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Novartis Institutes for BioMedical Research

LYS006

Clinical Trial Protocol CLYS006X2201
ClinicalTrials.gov Identifier: NCT03497897

A randomized, subject and investigator blinded, placebo-controlled, multi-center study in parallel groups to assess the efficacy and safety of LYS006 in patients with moderate to severe inflammatory acne

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO& PS) department **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

5-LO	5-lipoxygenase
ACR	Albumin-creatinine ratio
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	Breast cancer resistance protein
BID	*Bis in die* (twice daily)
BMI	Body Mass Index
BUN	blood urea nitrogen
CAH	Congenital adrenal hyperplasia
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CFR	U.S. Code of Federal Regulations
CHF	Congestive heart failure
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
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DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
e-GFR	estimated glomerular filtration rate
ECG	Electrocardiogram
EDC	Electronic Data Capture
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EoT	End of Treatment

ERCP	Endoscopic retrograde cholangiopancreatogram
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FDA	Food and Drug Administration
FIH	First in human
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GPDR	General Data Protection Regulation
h	Hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
HV	Healthy volunteer
i.v.	Intravenous
IA	Interim Analysis
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
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IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra-uterine device
IUS	Intra-uterine system
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
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LOCF	Last Observation Carried Forward
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MAD	Multiple Ascending Dose
MAR	Missing at Random
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed effect Model for Repeated Measures
MPO	Myeloperoxidase
MRI	Magnetic resonance imaging
NASH	non-alcoholic steatohepatitis
NOAEL	No observable adverse effect level
OAT	organic anion transporter
p.o.	Oral
PAPA	Pyogenic arthritis, Pyoderma gangrenosum and acne (syndrome)
PASH	pseudoangiomatous stromal hyperplasia
PCR	Protein-creatinine ratio
PD	pharmacodynamic(s)
PDT	Photodynamic therapy
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pH	Potential of hydrogen
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PoC	Proof-of-concept
PRIDE	Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to Epidermal growth factor receptor inhibitors (syndrome)
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PSTPIP1	proline-serine-threonine phosphatase interacting protein 1
PT	prothrombin time

QD	*Quaque die* (once daily)
QM	Quality management
RBC	red blood cell(s)
RCM	Reflectance Confocal Microscopy
RDC	Remote Data Capture
SAD	Single Ascending Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAPHO	Synovitis acne pustulosis hyperostosis osteitis (syndrome)
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sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
ULQ	upper limit of quantification
UV	Ultra-violet
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of child-bearing potential

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment

Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

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Protocol summary

Protocol number	CLYS006X2201
Full Title	A randomized, subject and investigator blinded, placebo-controlled, multi-center, parallel group study to assess the efficacy and safety of LYS006 in patients with moderate to severe inflammatory acne
Brief title	Study of pharmacodynamics, pharmacokinetics, safety and tolerability of LYS006 in patients with moderate to severe inflammatory acne
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	The main aim of the study is to assess preliminary efficacy, safety, tolerability of LYS006 in patients with moderate to severe inflammatory acne and to determine if LYS006 has an adequate clinical profile for further clinical development.
Primary Objective(s)	To assess the efficacy of LYS006 versus placebo on facial inflammatory lesion counts in patients with moderate to severe inflammatory acne.
Secondary Objectives	To assess the safety and tolerability of LYS006 in patients with moderate to severe inflammatory acne.
Study design	This is a randomized, placebo-controlled, subject and investigator blinded, multicenter, non-confirmatory, parallel group, proof of concept study in patients with moderate to severe inflammatory acne. After an initial screening period (up to 4 weeks), the patients will be treated with LYS006 or matching placebo for 12 consecutive weeks to assess preliminary clinical efficacy, safety, and tolerability in the targeted patient population. At the beginning of the treatment period, patients will be randomized to one of 3 following treatment groups: • CCI LYS006 (high dose) • CCI LYS006 (low dose) • matching placebo CCI Within the three treatment groups, patients will be stratified by type of center (selected or non-selected for additional exploratory assessments). Exposure to placebo will be limited to a maximum of 12 weeks.
Population	The patients included in the study will be patients with moderate to severe inflammatory acne who are candidate for systemic therapies and for whom an appropriate previous treatment with topical anti-acne medication failed or was not well tolerated, or is not indicated. Such patients should have 20 to 100 facial inflammatory lesions and no more than 2 facial inflammatory nodules or cysts to exclude severe cases of nodulocystic acne.

Key Inclusion criteria	Male and female subjects aged 18 to 45 years of age included, presenting with papulo-pustular acne vulgaris (inflammatory acne) at baseline with: • no more than 2 facial inflammatory nodules or cysts • and a minimum number of 10 non-inflammatory facial lesions (open and closed comedones) • who are candidates for systemic treatment and for whom in the opinion of the investigator, an appropriate previous treatment with topical anti-acne medication failed, or was not well tolerated, or is not indicated (generally due to large body surface area affected, e.g., on the back) • Grade 3 (moderate) or Grade 4 (severe) IGA score assessed by the investigator at screening and baseline.
Key Exclusion criteria	• Previous treatment with investigational drugs at the time of screening, or within 4 weeks or 5 half-lives of baseline, whichever is longer; or more as required by local regulations. • Previous treatment with any topical anti-acne therapy: prescription treatment within 2 weeks prior to baseline OR Over-The-Counter (OTC) treatment within 1 week prior to baseline. • Previous treatment with any oral/systemic anti-acne therapy, corticosteroids, or immune-modulators (such as, but not limited to, cyclosporine, methotrexate, azathioprine) within 4 weeks prior to baseline OR previous treatment with biologics (such as anti-TNFα agents, anti-IL-1, or anti--IL-17) within 3 months or 5 half-lives (whichever is longer) prior to baseline OR previous treatment with anti-IL-12/23 blocking agents within the last 6 months prior to baseline OR previous surgical, physical light or laser therapy within 4 weeks prior to baseline OR previous facial treatment with medium depth chemical peels within 3 months prior to baseline. • Patients receiving concomitant medication(s) that is/are known to inhibit OAT3 (see Table 5-1) and that cannot be discontinued or replaced by safe alternative medication within 5 half-lives or 1 week (whichever is longer) prior to baseline and for the duration of the study. • Any other forms of acne, Commercially Confidential Information • Active systemic infections (other than common cold) within 2 weeks prior to baseline. Commercially Confidential Information
Study treatment	LYS006 CCI (high dose): 12 weeks • LYS006 CCI (low dose): 12 weeks • Matching placebo CCI: 12 weeks

Key safety assessments	• AE monitoring using CTCAE grading • Physical examinations • Monitoring of laboratory markers in blood and urine • ECG • Vital signs
Data analysis	The natural log transformed inflammatory facial lesion count will be analyzed using a Bayesian mixed effect model for repeated measures (MMRM), with log transformed baseline inflammatory facial lesion count as a continuous covariate; treatment group, visit, treatment group by visit interaction, log transformed baseline inflammatory facial lesion count by visit interaction and type of center (selected/non-selected for additional exploratory assessments) as fixed effects and an unstructured covariance structure will be used
Key words	Acne, efficacy, safety.

