Supplementary Information Table of Contents

Pharmacokinetics

Supplemental Figure S7 shows the mean plasma concentrations of dapansutrile per cohort for each visit. Plasma dapansutrile concentrations on day 3 were only slightly lower than those on day 7 and indicate that all patients were exposed to the drug over the 8-day treatment period. Exposures increased as the daily dose increased, with mean plasma concentrations ranging from < 5 μg/mL in cohort 4 (100 mg/day) to between 50 and 60 μg/mL in cohort 2 (2000 mg/day). At the day 14 visit, plasma concentrations had fallen to below 5 ng/mL in all subjects. These results are consistent with the previously reported half-life of dapansutrile and plasma concentrations in healthy volunteers after an 8-day treatment period[1].

References

1. Marchetti C, Swartzwelter B, Gamboni F, et al. OLT1177, a beta-sulfonyl nitrile compound, safe in humans, inhibits the NLRP3 inflammasome and reverses the metabolic cost of inflammation. *Proc Natl Acad Sci U S A* 2018; **115**(7): E1530-E9.

Summary of Protocol changes

(Versions 1.0 and 2.0 were submitted for Ethics Committee (EC) review/approval but required additional changes)
Version 3.0 dated 24 January 2017:

- first version approved by EC

Version 3.1 dated 02 March 2017:

- changed chemistry testing: amylase removed and lipase added. Rationale: lab no longer performed amylase testing and instead performed lipase testing, which was determined by Study team and Sponsor to be an acceptable alternative.
- clarified dispensation and return of study materials.

Version 3.2 dated 06 June 2017:

- changed visit window for Day 3 visit to allow visit to occur a day after Day 3 (i.e., Day 3 visit window changed to "+/- 1 day" from "- 1 day"). Rationale: to avoid study visits during the weekends.

Version 4.0 dated 08 September 2017:

- changed prohibited use of paracetamol to within 4 hours of baseline visit (from within 12 hours of baseline visit). Rationale: to increase speed of inclusions. Short half-life of paracetamol (1-4 hours) supported a decreased timespan.

Version 5.0 dated 22 March 2018:

- added exclusion criteria for known diagnosis of chronic kidney disease or known history of renal impairment (e.g. calculated glomerular filtration rate [GFR] less than 40 mL/min). Rationale: It was noted that one subject had relatively elevated plasma levels of dapansutrile with a history of a moderate decline in renal function. The GFR requirement was added as a safety factor while non-clinical studies were undertaken to identify and quantify the route of excretion.
- changed Cohort 2 dose administration to 500mg QID (from 1000mg BID). Rationale: the dosage form was 100 mg capsules. The number of 100 mg capsules needed for 1000mg BID for each dose was difficult to take and potentially increased the risk of diarrhoea from gel capsule shells and capsule excipients. To prevent any possible side effect and to assure full dose compliance, the dose was spread over 4 timepoints.
- changed urate lowering therapy (a prohibited concomitant medication/therapy) stable dosing condition to 1 month (from 3 months). Rationale: to optimize inclusion without increasing risk
- allowed usage of medical data from synovial fluid collection/analysis from within 24 hours prior to baseline visit as part of standard medical diagnosis to be used and reported in study CRFs. Rationale: to reduce the burden for participants who had already had synovial puncture the day before.
- added discretionary replacement of any subject who did not complete dosing through the Day 7 visit. Rationale: a minimal number of participants of 8 subjects per cohort was selected as the minimally sized cohort to ascertain preliminary clinical utility.
- removed requirement that at least three subjects per cohort must be enrolled with a gout flare that began within 36 hours of the baseline visit. Rationale: to increase speed of inclusion.
- added suggested (not required) subject contact for dosing compliance. Rationale: to promote dosing compliance.

Version 5.1 dated 22 August 2018:

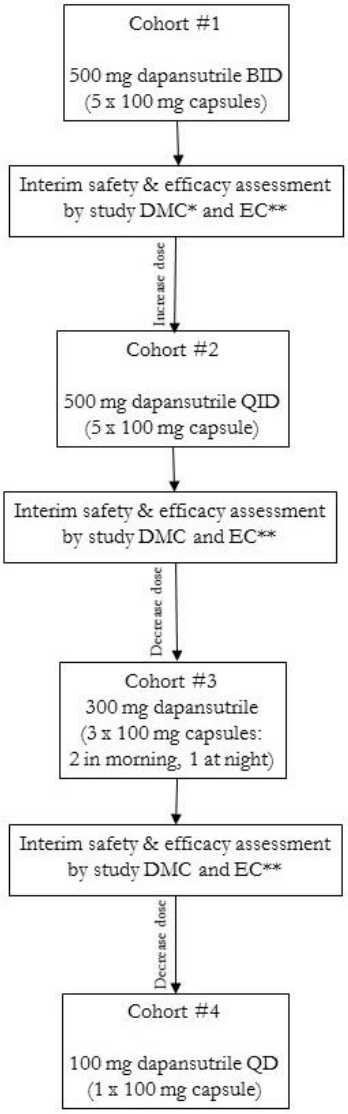
- changed decision tree for determination of dose schedule for Cohort 3 to decreased dose of 300mg per day (from 1600 mg per day) and removed increased dose option of 3000mg per day. Rationale: The safety and clinical response between 1000 mg and 2000 mg doses was approximately the same and achieved our primary and secondary endpoints. Therefore, rather than going to a higher dose, it was elected to explore clinical response activity at lower doses.

Version 6.0 dated 02 October 2018:

- added Cohort 4 with 8 patients dosing at 100mg per day thereby changing total enrolment to approximately 32 eligible subjects (from approximately 24 eligible subjects). Rationale: we observed clinically important effects, but without a clear dose response effect in the 1000mg-2000mg-300mg groups. The Study team and Sponsor elected, therefore, to expand the study to include a fourth cohort receiving a lower dose to explore its safety and clinical activity.

- decision tree for determination of dose schedules was removed and replaced with a table to reflect actual trial dosages

Tables and figures



Supplemental Figure S1 Study flow for dose selection *The DMC convened and reviewed all relevant safety and efficacy data (after completion of the day 7 visit for all subjects in a cohort) to determine whether an increase or decrease in total daily exposure is warranted. If adverse events or other safety concerns preclude an increase in total daily exposure or if pain reduction of ≥ 60% is achieved for at least 75% of subjects in a cohort at the day 3 (evening) timepoint, then the total daily exposure was decreased for the next cohort. If no adverse events or other safety concerns preclude an increase in dose and pain reduction of ≥ 60% was not achieved for at least 75% of subjects in a cohort at the day 3 (evening) timepoint, then the total daily exposure was increased for the next cohort. Practically, this meant the following decisions were made: while effective pain relief and reduction in cytokines were noted at 1000 mg/day without any significant safety findings, it was elected by the DMC to double the dose to 2000 mg/day. Since there was no incremental change in clinical response, it was chosen not to increase the dose even further, but to go on to the de-escalation phase. The 3rd cohort was given 300 mg/day with remarkably approximately the same clinical benefit. The study was then amended to explore the use of 100 mg/day.

**The interim analysis and DMC recommendation was submitted to the Ethics Committee upon completion. Documented Ethics Committee approval/agreement had to be obtained prior to progression to the subsequent cohort, regardless of the decision to decrease or increase dose.

Abbreviations: DMC, Data Monitoring Committee; EC, Ethics Committee; BID, bis in die/twice daily; QID, quarter in die/four times a day; QD, quaque die/daily

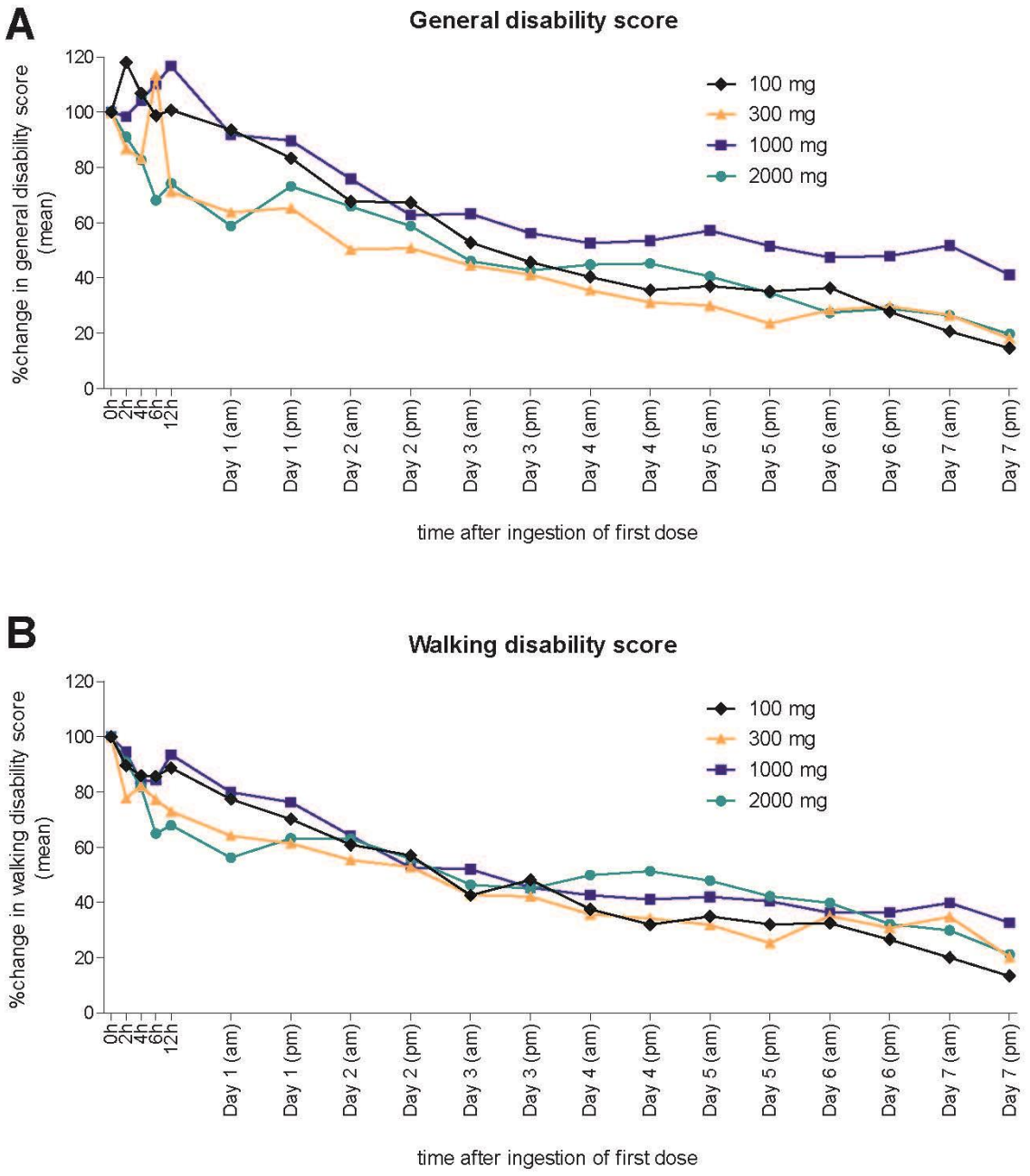
Supplemental Table S1 In- and exclusion criteria

Principal inclusion criteria 1) Male and female subjects between 18 and 80 years old, inclusive 2) Gout in a joint of a subject's lower limbs (e.g. ankle, foot, knee, toe) as indicated by the presence of monosodium urate (MSU) crystals by microscopic evaluation of synovial fluid from the target joint and in accordance with ACR/EULAR 2015 Gout Classification Criteria 3) Confirmation of a gout flare in the target joint that began within 96 hours prior to the baseline visit, based on presence of subject-reported joint pain at rest of ≥ 50 mm on a 0 - 100 mm VAS and at least two of the following criteria in the target joint: a. Subject-reported flare b. Subject-reported warm joint c. Subject-reported swollen joint 4) Acceptable overall medical condition to be safely enrolled in and to complete the study (with specific regard to cardiovascular, renal and hepatic conditions) in the opinion of the investigator 5) Ability to provide written, informed consent prior to initiation of any study-related procedures, and ability, in the opinion of the investigator, to understand and comply with all the requirements of the study, which includes abstaining from use of pain or rescue medication and other prohibited medications*.
Principal exclusion criteria 1) Women of childbearing potential, or men whose sexual partner(s) is a woman of childbearing potential, who: a. Are or intend to become pregnant (including use of fertility drugs) during the study b. Are nursing [female subjects only] c. Are not using an acceptable, highly effective method of contraception until all follow-up procedures are complete. 2) Presence of an acute gout flare in more than one joint at the baseline visit 3) Presence of another inflammatory arthritis in addition to gout 4) Presence or known history of other autoimmune conditions (e.g. systemic lupus erythematosus, hypophysitis, etc.) 5) Clinically significant general pain or non-gout related joint pain that would interfere with the subject's ability to accurately assess pain in the target joint, at the discretion of the investigator 6) Use of any prohibited concomitant medications/therapies or planned use of any concomitant medications/therapies* during the Treatment Period (including the use of paracetamol within 4 hours prior to the baseline visit or other pain medications within 12 hours prior to the baseline visit) 7) Active infection within 3 days prior to the baseline visit 8) History of or known positive for HIV, Hepatitis B surface antigen (HBsAg) or antibodies to Hepatitis C Virus (HCV) 9) Diagnosed with any form of internal cancer within the past 5 years 10) Any other concomitant medical or psychiatric conditions, diseases or prior surgeries that in the opinion of the investigator would impair the subject from safely participating in the trial and/or completing protocol requirements 11) History of alcohol or substance abuse within the 12 months prior to the baseline visit 12) Enrolment in any trial and/or use of any investigational product or device within the immediate 30-day period prior to the baseline visit 13) Enrolment in any study previously sponsored by Olatec Therapeutics LLC, specifically Study OLT1177-01, Study OLT1177-02, Study OLT1177-03 or Study OLT1177-04 14) Known diagnosis of chronic kidney disease or known history of renal impairment (e.g. calculated glomerular filtration rate [GFR] less than 40 mL/min)

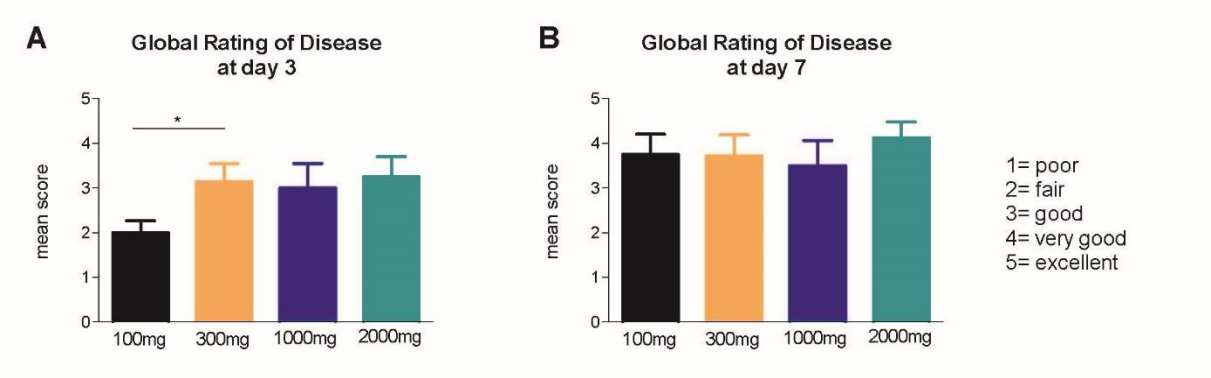
*prohibited concomitant medications: paracetamol (rescue medication, only allowed 12 hours after the first dose of dapansutrile), pain medications (except stable dose ASA for cardiovascular prophylaxis), icing therapy, colchicine, systemic or intraarticular steroids, other investigational products, chemotherapeutic drugs, immunotherapies, SSRIs, SSNRIs or TCAs (unless stable dose to treat depression for ≥ 3 months, narcotics, NSAIDs.

Supplemental Table S2 Use of Rescue Medication for gout in per-protocol population. Beginning 12 hours after the first dose of dapansutrile, subjects were allowed to take up to 4 g paracetamol orally per day as Rescue Medication.

	100 mg n=8	**300 mg n=7**	**1000 mg n=6**	**2000 mg n=8**
Rescure Medication Given n(%)				
Yes	4 (50·0)	2 (28·6)	3 (50·0)	4 (50·0)
No	4 (50·0)	5 (71.4)	3 (50·0)	4 (50·0)
Time to Rescue Calculations for Subjects taking RM				
Mean (SD)	31·0 (26·1)	23·0 (15·1)	25·2 (19·3)	31·0 (7·5)
Median	21·6	23·0	15·0	33·5
Min, Max	12·0, 68·7	12·3, 33·8	13·1, 47·5	20·0, 36·8



Supplemental Figure S2 General disability and Walking disability declined during treatment with dapansutrile. General disability (A) and Walking disability (B) were scored on a 0-100 mm VAS scale twice daily. Mean of percent reduction for all timepoints are shown for each cohort. Baseline values were set at 100%.



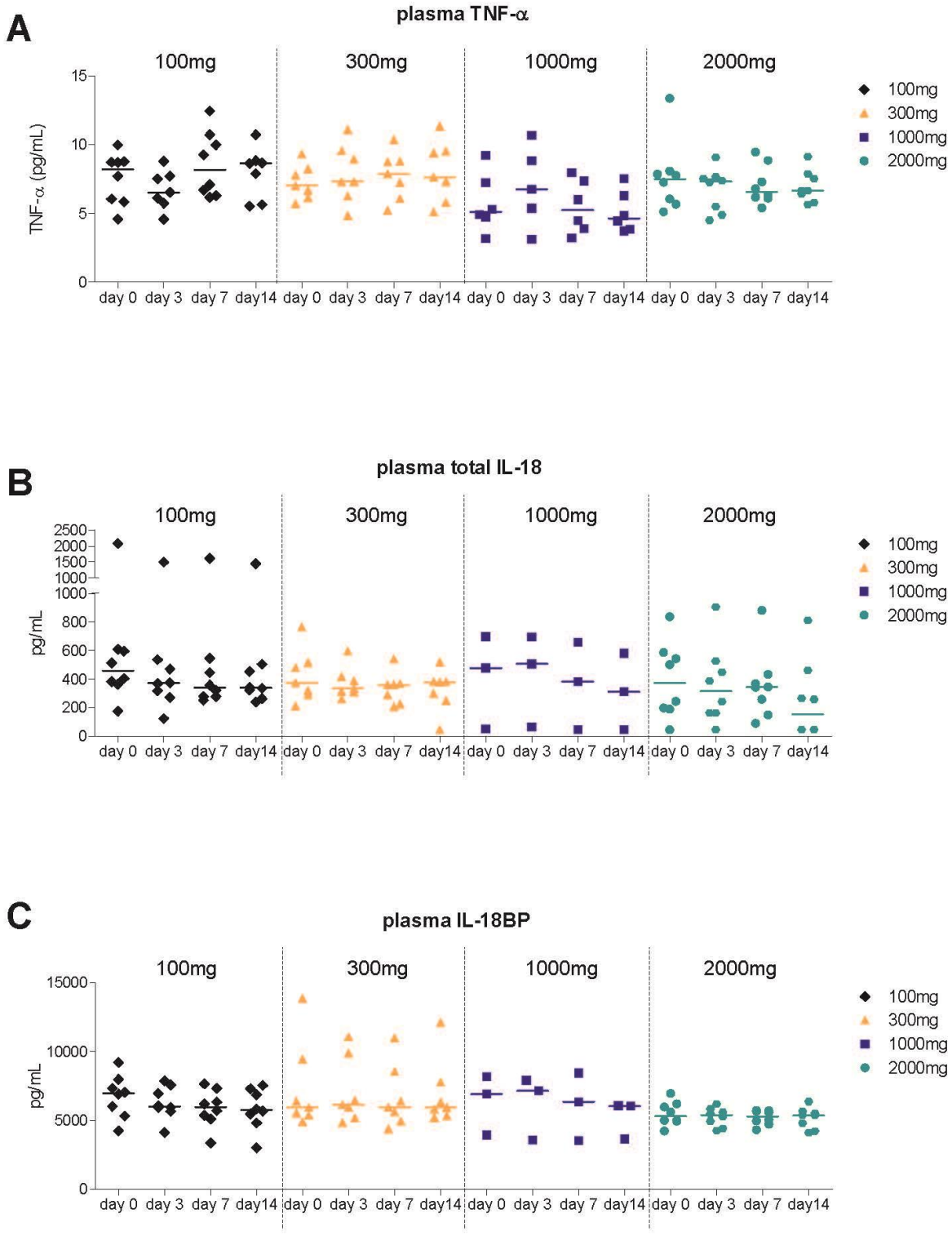
Supplemental Figure S3 Global rating of disease at day 3 and 7. Global rating of disease was scored at day 3 and 7 by investigator. 1=poor; 2=fair; 3=good; 4=very good; 5=excellent. Data are expressed as mean ± SEM. Mann-Whitney test for differences between cohort 100mg and 300mg demonstrated p=0.044.

