CLINICAL TRIAL PROTOCOL

A Phase II, Multicenter, Double-blind, Double-dummy, Placebo controlled, Randomized, Study to Evaluate the Efficacy and Safety of two doses of AUR101 in patients with Moderate-to-Severe Psoriasis (INDUS-2)

Trial Phase	Phase II
Protocol Number	AUR101-201
Investigational Product	AUR101 (Inhibitor of RORγ)
Sponsor	**Aurigene Discovery Technologies Limited** (Subsidiary of Dr. Reddy's Laboratories Limited) 39-40, KIADB Industrial Area, Phase II, Electronic City Hosur Road, Bangalore- 560100, Karnataka, India
Clinical Trial Protocol Version	1.0
Issue Date	07 Aug 2019

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SPONSOR SIGNATURE

Study Title:	A Phase II, Multicenter, Double-blind, Double-dummy, Placebo controlled, Randomized, Study to Evaluate the Efficacy and Safety of two doses of AUR101 in patients with Moderate-to-Severe Psoriasis (INDUS-2)
Protocol Number:	AUR101-201
Final Version and Date	Version 1.0, 07 Aug 2019

This study will be conducted in compliance with the clinical trial protocol approved by the Ethics Committee(s) (ECs) / Institutional Review Boards (IRBs) of the respective sites. The study will comply with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and current revision of the Declaration of Helsinki. In addition, this study will be conducted in compliance with all local regulatory and ethical requirements, US FDA guidelines and the New Drugs and Clinical Trials Rules, 2019 of the Department of Health and Family Welfare, India. The investigator will be provided with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

07 -Aug -2019

Dr. Divyesh Mandavia, MBBS, MD
Manager - Clinical Development
Aurigene Discovery Technologies Limited
(Subsidiary of Dr. Reddy's Laboratories Limited)

Dated

Approved By

Akhil Kumar

07 - AUG - 2019

Dr. Akhil Kumar, MBBS, MD, DM
Head - Clinical Development
Aurigene Discovery Technologies Limited
(Subsidiary of Dr. Reddy's Laboratories Limited)

Dated

PROTOCOL SIGNATURE PAGE

Title of Study: A Phase II, Multicenter, Double-blind, Double-dummy, Placebo controlled, Randomized, Study to Evaluate the Efficacy and Safety of two doses of AUR101 in patients with Moderate-to-Severe Psoriasis (INDUS-2)

I confirm that I have read, and I understand this protocol and other appropriate related documentation, including the Investigator's Brochure for AUR101. I agree that the available nonclinical information on the investigational product and the clinical data from Phase I are adequate to support the proposed Phase II clinical trial. This study will be conducted in compliance with the clinical trial protocol approved by the EC/IRB overseeing the study at the Clinical Site. The study will comply with the International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and current revision of the Declaration of Helsinki. In addition, this study will be conducted in compliance with local regulatory and ethical requirements as well as US FDA guidelines and the New Drugs and Clinical Trials Rules, 2019 of the Department of Health and Family Welfare, India. I will also appropriately direct and assist the personnel at the trial site who will be involved in the conduct of the study.

Principal Investigator or Clinical Site Investigator:

Signature _____ Date _____

Name:	
Title:	
Name of the site:	

1.0 SYNOPSIS

Sponsor: Aurigene Discovery Technologies Limited

Name of Study Therapy: AUR101 – An oral RORγT inhibitor for anti-inflammatory disorders

Protocol ID: AUR101-201

Title of Study: A Phase II, Multicenter, Double-blind, Double-dummy, Placebo controlled, Randomized, Study to Evaluate the Efficacy and Safety of two doses of AUR101 in patients with Moderate-to-Severe Psoriasis (INDUS-2).

Study Centers: 15-25	**Phase of Development:** Phase II

Study Objectives:

Primary:

- To assess efficacy of AUR101 in patients with moderate-to-severe psoriasis

Secondary:

- To evaluate the safety and tolerability of two oral doses of AUR101 in patients with moderate-to-severe psoriasis
- To evaluate the plasma pharmacokinetics of AUR101 in patients with moderate-to-severe psoriasis
- To evaluate effect of AUR101 on quality of life in patients with moderate-to-severe psoriasis

Study Design and Investigational Plan:

This will be a multicenter, double-blind, double-dummy, placebo controlled, randomized study to evaluate efficacy and safety of two doses of AUR101 in patients with moderate-to-severe psoriasis

- Approximately 90 patients with chronic moderate-to-severe plaque psoriasis (defined as Psoriasis Area and Severity Index (PASI) ≥12 and Body Surface Area (BSA) involved ≥10%) will be randomized to the 2 dose groups of AUR101 and placebo in the ratio of 1:1:1.
- The patients in each arm will receive AUR101 of 400 mg twice daily or AUR101 600 mg twice daily or matching placebo twice daily for 12 weeks in a double blind, double dummy fashion. All the patients will be followed up for 14 ± 2 days of their last dose for safety assessment.
- A subset of approximately 25 patients, who consent, will be asked to come for plasma PK assessment in week 4 of dosing.

Inclusion Criteria

1. Confirmed diagnosis of chronic plaque-type psoriasis, diagnosed at least 6 months before screening
2. Psoriasis of at least moderate severity, defined as PASI≥12 and involved BSA≥10 % at screening and Day 1

3. Adult males or females, ≥ 18 to ≤ 65 years of age,
4. Ability to communicate well with the investigator and to comply with the requirements of the entire study
5. Willingness to give written informed consent (prior to any study related procedures being performed) and ability to adhere to the study restrictions and assessments schedule.

Exclusion Criteria:

1. History of erythrodermic, guttate, or pustular psoriasis within last 12 months
2. Efficacy failure on any biologic (e.g. interleukin (IL) -17 antibodies like brodalumab or ixekizumab or anti-TNF agents. like etanercept, infliximab or adalimumab) for the treatment of psoriasis

   Note: Efficacy failure is defined as: A) Failure to achieve static Physician/ Investigator Global Assessment (PGA/IGA) of 0 to 2 (i.e. clear to mild) despite a continuous treatment with biologic at the approved (as in package insert) dose for at least 8 weeks And / Or B) After having an efficacious response, PGA/IGA increased to 3 or higher while receiving the approved (as in package insert) dose as maintenance
3. Static 5-point IGA mod 2011 scale of 0 to 2 at screening or Day 1.
4. BMI ≥ 35 kg/m^2
5. Current treatment or history of treatment for psoriasis with IL-17 or IL-12/23 antagonist biological agents (e.g. secukinumab, briakinumab, tildrakizumab, ustekinumab etc.) within 6 months prior to study day 1
6. Current treatment or history of treatment for psoriasis with other biological agents (e.g. adalimumab, etanercept, infliximab, alefacept etc.) within 3 months prior to study day 1
7. Current treatment or history of treatment for psoriasis with non-biological systemic medications (including systemic steroids, methotrexate, cyclosporine etc.) or phototherapy within 4 weeks prior to study day 1.
8. Treatment with medicated topical agents (having active pharmaceutical ingredient that can impact the interfere with effect of the study drug; See Section 8.11) within 2 weeks prior to study day 1.
9. History or presence of any medical or psychiatric disease, or clinically significant laboratory / ECG abnormalities at screening, any or a combination of illnesses, which, in the opinion of the PI, may either put the patient at risk because of participation in the study, or influence the results or the patient's ability to participate in the study.

10. Evidence of organ dysfunction (e.g. liver dysfunction ≥ 1.5 X of ULN for ALT, AST or ALP or Total Bilirubin, or renal dysfunction of 1.5X of ULN of serum creatinine)
11. Any surgery requiring general anesthesia within 3 months prior to screening
12. Known or suspected history of alcohol or drug abuse, as judged by the investigator
13. History or presence of malignancy except patients with non-melanoma skin cancer or carcinoma in situ of cervix who are allowed to participate in the study
14. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV Ab) at screening
15. Patient with known past history of systemic tuberculosis or currently suspected or known to have tuberculosis
16. Patient expected to be started on anti-tubercular therapy either for treatment or prophylaxis of tuberculosis
17. Suspected tuberculosis infection as evident from a positive QuantiFERON TB-Gold test (QFT) at screening. Patients with a positive QFT test may participate in the study if further work up as per the opinion of the investigator (like X-ray or CT scan or other locally acceptable method for diagnosing active tuberculosis) establishes that patient does not have active tuberculosis.
18. History of hypersensitivity or idiosyncratic reaction to any investigational ROR-gamma inhibitors or any of the excipients of study drug
19. Any previous gastrointestinal surgery or recent (within 3 months) / current history of gastrointestinal disease, that in the opinion of investigator, could impact the absorption of the study drug
20. Positive pregnancy test for women of child bearing potential (WOCBP) at the screening or randomization visit
21. Male patients with partners of childbearing potential not willing to use reliable contraception methods.
22. Pregnant or lactating women or WOCBP who are neither surgically sterilized nor willing to use reliable contraceptive methods (hormonal contraceptive, IUD or any double combination of male or female condom, spermicidal gel, diaphragm, sponge, cervical cap)
23. Has received another new chemical entity/investigational drug within 28 days or 5 half-lives of investigational drug (whichever is longer) prior to study day 1.
24. Use of herbal remedies, mega dose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the first

administration of investigational product.

25. Patients who have received live or attenuated vaccine in the 4 weeks prior to study day 1.

Outcome Measures

Primary End-point

1. Proportion of patients achieving PASI 75 response (i.e. 75% reduction from baseline PASI score) at the end of week 12.

Secondary End-points:

1. Proportion of patients achieving PASI 75 response (i.e. 75% reduction from baseline PASI score) at the end of week 4 and 8.
2. Proportion of patients achieving PASI 50 response (i.e. 50% reduction from baseline PASI score) at week 4, 8 and 12.
3. Proportion of patients achieving IGA 0 or 1 at week 4, 8 and 12.
4. Percent change from baseline in PASI score at week 4, 8 and 12
5. Change from baseline in IGA scale at week 4, 8 and 12
6. Change from baseline to week 4, 8 and 12 in percent Body Surface Area (BSA) involved
7. Change from baseline to week 4, 8 and 12 in Dermatology Life Quality Index (DLQI)

Safety and tolerability Assessment

1. Treatment Emergent Adverse Events (TEAEs), changes in vital signs, electrocardiograms (ECGs), laboratory assessments and physical examinations

Pharmacokinetics

Intensive PK will be done in a subset of approximately 25 patients at week 4 (±2 days) visit

Time points**:** Pre-dose and 1, 3, 4, 5, 6, 8, 12 hours post-morning dose

Efficacy criteria

Total PASI score, IGA, DLQI will be measured at baseline (Day 1), weeks 2, 4, 6, 8, and 12. PASI and IGA efficacy endpoints will be evaluated both by the PI as well as by an independent dermatologist. For the primary endpoint, the assessment by the independent dermatologist will supersede the assessment by the PI.

Safety Assessment will be done by evaluation of AEs/SAEs, changes in laboratory

parameters, ECG, vital signs and physical examination.

Prohibited medication

- Treatment with topical corticosteroid, topical vitamin D analogues, pimecrolimus, retinoids, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive or immunomodulator drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), phototherapy
- Treatment with any drug, including any biological agents which can affect psoriasis
- Any live virus vaccination

Note: Only bland emollients will be allowed during the study participation. It means that all topical medications that contain pharmacologically active ingredients such as (but not limited to) lactic acid, salicylic acid, urea, α-hydroxy acids or fruit acids etc. will not be allowed during the study.

If patient has received any of the above-mentioned therapy before randomization, adequate gap between initiation of study treatment and last dose of prohibited medication should be ensured as mentioned in exclusion criteria no. 5 to 8.

Rescue Medication

If patient's PASI score increases by at least 50% from baseline level after at least 6 weeks of therapy, patient can be given rescue medication as considered appropriate according to investigator. In other situations, if medically necessary (i.e. to control intolerable psoriasis symptoms), rescue treatment for psoriasis may be provided to study patients at the discretion of the investigator after discussion with sponsor medical monitor. In addition, even within first 6 weeks of therapy, if a patient has intolerable symptoms from psoriasis, then rescue medications can be administered. The investigator can choose any available medication as rescue medication to treat psoriasis. In this case, investigator should discuss with sponsor medical monitor.

For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures with the last efficacy assessment deemed as Last Observation Carried Forward (LOCF) for the primary endpoint and other secondary efficacy endpoints relevant at other future time-points. Investigators should make every attempt to conduct efficacy and safety assessments (e.g. disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary. **Patients who receive "Rescue Medication" will be discontinued from the trial.** All such patients

should be followed up after 14 ±2 days of study drug discontinuation for safety assessment.

Statistical Analysis

Sample Size

AUR101 doses will be tested versus placebo with respect to the primary endpoint (PASI75 response). A sample size of 25 in each of the three arms will provide an 80% power with a one-sided Type I error of 0.05, if the true placebo response rate is 7% and the response rate on investigational arm(s) is 35%. The sample size is increased to 30 to account for ~ 15-20% drop outs over the study period.