1 Introduction

1.1 Background

Moderate to severe inflammatory acne is a debilitating disease, with visible inflammatory lesions on the face and subsequent risk of permanent scars. Available treatments are either associated with serious side effects (such as isotretinoin) or are modestly effective even after long term treatment (such as systemic antibiotics, oral zinc, and hormonal therapies). Acne is recognized as a chronic inflammatory skin disease, in which innate immunity play critical roles (Das and Reynolds 2014). Systemic antibiotics are associated with the rise of microbiological resistance and their long term use is more and more under critique, as most used tetracyclines are bacteriostatic rather than bactericidal and antibiotic resistance is a growing concern (Adler et al 2017). Thus, the development of a non-antibiotic, anti-inflammatory and well-tolerated oral agent would respond to this medical need.

Zouboulis showed that in an open label Phase IIa clinical trial including 10 patients that treatment with the 5-LO inhibitor zileuton showed highly clinically relevant improvement of acne severity scores and reduction in inflammatory lesions (Zouboulis et al 2003, Zouboulis 2009). A multicenter placebo controlled study with 101 patients treated 4 times daily with 600 mg zileuton for 12 weeks showed significant reduction in inflammatory lesions in the subset of patients with more severe acne (Critical Therapeutics 2005). This pointed to the potential implication of the leukotriene A4 hydrolase (LTA4H) pathway in acne and led to the proposal of testing a specific LTA4H inhibitor, LYS006, in moderate to severe inflammatory acne.

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure (IB).

Relevant data summary

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Inflammatory acne is characterized by high numbers of neutrophils in the inflamed skin and upregulation of LTB4 and its biosynthetic enzymes. In acne, an approximately 70-fold less potent LTB4 inhibitor (the 5-LO inhibitor zileuton) demonstrated some clinical efficacy (Zouboulis 2009, Collawn et al 1992). LTB4 inhibitors, however, have not been developed for these indications yet, and no LTA4H inhibitor is currently marketed in this indication. LYS006 would therefore constitute a new therapeutic approach for this chronic inflammatory skin disease.

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1.2.1 Teratogenicity and reproductive toxicity data

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1.2.2 Pharmaceutical properties

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1.2.3 Pharmacology

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1.2.4 Toxicology

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1.2.5 Non-clinical pharmacokinetics and metabolism

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1.3 Clinical data

The most relevant data for the present study are summarized below. For detailed information, please refer to the IB.

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In parallel to the Phase 2 study in Acne, LYS006 is being evaluated in ulcerative colitis, hidradenitis suppurativa and, nonalcoholic steatohepatitis (all phase 2 studies).

1.4 Study purpose

The study is designed to assess clinical efficacy and safety of LYS006 in adult patients with moderate to severe inflammatory acne as well as exploring dose relationship. This information will support the decision to initiate a dose ranging study in inflammatory acne and guide dose selection for that planned study.

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	*Endpoints related to primary objective(s)*
• To assess the efficacy of LYS006 versus placebo on facial inflammatory lesion counts in patients with moderate to severe inflammatory acne	• Baseline-adjusted total inflammatory facial lesion count at Week 12

2.2 Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• To assess the safety and tolerability of LYS006 in patients with moderate to severe inflammatory acne	• Number and severity of AEs

2.3 Exploratory objective(s)

Exploratory objective(s)	*Endpoints related to exploratory objective(s)*

Exploratory objective(s)	***Endpoints related to exploratory objective(s)***
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Exploratory objective(s)	***Endpoints related to exploratory objective(s)***

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3 Investigational plan

3.1 Study design

This is a randomized, placebo-controlled, subject and investigator blinded, multicenter, non-confirmatory, parallel-group, proof-of-concept study in adult patients with moderate to severe facial inflammatory acne. After an initial screening period (up to 4 weeks), the study will be conducted over a treatment period of 12 weeks to evaluate the clinical efficacy of LYS006 versus placebo. Fifty-six patients will be randomized in a 3:1:3 ratio to one of the following treatment groups:

- Group 1: LYS006 capsules, high dose CCI , n=24
- Group 2: LYS006 capsules, low dose CCI , n=8
- Group 3: matching placebo CCI , n=24

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Exposure to placebo will be limited to a maximum of 12 weeks.

After treatment period completion, all patients will enter a post-treatment safety follow-up period of 4 weeks without study drug administration.

The maximum duration of study participation will be 20 weeks.

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3.2 Rationale for study design

Study population

The patients included in the study are adults with moderate to severe inflammatory acne. Disease severity is defined with a minimal count of 20 facial inflammatory lesions (papules, pustules, nodules) at baseline, a minimum of 10 non-inflammatory facial lesions at baseline and screening, and an IGA score of 3 (moderate) or 4 (severe) assessed by the investigator at screening and baseline. Patients should have no more than 2 facial nodules, in order to exclude cases of nodulocystic acne Commercially Confidential Information

In line with the observed activity of zileuton in previous studies (Zouboulis et al 2003, Critical therapeutics 2005), Commercially Confidential Information

Included patients should be candidates for a systemic treatment and should respect specified washout periods for systemic and topical anti-acne treatments (see Section 4.2 and Section 5.2). Patients are eligible for this study, if topical treatment alone or in combination with another topical treatment was not sufficient and/or was contraindicated. As an example, often involvement of the back alone may be considered an indication to systemic treatment, as topical treatment is difficult to apply by the subject himself. However, for this study, facial involvement is mandatory for inclusion. Washout periods have been defined based on other recent Phase 3 clinical studies in moderate to severe inflammatory acne such as Fleischer et al 2006, ClinicalTrials.gov NCT02320149 2014, and ClinicalTrials.gov NCT02322866 2014.