Supplemental Table S3 Target joint scores for baseline, day 3 and day 7 for intention-to-treat population. Target joint pain was scored on a 0-100 mm VAS scale twice daily, i.e., in the morning (AM) and in the evening (PM). The primary efficacy analysis was performed on the day 3 evening scores as per the study's Statistical Analysis Plan. For the day 7 visit, if the subject's study visit occurred on day 7 and subjects did not record PM VAS measurements, the AM VAS measurement was used for analysis. Wilcoxon matched-pairs signed rank test two-tailed for differences between baseline and day 3 or day 7. Data presented as mean (SD).

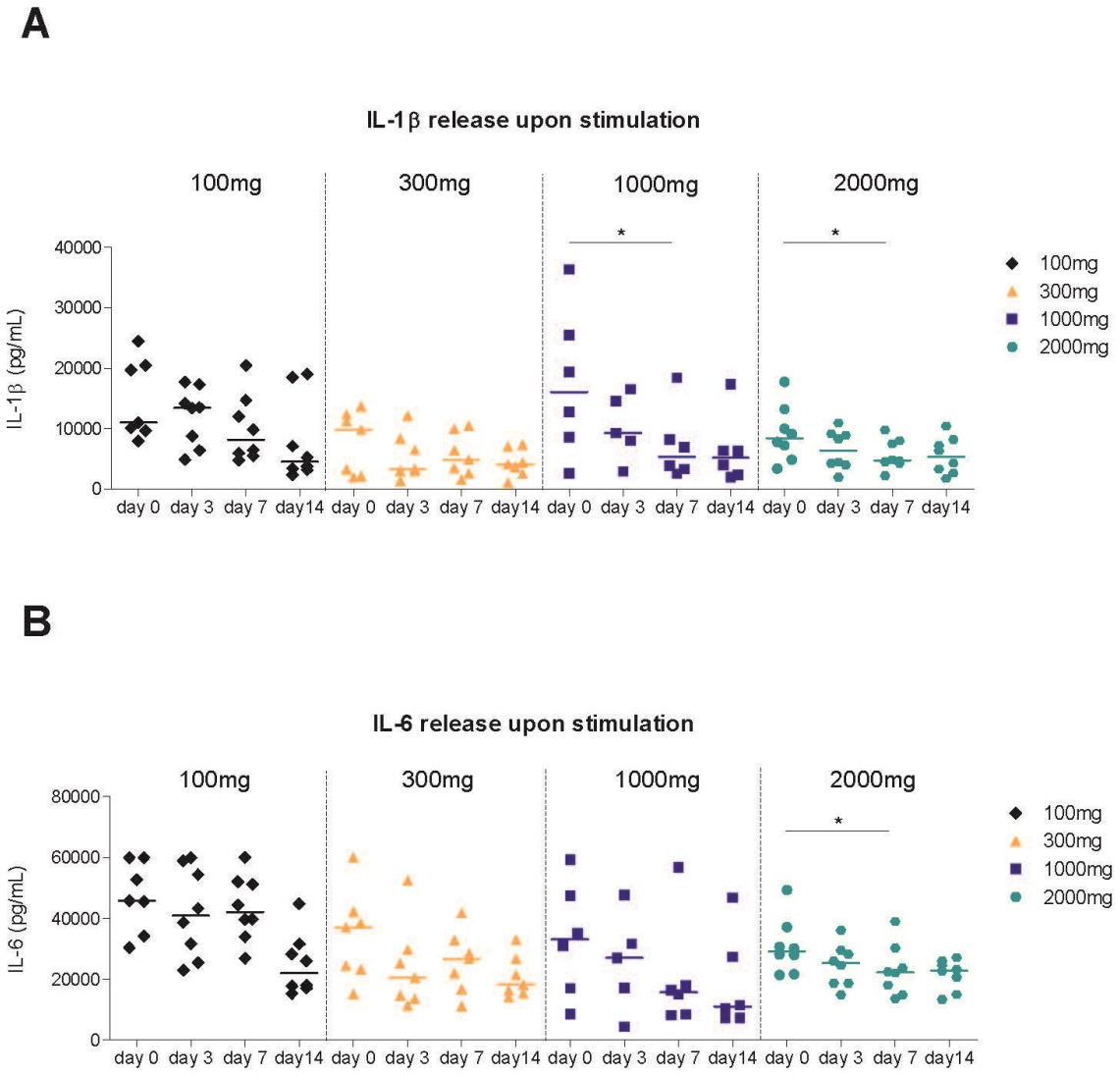
	100 mg n=8	**300 mg n=8**	**1000 mg n=10**	**2000 mg n=8**
Day 3 (pm)				
N in analysis	8	7	7	8
% Change from baseline, mean (SD)	-52·4 (32·94)	-68·4 (34·29)	-41·8 (55·36)	-57·6 (38·72)
p-value	p=0·016	p=0·016	p=0·109	p=0·016
Day 7 (pm)				
N in analysis	6	8	6	8
% Change from baseline, mean (SD)	-82·1 (22·68)	-85·5 (15·60)	-68·9 (34·89)	-83·9 (15·44)
p-value	p=0·031	p=0·008	p=0·031	p=0·008

Supplemental Table S4 Acute phase proteins and white blood cell counts Wilcoxon signed rank test were performed to detect differences between baseline and day 3 or day 7. *p<0·05.

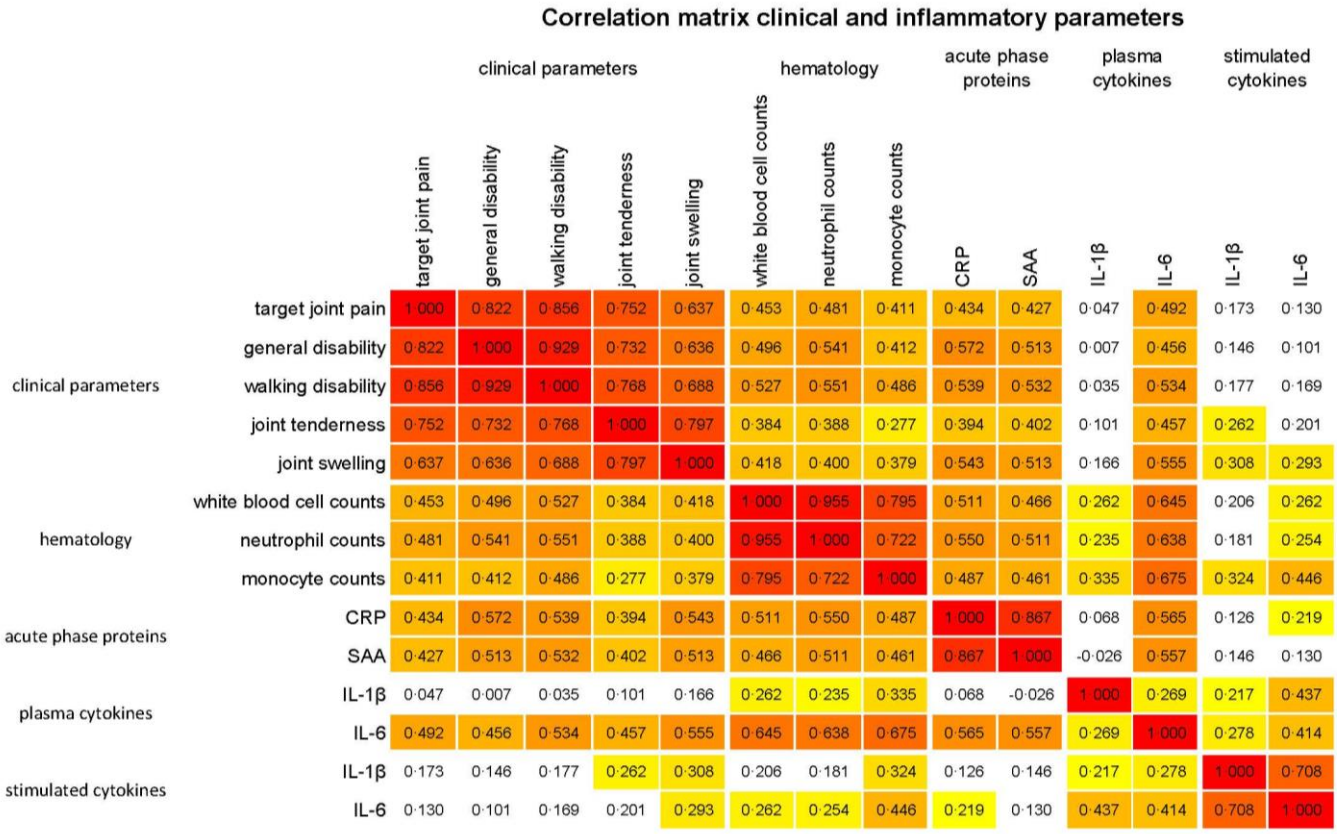
	100 mg n=8	300 mg n=7	1000 mg n=6	2000 mg n=8
CRP mg/L. mean (SD)				
Baseline	30·53 (63·84)	19·60 (16·27)	22·78 (31·20)	11·06 (8·57)
Day 3	39·95 (57·47)	41·03 (49·53)	39·54 (58·10)	9·18 (7·05)
Day 7	32·58 (52·53)	9·91 (11·41)	6·10 (3·86)	4·93 (3·85)
Day 14	2·99 (2·31)	6·57 (8·82)	1·37 (0·57)	4·43 (1·70)
SAA mg/L. mean (SD)				
Baseline	228·51 (614·86)	49·26 (63·86)	96·20 (192·72)	15·25 (14·12)
Day 3	293·15 (508·94)	259·11 (397·83)	275·38 (502·15)	15·35 (17·42)
Day 7	216·19 (381·39)	6·84* (6·18)	9·88* (7·32)	7·01* (7·36)
Day 14	6·78 (7·63)	10·83 (19·05)	2·70 (1·76)	5·91 (2·89)
WBC count 10^9/L. mean (SD)				
Baseline	9·75 (3·51)	9·70 (3·16)	8·55 (2·89)	8·54 (2·38)
Day 3	7·99* (1·93)	7·83* (2·62)	6·58 (2·13)	7·13 (1·74)
Day 7	7·86 (2·43)	7·31* (2·19)	6·93 (2·45)	7·34 (1·11)
Day 14	7·01 (1·50)	7·09 (1·59)	7·25 (3·14)	6·88 (1·43)
Monocyte count 10^9/L. mean (SD)				
Baseline	0·81 (0·25)	0·85 (0·35)	0·76 (0·30)	0·66 (0·15)
Day 3	0·76 (0·23)	0·64 (0·29)	0·59 (0·30)	0·58 (0·18)
Day 7	0·72 (0·23)	0·60* (0·21)	0·51 (0·20)	0·60 (0·17)
Day 14	0·59 (0·19)	0·57 (0·16)	0·54 (0·25)	0·50 (0·08)
Neutrophil count 10^9/L. mean (SD)				
Baseline	6·78 (3·78)	6·70 (2·70)	5·68 (2·25)	5·81 (1·93)
Day 3	5·31 (2·01)	5·02* (2·27)	4·33 (1·66)	4·24* (1·52)
Day 7	5·15 (2·13)	4·58 (1·46)	4·28 (1·93)	4·58 (0·80)
Day 14	3·99 (1·14)	4·39 (1·08)	4·72 (2·51)	4·34 (1·37)



Supplemental Figure S4 Plasma TNF-α, total IL-18 and IL-18BP during treatment with dapansutrile. At all timepoints (baseline, t=3, t=7 and t=14) EDTA plasma was collected and plasma TNF-α (A) was determined by Ella (Protein Simple) and total IL-18 (B) and IL-18BP (C) by R&D quantikine kits. For three individuals from the cohort of 1000mg/day insufficient amount of plasma was available for IL-18 and IL-18BP measurements.



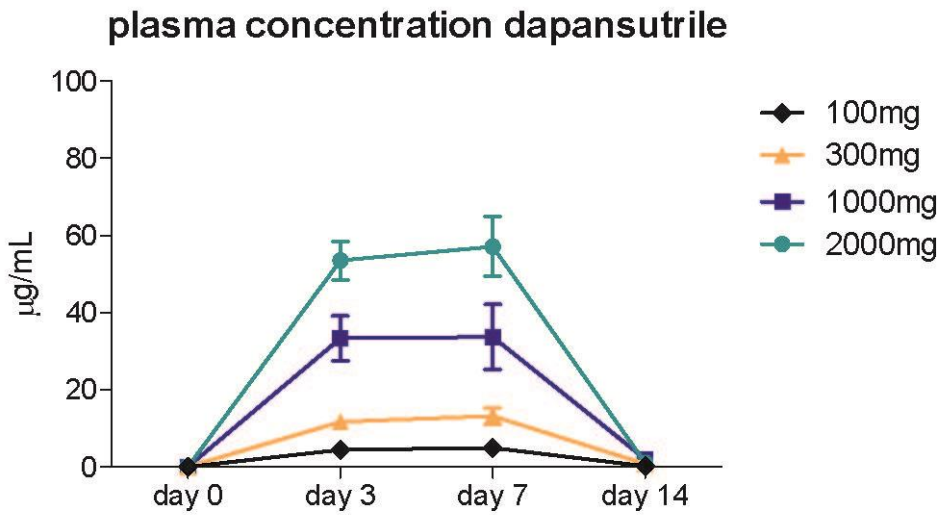
Supplemental Figure S5 Cytokine release from patients' stimulated PBMCs decline during treatment with dapansutrile. At each timepoint (day 0, 3, 7 and 14) PBMCs were isolated by density gradient isolation using Ficoll-paque. PBMCs were subsequently stimulated with the combination of LPS (10 ng/mL) and MSU crystals (300 µg/mL) for 24h. IL-1β (A) and IL-6 (B) were measured by ELISA Duoset (R&D Systems) in the supernatant. Data are presented as scatterplot and median. *p<0·05 (Wilcoxon matched-pairs signed rank test for differences between baseline and day 7).



Supplemental Figure S6 Correlation matrix clinical and inflammatory parameters. At timepoints baseline, day 3 and day 7 clinical parameters (subject-reported target joint pain, general and walking disability, and investigator-assessed joint tenderness and swelling) and markers of inflammation were assessed. Spearman's correlation was performed to analyse the correlation between all variables. Numbers present the correlation coefficient rho. Uncoloured boxes are not statistically significant. Significant correlations are coloured on a two-coloured scale with in yellow significant correlations with the lowest rho and in red the highest correlation coefficient.

Supplemental Table S5 Description of serious adverse events

Case 1 A 68-year-old male subject was enrolled in cohort 1 (Subject #032-002) and received 2000 mg QD of dapansutrile capsules (5 x 100 mg capsules per dose) over 3 days. Two days after the last dose of investigational product, the subject was hospitalized due to worsening gout flare. He was treated with diclofenac 100 mg orally twice a day for four days and methylprednisolone 500 mg intravenously (IP) once a day for three days. The subject's medical history is relevant for severe tophaceous gout, hypertension and prostatic hypertrophy. Concomitant medications taken within 2 weeks of the SAE included allopurinol 300 mg orally (PO) QD, prednisone 30 mg PO QD, nifedipine 30 mg PO QD, and pantoprazole 20 mg PO QD. The suspected cause of this SAE was the initiation of allopurinol therapy 3 weeks prior to enrolment, which was a major protocol deviation (i.e., allopurinol was prohibited unless the subject was on a stable dose for at least 3 months prior to the baseline visit). In the principal investigator's opinion, the gout flare was of moderate severity, unrelated to the investigational product and unexpected. The event resolved without sequelae 3 days after it began. Investigational Medicinal Product (IMP) was discontinued due to the SAE.
Case 2 On 09 February 2018, 18 days after the last dose of dapansutrile capsules, this subject was admitted in the hospital due to chest pain after an elective percutaneous coronary intervention (PCI). The chest pain he experienced was attributed to post-PCI infarction due to 99% stenosis of the D1 branch of the left coronary artery. During admission his ECG showed several times that he had (non-sustained) ventricular tachycardia and he remained in the hospital for a few days for observation. He was started on treatment with spironolactone and acetylsalicylic acid. His cardiac rhythm returned to normal and the cardiac symptoms resolved. The event was considered resolved, and he was discharged from the hospital, on 14 February 2018. Spironolactone and acetylsalicylic acid were continued after discharge. During hospitalization he had a gout flare in the right first metatarsophalangeal joint, which started on 13 February 2018. On evaluation it was found to be mild in severity and was not considered an SAE. He was started on treatment with prednisolone. The gout flare was not resolved at the time of hospital discharge and prednisolone was continued. In the principal investigator's opinion, the post-PCI infarction was considered moderate in severity, unrelated to the IMP, and unexpected.



Supplemental Figure S7 Plasma dapansutrile concentrations measured during the eight day dosing period (baseline, day 3 and day 7) and one week after stopping study drug (day 14). Data is plotted as mean ± SEM.

CLINICAL TRIAL PROTOCOL

OLT1177-05

English Title: A Phase 2 Single-Center, Proof-of-Concept Safety and Efficacy Study of Orally Administered OLT1177 Capsules with Successive, Result-Dependent Dose Adaptation in Subjects with an Acute Gout Flare

Dutch Title: Een fase 2, mono-centrische, proof-of-concept studie om de veiligheid en werkzaamheid te bepalen van oraal toegediende OLT1177 capsules in proefpersonen met een acute jichtaanval, waarbij resultaat-afhankelijk de dosis opeenvolgend wordt aangepast

Drug Development Phase:	Phase 2
Investigational product:	OLT1177
Indication:	Acute Gout Flare
Sponsor:	Olatec Therapeutics LLC
Protocol Version:	3.1

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

CONFIDENTIAL INFORMATION

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: OLATEC THERAPEUTICS LLC

I have read and understand the contents of this clinical protocol for Study OLT1177-05 (Version 3.1 dated 02 March 2017) and agree to meet all obligations as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this clinical trial.

Approved By:

Damaris Skouras
Chief Executive Officer, Olatec Therapeutics LLC

09 March 2017
Date

Robert B. Barrow

09/MAR/2017
Date

Robert Barrow
Chief Operating Officer & Sponsor Representative,
Olatec Therapeutics LLC

Curtis L. Scribner, MD
Chief Medical Officer & Medical Monitor
Olatec Therapeutics LLC

Date

Dianne Ekkel
Study Project Manager & CRA
Clinical Trial Service

10/Mar/2017
Date

Amy K. Poshusta, PhD
Regulatory Affairs

09 March 2017
Date

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: OLATEC THERAPEUTICS LLC

I have read and understand the contents of this clinical protocol for Study OLT1177-05 (Version 3.1 dated 02 March 2017) and agree to meet all obligations as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this clinical trial.

Approved By:

Damaris Skouras **Chief Executive Officer, Olatec Therapeutics LLC**	Date
Robert B. Barrow	09/MAR/2017
Robert Barrow **Chief Operating Officer & Sponsor Representative, Olatec Therapeutics LLC**	Date
Curtis L. Scribner	09 MAR 2017
Curtis L. Scribner, MD **Chief Medical Officer & Medical Monitor** **Olatec Therapeutics LLC**	Date
Dianne Ekkel **Study Project Manager & CRA** **Clinical Trial Service**	Date
Amy K. Poshusta, PhD **Regulatory Affairs**	Date

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study OLT1177-05 (Version 3.1 dated 02 March 2017) and will adhere to the clinical trial requirements as presented, including all statements regarding confidentiality.

By signing the protocol, I agree to keep all information provided by Olatec Therapeutics LLC ("Olatec") in strict confidence and to request the same from my personnel and the Ethics Committee ("EC"). Clinical trial documents provided by Olatec (protocols, Investigator's Brochure, CRFs and other materials) will be stored appropriately to ensure their confidentiality. I understand that information provided by Olatec may not be disclosed to others without direct written authorization from Olatec. In addition, I will conduct the clinical trial in accordance with current Good Clinical Practices and applicable local and European Union regulatory requirements:

Principal Investigator's Signature: _____

Principal Investigator's Name: _____

Institution: _____

Date: _____

PROTOCOL SYNOPSIS

Sponsor: Olatec Therapeutics LLC	**Investigational Medicinal Product:** OLT1177	**Developmental Phase:** Phase 2

Title of Clinical Trial: A Phase 2 Single-Center, Proof-of-Concept Safety and Efficacy Study of Orally Administered OLT1177 Capsules with Successive, Result-Dependent Dose Adaptation in Subjects with an Acute Gout Flare

Protocol Number: OLT1177-05

Indication: Acute Gout Flare

Objectives:

1. To assess the safety and tolerability of OLT1177 Capsule after oral administration in subjects with an acute gout flare
2. To assess the clinical activity of various doses of OLT1177 Capsule in treating signs and symptoms resulting from an acute gout flare
3. To assess OLT1177-induced changes in inflammatory biomarkers.

Methodology: This is an open-label Phase 2, single-center, sequential, result-dependent dose adaptation proof-of-concept safety and efficacy study to be conducted in subjects with an acute gout flare. A total of approximately 24 eligible subjects will be enrolled sequentially in up to three cohorts of 8 subjects each.

