STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase II, Multicenter, Double-blind, Double Dummy, Placebo Controlled, Randomized, Study to Evaluate the Efficacy and Safety of two doses of AUR101 (600mg and 400mg) in patients with Moderate-to-Severe Psoriasis (INDUS-2)
Protocol No.:	AUR101-201
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Prepared By:

JSS Medical Research India Private Limited
Data Management
Tower 2, 1st Floor, South Wing
L&T Business Park
Plot no 12/4, Sector 27 D, Near Sarai Khawaja Metro Station
Delhi Mathura Road, Faridabad -121003, Haryana, India
Landline No. +(91)129 – 6613500
Fax No. +(91)129 - 6613520

Sponsor:

Aurigene Discovery Technologies Limited
(Subsidary of Dr. Reddy's Laboratories Limited)
39-40, KIADB Industrial Area, Phase II,
Electronic City Hosur Road,
Bangalore- 560100, Karnataka, India

Sponsor Signature

I hereby declare that I have reviewed the Statistical Analysis Plan and agree to its form and content. In addition, I confirm that the outlined **Statistical Analysis Plan** contains all relevant information for the data analysis to be performed in the Protocol No. AUR101-201 study by the Biostatistics Department.

Represented by: DocuSigned by: Divyesh Mandavia 601F37CC1CB142D... 26Mar2021

Date

Dr. Divyesh Mandavia
Senior Manager, Clinical Development
Aurigene Discovery Technologies Ltd.

Authorization Document

Anjali Yadav	Biostatistician	Anjali Yadav	25MAR2021
Author	**Designation**	**Signature**	**Date**
Ayush Srivastava	Biostatistician	Ayush	25MAR2021
Reviewer	**Designation**	**Signature**	**Date**
Devyani Kanojia	Project Lead	Devyani	25MAR2021
Reviewer	**Designation**	**Signature**	**Date**
Dr Vinay Gupta	Senior Manager-Biostatistics	Vinay Gupta	26 Mar 2021
Approver	**Designation**	**Signature**	**Date**

Revision History

Version #	Version Date	Author	Description of Modifications from Previous Version

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse Events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration
$AUC_{0-\infty}$	$AUC_{0-\infty}$ 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}	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	CL/F Plasma Clearance
Co-I	Co-Investigator
CDSCO	Central Drugs Standard Control Organization
Cmax	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	HBsAg
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
SAP	Statistical Analysis Plan
ITT	Intent to Treat
IUD	Intrauterine Device
IWRS	Integrated Web based Randomization system
JSS India	JSS Medical Research India Private Limited
Kel	Kel Elimination Rate Constant
LOCF	Last Observation Carried Forward
MCH	Mean Corpuscular Hemoglobin
MedDRA	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
SD	SD Standard Deviation
SAE	SAE Serious Adverse Event
SOC	SOC System organ class
t½	t½ Terminal elimination half-life
TEAEs	TEAEs Treatment emergent adverse events
TGF	TGF Transforming Growth Factor
TNF	TNF Tumor necrosis factor

Th	Th Helper T cells
Tmax	Tmax Time to reach Cmax
ULN	ULN Upper Limit of Normal
WBCs	WBCs White blood cells
WHO-DD	World Health Organization Drug Dictionary

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) describes a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for Aurigene Discovery Technologies Limited protocol AUR101-201. (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)).

This phase II study is conducted to assess the safety and efficacy of two doses of AUR101 – An oral RORγT inhibitor for anti-inflammatory disorders in patient with Moderate-to-Severe Psoriasis. The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study and the operational aspects of clinical assessments and timing for completing a patient in this study.

The purpose of this analysis is to evaluate early trends of efficacy signals arising from this Phase II study which can help to plan AUR101 clinical development program. The planned analyses identified in this SAP can be used for amendment of current protocol to change the sample size, manuscript writing or presentation at conferences, and/or regulatory submissions. In addition, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective report.