Data analysis

The Safety Population includes all patients in the study who receive at least one dose of AUR101. Efficacy population will include patients who do not have any major protocol or inclusion/exclusion violations, have a valid baseline and at least one post-baseline (follow up) assessment for PASI score (i.e. primary end-point) by the independent dermatologist. The Pharmacokinetic Population includes all patients in the study who receive any dose of AUR101 and provide samples for PK analysis.

For efficacy, safety and PK analysis, data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. Data will be presented by treatment arms.

For the efficacy analysis, appropriate statistical test will be applied to compare AUR101 treatment arms with placebo.

A comprehensive statistical analysis plan (SAP) will be finalized prior to final data analysis.

In addition, interim analysis may be done after 45 patients complete 12 weeks of treatment to evaluate early trends of efficacy or safety without affecting individual patient's blinding. A separate interim analysis plan will be prepared accordingly.

2.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERM

AE	Adverse Events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to t hours calculated using the linear trapezoidal rule
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the last measurable concentration at time (t) calculated using the linear trapezoidal rule
Beta-HCG	Beta-Human Chorionic Gonadotropin
BCRP	Breast Cancer Resistant Proteins
BID	Twice daily
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urine Nitrogen
CI	Confidence Interval
CL/F	Plasma Clearance
Co-I	Co-Investigator
CDSCO	Central Drugs Standard Control Organization
C_{max}	Maximum plasma drug concentration from plasma concentration time profile
CRF	Case Report Form
CT	Computerized tomography
CYP	Cytochromes P450
DCGI	Drugs Controller General of India
DBL	Data Base Lock
DLQI	Dermatology Life Quality Index
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
FIH	First in Human
FTIH	First Time in Human
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B Surface Antigen
HCV Ab	Hepatitis C Virus Antibody

HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
ICF	Informed Consent
ICH	International Conference on Harmonization
IGA	Investigator Global Assessment
IL-17	Interleukin-17
IL-23	Interleukin-23
IRB/ EC	Institutional Review Board /Ethics Committee
IUD	Intrauterine Device
IWRS	Integrated Web based Randomization system
K_{el}	Elimination Rate Constant
LOCF	Last Observation Carried Forward
MAD	Multiple Ascending Dose
MCH	Mean Corpuscular Hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-Observed-Adverse-Effect Level
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PGA	Physician Global Assessment
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetics
PO	Per oral
QD	Once a day
QFT	QuantiFERON TB-Gold test
RORγ	Retinoic Acid Related Orphan Receptor Gamma
SAD	Single-Ascending Dose
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System organ class
$t_{½}$	Terminal elimination half-life
TEAEs	Treatment emergent adverse events
TGF	Transforming Growth Factor
TNF	Tumor necrosis factor
Th	Helper T cells
T_{max}	Time to reach C_{max}
ULN	Upper Limit of Normal
US	United States of America
WBCs	White blood cells
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

WOCBP	Women of Childbearing Potential

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Table 1: Study Activities

Assessment	Screening visit (Up to Day -14)	Treatment Period						Follow-up visit: 14 ± 2 days after last dose
		Visit 2: Randomization visit (Day 1)	Visit 3: Week 2 ±2 days	Visit 4: Week 4 ±2 days	Visit 5: Week 6± 2 days	Visit 6: Week 8 ±2 days	Visit 7 (End of Treatment): Week 12 ±4 days	
Informed Consent	X							
Demographics	X							
Height (Only at Screening), BMI (only at screening), weight	X	X		X		X	X	
Medical history	X	X	X	X	X	X	X	X
Menstrual history in females	X							
Prior/concomitant medication check	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X
Vital signs [a]	X	X	X	X	X	X	X	X
QuantiFERON TB-Gold test[b]	X							
Inclusion & exclusion criteria check	X							
Inclusion & exclusion criteria verification		X						
12 lead ECG	X							X
Randomization		X						
Photographs of lesions		X	X	X	X	X	X	X
Blood sampling for PK[c]				X				
Clinical laboratory tests (Haematology, Biochemistry)	X	X		X		X	X	X
Urinalysis		X					X	
Viral Serology	X							
PASI score, IGA by independent evaluator and Investigator	X	X	X	X	X	X	X	X
DLQI		X	X	X	X	X	X	X
IP dispense [d]		X	X	X	X	X		
IP return and compliance check			X	X	X	X	X	
AE check		X	X	X	X	X	X	X
Pregnancy test [e]	X	X		X		X	X	X

AE = adverse event; ECG = electrocardiogram; PK = pharmacokinetic, IP= Investigational product, PASI= Psoriasis Area and Severity Index, IGA= Investigator Global Assessment

[a]Vital signs include body temperature, blood pressure and pulse rate

[b] Patients who are positive by QuantiFERON TB- Gold test, should undergo further workup according to investigator opinion (like Chest X-ray, CT scan of chest or any other locally acceptable method) to rule out active tuberculosis.

c Only in subset of approximately 25 patients

[d] As directed by IWRS; IP may be dispensed on additional or fewer days, as required by logistics

[e] Serum pregnancy test at screening, and urine pregnancy test at other visits will be done for women of child bearing potential only

3.0 INTRODUCTION

3.1 Background

Helper T cells (Th) have traditionally been divided into Th1 and Th2 subtypes. It was subsequently demonstrated that the third major Th cell class exists which was shown to be dependent upon interleukin 23 (IL-23) stimulation and produces IL-17 in response to antigen recognition, hence it was named Th17.[1, 2] The differentiation of this cell type and the consequent production of IL-17 is dependent upon the transcription factor Retinoic acid related orphan receptor gamma (RORγ). RORγ, together with its close neighbors RORα and RORβ, are considered orphan receptors where no single endogenous ligand has yet been identified, though several nonspecific oxy-sterols have been shown to bind and modulate RORγ transcription.[3-5] Among all the RORs, the subtype RORα is expressed in the liver, skeletal muscle, skin, lungs, adipose tissue, kidney, thymus, and brain, RORβ predominantly in the brain and liver, and RORγ is highly expressed in the thymus, but significant expression is also found in the liver, skeletal muscle, adipose tissue, and kidney.[3]

Different studies suggest a causative involvement of IL-23 immune axis and Th17 cytokines in different autoimmune diseases such as psoriasis, ankylosing spondylitis, psoriatic arthritis, atopic dermatitis, Crohn's disease, ulcerative colitis, multiple sclerosis, and non-infectious uveitis.[6-8] RORγ is therefore expected to have a central role in driving these pathologies. Clinical validation of the IL-17 pathway is already proven from the therapeutic efficacy of antibodies that neutralize Th17-associated cytokines and receptors (Secukinumab, Ixekizumab-IL-17, Ustekinumab-IL12/23, Guselkumab, Tildrakizumab-IL23 and Brodalumab-IL-17 receptor A) in moderate to severe psoriasis and other autoimmune disorders such as psoriatic arthritis and ankylosing spondylitis).[6, 7, 9] In view of all these, reducing IL-17 via inhibition of RORγ is also expected to add clinical value in these diseases.

A small molecule of RORγ could have multiple benefits over neutralizing antibodies for patients. As RORγ inhibitor reduces secretion of IL-17 as compared to only neutralizing circulating IL-17, hypothetically it may have better effect in disease pathology. Oral administration is generally preferred over the parenteral routes of administration required for antibodies, considering chronic nature of autoimmune disorders. It also offers the possibility to adjust dose in response to the therapeutic effect. In addition, the more rapid clearance and smaller half-life of orally administered small molecules allow for easier management of adverse events, like infectious complications, by getting the drug cleared from the body more quickly upon discontinuation.

- **Mechanism of AUR101**

AUR101 is an inhibitor of RORγ, which is essential for the development of Th17 cells in the thymus.[10] When naive undifferentiated T cells first encounter a specific antigen, presented to them by a dendritic cell, they become activated and simultaneously receive signals directing them to differentiate into a specific class of T helper cells. IL-23 secreted by macrophage and dendritic cells together with other cytokines such as Transforming Growth Factor (TGF) β and IL-6 promotes differentiation of helper T cells into Th17 cells. Th17 cells mainly up-regulate RORγ[9] and gain the ability to produce IL-17A, IL-17F, IL-21, IL-22 and other proinflammatory effector cytokines.[11-13]

AUR101 is a small molecule inhibitor of RORγ. By inhibiting RORγ, it reduces differentiation of naïve T cells to Th17 cells and subsequently secretion of various proinflammatory cytokines, predominantly IL-17.

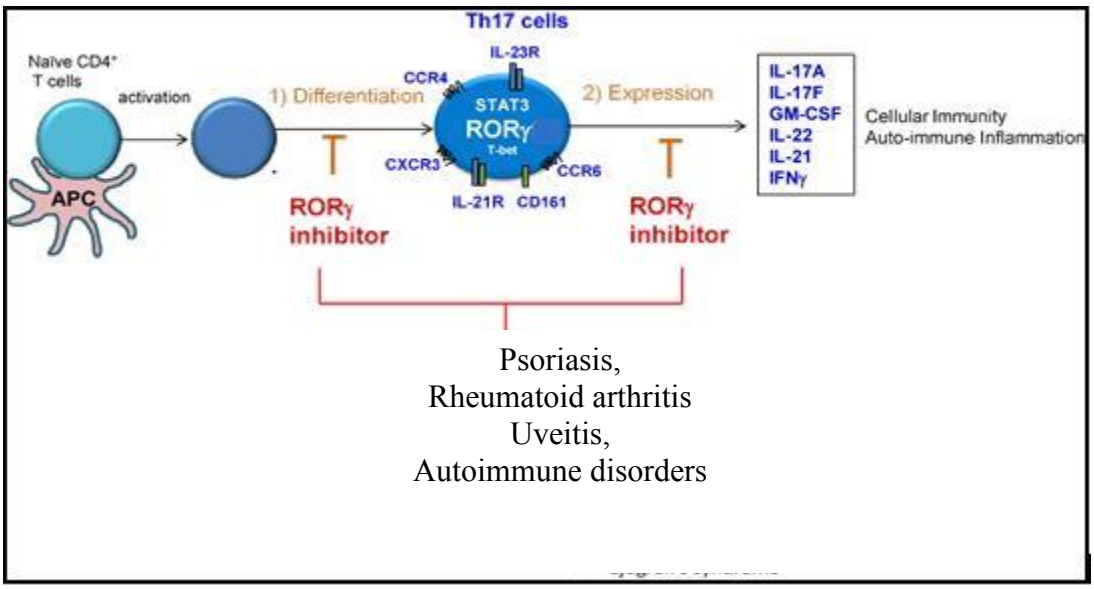


Figure 1: Schematic presentation of mechanism of action of AUR101

3.2 Summary of Nonclinical Experience

3.2.1 Nonclinical development

As discussed in Section 3.1, the RORγ is a key transcription factor that is required for the development and differentiation of Th17 cells. AUR101 has demonstrated dose-dependent inhibition of Th17 cells development and differentiation of both human and mouse in Th17 differentiation assays as determined by IL-17A production.

The efficacy of AUR101 has also been evaluated in two preclinical models of psoriasis. In Imiquimod induced psoriasis model oral AUR101 administration at 10 mg/kg to 150 mg/kg BID dose showed significant reduction in ear swelling at all test dosages. The maximal efficacy was observed at 75 mg/kg BID dose with 29% reduction in ear swelling with corresponding 37% reduction in ear skin histopathology score and 34% reduction in back skin swelling with corresponding 33% reduction in histopathology score. In a separate IL-23 induced psoriasis model, oral administration of AUR101 showed significant reduction in ear skin swelling at all test dosages (18%, 28%, 42 % at 3, 10, 30 mg/kg BID respectively) with corresponding reductions in ear skin histopathology scores of 35%, 43%, and 56%, respectively. The maximal efficacy observed in both the models (AUR101 75 mg/kg BID in Imiquimod induced psoriasis and 30 mg/kg BID in IL-23 induced psoriasis) are comparable with anti-IL-17A antibody administration in mouse.

3.2.2 Summary of Pharmacokinetics

Pharmacokinetics of AUR101 has been determined in male mice, rats, dogs and monkeys. The dose normalized absolute oral bioavailability of AUR101 in mice, rats, dogs and monkeys ranged from 89% to 100%. The volume of distribution at steady state was greater than whole blood volume indicating distribution of the compound into extravascular space in the tested species. The terminal elimination half-life after oral administration ranged from a low of 0.96 h in rats to a high of 6.30 h in dogs. Food administration has not shown any effect on the systemic availability of the compound in mice and rats. Intravenously and orally administered AUR101 in rat showed minimal excretion though urine and faces suggesting that metabolism is the primary route of elimination.

3.2.3 Nonclinical Safety and Toxicology studies

Non-clinical toxicology studies have been conducted with AUR101 for 2-weeks as well as 13-weeks in Wistar rats and Beagle dogs, and the current toxicological evaluation for AUR101 supports clinical studies for up to 13 weeks.