Subjects will be screened for eligibility at the Baseline visit and enrolled into the study. Following enrollment, Baseline safety and efficacy assessments will be conducted and the first dose of investigational product will be administered at the clinical site. Subjects will then self-administer investigational product twice daily for Cohorts 1 and 2 and either one, two or three times daily for Cohort 3 (see Section 5.4.3) for up to eight (8) consecutive days beginning at the Baseline visit (Day 0) and continuing through the planned Day 7 visit. Subjects will return to the study clinic on Days 3, 7 and 14 for follow-up visits[1] and will be contacted by telephone on Day 35 (± 3 Days) for additional follow-up.

Safety assessments will be conducted at each visit and efficacy assessments will be captured by a paper study diary. Safety and tolerability will be evaluated by monitoring the occurrence of adverse events (AEs) and changes in abbreviated physical examination findings, vital signs and clinical safety laboratory test results (chemistry, hematology and urinalysis). Clinical activity will be evaluated by subject-reported pain and disability scales,

[1] Clinic visits occurring a day after the indicated Day 3 visit day (e.g., on study day 4 for the Day 3 visit) will be considered within the visit window and will not be a deviation from the protocol. Clinic visits occurring a day before or after the indicated Day 7 and 14 visit days (e.g., on study day 6 or 8 for the Day 7 visit) will be considered within the visit window and will not be a deviation from the protocol.

Sponsor: Olatec Therapeutics LLC	**Investigational Medicinal Product:** OLT1177	**Developmental Phase:** Phase 2
Investigator-assessed Index Joint Score and Global Rating of Disease, and analysis of biomarkers of inflammation.		

Diagnosis and Main Criteria for Inclusion:

1) Male and female subjects between 18 and 80 years old, inclusive
2) Gout in a joint of a subject's lower limbs (e.g., ankle, foot, knee, toe) as indicated by the presence of monosodium urate (MSU) crystals by microscopic evaluation of synovial fluid from the target joint and in accordance with ACR/EULAR 2015 Gout Classification Criteria
3) Confirmation of a gout flare in the target joint that began[2] within 96 hours prior to the Baseline visit[3], based on presence of subject-reported joint pain at rest of $\geq$ 50 mm on a 0-100 mm visual analog scale (VAS) and at least two of the following criteria in the target joint[4]:
    a. Subject-reported flare
    b. Subject-reported warm joint
    c. Subject-reported swollen joint
4) Acceptable overall medical condition to be safely enrolled in and to complete the study (with specific regard to cardiovascular, renal and hepatic conditions) in the opinion of the Investigator
5) Ability to provide written, informed consent prior to initiation of any study-related procedures, and ability, in the opinion of the Investigator, to understand and comply with all the requirements of the study, which includes abstaining from use of pain or Rescue Medication (for 12 hours after first dose of investigational drug) and other prohibited medications as outlined in Section 5.6.3 of the protocol.

[2] For the purposes of this study, the beginning of a gout flare is considered to be the time at which the subject reports having first experienced severe pain in the target joint. If a subject is unable to specify the exact time and date that the flare began, an approximation of time since beginning of flare shall be made and the subject's eligibility will be determined at the discretion of the Investigator.

[3] At least three subjects per cohort must be enrolled with a gout flare that began within 36 hours of the Baseline visit.

[4] This inclusion criterion requires that each subject meet the provisional definition of a gout flare as described in Gaffo et al., 2012.

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Main Criteria for Exclusion:

1) Women of childbearing potential, or men whose sexual partner(s) is a woman of childbearing potential who:
   a. Are or intend to become pregnant (including use of fertility drugs) during the study
   b. Are nursing [female subjects only]
   c. Are not using an acceptable, highly effective method of contraception until all follow-up procedures are complete. See Section 5.6.2 for more details on acceptable forms of contraceptives.
2) Presence of an acute gout flare in more than one joint at the Baseline visit
3) Presence of another inflammatory arthritis in addition to gout
4) Presence or known history of other autoimmune conditions (e.g., systemic lupus erythematosus, hypophysitis, etc.)
5) Clinically significant general pain or non-gout related joint pain that would interfere with the subject's ability to accurately assess pain in the target joint, at the discretion of the Investigator
6) Use of any prohibited concomitant medications/therapies over the periods defined in Section 5.6.3 or planned use of any concomitant medications/therapies during the Treatment Period (including the use of pain medications within 12 hours prior to the Baseline visit)
7) Active infection within 3 days prior to the Baseline visit
8) History of or known positive for HIV, Hepatitis B surface antigen (HBsAg) or antibodies to Hepatitis C Virus (HCV)
9) Diagnosed with any form of internal cancer within the past 5 years
10) Any other concomitant medical or psychiatric conditions, diseases or prior surgeries that in the opinion of the Investigator would impair the subject from safely participating in the trial and/or completing protocol requirements
11) History of alcohol or substance abuse within the 12 months prior to the Baseline visit
12) Enrollment in any trial and/or use of any investigational product or device within the immediate 30-day period prior to the Baseline visit
13) Enrollment in any study previously sponsored by Olatec Therapeutics LLC, specifically Study OLT1177-01, Study OLT1177-02, Study OLT1177-03 or Study OLT1177-04

Sponsor: Olatec Therapeutics LLC	**Investigational Medicinal Product:** OLT1177	**Developmental Phase:** Phase 2

Dose and Mode of Administration:

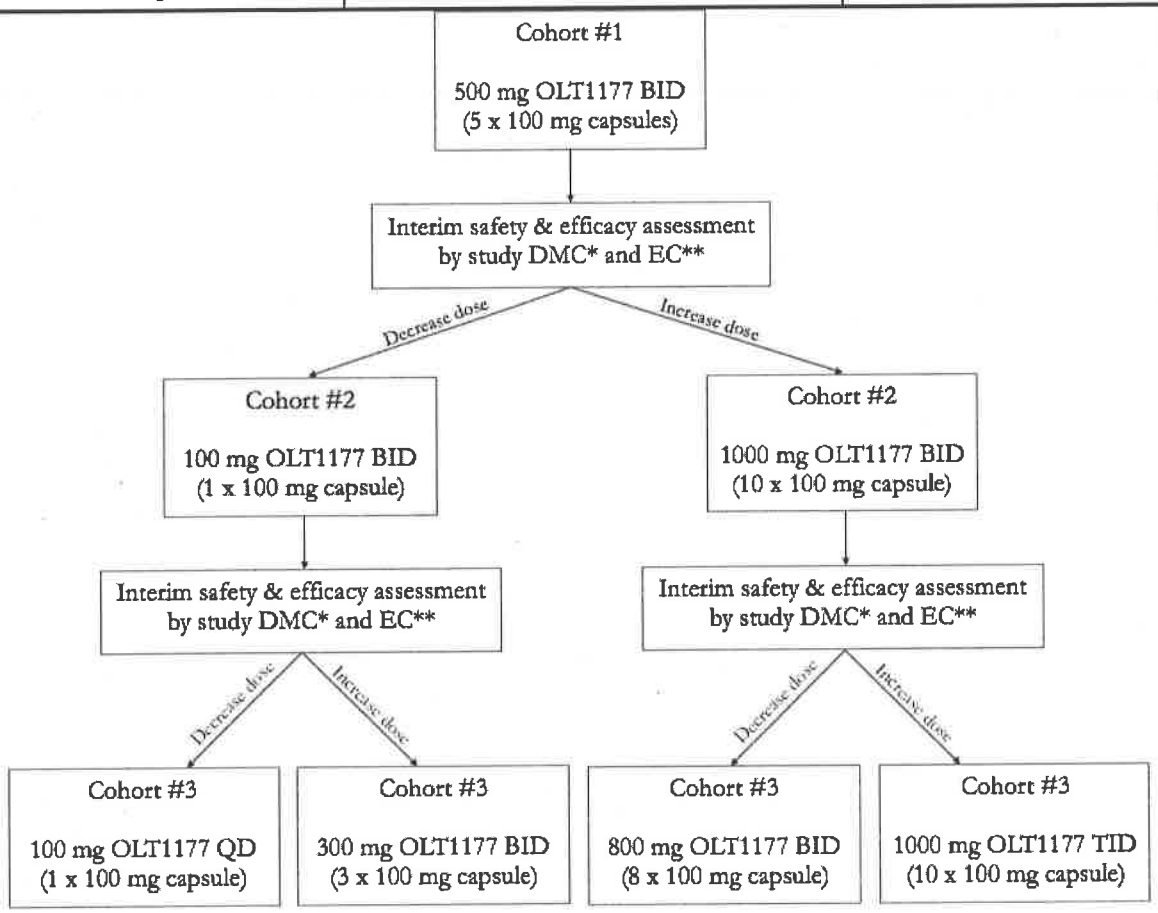
Investigational Product

Investigational product will be self-administered by mouth twice each day (BID) in Cohorts 1 and 2 beginning at the Baseline visit (Day 0) and continuing through the planned Day 7 visit. Investigational product will be administered either once (QD), twice (BID) or three (TID) times each day for Cohort 3, depending on the indicated dose and regimen in accordance with the dose selection flow chart (see Section 5.4.3). Depending on the time of the subject's Baseline visit and Day 7 visit, only one dose may be administered on those days. The first dose will be administered while in the study clinic under supervision of site personnel.

Dose Selection

The dose for Cohort 1 will consist of five 100 mg OLT1177 capsules dosed twice each day (for a total of 1,000 mg of OLT1177 drug substance per day). The dose for Cohorts 2 and 3 will be determined following analysis of safety and efficacy data of the preceding cohorts (after completion of the Day 7 visit for all subjects in a cohort) in the following manner and subject to determination by the Study Data Monitoring Committee (DMC):

Sponsor: Olatec Therapeutics LLC	Investigational Medicinal Product: OLT1177	Developmental Phase: Phase 2



*The DMC will convene and review all relevant safety and efficacy data (after completion of the Day 7 visit for all subjects in a cohort) to determine whether an increase or decrease in total daily exposure is warranted. If adverse events or other safety concerns preclude an increase in total daily exposure or if pain reduction of ≥ 60% is achieved for at least 75% of subjects in a cohort at the Day 3 (evening) timepoint, then the total daily exposure will be decreased for the next cohort. If no adverse events or other safety concerns preclude an increase in dose and pain reduction of ≥ 60% is not achieved for at least 75% of subjects in a cohort at the Day 3 (evening) timepoint, then the total daily exposure will be increased for the next cohort.

**The interim analysis and DMC recommendation will be submitted to the Ethics Committee upon completion. Documented Ethics Committee approval/agreement must be obtained prior to progression to the subsequent cohort, regardless of the decision to decrease or increase dose.

Rescue Medication

No Rescue Medication is allowed until 12 hours after the first dose of investigational drug.

At the Baseline visit, Rescue Medication (paracetamol, 1 g/dose) will be dispensed. Subjects will be instructed to record the amount and time of Rescue Medication use in the Study Diary. Beginning 12 hours after the first dose of investigational drug, subjects who are

Sponsor: Olatec Therapeutics LLC	Investigational Medicinal Product: OLT1177	Developmental Phase: Phase 2

unable to tolerate their pain will be allowed to take up to 4 g paracetamol orally per day (1 g QID) for the duration of the Treatment Period (through the Day 7 visit). No other pain, steroid or treatments for gout flare are allowed during the Treatment Period.

If at any time during the study a subject is unable to tolerate his/her pain and wishes to receive standard medical intervention for an acute gout flare, the subject will be withdrawn from the study, considered a Treatment Failure and treated with either prednisolone (30 mg QD) or colchicine (0.5 mg TID).

Permitted Concomitant Medication

No concomitant medication is allowed during the course of the study with the exception of Rescue Medication and those described in Section 5.6.1, specifically including contraceptives.

Reference Therapy:

OLT1177 Capsule consists of OLT1177 API and Avicel PH-101.

Clinical Trial Duration:

The trial duration will be approximately 36 days for all subjects enrolled, which will consist of four visits to the study site: Baseline (Day 0), Day 3 (+ 1 day), Day 7 (± 1 day) and Day 14 (± 1 day); with a follow-up telephone call on Day 35 (± 3 days).

Safety Criteria for Evaluation:

Safety criteria for evaluation are as follows:

- Physical examination (abbreviated general and site specific examination)
- Vital Signs (pulse, resting blood pressure, temperature, respiration rate)
- Safety laboratory measures (chemistry, hematology and urinalysis)
- Safety electrocardiograms (ECGs)
- Adverse Events (AEs) during the clinical trial

Clinical Activity Outcomes:

The primary clinical activity outcome will be:

- Change in subject-reported pain intensity score from Baseline (Day 0) to Day 3 (evening; approximately 72 hours after the first dose) in the target joint (100-mm VAS)

The principle secondary clinical activity outcome will be:

Sponsor: Olatec Therapeutics LLC	Investigational Medicinal Product: OLT1177	Developmental Phase: Phase 2

- Subject-reported Global Evaluation of Treatment at Day 7 (Likert scale)

The following secondary clinical activity variables will be collected at Baseline and through Day 7:

- Subject-reported pain intensity score in the target joint (100-mm VAS)[5]
- Subject-reported general disability score in the target joint (100-mm VAS)[5]
- Subject-reported walking disability score in the target joint (100-mm VAS)[5]
- Investigator-assessed Index Joint Score (tenderness, swelling, erythema, warmth)
- Investigator-assessed Global Rating of Disease (Likert scale)
- Blood levels of high sensitivity C-reactive protein (hsCRP), Serum Amyloid A protein (SAA) and inflammatory cytokines

If at any time during the study a subject is unable to tolerate his/her pain and wishes to receive standard medical intervention for an acute gout flare, the subject will be withdrawn from the study, considered a Treatment Failure and treated with either prednisolone (30 mg QD) or colchicine (0.5 mg TID). In addition to the clinical activity variables described above, the number and proportion of Treatment Failures in each cohort will be captured and summarized in the study results.

Statistical Methods:

The study is designed as an open-label Phase 2 proof-of-concept study to determine subjects' response to administration of OLT1177 Capsule during an acute gout flare. The sample size of eight subjects per cohort has been determined to be of sufficient size to provide a preliminary estimate of this effect. Descriptive statistics will be presented for the outcomes as defined in the Statistical Analysis Plan.

Two populations will be defined for this study: 1) the Intent to Treat Population will consist of all subjects who have taken at least one dose of investigational product; 2) the Per-Protocol Population (PPP) will consist of all subjects who take 80% or more of the total expected doses of investigational product and have no major protocol violations as determined by the Medical Monitor.

The primary efficacy population will be the Per-Protocol Population. Missing data will be imputed in accordance with the Statistical Analysis Plan, which will be based on a mixed

[5] This variable is also collected at the Day 14 visit

Sponsor: Olatec Therapeutics LLC	Investigational Medicinal Product: OLT1177	Developmental Phase: Phase 2

imputation strategy. With specific regard to Treatment Failures, clinical activity outcomes will be imputed using Worst Observation Carried Forward (WOCF) to eliminate the potential bias introduced by subjects who withdraw from the study due to lack of efficacy. The efficacy analysis will include a responder analysis for 20% and 60% reduction in symptoms at 3 and 7 days after first administration of investigational product.

The Statistical Analysis Plan for Study OLT1177-05 contains a complete description of all analyses to be performed.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABR Form	Dutch General Assessment and Registration Form
ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine transaminase (SGPT)
API	Active pharmaceutical ingredient
ASA	Acetylsalicylic acid (aspirin)
AST	Aspartate transaminase (SGOT)
AUC	Area under the concentration-time curve
BID	Twice a day
BUN	Blood urea nitrogen
CBC	Complete Blood Count
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
cm	Centimeter
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CRO	Contract Research Organization
CSF	Colony stimulating factor
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HbA1c	Glycated haemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
hsCRP	High sensitivity C-reactive protein

Abbreviation	Definition
ICF	Informed consent form
ICH	International Conference on Harmonisation
IL	Interleukin
kg	Kilogram
mg	Milligram
mL	Milliliter
MSU	Monosodium urate
NCE	Novel chemical entity
ng	Nanogram
NLRP3	NOD-like receptor family, pyrin domain containing 3
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OTC	Over-the-counter
QD	Once a day
PK	Pharmacokinetic
PPP	Per-protocol Population
PRN	As needed
RBC	Red blood cell
SAA	Serum amyloid A
SAE	Serious adverse event
SID	Subject identification number
SSNRIs	Serotonin-norepinephrine reuptake inhibitor
SSRIs	Selective serotonin reuptake inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TCAs	Tricyclic antidepressants
TID	Three times a day
VAS	Visual analog scale

1 ETHICS

1.1 ETHICS COMMITTEE (EC)

The protocol, protocol amendments, subject recruiting materials, the informed consent form and any other materials provided to subjects must be approved by the competent authority and Accredited Ethics Committee. A copy of the approval notification must be received by the Sponsor and/or CRO prior to shipment of drug supplies to the site.

Records of the Ethics Committee's review and approval of all documents pertaining to the study must be kept on file by the Investigator and are subject to Sponsor and regulatory inspection at any time. The Investigator will provide required progress reports and report all SAEs to the Sponsor, which will promptly notify the EC and competent authority (as required).

1.2 ETHICAL CONDUCT OF THE STUDY

This trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the trial protocol, Good Clinical Practices (GCPs) as defined in European Union Directive 2005/28/EC (applicable to studies conducted in the European Union), Title 21 of the US CFR Parts 50, 54, 56, 312 and Part 11 (applicable to studies conducted in the United States), as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

1.3 SUBJECT INFORMATION AND CONSENT

Informed consent will be obtained from all subjects prior to any trial procedures being performed. All subjects will be given ample time to review the informed consent form and ask questions. A signed ICF must then be obtained prior to any trial procedures being performed.

This study will enroll both first-time gout patients and recurrent gout patients (see Section 4.2.1). Recurrent gout patients are known to the Investigator and will be provided the Patient Information Form and should provide Informed Consent prior to the occurrence of a study-eligible gout flare. First-time gout patients will likely be unknown to the Investigator (e.g., those referred by a general practitioner or visiting the Investigator for initial diagnosis) and will be provided the Patient Information Form at their first visit to the study clinic. Prospective study participants will be given ample time to review the informed consent form and ask questions and may decline participation in the study. If the patient chooses to participate in the study, informed consent will be obtained at their initial visit, which will be the Baseline visit for this study. See Section 4.2 for precedent references and discussion of this study design.

2 INTRODUCTION AND RATIONALE

Gout is a chronic condition characterized by hyperuricemia and the presence of monosodium urate (MSU) crystals in affected joints. Gout is the most common inflammatory arthritis with an increasing incidence over the past several decades, due at least in part to the rise in comorbidities that promote hyperuricemia, including hypertension, obesity, metabolic syndrome, type-2 diabetes mellitus, and chronic kidney disease. Furthermore, demographic and behavioral trends suggest that a continued growth in the incidence of gout may be likely (Decision Resources Group, 2012).

Periodically, subjects suffering from gout have a sudden onset of symptoms, or a "flare," which can include severe pain, joint swelling, redness and/or warmth due to inflammation secondary to intraarticular MSU crystals. Acute gout flares are a primary factor in the decreased health-related quality of life reported by subjects with gout and can be debilitating and associated with decreased work productivity (Roddy and Doherty, 2010; Khanna et al., 2012). The inciting factor may not be known, but the biological mechanism underlying the symptoms of an acute gout flare is a sudden and marked increase in synovial fluid neutrophils in affected joints, a process that is mediated by the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome and pro-inflammatory cytokines, specifically interleukin (IL)-1β (Martinon et al., 2006; Pope and Tschopp, 2007; Hoffman and Wanderer, 2010).

The current standard of care for an acute gout flare is non-steroidal anti-inflammatory drugs (NSAIDs), steroids or colchicine. Each of these therapies suffers from limitations in their application, due to risks associated with NSAID use and common comorbidities, risks associated with chronic or recurrent high dose steroid use or the narrow therapeutic window with colchicine.

Recently, biologic therapies targeting IL-1β (e.g., canakinumab) have demonstrated efficacy in gouty inflammation and have been approved for the treatment of acute gout flares, though their use has been limited due to safety concerns and the high cost of treatment. Given the potential safety issues and limited efficacy of currently available therapies, new pharmaceutical therapies are warranted. Preferably, these new therapies should involve novel mechanisms of action or inhibition of new biological targets in order to achieve improved efficacy with safety and tolerability profiles that would not limit their use.

Olatec's investigational product (OLT1177 Capsules) is in clinical development for the treatment of acute gout flares. The active pharmaceutical ingredient (OLT1177) is a small molecule novel chemical entity (NCE) that is a selective inhibitor of the NLRP3 inflammasome, resulting in a reduction in IL-1β processing and release (Marchetti et al., submitted for publication). Additionally, OLT1177 has demonstrated anti-inflammatory

activity in the murine MSU crystal-induced model of acute gout in addition to several other models of local and systemic inflammation. OLT1177 at high concentrations *in vitro* is not a cyclooxygenase (COX)-1 or -2 inhibitor, and has not been shown to bind to opioid receptors. Unlike the biologics, which bind directly to and neutralize IL-1β, OLT1177 inhibits the expression of IL-1β via inhibition of the NLRP3 inflammasome. This mechanism of action suggests that OLT1177 may provide the desired anti-inflammatory effects in the treatment of an acute gout flare without the adverse effects observed with the currently available therapies.