2.0 DESCRIPTION OF THE PROTOCOL

2.1 Protocol Number

AUR101-201

2.2 Protocol 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).

2.3 Date and Version

07 Aug 2019, Version 1.0

2.4 Study Background

Helper T cells (Th) have traditionally been divided into Th1 and Th2 subtypes. A thirds subtype of Th17 cell was shown to be dependent upon interleukin 23 (IL-23) stimulation and produces IL-17 in response to antigen recognition.[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).

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, etc. [3-5] 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).[3,4,6] In view of all these, AUR101 being an RORγ inhibitor, reduces IL-17 and may prove effective in these diseases.

2.5 Study Rationale

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 animal models. Toxicology studies with the compound have also demonstrated a favorable safety profile at the exposures showing efficacy in animal models. A completed FIH study has determined a desirable safety, PK and optimal IL-17 inhibition, when AUR101 is administered at 600 mg BID.

In view of favorable preclinical safety, preclinical efficacy, and PK, PD and safety data derived from FIH study, the current Phase II Proof of Concept (POC) study has been planned in moderate-to-severe psoriasis.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1.1 Primary Objectives

The primary objective of the study is to assess efficacy of AUR101 in patients with moderate-to-severe psoriasis.

3.1.2 Secondary Objectives

The secondary objectives of the study are as follows,

1. To evaluate the safety and tolerability of two oral doses of AUR101 in patients with moderate-to-severe psoriasis.

2. To evaluate the plasma pharmacokinetics of AUR101 in patients with moderate-to-severe psoriasis

3. To evaluate effect of AUR101 on quality of life in patients with moderate-to-severe psoriasis.

3.2.0 End Points

3.2.1 Primary Endpoint(s)

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

3.2.2 Secondary Endpoint(s)

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)

3.2.3 Secondary Safety Endpoint

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.

3.2.4 Pharmacokinetic Endpoints

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 noncompartmental models. Summaries of PK parameters will be presented by dose group.

3.2.5 Exploratory Endpoints

While not stated in the study protocol, the sponsor will also explore the effects of AUR101 on PASI-90 as well as PASI-100 in the study.

3.2.6 Efficacy & Safety Evaluation score description

3.2.6.1 PASI (Psoriasis Area and Severity Index)

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). A PASI score will be derived as indicated in Table 1.

The following definitions are used in this study according to Committee for medicinal products for human use (CHMP) guidelines:

- 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.
  PASI 90 response: patients achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders
  PASI 100 response: patients achieving 100% improvement (reduction) in PASI score (i.e. achieving PASI score of 0) compared to baseline are defined as PASI 100 responders.

Table 1. Psoriasis Area and Severity Index

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	0=none 1=slight	0=none 1=slight	0 = 0% 1 = 1% - 9%

	2=moderate 3=severe 4=very severe	2=moderate 3=severe 4=very severe	2=moderate 3=severe 4=very severe	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.

3.2.6.2 Investigator Global Assessment (IGA)

The 5-point IGA mod 2011 rating scale is provided in Table 2. Based on this scale, a patient will be considered as IGA 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 2. Investigator Global Assessment

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

3.2.6.3 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. 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.
In DLQI score, Minimal Clinically Important Difference (MCID) is considered as 5-points reduction from baseline. [7-8]

4.0 STUDY METHODS

4.1 Study Design and Plan

This is 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 are three arms – two arms of AUR101 (400 and 600 mg BID) and one arm of placebo.

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

A subset up to 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.

4.1.1 Number of Patients and Duration of Treatment

Approximately 90 patients with chronic moderate-to-severe chronic plaque psoriasis are randomized to each of the three arms (1:1:1) by IWRS as mentioned below:

- AUR101 400 mg BID
- AUR101 600 mg BID
- Placebo BID

All the patients will receive study drugs for 12 weeks in a double blind, double dummy fashion.

4.1.2 Formulation and Mode of Administration

AUR101 is 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.

4.2 Study Initiation and Completion

This study is of approximately of 14 weeks from the screening through end of study. There will be seven scheduled visits and one follow up visit in the study. Follow-up visit will be 14 ±2 days after last dose tablet taken by the patients.

