ClinBAY

Statistical Analysis Plan (SAP)

M1095

M1095 phase 2b psoriasis study

A phase 2b randomized, double-blind, placebo controlled, multicenter 12-week study with an additional 40-week follow-up assessment of efficacy, safety and tolerability of M1095 in subjects with moderate to severe chronic plaque-type psoriasis.

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Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CC	Complete Cases
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
CSR	Clinical Study Report
csv	Comma-separated values
CV	Coefficient of Variation
DAG	Data Analysis Group
DBL	Database Lock
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EQ-5D-5L	Euro-Quality of Life-5 dimension-5 levels
EQ-POS	Euro-Quality of Life Questionnaire for Psoriasis
HR	Heart Rate
IA	Interim Analysis
IA1	First Interim analysis
IA2	Second Interim analysis
IGA	Investigator's Global Assessment
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ITT	Intent to Treat
LLOQ	Lower Limit Of Quantification
LOCF	Last Observation Carried Forward
LOQ	Limit Of Quantification
LS	Least-Squares
LSM	Least-Squares Means
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MITT12	Modified Intent to Treat up to Week 12
MITT24	Modified Intent to Treat up to Week 24
MITT48	Modified Intent to Treat up to Week 48
N/A	Not Applicable
NRI	Non-Responder Imputation
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PHQ-8	Personal Health Questionnaire-8
PK	Pharmacokinetics

PP	Per Protocol
PP12	Per Protocol up to Week 12
PP24	Per Protocol up to Week 24
PP48	Per Protocol up to Week 48
PRO	Patient Reported Outcomes
PT	Preferred Term
Q2W	Every 2 weeks
Q4	Every 4 weeks
Q4W	Every 4 weeks
Q8	Every 8 weeks
Q8W	Every 8 weeks
QC	Quality Control
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SF-36	Short-Form 36
SI	International System of Units
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures, Listings
TPA	Tipping Point Analysis
VAS	Visual Analog Scale
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
wk	week

Revision History

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Section title impacted (Current number): Outline of change
29-JAN-19	Prior to unblinding at Week 12 (first Interim Analysis)	Creation of initial version	NA
17-MAY-19	Prior to unblinding at Week 12 (first Interim Analysis)	The SAP was amended to clarify/modify some analyses.	**Section 1.3.2 Secondary Objectives:** Clarification of the key secondary objectives for consistency purposes with the protocol. **Section 1.4 Study Design:** Clarification of treatment groups in the response assessment/dose hold period. **Section 2 Interim Analyses (Table 2.1):** • Clarification of data presented for each interim analysis (IA). • Clarification of DMC meetings occurring before IA1. **Section 3 Analysis Populations:** Clarification of the period for the three per protocol populations. **Section 4.1 General Considerations (Table 4.2 and Table 4.3):** • Clarification of derivation of actual treatments for the safety analyses of the induction and overall periods. • Clarification of reporting of efficacy and QOL data. **Section 4.1.1 Imputation Methods for Missing Data:** • **Table 4.4**: Clarification of the timeframe for each IA and of the variables and changes in the planned analyses for these IA. • Clarification of the use of stratifications factors as assigned at randomization (in IRT) in the efficacy analyses. • Clarification of the definition of missing data. **Section 4.1.1.3 Last-Observation Carried Forward (LOCF):** Clarification of the assumption made for LOCF approach in case a subject misses a visit.

Date	Time point	Reason for update	Section title impacted (Current number): Outline of change
			Section 4.1.1.5.1 Imputation Phase: Clarification regarding the fact that the response probabilities specified in this section are provided to explain the methodology. **Section 4.2 Efficacy**: Clarification of using the stratifications factors as assigned at randomization (in IRT) **Section 4.2.1.3 Inferential Analyses:** Clarification of using the stratifications factors as assigned at randomization (in IRT) in the analyses. **Section 4.2.1.4 Sensitivity Analyses:** Clarification that sensitivity analyses are optional. **Section 4.2.2.1 Variables (Table 4.5):** Clarification of endpoints and their type. **Section 4.2.2.2 Descriptive and Inferential Analyses:** Addition of a sensitivity analysis because the subgroup analysis per actual stratification factors cannot serve as sensitivity analysis in case of stratification errors. **Section 4.2.2.2.2 Time-to-event Variables:** Clarification of the time to be used if median time is not estimable. **Section 4.2.3 Exploratory Analyses:** Clarification regarding the fact that sensitivity analyses of the exploratory analyses may not be performed. **Section 4.2.3.1.1 Variables (Table 4.6):** Clarification of type of variables. **Section 4.2.3.1.2 Descriptive Analyses (Table 4.7):** Clarification of the descriptive comparisons and of the displayed treatments for exploratory analyses after Week 12. **Section 4.2.3.1.5 Time-to-event Variables:** Clarification of the time to be used if median time is not estimable. **Section 4.2.3.1.6 Subset Analyses:** Clarification of the reasons to use the MITT48 population for exploratory analyses after Week 12.

Date	Time point	Reason for update	Section title impacted (Current number): Outline of change
			Section 4.2.3.2.1 Variables (Table 4.9): Clarification of type of variables. **Section 4.2.3.2.2 Descriptive Analyses:** • Clarification of the analysis population for the exploratory analyses after Week 24. • **Table 4.10**: Clarification of the treatments presented in the exploratory analyses after Week 24. • **Table 4.15**: Clarification of treatment labels for M1095 120mg. **Section 4.3.2: Descriptive Analyses and Inferential Analyses:** Clarification of the use of stratifications factors as assigned at randomization (in IRT) in the analyses of quality of life data. **Section 4.4.1 Variables:** • Clarification of the variables and/or visits to be presented in the table of demographics and other baseline characteristics • Clarification of the analysis populations for the laboratory assessments. **Section 4.5.1 Variables:** Correction of the analysis populations to be presented in the disposition table. **Section 4.7: Treatment Compliance:** Clarification of the definition of subject-years. **Section 4.8: Previous and Concomitant Therapy:** Change in the analysis population. **Section 4.9 Safety and Tolerability Data:** • **Table 4.13, Table 4.14 and Table 4.15**: Clarification of derivation of actual treatments. • **Table 4.15**: Clarification of treatment labels for M1095 120mg. **Section 4.9.2.5 Adverse Events:** • Clarification of TEAEs per treatment period. • Change of wording for actual treatments. • Clarification that only serious TEAEs will be presented in summary tables and that incidence tables by PT will not be produced. • The identification of common TEAEs were clarified.