In the **2-week GLP repeat dose study in Wistar rats,** daily doses of 0 (vehicle), 100, 300, 600, and 1000 mg/kg/day were utilized. There were no adverse clinical signs of toxicity observed during the treatment or the recovery period. There were no adverse changes in any of the clinical pathology parameters either.

In the **13-week GLP repeat dose study in Wistar rats,** doses of 0 (vehicle), 70, 150 and 450 mg/kg/day were utilized. There was no mortality in the study. AUR101 related but non-adverse clinical signs included transiently observed mild salivation at all the tested doses during the treatment period, a localized or generalized alopecia in the ventral parts of the body in 450 mg/kg/day dose group and a mild abdominal distension at 450 mg/kg/day in a few animals. These clinical signs gradually recovered to normalcy in all animals during the recovery period and are considered non-adverse. No AUR101 related neurobehavioral or ocular abnormalities were observed. There were no AUR101 related adverse changes in any of the laboratory parameters. Based on the results, the NOAEL in Wistar rats is considered to be 450 mg/kg/day.

In the **2-week GLP repeat dose study in Beagle dogs,** animals received daily doses of 0 (vehicle), 25, 50 and 100 mg/kg/dose, BID which is equivalent to 0, 50, 100 and 200 mg/kg/day for control, low, mid and high dose groups, respectively. Because of overt signs of toxicity during first 5 days of treatment, the high dose was reduced from 200 mg/kg/day (100 mg/kg/dose, BID) to 150 mg/kg/day (75 mg/kg/dose, BID) from Day 6 onwards. There were no mortalities in any of the AUR101 treated groups. Clinical observations were generally limited to 200/150 mg/kg/day dose group which exhibited reduced food consumption, reduction in body weight, decreased activity, soft stool, salivation, tremors and emesis. In the mid dose groups, emesis was infrequently observed only at some occasions. There were no test article-related ophthalmologic changes. No adverse or biologically significant changes in body temperature, quantitative or qualitative ECG parameters, blood pressure or respiration rate were observed. All the findings noticed during the treatment period were reversed to normalcy during treatment free period. Test article related changes in clinical pathology was limited to increased ALT in both genders; and AST, ALP, GGT and total bilirubin in males of high dose group (200/150 mg/kg/day). In conclusion, oral administration of AUR101 to male and

female Beagle dogs at 50 as well as 100 mg/kg/day followed by a 14-day recovery period was well tolerated and did not result in mortality or any adverse changes. Treatment related adverse findings were noted at 200→150 mg/kg/day, including severe clinical signs, body weight losses, low food consumptions, and remarkably increased ALT and AST. Based on the results, the NOAEL in this study is considered to be 100 mg/kg/day.

In **the 13-week repeat dose GLP study in Beagle dogs**, doses of 0 (vehicle), 10 mg/kg BID, 30 mg/kg BID, or 60→50→40 mg/kg BID were utilized. Due to observed toxicity, the dosage of the high dose group (Group 4) was reduced from 60 mg/kg BID to 50 mg/kg BID on Day 8 for both sexes, and then further reduced to 40 mg/kg BID from Day 34 after a 5-day dosing holiday from Day 29 to Day 33. It is referred as 60→50→40 mg/kg BID group. There was no mortality in the study. At 10 mg/kg BID and 30 mg/kg BID dose groups, there were no adverse clinical signs or changes in body weight and food consumption. The observed clinical signs at 10 and 30 mg/kg BID dose group were either transient or of lower magnitude. At 60→50→40 mg/kg BID dose, AUR101 related clinical signs included inappetence, prostration, decreased activity, salivation, thinness, tremors, cold to touch, unkempt fur, abnormal stool, vomitus, ocular discharge, ptosis, and/or pale gums during the dosing period, but were resolved at the end of the recovery period. Increases in liver enzymes (AST/ALT) occurred at 30 mg/kg BID as well as at 60→50→40 mg/kg BID. However, the increase at 30 mg/kg BID was mild and reversible and considered non-adverse. The majority of clinical signs noted at 60→50→40 mg/kg BID as well as increase in liver enzymes in this dose group were considered adverse due to the high frequency and/or severity. Consequently, the no-observed-adverse-effect level (NOAEL) in dogs is considered to be 30 mg/kg/dose BID (i.e. 60 mg/kg/day).

In addition to above toxicology studies, the genetic toxicity assessment of AUR101 has also been investigated. Results of an *in vitro* Bacterial Reverse Mutation Test have indicated that AUR101 is non-mutagenic. Similarly, the results of an *in vivo* micronucleus test in Wistar rats and *in vitro* chromosomal aberration test in human peripheral lymphocytes have indicated that AUR101 does not induce clastogenicity.

3.3 Summary of Clinical Experience

First Time in Human (FTIH) Phase I study (AUR101-101) has been completed at CMAX, a Phase I unit in Adelaide, Australia. This was a randomized, placebo-controlled study and included Single Ascending Dose (SAD) followed by Multiple Ascending Dose (MAD) cohorts among healthy volunteers. The study evaluated safety, tolerability, pharmacokinetics and pharmacodynamic (IL-17 inhibition) effects, and included 4 SAD cohorts (31 subjects; 23 active and 8 placebo), 3 MAD cohorts (24 subjects; 18 active and 6 placebo) and an open label Comparative PK part (6 subjects). The maximum dose evaluated is 600 mg BID for 14 days.

The study was initiated with enteric coated AUR101 or placebo tablets in SAD cohorts. First 3 SAD cohorts were completed with enteric coated formulation at 100, 300 and 600 mg respectively. The pharmacokinetic data from the first 3 SAD cohorts, done with enteric coated AUR101 tablets, were deemed inadequate with no dose-dependent increase in exposures and a highly variable half-life. Since pre-clinical investigation also showed that AUR101 absorption is expected to be largely from stomach, it was decided to test instant release AUR101 formulation (AUR101 suspension) by dissolving

AUR101 enteric coated tablet in water in SAD Cohort 4. SAD Cohort 4 (at 600 mg) also studied the Food Effect with AUR101 suspension. AUR101 or matching placebo suspension was then evaluated in MAD cohorts at 500 mg QD x14 days, 1000 mg x14 days and at 600 mg BID x14 days.

As desirable PK and PD was observed with AUR101 suspension, it was decided to take forward instant release formulation for further clinical development. Therefore, instant release film coated (i.e. non-enteric coated) AUR101 tablet formulation was prepared to improve patient compliance and ease of administration instead of preparing suspension on daily basis. An open label comparative PK part has also been done in 6 subjects to compare the PK of AUR101 suspension with the PK of AUR101 film coated tablet. In total, 47 subjects have received active AUR101 (23 in SAD, 18 in MAD and 6 in Comparative PK part) and 14 subjects (8 in SAD and 6 in MAD) have received placebo in the FIH Phase 1 study (INDUS).

The study did not reveal any clinically relevant hepatic, renal, cardiac, respiratory, or neurological adverse events at any of the dosages in SAD. MAD and Comparative PK cohorts. There is no evidence of any remarkable effect of AUR101 on any clinical laboratory parameters, including hemoglobin, blood counts, liver function or kidney function or on ECG, vitals or physical examination. There were two cases of altered liver function parameters, one occurred in placebo treated subject (Grade 2) in MAD cohort and the other one in comparative PK part with open label AUR101 film coated tablet (Grade 1). Both of these events were deemed as related by the investigator, resolved and did not require any intervention. There were no Grade 3 or higher AEs or serious adverse events (SAEs) or any interruption or discontinuation of the study drug due to AE.

Most commonly reported non-catheter associated Treatment-Emergent Adverse Events (TEAEs; reported ≥2 subjects receiving any dose of AUR101 or placebo) in SAD part were fatigue, headache, dizziness, nausea, vomiting, arthralgia, cough and backpain. In MAD part, most commonly reported non-catheter associated TEAEs were headache, abdominal pain, abdominal distension, abdominal discomfort, diarrhea and back pain. In comparative PK part, only headache was reported in ≥2 subjects. All of the AEs were mild to moderate in nature and resolved to the satisfaction of the PI. There was no relevant difference between placebo and the AUR101 arms with respect to the nature, severity or frequency of AEs. There is also no pattern or relationship of AEs with AUR101 dose, schedule or formulation.

The study findings from SAD cohorts also confirm that AUR101 is primarily absorbed in the stomach and minimal from intestine. Moreover, food increases the exposure by ~2.5 times, further re-confirming that retention of AUR101 in stomach leads to increased absorption.

The MAD cohorts done with AUR101/placebo suspension in fed condition (with standard meal) showed T_{max} of 4-5 hours with mean terminal elimination half-life ranging from 14 to 22 hours. Based on C_{max}, AUC_{0-24} and AUC_{0-12}, minimal increase in exposures was observed between 500 mg versus 1000 mg, suggesting that with a single time dose, peak in absorption likely occurs somewhere between 500 mg and 1000 mg. With BID dosing (600 mg BID), the C_{max} and AUC_{0-12} substantially increased, when compared to both 500 mg and 1000 mg QD once daily regimens (**Table 2**). This is likely

because with increase in frequency of dosing (such as from QD to BID), AUR101 drug substance got two opportunities to be absorbed from the stomach, over 24-hour period, when an absorption kinetics plateau between 500 mg and 1000 mg with a single time dosing.

Table 2: Key PK parameters from MAD cohorts

Parameter	Statistics	500 mg QD x14 days (N=6)		1000 mg QD x14 days (N=6)		600 mg BID x14 days (N=6)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C_{max} (ng/mL)	Mean (SD)	3711.95 (914.71)	4480.74 (877.35)	4394.89 (765.09)	5052.64 (1239.83)	3597.27 (1041.71)	7837.99 (2945.57)
	Geometric Mean (95% CI)	3614.32 (2763.07, 4727.82)	4412.66 (3615.22, 5385.99)	4338.06 (3597.84, 5230.57)	4899.70 (3629.81, 6613.86)	3469.26 (2538.19, 4741.87)	7462.85 (5287.23, 1.05E+04)
T_{max} (h)	Mean (SD)	3.67 (0.52)	4.33 (0.82)	4.67 (0.52)	4.17 (0.98)	3.67 (0.82)	4.83 (0.41)
	Geometric Mean (95% CI)	3.63 (3.11, 4.25)	4.26 (3.44, 5.28)	4.64 (4.11, 5.24)	4.06 (3.12, 5.28)	3.60 (2.87, 4.50)	4.82 (4.38, 5.30)
AUC_{last} (h*ng/mL)	Mean (SD)	-	103718.11 (41883.94)	-	113826.95 (41124.24)	-	193019.87 (134249.01)
	Geometric Mean (95% CI)	-	96480.30 (6.19E+04, 1.50E+05)	-	107604.42 (7.29E+04, 1.59E+05)	-	168381.87 (9.81E+04, 2.89E+05)
AUC_{0-12} (h*ng/mL)	Mean (SD)	26977.52 (8038.07)	39513.84 (10193.30)	31584.64 (5962.66)	40487.02 (10377.74)	26713.79 (8654.54)	71386.18 (30233.01)
	Geometric Mean (95% CI)	25928.42 (1.87E+04, 3.60E+04)	38508.93 (2.98E+04, 4.97E+04)	31054.65 (2.50E+04, 3.86E+04)	39111.81 (2.84E+04, 5.39E+04)	25557.68 (1.81E+04, 3.60E+04)	67485.43 (4.72E+04, 9.65E+04)
AUC_{0-24} (h*ng/mL)	Mean (SD)	41323.55 (13348.11)	64369.19 (19024.52)	49727.38 (10147.46)	65710.45 (20131.72)	-	115400.32 (57173.33)
	Geometric Mean (95% CI)	39527.50 (2.80E+04, 5.58E+04)	62152.73 (4.60E+04, 8.40E+04)	48780.80 (3.87E+04, 6.15E+04)	62758.16 (4.35E+04, 9.05E+04)	-	107285.97 (7.18E+04, 1.60E+05)
$AUC_{0-\infty}$ (h*ng/mL)	Mean (SD)	-	104487.16 (42591.29)	-	116118.57 (41138.27)	-	196048.96 (139777.93)
	Geometric Mean (95% CI)	-	97050.25 (6.19E+04, 1.52E+05)	-	110101.95 (7.55E+04, 1.61E+05)	-	169987.05 (9.79E+04, 2.95E+05)
$t_{1/2}$ (h)	Mean (SD)	-	14.98 (3.99)	-	22.43 (7.44)	-	16.18 (4.66)
	Geometric Mean (95% CI)	-	14.48 (10.63, 19.72)	-	21.37 (14.85, 30.76)	-	15.67 (11.77, 20.85)

SD = Standard Deviation; CI = Confidence Intervals; QD = once a day; BID = twice a day; C_{max} = Maximum Concentration; T_{max} = Time to reach C_{max}; AUC = Area Under the Curve; $t_{1/2}$ = Terminal elimination half-life;