4.3 Selection of Study Population

Adult males or females of age group between (18-65) years and confirmed diagnosis of chronic plaque-type psoriasis at least moderate severity, defined as (Psoriasis Area and Severity Index) PASI≥12 and involved Body Surface Area (BSA) ≥10 % at screening, diagnosed at least 6 months before screening and have willingness to give written informed consent and ability to adhere to the study restrictions and assessments schedule.

4.3.1 Screened Population

The population will include all patients in the study who have signed Inform Consent Form.

4.3.2 Randomized Population

The Population will include all patients in the study who have signed Inform Consent Form and satisfied all inclusion and exclusion criteria.

4.3.3 Safety Population

The Safety Population will include all patients in the study who receive at least one dose of study treatment.

4.3.4 Efficacy population

Efficacy population will include patients who

- have a valid baseline and at least one post-baseline (follow up) assessment for PASI score by the independent dermatologist or withdrawal is associated with lack of effect by the patient before post-baseline assessment.
- do not have any major protocol or inclusion/exclusion violations,

Efficacy population will provide sample for analysis of primary, secondary and exploratory endpoints. 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.
Efficacy data collected solely based on the photographs without on-site examination by the investigator/independent dermatologist will not be considered for the analysis and this data will also be imputed with LOCF approach.

4.3.5 Major Protocol Deviations

The protocol deviations in the study will be evaluated on a case-to-case basis and will be categorized as major or minor. A major protocol deviation is defined as any deviation that may affect the efficacy outcome or patient's safety. Subjects having major protocol deviation will be finalized prior to the soft lock.

Following are some protocol deviations.

1. Violation of major inclusion/ exclusion criteria assessment

2. Use of prohibited concomitant medication
3. Treatment non-compliance
4. Non-compliance/non-assessment of study procedure
5. Visit out of the window period

4.3.6 Pharmacokinetic (PK) Population

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

4.4 Schedule of Visits and Procedures

There will be seven scheduled visits and one follow up visit in the study mentioned as below:

- Screening visit (Up to Day -14)
- 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

Follow-up visit: 14 ±2 days after last dose

All the procedures that will be conducted in different visits are shown in table 3.

Table 3. 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	

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	
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 sign includes 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 childbearing potential only

4.5 Permitted therapy for psoriasis

Only bland emollients or shampoos (for scalp psoriasis) will be allowed during the study participation. No active drug (topical or systemic) affecting psoriasis will be allowed during the treatment period.

4.6 Rescue Medication

Rescue medication can be given if patient's PASI score is increasing by at least 50% from baseline level at or after 6 weeks of therapy. In addition to above, if a patient has intolerable symptoms from psoriasis, then any available medication, including any biologic medications, such as secukinumab or adalimumab, can be administered as srescue medications.

Patients who receive rescue treatment during the study treatment period will be considered treatment failures for the purpose of efficacy analysis. To conduct efficacy and safety assessments (e.g. disease severity scores, safety labs) immediately before administering any rescue treatment. 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.

5.0 GENERAL CONSIDERATIONS FOR STATISTICAL ANALYSIS

Data on continuous scale will be expressed as mean, standard deviation, standard error, median, 95%CI and number of patients in each treatment group. Categorical type of data will be presented with frequency and the percentages of patients in each treatment group. Statistical Analysis. Software (i.e. SAS® 9.4 or higher) will be used to perform all analyses.

5.1 Sample Size Determination

AUR101 doses will be tested versus placebo with respect to the primary endpoint (PASI 75 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% dropouts over the study period. Placebo response rates from previous studies was 4-7% in most of the studies in similar patient population. No multiplicity adjustments were considered in the sample size calculation as it is a POC study.

A subset of approximately 25 consenting patients will participate in the pharmacokinetic part in addition to main study.

5.2 Compliance

IP return and compliance check will be assessed at visit 3, visit 4, visit 5, visit 6 and visit 7. Subjects will be dispensed 3 bottles at each visit. Each bottle contains total 30 tablets and patients will have to take 3 tablets in the morning and 3 tablets in the evening.
Total Compliance will be calculated by using formula:

Total Compliance = Number of actual doses taken / (Number of expected doses to be taken) *100

Overall compliance at each visit and during study period will also be calculated by using the above formula as given above. Descriptive statistics by treatment groups will be reported for treatment overall compliance using safety population. A listing will be provided.