Treatment arms and study methodology

The following treatment groups will be compared in the primary efficacy analysis: LYS006 high dose CCI versus placebo on baseline-adjusted facial inflammatory lesion count at Week 12. Other time-points may be explored. Moderate to severe acne is associated with an increased risk of scarring on the face. A placebo-controlled study of more than 12 weeks is therefore not considered. In this clinical setting, it is known that a placebo effect could occur with up to 30-40% spontaneous reduction in inflammatory lesion count at Week 12. In this context, a blinded study is deemed optimal to generate reliable data, which are not influenced by investigators' or patients' perception. Due to possible carry-over effects and the need for a wash-out period, a cross-over design is not considered appropriate for this proof-of-concept study.

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Clinical endpoints

It is assumed that the anti-inflammatory effect with the LTA4H inhibitor LYS006 is the clinically most pronounced effect. Consequently, baseline-corrected facial inflammatory lesion count is chosen as the primary endpoint (US department of Health and Human Services 2005). Inflammatory

lesions (IL) are defined as papules, pustules and nodules. As counts on the face are best validated, the IL count will focus on the face similarly to other clinical studies in the same clinical setting. Commercially Confidential Information

3.3 Rationale for dose/regimen, route of administration and duration of treatment

In the present study, doses CCI are proposed to explore safety and efficacy in the moderate to severe acne population.

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Treatment duration is referenced by the FDA draft guidance for industry on acne vulgaris (US department of Health and Human Services 2005) to be at least 12 weeks despite the recognized fact that maximum effects may not yet be achieved. Currently ongoing or completed studies with systemic treatments have used a similar duration (for example, antibiotics such as minocycline in Fleischer et al 2006, or sarecycline in ongoing pivotal studies (ClinicalTrials.gov NCT02320149 2014, ClinicalTrials.gov NCT02322866 2014). It is generally accepted to include placebo controls in these studies in similar patient populations.

3.4 Rationale for choice of comparator

In this proof-of-concept study, the preliminary efficacy CCI of LYS006 will be assessed using a subject-blinded and investigator-blinded study design as compared to placebo. Moderate to severe inflammatory acne is associated with a pronounced potential placebo effect. In addition, lesion counts CCI are subjective assessments with a potential risk of substantial variability. Therefore, the proposed study design should mitigate the potential biases associated with the clinical setting and the endpoints related to the study objectives.

3.5 Rationale for choice of background therapy

Acne is a disease where the visible inflammatory lesions, papules and pustules, appear and disappear in irregular intervals and numbers. The minimal treatment duration is considered to be 12 weeks.

No background therapy is needed in this trial, in order to evaluate the effect of an oral therapy alone. In order to avoid as much as possible potential confounders, all medications to treat acne or acne inflammation are to be washed out before randomization (see relevant exclusion criteria (Section 4.2) and prohibited treatment (Section 5.2)). Adherence for anti-acne therapies is considered generally as poor (Thiboutot et al 2009).

3.6 Purpose and timing of interim analyses/design adaptations

The following interim analysis (IA) may be conducted during this trial:

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3.7 Risks and benefits

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and adequate post-treatment safety follow-up to capture any potential late occurring AEs.

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In addition, women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if a pregnancy was to occur during the study, and agree that, in order to participate in the study, they must adhere to the contraception requirements outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subjects will not reliably comply, they should not be entered or continue in the study.

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Treatment for AEs should follow general guidelines for standard-of-care, and is at the discretion of the investigator or treating physician. There are no specific treatment recommendations for AEs that may possibly occur in in this trial.

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Due to early stage of development, there may be unknown risks of LYS006 which may be serious.

3.7.1 Blood sample volumes

A maximum of approximately 207 mL of blood from each subject is planned to be collected over a period of 20 weeks from Screening until EOS as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and central Laboratory Manual.

All blood samples will be taken by direct venipuncture in a forearm vein. Each sample should have a unique sample number. The actual sample collection date and time will be recorded on the eCRF. Sampling problems will be noted on the comments field of the eCRF.

See Section 8.9 regarding the potential use of residual samples.

4 Population

4.1 Inclusion criteria

The patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female subjects aged 18 to 45 years of age inclusive, and otherwise in good health as determined by medical history, physical examination, and vital signs
3. Body weight between 50 and 120 kg, both inclusive, at screening.
4. Patients with papulo-pustular acne vulgaris (inflammatory acne):
    - presenting at baseline with :
        - 20 to 100 facial inflammatory lesions (papules, pustules and nodules),
    - presenting at baseline and screening with
        - no more than 2 facial inflammatory nodules or cysts,
        - and a minimum number of 10 non-inflammatory facial lesions (open and closed comedones)

- who are candidates for systemic treatment and for whom in the opinion of the investigator, an appropriate previous treatment with topical anti-acne medication :
  - failed,
  - or was not well tolerated,
  - or is not indicated (e.g., due to large body surface area affected, e.g., on the back)

5. Patients with Grade 3 (moderate) or Grade 4 (severe) IGA score assessed by the investigator at screening and baseline.
6. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

The patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Previous treatment with investigational drugs at the time of screening, or within 4 weeks or 5 half-lives of baseline, whichever is longer; or more as required by local regulations.
2. Previous treatment with any topical anti-acne therapy:
   - prescription treatment within 2 weeks prior to baseline
   - Over-The-Counter (OTC) treatment within 1 week prior to baseline

   The use of medicated anti-acne creams, medicated cleansers or medicated soaps will remain prohibited for the duration of the study.
3. Previous treatment with any oral/systemic anti-acne therapy:
   - oral antibiotics, dapsone, oral zinc within 4 weeks prior to baseline
   - retinoids, e.g., isotretinoin, within 3 months prior to baseline
   - hormonal therapy (in particular anti-androgen for example spironolactone, finasteride, and cyproterone acetate alone or in combination with estrogen derivatives) within 1 month prior to baseline.

   If women of child-bearing potential are using oral contraception, this contraception can be used under certain conditions (see prohibited treatments for further guidance on oral contraception in women of child-bearing potential [WOCBP]).
4. Previous treatment with systemic corticosteroids or immunomodulators (such as, but not limited to, cyclosporine, methotrexate, azathioprine) within 4 weeks prior to baseline.