To support the clinical trials of OLT1177, a comprehensive nonclinical safety evaluation program was conducted for up to 14 days (oral administration) and 91 days (topical administration) in two species. Toxicology and safety pharmacology studies in rodents, minipigs and dogs have demonstrated that OLT1177 is well tolerated with no significant adverse events (local/dermal or systemic) after topical and oral administration and support administration of OLT1177 at doses of up to approximately 10 g per day.

Earlier clinical studies have shown that OLT1177 Capsules by oral administration are safe for durations of up to 8 days (1 g OLT1177 per day). Additionally, the topical dosage form of OLT1177 (OLT1177 Gel) has been shown to be safe for durations up to six weeks (18 g gel per day). This clinical trial is designed to investigate the clinical activity and safety of OLT1177 Capsules in subjects with an acute gout flare.

2.1 CLINICAL EXPERIENCE

One clinical study has been completed with OLT1177 Capsules to date (Study OLT1177-04). This study was a Phase 1 single- and multi-dose safety and pharmacokinetic study of orally administered OLT1177 Capsule for up to eight consecutive days at doses ranging from 100 mg QD to 1,000 mg QD in normal healthy volunteers and conducted in a single clinical site in the United States.

Additionally, three clinical studies have been completed with the investigational product in a topical dosage form (OLT1177 Gel), consisting of a Phase 1 topical dose-escalation safety study in normal healthy subjects (Study OLT1177-01), a Phase 2a 14-day topical safety and efficacy study (Study OLT1177-02) in subjects with mild-to-moderate osteoarthritis of the knee and a Phase 2b 6-week topical efficacy and safety study (Study OLT1177-03) in subjects with mild-to-moderate osteoarthritis of the knee. These studies were conducted at multiple clinical sites in the United States.

A summary of the known and potential risks and benefits, if any, to human subjects is contained in the Investigators Brochure for OLT1177.

2.1.1 Study OLT1177-04 – OLT1177 Capsules

Study OLT1177-04 was a Phase 1 single-center, placebo-controlled, sequential group, dose-escalation study of the safety and PK of 3 dosages of OLT1177 Capsules in 35 healthy male and female subjects aged 18 to 60 years. OLT1177 Capsules were administered orally at doses of 100, 300 and 1,000 mg OLT1177 in single-dose, fasted (Part A), single-dose, fed (Part B, 1,000 mg dose only) and multiple-dose (Part C) regimens. In Part A, 18 healthy volunteer subjects in 3 dose escalating cohorts were randomized to receive a single dose of the investigational drug (5 subjects OLT1177 Capsules and 1 subject Placebo Capsules in each cohort). Upon completion of Part A, subjects from the high dose group (1,000 mg) received a test (high fat) meal and single dose of OLT1177 Capsules 1,000 mg in Part B of the study. Upon completion of Part B, a new subject population of 17 subjects in 3 dose escalating cohorts was randomized in Part C of the study. Part C subjects received a total of 8 doses over 8 consecutive days given once per day and were followed for up to 30 days for safety assessment.

The primary objective of the study was to assess the safety and tolerability of OLT1177 Capsules in healthy subjects after oral administration. Secondary objectives were to: characterize and compare the pharmacokinetic profile of OLT1177 following single ascending doses by oral administration; evaluate the effect of food on the single-dose pharmacokinetics of OLT1177; and characterize and compare the multiple-dose PK profiles of OLT1177 following 8 consecutive days of oral administration.

Safety and tolerability was assessed by physical examination and measurement of vital signs, ECGs and clinical laboratory tests (e.g., chemistry, hematology, lipid profile, coagulation factor and urinalysis). Further, adverse events and concomitant medications were recorded. Blood was drawn for plasma OLT1177 PK analysis at pre-dose, 30 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 23, 48, 72, 96 and 168 hours post-dose in Part A. For Part B, blood was drawn prior to dosing and after 30 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 23, 48, 72, 96 and 168 hours post-dose. For Part C, blood was drawn prior to dosing and 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 23 hours post-dose on Day 1, pre-dose on Days 6 and 7; and on Day 8 prior to dosing and after 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 23 hours post-dose.

A total of 35 subjects were randomized in the study. Five subjects in each of the 3 active treatment groups and 1 in each of the 3 placebo groups in Parts A and C of the study were enrolled, with the exception of Cohort 5 for which only 4 subjects were enrolled. All enrolled subjects completed the study, with no discontinuations, and safety data were collected for all subjects enrolled. PK data were collected and reported only for subjects in the active treatment groups.

No deaths or serious adverse events occurred during the study. A total of 7 out of 35 (20.0%) subjects reported a total of 7 treatment-emergent adverse events with six occurring in the OLT1177 Capsules treatment group and one occurring in the Placebo Capsules group. The observed TEAEs in the OLT1177 Capsule treatment group were one instance each of: diarrhea, back pain, migraine, contact dermatitis, eczema and headache. Five of the seven events occurred in Parts A and B of the study, and two occurred in Part C (both in the low dose group). None of the events were considered to be drug-related, and all resolved. The severities of the events ranged from mild to moderate.

Results from all the clinical laboratory evaluations were variable, but showed no relevant changes with regard to the change from baseline or study drug administration timing or dose or between the active treatment groups and placebo. ECG findings were either normal or not considered to be clinically significant. QT and QTcF durations remained stable throughout the study in all parts of the study. Respiration rates remained largely consistent throughout the study.

Overall, OLT1177 Capsules were found to be safe and well tolerated in healthy subjects. No treatment-emergent serious adverse events or deaths occurred. The few adverse events that did occur were mild to moderate in severity, deemed to be unrelated to study drug, and all resolved. None of the laboratory parameters, or cardiac or respiratory measures indicated any issues with the drug.

Single- and multiple-dose PK profiles were determined as a secondary endpoint of Study OLT1177-04. After a single oral dose of OLT1177 Capsules, equivalent to 100, 300 or 1,000 mg of OLT1177, to fasted healthy subjects, OLT1177 was rapidly absorbed with mean peak plasma concentrations of 2,700, 9,800 and 32,000 ng/mL, respectively, reached at approximately 1.8 hours. Plasma OLT1177 concentrations were detectable in all subjects and all OLT1177-dosed treatment groups at all time points. Seven days after OLT1177 Capsules administration, plasma OLT1177 concentrations were still detectable for all subjects but mean concentrations had fallen to 14.8, 69.9 and 270 ng/mL at the 168 hour time point for subjects that received 100, 300 and 1,000 mg OLT1177. Systemic exposure (AUC and C_{max}) increased linearly with dose. The median terminal half-life ranged from 21 to 24 hours for all dose groups.

For characterization of multi-dose PK in Part C, OLT1177 Capsules were administered once daily over the course of 8 days to 3 cohorts in a sequential dose-escalation design. Doses of 100, 300 or 1,000 mg were administered orally. Blood samples were collected for PK analysis at the following time points: prior to dosing and 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 23 hours post-dose on Day 1, pre-dose on Days 6 and 7; and on Day 8 prior to dosing and after 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 23 hours post-dose.

After 8 daily doses of OLT1177 Capsules over 8 days, the mean maximum plasma OLT1177 concentrations were reached 1 to 2 hours after the final dose was administered for all dose groups. The mean C_{max} increased linearly with dose for the groups receiving 100, 300 or 1,000 mg OLT1177 per day (4,800, 15,800 and 41,400 ng/mL, respectively). Plasma concentrations on Day 6 and 7 and pre-dose on Day 8 corresponded to trough levels of 1,400-1,900, 6,600-7,300 and 1,900-19,500 ng/mL for the low, mid and high dose groups, respectively. Systemic OLT1177 exposure following the last dose (AUC) also increased linearly with dose. The median terminal half-life ranged from 14 to 21 hours for all dose groups.

Overall, OLT1177 Capsules were found to be safe and well tolerated in healthy subjects and Study OLT1177-04 is supportive of continued research with the OLT1177 investigational product.

2.1.2 Study OLT1177-01 – OLT1177 Gel

Study OLT1177-01 was a Phase 1 safety study of OLT1177 Gel in 36 healthy subjects (30 subjects OLT1177 Gel [3 or 5%], 6 subjects vehicle control). The study was performed with two parts (Parts A and B) with subjects receiving a single-dose of investigational product during Part A and multiple doses (8 doses over 3 days, TID on Days 1 and 2 with one dose on Day 3) during Part B. OLT1177 Gel was found to be very safe and well tolerated in all of the six cohorts in OLT1177-01. No serious adverse events or deaths occurred. The six adverse events reported were mild to moderate in severity, specifically: sinus infection, toothache, cold, migraine, neck pain and insomnia. All adverse events were deemed by the Investigator to be unrelated to the investigational product, and all resolved. Local skin tolerability was excellent with no signs of irritation in any subject. None of the laboratory parameters, or cardiac or respiratory measures indicated any issues with the investigational product, nor presented any clinically significant changes from Baseline. Vital sign changes from Baseline were variable, but not considered to be clinically significant. No physical examination results considered to be related to the investigational product.

2.1.3 Study OLT1177-02 – OLT1177 Gel

Study OLT1177-02 was a Phase 2a 14-day safety and efficacy study in 79 subjects with moderate to severe pain associated with osteoarthritis (OA) of the knee following cessation of pain therapy. Subjects were randomized 2:1 to receive OLT1177 Gel (5%) or Placebo Gel TID. No serious adverse events or deaths occurred. The 24 adverse events reported (by 17 subjects total) in the OLT1177 Gel treatment group were mild to moderate in severity, specifically: pharyngitis, upper respiratory infection, gastritis, conjunctivitis, bilateral leg pain, hip pain, left thigh contusion, influenza, viral syndrome, headache, diarrhea, edema on knee, rib fracture, neuropathy, bilateral varicose veins, gastroenteritis, nasal congestion, chronic cough and anemia. All of these adverse events were deemed by the Investigator to

be unrelated to the investigational product. A total of six adverse events were reported for the vehicle control treatment group, including one severe adverse event (atrial fibrillation), which was not related to treatment.

None of the laboratory parameters or cardiac or respiratory measures indicated any issues with the investigational product, nor presented any clinically significant changes from Baseline. Vital sign changes from Baseline were variable, but not considered to be clinically significant. No physical examination results were considered related to the investigational product. With regards to local skin tolerability, OLT1177 Gel was well tolerated with a small number of reported mild edema, erythema and scaling/dryness, and no reports of pruritus or stinging/burning at the administration site.

OLT1177 Gel demonstrated the potential for clinical benefit in Study OLT1177-02 with preliminary analysis showing improvement in multiple dimensions of pain and physical functioning.

2.1.4 Study OLT1177-03 – OLT1177 Gel

Study OLT1177-03 was a Phase 2b randomized, double-blind, vehicle-controlled, repeat-dose, multi-center efficacy and safety clinical trial of subjects with moderate to severe pain associated with OA of the knee. Two hundred and two subjects, randomized in a 1:1 ratio (OLT1177 Gel 5% to Placebo Gel) received approximately 125 doses of the investigational product (102 subjects OLT1177 Gel 5% and 100 subjects Placebo Gel) over 6 consecutive weeks given TID (6 mL per dose). Safety data were collected through Week 8.

Safety was assessed by physical examination, measurement of vital signs, ECGs, clinical laboratory tests (e.g., chemistry and hematology), adverse events and concomitant medications.

A total of 71 treatment-emergent adverse events (TEAEs) were reported for the OLT1177 Gel treatment group and a total of 65 TEAEs were reported for the Placebo Gel treatment group. Only one TEAE was considered related to treatment in the OLT1177 Gel treatment group. Headache and Back Pain were the only TEAEs for the OLT1177 Gel treatment group with incidences greater than 5.0% with 17.6% (vs. 8.0% for Placebo Gel) and 6.9% (vs. 5.0% for Placebo Gel), respectively. (Incidence of TEAEs is reported as percent of subjects experiencing.)

The Investigator's Brochure includes a complete description of the clinical experience of OLT1177 in both dosage forms.

3 TRIAL OBJECTIVES

The objectives of this clinical trial are as follows:

1. To assess the safety and tolerability of OLT1177 Capsule after oral administration in subjects with an acute gout flare
2. To assess the clinical activity of various doses of OLT1177 Capsule in treating signs and symptoms resulting from an acute gout flare
3. To assess OLT1177-induced changes in inflammatory biomarkers.

These objectives will be addressed by the specific outcomes outlined in Section 6.1 of this protocol.

4 INVESTIGATIONAL PLAN

4.1 OVERALL STUDY DESIGN AND PLAN

This is an open-label Phase 2 single-center, successive, result-dependent dose adaptive proof-of-concept safety and efficacy study to be conducted in subjects with an acute gout flare. A total of approximately 24 eligible subjects will be enrolled sequentially in up to three cohorts of 8 subjects each.

Subjects will be screened for eligibility at the Baseline visit and, if eligible, enrolled into the study. Following enrollment, Baseline safety and efficacy assessments will be conducted and the first dose of investigational product will be administered. Subjects will self-administer investigational product for up to eight (8) consecutive days beginning at the Baseline visit (Day 0) and continuing through the planned Day 7 visit. Subjects will return to the study clinic on Days 3, 7 and 14 for follow-up visits[6] and will be contacted by telephone on Day 35 (± 3 days) for further follow-up. Upon completion of the Day 14 visit, the subject will return to the care of his/her standard/referring physician.

Safety assessments will be conducted at each visit and efficacy assessments will be captured by a paper study diary. Safety and tolerability will be evaluated by monitoring the occurrence of AEs and changes in abbreviated physical examination findings, vital signs, clinical safety laboratory test results (chemistry, hematology and urinalysis) and ECGs.

[6] Clinic visits occurring a day after the indicated Day 3 visit day (e.g., on study day 4 for the Day 3 visit) will be considered within the visit window and will not be a deviation from the protocol. Clinic visits occurring a day before or after the indicated Day 7 and 14 visit days (e.g., on study day 6 or 8 for the Day 7 visit) will be considered within the visit window and will not be a deviation from the protocol.

Efficacy will be evaluated by subject-reported pain and disability scales, Investigator-assessed Index Joint Score and Global Rating of Disease, and analysis of biomarkers of inflammation.

At the Baseline visit, Rescue Medication (paracetamol, 1 g/dose) will be dispensed. Subjects will be instructed to record the amount and time of Rescue Medication use in the Study Diary. No Rescue Medication is allowed until 12 hours after the first dose of investigational drug. Beginning 12 hours after the first dose of investigational drug, subjects who are unable to tolerate their pain will be allowed to take up to 4 g paracetamol orally per day (1 g QID) for the duration of the Treatment Period (through the Day 7 visit). No other pain, steroid or treatments for gout flare are allowed during the Treatment Period.

If at any time during the study a subject is unable to tolerate his/her pain and wishes to receive standard medical intervention for an acute gout flare, the subject will be withdrawn from the study, considered a Treatment Failure and treated with either prednisolone (30 mg QD) or colchicine (0.5 mg TID).

4.2 STUDY DESIGN RATIONALE

This trial is being performed to assess the clinical activity, dose-response relationship and safety of OLT1177 Capsules when orally administered to subjects with an acute gout flare for eight consecutive days. This trial will be conducted in compliance with this protocol, Good Clinical Practices (GCP) and all applicable regulatory requirements.

The primary clinical activity assessment will be change in subject-reported pain intensity score from Baseline (Day 0) to Day 3 (evening; approximately 72 hours after the first dose) in the target joint (100-mm VAS). This endpoint is relevant, well established, accepted and validated in pain studies (Todd et al., 1996). Additional clinical activity variables will also be collected as described in Section 6.1 of this protocol.

This is the first clinical activity/proof of concept study for oral OLT1177. Based on preclinical toxicology testing, OLT1177 has a clean safety profile to a human equivalent dose of 10 g/day. A clean human safety profile was additionally demonstrated in the Phase 1 single and multiple dose escalation study of OLT1177 Capsules (up to 1 g/day for 8 days) in normal healthy volunteers. Therefore, the doses selected for study have been qualified through preclinical and/or clinical trials. However, as subject safety is paramount, in the event that the dose to be administered in any cohort is in excess of 1 gram per day (the highest dose studied in humans to date), enrollment and administration of investigational drug will be staggered such that no more than 2 subjects are in the Treatment Period (actively administering investigational drug) at any one time.

OLT1177 has been shown in multiple *in vitro, in vivo* and *ex vivo* studies to rapidly down regulate the release of IL-1β via the NLRP3 inflammasome. In both a prophylactic and a treatment model of MSU crystal-induced arthritis in mice, OLT1177 rapidly decreased IL-1β levels, minimized granulocyte entrance into the joint, and led to a rapid response to treatment. Based on these data, a study in subjects with an acute gout flare was selected for the initial trial because it is an IL-1-driven disease. Therapy with canakinumab and anti-IL-1 receptor antibodies has been shown to be effective in the treatment of acute gout.

Since there have been no safety signals seen with OLT1177, even at high doses, the starting dose of 500 mg given by mouth twice a day was selected as the human equivalent dose based on an approximation of preclinical exposures that demonstrated a 50% reduction in clinical findings in the MSU crystal induced mouse model of gout flare. The total daily exposure of this starting dose (1,000 mg per day) is the same as the dose tested in the Phase 1 safety and PK study of OLT1177 (1,000 mg QD) with no associated adverse findings. Twice a day (BID) dosing was selected as the starting dose to achieve a more consistent plasma-concentration exposure. A total of 8 subjects per cohort was selected as the minimally sized cohort to ascertain preliminary clinical utility based on the inherent variability between onset of signs and symptoms being seen at the clinical center and the evolution of gout flare signs and symptoms over time. To optimize the assay sensitivity of this study, two additional entry criteria are being employed, specifically: the inclusion of only subjects with monoarticular gout flare and the requirement that the flare started no more than 96 hours prior to the Baseline visit[7]. The first of these criteria is intended to eliminate the risk that sources of pain other than the target joint could interfere with a subject's ability to accurately rate their target joint pain. The second criterion is intended to minimize the possible confounding influence of gout flare self-resolution that can occur beginning at approximately 7 days into a gout flare.

This study has been designed to include both first-time and recurrent gout patients, with the former expected to represent the majority of enrolled study participants. The majority of patients with chronic gout are well-controlled on urate-lowering therapy (ULT) and therefore do not experience regular acute gout flares. As such, it is necessary to enroll first-time gout patients in clinical trials studying acute gout flares. Regardless of patients' gout history, past studies of known and experimental treatments for acute gout flare have enrolled patients while they have an active painful gout flare, which is the design implemented for this study (see Janssens et al., 2008 and Schlesinger et al., 2012).

This study has been designed to employ a result-dependent dose adaptation scheme, in which the escalation or de-escalation of total daily exposure for subsequent cohorts (i.e., Cohorts 2 and 3) is determined based on the safety and efficacy observed in the preceding cohort(s).

[7] At least three subjects per cohort must be enrolled with a gout flare that began within 36 hours prior to the Baseline visit.

The determination of total daily exposure (i.e., dose and regimen) will be made by the Study DMC based on the following criteria (see Section 5.4.3 for additional information): If adverse events or other safety concerns preclude an increase in total daily exposure or if pain reduction of $\geq 60\%$ is achieved for at least 75% subjects at the Day 3 (evening) timepoint, then the total daily exposure will be decreased for the next cohort. If no adverse events or other safety concerns preclude an increase in dose and pain reduction of $\geq 60\%$ is not achieved for at least 75% subjects at the Day 3 (evening) timepoint, then the total daily exposure will be increased for the next cohort.

The interim analysis and DMC recommendation will be submitted to the Ethics Committee upon completion. Documented Ethics Committee approval/agreement must be obtained prior to progression to the subsequent cohort, regardless of the decision to decrease or increase dose.

The selection of a 60% reduction in pain score as a cutoff was chosen based on the level of response shown in acute gout trials with NSAIDs, oral prednisolone and canakinumab. At the end of the study, all safety and clinical activity data from all cohorts will be evaluated, and if supportive, a subsequent controlled study in a larger population will be planned.

4.2.1 Selection of Study Population

4.2.1.1 Overview

One site will enroll a total of approximately 24 subjects in the southeast area of the Netherlands. Enrolled subjects who do not complete the study through the Day 7 visit may be replaced.

The study population will be comprised of Dutch-speaking male and female subjects between 18 and 80 years old (inclusive) with a monoarticular gout flare. Factors known to be associated with gout include: hyperuricaemia, genetic factors, dietary factors, alcohol consumption, metabolic syndrome, hypertension, obesity, diuretic use and chronic renal disease. This population was selected as the investigational drug, OLT1177, is being developed as a new therapy for the treatment of gout flares. The study population will include both patients who have not been previously diagnosed with gout or an acute gout flare (referred to as 'first-time gout patients') and patients who have been previously diagnosed with gout, but continue to experience periodic gout flares (referred to as 'recurrent gout patients').