Date	Time point	Reason for update	Section title impacted (Current number): Outline of change
			Section 4.10 Pharmacokinetic (PK) Parameters: • Clarification regarding the fact that the PK analyses may be reported in a separate report. • Clarification of treatment groups to be used for PK analyses. **Section 4.12 Subgroup Analyses:** • Clarification of using the actual stratifications factors in the subgroup analyses. • Clarifications that the subgroup analyses can be used as sensitivity analyses only if there were no stratifications errors. **Section 4.12.1 Variables (Table 4.16):** Clarifications of type of variables. Editorial and administrative changes have been made throughout the document.
17-JUL-19	Prior to unblinding at Week 12 (first Interim Analysis)	The SAP was amended to clarify/modify some analyses.	**Section 2 Interim Analyses (Table 2.1)**: Clarification of analyses to be performed at Interim Analyses 1 and/or 2. **Section 3 Analysis Populations**: Adding a reference to a supplement to the SAP. **Section 4.1.1 Imputation Methods for Missing Data**: • Table 4.4: Clarification of analyses to be performed at Interim Analysis 2. • Change of the factors to be used for the efficacy analyses: use of weight category and prior use of biologic therapy stratum derived from the observed values rather than the stratum as assigned at randomization. **Section 4.2 Efficacy**: Use of the actual stratification factors for all efficacy analyses using a CMH test or an ANCOVA and for the descriptive analyses presenting the stratification factors. **Section 4.2.1.4.1 Sensitivity Analysis to Stratification Factors**: Addition of a sensitivity analysis of the primary endpoint using the randomized stratum in case of a large number of stratification errors. **Section 4.2.1.1 Variables**: Clarification of the IGA categories for the shift analysis.

Date	Time point	Reason for update	Section title impacted (Current number): Outline of change
			Section 4.2.1.4.3 Sensitivity Analyses to Missing Data: Clarification of how the extent of missing IGA data will be summarized. **Section 4.2.2.2.1 Binary and Categorical Variables**: • Addition of a sensitivity analysis of the key secondary endpoints in case of a large number of stratification errors. • Removal of the assessment of the homogeneity assumption because this assessment is covered by the subgroup analyses. • Removal of the pairwise comparisons for the shift analyses to keep all possible shift categories. **Section 4.2.3.1.1 Variables and Section 4.2.3.2.1 Variables**: Clarification of the IGA categories for the shift analysis. **Section 4.3 Quality of Life**: Use of the actual stratification factors for all analyses using an ANCOVA. **Section 4.9.2.1 Vital Signs**: Clarifications of the way to identify vital signs abnormalities. **Section 4.12 Subgroup Analyses**: Clarification of the subgroup analyses that can be used for sensitivity analyses due to the change of efficacy analyses. Editorial and administrative changes have been made throughout the document.
24-SEP-19	Prior to unblinding of study statistician, programmers and designated sponsor team members at Week 24 (second Interim Analysis)	The SAP was amended to clarify some points.	**Section 2 Interim Analyses:** • Clarification of tasks to be performed for each designated role (study statistician, statistical programmers and designated sponsor team members). • Table 2.1: Clarification that shift analysis from baseline in IGA (secondary endpoint) as well as PK and immunogenicity analyses (exploratory endpoint) will not be reported after Week 24 for Interim Analysis 2. **Section 4.1.1 Imputation Methods for Missing Data (Table 4.4):** • Correction of the imputation method of the secondary analysis of PASI responses and IGA score of 0 or 1 from Week 24 in the MITT48

Date	Time point	Reason for update	Section title impacted (Current number): Outline of change
			population. • Completion of the imputation method when there was a change in the population but not in the analysis period (exploratory (escalation): IGA score of 0 or 1, IGA score of 0, PASI responses from Week 12 to Week 24 and exploratory (escalation): shift from Week 12 in IGA score category from Week 12 to Week 24), • Removal of the reporting of the shift from baseline in IGA imputed with LOCF from Week 24 to Week 52 for Interim Analysis 2. **Section 4.2.2.2.1 Binary and Categorical Variables**: Correction of the presented visits for the categorical analyses displaying the shift from baseline in IGA score category to be consistent with Table 4.5. **Section 4.9.1 Variables**: Clarification of the data presented in the section. **Section 4.12 Subgroup Analyses**: Clarification of the subgroups of IGA at baseline. Editorial and administrative changes have been made throughout the document.

1 Introduction

1.1 Scope of Document

The Statistical Analysis Plan (SAP) describes the implementation of the planned statistical analysis that will be included in the Clinical Study Report (CSR) for protocol No. AV002: A phase 2b randomized, double-blind, placebo controlled, multicenter 12-week study with an additional 40-week follow-up assessment of efficacy, safety and tolerability of M1095 in subjects with moderate to severe chronic plaque-type psoriasis.

1.2 Study Reference Documentation

Final study protocol (Version 3.0, incorporating CZE-1, dated 16th October 2018) is available at the time of finalization of the SAP.

1.3 Study Objectives

1.3.1 Primary Objective

Type of Objective	Study Objective
Primary Objective	• To evaluate the efficacy of four dose regimens of M1095 compared to placebo on achievement of an Investigator's Global Assessment (IGA) score of 0 or 1 after 12 weeks of treatment in subjects with moderate to severe chronic plaque-type psoriasis.

1.3.2 Secondary Objectives

Type of Objective	Study Objective
Key Secondary Objectives	• To evaluate the efficacy of four dose regimens of M1095 compared to placebo during a 12-week treatment period on secondary endpoints: Psoriasis Area and Severity Index (PASI) 75, PASI 90, PASI 100, change in PASI and shift in IGA.
Secondary Objectives	• To assess the dose-regimen efficacy relationship for M1095 after 12, 24, 36 and 48 weeks of treatment. • To evaluate the longer-term efficacy of M1095 at Week 24 and at Weeks 36 and 48. • To assess the safety and tolerability of M1095.