   This includes as well lesional injections of the above medications in acne prone areas (such as corticosteroids).
5. Previous treatment with biologics (such as anti-TNFα agents, anti-IL-1, or anti-IL-17) within 3 months or 5 half-lives (whichever is longer) prior to baseline.
6. Previous treatment with anti-IL-12/23 blocking agents (such as briakinumab and ustekinumab or p19 antibodies) within 6 months prior to baseline.
7. Previous surgical, physical (such as ThermaClear™), light (including blue or UV light, photodynamic therapy [PDT]) or laser therapy within 4 weeks prior to baseline.

8. Previous facial treatment with medium depth chemical peels (excluding home regimens) within 3 months prior to baseline.
9. Patients receiving concomitant medication(s) that is/are known to inhibit OAT3 (see Table 5-1) and that cannot be discontinued or replaced by safe alternative medication within 5 half-lives or 1 week (whichever is longer) to baseline and for the duration of the study.
10. Any other forms of acne, such as:

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11. Any severe, progressive or uncontrolled medical or psychiatric condition or other factors at randomization that in the judgment of the investigator prevents the patient from participating in the study.

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13. Active systemic infections (other than common cold) within 2 weeks prior to baseline

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15. Subjects with estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73m (estimated by MDRD) at screening.
16. History of kidney stones and/or repeated presence of crystals in urine before drug administration.
17. History or symptoms of malignancy of any organ system, treated or untreated, within the past 5 years,

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18. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV).

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19. History of auto-immune or immunodeficiency diseases, or a positive human immunodeficiency virus (HIV) test result (for example, Chemiluminescence and Polymerase Chain Reaction) at screening.
20. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of study treatment. Commercially Confidential Information

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23. History of drug abuse or unhealthy alcohol use[#] Commercially Confidential Information

24. Donation or loss of 400 ml or more of blood within 8 weeks prior to baseline, or longer if required by local regulation.

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The study population will be comprised of male and female subjects, aged 18-45 years, with moderate to severe inflammatory acne. A total of approximately 56 patients will be randomized. The sample size may be re-assessed at time of IA and the number of randomized patients may be increased.

The investigators must ensure that all patients being considered for the study meet the eligibility criteria. No additional criterion should be applied by the investigators, in order to ensure that the study population is representative of all eligible patients. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Commercially Confidential Information women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

If there is any question that the subject will not reliably comply, the subject should not be entered or continue in the study. Please refer to Section 4.2 (Exclusion criteria) for details of contraception requirements for the study.

5.2 Prohibited treatment

Table 5-1 Prohibited medication

Medication	Action to be taken	Requested wash-out (prior to randomization/first treatment)
IL-12 or IL-23 blocking agents such as briakinumab and ustekinumab, including p19 blocking antibodies	Discontinue study treatment	Wash-out: 6 months
Any biologics, other than above, in particular, IL-1 and IL-17 blockers	Discontinue study treatment	Wash-out: 3 months or at least 5 times the half-life, whichever is longer
Any systemic immunosuppressant or immunomodulator, such as cyclosporine, methotrexate, cyclophosphamide, azathioprin, corticosteroids (includes local injections), etc.	Discontinue study treatment	Wash-out: 1 month
Any systemic treatment with antibiotics, in particular tetracyclines and/or macrolides, but as well other oral anti-acne treatment such as dapsone and zinc.	Discontinue study treatment if antibiotic treatment (not for acne) is significantly longer than 2 weeks. All other cases to be discussed with Sponsor on case-by-case basis.	Wash-out: 1 month
Use of any systemic hormonal treatment (including anti-androgens, for example spironolactone, finasteride, and cyproterone acetate alone or in combination with estrogen derivatives) within 1 month before baseline.	To be discussed with Sponsor on case by case basis	Wash-out: 1 month
Oral contraceptives can be continued if stable for the last 3 months before baseline if stable in dose and dosing regimen and type (brand) and if the patient plans to continue throughout the study treatment period.	To be discussed with Sponsor on case by case basis (in particular of dose and brand changes)	Wash out in case of change in dose, regimen or type: 3 months
Systemic retinoids, in particular isotretinoin	Discontinue study treatment	Wash-out: 3 months

Medication	Action to be taken	Requested wash-out (prior to randomization/first treatment)
Surgical or physical CCI light and laser therapy (including blue light, use of handheld devices, tanning devices or photodynamic therapy) on area of evaluation. After baseline, use of any tanning device, or excessive exposure to sun [with intention to tan], any handheld light device to treat skin or procedures for hair removal in the evaluation areas are not permitted.	Discuss with Sponsor on case by case basis	Wash-out: 1 month
Any topical for acne on area for evaluation (face, back, chest, shoulder, neck), including retinoids (such as adapalene, tazarotene, isotretinoin or tretinoin), antibacterial and antibiotics (such as benzoyl peroxide, clindamycine or erythromycine) and any other topical keratolytic or peeling agents (such as salicylic acid, or lactic acid) or any other anti-acne drug (such as dapsone, azelaic acid). These topicals include over the counter products for acne, such as medicated emollients, cleansers or soaps.	To be discussed with Sponsor on case-by-case basis.	CCI

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Decisions regarding drop-outs and replacements will be discussed with the sponsor on a case-by-case basis.

5.3 Dietary restrictions and smoking

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5.4 Other restrictions

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6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational treatment and control drug(s)

The investigational drug, LYS006 1 mg and 5 mg, and matching placebo will be prepared and supplied by Novartis to investigator`s site as double blinded patient kits. Drug will be administered orally in accordance with the specified study procedures (see Section 6.5).

Table 6-1 Overview of study medication

Study drug name	Formulation	Unit dose	Packaging	Provided by
LYS006	Hard Gelatin Capsule	1 mg	Double blind patient kits	Novartis
LYS006	Hard Gelatin Capsule	5 mg	Double blind patient kits	Novartis
Placebo	Hard Gelatin Capsule	0 mg	Double blind patient kits	Novartis

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

6.2 Treatment arms

Subjects will be assigned to one of the following 3 treatment groups in a ratio of 3:1:3:

- Group 1: LYS006 CCI (high dose) for a total of 12 weeks
- Group 2: LYS006 CCI (low dose) for a total of 12 weeks
- Group 3: placebo CCI for a total of 12 weeks

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6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual patients by way of a randomization number on Day 1. Randomization of patients will be carried out by Interactive Response Technology (IRT) system.

The randomization number is only used to identify which treatment the patients have been randomized to receive. The Subject number assigned to a patient at screening remains the unique identifier for the patient throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

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The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A subject randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of patients.

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling and schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

Sponsor staff

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Statistical programmers and other personnel involved in study data analysis (e.g. drug supply manager) are allowed to access treatment assignment information for the purpose of data analysis.