5.3 Definition and Derived Variables

5.3.1 Baseline

Baseline value is defined as the last non-missing assessment prior to the first study treatment exposure. If the last non-missing assessment is performed on the same date as the first study treatment and time is not available, the assessment will be considered as baseline. In this study, drug is dispensed at visit 2 that is randomization visit which will serve as baseline for efficacy variables.

5.3.2 Change from Baseline

Value of change from baseline at any post baseline visit is defined as the difference of the post-baseline value to the baseline value

i.e. Change from baseline (Δ) = post baseline value- baseline value

Percent change from baseline is defined as percentage difference of the post-baseline value to the baseline value, relative to baseline value

i.e. Percent Change from baseline at respective time =

$$\frac{\text{(Post baseline value at respective time - Baseline value) x 100}}{\text{Baseline value}}$$

5.3.3 End of Treatment

End of treatment value is defined as the last non-missing assessment at the end of study treatment visit i.e. visit 7 (week 12 ± 4 Days). If the subject has not completed the treatment as per protocol, then the last available non-missing value prior to the end of study treatment visit will be used as end of study value and that visit will be considered as early termination visit.

5.3.4 Treatment Start Day

Date of first study treatment date is used for treatment start day i.e. visit 2 (day 1) in this study.

5.3.5 Treatment End Day

Date of last study treatment date is used for treatment end day until unless the subjects has not prematurely discontinued from the study, then the last date of treatment taken prior to the week 12 ± 4 Days will be used for treatment end day.

5.3.6 Duration of Treatment Exposure

Duration of treatment exposure is defined as the time period in which the subjects was on treatment during the study and will be calculated as follows: number of days between the last dose date and the first dose date plus one i.e.

Treatment duration=date of last dose -date of first dose +1.

5.4 Methods for Withdrawals, Missing Data, and Outliers

In case of a patient's withdrawal from the study without any major protocol deviation, its values on subsequent visits will be considered missing.

The last observation carried forward (LOCF) method will be applied to all efficacy measurements (PASI score, IGA mod 2011 score, DLQI score etc.) 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. If withdrawal prior to first post-baseline assessment is considered due to lack of effect of the study drug by the investigator, then the respective patient will be considered as non-responder in PASI and IGA responder analysis, and no change (i.e. post-baseline difference of 0) will be considered for percent or absolute change in PASI, IGA or DLQI parameters.

For missing safety variables, when repeat assessment data is available for the respective visit, then these repeat assessment data will be imputed. E.g. The hematology parameters are not available for Visit 4 for any patient and repeat hematology assessment is done prior to next scheduled visit, then hematology parameters during Visit 4 will be replaced with repeat assessment parameters.
However, no values will be replaced if the parameter value is available. For example, if only ALT and AST are not available for a specific visit in biochemistry panel and repeat assessment prior to next visit is done with all liver function tests (ALT, AST, ALP, bilirubin, etc.), then only ALT and AST values will be replaced and other liver function values will not be replaced.

For the efficacy variables (PASI score, IGA mod 2011 score, DLQI score), no observed values will be considered as outliers. For safety parameters like vital signs, lab parameters etc., any value which is out of range will be summarized as observed. However, it will be checked whether it is a normal or abnormal finding and will be

reported accordingly. For abnormal observed value we further summarized as clinically significance and non- clinically significance.

5.5 Analysis Software

Statistical processing will be performed using Statistical Analysis System (SAS®) 9.4. (Please refer section 6.0).

6.0 GENERAL CONSIDERATIONS FOR STATISTICAL ANALYSIS

The statistical analysis will be performed using the SAS version 9.4. The descriptive statistics for the continuous data will be presented using mean, standard deviation, standard error, median and 95% CI, whereas, for the categorical data it will be presented using number of observations (n) and percentages (%) For continuous data, normality will be tested though "Kolmogorov-Smirnov Goodness-of-Fit Test". If normality assumption will not fulfil then non-parametric methods such as Mann Whitney U/ Kruskal Wallis Test will be used.