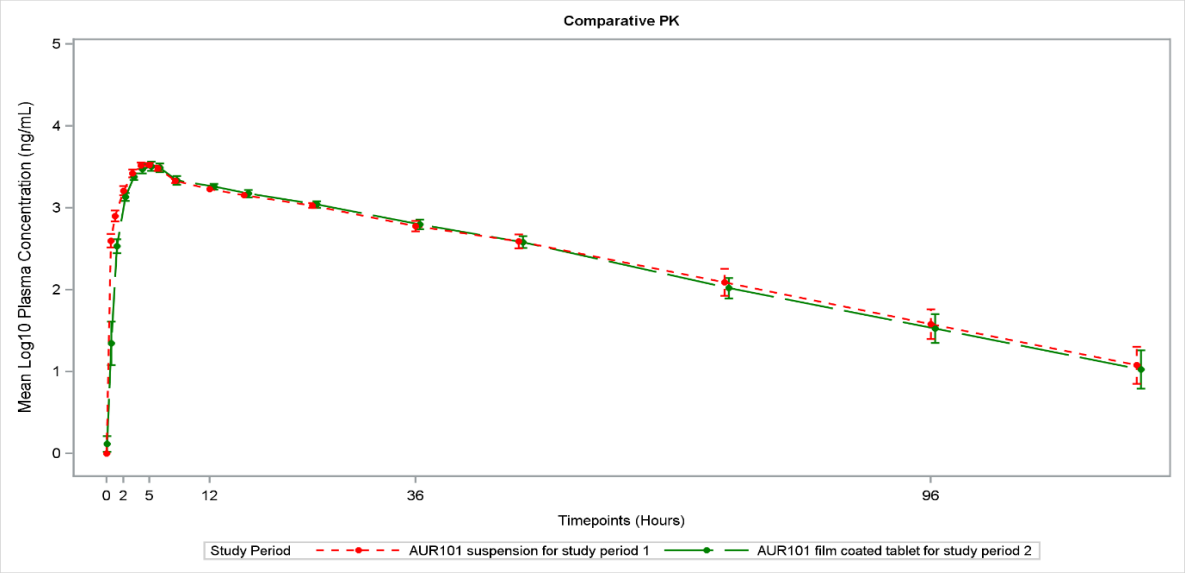
The Comparative PK part showed near identical exposures with AUR101 film-coated tablet and AUR101 suspension, confirming that the new film-coated formulation could be utilized in future clinical development and will provide same results as AUR101 suspension, utilized in MAD cohorts (**Table 3** and **Figure 2**).

Table 3: Key PK parameters from Comparative PK Cohort

Parameter	Statistic	Treatment Group (600 mg AUR101)	
		AUR101 suspension (period 1)	AUR101 film coated tablet (period 2)
		(N=6)	(N=6)
C_{max} (ng/mL)	Mean (SD)	3585.92 (696.12)	3542.55 (1140.98)
	Geometric Mean (95% CI)	3530.27 (2880.29, 4326.93)	3377.50 (2347.05, 4860.36)
T_{max} (h)	Mean (SD)	4.50 (0.84)	4.68 (1.23)
	Geometric Mean (95% CI)	4.44 (3.71, 5.32)	4.54 (3.40, 6.05)
AUC_{last} (h*ng/mL)	Mean (SD)	71114.81 (12818.65)	70901.59 (19544.84)
	Geometric Mean (95% CI)	70182.00 (5.83E+04, 8.45E+04)	68948.03 (5.30E+04, 8.98E+04)
AUC_{0-12} (h*ng/mL)	Mean (SD)	26581.99 (4979.52)	26024.40 (6722.43)
	Geometric Mean (95% CI)	26218.91 (2.17E+04, 3.16E+04)	25284.64 (1.91E+04, 3.34E+04)
AUC_{0-24} (h*ng/mL)	Mean (SD)	42879.12 (5053.75)	43561.44 (10512.65)
	Geometric Mean (95% CI)	42648.90 (3.79E+04, 4.80E+04)	42511.01 (3.30E+04, 5.48E+04)
AUC_{0-48} (h*ng/mL)	Mean (SD)	59675.79 (6429.20)	60835.15 (14969.02)
	Geometric Mean (95% CI)	59388.29 (5.30E+04, 6.65E+04)	59418.11 (4.65E+04, 7.60E+04)
$AUC_{0-\infty}$ (h*ng/mL)	Mean (SD)	71686.12 (13439.29)	71390.11 (20010.01)
	Geometric Mean (95% CI)	70675.66 (5.83E+04, 8.57E+04)	69368.84 (5.31E+04, 9.06E+04)
$t_{1/2}$ (h)	Mean (SD)	14.74 (3.40)	15.14 (4.03)
	Geometric Mean (95% CI)	14.39 (11.12, 18.61)	14.61 (10.62, 20.10)

SD = Standard Deviation; CI = Confidence Intervals; C_{max} = Maximum Concentration; T_{max} = Time to reach C_{max}; AUC = Area Under the Curve; $t_{1/2}$ = Terminal elimination half-life;

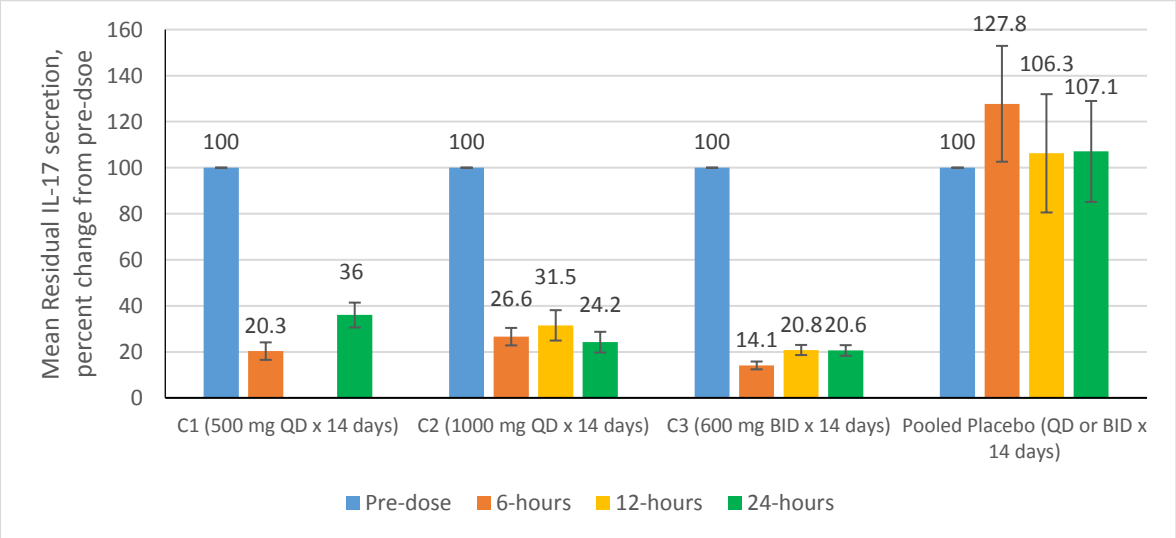
Figure 2: Plasma concentration profile of AUR101 suspension (Period 1) vs. AUR101 film coated tablet (Period 2) in Comparative PK part



Error bars represents standard errors of mean.

With respect to PD biomarker evaluation, IL-17 inhibition correlated well with exposures in the Phase 1 study .Better, sustained and consistent IL-17 inhibition (≥ ~80% IL-17 inhibition throughout the day) was observed with BID dosing as compared QD dosing (Figure 3), and forms the basis for the dosing regimen for future clinical studies.

Figure 3: Mean IL-17 secretion in MAD cohorts



C1- Cohort 1, C2- Cohort 2, C3- Cohort 3. Error bars represents standard errors of mean.

3.4 Rationale for Current Study

AUR101 is a potent and selective inhibitor of RORγ with good cellular activity in Th17 differentiation assays. The compound has also demonstrated good efficacy in relevant in vivo models. Toxicology studies with the compound have also

demonstrated a favorable safety profile at the exposures showing efficacy in animal models. The FIH study has determined a desirable safety, PK and optimal IL-17 inhibition, when AUR101 is administered up to 600 mg PO BID.

In view of favorable preclinical safety, preclinical efficacy, and PK, PD and safety data derived from FIH study, there is a strong scientific rationale for continued clinical development of AUR101. The Phase II development plan will initially evaluate efficacy and safety of AUR101 in patients with moderate to severe psoriasis at 600 mg PO BID as well as 400 mg PO BID, with both dosages administered for 12 weeks and compared with matching placebo in a double blind, double dummy study (AUR101-201; Current Study). In future, additional Phase II studies in other autoimmune diseases, such as atopic dermatitis, and non-infectious auto-immune uveitis, either as single agent or in combination with standard of care, may be done.

3.4.1 Basis for Dose Selection

Repeat dose toxicology studies in rats and dogs for 13-weeks showed NOAEL doses of 450 mg/kg/day and 60 mg/kg/day (30 mg/kg BID) respectively. At higher doses in dogs (60→50→40 mg/kg BID), treatment related adverse findings were observed including severe clinical signs, body weight losses, low food consumptions, and increased ALT and AST. So, dog is considered more relevant and sensitive species.

The dosage and dosing schedule (BID) in the current Phase II study (AUR101-201) in patients with moderate to severe psoriasis is determined from the level and consistency of IL-17 modulation in the Phase I study (AUR101-101) (See Section 3.3) at different MAD cohorts. Specifically, in MAD Cohort 3 (600 mg PO BID x 14 days), the mean IL-17 level on Day 15 was ~ 80% below baseline value (Figure 3). This dose is, therefore, chosen as one of the two dosages in the proposed (AUR101-201) Phase II study. A lower dose (400 mg PO BID) is also proposed as investigating two separate dosages in Phase II will provide the risk-benefit analysis for two separate dosages and will help decide the dosage for Phase III.

The Day 14 human exposures, at 600 mg PO BID, is also compared with the NOAEL exposures, on Day 91 from the 13-week toxicology study in dogs. This comparison provides a 2.5-fold safety window (for 600 mg PO BID dose) and thus considered acceptable from safety perspective.

Table 4: Summary of Safety margin calculation based on NOAEL exposure in animals and MAD exposure in humans

Study	Findings	Mean Exposure (AUC0-24h) at NOAEL on the last day of dosing or Day 14 in MAD cohort 3 (hr*ng/mL)	Safety margin in humans with respect to NOAEL exposure
13-week oral rat toxicity study	NOAEL 450 mg/kg/day	473472	3.3
13-week oral dog toxicity study	NOAEL 60 mg/kg/day	364160	2.5
MAD cohort 3 for 14 days	Dose 600 mg BID	142764[#]	-

HED = Human Equivalent Dose; NOAEL = No-Observed-Adverse-Effect Level. BID-= twice a day, MAD = Multiple Ascending Dose

[#]Mean AUC_{0-12} on Day 14 was 71386.18 hr*ng/mL. Hence, AUC_{0-24} is calculated as $2xAUC_{0-12}$

3.4.2 Basis for Placebo controlled study

Psoriasis is a chronic immune-mediated disorder, characterized by relapses and remission. The disease persists throughout the life, and may manifest at unpredictable intervals. Spontaneous remissions may also occur. Moreover, presentation of the disease is influenced by various environmental (e.g. weather), genetic and psychosocial factors [14]. Since the disease is not life-threatening and there are possibilities of natural improvement of the disease, only a placebo-controlled study can reliably provide proof of effect in this scenario. ICH guidelines confirm this rationale [15]. Consistent with ICH guidelines and regulatory recommendations [16], several drugs (apremilast, secukinumab, ustekinumab etanercept, adalimumab etc.) have been evaluated in psoriasis in placebo-controlled Phase II and Phase III studies, with similar eligibility criteria and duration as the current study. Not surprisingly, in almost all these studies, 75% reduction from baseline PASI score (i.e. PASI75) was achieved in 4-10% of the placebo population, confirming the necessity of a placebo-control in this disease [17-24].

In addition to efficacy, placebo-controlled study will provide maximum ability to distinguish adverse effects caused by a drug from those resulting from underlying disease or intercurrent illness (i.e. by chance).

With this background, it is important to perform placebo-controlled study with AUR101 in moderate to severe psoriasis patients to get objective evidence of safety and efficacy.

In addition, frequent study visits as well as rescue therapies are allowed by the protocol to ensure adequate safety of the patients during the study period.

4.0 OBJECTIVES

4.1 Primary Objective

- To assess efficacy of AUR101 in patients with moderate-to-severe psoriasis

4.2 Secondary Objectives

- To evaluate the safety and tolerability of two oral doses of AUR101 in patients with moderate-to-severe psoriasis
- To evaluate the plasma pharmacokinetics of AUR101 in patients with moderate-to-severe psoriasis
- To evaluate effect of AUR101 on quality of life in patients with moderate-to-severe psoriasis.