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All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-2 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis
Subjects/Patients	B	B	UI	CCI
Site staff	B	B	UI	
Drug Supply and Randomization Office	UI	UI	UI	
Unblinded sponsor staff (see text for details)	UI	UI	UI	
Statistician/statistical programmer/data analysts	B	B	UI	
All other sponsor staff including external experts not identified above	B	B	UI	

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Treating the subject

LYS006 and its matching placebo will be administered to the subject via oral route

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6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted. Occasional interruptions in study treatment must be recorded as protocol deviations.

These changes must be recorded on the Dosage Administration Record page of the eCRF.

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely or in case of pregnancy confirmed by a positive serum pregnancy test. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system

to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time (select as applicable) in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- subject number.

In addition, the investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject.

6.8 Treatment exposure and compliance

Pre-dose LYS006 blood and plasma concentrations (measures of treatment exposure) will be determined in all subjects treated with LYS006, as detailed in Section 8.7.

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The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be assessed by the investigator and/or study personnel using pill counts at visits 104, 105 and 106 and information provided by the subject at visits 102 and 103. This information should be captured in the source document at the respective visit and in the eCRF. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.9 Recommended treatment of adverse events

There are no known expected AE associated with LYS006 that would warrant specific treatment. Necessary medication as well as surgical or physical treatment used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

No specific rescue treatments are planned for this study. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

If during the treatment period, the acne condition would worsen significantly and rescue treatment is medically indicated, the patient should be discontinued from the study treatment. If the acne condition worsens after the treatment period is finished, any medically indicated rescue medications can be prescribed during the follow up period.

6.11 Concomitant treatment

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions and any physical anti-acne therapy including light, laser) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes his/her Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

All treated subjects should have a safety follow-up visit conducted 30 days after last administration of study treatment. All SAEs reported during this time period must be reported as described in Section 9.2 and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

7.2 Discontinuation of study treatment

Individual Treatment Discontinuation Rules

Patients may voluntarily discontinue the study for any reason at any time. The investigator must discontinue study treatment for a given subject, if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment **must** be discontinued under the following circumstances:

- Subject withdraws consent
- Pregnancy

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- Any other protocol deviation that results in a significant risk to the patient's safety

Subjects who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Where possible, they should return for the assessments as defined in the Assessment schedule (Table 8-1). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in Section 7.4.

7.2.1 Replacement policy

Replacement patients may be enrolled to replace patients who discontinue from study treatment before completion of Week 12 assessments. Decisions regarding drop-outs and replacements will be discussed with the sponsor on a case-by-case basis.

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For the United States and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For all the other countries: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study stopping rules

The study may be put on hold pending full safety data review if one or more of the following criteria are met:

- Two or more investigational drug (LYS006) related SAEs are reported
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- Other clinically significant events that in the opinion of the investigator or sponsor preclude to continue dosing Commercially Confidential Information

In these cases, ad hoc internal experts will carefully evaluate the safety data of the entire study. The experts will recommend whether the study can be continued, should be stopped or if other safety measures need to be taken. The findings and recommendations of the internal experts will be documented and will be made available to the respective Ethics Committees/Review Boards.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued subject.

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the Assessment schedule (Table 8-1) or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study treatment for any reason should be scheduled for a visit as soon as possible. Where possible, they should return for the assessments as defined in the assessment table. If not possible, all of the assessments listed for the final visit should be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsultation) or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Epoch	Screening		Treatment						Post-Treatment Follow-Up
Visit Name	Screening	Baseline	Treatment						EOS
Visit Numbers[1]	1	2	101	102	103	104	105	106	299[2]
Days	-30 to -2	1	1		15 -8 +5	29 ±5	57 ±5	85 ±5	115 -5 +15
Time (post-dose)	-	-	-		-	-	-	-	-
Informed consent	X								
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Inclusion / Exclusion criteria	X	X							
Pregnancy test[3]	X	X			X	X	X	X	X
Physical Examination	S	S						S	S
Medical history/current medical conditions	X								

Epoch	Screening		Treatment						Post-Treatment Follow-Up
Visit Name	Screening	Baseline	Treatment						EOS
Visit Numbers[1]	1	2	101	102	103	104	105	106	299[2]
Days	-30 to -2	1	1		15 -8 +5	29 ±5	57 ±5	85 ±5	115 -5 +15
Time (post-dose)	-	-	-		-	-	-	-	-
Demography	X								
Body Height	X								
Body Weight	X								X
Body Temperature	X	X			X	X	X	X	X
Pulse rate	X	X			X	X	X	X	X
Blood Pressure	X	X			X	X	X	X	X
Electrocardiogram (ECG)	X	X			X	X	X	X	X
Hepatitis and HIV Screen	X								
Clinical Chemistry	X	X			X	X	X	X	X
Hematology	X	X			X	X	X	X	X
Urinalysis	X	X			X	X	X	X	X
Commercially Confidential Information	X	X[16]			X	X	X	X	X
Commercially Confidential Information		X			X	X	X	X	
Drug dispensation			X			X	X		
Compliance check (pill count[17] and patient's information)					X	X[17]	X[17]	X[17]	
Drug administration record			X		X	X	X	X	
Concomitant medications	As required								
Adverse Events	As required								
Serious Adverse Events[4]	As required								
Facial inflammatory lesion count (papules, pustules, inflammatory nodules, including nodulocysts)	X	X			X	X	X	X	X
Commercially Confidential Information	X	X				X		X	X
Commercially Confidential Information		X				X		X	X

Epoch	Screening		Treatment						Post-Treatment Follow-Up
Visit Name	Screening	Baseline	Treatment						EOS
Visit Numbers[1]	1	2	101	102	103	104	105	106	299[2]
Days	-30 to -2	1	1		15 -8 +5	29 ±5	57 ±5	85 ±5	115 -5 +15
Time (post-dose)	-	-	-		-	-	-	-	-
Commercially Confidential Information		X				X	X	X	X
	X	X			X	X	X	X	X
		X				X	X	X	X
		X							X
		X							X
		X				X		X	X
	X	X				X	X	X	X
			X		X	X	X	X	X
								X	
					X	X	X	X	X
	X	X				X		X	X
		X			X	X	X	X	X
		X			X	X	X	X	X
		X			X	X	X	X	X
	X	X				X		X	X
		X						X	
			X						
Study completion information									X

[1] Visit structure given for internal programming purpose only.
[2] Patients who discontinue the study early, should have the same assessments performed as for the end of treatment Visit 106 and EOS performed.
[3] Blood test at screening and EoS or last visit; additional urine tests must be done throughout the study.
[4] SAEs collected up to 30 days following the End of Treatment Visit.

