completed the study and 3 subjects from the LOU064 group discontinued the study due to the worsening of the disease (physician's decision).

Diagnosis and main criteria for inclusion:

Key inclusion criteria

- 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.
- 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.
- Hemoglobin levels below 12.0 g/dL at screening or first baseline.
- Platelet count outside of the normal range (below 150 x 10^9/L or above 450 x 10^9) 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.
- 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.

Duration of treatment: Multiple oral doses of 100 mg LOU064 or matching placebo in a bid regimen (morning and evening dose) with a total treatment period of 28 days. On the last day, only the morning dose was given.

Test and reference therapies, dose and mode of administration, batch number:

The investigational drug, LOU064 and matching placebo were prepared by Novartis and supplied as single-blind packaging to an unblinded site Pharmacist. The batch numbers of the study treatment and placebo are presented below:

Study drug and strength	Batch number
LOU064 50 mg	2033160
Placebo	2033161

Criteria for evaluation

Safety:

Safety assessments included all AEs, serious AEs (SAEs), with their severity and relationship to study drug, regular monitoring of hematology, blood chemistry and urine performed at the study center, and regular assessments of vital signs, physical examination, and 12-lead ECGs.

Pharmacokinetics:

Pharmacokinetic samples were obtained in blood and evaluated in all subjects who received active treatment. LOU064 concentrations were determined in blood by a validated LC-MS/MS method.

Blood (Day 1): Cmax, Tmax, AUClast, AUC0-12h and T1/2.

Blood (Day 29, steady state): Cmax, Tmax, AUCtau, AUClast and T1/2.

Exploratory pharmacodynamic assessments:

BTK occupancy in whole blood and basophil activation (Basotest):

Exploratory assessments including free BTK in whole blood and basophil activation (Basotest) were performed.

Soluble biomarkers:

The following soluble biomarkers were analyzed in serum samples: CXCL13 (BLC), eotaxin-3 (CCL26), TARC (CCL17), and IP 10 (CXCL10).

Immunoglobulins.

Immunoglobulins were collected as potential disease and treatment markers with the goal of determining 1) whether there was a difference in efficacy in low or high IgE subjects; 2) whether there was any influence of LOU064 on Ig levels, specifically IgE, IgG, and IgA.

Exploratory efficacy assessments:

EASI scores

The EASI (Eczema Area and Severity Index) was used to make an assessment of the extent and severity of AD in four body regions (head/neck, upper limbs, trunk, and lower limbs).

Investigator's global assessment (IGA)

The IGA scale used in the study was vIGA-AD™ (Validated Investigator Global Assessment scale for atopic dermatitis). The IGA rating scale was used to determine the severity of AD symptoms and clinical response to treatment.

SCORAD

Severity scoring of atopic dermatitis (SCORAD) is a clinical tool used to assess the extent and severity of AD. This score integrated the Investigator's assessment of body area affected and the intensity of symptoms, as well as subject's reported itch and sleep loss.

There are 3 parameters (A, B and C):

- A: The extent of AD was a percentage of body surface affected by AD, with a maximum score of 100%.
- B: The severity of 6 specific symptoms of AD (of average representative area) was assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points). Note dryness is evaluated on uninvolved area.
- C: Subjective assessment of itch and sleep loss (average value for the last 3 days/ nights) was recorded for each symptom by the patient on a visual analogue scale (VAS), where 0 is no itch (or sleep loss) and 10 is the worst imaginable itch (or sleep loss), with a total maximum possible score of 20.The SCORAD was calculated as: A/5 + 7B/2 + C.

Numerical Rating Scale for Itch

Subjects were asked to respond to the question: “How would you rate your itch at the worst moment during the previous 24 hours?”. The subjects responded by rating on a numerical scale from minimum 0 (no itch) to maximum 10 (worst itch imaginable). Starting from the baseline visit until the end of study visit, each subject completed this assessment every day, recording the rating in a diary.

Statistical methods:

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. Summary statistics included mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum and the frequency (n, %) of concentrations below the LLOQ and reported as zero. Descriptive summary statistics were provided for blood PK parameters. An exception for this was Tmax where median, minimum and maximum were presented. Concentrations below LLOQ were treated as zero in summary statistics and for PK parameter calculations. A geometric mean was not reported if the dataset included zero values.

Since LOU064 is an irreversible inhibitor of BTK, the PD effects were determined by the extent and duration of BTK target occupancy by LOU064. Free BTK levels (not bound to LOU064) were measured in whole blood by ELISA.

Basophil activation, soluble biomarkers, immunoglobulins (IgE, IgG and IgA levels) and the exploratory hematology assessments data (TEG) were listed by treatment, subject, and visit/time. Summary statistics were provided by treatment and visit/time.