5.0 ENDPOINTS

5.1 Primary Endpoint

1. Proportion of patients achieving PASI 75 (i.e. 75% reduction from baseline PASI score) at the end of week 12.

5.2 Secondary Endpoint

1. Proportion of patients achieving PASI 75 (i.e. 75% reduction from baseline PASI score) at the end of week 4 and 8.
2. Proportion of patients achieving PASI 50 (i.e. 50% reduction from baseline PASI score) at week 4, 8 and 12.
3. Proportion of patients achieving IGA 0 or 1 at week 4, 8 and 12.
4. Percent change from baseline in PASI score at week 4, 8 and 12
5. Change from baseline in IGA scale at week 4, 8 and 12
6. Change from baseline to week 4, 8 and 12 in percent Body Surface Area (BSA) involved
7. Change from baseline to week 4, 8 and 12 in Dermatology Life Quality Index (DLQI)

Safety and tolerability Assessment

1. Safety will be evaluated based on the nature and incidence of treatment emergent adverse events (AEs), vital signs, electrocardiograms (ECGs), laboratory assessments and physical examinations in patients treated with AUR101 or placebo

6.0 STUDY DESIGN

6.1 Overview

This will be a multicenter, double-blind, double-dummy, placebo controlled, randomized study to evaluate efficacy and safety of two doses of AUR101 in patients with moderate-to-severe psoriasis

There will be three arms – two arms of AUR101 (400 and 600 mg BID) and one arm of placebo.

All the patients will be followed up for 14 ± 2 days of their last dose for safety assessment.

A subset of approximately 25 consenting patients will participate in the pharmacokinetic part in addition to main study. Separate consent will be taken. If patient consents for PK, samples will be collected at week 4 (±2 days) visit of dosing.

6.2 Number of Patients and Duration of Treatment

Approximately 90 patients with chronic moderate-to-severe plaque psoriasis will be randomized to each of the three arms (1:1:1 randomization). All the patients will receive study drugs for 12 weeks in a double blind, double dummy fashion.

6.3 Formulation and Mode of Administration

AUR101 will be formulated as 100 and 300 mg film coated tablets. Patients will take study drugs orally with water, twice daily after meals (breakfast and dinner), preferably same time each day.

6.4 Schedule of Visits and Assessments

See **Table 1** for the Schedule of Events.

6.4.1 Screening Visit (Up to Day -14)

All Screening assessments will occur within 14 days prior to administration of the first dose of study drug

Informed consent must be obtained at this visit before study procedures are performed. Further details regarding informed consent are provided in Section 13.3.

A screening log will be kept to record patients who sign the informed consent form and who will be screened. For those patients who will be screen failures, a reason will be documented.

Rescreening of subjects who have been declared screen failure is not advocated. If rescreening of any patient is required, site staff should discuss with sponsor medical monitor.

The following assessments/information will be performed/ recorded:

- Obtain patient demographics, medical history, previous anti-psoriasis therapies

and prior/concomitant medication data (medications taken up to 4 weeks prior to screening

- Conduct complete physical exam, 12-lead ECG, and vital sign (temperature, pulse rate, blood pressure) assessments, including weight and height.
- Menstrual history in females
- Check inclusion/exclusion criteria
- Clinical laboratory tests (blood sample for hematology and biochemistry tests) including QuantiFERON TB-Gold test
- Viral serology for hepatitis B (HBsAg), hepatitis C (Anti-HCV Ab), HIV I and II antibody test
- Perform area and severity assessment of psoriasis. Independent dermatologist should perform PASI, involved BSA and IGA assessment in addition to Principal Investigator (PI) or Co-Investigator (Co-I).
- Perform serum pregnancy test for females of childbearing potential.

6.4.2 Visit 2: Randomization Visit (Day 1)

Those patients who are eligible for the study, based on the inclusion and exclusion criteria, will be invited for the next visit. At this visit, randomization will be performed by Integrated Web based Randomization System (IWRS).

The following assessment/information will be performed /recorded.

- Verification of inclusion/exclusion criteria
- Conduct physical exam and vital sign (temperature, pulse rate, blood pressure) assessments, including weight.
- Check medical history
- Check prior and concomitant medications
- AEs (illnesses that started between informed consent and the first dosing occasion will be recorded in AE page but will be considered as non-treatment emergent AE) assessment
- Independent dermatologist should perform PASI and involved BSA evaluation in addition to Principal Investigator (PI) or Co-Investigator (Co-I).
- Investigator should mark 1-2 major psoriasis lesions (Index lesions) for taking photographs. The lesions should be representative of overall severity, easily accessible and re-evaluable at subsequent study visits
- DLQI questionnaire should be explained to the patient and needs to be filled by the patient.
- Urine pregnancy test for females of childbearing potential only (Beta-hCG)
- Perform clinical laboratory tests as per Section 9.2.3.

- Dispense study drug as directed by IWRS

6.4.3 Treatment Visits (Visits 3-7)

On treatment, patients will be asked to come at Week 2 (±2 days), Week 4 (±2 days), Week 6 (±2 days), Week 8 (±2 days) and Week 12 (±4 days).

The following assessments/information will be performed/ recorded at respective visit according to **Table 1**: (see Section 9.0 for more details):

- Conduct physical exam and vital sign (temperature, pulse rate, blood pressure) assessments at every visit, and weight at visit 4 and 6, 7.
- Check medical history at every visit.
- Check prior and concomitant medications at every visit.
- Independent dermatologist should perform PASI, involved BSA and IGA evaluation in addition to Principal Investigator (PI) or Co-Investigator (Co-I) at every visit.
- DLQI questionnaire should be filled by the patient at every visit.
- Photographs of the designated lesions should be taken at every visit.
- Perform clinical laboratory tests as per Section 9.2.3 at Week 4, 8 and 12 visits only.
- AE assessment at every visit
- Dispense study drug as directed by IWRS except visit 7.
- Count unused study drugs and evaluate compliance at every visit.
- Perform urine pregnancy tests at Week 4, 8 and 12 visits only.
- Perform PK sampling at Week 4 visit in consenting patients. These patients will be advised to come to the site without taking study drug for the respective visit. Study drug will be given at the site (after breakfast), followed by PK sampling.

6.4.4 Follow up visit (Visit 8)

Patients will return to the site 14 ± 2 days after their last dose for a follow up visit.

The following assessment/information will be performed/ recorded:

- Conduct physical exam, 12-lead ECG, and vital sign (temperature, pulse rate, blood pressure) assessments.
- Check medical history

- Check prior and concomitant medications
- Independent dermatologist should perform PASI and BSA evaluation in addition to Principal Investigator (PI) or Co-Investigator (Co-I)
- DLQI questionnaire should be filled by the patient
- Photographs of the designated lesions should be taken.
- AE assessment
- Clinical laboratory tests for follow up visit (as mentioned in **Table 6**)
- Urine pregnancy test for females of childbearing potential only (Beta-HCG)

For patients who are withdrawn from the study for any reason, withdrawal procedures as defined in Section 7.4 will be followed.

7.0 STUDY ENROLLMENT AND WITHDRAWAL

7.1 Inclusion Criteria

1. Confirmed diagnosis of chronic plaque-type psoriasis, diagnosed at least 6 months before screening
2. Psoriasis of at least moderate severity, defined as PASI≥12 and involved BSA≥10 % at screening and Day 1
3. Adult males or females, ≥ 18 to ≤ 65 years of age,
4. Ability to communicate well with the investigator and to comply with the requirements of the entire study
5. Willingness to give written informed consent (prior to any study related procedures being performed) and ability to adhere to the study restrictions and assessments schedule.

7.2 Exclusion Criteria

1. History of erythrodermic, guttate, or pustular psoriasis within last 12 months
2. Efficacy failure on any biologic (e.g. IL-17 antibodies like brodalumab or ixekizumab or anti-TNF agents. like etanercept, infliximab or adalimumab) for the treatment of psoriasis

   Note: Efficacy failure is defined as: A) Failure to achieve static Physician/Investigator Global Assessment (PGA/IGA) of 0 to 2 (i.e. clear to mild) despite a continuous treatment with biologic at the approved (as in package insert) dose for at least 8 weeks B) After having an efficacious response, PGA/IGA increased to 3 or higher while receiving the approved (as in package insert) dose as maintenance

3. Static 5-point IGA mod 2011 scale of 0 to 2 at screening or Day 1.

4. BMI ≥ 35 kg/m2

5. Current treatment or history of treatment for psoriasis with IL-17 or IL-12/23 antagonist biological agents (e.g. secukinumab, briakinumab, tildrakizumab, ustekinumab etc.) within 6 months prior to study day 1

6. Current treatment or history of treatment for psoriasis with other biological agents (e.g. adalimumab, etanercept, infliximab, alefacept etc.) within 3 months prior to study day 1

7. Current treatment or history of treatment for psoriasis with non-biological systemic medications (including systemic steroids, methotrexate, cyclosporine etc.) or phototherapy within 4 weeks prior to study day 1.

8. Treatment with medicated topical agents (having active pharmaceutical ingredient that can impact the interfere with effect of the study drug; See section 8.11) within 2 weeks prior to study day 1

9. History or presence of any medical or psychiatric disease, or clinically significant laboratory / ECG abnormalities at screening, any or a combination of illnesses, which, in the opinion of the PI, may either put the patient at risk because of participation in the study, or influence the results or the patient's ability to participate in the study.

10. Evidence of organ dysfunction (e.g. liver dysfunction ≥ 1.5 X of ULN for ALT, AST or ALP or Total Bilirubin, or renal dysfunction of 1.5X of ULN of serum creatinine)

11. Any surgery requiring general anesthesia within 3 months prior to screening

12. Known or suspected history of alcoholism or drug abuse, as judged by the investigator

13. History or presence of malignancy except patients with non-melanoma skin cancer or carcinoma in situ of cervix who are allowed to participate in the study

14. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV Ab) at screening

15. Patient with known past history of systemic tuberculosis or currently suspected or known to have tuberculosis

16. Patient expected to be started on anti-tubercular therapy either for treatment or prophylaxis of tuberculosis

17. Suspected tuberculosis infection as evident from a positive QuantiFERON TB-Gold test (QFT) at screening. Patients with a positive QFT test may participate in the study if further work up as per the opinion of the investigator (like Chest

X-ray or CT scan of chest or other locally acceptable method for diagnosing active tuberculosis) establishes that patient does not have active tuberculosis.

18. History of hypersensitivity or idiosyncratic reaction to any investigational ROR-gamma inhibitors or any of the excipients of study drug

19. Any previous gastrointestinal surgery or recent (within 3 months) / current history of gastrointestinal disease, that in the opinion of investigator, could impact the absorption of the study drug

20. Positive pregnancy test for women of child bearing potential (WOCBP) at the screening or randomization visit

21. Male patients with partners of childbearing potential not willing to use reliable contraception methods.

22. Pregnant or lactating women or WOCBP who are neither surgically sterilized nor willing to use reliable contraceptive methods (hormonal contraceptive, IUD or any double combination of male or female condom, spermicidal gel, diaphragm, sponge, cervical cap)

23. Has received another new chemical entity/investigational drug within 28 days or 5 half-lives of investigational drug (whichever is longer) of the first administration of investigational product in this study prior to study day 1.

24. Use of herbal remedies, mega dose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the first administration of investigational product.

25. Patients who have received live or attenuated vaccine in the 4 weeks prior to study day 1.

7.3 Withdrawal of Patients from Study Treatment

Patients may decide to withdraw from the study at any time without prejudice to any benefits. Although a patient is not obliged to give his reason(s) for withdrawing prematurely from the trial, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the patient's rights.

The investigator may withdraw a patient for any of the following reasons:

- Intolerable adverse event
- If patient's condition is deteriorating, continued participation of the patient would be an unnecessary risk to the patient's health, in the opinion of the investigator
- Use of rescue medication
- PASI increases by 50% from baseline, after 6 weeks of trial participation (from Day 1)
- Non-compliance
- Major protocol deviation/violation
- Lost to follow-up

- Study blind is broken
- Termination of the study by the Sponsor.
- Sponsor's request
- Other as per investigator's discretion

7.4 Withdrawal Procedures

If a patient is withdrawn from the study, the primary reason for withdrawal must be recorded in the eCRF. If a patient is withdrawn during the study period after dosing, all safety assessments (e.g. AEs, vitals, ECG, laboratory assessments etc.) according to "End of Treatment" (Week 12±4 days) visit should be performed. Patient will be asked to come 14±2 days after last dose for follow up visit assessments according to study activities **Table 1** If a patient is withdrawn before study drug administration, then safety assessments is not required.

The last date of study drug administration must be documented.

Appropriate follow-up of all withdrawn patients will be performed, as required. If a withdrawn patient does not follow up, then adequate attempts to contact the withdrawn patient must be documented before declaring a patient 'Lost to Follow up'.

7.5 Replacement of Withdrawals

If a patient is withdrawn after randomization without any safety or lack of efficacy issues, then he/she may be replaced after consultation with sponsor.