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[7] Pre-dose sample on dosing days, all patients. Sample will also be collected at EOS visit as indicated in the assessment schedule.

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[17] Pill count only at visits 104, 105 and 106.

8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH E14 (R2) GCP guideline (2016) and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

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A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

Refer to the Site Operations Manual for a complete list of Informed Consent Forms included in this study.

8.3 Subject screening

It is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed.

All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only be re-screened once for the study.

If a subject fails screening but is re-screened, the subject must be rescreened using the same subject number.

Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

All eligibility criteria must be re-checked, based on the most recent data available, and met prior to enrollment of the patient into the study.

If the rescreening is successful, the following information should be collected in the CRF:

- Date the study informed consent was first signed.
- All assessments done during the first screening period.
- All assessments repeated during the re-screening period (e.g. ECG, lab).
- Updated information as per latest status during the re-screening period, e.g., medical history, diagnosis.
- Adverse events based on the date of re-consent.

For screening failures (initial or after re-screening), information on what data should be collected is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Data to be collected will include general patient demographics, relevant medical history and current medical conditions prior to study entry, diagnosis, details of prior anti-acne, and any other assessments that are done for the purpose of determining eligibility for inclusion in the study. All medications and significant non-drug therapies (including herbal medicines, physical therapy and blood transfusions) taken within 4 weeks prior to first dose of study drug must be recorded on the eCRF. Details are outlined in the Site Operations Manual.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.5 Efficacy / Pharmacodynamics

Pharmacodynamic and efficacy assessments are specified below, with the methods for assessment and recording specified in the Study Operations Manual. As clinical efficacy measures are rater dependent, each evaluator should be appropriately trained and qualified for these assessments. In particular, **every effort should be made that the same evaluator assesses and counts the lesions throughout the study.**

Assessments will be performed and pharmacodynamic samples will be collected at the time-points defined in the Assessment schedule (Table 8-1). Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment.

In order to better define the Pharmacodynamic profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Pharmacodynamic samples will be obtained and evaluated in all subjects at all dose levels.

8.5.1 Clinical Outcome Assessments (COAs)

Clinical Outcome measures will assess the acne severity CCI and also the numbers of lesions and their type CCI Due to the inter- and intra- rater variability inherent to every subjective grading system, it is important that every effort should be made to keep the same evaluator per patient between baseline to Week 12. This evaluator needs to provide documentation that s/he was properly trained and whether s/he was previously involved in acne clinical studies.

The counting is to be done by lesion type CCI . The face will be separated into five areas: the forehead, the right cheek, the left cheek, the chin and the nose. For each assessment, the evaluator will be recorded in the source documentation and change of evaluator should be noted in CRF.

8.5.1.1 Lesion counts

Acne is characterized by inflammatory and non-inflammatory lesions situated in the face and non-facial areas, such as upper trunk (chest, back and shoulders). The most frequent inflammatory lesions include papules and pustules, both generally less than 0.5 cm in diameter, while nodules are larger, deeper dermal lesions and more typical for nodulo-cystic acne. All inflamed lesions are generally surrounded by a halo of erythema allowing for their characterization as inflammatory. Some lesions, in particular nodules, may be tender.

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8.5.1.1.1 Inflammatory lesion counts

For a therapeutic effect in inflammatory acne, a reduction in inflammatory facial lesions is considered the main endpoint. The inflammatory lesions include papules, pustules, and nodules (nodules and cysts are discussed below). Papules are red inflammatory lesions in general not larger than 0.5cm, while pustules have a yellow center, from the pus collection in the center of the inflammatory lesion. At pre-specified visits, the evaluator will count papules and pustules separately and by area on the face only. For this purpose, inflammatory lesions will be counted in five areas (right and left cheek, chin, forehead, and nose).

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8.5.3 Exploratory biomarkers

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8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule (Table 8-1) detailing when each assessment is to be performed.

8.6.1 Physical examination

A complete physical examination will be performed as per Assessment schedule (Table 8-1) and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological.

Further examination may be required based on medical history and/or symptoms.

Significant findings that were present prior to informed consent signature must be included in the Medical History page eCRF. Significant new findings that begin or worsen after informed consent signature must be recorded on the Adverse Event page eCRF.

8.6.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before dosing and as indicated in the Assessment schedule (Table 8-1) as per institutional standards.

Unscheduled assessment can be performed if clinically indicated.

8.6.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as indicated in the Assessment schedule (Table 8-1).

Height information will be collected at screening only.

8.6.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Central laboratories will be used for the analysis of scheduled hematology and clinical chemistry blood specimens collected as part of screening and safety monitoring (as detailed in the Assessment schedule (Table 8-1)). Only laboratory results from the central laboratory can be used to determine patient's eligibility for the study. During the course of the study, unscheduled assessment can be performed if clinically indicated.

Local laboratory assessments may be performed if medically indicated or when the treating physician cannot wait for central laboratory results for decision making. In this particular situation, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

The results of the local laboratory will be recorded in the eCRF as unscheduled visit if the following criteria are met:

- a treatment decision was made based on the local results, or
- there are no concomitant central results available

Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to the investigators in a separate Laboratory Manual.

Blood specimens

The following parameters will be analyzed from blood samples:

Table 8-6 Blood clinical laboratory parameters

Test category	Test name
Hematology	Hematocrit, hemoglobin, platelets, red blood cells, white blood cells (WBC), WBC morphology with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Clinical chemistry	Albumin, alkaline phosphatase, total bilirubin, calcium, cholesterol, chloride, creatinine, creatine kinase, C-Reactive Protein and hs-CRP, g-GT, glucose, lactate deshydrogenase, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST (SGPT), ALT (SGOT), sodium, triglycerides, blood urea nitrogen (BUN) and uric acid. For postmenopausal women, FSH is measured at screening to assist in confirming menopausal status. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.
Viral serology	Hepatitis B, Hepatitis C, HIV at screening

Urine specimens

During on-treatment visits at the clinic, a midstream urine sample (approx. 30 ml) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative “dipstick/bedside” evaluation for the following parameters will be performed by the central lab: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

All urine samples should be kept at room temperature until local and/or central analysis.