- Following statistical tests/procedure will be performed wherever required:

Clopper Pearson Method for Confidence Interval

The Proc Freq procedure of SAS will be used to find the 95% CI:

ods output;

binomial = <name of dataset containing p-value>;

PROC FREQ data=<dataset name>;

by <list of categorical variables>;

tables<values of the categorical variables >/binomial alpha=<significant level>;

weight <count>;

exact binomial;

run;

- ods output close;

Proc mixed for MMRM ANCOVA Model

proc mixed;

class var1 var2;

model var1 = var2;

random var1 var1*var2;

run;

-

The Proc Means procedure of SAS will be used to find the summary statistics

PROC means data=<dataset name>;

var < variable to be analyzed >;

OUTPUT OUT=<name of dataset containing all statistics>

N=n MEAN=mean STDERR=stderr LCLM=lclm Uclm=uclm;

- run;

Chi-square Test

The Proc Freq procedure of SAS will be used to find the p-value:

ods output;

Chi-square = <name of dataset containing p-value>;

PROC FREQ data=<dataset name>;

by <list of categorical variables>;

tables<values of the categorical variables >/CHISQ=<significant level>;

weight <count>;

run;

- ods output close;

Fisher Test

The Proc Freq procedure of SAS will be used to p-value:

ods output;

fisher = <name of dataset containing p-value>;

PROC FREQ data=<dataset name>;

by <list of categorical variables>;

tables<values of the categorical variables >/fisher=<significant level>;

weight <count>;

run;

ods output close;

Proc TTEST < options >;

class variable;

paired variables;

by variables;

var variables;

6.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Demographic and baseline characteristics, including age, sex, race, weight, BMI, medical history and conditions, prior anti-psoriasis therapy, duration of disease and any other study-appropriate data (e.g. PASI, BSA, IGA) will be tabulated and summarized by treatment groups. In addition, following parameters (by both independent dermatologist and investigator) will be summarized by number and percentages:

- Patients with PASI <20 and PASI ≥ 20.
- Patients with IGA of 3 and IGA of 4
- Patients with prior exposure to systemic therapy
- Patients with prior exposure of biologics

6.2 Prior and concomitant medication

Prior and concomitant medications will be summarized by treatment group. 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.

All prior, concomitant and prior/ concomitant medications that were recorded on the CRF will be coded and summarized, according to the generic names using the WHO drug classification (WHODD) dated September 1, 2019 or later, using the number and percentage of subjects for safety population. A listing of all prior, concomitant and prior/ concomitant medications will also be provided.

6.3 Baseline and Screening Conditions

6.3.1 Baseline Medical History

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. Medical/ surgical history will be coded according to the MedDRA dictionary version 22.1 or later and will be summarized using number (%) of subjects for safety population, corresponding subject data listing will also be provided.

6.3.2 Other Screening Assessments

Menstrual history of women, QuantiFERON TB-Gold test and viral serology that are assessed at screening only for inclusion and exclusion testing will not be presented separately. However, the frequency and percentage will be presented for patients who will be eligible to participate based on all screening conditions.

7.0 EFFICACY ANALYSES

7.1 Primary Efficacy Analysis

Summary statistics with 95% confidence interval will be presented for PASI. Comparison of percentage of patients achieving at least 75% reduction from Baseline

PASI score (PASI-75) to Week 12 between treatment arm and placebo will be evaluated using Chi-square/Fisher's exact test with responder and non-responder psoriasis type. Also, 95% CI for the responders within treatment will be evaluated by using Clopper-Pearson method and 95% CI for treatment difference will be evaluated by using Miettinen-Nurminen method.

Additional sensitivity analysis will be tested by using Cochran-Mantel-Haenszel (CMH) test after adjusting the sites and baseline PASI score. The analysis will be performed on efficacy population. No multiplicity adjustments will be done for the primary analysis.

Two sets hypotheses will be tested,

1. H_0: $P_1=P_0$ vs H_1: $P_1\neq P_0$
2. H_0: $P_2=P_0$ vs H_1: $P_2\neq P_0$

Where, P_0, P_1 and P_2 are the proportion of responders in placebo, 400 mg and 600 mg arms, respectively. Since, both hypotheses will be tested separately, no multiplicity adjustment will be done.