7.6 Early Study Termination

The Sponsor has the right to close the study at any time, although this should occur only after mutual consultation between the Sponsor and the Investigators. Events that may trigger early study termination include but are not limited to:

- Change in development plans for the study drug
- Slow recruitment.

8.0 INVESTIGATIONAL PRODUCT

8.1 Description:

AUR101 film coated tablet	
Laboratory Code	AUR101
Excipients	Microcrystalline cellulose, lactose monohydrate, Croscarmellose sodium, Hypromellose, Sodium lauryl Sulphate, Sodium Stearyl Fumarate and coating excipients (Opadry II white)
Formulation	Film Coated Tablet
Strengths	100 and 300 mg strengths
Route of	Oral

administration	

Placebo for film coated tablet	
Excipients	Microcrystalline cellulose, lactose monohydrate, Croscarmellose sodium, Hypromellose, Sodium lauryl Sulphate, Sodium Stearyl Fumarate and coating excipients (Hypromellose, Talc and Acryl-Eze coating powder
Formulation	Film Coated Tablet
Strengths	Placebo according to 100 and 300 mg strengths of AUR101
Route of administration	Oral

Placebo tablet will have an identical appearance corresponding to the strength of AUR101 film coated tablet.

8.2 Supply and Storage

The investigational products will be manufactured, handled and stored in accordance with Good Manufacturing Practice (GMP) and used in accordance with this protocol. Aurigene Discovery Technologies Ltd. (sponsor) will ensure the supply of investigational products and will also ensure that the drug supplies are suitable for human use.

The packaging supplied by the sponsor will be labelled as per local regulations.

On receipt of the study drugs at site, site staff will check the number of bottles and complete documentation of receipt.

The study drugs will be kept in a secure, temperature controlled, restricted access location and in accordance with applicable regulatory requirements. AUR101 and placebo tablets should be stored at a temperature of 2-8°C & in original package in order to protect from light and temperature logs will be maintained. Patients will be advised to store the study drug in refrigerator.

The investigator will ensure that the investigational products are used only in accordance with this protocol.

8.3 Blinding

This will be a double-blind, double-dummy study. As shape of 100 and 300 mg of AUR101 tablets are different, double-dummy design is adopted to ensure the blinding.

Each patient will receive one of the following combinations:

Table 5: Study drug administration according to treatment arms

Dose timing	Morning dose			Evening dose		
Arms	**100 mg active/ placebo**	**300 mg active/ placebo**	**300 mg active/ placebo**	**100 mg active/ placebo**	**300 mg active/ placebo**	**300 mg active/ placebo**
400 mg BID	100 mg active	300 mg active	300 mg placebo	100 mg active	300 mg active	300 mg placebo
600 mg BID	100 mg placebo	300 mg active	300 mg active	100 mg placebo	300 mg active	300 mg active
Placebo BID	100 mg placebo	300 mg placebo	300 mg placebo	100 mg placebo	300 mg placebo	300 mg placebo

So, every patient will receive one tablet of 100 mg active/placebo and 2 tablets of 300 mg of active/placebo as morning and evening dose. **To reiterate, every patient will receive 3 tablets in the morning and 3 tablets in the evening.**

8.4 Randomization

8.4.1 Preparation of randomization code

The randomization list will be generated by an Independent Statistician who will remain unblinded and will not be involved in the conduct of the study. The randomization list will be maintained as a password protected file and it will be shared to unblinded personnel of depot for preparation of individual kits for the patients. All randomization information will be secured and kept in a locked storage area, accessible only by authorized personnel.

8.4.2 Randomization of patients

Only patients who meet all the inclusion criteria and none of the exclusion criteria are eligible for randomization.

Randomization will take place on Visit 2. Each patient will be given a randomization number by IWRS. System will allocate the kit according to randomization number. Site staff will dispense the study kit accordingly.

8.4.3 Breaking the randomization code

There is no known antidote of AUR101 and in general a knowledge that a patient is on active drug or placebo will not help in the management of AEs or SAEs, and thus unblinding is discouraged. Still, if the PI believes that knowledge of randomization code may help in managing the patient in the face of an AE or SAE, then the same would be made available to the PI. In such a situation, the respective EC will also be notified if the code is broken during the study. The date, time and reason and the

name of the person who opened the code will be recorded. If the blind is broken, the patient must be withdrawn from the study.

8.5 Dispensing

Site staff will dispense the bottles according to IWRS direction. A dispensing log and accountability log will be maintained.

8.6 Method of Administration

AUR101 or matching placebo tablets will be supplied in bottles. The patients will be asked to swallow the tablets as whole with water, immediately after food in the morning and evening. It is necessary for the patient to take the study drug only after food (breakfast and dinner, respectively).

8.7 Compliance

As mentioned in **Table 1**, visit 3 onwards till end of treatment visits, study staff will count the unused tablets in the bottles and will assess the compliance of the patient.

Patients should also be advised to keep these tablets out of reach from children and also not to take the drug only as directed by the investigator.

8.8 Accountability

The study staff will be responsible for drug accountability. Records will be kept for:

- All study drugs delivered to the trial site
- All study drugs dispensed
- The administration to each patient
- All study drugs returned by the patients
- All study drugs remaining are returned to depot/destroyed.

These records will include dates, quantities, batch numbers, expiry dates, and the unique code numbers assigned to the investigational products and trial patients.

The sponsor or its designee will monitor the drug accountability records during the study and will perform drug reconciliation at the end of the study.

At the end of the study, unused study drugs will be returned to the pharmacy depot (designated by the sponsor) or destroyed, as directed by the sponsor (by written authorization). The return/destruction of all investigational medicinal products will be documented appropriately.

8.9 Treatment of Overdose

Based on the preclinical data and Phase I clinical data, the study drug is expected to

be well tolerated at currently recommended dosages. Still in the unforeseen event of an overdose of study drug, the patient should be given supportive treatment depending on the symptoms, and gastric lavage may also be done. There are no known antidotes for AUR101 or any other RORγ inhibitor.

8.10 Prior and Concomitant Medications

Concomitant medications and treatments will be collected from Screening through the Follow up visit. All prior and concomitant anti-psoriasis therapy will be collected, including biologics, non-biologic systemic therapies, phototherapy and topical treatments. In addition, other concomitant medications used for any indication (e.g. diabetes mellitus, hypertension, etc.) apart from psoriasis will be collected for at least 4 weeks prior to screening visit.

The patient should be asked to notify the study site about any new treatments (including over-the-counter drugs, supplements, calcium, vitamins and herbal drugs) he/she takes after signing informed consent. All medications and significant non-drug therapies (including physical therapy, procedures) administered, must be recorded.

No concomitant medication information will be collected following patient discontinuation from the study except for concomitant medication use associated with study drug-related adverse events or adverse events that lead to discontinuation from the study.

8.11 Prohibited Concomitant Medications

Use of any treatments that could confound the efficacy are not allowed during the study for any indication. Following drugs are not allowed during the study period:

- Treatment with topical corticosteroid, topical vitamin D analogues, pimecrolimus, tacrolimus, retinoids, salicylic acid, lactic acid, tar, urea, α-hydroxy or fruit acids
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive or immunomodulator drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) or phototherapy
- Treatment with any drug, including any biological immunomodulating agents like adalimumab, etanercept, secukinumab, ustekinumab etc. which can affect psoriasis

If the investigator use of any of above treatments is required, then the patient should not be randomized into the study. Additionally, any live virus vaccination during the study is not permitted.

If a patient receives any prohibited medication or live virus vaccination during the study period, he/she should be discontinued from the study by the investigator after consultation with sponsor medical monitor. Withdrawal procedures as mentioned in section 7.4 should be performed.

Patients are also advised to avoid extreme long exposures to sunlight like sun-bathing

during the study period.

If patient has received any of the above-mentioned therapy before randomization, adequate gap between initiation of study treatment and last dose of prohibited medication should be ensured as mentioned in exclusion criteria no. 5 to 8.

Whenever in doubt about confounding, investigators are recommended to discuss with sponsor medical monitor before starting any new drug during the study period.

8.12 Permitted therapy for psoriasis

Only bland emollients or shampoos (for scalp psoriasis) will be allowed during the study participation. It means that all topical medications that contain pharmacologically active ingredients will not be allowed during the study. Sponsor will provide bland topical preparations to maintain uniformity across the patients, as required.

8.13 Rescue Medication

If patient's PASI score is increasing by at least 50% from baseline level at or after 6 weeks of therapy, patient can be given rescue medication as considered appropriate according to investigator. In other situations, if medically necessary (i.e. to control intolerable psoriasis symptoms), rescue treatment for psoriasis may be provided to study patients at the discretion of the investigator after discussion with sponsor medical monitor. In addition, even within first 6 weeks of therapy, if a patient has intolerable symptoms from psoriasis, then rescue medications can be administered. The investigator can choose any available medication, including any biologic medications, such as secukinumab or adalimumab, as rescue medication to treat psoriasis. The choice of rescue medication is not part of the study and should be decided by the PI on an individualized assessment of the patient. With respect to the decision to use rescue medication, investigator should discuss with the sponsor medical monitor.

Considering the mechanism of action of study drug, it may take 4-6 weeks to show visible effects on the disease. Hence, investigators are advised to continue the study drug as long as possible unless the symptoms are intolerable and severely affect patient's health condition.

For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures. Investigators should make every attempt to conduct efficacy and safety assessments (e.g. disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose if necessary. Patients who receive "Rescue Medication" will be discontinued from the trial. All such patients should be followed up after 14 ±2 days of study drug discontinuation for safety assessment.

8.14 Contraception Methods

Women of childbearing potential and men who partner with a woman of childbearing potential must agree to use contraceptive methods which, in the Investigator's opinion,

are highly effective and adequate for the patient's circumstances while on investigational agent and at least 28 days after last dose. A woman of childbearing potential is defined as a premenopausal female or woman <1 year after the onset of menopause who is considered capable of becoming pregnant.

Highly effective methods of contraception for this study include:

- Hormonal implanted contraceptive
- Birth control pills (combined oral contraceptive)
- Intrauterine device
- Birth control patch
- Hormonal injected contraceptive
- Sterilization
- Abstinence (if in line with the patient's usual and preferred lifestyle)
- Double barrier method - Male condom with cervical cap/diaphragm, Male condom with vaginal spermicide or similar combination.

8.15 Drug Interactions/Precautions

AUR101 is metabolically stable molecule with low metabolism by CYP enzymes. It is neither a CYP inducer or inhibitor in in-vitro studies. So, drug interaction potential of AUR101 is low for CYP-mediated drug-drug interaction. Furthermore, AUR101 is neither a substrate nor an inhibitor of P-glycoprotein (P-gp) and Breast Cancer Resistant Proteins (BCRP) transporters.

9.0 STUDY ASSESSMENTS

This study is divided into 3 periods: Screening, Treatment, and Follow-up. The schedule of study procedures is presented in the Schedule of Events (**Table 1**). Window period for each visit is defined in the **Table 1**. All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 PM). A description of individual study assessments is provided below.

9.1 Demographics and Medical History

Demographics and medical history will be obtained by the Investigator or designee during the Screening Period. Demographics will include date of birth (or age), sex, ethnicity, and race. Relevant medical history should be recorded and should include prior/current medical conditions, including psoriasis diagnosis, and abnormal physical exam findings or clinically significant laboratory abnormalities (excluding study disease-related abnormalities) from the baseline assessment.

9.2 Safety and Tolerability Assessments

9.2.1 Adverse Events

Monitoring and recording of AEs will be conducted and recorded throughout the study, starting from signing the ICF. Treatment-related AEs/SAEs that are ongoing at the time of Follow-up visit should continue to be followed until resolution, return to baseline, or until the investigator considers that further follow-up is not necessary. Definitions, documentation, and reporting of AEs are described in detail in Section

10.0.

9.2.2 Physical Exam and Vital Signs

A complete physical exam will be performed at every visit. Vital signs include temperature (oral or axillary), pulse rate and blood pressure (seated or supine for at least 5 minutes) assessed at every visit. One temperature method should be selected for each patient and used consistently at each assessment throughout the duration of study.
Weight will be recorded at every visit except visit 3, 5 and follow up visit. Height will be captured at screening only.

9.2.3 Clinical Laboratory Test

A blood sample will be taken for measurement of hematology and biochemistry parameters, and a urine sample will be taken for urine analysis at the following time points:

- Screening visit
- Randomization visit (Visit 2)
- Week 4, 8 and 12 (Visits 4, 6 and 7)
- Follow-up visit

In addition, viral serology tests will be performed at the screening visit. Following parameters (**Table 6**) will be measured:

Table 6: List of Clinical Laboratory Tests

Haematology	**Biochemistry**
Red blood cells White blood cells (WBCs) Differential WBC count (absolute and %) including neutrophils, eosinophils, basophils, monocytes, lymphocytes Haemoglobin Haematocrit Platelets Mean corpuscular haemoglobin MCH concentration Mean corpuscular volume	Alkaline phosphatase ALT AST Potassium Serum Creatinine BUN Sodium Chloride Bicarbonate Phosphorus Calcium Total bilirubin Albumin Globulin Total Protein Albumin/Globulin ratio Glucose
Urinalysis (on Visit 2 and visit 7 only) Routine & microscopic examination	
Viral serology (For screening only) HBsAg, hepatitis C antibody, HIV I, HIV II	

9.2.4 Electrocardiogram

Standard, single 12-lead ECGs at Screening and Follow-up visits will be performed. Heart rate and PR, QRS, QT, and QTc (Bazett) intervals will be entered in eCRF. During Screening, if the ECG reading shows any abnormality, it must be repeated two more times to confirm the findings, and then the patient should be assessed if (s)he should be ineligible for the study.

