK, Bruton’s tyrosine kinase; CSU, chronic spontaneous urticaria; UAS7, weekly urticaria activity score
Materials and Methods

- A multicentre, randomized, double-blind, placebo-controlled Phase 2b dose-finding study to investigate the efficacy, safety and tolerability of LOU064 in adults with CSU inadequately controlled by H₁-antihistamines, is being conducted (NCT03926611)
- Participants are randomized to receive once- or twice-daily treatment with high-, medium- or low-dose LOU064, or placebo for 12 weeks followed by a 4-week treatment-free follow-up period
- Patients are required to be on a stable treatment regimen with a second generation H₁-antihistamine at locally approved doses throughout the entire study
- For treatment of intolerable CSU symptoms during the study, a second generation H₁-antihistamine (that differed from the background H₁-antihistamine) is available on an as needed basis as rescue medication
- Concomitant medications that might affect CSU (including but not limited to 1st generation H₁-antihistamines, leukotriene receptor antagonists and anti-IgE biologics such as omalizumab) are prohibited throughout the study

CSU, chronic spontaneous urticaria; IgE, immunoglobulin E

4 Business Use Only
Study design: Multicentre, randomized, double-blind, placebo-controlled Phase 2b dose-finding study

*Eligible subjects may roll-over into the extension study at Week 12 or at Week 16 (after completing all scheduled assessments planned at these visits), following roll-over criteria defined in the extension study protocol and approval from participating countries.

bid, twice daily; n, number of patients planned for inclusion in each group; BID, twice daily; n, number of patients; qd, once daily; R, randomization

# Key inclusion and exclusion criteria

<table>
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<tr>
<th>Inclusion</th>
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<tr>
<td>≥18 years of age</td>
<td>A clearly defined predominant or sole trigger of their chronic urticaria (i.e. chronic inducible urticaria)</td>
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<td>CSU for ≥ 6 months</td>
<td>Other diseases with symptoms of urticaria or angioedema</td>
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<tr>
<td>A UAS7 ≥ 16 and HSS7 ≥ 8 at randomization</td>
<td>Other skin disease associated with chronic itching that might influence in the investigators opinion, the study evaluations, and results</td>
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CSU, chronic spontaneous urticaria; HSS7, weekly Hives Severity Score; UAS7, weekly Urticaria Activity Score
Inhibition of basophil activation and reduction in average wheal diameter post treatment demonstrates the proof of mechanism for efficacy of LOU064

- Results from the first-in-human study and preclinical data were used to select doses for this Phase 2b study.
- In the first-in-human study, full inhibition of blood basophil CD63 expression was reached with daily doses of ≥ 50 mg LOU064 with a fast onset of action over the entire treatment period (Day 1–12) and several days beyond.
- In subjects with atopic diathesis, dose dependent inhibition of wheal formation after skin-prick-testing with an established allergen demonstrated pharmacodynamic effects on mast cells in the skin and served as proof-of mechanism for the efficacy of LOU064 in mast cell-driven diseases such as CSU.

Pharmacodynamic effects of LOU064 after multiple oral administrations 10–400 mg qd and bid over 12 days

- a) Inhibition of basophil activation (% CD63 expression)
- b) Change from baseline (CFB) in average wheal size between pre- and post-treatment skin prick test in atopic subjects

*Data taken from the first-in-human study poster presented at EAACI 2019. "LOU064: a highly selective and potent covalent oral BTK inhibitor with promising pharmacodynamic effects in skin".

### Study objectives and endpoints

- The primary and secondary objectives and endpoints are displayed in the table.
- Efficacy, safety and tolerability will be assessed over the entire period of the study.

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>Primary endpoint</th>
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<tr>
<td>To characterize the dose-response relationship of LOU064 administered once or twice daily in subjects with CSU</td>
<td>Change from baseline in UAS7 at week 4</td>
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<th>Secondary objectives</th>
<th>Secondary endpoints</th>
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<tr>
<td>To evaluate the efficacy of LOU064 compared to placebo</td>
<td>Change from baseline in UAS7 at Week 12 and over time</td>
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<tr>
<td>To evaluate the efficacy of LOU064 compared to placebo with respect to achievement of complete clinical response and disease control</td>
<td>The number of responders with UAS7=0 (clinical response) and UAS7≤6 (disease control) over time</td>
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<td>To evaluate the effect of LOU064 on disease- and CSU-related QoL</td>
<td>Dermatology Life Quality Index score of 0 or 1 (disease-related), and change from baseline in DLQI (CSU-related) at Week 4 and 12</td>
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<tr>
<td>To evaluate the effect of LOU064 on angioedema</td>
<td>The cumulative number of weeks free from angioedema with a 7-day angioedema activity score of 0 between baseline and Week 12</td>
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<td>To evaluate the PK of LOU064 resulting from oral dosing in the target population</td>
<td>Concentrations in blood and calculation of PK at Week 4 and 12</td>
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<tr>
<td>To evaluate the safety and tolerability of LOU064 in subjects with CSU</td>
<td>Occurrence of emergent adverse events and serious adverse events during the study</td>
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This poster describes the design of the Phase 2b study from which the results are expected to characterize the dose- and exposure-response relationships for once and twice daily dosing and enable the determination of the optimal dosing regimen for LOU064 in Phase 3 studies.
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