7.2 Secondary Efficacy Analysis

- Comparison of percentage of patients achieving at least 75% reduction from baseline PASI (PASI-75) score at 4 and 8 weeks between test and placebo will be evaluated using Chi-square/ Fisher's exact test with responder and non-responder psoriasis type. Also, 95% CI for treatment and for treatment difference will be evaluated by Clopper-Pearson method and Miettinen-Nurminen method, respectively.
- Comparison of percentage of patients achieving at least 50% reduction from baseline PASI (PASI-50) score at 4, 8 and 12 weeks between test and placebo will be evaluated using Chi-square/ Fisher's exact test with responder and non-responder psoriasis type. Also, 95% CI for treatment and for treatment difference will be evaluated by Clopper-Pearson method and Miettinen-Nurminen method, respectively.
- Comparison of percentage of patients with Investigator Global Assessment (IGA) scores of 0 or 1 at 4, 8 and 12 weeks of treatment (end of treatment) between test and placebo will be evaluated using Chi-Square test. Also, 95% CI for treatment and for treatment difference will be evaluated by Clopper-Pearson method and Miettinen-Nurminen method, respectively.

Absolute and percent change of PASI score at visit 4, 8 and 12 from baseline will be computed using given formula:

%Change of PASI Score for time T= (PASI score at T- PASI score at baseline) *100
PASI score at baseline

where time T can be week 4, week 8 and week 12.

Summary statistics of absolute & percent change from baseline in PASI score at week 4, 8 and 12 will be presented as n, mean median, SD, SE and 95% confidence interval for mean. Comparison of percent change in PASI scores from baseline to week 4, week 8 and week 12 between treatment groups i.e., from AUR 400mg to placebo and AUR 600mg to placebo will be analyzed using analysis of covariance (ANCOVA) model with baseline scores included as a covariate.

Summary statistics of IGA score at baseline (screening), week 4 (visit 4), week 8 (visit 6) and week 12 (visit 7) and also respective absolute and percent change at week 4, week 8 and week 12 from baseline will be presented as n, mean median, SD, SE, and 95% confidence interval for mean. Comparison of mean change in IGA scores from baseline to week 4, week 8 and week 12 between treatment groups will be analyzed using analysis of covariance (ANCOVA) model with baseline scores included as a covariate.

Summary statistics of BSA (Body Surface Area) score at baseline (screening), week 4 (visit 4), week 8 (visit 6) and week 12 (visit 7) and respective absolute and percent change at week 4, week 8 and week 12 from baseline will be presented as n, mean median, SD, SE and 95% confidence Baseline interval for mean. Comparison of mean change in BSA scores from to week 4, week 8 and week 12 between treatment groups will be analyzed using analysis of covariance (ANCOVA) model with baseline scores included as a covariate.

Summary statistics of DLQI score at (screening), week 4 (visit 4), week 8 (visit 6) and week 12 (visit 7) and absolute and percent change in DLQI score at week 4 (visit 4), week 8 (visit 6) and week 12 (visit 7) from baseline will be presented as n, mean, SD, SE, median and 95% confidence interval for mean. Comparison of mean change in DLQI scores from baseline to week 4, week 8 and week 12 between treatment groups will be analyzed using analysis of covariance (ANCOVA) model with baseline scores included as a covariate.

For MMRM ANCOVA model, change will be taken as dependent variable and the baseline value, treatment, visit (main effect) and visit *treatment (interaction effect) will be taken as independent variables.

$$\text{Change} = \beta_{0+} \beta_1 * \text{baseline} + \beta_2 * \text{treatment} + \beta_3 * \text{visit} + \beta_4 * (\text{visit} * \text{treatment}),$$

where Y=change from baseline in different scores and β_0, β_1, β_3, β_4=coefficients.

First, the covariance structure will be kept as unstructured. If the model will not converge then autoregressive AR(1) covariance structure will be used for covariance matrix.