Machine read normal ECGs are acceptable for the study. ECGs read as abnormal by machine must be read by the PI / local ECG reader for final results.

9.3 Efficacy Evaluations

9.3.1 Psoriasis Area and Severity Index (PASI)

PASI is widely used tool to measure the severity of psoriasis. It combines area of the lesions with severity of individual lesions by grading erythema, induration/thickness and scaling. It can be 0 (minimum) to 72 (maximum).

For this study, an independent dermatologist at each site will evaluate PASI score at every visit for patients of the respective site. Additionally, PI will also evaluate PASI score independently.

A PASI score [25-27] will be derived as indicated in **Table 7**. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region.

Table 7: PASI Score

Body part	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %)#
Head (H) including neck	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%
Trunk (T) Including axilla and groin area	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%

Upper Limbs (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%
Lower Limbs (L) Including buttocks area	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1% - 9% 2 = 10% - 29% 3 = 30% - 49% 4 = 50% - 69% 5 = 70% - 89% 6 = 90% - 100%

#Percentage (not score) of body region (not whole body) affected will be recorded.

Based on PASI, to be eligible a patient must have a score of 12 or more at screening and visit 2.

Based on total BSA, to be eligible, a patient must have 10% or more total BSA involved at screening and visit 2.

The following definitions are used in this study according to CHMP guidelines [16]:

- PASI 75 response: patients achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- PASI 50 response (partial response): patients achieving ≥ 50% improvement (reduction) in PASI score compared to baseline are defined as PASI 50 responders

9.3.2 Investigator Global Assessment (IGA)

The 5-point IGA mod 2011 scale has been developed based on a previous version of 6-point IGA/PGA Scale based on inputs received from regulatory agency [28].

The IGA mod 2011 used in this study is static, i.e. it refers exclusively to the patient's current disease state at the time of the assessments, and does not attempt a comparison with any of the patient's previous disease states, whether at baseline or at a previous visit. IGA mod 2011 will also be assessed by independent dermatologist and PI separately. Both the scores will be recorded in the eCRF.

The 5-point IGA mod 2011 rating scale is provided in **Table 8**. Based on this scale, a patient will be eligible to participate in the study if the patient has an IGA mod 2011 score of 3 or 4 at screening and Day 1.

Based on this scale, a patient will be considered as IGA 0 or 1 responder if the patient achieves a score of 0 or 1 and improves by at least 2 points on the IGA scale compared to baseline.

Table 8: The IGA mod 2011 rating scale [28]

Score	Short Descriptor	Detailed Description
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost Clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

9.3.3 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item general dermatology disability index designed to assess health-related quality of life in adult patients with skin diseases such as eczema, psoriasis, acne, and viral warts [29].

Scores range from 0 to 30, and higher scores indicate greater health-related quality-of-life impairment. Additionally, each subscale of the DLQI may be analyzed separately.

It will be completed in the language the patient is most familiar with, at the scheduled visit before he/she undergo clinical assessments by the investigator. The patient should be given sufficient space and time to complete the questionnaire. The principal investigator or designee should check the questionnaire for completeness and encourage the patient to complete any missing responses. The principal investigator or designee can explain the question, if required without influencing/guiding the response. The original questionnaires will be kept with the patient's file as the source document. Completed questionnaires will be reviewed and examined by the investigator at the site after the clinical examination and efficacy assessments for other parameters, for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed then the investigator must record the events as per section 10.0. Investigator should not encourage or influence the patient to change the responses reported in the completed questionnaire.

9.3.4 Photograph of the lesions

PI should identify 1-2 index psoriasis lesions in each of the patients. At each visit indicated in **Table 1**, photography will be performed of these 1-2 index psoriasis

lesion(s) only. Index psoriasis lesion should have adequate severity (representative of overall severity, accessibility and re-evaluable at subsequent visits. If face (not preferable) lesion is required to be taken, then eyes must be masked or closed in all photographs. These photographs will be submitted to the sponsor to be retained as part of the patient's medical record; however, they will not be analyzed proactively , will serve as supportive in terms of overall evaluation and may be analyzed retrospectively, after the study is complete, should there be gross differences in the PASI assessments by the PI and the independent dermatologists, at any site. In that case as well, this analysis will not override the independent dermatologists' assessments.

9.4 Pharmacokinetics Assessments

9.4.1 Blood sampling

Patients who will consent to participate in the PK part, samples will be collected at pre-defined period till 12 hours after the dosing of Week 4 (±2 days) visit. If required, metabolites of AUR101 can be assessed in the same samples.

Blood samples (4 ml) will be taken at the following time points relative to dosing, for PK analysis:

Time points: Pre-dose and 1, 3, 4, 5, 6, 8, 12 hours post-morning dose.

Window period for blood collection will be 15 minutes for pre-dose and ±15 minutes for remaining time-points.

It is expected that approximately 25 patients will provide the PK sampling. For these patients, evening dose should also be given after collection of 12^{th} hour sample.

Note: Dosing should be done after taking standard locally acceptable food.

9.5 Sequence of Assessments

During treatment visits (Visit 2 to 7), following sequence of assessments should be followed at the site:

- Patient related questionnaire – DLQI filling
- PASI, involved BSA and IGA assessment by Independent dermatologist
- PASI, involved BSA and IGA assessment by investigator
- Clinical examination, vitals, medical history, concomitant medication, AE assessment, photography and other study related procedures mentioned in **Table 1**
- IP compliance check (Visit 3 onwards)
- IP dispense according to IWRS
- Dosing at the site followed by PK sampling in consenting patients at week 4 (±2 days) visit.

10.0 ADVERSE EVENTS

10.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Changes in clinical laboratory test results, vital signs and ECG results are to be recorded as AEs if they are judged to be clinically significant.

Pre-planned or elective surgeries should be avoided during the conduct of the study. Pre-planned or elective surgeries or therapies should be recorded in the patient's source documents but are not be considered AEs unless there is any change to the patient's medical condition.

SAE is defined as any untoward medical occurrence that at any dose:

- results in death;
- is life threatening;
    - requires inpatient hospitalization or prolongation of an existing hospitalization; results in persistent or significant disability/incapacity; Day care or outdoor surgery/procedure (e.g. stenting, Ryle's tube insertion, tracheostomy cleaning, wound care, etc.) for prevention of any complication will not be considered as SAE but event leading to such procedure should be recorded as AE (if arise during the study period) or in medical history (if pre-existing condition)
    - Any planned hospitalization, such as hospitalization for PK sampling, will not be considered SAE.

Note: Complications that occur during hospitalization are adverse events and if a complication prolongs hospitalization, then the event is serious;

- results in a congenital anomaly/birth defect;
- results in another important medical event that may not be immediately life threatening or does not result in death or hospitalization, but which may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of important medical events which may meet the definition of a SAE include: intensive treatment in the emergency room or at home for allergic bronchospasm, certain abnormalities (e.g., blood dyscrasias), convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

10.1.1 Recording and follow-up

For each patient, all AEs will be collected from informed consent through to the follow-up visit. AE assessment will be continuous throughout the study period.

Pre-existing conditions (present at or before screening day; they will be recorded in medical history) are only to be recorded as AEs if the patient experiences a worsening or complication of the condition, and the description recorded in the CRF should clarify this. The onset of such an AE should correspond to the onset of the worsening of the pre-existing condition.

For each AE, the following information will be recorded:

- AE description/term
- Treatment start and stop dates and times
- Frequency i.e. single episode or intermittent
- Severity: mild (easily tolerated), moderate (interferes with daily activities) or severe (prevents normal daily activities)
- Relationship to study drug (definite, probable, possible, unlikely or not related)
- Outcome (resolved, resolved with sequelae, or ongoing)
- Whether serious or not

Definitions for the relationship to study drug assessment, to be made by the investigator, are as follows:

- **Definitely related:** This category applies when, after careful medical consideration, there is almost no consideration of other causation.
- **Probably related:** There is a clinically plausible time sequence between onset of the AE and study treatment administration. The AE is unlikely to be caused by a concurrent and/or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study drug.
- **Possibly related:** There is a clinically plausible time sequence between onset of the AE and study treatment administration, but the AE could also have been caused by the concurrent/underlying illness, other drugs, or procedures. Information regarding study drug withdrawal may be lacking or unclear. “Possible” should be used when study treatment administration is one of several biologically plausible causes of the AE.
- **Unlikely related:** The AE is most likely due to a non-study-treatment-related cause. However, association with the study treatment cannot be completely ruled out.
- **Unrelated:** Another cause of the AE is most plausible, and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study treatment administration and/or a causal relationship is considered biologically implausible.

For the purpose of regulatory reporting requirements, causal relationships of definite, probable, and possible will be considered treatment-related, while unlikely and unrelated will be considered not treatment-related.

All AEs should be followed up until the AE resolves or the investigator considers that further follow-up is not necessary.

Severity will be assessed by the investigator and will be graded as mild, moderate or severe.

10.1.2 Procedures for reporting SAEs

All SAEs, regardless of relationship to the study treatment, must be reported to the Sponsor or designee within 24 hours of the Investigator becoming aware of the event. Written SAE notification must follow within the 24-hour reporting timeframe, via an SAE Report submitted to the Sponsor's medical monitor via e-mail ID provided in Appendix A. Follow-up SAE reports must be submitted by the Investigator as new information becomes available. All treatment related SAEs should be followed until resolution, return to baseline, or stabilization.

If the investigator becomes aware of safety information involving a patient who participated in the study that appears to be drug related, even after an individual patient has completed the study, this should also be reported to the Sponsor immediately.

Sponsor will provide compensation for any drug related injury/death and medical management cost for drug related AEs, for a patient enrolled in India, according to applicable Central Drugs Standard Control Organization (CDSCO) regulations and as ordered by CDSCO, India.

10.1.3 Reporting to the IRB / ECs

SAEs will be reported to the local Institutional Review Board (IRB) / EC by the Investigator as per regulatory and IRB requirements. Sponsor will also report to IRB/IEC as per applicable regulations

10.1.4 Reporting to the Regulatory Agency

The Sponsor will be responsible for reporting all AEs and SAEs to the appropriate regulatory authority (e.g., U.S. Food and Drug Administration, CDSCO etc.) in accordance with respective guidelines.

Investigators, and IRB/EC in accordance with all applicable local regulations and guidance.

10.2 Pregnancy Reporting

Pregnancy testing must be performed in all female patients of childbearing potential throughout the study as specified in the Schedule of Events (**Table 1**), and the results of all pregnancy tests are to be recorded. In the event of a confirmed positive test

result, patients will be discontinued from study drug and will be followed for the outcome of their pregnancy.

If a female patient suspects she might be pregnant (e.g., missed or late menstrual period) or a male patient suspects he may have fathered a child at any time during the study through the Follow-up visit, they must notify the Investigator immediately. The Investigator will follow the patient or patient's partner to determine the outcome of the pregnancy.

Information regarding pregnancy must be reported immediately to the Sponsor and the outcome information provided once the outcome is known. The Sponsor will be responsible for reporting all pregnancy cases to the appropriate regulatory authority (e.g., U.S. Food and Drug Administration, CDSCO etc.), Investigators, and IRB/EC in accordance with all applicable local regulations and guidance.

11.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS

11.1 Sample Size Calculation

AUR101 doses will be tested versus placebo with respect to the primary endpoint (PASI75 response). A sample size of 25 in each of the three arms will provide an 80% power with a one-sided Type I error of 0.05, if the true placebo response rate is 7% and the response rate on investigational arm(s) is 35%. The sample size is increased to 30 to account for ~ 15-20% drop outs over the study period.

Placebo response rates from previous studies was 4-7% in most of the studies in similar patient population [17-19].

11.2 Data Handling

Data obtained in this study will be collected in eCRFs prepared by sponsor/designee. The eCRF will be completed and monitored in accordance with the principles of GCP.

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents are original documents, data and records, such as laboratory printouts, 12-lead ECG reports, dispensing records, and patient files. In case, any data is recorded directly into the eCRFs, then that will be considered as source and should be appropriately reflected in the study records.

AEs, medical history, and pre-existing (concurrent) conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary (WHO-DD).

11.3 Analysis Sets

11.3.1 Safety Population

The Safety Population includes all patients in the study who receive at least one dose of AUR101.