1.3.3 Exploratory Objectives

Type of Objective	Study Objective
Exploratory Objectives	• Assessment of the quality of life and health outcomes of subjects treated with M1095 over 48 weeks via quality of life instruments evaluated every 12 weeks. • Assessment of the population pharmacokinetics (PK) of various doses and dose regimens of M1095. • Assessment of the development of antidrug antibodies for various doses and dose regimens of M1095. • Assessment of change in efficacy from Week 12 to Week 24 in subjects who undergo dose escalation. • Assessment of M1095 being withheld in subjects with an IGA score of 0 at Week 24.

1.4 Study Design

This is a multi-center, randomized phase 2b study in subjects with moderate to severe chronic plaque-type psoriasis. Approximately 300 subjects will be enrolled at approximately 60 investigator sites in North America and Europe.

At the end of the initial 4-week screening period (Week -4 to Week 0), all eligible subjects will be randomized within strata of prior biologic use (yes/no) and weight (≤ 90 kg/> 90 kg) in a 1:1:1:1:1:1 ratio with approximately 50 subjects randomized into each of six treatment groups as shown below and in Figure 1.1:

1. Placebo at weeks 0, 1, 2, 3, 4, 6, 8, 10 / M1095 120mg at weeks 12, 14, 16 and Q4W.
2. M1095 (30 mg) at weeks 0, 2, 4, 8, 12 and Q4W.
3. M1095 (60 mg) at weeks 0, 2, 4, 8, 12 and Q4W.
4. M1095 (120 mg) at weeks 0, 2, 4, 8, 12 and Q8W.
5. M1095 (120 mg) at weeks 0, 2, 4, 6, 8, 10, 12 and Q4W.
6. Secukinumab (300 mg) at weeks 0, 1, 2, 3, 4, 8, 12 and Q4W.

After randomization at Week 0, the study will consist of:

- 3 consecutive treatment periods:

  A: Induction: a 12-week treatment period (Week 0 to Week 12), which is placebo-controlled,

  B: Maintenance/escalation: a 12-week maintenance/escalation period (Week 12 to Week 24) where all subjects are on active treatment,

C: Response assessment/dose hold: a 24 week response assessment/dose hold period (Week 24 to Week 48) where active treatment is withheld in subjects who have been administered M1095 during the maintenance period and have an IGA score of 0 at the start of this period i.e. at Week 24,

- followed by a final assessment period (Week 48 to Week 52) for safety/efficacy follow-up.

The study will be double-blinded, subject- and investigator- blinded, during all treatment periods up to Week 52 (refer to the unblinding plan for further information about the timepoints when specific teams will be unblinded during the study). Blinding will be maintained prior to Week 52 using masking techniques. Therefore, up to Week 24, subjects randomized to 30 and 60 mg M1095 (Arms 2 and 3) will be administered placebo at Weeks 1, 3, 6, 10 and 14 in order to preserve the blinding. Similarly, subjects randomized to 120 mg M1095 (Arm 4) will receive placebo at Weeks 1, 3, 6, 10, 14 and 16 and subjects randomized to 120 mg M1095 (Arm 5) will receive placebo at Weeks 1, 3 and 14. Subjects randomised to Secukinumab (Arm 6) will receive placebo at Weeks 6, 10 and 14.

At the end of the treatment induction period (Week 12), the subjects randomized to 30 mg or 60 mg M1095 who do not achieve an IGA score of 0 or 1 will be dose-escalated to 120 mg Q4W at Week 12.

Subjects who enter the maintenance/escalation period will receive one of the following treatments until Week 24 and before the dose injection at Week 24:

- **Placebo at weeks 0, 1, 2, 3, 4, 6, 8, 10** and M1095 120 mg at weeks 12, 14, 16 and Q4W.
- **M1095 30 mg at weeks 0, 2, 4, 8,** 12 and Q4W
- **M1095 60 mg at weeks 0, 2, 4, 8,** 12 and Q4W

} if IGA $_{Week12} \leq 1$

- **M1095 30 mg at weeks 0, 2, 4, 8** and M1095 120 mg at week 12 and Q4W
- **M1095 60 mg at weeks 0, 2, 4, 8** and M1095 120 mg at week 12 and Q4W

} if IGA $_{Week12} > 1$

- **M1095 120 mg at weeks 0, 2, 4, 8,** 12 and Q8W
- **M1095 120 mg at weeks 0, 2, 4, 6, 8, 10,** 12 and Q4W
- **Secukinumab 300 mg at weeks 0, 1, 2, 3, 4, 8,** 12 and Q4W.

At the end of the maintenance/escalation period (Week 24), any subjects on M1095 treatment groups who did not undergo dose escalation at Week 12 and achieve an IGA score of 0 at Week 24 will have the study treatment withheld. To maintain the blinding after Week 24, these subjects will receive placebo Q4W. Subjects receiving secukinumab in the first treatment period will continue to receive it at the same dose 300 mg Q4W throughout the study.