While gout flares are not specific to the geriatric population, the risk of gout and associated gout flares increase with age and the target population is likely to include a substantial number of geriatric patients. As such, the potential inclusion of geriatric patients in this study is warranted to discern early indications of any differences present in this population.

4.2.1.2 Recruitment

Recruitment of study participants will be conducted by the Investigator and/or site staff and will utilize the following methods:

- Request for referral from general practitioners in the Netherlands (e.g., telephone calls placed to general practitioners)
- Direct recruitment of participants, including patients of the Investigator and/or the study clinic
- Local advertisement at the study clinic and/or clinics of referring physicians with Ethics Committee-approved recruitment materials (e.g., flyer, poster, etc.)
- Word of mouth

4.2.2 Inclusion Criteria

A subject may be included in the study if he/she meets each of the criteria as presented below:

1) Male and female subjects between 18 and 80 years old, inclusive

2) Gout in a joint of a subject's lower limbs (e.g., ankle, foot, knee, toe) as indicated by the presence of monosodium urate (MSU) crystals by microscopic evaluation of synovial fluid from the target joint and in accordance with ACR/EULAR 2015 Gout Classification Criteria

3) Confirmation of a gout flare in the target joint that began[8] within 96 hours prior to the Baseline visit[9], based on presence of subject-reported joint pain at rest of ≥ 50 mm on a 0-100 mm VAS and at least two of the following criteria in the target joint[10]:

   a. Subject-reported flare

   b. Subject-reported warm joint

   c. Subject-reported swollen joint

[8] For the purposes of this study, the beginning of a gout flare is considered to be the time at which the subject reports having first experienced severe pain in the target joint. If a subject is unable to specify the exact time and date that the flare began, an approximation of time since beginning of flare shall be made and the subject's eligibility will be determined at the discretion of the Investigator.

[9] At least three subjects per cohort must be enrolled with a gout flare that began within 36 hours prior to the Baseline visit.

[10] This inclusion criterion requires that each subject meet the provisional definition of a gout flare as described in Gaffo et al., 2012.

4) Acceptable overall medical condition to be safely enrolled in and to complete the study (with specific regard to cardiovascular, renal and hepatic conditions) in the opinion of the Investigator

5) Ability to provide written, informed consent prior to initiation of any study-related procedures, and ability, in the opinion of the Investigator, to understand and comply with all the requirements of the study, which includes abstaining from use of pain or Rescue Medication (for 12 hours after first dose of investigational drug) and other prohibited medications as outlined in Section 5.6.3 of the protocol.

4.2.3 Exclusion Criteria

A subject may not be included if he/she meets one or more of the criteria presented below:

1) Women of childbearing potential, or men whose sexual partner(s) is a woman of childbearing potential, who:
   a. Are or intend to become pregnant (including use of fertility drugs) during the study
   b. Are nursing [female subjects only]
   c. Are not using an acceptable, highly effective method of contraception until all follow-up procedures are complete. See Section 5.6.2 for more details on acceptable forms of contraceptives.

2) Presence of an acute gout flare in more than one joint at the Baseline visit

3) Presence of another inflammatory arthritis in addition to gout

4) Presence or known history of other autoimmune conditions (e.g., systemic lupus erythematosus, hypophysitis, etc.)

5) Clinically significant general pain or non-gout related joint pain that would interfere with the subject's ability to accurately assess pain in the target joint, at the discretion of the Investigator

6) Use of any prohibited concomitant medications/therapies over the periods defined in Section 5.6.3 or planned use of any concomitant medications/therapies during the Treatment Period (including the use of pain medications within 12 hours prior to the Baseline visit)

7) Active infection within 3 days prior to the Baseline visit

8) History of or known positive for HIV, Hepatitis B surface antigen (HBsAg) or antibodies to Hepatitis C Virus (HCV)

9) Diagnosed with any form of internal cancer within the past 5 years

10) Any other concomitant medical or psychiatric conditions, diseases or prior surgeries that in the opinion of the Investigator would impair the subject from safely participating in the trial and/or completing protocol requirements

11) History of alcohol or substance abuse within the 12 months prior to the Baseline visit

12) Enrollment in any trial and/or use of any investigational product or device within the immediate 30-day period prior to the Baseline visit

13) Enrollment in any study previously sponsored by Olatec Therapeutics LLC, specifically Study OLT1177-01, Study OLT1177-02, Study OLT1177-03 or Study OLT1177-04

4.2.4 Early Termination of Subjects from Therapy

Subjects will be informed, prior to the trial's commencement, that they will have the right to withdraw from the trial at any time, for any reason, without prejudice to his/her safety or medical care. Moreover, Investigators will have the right to withdraw a subject from the trial if there is any reason, in the Investigator's opinion, that would impair the subject from safely participating in the trial, including completing any protocol requirements.

Notification of early termination due to adverse event or any other safety-related concerns will immediately be made to the Medical Monitor and Sponsor or Sponsor's Representative. The date the subject is withdrawn from the trial and the reason for discontinuation will be recorded in the source documents and in the subject's CRF. If a subject withdraws from the trial because of an adverse event, the principal specific event and any related test results will be recorded in the CRF in both the End of Study and the Adverse Event CRF pages. Follow-up of any persisting adverse event is required until the event resolves or stabilizes at a level acceptable to the Investigator or Investigator's designee.

Reasons for early termination may include, but are not limited to:

- Adverse Events (AEs)
- Worsening condition, as determined by the Investigator
- Withdrawal of consent
- Changes in the subject's condition that would impair the subject from safely participating in the trial, including but not limited to completing any protocol requirements, in the judgment of the Investigator

- Subject becomes pregnant (withdrawal is required)
- Subject is lost to follow-up

4.2.5 Early Discontinuation of the Trial

The Sponsor and the Medical Monitor reserve the right to discontinue the trial in accordance with applicable law. Reasons for discontinuation may include, but are not limited to:

- Approval by the Ethics Committee is irrevocably revoked
- In interest of the health of the trial subjects
- Determination that continuation of the trial cannot serve a scientific purpose
- Unremedied violation of applicable law, GCP or this study by the Investigator

4.3 INSURANCE

The Sponsor has insurance, which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides coverage for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

5 TREATMENTS

5.1 TREATMENTS ADMINISTERED

OLT1177 Capsule (100 mg each) will be self-administered for the duration of the Treatment Period beginning at the Baseline visit and will continue through the Day 7 visit. Investigational product will be self-administered orally two times per day for Cohort 1 and 2, and either one, two or three times per day for Cohort 3 based on the dose and regimen determined in accordance with Section 5.4.3.

5.2 IDENTITY OF INVESTIGATIONAL PRODUCT

5.2.1 Description of Investigational Product

OLT1177 Capsule consists of a blend of OLT1177 API and Avicel PH-101.

5.2.2 Packaging of Investigational Product

Investigational product (OLT1177 Capsule) will be packaged in bottles containing twenty 100 mg capsules. Each bottle will be labeled to display: Sponsor name and contact

information, name of investigational product, description of bottle contents, batch code/lot number, bottle number, protocol number, EudraCT number, center and Investigator identification, storage information, expiry date and appropriate disclaimers. Additionally, the bottle will contain space for the assigned Subject Identification Number and Cohort Number to be hand-written by site personnel.

5.3 DISPENSATION OF INVESTIGATIONAL PRODUCT

Investigational product will be dispensed to subjects at the Baseline visit and collected at the Day 7 visit. A sufficient number of bottles of investigational product will be dispensed to enable dosing until the subject's planned Day 7 visit.

5.4 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

5.4.1 Randomization

All subjects enrolled will receive OLT1177 Capsules; therefore, subjects will not be randomized in this clinical trial.

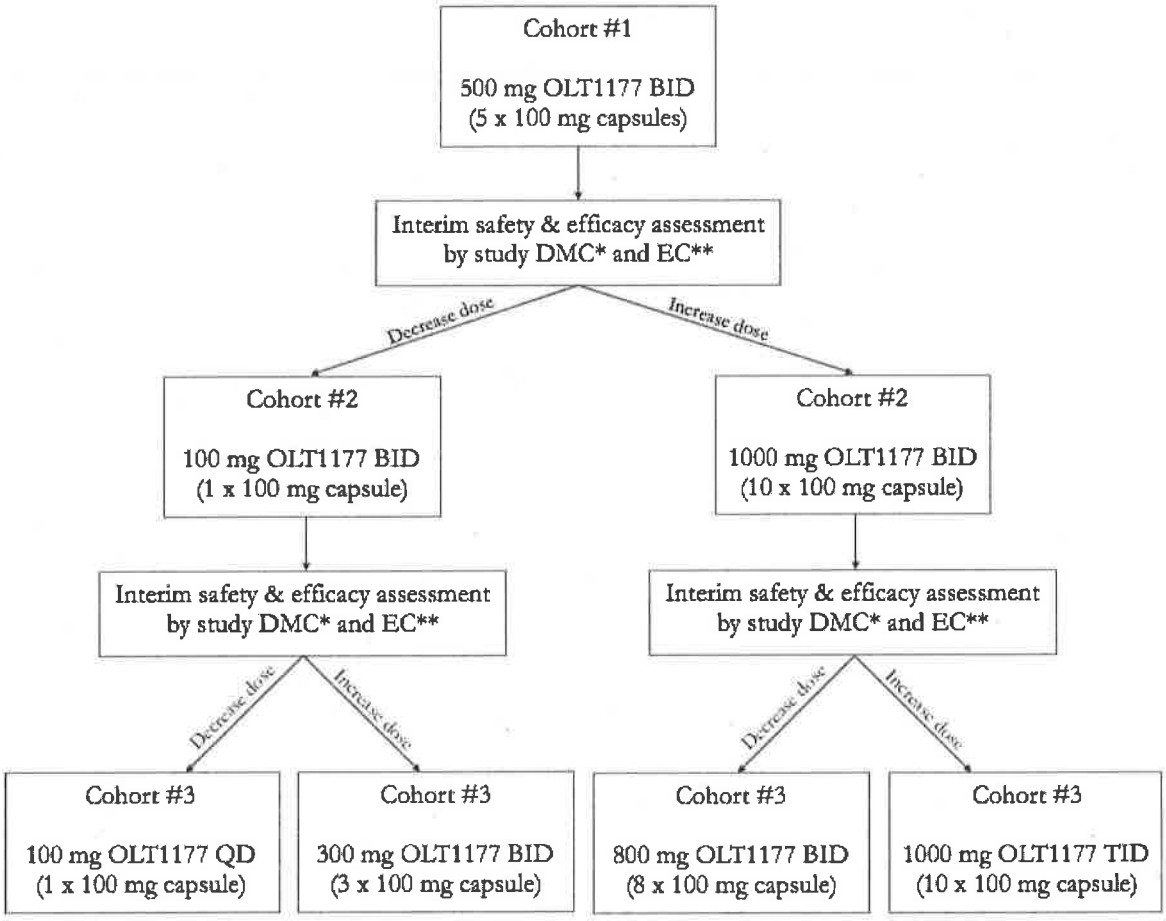
5.4.2 Subject Identification (SID) Number

All screened subjects will be assigned a six-digit subject identification (SID) number, of which the first three digits will be the clinical site identification number and the last three digits will be the subject number. The SID numbers at the clinical site will be assigned sequentially in the order subjects are screened. The SID number identifies the subject from the time of screening through the duration of the trial. For example, the fifth subject screened at the site assigned clinical site identification number 001 would be assigned SID: 001-005.

5.4.3 Cohort Progression

Subjects will be enrolled in the first cohort until a total of eight subjects have been enrolled. Subsequent determination of the dose schedules for Cohorts 2 and 3 will be made by the Study DMC and confirmed by the Ethics Committee in accordance with the following decision tree, at which time subjects will be enrolled into the subsequent cohort until the completion of the trial.

Decision Tree for Determination of Dose Schedules for Cohorts 2 and 3



*The DMC will convene and review all relevant safety and efficacy data (after completion of the Day 7 visit for all subjects in a cohort) to determine whether an increase or decrease in total daily exposure is warranted. If adverse events or other safety concerns preclude an increase in total daily exposure or if pain reduction of $\geq$ 60% is achieved for at least 75% of subjects in a cohort at the Day 3 (evening) timepoint, then the total daily exposure will be decreased for the next cohort. If no adverse events or other safety concerns preclude an increase in dose and pain reduction of $\geq$ 60% is not achieved for at least 75% of subjects in a cohort at the Day 3 (evening) timepoint, then the total daily exposure will be increased for the next cohort.

**The interim analysis and DMC recommendation will be submitted to the Ethics Committee upon completion. Documented Ethics Committee approval/agreement must be obtained prior to progression to the subsequent cohort, regardless of the decision to decrease or increase dose.

5.5 BLINDING OF THE STUDY

There will be no blind employed in this study; therefore, subjects, investigators and study personnel will be aware of treatment and dosage assignment (i.e., OLT1177).

5.6 PRIOR AND CONCOMITANT MEDICATIONS/THERAPIES

5.6.1 Allowed Concomitant Medications/Therapies

Any medical conditions during the Treatment Period of the trial will be treated at the discretion of the Investigator according to acceptable community standards of medical care. All concomitant medications and therapies will be documented in the subject's CRF.

At the Baseline visit, Rescue Medication (paracetamol, 1 g/dose) will be dispensed. Subjects will be instructed to record the amount and time of Rescue Medication use in the Study Diary. No Rescue Medication is allowed until 12 hours after the first dose of investigational drug. Beginning 12 hours after the first dose of investigational drug, subjects who are unable to tolerate their pain will be allowed to take up to 4 g paracetamol orally per day (1 g QID) for the duration of the Treatment Period (through the Day 7 visit). No other pain, steroid or treatments for gout flare are allowed during the Treatment Period.

If at any time during the study a subject is unable to tolerate his/her pain and wishes to receive standard medical intervention for an acute gout flare, the subject will be withdrawn from the study, considered a Treatment Failure and treated with either prednisolone (30 mg QD) or colchicine (0.5 mg TID).

Subjects will be allowed to continue taking non-analgesic/non-anti-inflammatory, concomitant medication/therapy, except those medications/therapies listed under "Prohibited Concomitant Medications/Therapies" in Table 5.1.

5.6.2 Contraception Protection

All women of childbearing potential enrolling in the trial must agree to use an acceptable, highly effective method of contraception. Men enrolling in the trial and whose sexual partner(s) is/are a woman of childbearing potential, must also agree to use an acceptable, highly effective method of contraception. Acceptable, highly effective forms of contraception are defined as: oral contraception, intrauterine device, systemic (injectable or patch) contraception, double barrier methods, naturally or surgically sterile, strict abstinence or partner has been sterilized. If hormonal-based birth control is being used, subject or subject's sexual partner(s) must be on a stable-dose for $\geq$ 3 months prior to the Baseline visit and maintained at the same dosing level throughout the study.

5.6.3 Prohibited Concomitant Medications/Therapies

The following concomitant medications/therapies are prohibited except under the specific conditions noted. Subjects taking these medications should either be excluded from the trial as noted in the entry criteria, or if on a permitted stable dose should continue on their stable-dose treatment for the full 8-day Treatment Period (under specific conditions noted). Subjects who enroll in this trial should not begin use of, or intermittently use, any prohibited concomitant medication/therapy during the 8-day Treatment Period. (PRN dosing is not considered a stable dose.)

Table 5.1 summarizes those medications/therapies that are prohibited (except as otherwise noted).

Table 5.1 Prohibited Concomitant Medications/Therapies

Medication / Therapy Class	Conditions for Enrollment/Allowance	Examples
Paracetamol (dispensed as Rescue Medication)	Not allowed beginning 12 hours before the Baseline visit. Study-provided rescue medication (which is paracetamol) is only allowed during the study beginning 12 hours after the first dose of study medication.	Paracetamol
NSAIDs (other than paracetamol)	Not allowed from 12 hours prior to Baseline visit until after completion of the Day 7 visit	Ibuprofen, naproxen, diclofenac, etc.
Pain medications (other than NSAIDs or Narcotics)	Not allowed until after completion of the Day 7 study visit Stable dose ASA therapy is allowed (up to 325 mg/day) for cardiovascular prophylaxis if on stable dose for ≥ 30 days prior to Baseline; maintain stable dose throughout the study	Any prescription, over-the-counter (OTC) or natural supplement intended to treat pain, other than study-provided Rescue Medication
Narcotics	Not allowed	Opioids, such as morphine, heroin and their derivatives, hydrocodone, etc.
Icing therapy	Not allowed until after completion of the Day 3 (evening) diary assessments	Ice pack or equivalent
Colchicine[1]	Not allowed until after completion of the Day 7 study visit	Not allowed including chronic prophylaxis with colchicine
Systemic corticosteroids[1]	Last dose taken must have been at least 1 month prior to Baseline visit	Prednisone, cortisone, methylprednisolone, etc.
Intraarticular steroids (in any joint)	Not allowed until after completion of the Day 7 study visit. Target joint: last dose must have been given at least 3 months before the Baseline visit. Other joints: last dose must have been given at least 30 days before the Baseline visit.	Betamethasone, methylprednisolone, triamcinolone, etc.

Medication / Therapy Class	Conditions for Enrollment/Allowance	Examples
Other investigational products	Not allowed	Any drug not approved by EMA
Chemotherapeutic drugs	Not allowed	Carboplatin, cisplatin, cyclophosphamide, doxorubicin, etoposide, fluorouracil, gemcitabine, irinotecan, methotrexate, paclitaxel, topotecan, vincristine, vinblastine, etc.
Immunotherapies	Not allowed	interferons, interleukins, monoclonal antibodies, colony stimulating factors (CSFs)
SSRIs, SSNRIs or TCAs	Stable dose for at least the last 3 months prior to Baseline to treat depression is allowed; the stable dose should be maintained throughout the study	Fluoxetine, paroxetine, sertraline, citalopram, venlafaxine, duloxetine, milnacipran, amitriptyline, imipramine, nortriptyline, etc.
Urate lowering therapies (ULTs)	Stable dose for at least the last 3 months prior to Baseline	Allopurinol, febuxostat, benzbromaron, etc.

[1] In the event a patient experiences an unacceptable level of pain (e.g. severe pain) with study medication and/or paracetamol (1g QID), he/she will be considered a Treatment Failure, withdrawn from the study and treated with either prednisolone (30 mg QD) or colchicine (0.5 mg TID).

Subject safety must always remain paramount. Therefore, if an Investigator deems that a subject requires a prohibited concomitant medication/therapy, at the Investigator's discretion and according to acceptable community standards of medical care, the subject will receive concomitant medication/therapy as specified. The subject may be withdrawn from the study at the discretion of the Investigator, in consultation with the Sponsor and Medical Monitor for use of concomitant medications/therapies that are prohibited.

5.7 TREATMENT COMPLIANCE

During the 8-day Treatment Period, subjects will report the administration of investigational product two times daily for Cohorts 1 and 2 and either one, two or three times daily for Cohort 3 (see Section 5.4.3) using the supplied diary. The site personnel will have access to each subject's diary at the required site visits and will track subject compliance with the investigational product on an ongoing basis.

5.8 INVESTIGATIONAL PRODUCT STORAGE & ACCOUNTABILITY

5.8.1 Storage

Investigational product should be stored in a secure area that is maintained at room temperature: 15°C-25°C (59°F-77°F). Slight deviations from this temperature range are acceptable. Significant deviations should be recorded and the Sponsor should be contacted to determine any effect on the investigational product.

5.8.2 Accountability

Upon receipt of the investigational product, the Investigator is responsible for ensuring that the designated site personnel conduct a complete inventory of trial materials and the Investigator assumes responsibility for their storage and dispensing. In accordance with applicable regulations, the Investigator must agree to keep all trial materials in a secure location with restricted access. The Investigator will keep a record of the inventory and dispensing of all investigational product. This record will be made available to the study monitor or other qualified representatives of the Sponsor for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the Investigator will be accounted for and, in no case, used in any unauthorized situation.

Used (empty), unused or expired bottles of the investigational product as well as all blister card(s) of Rescue Medication are to be collected and saved at the site for inspection by the study monitor of other qualified representatives of the Sponsor throughout the study. Thereafter, the investigational product will be returned to the Sponsor or Sponsor's Representative, along with the Drug Return Form.

6 CLINICAL ACTIVITY AND SAFETY VARIABLES

6.1 CLINICAL ACTIVITY OUTCOMES

6.1.1 Primary Clinical Activity Outcome

The primary clinical activity outcome will be:

- Change in subject-reported pain intensity score from Baseline (Day 0) to Day 3 (evening; approximately 72 hours after the first dose) in the target joint (100-mm VAS)

6.1.2 Principle Secondary Clinical Activity Outcome

The principle secondary clinical activity outcomes will be:

- Subject-reported global evaluation of treatment at Day 7 (Likert scale)

6.1.3 Other Secondary Clinical Activity Variables

The following secondary clinical activity variables will also be collected at Baseline and all post-Baseline visits during the Treatment Period:

- Subject-reported pain intensity score in the target joint (100 mm-VAS)[11]
- Subject-reported general disability score in the target joint (100 mm-VAS)[11]
- Subject-reported walking disability score in the target joint (100 mm-VAS)[11]
- Investigator-assessed Index Joint Score (tenderness, swelling, erythema, warmth)
- Investigator-assessed Global Rating of Disease (Likert scale)
- Blood levels of high sensitivity C-reactive protein (hsCRP) and Serum Amyloid A protein (SAA)

If at any time during the study a subject is unable to tolerate his/her pain and wishes to receive standard medical intervention for an acute gout flare, the subject will be withdrawn from the study, considered a Treatment Failure and treated with either prednisolone (30 mg QD) or colchicine (0.5 mg TID). In addition to the clinical activity variables described above, the number and proportion of Treatment Failures in each cohort will be captured and summarized in the study results.