7.3 Additional Analysis

- Comparison of PASI-75 and PASI-50 at week 2, 6 and 14 by Chi-square/ Fisher's exact test also. Also, 95% CI for treatment and for treatment difference will be evaluated by Clopper-Pearson method and Miettinen-Nurminen method, respectively.
- Comparison of percentage of patients achieving at least 90% reduction from baseline PASI (PASI-90) score at 2, 4, 6, 8, 12 and 14 weeks between test and placebo will be evaluated using Chi-square/ Fisher's exact test with responder and non-responder psoriasis type. Also, 95% CI for treatment and for treatment difference will be evaluated by Clopper-Pearson method and Miettinen-Nurminen method, respectively.
- Comparison of percentage of patients achieving 100% reduction from baseline PASI (PASI-100) score at 2, 4, 6, 8, 12 and 14 weeks between test and placebo will be evaluated using Chi-square/ Fisher's exact test with responder and non-responder psoriasis type. Also, 95% CI for treatment and for treatment difference will be evaluated by Clopper-Pearson method and Miettinen-Nurminen method, respectively.
- IGA responder (IGA of 0 or 1) will be compared across treatment groups at week 2, 6 and 14 by Chi-square/ Fisher's exact test also.
- Absolute change in IGA, percent change in PASI & BSA and absolute change in DLQI will also be compared across treatment groups at week 2, 6 and 14 by ANCOVA with baseline as covariate
- Percentage of patients achieving MCID (≥ 5-points reduction from baseline) in DLQI will be compared across the treatment groups by Chi-square/ Fisher's exact test at week 2, 4, 6, 8, 12 and 14
- Percentage of patients achieving DLQI score of 0 or 1 at week 2, 4, 6, 8, 12 and 14 will be compared across the treatment groups by Chi-square/ Fisher's exact test
- An analysis of combined active arms (i.e. 400 mg BID and 600 mg BID) vs. placebo arms will be done for PASI75, PASI90, PASI100 and IGA responders (i.e. IGA of 0 or 1) at week 4, 8 and 12 by Chi-square/ Fisher's exact test. For this assessment, only independent dermatologist evaluation will be considered.

7.4 Subgroup Analysis

1. Following analysis will be repeated for subgroup of PASI <20 and PASI≥ 20 and IGA of 3 and IGA of 4:

   - PASI-50, PASI-75, PASI-90 and PASI-100 responder (as per independent dermatologist assessment only) comparison at week 4, 8, and 12 by Chi-square/ Fisher's exact test
   - Change in PASI score (as per independent dermatologist assessment only) at week 4, 8 and 12 from baseline will assessed by ANCOVA with baseline as covariate.
   - IGA responder (IGA of 0 or 1; as per independent dermatologist assessment only) comparison by week 4, 8 and 12 by Chi-square/ Fisher's exact test
   - IGA reduction (as per independent dermatologist assessment only) analysis by week 4, 8 and 12 i.e. proportion of the patients with at least 1-point reduction, 2-points reduction, 3-points reduction and 4-points reduction (Only for baseline IGA of 4)

2. Patient with Head & neck PASI of 12

   PASI-50, PASI-75, PASI-90 and PASI-100 responder (as per independent dermatologist assessment only) comparison at week 4, 8, and 12 by Chi-square/ Fisher's exact test

7.5 Pharmacokinetic (PK) Analysis

PK analysis will be performed on PK population.

Individual plasma PK parameters, including area under the concentration-time curve (AUC_{0-12}), terminal elimination half-life ($t_{1/2}$), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), elimination rate constant (Kel) and clearance (Cl) will be summarized and presented as described for continuous variables. Along with mean, SD, median and geometric mean concentration (GMC) and 95% GMC will also be provided by treatment arms.

Pharmacokinetic analysis will be performed only of sufficient patient's data are available.

8.0 SAFETY & TOLERABILITY ASSESSMENT ANALYSIS

The analysis of safety assessments in this study will include summaries of the following categories of safety data collected for each subject

- Adverse Events
- Physical Examination

-
-
- Vital Sign
-
- ECG Record

Laboratory Test

Treatment emergent adverse events (AEs) and serious adverse events (SAEs) will be reported by frequency analysis with respect to incidence, severity as well as seriousness. Clinically significant alterations in clinical laboratory parameters, vital signs and ECG will be reported.
All safety parameters (e.g. AEs, physical examination, vital signs, ECG parameters, Laboratory evaluations) will be summarized descriptively and by treatment. Continuous variables will be described by number (n) of non-missing observations, arithmetic mean, standard deviation, standard error, median and 95%CI. Categorical variables will be described by frequency tables (counts and percentages), however in case of very low occurrences instead of tables with zero proportions, note statement will be added in respective section of table. Safety evaluations will be done on safety population. No formal statistical testing will be performed on the safety data.