11.3.2 Efficacy Population

Efficacy population will include patients who do not have any major protocol or inclusion/exclusion violations, have a valid baseline and at least one post-baseline (follow up) assessment for PASI score by the independent dermatologist.

11.3.3 Pharmacokinetic Population

The Pharmacokinetic Population includes all patients in the study who receive any dose of AUR101 and provide samples for PK analysis.

11.4 Description of Statistical Analyses

11.4.1 General Considerations

Data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. Data will be presented by treatment arms.

A comprehensive statistical analysis plan (SAP) will be finalized prior to final data analysis.

11.4.1.1 Medical history

Any condition entered as medical history or current medical conditions at baseline will be coded using the MedDRA dictionary. They will be summarized by system organ class and preferred term of the MedDRA dictionary.

11.4.1.2 Prior and concomitant medication

Prior and concomitant medications will be summarized by treatment group in separate tables.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the last day of study visit will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period.

Medications will be coded by WHO-DD.

11.4.1.3 Handling of missing values

The last observation carried forward method will be applied to all efficacy measurements (PASI score, IGA mod 2011 score, DLQI score etc.) that are missing for the respective visits when at least one post-baseline assessment is available.

If all post baseline efficacy values are missing for one efficacy parameter then these missing values will not be imputed and this patient will be removed from the analysis

of the corresponding variable, i.e. it might be that the number of patients providing data for one variable is smaller than efficacy population.

For patients who dropped out during study treatment period due to any reason, data from the last efficacy assessment will be considered for the primary endpoint and other secondary efficacy endpoints relevant at other future time-points as per Last Observation Carried Forward (LOCF) approach. Following the intent-to-treat principle for patients who prematurely discontinue treatment, but who are observed in the follow-up period, efficacy data collected in follow-up periods will be linked to planned but missed study visits as well. Detailed imputation schemes will be described in SAP.

11.4.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics, including age, sex, race, weight, medical history and conditions, prior anti-psoriasis therapy, and any other study-appropriate data will be tabulated and summarized.

11.5 Efficacy Analysis

Summary statistics with 95% confidence interval will be presented for PASI, IGA DLQI scores. PASI 75, PASI 50 responses, IGA responders (patients achieving IGA 0 or 1) will be summarized by treatment groups. Change from baseline in DLQI scores will be summarized by the treatment groups. Appropriate parametric or non-parametric tests will be applied to test the significance between active arms vs. placebo. No multiplicity adjustments will be done.

11.6 Pharmacokinetic Analysis

Individual plasma PK parameters, including but not limited to $t_{1/2}$, AUC_{0-12}, Kel, and CL/F. C_{max}, and T_{max} will be estimated using appropriate compartmental or non-compartmental models. Summaries of PK parameters will be presented by dose group.

11.7 Safety Analysis

Safety observations and measurements will include AEs, vital signs and ECGs and clinical laboratory tests

11.7.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are signs or symptoms that occur during treatment or within 14 days of the last dose of study drug. These include new events absent at baseline or worsening of baseline conditions. Any adverse event considered related to treatment will also be considered a treatment-emergent adverse event (TEAE), regardless of the elapsed time since the last dose of study drug.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentages of patients experiencing AEs will be tabulated by system organ class (SOC), preferred term, maximum severity, and

relationship to AUR101. Summaries of the number of patients with DLTs, dose reductions/interruptions, SAEs, treatment-related AEs, AEs resulting in treatment/trial discontinuation, and deaths will be presented by dose cohort.

11.7.2 Vital Signs and ECG

Vital signs at each visit and the change from baseline to each post-baseline assessment (after the first dose of study drug) will be summarized by treatment groups using descriptive statistics. This will include height (at screening only), weight, temperature, pulse rate, and blood pressure.

ECG results will also be summarized by treatment groups. The percentage of patients with abnormal changes in vital signs during study drug administration will be summarized at each assessment.

11.7.3 Clinical Laboratory Tests

Clinical laboratory test results will be summarized by treatment groups using descriptive statistics and will include hematology, chemistries, and urinalysis. Laboratory test values which are outside the normal range will be flagged as H (above high normal limit), L (below low normal limit), or A (abnormal) in the data listings. Laboratory values deemed clinically significant by the Investigator should be reported as AEs.

11.8 Interim Analysis

An interim analysis may be done after 45 patients complete 12 weeks of treatment depending on the recruitment to evaluate early trends of efficacy or safety. It will be performed in such way that study team and sponsor will remain blinded for individual patients. A separate interim analysis plan will be prepared. Unblinded statistician will perform interim analysis who will not be part of the study statistical team. Sample size may be adjusted, if required based on the results of the interim analysis.

12.0 STUDY ADMINISTRATION

12.1 Case Report Forms and Source Documentation

For each patient, CRF and corresponding source records will be maintained at each clinical site. Case report forms should be completed in a timely manner, and every effort should be made to have forms completed and up-to-date in anticipation of a visit by the Sponsor's monitor.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertaining to the clinical study for each study participant. All aspects of the study will be carefully monitored with respect to GCP and standard operating procedures for compliance with applicable government regulations. The study monitor will be an authorized individual designated by the Sponsor. The study monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

An electronic data capture system to manage data collection will be utilized during this trial. The electronic data capture system is a software tool designed to ensure quality assurance and facilitate data capture during clinical trials. The system is fully compliant with US Code of Federal Regulations 21 Part 11.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator (or designee) will cooperate with the Sponsor (or its representative(s)) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

12.2 Investigator Documentation

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of patients. Study staff will permit authorized representatives of regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

The Investigator will provide the Sponsor with an Investigator's Undertaking according to Indian regulatory requirements, in addition to the fully executed FDA Form 1572 and his/her curriculum vitae. The investigator will indicate on Form 1572 the name and location of the clinical laboratory which will be used for patient evaluation. The laboratory's certification, certification number, and date of certification and the laboratory normal values will be provided. Any changes in the clinical laboratory will be provided promptly to the Sponsor who will report the changes to the FDA as required.

12.3 Record Retention

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Trial Master File and Site Master Files will be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

The Investigator will also retain a copy of all study records in a secure location for a period as mutually agreed with sponsor in the Clinical Trials Agreement. Investigator will be advised when the record retention is complete and no longer needed.

12.4 Audit and Inspection Procedures

Regulatory authorities, the Institutional Review Board (IRB)/Ethics Committee (EC), and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

12.5 Protocol Deviations and Amendment

The Investigator is not permitted to alter or deviate from the protocol except when immediate health care concerns mandate it. All the protocol deviations should be appropriately documented.

All protocol revisions (amendments) must originate with and be documented by the Sponsor. The Investigator must submit the amendment to his/her IRB/EC for review and approval prior to implementation. Documentation of approval signed by the chairperson or designee must be sent to the Sponsor.

12.6 Sponsor Monitoring

Monitoring and auditing procedures approved by the Sponsor will be followed in order to comply with GCP guidelines. After satisfactory receipt of all necessary regulatory paperwork, the

Sponsor's monitor will arrange that all study material be delivered to the study site at a mutually convenient time. An initiation visit by the Sponsor/designee and its monitoring personnel will be made. At this meeting, all personnel expected to be involved in the conduct of the study will undergo an orientation to include review of study protocol, instruction for eCRF completion and overall responsibilities, including those for drug accountability and study file maintenance.

Throughout the course of the study, the Sponsor or its designee's monitor will make frequent contact with the Investigator. This will include telephone and/or on-site visits. On-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. As part of the data audit, it is expected that source documents (e.g., hospital records, office records) will be made available for review by the monitor. The monitor also will perform drug accountability checks, and may periodically request review of the Investigator's study file to assure completeness of documentation in all respects of study conduct.

Upon study completion, the monitor will arrange for a final review of the study files, after which the file should be secured by storage for the appropriate period as specified in Section 12.3.

The Investigator or appointed delegate will receive the Sponsor's representative during these on-site visits and will cooperate in providing the documents for inspection and responding to inquiries that may arise as part of this review. The Investigator will also permit inspection of the study files by authorized representatives of the FDA and regulatory authorities of other countries.

12.7 Publication/Data Sharing Policy

Publication by the sites of any data from this study must be in accordance with the clinical trial agreement.

12.8 Reports and Publications

Upon completion of the trial (or early termination), the sponsor should provide the EC/IRB with a summary of the trial's outcome. All the regulatory authorities will also be provided with reports, as required per local regulations.

A clinical study report will be prepared by the sponsor or its designee in accordance with the ICH guidelines.

13.0 ETHICS/PROTECTION OF HUMAN PATIENTS

13.1 Ethical Conduct of the Study

The study will be conducted in accordance with ethical principles that have their origin in the

Declaration of Helsinki and are consistent with International Conference on Harmonisation, Good Clinical Practice guidelines, applicable regulatory requirements, and Sponsor policies. The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Patients of Research, as drafted by the US National Commission for the Protection of Human Patients of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

13.2 Institutional Review Board (IRB)/Ethics Committee (EC)

The protocol, informed consent form(s), recruitment materials, and all patient materials will be submitted to the IRB/EC by the investigator for review and approval. Approval of all Essential Documents including the protocol, informed consent form, and other patient pertinent documents etc. must be obtained before any patient is enrolled at any given investigative center, and a copy of the approval letter supplied to the Sponsor or Sponsor's designee. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented in the study. All ongoing patients shall be notified about the changes and asked to sign amended version of the informed consent form.

During the course of the study, the Investigator shall make timely and accurate reports to the IRB/EC on study progress at intervals as advised by the investigative site or IRB/EC standard operating procedures. Copies of all reports to, and correspondence with, the IRB/EC must be provided to the Sponsor or Sponsor's designee. Further, after the completion or early termination of the study, a final report should be submitted by the Investigator to the respective IRB/EC following the IRB/EC SOP and share the notification and acknowledgement with the Sponsor.

It is the Investigator's obligation to maintain an IRB/EC correspondence file and to make this available for review to Sponsor representatives as part of the routine study monitoring process.

13.3 Informed Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to patients and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the patient. Before each patient is enrolled in the clinical study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. Specifically, for any patients enrolled from sites in India (as per the regulatory requirement), the Informed Consent Form (ICF) will also contain the language that patients enrolled in the trial will receive free medical management for any injury occurring to him/her while participating in the study, as long as required in the opinion of the investigator, or till such time it is established that the injury is not related to the clinical trial, whichever is earlier. Further the ICF, for patients enrolled in India, will also state that in case of study related injury or death or permanent disability, the Sponsor / designee will provide financial compensation to the patient / nominee as per the order of the licensing authority.

The patient will receive all information that is required by regulatory authorities and ICH guidelines. The Investigator (or designee) will provide the Sponsor with a copy of the IRB/EC approved ICF prior to the start of the study. The ICF must be signed and dated by investigator and patient; one copy will be given to the patient for their records whereas original will be retained by the Investigator as part of the clinical study records. Impartial witness should sign and date the ICF, if consenting patient is illiterate and patient's thumb impression should also be taken. The investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented. Patients will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/EC and signed by all patients subsequently enrolled in the clinical study as well as those ongoing in the clinical study before implementing revised ICF.

Written informed consent will be obtained and documented from each patient prior to entry into the study. The consent process will be documented in the source and applicable details should be transcribed in the e-CRF. Additionally, for patients enrolled in India, Audio-Visual consenting, for patients deemed vulnerable by the investigator, will also be required, as per CDSCO regulations.

13.4 Confidentiality and Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, Investigator's Brochures, and other materials) will be stored

appropriately to ensure their confidentiality. Patient data will be made available upon request to monitors from the Sponsor, the Food and Drug Administration, the Institutional Review Board, and to other government agencies that have responsibility for clinical research activities.

The anonymity of participating patients must be maintained. Data that is released by the Investigator to the Sponsor, the FDA, or IRB will not be directly traceable to the patient.

Documents that identify the patient (e.g., the signed informed consent document) must be maintained in confidence by the Investigator. In the event that a publication of this research incorporates a patient's medical data, that data will not identify the patient.

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Appendix A: Pharmacovigilance Contact Details

Pharmacovigilance Department
Veeda Clinical Research
Nr. YMCA club, S. G. Highway,
Ahmedabad- 380015, Gujarat, India
Email: drugsafety@aurigene.com (SAE form is to be sent on this e-mail ID)
Fax Number: +91 7930013010

Appendix B: Clinical Laboratories and Other Departments and/or Facilities Participating in the Study

Clinical Laboratory Facility (Central Laboratory)
Metropolis Healthcare Limited,
250-D, Udyog Bhavan,
Hind Cycle Marg,
Behind Glaxo,
Worli, Mumbai – 400030
Customer care: 022-33993939

Bioanalytical Laboratory Facility for Pharmacokinetic samples
Veeda Clinical Research Pvt Ltd.,
2nd, 3rd, 4th Floor Shivalik Plaza-A, Nr. ATIRA, IIM Road,
Ahmedabad-380015, Gujarat, India
Phone: +91 79 3001 3000

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This and any "Appendix" can be changed administratively, without the need for an amendment.