[11] This variable is also collected at the Day 14 visit

6.2 SAFETY VARIABLES

Safety variables collected in the study will be:

- Physical examination (abbreviated general and site specific examination)
- Vital Signs (pulse, resting blood pressure, temperature, respiration rate)
- Safety laboratory measures (chemistry, hematology and urinalysis)
- Safety electrocardiograms (ECGs)
- Adverse Events (AEs) during the clinical trial

7 TRIAL ASSESSMENTS

7.1 ELIGIBILITY & DISEASE CHARACTERIZATION

7.1.1 Synovial Fluid Sample & Evaluation

The gold standard for diagnosing acute gout is the identification of birefringent crystals in joint fluid. This is a standard procedure that is practiced by rheumatologists around the world on a daily basis. In accordance with Step 2 of the ACR/EULAR 2015 Gout Classification Criteria, the presence of MSU crystals in the synovial fluid of the target joint will serve as confirmation of gout (see Inclusion Criterion #2). Only those subjects determined to have gout by this method will be enrolled in this study.

At the Baseline visit, synovial fluid from the target joint will be collected and analyzed by the Investigator under a polarizing microscope to confirm the presence of intraarticular MSU crystals. The Investigator's determination will be captured in the source documents and/or CRFs.

The procedure for synovial fluid sampling and evaluation is as follows:

1. The acutely inflamed and tender joint (i.e., target joint) is gently cleaned with an alcohol swab or equivalent decontamination agent.
2. Using aseptic technique, the joint space is punctured using a syringe with a 25 or 23 gauge needle and a small amount of joint fluid is aspirated. Given that one of the most often affected joints is the great toe, the maximum amount of fluid that can be withdrawn is very limited. The average amount of fluid aspirated is often less than 0.04 to 0.1 mL.
3. The aspirate is put on a microscope slide and searched using a polarized light microscope.

4. A positive diagnosis of gout is made when birefringent crystals are seen. If no crystals are seen or if crystals are observed but they are not birefringent, then the diagnosis of gout cannot be made.

7.2 EFFICACY

7.2.1 In-Clinic Efficacy Assessments

7.2.1.1 Global Evaluation of Treatment | Likert Scale

Global Evaluation of Treatment is one general question the subject is asked to answer about the overall perceived quality of the investigational product in treating the subject's symptoms. Specifically, each subject will be asked to respond to the following instruction and question:

Zet een "X" in het vierkant naast de term die u het best passend vindt om de onderstaande vraag te beantwoorden: Hoe omschrijft u van het effect van de behandeling voor de jicht?

[English: How would you describe the effects of the gout treatment?]

The Global Evaluation of Treatment will be completed at the Day 7 visit and will be assessed on a 5-point Likert scale, with numerical values to be assigned as follows: (0 = Slecht, 1 = Redelijk, 2 = Goed, 3 = Heel goed and 4 = Uitstekend) [English: 0 = poor, 1 = reasonable, 2 = good, 3 = very good and 4 = excellent]

7.2.1.2 Investigator-Assessed Index Joint Score | Likert Scale

The Investigator-assessed Index Joint Score is a combined assessment of individual assessments for the following outcome domains: tenderness, swelling, erythema and warmth.

This assessment will be completed at the Baseline (pre-dose and 2 hours[1] post-dose), Day 3 and Day 7 visits and will be assessed as indicated below.

[1] Assessments can be taken within 30 minutes of indicated time

Tenderness

Investigator assessment of index joint tenderness, with numerical values to be assigned as follows: 0 = no pain; 1 = mild pain / patient states there is pain when touched, 2 = moderate pain / patient states there is pain and winces, 3 = severe pain / patient states there is pain, winces and withdraws.

Swelling

Investigator assessment of index joint swelling, with numerical values to be assigned as follows: 0 = no swelling; 1 = mild swelling; 2 = moderate swelling; 3 = severe swelling (or bulging beyond joint margins).

Erythema

Investigator assessment of index joint erythema, with values to be assigned as follows: present, absent, and non-assessable.

Warmth

Investigator assessment of index joint warmth, with values to be assigned as follows: present, absent, and non-assessable.

7.2.1.3 Investigator-Assessed Global Rating of Disease | Likert Scale

Global Rating of Disease is one general question the Investigator is asked to answer about the overall perceived status of the subject's symptoms. Specifically, the Investigator will be asked to respond to the following question:

Considering all of the patient's signs and symptoms, how well are they doing?

The Global Rating of Disease will be completed at the Baseline (pre-dose and 2 hours[1] post-dose), Day 3 and Day 7 visits and will be assessed on a 5-point Likert scale, with numerical values to be assigned as follows: (0 = poor, 1 = fair, 2 = good, 3 = very good and 4 = excellent).

[1] Assessments can be taken within 30 minutes of indicated time

7.2.2 Diary Efficacy Assessments | 100-mm VAS

Subjects will be given a Study Diary in which they will be asked to record their response to three assessments according to the following schedule during the Treatment Period, from Baseline (Day 0) through the Day 7 visit, and at the Day 14 visit:

- Baseline (Day 0): Pre-dose, 2 h, 4 h, 6 h and 12 h post-dose[12]
- Days 1-7: morning and evening at approximately 9 a.m. and 9 p.m.
- Day 14: during study visit

Note 1: Assessments in the first 24 hours should be collected within 30 minutes of the indicated time relative to dosing. Assessments after 24 hours should be collected within 1 hour of the indicated time.

Note 2: Depending on the time of the subject's Baseline (Day 0) and Day 7 visits fewer assessments may be collected on those days.

[12] Depending on the time of the subject's Baseline (Day 0) visit, the 12-hour and/or 6-hour diary assessments may not be completed. Diary assessments not done at these time points will not be considered a protocol deviation.

Subjects will provide responses to assess: target joint pain, general disability and walking disability and will record the time at which the assessments were completed.

At the Baseline visit, site personnel will review the diary completion instructions with each subject and subjects will complete their first assessment in the presence of site personnel. Subjects will return the Study Diary at the Day 7 visit.

7.2.2.1 Pain

Subjects will be instructed to record the pain in their target joint on a 100-mm Visual Analog Scale (with anchors 0 = Geen enkele pijn [English: no pain]; 100 = Nog nooit zoveel pijn gehad [English: never experienced this much pain before]) and in response to the following question (in Dutch):

Hoeveel pijn *ervaart U* ***nu****, deze [invoegen tijdstip], in het jichtgewricht?*

[English: How much pain are you experiencing now, this [insert time of day], in your gout joint?]

7.2.2.2 General Disability

Subjects will be instructed to record their level of general disability on a 100-mm Visual Analog Scale (with anchors 0 = Kan alles wat ik ook kon vóórdat deze jichtaanval begon [English: I can do everything I was able to do before this gout attack started]; 100 = Kan niets [English: I cannot do anything]) and in response to the following question:

Hoe beperkt *voelt U zich* ***nu****, deze [invoegen tijdstip], bij uw dagelijkse bezigheden ten gevolge van deze jichtaanval?*

[English: How limited do you feel right now, this [insert time of day,] in your daily activities as a result of this gout attack?]

7.2.2.3 Walking Disability

Subjects will be instructed to record their level of walking disability on a 100-mm Visual Analog Scale (with anchors 0 = Ervaar geen enkele verslechtering van het lopen [English: I am not experiencing any deterioration in walking]; 100 = Kan absoluut niet lopen [English: I can absolutely not walk]) and in response to the following question:

Hoe ***loopt*** *U* ***nu****, deze [invoegen tijdstip]?*

[English: How are you walking now, this [insert time of day]?]

7.3 SAFETY

7.3.1 Medical History and Concomitant Medications/Therapies Review

A review of each subject's medical history, including medication history, within the past 5 years, taking into account all recent and pertinent medical conditions, will be recorded at the Baseline visit.

All concomitant medications/therapies and past medications/therapies will be reviewed and recorded in the CRF at the following visits: Baseline (prior to dosing; including those taken within the past 30 days), Day 3, Day 7 and Day 14.

7.3.2 Physical Examination

A full physical examination will be performed at the Baseline visit (prior to dosing). An abbreviated / targeted physical examination will be performed at the Day 14 visit or at an early termination visit (if before the Day 14 visit) based on the subject's reported symptoms. Additional targeted physical examinations may be conducted at the discretion of the Investigator, if required by the subject's signs and symptoms. Height and weight will be recorded as part of the physical examination at the Baseline (pre-dose) visit only.

7.3.3 Vital Signs

Vital signs (pulse, resting blood pressure [must be resting for 10 minutes], temperature and respirations) will be recorded at the following visits: Baseline (prior to dosing), Baseline (2 hours[1] post-dose), Day 3, Day 7 and Day 14 or early termination (if before Day 14 visit).

[1] Assessments can be taken within 30 minutes of indicated time

7.3.4 Urine Pregnancy Test

Women who have undergone hysterectomy, bilateral oophorectomy, bilateral tubal ligation or have been without menses for 12 months are considered to be of non-child bearing potential. All other women will require a urine pregnancy test during each of the following visits: Baseline (prior to dosing) and Day 14 or at an early termination visit (if before Day 14 visit).

7.3.5 Safety Laboratory Measures

Blood will be drawn and urine collected for safety laboratory measures (hematology and chemistry) at the following visits: Baseline (prior to dosing), Day 3, Day 7 and Day 14 or at an early termination visit (if before the Day 14 visit). Confirmatory or follow-up laboratory measurements may be taken at the discretion of the Investigator as warranted by the subject's signs and symptoms (e.g., clinically significant abnormal laboratory values at previous visit).

7.3.5.1 Hematology

The following hematology testing should be performed at each time point: CBC with 5-part differential, RBC statistics and platelet count.

7.3.5.2 Chemistry

The following chemistry testing should be performed at each time point: total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), total protein, albumin, lipase, sodium, potassium, calcium, blood urea nitrogen (BUN), creatinine, glucose, chloride, glycated haemoglobin (HbA1c), high sensitivity C-reactive protein (hsCRP), serum amyloid A (SAA) and serum uric acid (UA).

hsCRP and SAA are inflammatory biomarkers and may be analyzed for changes from Baseline as part of the efficacy analysis.

7.3.5.3 Urinalysis

Urine samples will be collected at each time point and analyzed for measurements of: urinary protein, glucose, ketones, hemoglobin, bilirubin, pH, specific gravity, red cell count, white cell count, epithelial cells, casts and crystals.

7.3.6 Safety ECGs

Single digital 12-lead ECGs will be collected at the following visits: Baseline (pre-dose) and Day 7. Subjects must be resting for at least 10 minutes prior to obtaining ECGs.

7.3.7 Adverse Events

Adverse events will be collected starting immediately after the subject signs the ICF and continuing through Day 35. Any AEs ongoing at the Day 14 visit will be followed until resolution or stabilization or until the subject is lost to follow-up.

7.4 PHARMACOKINETIC ASSESSMENTS

Blood will be drawn for plasma PK analysis at the following time points:

- Baseline visit (Day 0): pre-dose
- Day 3 visit
- Day 7 visit
- Day 14 visit

Blood samples for plasma PK analysis will be collected into 4 mL K_2-EDTA (lavender top) anticoagulation tubes at each time point. Samples should be centrifuged and plasma collected, equally divided into two separate aliquots, and placed in 2 mL cryovials. Shipping materials will be provided for frozen shipment to the Sponsor's designated bioanalysis laboratory. Detailed instructions on handling PK samples will be provided in the PK manual.

7.5 OTHER ASSESSMENTS & PROCEDURES

7.5.1 Photographs of Target Joint

Subjects who have provided consent for photographic documentation of their target joint will have photographs taken of their target joint at the Baseline (Day 0, pre-dose and 2 hours[1] post-dose), Day 3, Day 7 and Day 14 visits. Photographs will be taken according to Appendix 4 and attention should be paid to the position of subject's target joint, lighting, and camera set-up to ensure standardization.

Subjects who do not agree to have their target joint photographed will still be permitted to participate in the study.

[1] Photographs can be taken within 30 minutes of indicated time

7.5.2 Blood Samples for Future Analysis

Subjects will have approximately 25 mL of blood collected at each blood draw (Baseline (pre-dose), Day 3, Day 7 and Day 14) and stored by Sponsor or designee for a period of up to 5 years for future analysis, including but not limited to *ex vivo* cytokine and biomarker assays.

Table 7.1 Schedule of Trial Activities & Assessments

Trial Period:		Eligibility	Treatment & Follow-up Period				
Assessment	Visit:	Baseline (Day 0)		Day 3 (+ 1 day)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 35 (± 3 days)
		Pre	Post				
Informed Consent Form		X					
Eligibility							
Microscopic Analysis of Synovial Fluid		X					
Inclusion and Exclusion Criteria[a]		X					
Baseline Characteristics							
Medical History / Concomitant Medications		X		X	X	X	
Demographics		X					

Trial Period:		Eligibility	Treatment & Follow-up Period				
Assessment	Visit:	Baseline (Day 0)		Day 3 (+ 1 day)	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 35 (± 3 days)
		Pre	Post				
Safety Assessments							
Physical Examination		X				X	
Vital Signs[b]		X	X[e]	X	X	X	
Safety Laboratory Measures[c]		X		X	X	X	
Safety Electrocardiograms		X			X		
Adverse Event Reporting		*Adverse Events will be recorded via study diary and reviewed at each site visit*					
Follow-up Telephone Call							X
Clinical Activity Assessments[d]							
Pain (diary)		X	*ongoing*			X	
General Disability (diary)		X	*ongoing*			X	
Walking Disability (diary)		X	*ongoing*			X	
Global Evaluation of Treatment (in-clinic)					X		
Investigator-assessed Index Joint Score		X	X[e]	X	X		
Investigator-assessed Global Rating of Disease		X	X[e]	X	X		
Other Assessments							
Blood Draw for PK analysis		X		X	X	X	
Blood Draw for *ex vivo* analysis		X		X	X	X	
Photographic Assessment of Target Joint		X	X[e]	X	X	X	
Dispensation & Return of Study Materials							
Investigational Product Dispensed (D) / Returned (R)		D			R		
Study Diary including Dosing Diary and instructions Dispensed (D) / Returned (R)		D		R/D	R		
Rescue Medication Dispensed (D) / Returned (R)		D			R		
Dosing							
Investigational product Administered			X				

[a] **Inclusion and Exclusion Criteria:** all criteria should be met at Baseline visit
[b] **Vital Signs:** pulse, 10-minute resting blood pressure, temperature, respiration rate
[c] **Safety Laboratory Measures:** chemistry, hematology and urinalysis will be performed each time. Urine Pregnancy Test will be completed at Baseline (pre-dose) and Day 14 visits, if applicable
[d] **Efficacy Assessments:** Diary assessments will be captured in accordance with the schedule in Section 7.2.2
[e] **Post-dose Assessments:** Assessments to be completed 2 hours post-dose (±30 minutes)

8 ADVERSE EVENTS

An adverse event (AE) can be any unfavorable, unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of the investigational product, whether or not considered related to the medicinal product.

It is the responsibility of the Investigator to document all AEs that occur during the course of the trial. Adverse events should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the subject at each trial visit.

Adverse events occurring after the signing of the ICF will be recorded. The Investigator will follow subjects with any adverse events until one of the following conditions occurs:

- AE is stabilized and/or resolved
- Subject is lost to follow-up

All AEs will be classified by intensity according to Table 8.1, and guidelines for determining the relationship between any AE and the investigational product will be according to Table 8.2. If the relationship between an adverse event and the investigational product is classified as "related", "probable" or "possible, the event will be regarded as a reaction to the investigational product.

Table 8.1 Classification of Adverse Events by Intensity

Grade 1 (MILD): The symptom is barely noticeable to the subject and does not influence performance or functioning. Allowed concomitant medication is not ordinarily indicated for relief of mild AEs. Examples specific to the trial would include: Transient, barely noticeable headache.
Grade 2 (MODERATE): The symptom is of sufficient severity to make the subject uncomfortable and to influence performance of daily activities. Allowed concomitant medication may be indicated for relief of moderate AEs. Examples specific to the trial would include: Dull persisting headache.
Grade 3 (SEVERE): The symptom causes severe discomfort, sometimes of such severity that the subject cannot continue in the trial. Daily activities are significantly impaired or prevented by the symptom. Allowed concomitant medication may be indicated for relief of severe AEs. Examples specific to the trial would include: Excruciating migraine.

Table 8.2 Guidelines for Determining the Relationship Between Any Adverse Event and the Investigational Product

Related:	There is a reasonable causal relationship between the investigational product administration and the adverse event. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible.
Probable:	There is a reasonable temporal sequence from investigational product administration. The event abates upon discontinuation of the investigational product, and cannot be reasonably explained by the known characteristics of the subject's clinical state.
Possible:	The event may or may not follow a reasonable temporal sequence from investigational product administration. The event could have been produced or mimicked by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.
Unlikely:	There is no reasonable temporal association between the investigational product administration and the event. The event could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.
Unrelated:	There is not a temporal relationship to investigational product administration or there is a reasonable causal relationship between another therapy, concurrent disease, or circumstance and the event.

8.1 SERIOUS ADVERSE EVENTS

An SAE or serious adverse event is defined as any untoward medical occurrence that:

- Results in death;
- Is immediately life-threatening, (the term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires in-patient hospitalization or prolongation of existing hospitalization (hospitalization for elective surgery for a baseline condition is not considered an AE);
- Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect; or
- Is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the above listed outcomes.

8.2 UNEXPECTED ADVERSE EVENT

An unexpected adverse event is defined as any adverse drug experience (i.e., untoward or unintended response) that has not been previously observed (e.g., included in the Investigator's Brochure).

8.3 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS)

Unexpected adverse reactions are suspected unexpected serious adverse reactions if the following three conditions are met:

1. The event must be serious (see Section 8.1);
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose; and
3. The adverse reaction must be unexpected (see Section 8.2).

8.4 ADVERSE EVENTS PROCEDURES

The Investigator should obtain any information regarding the occurrence of adverse events through open-ended questioning of the subject, physical examination and review of laboratory results.

All adverse events, whether serious or not, will be recorded in the Adverse Event page of the subject's CRF and any other related documents.

Information to be described for any adverse event includes:

- Date of onset of the AE
- Medical diagnosis of the AE (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded). Action taken for the AE, such as: none; change in the investigational product administration (e.g., temporary interruption in dosing); drug treatment required; non-drug treatment required; hospitalization or prolongation of hospitalization required; diagnostic procedure performed, subject discontinued from the trial
- Outcome of the AE, such as: subject recovered without sequelae; subject recovered with sequelae; event ongoing; subject died (notify the Sponsor immediately, and complete the Serious Adverse Event page and the Final Visit section of the CRF)
- Date of resolution of the AE and whether or not it was an SAE

8.4.1 Reporting Serious Adverse Events (SAEs)

Full details regarding the collection and reporting procedures for this study are contained in the Safety Management Plan for Study OLT1177-05.

8.4.1.1 Reporting SAEs to the Sponsor

Any fatal or life-threatening serious adverse events must be reported to the Medical Monitor immediately when known by phone, e-mail or the study safety web portal. Any other serious adverse events must be reported to the Medical Monitor within 24 hours of knowledge by phone, e-mail or the study safety web portal. A full description of procedures for the reporting of SAEs is contained in the Safety Management Plan.

Within 24 hours of knowledge, the Serious Adverse Event Form must be sent to the Medical Monitor whether full information regarding the event is known or not. If full information is not known, additional follow-up by the Investigator will be required.

All SAEs occurring by Day 35 of the study (28 days after the last dose of investigational drug) must be reported to the Sponsor.

8.4.1.2 Reporting SUSARs and SAEs to the Ethics Committee and Regulatory Authorities

The Sponsor (or designee) will report all SAEs through the web portal *ToetsingOnline* to the accredited EC that approved the protocol and through the EudraVigilance Clinical Trial Module, within 15 days after the Sponsor has first knowledge of the serious adverse events.

All SUSARs and SAEs that are considered related to the investigational drug and result in death or are life-threatening will be reported expedited. The expedited preliminary reporting will occur not later than 7 days after the Sponsor has first knowledge of the adverse event. The final expected reporting will be submitted no later than 8 days following submission of the preliminary report.