Pregnancy tests

At screening and EOS (or last visit), a serum pregnancy test will be performed centrally.

Throughout the study, local urine pregnancy test are sufficient. Additional urine pregnancy tests may be required, if a reason occurs such as patient reports delay in menstruation. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. See Section 9.6 for guidance on pregnancy reporting and follow-up.

8.6.5 Electrocardiogram (ECG)

A central reading of standard 12-lead ECGs will be implemented. Full details of all procedures relating to the ECG collection and reporting are contained in the core laboratory technical manual or in the Site Operations Manual.

PR interval, QRS duration, heart rate, RR, QT, QTcF (Fridericia QT) will be collected.

The preferred sequence of data collection during study visits is ECG collection first (10 min rest, ECG recording over next 5 min suggested), followed by vital signs, and blood sampling.

Clinically significant abnormalities must be reported in the AE CRF.

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8.8 Other assessments

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8.9 Use of residual biological samples

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9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject after *providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.6 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The Common Toxicity Criteria (CTC) for AE grade (version 4.0 or higher). A copy of the CTCAE grading will be provided separately.

   If CTCAE grading does not exist for an adverse event, use:

   1=mild,

   2=moderate,

   3=severe

   4=life threatening* (see Section 9.2 for definition of a serious adverse event (SAE))

   *Note: There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).

   CTCAE grade 5 (death) is not used, but is collected as a seriousness criteria and also collected in other CRFs (e.g. Study Completion, Death/Survival).
2. its relationship to the study treatment
   - Yes or
   - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.

   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

*Refer to the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to ICH E14D Guideline 2003).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to ICH E14D Guideline 2003).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2

9.2.2 SAE reporting

Screen Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized / Treated Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO& PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 1should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and GGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 15-3-Appendix 1.
- Imaging such as abdominal US, CT or MRI, as appropriate

- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

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9.6 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO& PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO& PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing treatment errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.7 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO& PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.8 Early phase safety monitoring

The investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eCRFs) with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis or the CRO working on behalf of Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Certain data may be captured via other source documentation (such as safety laboratory data report, imaging) and then transcribed, uploaded or transferred to the CRO working on behalf of Novartis or to Novartis. This, and any additional data treated in this manner, will be source data verified by the study monitor per the monitoring plan and the location of source data (i.e., Source, paper or a local electronic system) will be documented prior to study start in the Data Handling Plan. When using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application; rather, the electronic source record directly populates the study database.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the vendor working on behalf of Novartis.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

The investigator must certify that the data entered into the eCRF are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule (Table 8-1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

10.3 Database management and quality control

Novartis staff and the CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or to the CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

10.4 Data Monitoring Committee

In this proof-of-concept study, there is no a priori information as per the FDA Guidance of "situations in which safety concerns may be unusually high" or the patient population being studied is "potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity." Thus, an independent data monitoring committee will not be constituted.

The Novartis clinical team will review the safety data on a regular basis. A preliminary review of the safety data and assessment of efficacy, based on the calculated Bayesian probability of success will be performed at the first interim analysis by the Novartis clinical trial team and the overall recommendations on study continuation shared with the investigators. A re-assessment of the sample size based on the observed coefficient of variation in the primary endpoint between patients may also be performed.

At the time of the first interim analysis, the inflammatory facial lesion counts performed by the investigator will be used to compare the CCI high dose group with the placebo group. A Bayesian analysis will be performed to estimate the probability of success of the trial given the current data.

It is envisioned that the team may make three types of recommendations at the first interim analysis, namely:

- No safety or efficacy issues, ethical to continue the study as planned,
- Substantial coefficient of variation between patients in the primary endpoint requiring re-assessment of the sample size,
- Serious safety concerns precluding further treatment in the study, regardless of efficacy.

10.5 Adjudication Committee

Not required.

11 Data analysis

The analyses will be conducted on all subject data at the time when interim analysis occurs and also when the trial ends. Study data will be analyzed by Novartis and/or a designated contract research organization (CRO). Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The following study data will be summarized: demographic and baseline characteristics, efficacy assessments, safety assessments, pharmacokinetic and biomarker assessments.

Categorical data will be presented as contingency tables (frequencies and percentages). For continuous data, summary statistics including mean, standard deviation, median, minimum, and maximum will be presented if not otherwise specified. In addition, individual listings of all raw data captured in the clinical database will be presented by treatment group and patient. All data from participating clinical sites will be combined, so that an adequate number of patients will be available for analysis.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The following analysis sets will be used and will be derived prior to database lock. As required, additional analysis sets will be defined in the Statistical Analysis Plan (SAP).

Safety Analysis Set

The safety analysis set will include all subjects that received at least one dose of study drug.

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Pharmacodynamic (PD) Analysis Set

The PD analysis set will include all subjects with available PD data, who received any study drug and with no protocol deviations with relevant impact on PD data. Protocol deviations leading to exclusion from the PD analysis set will be added in the SAP.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group. Subject demographics will include age, sex, race, ethnicity, country, height, weight and BMI. Baseline disease characteristics include but are not limited to: facial inflammatory lesion counts (papules, pustules, nodules),

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Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

11.3 Treatments

Data for study drug administration and concomitant therapies will be listed by treatment group and subject.

Duration of exposure to study drug in days, as well as actual total doses, actual dose intensities (total amount of drug administered per unit of time), and relative dose intensities (ratio of actual dose intensity to planned dose intensity) will be summarized using descriptive statistics by treatment group for the safety analysis set.

Compliance to the study treatment will be assessed by the number of dose interruptions and percent of days with received planned dose by treatment group for the safety analysis set.

Concomitant therapies prior to and after the start of study treatment will be listed and summarized by treatment group for the safety analysis set.

11.4 Analysis of the primary variable(s)

The primary aim of this study is to assess the efficacy of LYS006 versus placebo on inflammatory facial lesion counts in patients with moderate to severe inflammatory acne. Therefore, a statistical analysis will be performed on the log transformed inflammatory facial lesion count after 12 weeks. The primary analyses will be based on on-treatment data. Data recorded after a patient discontinues study treatment will not be included in the primary analyses. Commercially Confidential Information

11.4.1 Primary Variable(s)

The primary variable is the natural log transformed total inflammatory facial lesion counts (sum of papules, pustules, and nodules) at Week 12.