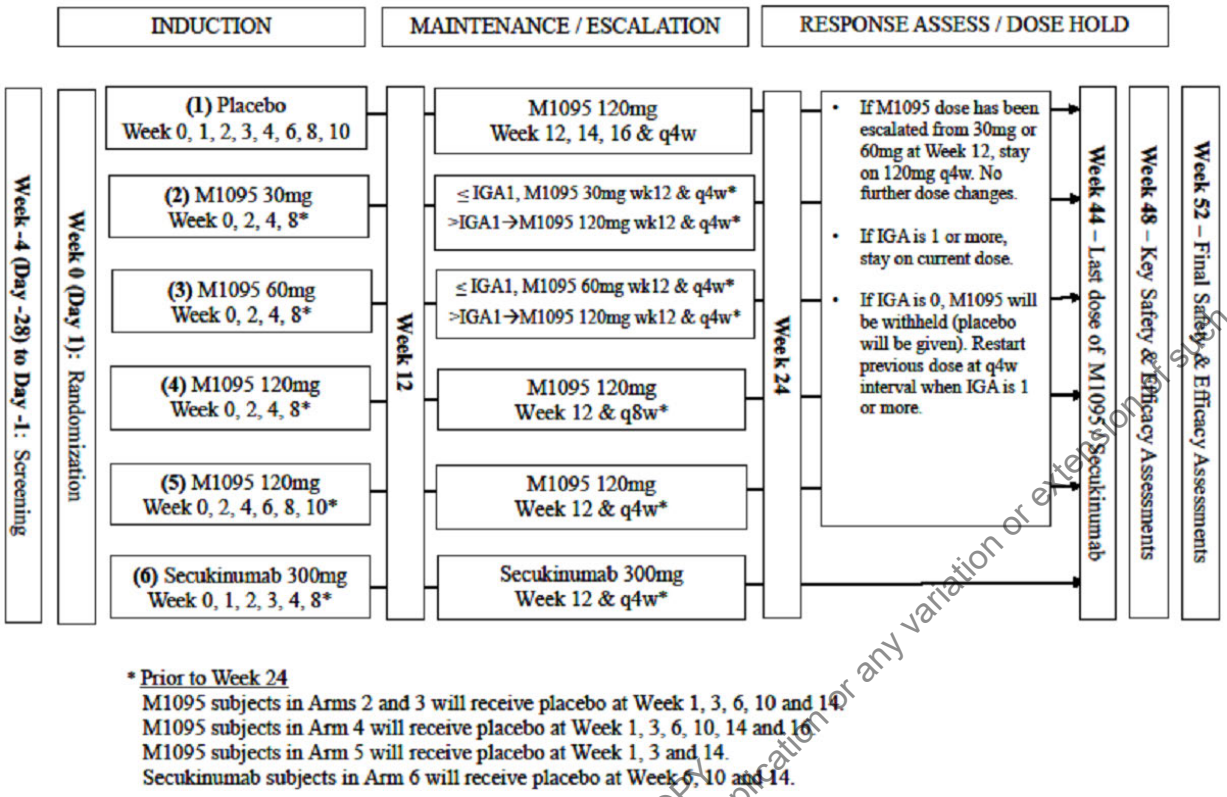
Subjects who enter the response assessment/dose hold period will receive one of the following treatments until Week 44 (or until when the IGA score of subjects with M1095

treatment held at Week 24 subsequently increases to 1 or more* at which time these subjects will be re-administered the study treatment M1095 at the dose they received prior to Week 24):

- **Placebo at weeks 0, 1, 2, 3, 4, 6, 8, 10** and M1095 120 mg at weeks 12, 14, 16 and Q4W } if $IGA_{Week24} > 0$
- **Placebo at weeks 0, 1, 2, 3, 4, 6, 8, 10** and M1095 120 mg at weeks 12, 14, 16 and Q4W until Week 20 and Placebo Q4W* } if $IGA_{Week24} = 0$
- **M1095 30 mg at weeks 0, 2, 4, 8,** 12, and Q4W until Week 20 and Placebo Q4W*
- **M1095 60 mg at weeks 0, 2, 4, 8,** 12, and Q4W until Week 20 and Placebo Q4W* } if $IGA_{Week12} \leq 1$ and $IGA_{Week24} = 0$
- **M1095 30 mg at weeks 0, 2, 4, 8,** 12 and Q4W
- **M1095 60 mg at weeks 0, 2, 4, 8,** 12 and Q4W } if $IGA_{Week12} \leq 1$ and $IGA_{Week24} > 0$
- **M1095 30 mg at weeks 0, 2, 4, 8** and M1095 120 mg at week 12, and Q4W
- **M1095 60 mg at weeks 0, 2, 4, 8** and M1095 120 mg at week 12, and Q4W } if $IGA_{Week12} > 1$
- **M1095 120 mg at weeks 0, 2, 4, 8,** 12 and Q8W until Week 20, and Placebo Q4W*
- **M1095 120 mg at weeks 0, 2, 4, 6, 8, 10,** 12 and Q4W until week 20, and Placebo Q4W* } if $IGA_{Week24} = 0$
- **M1095 120 mg at weeks 0, 2, 4, 8,** 12 and Q8W
- **M1095 120 mg at weeks 0, 2, 4, 6, 8, 10**, 12 and Q4W } if $IGA_{Week24} > 0$
- Secukinumab 300 mg at weeks 0, 1, 2, 3, 4, 8, 12 and Q4W

*If the IGA score of these subjects subsequently increases to 1 or more at any time after Week 24, these subjects will be re-administered the study treatment M1095 at the dose they received prior to Week 24 on a Q4W regimen at the scheduled visits as per protocol until the end of the treatment period. Dose will not be withheld for a second time, irrespective of subsequent IGA scores.

Figure 1.1: Flow chart / Study Design Diagram



* Prior to Week 24
M1095 subjects in Arms 2 and 3 will receive placebo at Week 1, 3, 6, 10 and 14.
M1095 subjects in Arm 4 will receive placebo at Week 1, 3, 6, 10, 14 and 16.
M1095 subjects in Arm 5 will receive placebo at Week 1, 3 and 14.
Secukinumab subjects in Arm 6 will receive placebo at Week 6, 10 and 14.

Exposure to Placebo will be limited to a maximum of 12 weeks during the induction period and a maximum of 20 weeks after Week 24 (i.e. during the response assessment/dose hold period) provided that the subjects maintain a complete remission (i.e. achieving an IGA = 0).

All subjects, irrespective of whether they completed or discontinued the study, will be followed up for safety and potential sustainability of efficacy, for an additional 8 weeks (56 days) after receiving the last dose of study treatment. In addition, subjects who discontinued prior to Week 52 will be contacted monthly as per the study schedule (up to Week 52) to report any AEs, concomitant medications and any new psoriasis treatments.

2 Interim Analyses

Two Interim Analyses (IAs) are planned during this trial:

1. IA1: the first unblinded IA of complete 12-week data for all randomized subjects will occur at the end of the induction period, while the study is still ongoing,

2. IA2: the second IA will occur at the completion of the maintenance/escalation period at Week 24, while the study is still ongoing.

The purpose of both interim analyses is to closely monitor the safety and tolerability data throughout the study. The study will not be terminated early on the basis of either positive efficacy or futility after the review of the first or the second interim analyses. The two interim analyses are also conducted to gather preliminary efficacy information to make possible executive decisions concerning the clinical project.