8.4.1.3 Contact Information for Reporting Serious Adverse Event

Investigator will report any serious adverse events to Medical Monitor, as follows:

Curtis Scribner, MD
4287 Howe Street
Oakland, CA 94611

Main/Mobile Tel: +1 510-914-8368
Main Fax: +1 510-985-1665

E-mail: curt@clscribs.com and operations@olatec.com

8.4.2 Reporting Pregnancies

Any pregnancies occurring during the study must be reported to the Sponsor within one business day of the clinical site becoming aware of it. Initial and follow-up pregnancy reporting will be performed in accordance with the Safety Management Plan for Study OLT1177-05. All pregnancies will be followed through birth.

8.4.3 Annual Safety Report

The Sponsor (or representative) will submit, once a year throughout the clinical trial, a safety report to the accredited EC, competent authority, and competent authorities of the concerned Member States.

This safety report will consist of:

- A list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study; and
- A report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9 STATISTICAL METHODS

9.1 GENERAL CONSIDERATIONS

9.1.1 Determination of Sample Size

A total of approximately 24 eligible subjects will be enrolled sequentially in three cohorts of up to 8 subjects each.

9.1.2 Statistical and Analytical Plans

9.1.2.1 Study Populations

Subjects will be screened for eligibility at the Baseline visit and enrolled into the study. Following enrollment, Baseline safety and efficacy assessments will be conducted and the first dose of investigational product will be administered at the clinical site. Subjects will then self-administer investigational product, twice daily for Cohorts 1 and 2 and either one, two or three times per day for Cohort 3 (see Section 5.4.3), for up to eight (8) consecutive days beginning at the Baseline visit (Day 0) and continuing through the planned Day 7 visit. Subjects will return to the study clinic on Days 3 (+1 day), 7 (±1 day) and 14 (±1 day) for

follow-up visits and will be contacted by telephone on Day 35 (± 3 Days) for additional follow-up.

9.1.2.2 Planned Efficacy Analysis

Descriptive statistics will be presented for all outcomes including but not limited to: number of datapoints (n), mean, standard deviation, range, median, and interquartile range. Statistical inference tests will not be conducted.

The study is designed as an open-label Phase 2 proof-of-concept study to determine subjects' response to administration of OLT1177 Capsule during an acute gout flare. The sample size of eight subjects per cohort has been determined to be of sufficient size to provide a preliminary estimate of this effect. Descriptive statistics will be presented for the outcomes as defined in the Statistical Analysis Plan.

Two populations will be defined for this study: 1) the Intent to Treat Population will consist of all subjects who have taken at least one dose of investigational product; 2) the Per-Protocol Population will consist of all subjects who take 80% or more of the total expected doses of investigational product and have no major protocol violations as determined by the Medical Monitor.

The primary efficacy population will be the Per-Protocol Population (PPP). The efficacy analysis will include a responder analysis for 20% and 60% reduction in symptoms at 3 days and 7 days after first administration of investigational product.

The Statistical Analysis Plan (SAP) for Study OLT1177-05 contains a complete description of all populations and analyses to be performed, including a description of the procedures for accounting for missing, unused and spurious data and for reporting any deviation from the SAP. Missing data will be imputed using a mixed imputation strategy. With specific regard to Treatment Failures, missing clinical activity outcome data for such subjects will be imputed using Worst Observation Carried Forward (WOCF; e.g., the highest or most undesirable score will be carried forward for all missing data points) to eliminate the potential bias introduced by subjects who withdraw from the study due to lack of efficacy.

9.1.2.3 Planned Safety Analysis

Summary statistics for the safety data collected during this trial will be presented for all subjects to give a general description of the subjects studied and an overview of baseline results and safety measures. For safety measures (AEs, clinical laboratory, physical examinations, vital signs), categorical variables will be summarized. Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum values.

10 REGULATORY AND LEGAL OBLIGATIONS

10.1 PROTOCOL AMENDMENTS

The Sponsor will immediately inform the EC and Principal Investigator(s) of any required protocol changes, such as to eliminate any hazard to a subject. Changes to the protocol must be in the form of a written amendment prepared and approved by Sponsor. Such changes will require the written approval of the EC and finding of "No grounds for non-acceptance" by the CCMO and will only be implemented following receipt of such approval. The Sponsor, as required by local regulation, will also submit all amendments to local regulatory authorities. Amendment to the protocol may also require Sponsor to revise the ICF. Such a revised ICF must then be submitted to the EC and CCMO for review and approval; the revised ICF must be used to obtain consent from subjects currently randomized/enrolled in the trial if they are affected by the amendment and to obtain consent from new subjects prior to enrollment.

10.2 MONITORING

Qualified representative(s) of the Sponsor or Sponsor designees, "study monitor(s)," will monitor the trial according to a predetermined monitoring plan.

The Investigator must allow the study monitor(s) to periodically review, at mutually convenient times, during the trial and after the trial has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the trial. The CRFs and other documentation supporting the trial must be kept up-to-date by the Investigator and the site personnel at the investigative site. The Investigator will ensure that the study monitor or other qualified representatives of the Sponsor are given access to all study-related documents and has adequate time and space to conduct the monitoring visit including availability of the Investigator and site personnel to discuss findings.

The study monitor will review the various records of the trial (CRFs, subject medical and laboratory records, and other source documents). The study monitor will verify the CRF data against original source documentation for accuracy and completeness. The study monitor will identify data discrepancies and collaborate with the Investigator and site personnel to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log." The study monitor will ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner.

In addition to the above, Representatives of the Sponsor's auditing staff or government inspectors may review the conduct/results of the trial at the site. The Investigator must promptly notify the Sponsor of any audit requests by regulatory authorities.

10.3 PRE-TRIAL DOCUMENTATION

Prior to initiating the trial, the Sponsor will obtain the following documentation:

- A current (within 2 years), dated and signed curriculum vitae for the Principal Investigator and each Sub-Investigator listed on the ABR Form
- A Research Declaration from the head of the department (or equivalent) conducting the research
- A copy of the medical license from the governing body of the locality in which the trial is being conducted for the Principal Investigator and each Sub-Investigator
- Written confirmation from the EC stipulating approval of the protocol, the ICF and any other material provided to potential trial subjects with information about the trial (e.g., instruction sheets, advertisements, etc.)
- A copy of the EC-approved Informed Consent Form
- A Protocol Agreement signed by the Principal Investigator
- A completed Financial Disclosure Form for the Principal Investigator and each Sub-Investigator

Additionally, prior to initiating the trial, the Sponsor will obtain copies of the following documentation from the central laboratory:

- Current laboratory certification for the reference laboratory along with a copy of the laboratory director's CV
- A list of current laboratory normal values for the reference laboratory

10.4 SUBJECT CONFIDENTIALITY AND DISCLOSURE

It is the responsibility of the Principal Investigator to ensure that the confidentiality of all subjects participating in the trial and all of their medical information is maintained at all times prior to, during and following completion of the trial. CRFs and all other documents will identify each subject by SID. All CRFs and any identifying information must be kept in a secure location with access limited to designated site personnel.

Personal medical information may be reviewed by the study monitor or other qualified representatives of the Sponsor, the EC or regulatory authorities in the course of monitoring the progress of the trial. Every reasonable effort will be made to maintain such information as confidential.

The results of the trial may be presented in reports, published in scientific journals or presented at medical meetings in consultation with the Sponsor and Principal Investigator in

accordance with applicable law (see Section 10.7); however, in all cases no reference will be made to any subject by name.

10.5 SOURCE DOCUMENTS

The Principal Investigator will maintain trial-related source documents, which are separate from the CRFs, including: clinical charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The Principal Investigator will document the name and number of the trial and the date on which the subject signed the ICF in the clinic chart or medical record. Source documents will contain a complete description of each subject's medical care, and must be available for source document verification against entries in the CRFs when the Project Manager or study monitor visits the site. All information obtained from source documents will be kept in strict confidentiality.

10.6 RECORD RETENTION

Site shall maintain all such information until the earlier of (i) two (2) years after the first regulatory approval of the investigational product by the FDA, EMA or another regulatory authority or (ii) two (2) years after Sponsor has notified Site and the Principal Investigator that clinical development of the investigational product has been discontinued, or (iii) 15 years, but in any event for the full duration required by Applicable Laws. Site shall not destroy any such information without the prior written permission of Sponsor. Trial records that must be retained include copies of: CRFs, signed ICFs, correspondence with the EC, investigational product dispensing and inventory records, source documents, clinic charts, medical records, laboratory results, radiographic reports and screening/enrollment logs.

Should the Principal Investigator relocate or retire, or should there be any changes in the archival arrangements for the trial records, the Sponsor must be notified. The responsibility for maintaining the trial records may be transferred to another suitable individual, but the Sponsor must be notified of the identity of the individual assuming responsibility for maintaining the trial records and the location of their storage. If no other individual at the site is willing to assume this responsibility, the Sponsor will assume responsibility for maintaining the trial records.

10.7 PUBLICATION POLICY

All information and data obtained in the course of the trial are the property of the Sponsor and are considered confidential. Publication of information and data will be determined in consultation with the Sponsor and Principal Investigator, and in accordance with applicable law will not include unreasonable restrictions on publications.

11 REFERENCES

1. Decision Resources Group, 2012

2. Gaffo AL, et al. Developing a Provisional Definition of Flare in Patients With Established Gout. Arthritis Rheum 2012;64(5):1508-1517.

3. Hoffman HM, Wanderer, AA. Inflammasome and IL-1β-Mediated Disorders. *Curr Allergy Asthma Rep*. 2010 Apr; 10: 229-235.

4. Janssens HJEM, Janssen M, van de Lisdonk EH, van Riel PLCM and van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial; Lancet. 2008 May; 371: 1854-60.

5. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia; Arthritis Care Res (Hoboken). 2012 Oct;64(10):1431-46.

6. Marchetti C, Swartzwelter B, Gaboni F, Neff CP, Richter K, D'Alessandro A, et al. The Novel Pharmaceutical Compound OLT1177 Reduces Inflammation by Preventing Activation of the NLRP3 Inflammasome. Submitted.

7. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006 Mar 9;440(7081):237-41.

8. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al.; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: blood pressure measurement in humans. Hypertension 2005;45:142–61

9. Pope RM, Tschopp J. The Role of Interleukin-1 and the Inflammasome in Gout. Arthritis Rheum 2007;56(10):3183-88.

10. Roddy E, Doherty M. Epidemiology of gout. Arthritis Res Ther 2010;12:223.

11. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, Krammer G, Murphy V, Richard D, and So AK. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012; 71: 1839-48.

12. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996; **27:** 485–89.

APPENDIX 1 DETAILED DESCRIPTION OF STUDY DAYS

1 CLINICAL VISITS

1.1 Baseline Visit (Day 0)

1.1.1 Prior to Drug Administration

The following evaluations and procedures will be performed at this visit:

- Informed Consent: review, explanation and signature on ICF
- Demographics: race, gender, age (years)
- Review of inclusion/exclusion criteria, including microscopic assessment of synovial fluid
- Medical history: A full medical history, including medication history, will be taken, and all concomitant medications/therapies taken prior to the Baseline visit should be recorded on the concomitant medications/therapies source document and CRF page
- Urine pregnancy test for all females of childbearing potential
- Physical examination (including height (cm) and weight (kg) measurements)
- Vital signs (pulse, resting blood pressure [must be resting for 10 minutes], respiration rate, and temperature)
- Blood and urine samples for safety laboratory (hematology, chemistry and urinalysis), pharmacokinetic and biomarker analysis
- Blood samples for *ex vivo* analysis
- Electrocardiogram (Single 12-lead digital ECG)
- Photograph of target joint, if consented
- Investigator-assessed Index Joint Score
- Investigator-assessed Global Rating of Disease
- Efficacy assessments (recorded in Study Diary)
  - Pain
  - General Disability
  - Walking Disability

The Principal Investigator or designated Sub-Investigator will only enroll subjects who meet all protocol eligibility criteria.

1.1.2 Drug Administration

Subjects meeting all entry criteria will have the following procedures performed:

- Dispense investigational product
- Dispense Study Diary including Dosing Diary and subject instructions
- Dispense blister card(s) of Rescue Medication

Site personnel will observe the first administration of the investigational product.

1.1.3 Post Drug Administration

Following first administration of investigational product, subjects will remain at the study clinic for approximately 2 hours at which time the following assessments will be completed:

- Vital signs (pulse, resting blood pressure [must be resting for 10 minutes], respiration rate, and temperature)
- Photograph of target joint, if consented
- Investigator-assessed Index Joint Score
- Investigator-assessed Global Rating of Disease
- Efficacy assessments (recorded in Study Diary)
  - Pain
  - General Disability
  - Walking Disability
- Assessment of adverse events

1.2 Day 3 Visit (+ 1 Day)

- Collect study diary and remove completed pages (for storage in study files)
- Return/dispense study diary
- Assessment of adverse events and concomitant medications/therapies
- Vital signs (pulse, resting blood pressure [must be resting for 10 minutes], respiration rate, and temperature)
- Blood and urine samples for safety laboratory (hematology, chemistry and urinalysis), pharmacokinetic and biomarker analysis
- Blood samples for *ex vivo* analysis

- Investigator-assessed Index Joint Score
- Investigator-assessed Global Rating of Disease
- Photograph of target joint, if consented

A targeted physical examination may be completed if necessary (at the discretion of the Investigator), as required by a subject's signs and symptoms.

1.3 Day 7 Visit (± 1 Day)

- Subject will return completed Study Diary
- Collect study diary and remove completed pages (for storage in study files)
- Subjects will return used and unused bottles of investigational product, for reconciliation
- Subjects will return remaining Rescue Medication to the site, for reconciliation
- Efficacy assessments:
  - Global Evaluation of Treatment
- Assessment of adverse events and concomitant medications/therapies
- Vital signs (pulse, resting blood pressure [must be resting for 10 minutes], respiration rate, and temperature)
- Blood and urine samples for safety laboratory (hematology, chemistry and urinalysis), pharmacokinetic and biomarker analysis
- Blood samples for *ex vivo* analysis
- Electrocardiogram (Single 12-lead digital ECG)
- Investigator-assessed Index Joint Score
- Investigator-assessed Global Rating of Disease
- Photograph of target joint, if consented

An abbreviated physical examination may be completed if necessary (at the discretion of the Investigator), as required by a subject's signs and symptoms.

1.4 Day 14 (± 1 Day) Visit or Early Termination Visit

- Assessment of adverse events and concomitant medications/therapies
- Physical examination

- Vital signs (pulse, resting blood pressure [must be resting for 10 minutes], respiration rate, and temperature)
- Blood and urine samples for safety laboratory (hematology, chemistry and urinalysis), pharmacokinetic and biomarker analysis
- Blood samples for *ex vivo* analysis
- Photograph of target joint, if consented
- Urine pregnancy test for all females of childbearing potential
- Efficacy assessments (recorded in Study Diary)
  - Pain
  - General Disability
  - Walking Disability

1.5 Day 35 (± 3 Days) Follow-up Telephone Call

A safety follow-up call will be placed by site staff to each subject to assess if they have experienced any adverse events. Any adverse events that have occurred since the Day 14 visit will be recorded in study documentation and CRFs.

1.6 Additional Follow-up for Adverse Events

If a subject has an ongoing treatment-related adverse event at the Day 14 or early termination visit, he/she will be followed by the site personnel until resolution or stabilization.

APPENDIX 2 DATA MONITORING COMMITTEE (DMC)

A Data Monitoring Committee has been arranged for this study. The Charter for this DMC is incorporated into this protocol by reference.

APPENDIX 3 AMERICAN HEART ASSOCIATION GUIDELINES FOR COLLECTION OF BLOOD PRESSURE

- Patient should be seated comfortably, with back supported, legs uncrossed, and upper arm bared.
- Patient's arm should be supported at heart level.
- Cuff bladder should encircle 80 percent or more of the patient's arm circumference.
- Mercury column should be deflated at 2 to 3 mm per second.
- The first and last audible sounds should be recorded as systolic and diastolic pressure, respectively. Measurements should be given to the nearest 2 mmHg.
- Neither the patient nor the person taking the measurement should talk during the procedure.

Reference: Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al.; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: blood pressure measurement in humans. Hypertension 2005;45:142–61

APPENDIX 4 PHOTOGRAPHIC PROCEDURE DETAILS

Photographs of the target joint (subject to consent being obtained) will be taken at the clinical site at the Baseline (Day 0: pre-dose and 2 hours[1] post-dose), Day 3, Day 7 and Day 14 visits.

A good medical photograph should accurately portray the subject's target joint, maximize clinically significant information, and minimize extraneous factors. Therefore, any extraneous factors (clothing, furniture, walls, etc.) are to be eliminated from the fields to be photographed. The necessity of good study photos should be stressed to the subjects.

Always use the same, Sponsor-provided digital camera with consistent settings, flash, lens, lighting, and subject position.

Backgrounds should be covered with flat blue material (cloth or paper). The pictures are to be taken with autofocus, in neutral zoom position, at a distance such that no more than 80% of the viewfinder screen is occupied by the subject's target joint. An identifying card or piece of paper containing the subject's SID number should be included in the field of each photograph. The target joint should be photographed while the subject is seated or laying on his/her back in front of a blue colored background.

The following photographs will be taken:

1. One exposure with subject's Subject Identification Number card
2. Two dorsal exposures of subject's target joint
3. Two ventral exposures of subject's target joint
4. Two lateral exposures of subject's target joint
5. Two medial exposures of subject's target joint

Photographs will be transferred to the Sponsor. All supplied photographic equipment will remain the property of the Sponsor.

[1] Assessments can be taken within 30 minutes of indicated time

APPENDIX 5 CONTACT LIST

SPONSOR:

Olatec Therapeutics LLC
800 Fifth Avenue, Fl 25
New York, NY 10065

Office: +1 917-324-7474
Fax: +1 888-418-9873
Email: operations@olatec.com

PRIMARY SPONSOR CONTACT:

Robert Barrow
Olatec Therapeutics LLC
800 Fifth Avenue, Fl 25
New York, NY 10065

Main/Mobile Tel: +1 919-414-3442
Fax: +1 888-418-9873
Email: robert.barrow@olatec.com

MEDICAL MONITOR:

Curtis Scribner, MD
4287 Howe Street
Oakland, CA 94611

Main/Mobile Tel: +1 510-914-8368
Fax: +1 510-985-1665

E-mail: curt@clscribs.com and curt.scribner@olatec.com

STATISTICAL ANALYSIS PLAN

OLATEC THERAPEUTICS LLC

Version 1.0

26 February 2019

Protocol ID: OLT1177-05

Protocol Title: A Phase 2 Single-Center, Proof-of-Concept Safety and Efficacy Study of Orally Administered OLT1177™ (rINN Dapansutrile) Capsules with Successive, Result-Dependent Dose Adaptation in Subjects with an Acute Gout Flare

APPROVALS

Author		
Printed Name & Title:	**Signature:**	**Date:**
Heather Kapushoc Sr. Biostatistician, SSS	Heather Kapushoc	26Feb2019

Reviewer		
Printed Name & Title:	**Signature:**	**Date:**
Suzanne Hackett Sr. Biostatistician, SSS	Suzanne Hackett	26Feb2019

Sponsor Representative		
Printed Name & Title:	**Signature:**	**Date:**
Damaris B. Skouras CEO	Damaris Skouras	26 February 2019

Sponsor Representative		
Printed Name & Title:	**Signature:**	**Date:**
Curtis L. Scribner, MD CMO	C L Scribner	26Feb2019

TABLE OF CONTENTS

1. REVISION HISTORY

Version #	Implemented By	Revision Date	Reason
0.1	Heather Kapushoc	24 January 2019	Initial Creation
0.2	Heather Kapushoc	05 February 2019	Updates throughout, additional figures
0.3	Heather Kapushoc	13 February 2019	Added Trade Mark, clarified Per Protocol definition
0.4	Heather Kapushoc	15 February 2019	Finalized all decisions, added figures
0.5	Heather Kapushoc	22 February 2019	Incorporated comments from statistical reviewer
0.6	Heather Kapushoc	25 February 2019	Replaced Day 7 in clinical activity summary; added PK section; updated formatting
0.7	Heather Kapushoc	26 February 2019	Clarified PK summary
1.0	Heather Kapushoc	26 February 2019	Final Version 1.0

2. ABBREVIATIONS AND ACRONYMS

Some common abbreviations may not be listed.

AE	Adverse Event
CRF	Case Report Form
DMC	Data Monitoring Committee
ECG	Electrocardiogram
hsCRP	High sensitivity C-reactive protein
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
SAA	Serum Amyloid A protein
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SSS	Social and Scientific Systems, Inc.
VAS	Visual Analog Scale
WBC	White Blood Cell

3. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed on data from the Study OLT1177-05, "A Phase 2 Single-Center, Proof-of-Concept Safety and Efficacy Study of Orally Administered OLT1177™ (rINN dapansutrile) Capsules with Successive, Result-Dependent Dose Adaptation in Subjects with an Acute Gout Flare." OLT1177™ is a small molecule new chemical entity that has demonstrated the potential for safety and clinical benefit in this Phase 2 trial of symptoms and inflammatory biomarkers associated with acute gout flare. Social & Scientific Systems, Inc. (SSS) is responsible for developing the SAP and carrying out the statistical analyses, including the production of all tables, figures and listings.