11.4.2 Statistical model, hypothesis, and method of analysis

Data up to Week 12 will be included in a Bayesian mixed effect model for repeated measures (MMRM) for the comparison of LYS006 high dose group versus placebo group at 12 weeks, which is of primary interest. Data from the LYS006 low dose group will also be included in this primary model at the time of IA and later analyses, but will mainly be summarized as described in Section 11.6.

The natural log transformed inflammatory facial lesion count is expected to be approximately normally distributed. It will be analyzed using a Bayesian mixed effect model for repeated measures (MMRM) using Proc MCMC in SAS software (Chen 2011). Baseline adjustment will be implemented by including the log transformed baseline inflammatory facial lesion count in the model as a continuous covariate. The model will also include treatment group, visit, treatment group by visit interaction, log transformed baseline inflammatory facial lesion count by visit interaction and type of center Commercially Confidential Information as fixed effects. Non-informative priors will be utilized for the fixed effects and for the covariance. An unstructured covariance will be assumed; other covariance structures will be investigated if there is a convergence issue. As supportive analyses, other factors such as gender, race, center and assessor may also be considered in the primary analysis model either as a fixed effect or as a sub-group analyses variable to investigate for potential heterogeneity. The log transformed baseline inflammatory facial lesion count will be centered and standardized prior to being included in the model.

Bayesian posterior probabilities will be used to assess the following PoC criteria as a guidance for decision making (Fisch et al 2015), though other criteria may be taken into account:

Efficacy criteria (only for primary objective) at IA and at the final analysis:

- If there is at least 90% probability that the treatment effect of LYS006 at 12 weeks is better than placebo, i.e., Prob (y_LYS006 - y_placebo < 0) > 90%, and
- If there at least 50% probability that the treatment effect at 12 weeks is at least 25% in favor of LYS006, i.e., Prob (y_LYS006 - y_placebo < - 0.288) > 50%.

where y is the log transformed facial inflammatory lesion count.

The posterior estimates of the treatment effect and the treatment difference (along with its 90% credible interval) at each post baseline visit (with Week 12 being of primary interest) will be provided. The results will be reported in terms of adjusted absolute and percent changes from baseline by back-transforming the estimates from the log-scale. The absolute change from baseline and the percentage change from baseline in total inflammatory facial lesion count will also be summarized by group and visit. Data will also be presented in graphics such as spaghetti plots.

11.4.3 Handling of missing values/censoring/discontinuations

All patients with available data after baseline and until Week 12 will be included in the interim and in the primary analyses. If study drug is permanently discontinued before Week 12, data collected after permanent discontinuation will not be considered for the purpose of the primary analyses. The primary variable analysis model is known to give unbiased results under the assumption that missing data are at random (MAR), i.e. given observed data the missingness does not depend on unobserved data. In the event that many patients discontinue treatment, alternative estimands considering the effect of LYS006 versus placebo may also be investigated. Further details will be provided in the Statistical Analysis Plan (SAP).

11.4.4 Sensitivity analyses

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11.5 Analysis of secondary variable(s)

11.5.1 Safety

For all safety analyses, the safety analysis set will be used if not otherwise specified. All listings and tables will be presented by treatment group.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

For laboratory tests covered by the CTCAE version 4.0 or higher, the laboratory data will be graded accordingly. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

Adverse events (AEs)

All information obtained on AEs will be displayed by treatment group and subject.

Summary tables for AEs include only AEs that started or worsened after first dose, the ***treatment-emergent*** AEs (TEAEs). However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged. Listings of all AEs will be provided.

The incidence of TEAEs (new or worsening after first dose) will be summarized by system organ class or preferred term, severity and by treatment group.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and treatment group.

SAEs, non-serious AEs and AEs of special interest CCI will be tabulated.

A subject with multiple AEs within a body system is only counted once towards the total of this body system.

Study drug compliance assessment

Study drug compliance will be assessed by summarizing the duration of exposure, the actual total doses, frequency of dose interruption, and actual and relative dose intensities. Reason for dose interruption will be listed by patient and summarized.

Other safety evaluations

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Pregnancy test results will be listed by treatment group, subject and visit/time.

11.5.2 Other assessments

Not applicable.

11.6 Analysis of exploratory variables

Details of statistical methodologies for exploratory variables will be described in the SAP. Graphical presentation of the data will be performed where applicable.

11.6.1 Clinical Outcome Assessments

Facial inflammatory lesion count over time

Total inflammatory facial lesion count data over time will be visualized via individual profile plots for all subjects, where group allocation and responder status at Week 12 will be indicated. Individual facial inflammatory lesion counts (papules, pustules and nodules) over time will be summarized by lesion type, treatment group and visit/time and also be visualized by spaghetti plots and group summary plots. Estimates of the treatment effect over time will be taken from a MMRM model as described for the primary variable.

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11.6.5 Exploratory biomarkers

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11.7 Sample size calculation

In total approximately 56 subjects are to be randomized with a 3:1:3 ratio to LYS006 high dose, low dose and placebo group. This should provide complete 12-week data of approximately 20 patients in the LYS006 high dose and placebo groups, with the assumption of around 20% dropout rate.

The table below shows the cumulative operating characteristics of the trial for the primary endpoint (LYS006 high dose versus placebo) at the interim analysis (IA), when approximately 15 patients in the LYS006 high dose group and 15 patients in the placebo group have completed 12 weeks (at about 75% enrolment); and at the final analysis when all patients have completed 12 weeks. The operating characteristics are presented with the probabilities to declare preliminary efficacy at IA and final analysis under different true difference in lesion counts between treatment groups (active-placebo/placebo).

With the log-normal assumption and a median of 20 lesions in the placebo group at Week 12, the 25% effect (active minus placebo being -0.288 on the log scale) corresponds to approximately 5 lesions difference in the median, which is considered the targeted difference from placebo (Section 11.4.2). If the true effect is 35% over placebo (active minus placebo

being -0.431 on the log scale), the probability of meeting the efficacy criteria is 87%, with 20 subjects from either LYS006 high dose group or placebo group. Effect of 35% corresponds to approximately 7 lesions difference in median, assuming a median of 20 lesions in the placebo group at week 12. If the true effect over placebo is 0, there is approximately 5% chance of declaring efficacy.

Table 11-1 Operating characteristics of decision rules

	15:15 (IA)	**20:20 (final analysis)**
Sample size*	**Chance of meeting both efficacy criteria**	**Chance of meeting both efficacy criteria**
True effect = 0	5%	5%
True effect = 35%	80%	87%

11.8 Power for analysis of key secondary variables

Not Applicable.

11.9 Interim analyses

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12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

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