The first unblinded IA will be managed by an independent Data Monitoring Committee (DMC) and an independent Data Analysis Group (DAG) to preserve the blinding. This data will be shared with firewalled individuals who are not directly involved in the conduct of the study. The DMC will be operational prior to enrolment of the first subject into the study. The composition and operation of the DMC will be described in a DMC charter. The charter will also detail how the communication between the DMC and the sponsor will be firewalled to preserve the blinding and integrity of the study. The analyses that will be included in the first interim analysis are described in Table 2.1 (refer to the corresponding sections of this SAP for further information about the analyses and to Table 4.4 for the imputation methods to be used for each assessment of this planned interim analysis). Unblinded results of IA1 will be reviewed by the DMC members.

The DMC members will meet regularly to review blinded safety data and may decide to carry out additional unblinded safety review, as necessary. In addition, the DMC members will hold two DMC meetings with review of unblinded safety data before IA1.

Laboratory personnel performing the bioanalytical PK sample analysis may receive an open randomization list to enable analysis of relevant samples prior to IA2. In addition, a PK analyst and modelling/simulation scientist may receive an open randomization list to enable preparation of modelling/simulation activities. These individuals will not interact with site or CRO personnel, who is blinded.

For the second unblinded IA, all investigators and subjects will remain blinded to treatment assignments. Once the second interim database lock has occurred after the last subject completed the visit at Week 24 or early discontinued before Week 24 and all data up to Week 24 are cleaned, the study statistician, statistical programmers and designated sponsor team members will be unblinded to perform and/or review analysis of key study endpoints (please refer to the unblinding plan for further details). All sponsor or CRO personnel in direct contact with study sites will remain blinded and be firewalled to prevent accidental unblinding. The second interim analysis will consist of all planned analyses described in Table 2.1. It will present data for all subjects up to Week 24 (Visit 13) that is the minimum analysis cutoff visit for interim 2 and data beyond Week 24 (please refer to Table 4.4 for

further details about the imputation methods). The exact cut-off date for IA2 will be specified at a later stage before unblinding.

Table 2.1 List of assessments and timeframes analyzed for interim analyses

		Timeframe	
Purpose	**Assessment**	**Interim 1**	**Interim 2[a]**
Subject Status	Subject demographics and other baseline characteristics	Screening/ Baseline	Screening/ Baseline
	Analysis populations and/or subject disposition	Up to Week 12	> Week 24
	Medical history, previous and concomitant medications	N/A	> Week 24
	Treatment compliance and/or treatment exposure	Up to Week 12	Up to Week 24
	Protocol deviations	Up to Week 12	Up to Week 24
Efficacy	IGA response: proportion of subjects achieving an IGA score of 0, 1 with an IGA reduction of at least 2 points from baseline (primary endpoint at Week 12)	Up to Week 12	> Week 24
	Proportion of subjects achieving PASI 75/PASI 90/PASI 100	Up to Week 12	> Week 24
	Shift analysis from baseline in IGA	Up to Week 12	Up to Week 24
	Time to first IGA response	N/A	> Week 24
	Absolute change and percent change from baseline in PASI	Up to Week 12	> Week 24
	Absolute change from baseline in percentage of total BSA affected by psoriasis	N/A	> Week 24
	Subgroup analyses	N/A	Up to Week 24
Exploratory Analyses	Exploratory analyses after Week 12	N/A	> Week 24
	Exploratory analyses after Week 24	N/A	> Week 24
	Analyses of Quality of Life (QOL) data	N/A	Up to Week 24
PK Analyses	PK and immunogenicity analyses	N/A	Up to Week 24
Safety and Tolerability	Absolute change from baseline in vital signs and/or vital signs abnormalities and absolute change from baseline in ECG and/or ECG abnormalities.	Up to Week 12	> Week 24
	Clinically laboratory abnormalities	Up to Week 12	> Week 24
	Adverse events (TEAE, serious TEAE, AESI)	Up to Week 12	> Week 24
	Mortality and suicidality and self-injurious behavior	Up to Week 12	> Week 24
	Subgroup analyses	N/A	Up to Week 24
	Any other safety data that may deemed required at the time of IA1/IA2	Up to Week 12	> Week 24

[a]: For IA2, the data presented will be all data up to a cutoff date, which is beyond Week 24 (Visit 13) for the last subject unless specified otherwise. This list of planned analyses for IA2 will be confirmed before unblinding at Week 24.

Information that may unblind the study during the interim analyses must not be reported to study sites or any blinded teams as per the separate unblinding plan until the study has been unblinded.

3 Analysis Populations

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign informed consent.
Intent-to-Treat (ITT)	The Intent-to-Treat (ITT) population includes all subjects randomly allocated to a treatment. Subjects will be analyzed according to planned treatment in the induction period (up to Week 12).
Modified Intent-To-Treat (MITT) including MITT12, MITT24 and MITT48	The Modified Intent-to-Treat up to Week 12 (MITT12) population includes all subjects in the ITT population who receive at least one injection, have a baseline, and at least one post-baseline efficacy assessments up to Week 12. Two additional MITT populations will be defined for exploratory analyses after Week 12 and after Week 24: • MITT24 that includes all MITT12 subjects who received at least one injection during the escalation/maintenance period from Week 12 to Week 24, • MITT48 that includes all MITT12 subjects who received at least one injection during the response assessment/dose hold period from Week 24 to Week 48. Subjects will be analyzed according to planned treatment: • in the induction period (up to Week 12) for MITT12, • in the maintenance/escalation period (from Week 12 to Week 24) for MITT24, • in the response assessment/response hold period (from Week 24 to Week 48) for MITT48.
Per-Protocol (PP) including PP12, PP24 and PP48	The Per-Protocol (PP) population includes all subjects in the MITT population who have no important clinical protocol deviations affecting the assessment of efficacy. Three PP populations will be defined: • PP12 population: PP population up to Week 12 including subjects in the MITT12 population • PP24 population: PP population up to Week 24 including subjects in the MITT24 population • PP48 population: PP population up to Week 48 including subjects in the MITT48 population.

Population	Description
Per-Protocol (PP) including PP12, PP24 and PP48	The PP populations up to Week 12 and Week 24 will be defined during the blinded data review meeting prior to unblinding at Weeks 12 and 24 respectively. Membership of the PP population after Week 24 will be determined based on new protocol deviations occurring after Week 24. Subjects will be analyzed according to planned treatment: • in the induction period (up to Week 12) for PP12, • in the maintenance/escalation period (from Week 12 to Week 24) for PP24, • in the response assessment/response hold period (from Week 24 to Week 48) for PP48.
Safety	The Safety population includes all subjects who receive at least one dose of study treatment. The Safety population will be analyzed per the actual treatment received using a conservative approach that will be described further in Section 4.1.
Pharmacokinetic (PK)	The Pharmacokinetic (PK) population includes all subjects who receive at least one dose of M1095 with valid (i.e. not flagged for exclusion) PK data and with no occurrence of important protocol deviation impacting the PK results during the study. The PK population will be analyzed per the actual treatment received.