4. PURPOSE OF THE ANALYSES

The focus of this SAP will be to evaluate the safety profile, inflammatory biomarkers and clinical activity of oral OLT1177™ Capsules in Cohorts 1 through 4. Further exploratory analyses not described in this SAP may be performed upon completion of these analyses.

The results from this study are intended to support future clinical investigation of oral OLT1177™ Capsules for safety and effectiveness in subjects with acute gout flare.

5. STUDY DESCRIPTION

5.1 Brief Description of Study Design

This is an open-label Phase 2, single-center, sequential, result-dependent dose adaptation proof-of-concept safety, biomarker, and efficacy study to be conducted in subjects with an acute gout flare. A total of approximately 32 eligible subjects will be enrolled in up to four cohorts of approximately 8 subjects each.

OLT1177™ Capsules (100 mg each) will be self-administered for the duration of the Treatment Period, beginning at the Baseline visit (Day 0) and continuing through the Day 7 visit. Following completion of each cohort, the Study Data Monitoring Committee (DMC) reviewed the data and determined the dosing regimen for the next cohort. The dose for Cohort 1 will consist of five 100 mg OLT1177™ Capsules administered twice each day, for a total of 1000 mg of OLT1177™ drug substance per day. Thereafter, subsequent doses in each cohort will be determined by an adaptive dosing scheme as detailed in the protocol. From the responder-type metrics, Cohort 2 consisted of five 100 mg Capsules 4 times per day, for a total of 2000 mg per day. Cohort 3 consisted of 300 mg per day dosed as two OLT1177™ Capsules in the morning and one OLT1177™ Capsule in the evening. Cohort 4 consisted of one 100 mg OLT1177™ Capsule per day.

Subjects will be screened for eligibility at the Baseline visit and enrolled into the study. Following enrollment, Baseline safety, biomarker, and efficacy assessments will be conducted and the first dose of OLT1177™ Capsules will be administered at the clinical site. Subjects will then self-administer OLT1177™ Capsules for up to eight (8) consecutive days beginning at the Baseline visit (Day 0) and continuing through the planned Day 7 visit. Subjects will return to the study clinic on Days 3 (± 1 day), 7 (± 1 day), and 14 (± 1 day) for follow-up visits and will be contacted by telephone on Day 35 (± 3 Days) for additional follow-up.

Safety, efficacy and biomarker assessments will be conducted at each visit and efficacy assessments will also be captured by a subject-reported paper study diary throughout the duration of treatment.

Safety and tolerability will be evaluated by monitoring the occurrence of adverse events (AEs) and changes in abbreviated physical examination findings, vital signs, clinical safety laboratory test results (chemistry, hematology, SAA, and urinalysis), and ECGs.

Clinical activity will be evaluated by both: 1) subject-reported pain and disability scales and 2) Investigator-assessments, including Index Joint Score and Global Rating of Disease. Biomarkers of inflammation activity will be assessed by changes in: 1) clinical laboratory test results (e.g., WBC, RBC, hsCRP, SAA) and 2) assessment of inflammatory biomarkers, including plasma cytokine analysis as well as ex vivo sample analyses.

6. STUDY OBJECTIVES

The overall study objectives are three-fold:

1. To assess the safety and tolerability of OLT1177™ Capsules after oral administration in subjects with an acute gout flare.
2. To assess the clinical activity of various doses of OLT1177™ Capsules in treating signs and symptoms resulting from an acute gout flare.
3. To assess OLT1177-induced changes in inflammatory biomarkers.

7. STUDY ENDPOINTS

7.1 Clinical Activity Variables

- The primary clinical activity outcome is: Change in subject-reported pain intensity score from Baseline (Day 0) to Day 3 (evening, approximately 72 hours after the first dose) and to Day 7 (evening) in the target joint (100-mm VAS).
- The principle secondary clinical activity outcome is: subject-reported global evaluation of treatment at Day 7.
- Other secondary clinical activity outcomes are:
    - Subject-reported pain intensity score in the target joint
    - Subject-reported general disability score in the target joint
    - Subject-reported walking disability score in the target joint
    - Investigator-assessed Index Joint Score
    - Investigator-assessed Global Rating of Disease
    - Blood levels of high sensitivity C-reactive protein (hsCRP) and Serum Amyloid A protein (SAA)

7.2 Safety Variables

- Safety laboratory measures (chemistry, hematology, SAA, and urinalysis)
- Safety electrocardiograms (ECGs)
- Adverse events (AEs) and serious adverse events (SAEs)
- Physical examination (abbreviated general and site specific examination)
- Vital signs (pulse, resting blood pressure, temperature, respiration rate)

7.3 Biomarker Activity Variables

- Changes in blood levels, e.g. hsCRP, SAA, RBC, WBC
- Circulating inflammatory cytokines in plasma, e.g. IL-1β, IL-6 (these endpoints are the subject of a separate analysis plan; see Cytokine Analysis Plan for Study OLT1177-05)
- *Ex Vivo* sample analyses (these endpoints are not covered by this SAP)

The analyses of levels of cytokines in plasma and *ex vivo* assays are described separately from this SAP and will be reported separately.

8. STUDY SAMPLE SIZE

The sample size of approximately 8 subjects per cohort has been determined to be of sufficient size to provide a preliminary estimate of clinical activity, as well as an assessment of safety and tolerability.

8.1 Randomization

All enrolled subjects will receive OLT1177™ Capsules; therefore, subjects will not be randomized in this clinical trial.

9. ANALYSIS POPULATIONS

The All Enrolled Population includes all subjects who signed an informed consent and were enrolled in OLT1177-05. All subjects who have taken at least one dose of OLT1177™ Capsules will be included in the Safety Population.

Two efficacy populations will be used for this study: Intent to Treat (ITT) and Per-Protocol (PP). The primary efficacy analysis will be performed on the Per-Protocol Population and the safety analysis will be performed on the Safety/ITT population. All enrolled subjects will be included in the subject data listings.

A by-subject listing will be provided for the analysis populations.

9.1 Intent to Treat

The Intent to Treat (ITT) Population will consist of all subjects who have taken at least one dose of OLT1177™ Capsules. For this open-label study, the Intent to Treat Population is synonymous with the Safety Population.

9.2 Per Protocol Population

The Per-Protocol (PP) Population will consist of all subjects who take at least 80% of the intended dose of OLT1177™ Capsules through Study Day 3 and have no major protocol violations as determined by the Medical Monitor. Exposure will be derived using data collected on the Study Drug Administration CRF page. Percent of intended doses will be calculated according to the number of dosing days the subject is on the study as: (number of capsules taken through Study Day 3 / number of capsules intended through Study Day 3) * 100. Table 1 in Section 11.3 shows the intended number of capsules through Study Day 3 for each cohort. If a subject discontinues the study prior to their evening dose, the intended dose for their final dosing day will be considered as half of a day.

10. STATISTICAL METHODS AND GENERAL CONSIDERATIONS

The purpose of this analysis is to assess a small number of subjects exposed for safety, tolerability and clinical and inflammatory biomarker activity of oral OLT1177™ Capsules in the treatment of acute gout flare. As such, no formal statistical testing will be performed. Moreover, all biomarker analyses are described and will be reported separately from this SAP.

Baseline characteristics will be summarized by dose cohort. Baseline for any given parameter is defined as the observation immediately prior to administration of OLT1177™ Capsules. The date of first administration of OLT1177™ Capsules, treatment start date, is considered Day 0. Study day is calculated as 'event date – treatment start date'.

Summary statistics for all data collected during this study will be presented by cohort and overall. For measures which are categorical, the results will be summarized by the number and percentage of subjects in each category. Continuous variables will be presented with summary statistics and will include the number of observations (n), mean, standard deviation (SD), median, 25th and 75th percentiles, and minimum (min) and maximum (max) values.

For continuous variables, change from baseline is defined as the value at a post-baseline time point minus the baseline value. Percent change from baseline is defined as the change from baseline divided by the baseline value multiplied by 100.

All analyses will be performed using SAS 9.3 or higher.

10.1 Missing and Spurious Data

There will be no imputation of missing data for the analysis of this proof-of-concept study.

Data from unscheduled visits will not be included in statistical summaries. However, the data from unscheduled visits will be presented in applicable listings.

10.2 Protocol Clarification

In order to determine the doses in Cohorts 2-4, a responder-type adaptive dosing scheme was developed for the DMC and described in the protocol. This included a responder analysis for percent reduction in symptoms at 3 days and 7 days after first administration of OLT1177™ Capsules. As this responder analysis was intended to be used only by the DMC, the responder analysis will not be performed as part of the final analysis of the study and is not included in this SAP. In addition, no imputation of missing data will be performed. Instead, to assess clinical activity of OLT1177™ Capsules, the primary clinical activity outcome of change in subject-reported pain intensity score in the target joint will be summarized at both the Day 3(PM) visit and the Day 7(PM) visit.

11. STATISTICAL ANALYSES

11.1 Subject Disposition

A summary table will be produced detailing the number of subjects enrolled, the number of subjects treated, and the number of subjects who completed the study or withdrew by cohort and overall.

11.2 Demographic and Baseline Characteristics

Demographics such as sex, age (yrs.), height (cm), weight (kg) and body mass index (BMI (mg/kg^2)) will be presented in summary tables.

Age will be calculated as the number of completed years between birth and informed consent date. The BMI will be calculated as weight/height^2, with weight expressed in kilograms and height in meters.

The Target Joint specified at baseline will be summarized as the number and percent of subjects reporting each joint.

A by-subject listing will be provided for demographic and baseline characteristics.

11.3 Investigational Product Exposure and Compliance

Exposure to OLT1177™ Capsules will be summarized by cohort and overall for all subjects. Descriptive statistics of the number of doses taken, percent of total intended dose, and total dose (mg) will be presented through Study Day 3 and for the entire study. The percent of total intended dose will be calculated as the number of capsules taken divided by the intended number of capsules prescribed, multiplied by 100. The intended number of capsules for each cohort is shown in Table 1 for the period through Study Day 3 and for the entire study. If a subject discontinues the study prior to their evening dose, the intended dose for their final dosing day will be considered as half of a day. The number and percent of subjects who took <80% and ≥80% of total intended doses through Study Day 3 and over the entire Treatment Period will be presented.

A by-subject listing will be provided for exposure and compliance.

Table 1 Prescribed Number of Capsules per Cohort

Cohort	Dose (mg) per Day	Number of Capsules Per Day	Number of Capsules Through Study Day 3	Total Number of Capsules Through End of Treatment
1	1000	10	40	80
2	2000	20	80	160
3	300	3	12	24
4	100	1	4	8

11.4 Clinical Efficacy Analyses

The primary efficacy analyses will be performed on the PP population. Additional efficacy analyses may also be provided for the ITT population for specified endpoints. All efficacy analyses will be presented by cohort and overall.

Pain intensity, walking disability and general disability were recorded on a 0 – 100 mm VAS with anchors 0 = ["no pain", "I can do everything I was able to do before this gout attack started", "I am not experiencing any deterioration in walking"] and 100 = ["never experienced this much pain before", "I cannot do anything", "I can absolutely not walk"] on the respective scales.

11.4.1 Pain Intensity Score

Descriptive statistics for the observed value, change from baseline and percent change from baseline values will be presented for the Day 3 (PM) visit and the Day 7 (PM) visit for the Target Joint Pain VAS (mm) measure. Pain Intensity of the Target Joint will be summarized for the PP and ITT populations.

11.4.2 Subject Reported Global Evaluation of Treatment

Summaries of the count and percentage of subjects will be presented by visit for each of the Global Evaluation of Treatment categories:

- Poor
- Fair
- Good
- Very Good
- Excellent

A by-subject listing will be provided for Global Evaluation of Treatment. Global Evaluation of Treatment will be summarized for the PP and ITT populations.

11.4.3 Target Joint Pain

Descriptive statistics of the Target Joint Pain VAS (mm) measures will be provided by visit for the observed value, change from baseline and percent change from baseline. Target Joint Pain VAS will be summarized for the PP and ITT populations. Figures of the mean scores by cohort, mean percent change by cohort, percent change by subject and percent change by subject within cohort in Target Joint Pain VAS over time will be provided for the PP population. A by-subject listing of Target Joint Pain VAS will be provided.

11.4.4 General Disability

Descriptive statistics of the General Disability VAS (mm) measures will be provided by visit for the observed value, change from baseline and percent change from baseline. General Disability VAS will be summarized for the PP and ITT populations. Figures of the mean scores by cohort, mean percent change by cohort, percent change by subject and percent change by subject within cohort in General Disability VAS over time will be provided for the PP population. A by-subject listing of General Disability VAS will be provided.

11.4.5 Walking Disability

Descriptive statistics of the Walking Disability VAS (mm) measures will be provided by visit for the observed value, change from baseline and percent change from baseline. Walking Disability VAS will be summarized for the PP and ITT populations. Figures of the mean scores by cohort, mean percent change by cohort, percent change by subject and percent change by subject within cohort in Walking Disability VAS over time will be provided for the PP population. A by-subject listing of Walking Disability VAS will be provided.

11.4.6 Investigator-Assessed Index Joint Score

The four measures of Tenderness, Swelling, Erythema, and Warmth for the Investigator-Assessed Index Joint Score will be summarized by the number and percent of subjects at each response level. For Tenderness and Swelling the response levels are:

- No Pain
- Mild Pain
- Moderate Pain
- Severe Pain

For Erythema and Warmth the response levels are:

- Absent
- Present
- Non-assessable

Investigator-Assessed Index Joint Score will be summarized for the PP and ITT populations. A by-subject listing will be provided.

11.4.7 Investigator-Assessed Global Rating of Disease

Summaries of the count and percentage of subjects will be presented by visit for each of the Global Rating of Disease categories:

- Poor
- Fair
- Good
- Very Good
- Excellent

Investigator-Assessed Global Rating of Disease will be summarized for the PP and ITT populations. A by-subject listing will be provided.

11.4.8 High Sensitivity C-reactive Protein and Serum Amyloid A Protein

Descriptive statistics of high sensitivity C-reactive protein (hsCRP) and serum amyloid A protein (SAA) laboratory results will be presented for the reported values, change from baseline and percent change from baseline values by visit. The summary of hsCRP and SAA will be performed on the PP and ITT populations. Figures of the mean scores by cohort, mean percent change by cohort, percent change by subject and percent change by subject within cohort of hsCRP and SAA laboratory results will be provided for the PP Population.

11.4.9 Treatment Failures

A **Treatment Failure** is defined as a subject who at any time during the study is unable to tolerate his/her pain and wishes to receive standard medical intervention for an acute gout flare and is either withdrawn from the study or withdrawn from treatment.

The number and proportion of Treatment Failures will be summarized by cohort and overall for the PP population and for the ITT population.

11.5 Biomarker Efficacy Analyses

An integral part of the efficacy analysis for this study is the analysis of inflammatory biomarkers (hsCRP, SAA, RBC and WBC and plasma cytokines). In addition, supplemental analyses will be done on blood samples collected for *ex vivo* PBMC isolation, stimulation and cytokine production, which will be described and reported separately.

11.6 Safety Analysis

All safety analyses will be conducted on the Safety Population. The applicable definition of an Adverse Event (AE) can be found in the study protocol. All AEs occurring from when the subject signs informed consent to when the subject exits the study will be accounted for in the listings. A treatment emergent AE (TEAE) is an event with onset on or after the first administration of OLT1177™ Capsules through day 35.

11.6.1 Adverse Events

An overall summary of treatment emergent adverse events will be provided including the number and percent of unique subjects with at least one AE, serious adverse events (SAE), related AEs, related SAEs, AE leading to withdrawal, and deaths. Additionally, a summary of unique subjects with AEs (number and %) and actual AE event counts will be presented by MedDRA system organ class and preferred term. Related adverse event incidence will be presented by maximum relationship. Related events are those classified as ‘related’, ‘probably’ or ‘possible’ for relationship. Additionally, the incidence of adverse events by maximum severity will be presented.

The incidence and event count for Serious Adverse Events (SAE) will be provided as well as SAE incidence by maximum relationship and SAE incidence by maximum severity.

Adverse events will be listed by subject. Additionally, subject listing of deaths and AEs leading to withdrawal will be provided.

11.6.2 Laboratory Evaluations

Laboratory data for hematology, chemistry, and urinalysis parameters, will be presented by cohort. At each assessed visit, summary statistics will be presented as well as the change and percent change from baseline at each post-baseline visit. Figures of the mean value, mean percent change by cohort, percent change by subject and percent change by subject within cohort will be provided for the following laboratory parameters:

- Hematology: WBC, RBC, Hemoglobin, Hematocrit, Platelets, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, MCV, and MCH
- Serum Chemistry: Sodium, Potassium, Glucose, BUN, Creatinine, Albumin, Calcium, Chloride, Total Bilirubin, Total Protein, ALT (SGPT), AST (SGOT), Lipase, HbA1c, and Serum Uric Acid

11.6.3 Electrocardiogram (ECG)

Summary statistics will be presented by visit for quantitative ECG results, along with change and percent change from baseline. The following ECG parameters will be summarized:

- Vent Rate (bpm)
- PR interval (ms)
- QRS duration (ms)
- QT (ms)
- QTcF (ms)
- Average RR (ms)

ECG findings of normal, abnormal - not clinically significant, and abnormal - clinically significant will be summarized by subject count and percentage at each visit. Figures for the mean percent change by cohort for each of the above ECG parameters will be provided.

11.6.4 Physical Examination

Physical Examination findings of Normal and Abnormal will be summarized for each body system as counts and percentages by visit.

11.6.5 Vital Signs

Summary statistics of reported values, change from baseline and percent change from baseline will be presented for each visit for the following vital signs:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse (bpm)
- Temperature (C)
- Respiratory Rate (breaths per minute).

Figures of mean percent change by cohort for each of the above vital signs parameters will be provided.

11.6.6 Concomitant Medications

Concomitant medications/therapies and past medications/therapies taken within 30 days prior to the first dose will be provided in a by-subject listing.

12. PHARMACOKINETICS

Plasma concentration levels will be summarized by descriptive statistics for the concentration levels by group at each time point. A by-subject listing will be produced.

13. PRESENTATION OF RESULTS

The following sections are numbered in accordance with the numbering that will be used in the Clinical Study Report per ICH Guidelines and, therefore, do not follow the numbering in the preceding body of the SAP. The Biomarker Analysis will be reported separately.

Disposition and Demographic Data Tables		
Table 14.1.1	Subject Disposition	All Enrolled
Table 14.1.2.1	Demographics Summary	PP Population
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Table 14.1.3.1	Baseline Characteristics	PP Population
Table 14.1.3.2	Baseline Characteristics	ITT Population
Table 14.1.4	Study Drug Exposure and Compliance	ITT Population
Table 14.1.5	Pharmacokinetic Concentration Levels	ITT Population
Efficacy Summary Tables		
Table 14.2.1.1	Pain Intensity Score	PP Population
Table 14.2.1.2	Pain Intensity Score	ITT Population
Table 14.2.2.1	Global Evaluation of Treatment	PP Population
Table 14.2.2.2	Global Evaluation of Treatment	ITT Population
Table 14.2.3.1	Target Joint Pain VAS (mm) by Visit	PP Population
Table 14.2.3.2	Target Joint Pain VAS (mm) by Visit	ITT Population
Table 14.2.4.1	General Disability VAS (mm) by Visit	PP Population
Table 14.2.4.2	General Disability VAS (mm) by Visit	ITT Population
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Figure 14.3.28.1	Systolic Blood Pressure (mmHg) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.28.2	Diastolic Blood Pressure (mmHg) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.28.3	Pulse (bpm) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.28.4	Temperature (C) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.28.5	Respiratory Rate (breaths per minute) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.29.1	ECG Vent Rate (bpm) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.29.2	ECG PR Interval (ms) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.29.3	ECG QRS Duration (ms) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.29.4	ECG QT (ms) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.29.5	EG QTcF (ms) - Mean Percent Change from Baseline by Time	Safety Population
Figure 14.3.29.6	ECG Average RR (ms) - Mean Percent Change from Baseline by Time	Safety Population

Subject Data Listings		
Listing 16.2.1	Subject Disposition	All Enrolled
Listing 16.2.2	Protocol Deviations	All Enrolled
Listing 16.2.3	Analysis Populations	All Enrolled
Listing 16.2.4	Subject Demographics	All Enrolled
Listing 16.2.5	Study Drug Exposure and Compliance	All Enrolled
Listing 16.2.6.1	Target Joint Pain	ITT Population
Listing 16.2.6.2	Global Evaluation of Treatment	ITT Population
Listing 16.2.6.3	General Disability Score	ITT Population
Listing 16.2.6.4	Walking Disability Score	ITT Population
Listing 16.2.6.5	Investigator-Assessed Index Joint Score	ITT Population
Listing 16.2.6.6	Investigator-Assessed Global Rating of Disease	ITT Population
Listing 16.2.7.1	Adverse Events	Safety Population
Listing 16.2.7.2	Adverse Events Leading to Withdrawal	Safety Population
Listing 16.2.8	Concomitant Medications	Safety Population
Listing 16.2.8	Pharmacokinetic Concentration Levels	ITT Population

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