To allow for a pairwise comparison of LOU064 group versus placebo group, the percent change from baseline in EASI total score was analyzed using a Bayesian mixed effect model for repeated measures (MMRM) with treatment group, baseline EASI and baseline IGA (baseline adjustment for covariates), visit, baseline EASI*visit, baseline IGA*visit and treatment group*visit as fixed effects. Non-informative priors were utilized for the fixed effects and weakly informative prior for the covariance. An unstructured covariance was assumed. Note that the baseline IGA*visit interaction had to be excluded from the MMRM so that the model would converge. The posterior estimates of the treatment effect and the treatment difference (along with its 90% credible interval) at each post baseline visit (with Week 4 being of primary interest) were provided.

Summary – Results

Demographic and background characteristics:

The mean/median age of the subjects was 24.8/23.0 years with a range between 19 and 42 years. The mean age in the LOU064 group was similar (25.2 years) to the placebo group (23.5 years). There were more females (58.3%) as compared to males (41.7%) in the LOU064 group whereas there were more males (75.0%) as compared to females (25.0%) in the placebo group. The majority of subjects in both groups were white (81.3%). Body weight (mean 71.86 kg across both groups), body height, and BMI (24.024 kg/m^2 across both groups) were balanced between the treatment groups.

The mean baseline EASI total scores in the LOU064 group (19.888) were higher as compared to the placebo group (16.375). Similarly, the mean baseline SCORAD total scores were higher in the LOU064 group (55.9) as compared to placebo group (45.5) and the mean NRS for itch scores were higher in the LOU064 group (7.2) as compared to the placebo group (4.5). However, the mean baseline IGA scores were similar in both groups.

Pharmacokinetic results:

- LOU064 was found to have a rapid absorption (Tmax, ranging between 0.5 h - 4.23 h) following the initial dose of 100 mg. Higher exposure increase in Cmax and AUC and a slightly longer Tmax was observed at Day 29 compared to the first dose.
- The median elimination half-life (T1/2) calculated after bid dosing at steady state (D29), amounted to about 2.89 hr.

Pharmacodynamics and efficacy exploratory results:

- After the first dose, free BTK levels dropped to zero and remained undetectable throughout the 4-week treatment period and up to 24 hrs after the last dose. Free BTK levels rose to almost pre-study level at the EOS Visit suggesting full occupancy by LOU064 during the entire treatment period with recovery to pre-dose levels thereafter. Free BTK levels in the placebo group remained unaffected.
- In the LOU064 100 mg bid, the dose percent inhibition of stimulated basophils (monitored by CD63 surface marker expression) was near complete from Day 1, 8 hrs to Day 30, 24 hrs. In the placebo group, basophil activation as measured by CD63 was not affected.
- The percent change from baseline in the EASI total score showed a similar trend for both the active and the placebo group. None of the analyses based on the overall EASI scores indicated any meaningful clinical efficacy of LOU064 over placebo.
- Similarly, for the IGA scores and SCORAD total scores no noteworthy effect was observed in the comparison between the groups.
- There was a decline in itch symptoms as measured by numerical rating scale change (average change from baseline) for the LOU064 group in contrast to the placebo group, which showed an increase. This was both apparent in change from baseline as well as in the MMRM model.

Safety results:

- LOU064 was safe and well tolerated in the dose tested (100 mg bid) over the entire treatment period of four weeks in subjects with AD.
- There were no SAEs, deaths, or severe AEs in the study and none of the AEs led to study treatment discontinuation.
- No clinically significant changes were observed in the hematology, biochemistry, or urinalysis parameters after administration of LOU064.
- No clinically significant changes were observed in the vital signs and ECG parameters after administration of LOU064

Conclusion:

- Small patient population (17 randomized, 16 exposed) with baseline imbalance in gender distribution and itch score
- Complete and maximum PD effect on BTK occupancy and Basophil activation throughout the 4 week treatment in the active group was observed
- 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, this is not considered relevant
- No apparent effect on typical clinical disease scores for AD (EASI, SCORAD, IGA)
- Probability for a relevant treatment effect of LOU064 on clinical parameters in AD (EASI-reduction compared to Placebo -15%) is low (26%)
- Possible isolated effect on itch symptom, potentially related to inhibition of basophil degranulation provides a basis for further Biomarker assessment to better understand itch pathophysiology
- No new safety signals and no major infections were reported.

History of changes to the synopsis			
Version	Date (content final)	Summary of Changes	Change to overall conclusion
1.0	14-Aug-2020	Original version	