Table 3.1: Definition of Analysis Populations

The primary population for efficacy data will be the ITT population. The primary analysis will be repeated on the MITT12 and PP12 analysis populations.

Safety data will be analyzed using the Safety population and PK data using the PK population.

All protocol deviations (PDs) will be tracked and their categorization will be reviewed and evaluated during the blinded data review meetings. Important PDs are defined as deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis. However, only selected clinically important PDs affecting the assessment of efficacy will be excluded from statistical analyses in the PP populations (refer to the supplement to the SAP: Protocol Deviations Exclusion List).

The PP12 and PP24 populations and the PK population will be finalized during the blinded data review meetings.

The precise list of important PDs will be documented and approved at Weeks 12 and 24 before unblinding and at Week 48.

4 Statistical Methods

4.1 General Considerations

Treatment groups (and their labels to be displayed in Tables, Figures, Listings) are defined as follows:

- for all primary and secondary efficacy analyses and analyses of QoL variables unless otherwise indicated:

Randomized Planned Treatment Group	Treatment Label Induction Period / Maintenance /Escalation Period / Response Assessment/ Dose Hold Period / Final Assessment Period 0 12 24 36 48 52 (in weeks)
(1) - Placebo at Week 0, 1, 2, 3, 4, 6, 8 (and / M1095 120 mg at Week 12, 14, 16 and Q4W)	Plac/120mg (x4), Q4
(6) - Secukinumab 300 mg at Week 0, 1, 2, 3, 4, 8 (and 12 and Q4W)	Secukinumab
(2) - M1095 30 mg at Week 0, 2, 4, 8 (and (2a) Q4W if no escalation at Week 12) (2b) M1095 120 mg Q4W if escalation at Week 12)	30mg (x4), Q4
(3) - M1095 60 mg at Week 0, 2, 4, 8 (and (3a) Q4W if no escalation at Week 12) (3b) M1095 120 mg Q4W if escalation at Week 12)	60mg (x4), Q4
(4) - M1095 120 mg at Week 0, 2, 4, 8 (and 12 and Q8W)	120mg (x4), Q8
(5) - M1095 120 mg Q2W at Week 0, 2, 4, 6, 8, 10 (and 12 and Q4W)	120mg (x6), Q4

Table 4.1: Randomized Planned Treatment Groups and their Labels for each Treatment Period for Primary, Secondary Efficacy Analyses and Exploratory Analyses of QoL Variables.

- for all safety analyses unless otherwise indicated:

Table 4.2: Actual Treatment Groups for the Induction Period and their Labels for Safety Analyses of the Induction Period

Actual Treatment Group[a]	Treatment Label Induction Period (Week 0-12)
(1) - Placebo at Week 0, 1, 2, 3, 4, 6, 8	Placebo
(6) - Secukinumab 300 mg at Week 0, 1, 2, 3, 4, 8	Secukinumab
(2) - M1095 30 mg at Week 0, 2, 4, 8	30mg (x4), Q4
(3) - M1095 60 mg at Week 0, 2, 4, 8	60mg (x4), Q4
(4) - M1095 120 mg at Week 0, 2, 4, 8	120mg (x4), Q8
(5) - M1095 120 mg Q2W at Week 0, 2, 4, 6, 8, 10	120mg (x6), Q4
	Total M1095[b]

[a]: Subjects will be assigned to a treatment group based on the actual treatment they received most during the induction period.
[b]: Total M1095 will include the subjects who receive M1095 treatment during the induction period i.e. (2), (3), (4) and (5).

Table 4.3: Actual Treatment Groups for the Overall Period and their Labels for Safety Analyses of the Overall Period

Actual Treatment Group[a]	Treatment Label Overall Period (Week 0-52)
(1) - Placebo at Week 0, 1, 2, 3, 4, 6, 8 (and M1095 120 mg at Week 12, 14, 16 and Q4W)	Plac/120mg (x4), Q4[b]
(6) - Secukinumab 300 mg at Week 0, 1, 2, 3, 4, 8 (and 12 and Q4W)	Secukinumab
(2) - M1095 30 mg at Week 0, 2, 4, 8 (2a) and Q4W if no escalation at Week 12 (2b) and M1095 120 mg Q4W if escalation at Week 12	30mg (x4), Q4
(3) – M1095 60 mg at Week 0, 2, 4, 8 (3a) and Q4W if no escalation at Week 12	60mg (x4), Q4
(3b) and M1095 120 mg Q4W if escalation at Week 12	
(4) - M1095 120 mg at Week 0, 2, 4, 8 (and 12 and Q8W)	120mg (x4), Q8
(5) - M1095 120 mg Q2W at Week 0, 2, 4, 6, 8, 10 (and 12 and Q4W)	120mg (x6), Q4
	Total M1095[c]

[a]: Subjects will be assigned to a treatment group based on the actual treatment they received most during the overall period for all treatment groups except for (1), (2b) and (3b). Regarding (2b) and (3b), subjects will be assigned to a treatment group based on the actual treatment they received most during the induction period.
[b]: Plac/120 mg (x4), Q4 include all subjects who were mostly administered M1095 120 mg from Week 12 to Week 44 having received placebo during the induction period. The data will only be presented from Week 12 onwards for this treatment group.
[c]: Total M1095 will include all subjects who received M1095 at any time during the study i.e. (1), (2), (3), (4) and (5).

All pairwise treatment comparisons will be two-sided at the 5% level, without adjustment for multiplicity unless otherwise specified.