8.1 Adverse Events

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.

8.2 Physical Examination

The baseline medical history of subjects includes information regarding physical history for different body systems (General Appearance, Skin, Neck, Eyes, Lungs etc.). Weight will be recorded at every visit except visit 3, 5 and follow up visit. Height will be captured at screening only. Change in weight and BMI from baseline will be calculated and descriptive statistics (Mean, SD, SE, median) will be presented in dose-wise groups. For rest of the physical examination data, a listing will be presented

8.3 Vital Signs

Standard vital signs will include the blood pressure, pulse rate, respiratory rate, and body temperature. Vital signs at each visit and the change from baseline to each post-baseline assessment will be summarized using descriptive statistics.
These parameters will be analyzed using number (n) of non-missing observations, mean, standard deviation (SD), SE, median and 95%CI. Change from baseline in vital sign parameters will also be reported.

8.4 ECG

Overall interpretation of 12 lead ECG will contain within normal limits, abnormal but not clinically significant, or abnormal and clinically significant categories.
The ECG data will be analyzed by treatment groups at each visit using frequency count and percentage of subjects by treatment groups.

8.5 Laboratory Parameters

The laboratory parameters will include Hematology, Liver function Test, and Renal Function Test samples by visits.

The categorical variables will be analyzed using frequency count and percentage of subjects, and continuous variables will be analyzed using number (n) of non-missing observations, mean, standard deviation, SE and median (IQR) by groups. Any change from baseline in laboratory parameters in terms of normal or abnormal (clinically significant or not significant) findings will also be reported through shift tables for overall data without mentioning the groups. Descriptive statistics (Mean, median, SD, SE and 95% CI) will be presented for change from baseline to the respective visit.

8.6 Urine Pregnancy Test

For Urine Pregnancy Test listing will be provided.

9.0 REPORTING CONVENTIONS

9.1 Reporting of Numeric Values

All data will be presented by treatment group. Where appropriate, data will be presented including a total overall column and by visit in addition to treatment group.

- Summary descriptive statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean, median, standard deviation (SD), SE, median and 95% confidence interval for continuous variables.
- Mean and Median values will be reported to one decimal place. Standard deviation, standard error and 95% confidence interval values will be reported to two decimal places.
- Percentages will be rounded to one decimal place. Where appropriate, the number and percentage of responses will be presented in the form XX (XX.X %).
- All Adverse Events (AE) and Serious Adverse Events (SAE) will be presented: Number of events, Number of subjects and %(n/N) of subjects.
- P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables. P-values greater than 0.999 will be reported as >0.999.
- P value <0.05 will be considered significant.
- All listings will be sorted for presentation in order of site number, patient number, date of procedure or event.

  All categories of variables will be presented even if there is no data. Zero frequencies are going to be represented as “0 (0.0%) “in reporting of results.

10.0 OUTPUT (TABLES, LISTINGS AND GRAPHS) CONSIDERATIONS

The default Tables, Listings and Graphs (TLG) layout will be as follows.

Orientation	All pages should preferably be landscape.
Paper Size	Legal size
Margins	Top: 1 in Bottom: 0.75 in Left: 0.75 in Right: 0.75 in
Font	Font style (preferably Times New Roman) of the Text

Headers	**Titles of Table/Listing will be center** **Left** Sponsor: Study Name: Protocol No:
Footers	**Left** Analyst Initials: Program Name: Program Run date: time: **Right** Datasets Used: Page XXX of YYY

The margin may be reduced as necessary to allow additional rows to be presented, but not at the expense of clarity. In addition, the orientation may be changed to portrait if appropriate. The date format for all presentations will be 'DDMMMYYYY'.

11.0 REFERENCES

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