All primary/secondary efficacy and exploratory QoL endpoints will be presented in tables including visits from Week 0 to Week 52 as follows: 0, **1**, **2**, **3**, **4**, **6**, **8**, **10**, **12**, // 14, 16, 20, **24**, // 28, 32, **36**, 40, 44, **48** and 52 (each week number, written in bold, indicates the weeks, at which the pairwise treatment comparisons will be made and // indicates the boundary for the study periods). In regard to interim analyses, only visits up to Week 12 will be included for IA1. IA2 will include data up to Week 24 for all subjects and beyond Week 24 for some subjects depending on the cut-off date (see Section 2). The analyses may be split by period or by combined periods depending on the tables produced for IA1 and IA2.

For all efficacy and quality of life analyses unless specified otherwise, baseline will be defined as the last non-missing assessment prior to the first dose of study medication (planned at Week 0).

For safety analyses, baseline will be defined differently according to the treatment period:

- Induction period: baseline will be defined as the last non-missing assessment prior to the first dose of study medication (planned at Week 0).
- Maintenance/Escalation period, Response Assessment/Dose Hold period and Overall study (all combined periods): baseline will be defined as the last non-missing assessment prior to the first dose of study medication (planned at Week 0) for all subjects randomized to M1095 or Secukinumab. For the subjects randomized to placebo, baseline will be the last non-missing assessment prior to the first dose of M1095 (planned at Week 12).

Unless otherwise stated, continuous data will be summarized by treatment group at each scheduled visit (including baseline) using the following summary statistics: number of non-missing observations (n), arithmetic mean, standard deviation, median, minimum and maximum. In general, summary plots over time will present means and standard errors. The number of decimal places for these statistics will be determined by the number of decimal places of the raw data or derived data where applicable: minimum and maximum will be presented with the same number of decimal places as for the raw data, mean and median with an additional decimal place and the standard deviation and/or standard error with two additional decimal places compared to the raw data.

Categorical data will be summarized in terms of the number of non-missing observations in the analysis population, frequency counts and percentages. Percentages will be displayed with one decimal place.

All statistical analyses will be performed using SAS v9.4 or higher.

4.1.1 Imputation Methods for Missing Data

Intercurrent events, inducing missing assessments, may occur during the course of the study for various reasons such as:

- treatment discontinuation due to an adverse event or a lack of efficacy,
- treatment discontinuation due to subject noncompliance (protocol deviations, missing two consecutive visits).

The potential impact of missing data due to missing a visit, treatment/study discontinuation or loss-to-follow-up on the trial conclusions may be evaluated with several approaches based on different plausible assumptions that account for the uncertainty due to this unobservable data.

These approaches will be Non-Responder Imputation (NRI), Last Observation Carried Forward (LOCF), Multiple Imputation (MI) and Tipping Point Analysis (TPA).

The extent of missing data will be documented with descriptive analyses (refer to Section 4.6.3) and may be assessed with complete case analyses.

The sensitivity analyses for the efficacy endpoints (using the approaches below) that are not pre-planned in Table 4.4 will only be performed if the extent of missing data is greater than 10%. Missing data include any data that are imputed i.e. any missing assessments or subjects who discontinue study treatment but remain in the study.

The methods to handle missing efficacy variables are summarized in Table 4.4.

Table 4.4: Analysis Populations and Imputation Approaches to Handle Missing Data in Function of Efficacy Variables

Type of Variables	Variables	Period (Week – Week)	Analysis Population	Imputation (See Section 4.1.1)	IA1	IA2*	Final
Binary	Primary: IGA score of 0 or 1 at Week 12	0-12	ITT	NRI	●		●
				None (CC)			(●)
				LOCF	●		●
				TPA			(●)
				MI			(●)
			MITT12	NRI	●		●
			PP12	NRI	●		●
	Secondary: PASI responses	0-12	ITT	NRI	●		●
				None (CC)			(●)
				MI			(●)
			MITT12	NRI	●		●
			PP12	NRI	●		●
	Secondary: PASI responses and IGA score of 0 or 1 after Week 12	12-24	ITT	NRI		●	●
				None (CC)			(●)
				LOCF (IGA only)		●	●
			MITT24	NRI		●	●
			PP24	NRI		●	●
		24-52	ITT	NRI			●
				None (CC)		●+	(●)
				LOCF (IGA only)			●
			MITT48	NRI			●
			PP48	NRI			●
	Exploratory: Achievement DLQI of 0 or 1	0-24	ITT	NRI		●	●
		24-48	ITT	NRI			●

Type of Variables	Variables	Period (Week – Week)	Analysis Population	Imputation (See Section 4.1.1)	IA1	IA2*	Final
Binary	Exploratory (escalation): IGA score of 0 or 1, IGA score of 0, PASI responses	12-24	MITT24 & subjects who escalated due to IGA > 1	NRI		●	●
			Week 12 IGA non-responder	NRI			(●)
		12-52	MITT48 & subjects who escalated due to IGA > 1	NRI			●
	Exploratory (dose hold): IGA score of 0 or 1, IGA score of 0, PASI responses, PASI responses during the M1095 dose hold interval, PASI responses after M1095 restart	24-52	MITT48 & subjects who are eligible to dose hold	None (CC)		●+	●
Categorical	Secondary: Shift from baseline in IGA score category	0-12	ITT	LOCF	●		●
		12-24	ITT	LOCF		●	●
		24-52	ITT	LOCF			●
	Exploratory (escalation): Shift from Week 12 in IGA score category	12-24	MITT24 & subjects who escalated due to IGA > 1	LOCF		●	●
			Week 12 IGA non-responder	LOCF			(●)
		12-52	MITT48 & subjects who escalated due to IGA > 1	LOCF			●
	Exploratory (dose hold): Shift from Week 24 in IGA score category	24-52	MITT48 & subjects who are eligible to dose hold	None (CC)			●
Time-to-event	Secondary: Time to first IGA/complete IGA response from baseline	0-52	ITT	None		●+	●
	Exploratory (escalation): Time to first IGA/complete IGA response from Week 12	12-52	MITT24 & subjects who escalated due to IGA > 1	None		●+	●
	Exploratory (dose hold): Time to first IGA ≥ 1 from Week 24, time to first complete IGA response from M1095 restart	24-52	MITT48 & subjects who are eligible to dose hold	None		●+	●

Type of Variables	Variables	Period (Week – Week)	Analysis Population	Imputation (See Section 4.1.1)	IA1	IA2*	Final
Continuous	Secondary: change and percent change from baseline in PASI	0-12	ITT	LOCF	●		●
				None (CC)			(●)
				MI			(●)
		12-24	ITT	LOCF		●	●
				None (CC)			(●)
		24-52	ITT	LOCF			●
				None (CC)		●+	(●)
	Secondary: Absolute change from baseline in percentage of total BSA affected by plaque-type psoriasis	0-12	ITT	LOCF		●	●
				None (CC)			(●)
		12-24	ITT	LOCF		●	●
				None (CC)			(●)
		24-52	ITT	LOCF			●
				None (CC)		●+	(●)
	Exploratory: change from baseline in DLQI, SF-36, EQ-PSO	0-12	ITT	LOCF		●	●
		12-24	ITT	LOCF		●	●
		24-48	ITT	LOCF			●
	Exploratory (escalation): change and percent change from baseline/Week 12 in PASI	12-24	MITT24 & subjects who escalated due to IGA > 1	LOCF		●	●
			Week 12 IGA non-responder	LOCF			(●)
		24-52	MITT24 & subjects who escalated due to IGA > 1	LOCF		●+	●
			Week 12 IGA non-responder	LOCF			(●)
		12-52	MITT48 & subjects who escalated due to IGA > 1	LOCF			●
	Exploratory (dose hold): raw PASI scores, raw PASI scores during the M1095 dose hold interval, after M1095 restart by visits and as a function of time in weeks, change and percent change in PASI from baseline/Week 24	24-52	MITT48 & subjects who are eligible to dose hold	None (CC)		●+	●

Note: (●) indicates the sensitivity analyses that are optional and may be performed.
*: The list for IA2 may not be exhaustive and additional analyses planned for final analysis may be included in IA2 if deemed necessary – this will be confirmed before unblinding.
+: Only data up to a cutoff date, which is beyond Week 24 (Visit 13) for the last subject are presented.

4.1.1.1 Complete Cases (CC)

Where stated, efficacy and quality of life data will be analyzed without any imputation using complete cases to assess the imputation approaches. A complete case will be a subject with no missing data at the considered timepoint and who did not discontinue treatment during this period before this timepoint.

4.1.1.2 Non-Responder Imputation (NRI)

Where specified, missing dichotomous categorical efficacy data (such as clinical response) will be imputed with Non-Responder Imputation (NRI). NRI will assume a non-response for the considered endpoint at any assessment that is missing. This may arise because of a missed assessment, discontinuation due to any reasons from study treatment or study at any time point prior to the cutoff analysis date regardless of whether the subject was a responder at the time of dropout.

NRI will be the primary imputation approach for the primary and key secondary analyses (as specified in Table 4.4).

4.1.1.3 Last-Observation Carried Forward (LOCF)

Where stated, missing categorical and continuous efficacy data will be imputed with Last Observation Carried Forward (LOCF). LOCF approach will consist in carrying forward the value of the last observed non-missing post-baseline assessment to the subsequent scheduled and missing assessment. In case of missing baseline i.e. of absence of an observed assessment prior to the first administration of treatment at Week 0, no imputation of baseline will be performed. In addition, if a subject did not have at least one observed post-baseline assessment during the considered period, no LOCF will be performed on the missing post-baseline assessments.

This approach will assume that any subjects who withdraw the treatment or study due to any reasons maintain the same value that was observed at the last non-missing post-baseline assessment before withdrawing. Similarly, for subjects who miss an assessment, the approach will assume that they maintain the same value that was observed at the last non-missing post-baseline assessment until they return to a visit and a new value is observed.

4.1.1.4 Multiple Imputation (MI)

Missing pre-specified categorical and continuous efficacy data will be imputed with MI under Missing at Random (MAR) assumption using the ITT population (Enders, 2010). MI method will be applied on the data of a given endpoint that are assumed to be MAR.

The current assumption on which the primary analysis is based is that all subjects with a missing response at a given timepoint and/or with missing responses after treatment withdrawal are regarded as non-responder, non-response is assumed regardless of whether the subject responded to the treatment at the time of the drop-out. The secondary analyses using LOCF approach assume that all subjects with missing data at a given timepoint and/or after treatment withdrawal maintain their last observed assessment over time.

MI under MAR assumption assumes that dropouts behave similarly to other subjects in the same treatment group who did not withdraw and continued to be treated with the study treatment. In terms of efficacy, this will estimate the effect of treatment as if all subjects were treated as randomized.

MI will be implemented in three steps using SAS®, version 9.4 or higher (see Figure 4.1.). Depending on the nature of data, some of the steps may have some specificities (Demirtas et al., 2008). MI method assumes a multivariate normal distribution for the continuous variable of interest (e.g. PASI percent change) at each visit.

4.1.1.4.1 Step 1: Imputation Phase

1.a. Initialization

Create a dataset with only one record per subject containing all scheduled assessments at each visit including the baseline assessment, the planned treatment group and all covariates of the imputation model to use SAS® PROC MI. The covariates of the imputation model will be the stratification factors as randomized at the least. Other covariates such as sites, gender may be considered to be added.

1.b. Exploration of the Missing Data Pattern

Check the pattern of missing data. The pattern of missing data may be intermittent or non-monotone, i.e. that a subject may miss an assessment at a planned visit and may return for assessment at the subsequent visits before study completion or treatment withdrawal. That will be the assumption by default. However, the pattern might be monotone for shorter periods such as the induction period up to Week 12 i.e. no subjects miss a scheduled visit before withdrawing treatment or completing the period.

If the pattern for the considered period is intermittent, please go to Step 1.c. Otherwise, go to Step 1.d.

1.c. Partial Imputation of intermittent Missing Data

Generate *n* datasets with a monotone missing pattern using a Markov Chain Monte Carlo (MCMC) method with one single chain, 1000 burn-in iterations at least, and a non-informative Jeffreys prior for each treatment group. The model will include weight category and prior use of biologic therapy stratum derived from the observed values (actual stratum), the baseline and post-baseline assessments. Each intermittent missing value will be imputed using independent samples that are generated by MCMC from the posterior distribution.

The chosen *n* will be 100 imputed datasets at least. A larger number for *n* such as 500 or 1000 might be considered depending on the computational cost. If the baseline assessment was missing, the baseline will be imputed at this step.

1.d. Imputation of Monotone Missing Data

Impute the monotone missing data using a Bayesian framework for each treatment group. The model will include the explanatory variables of actual weight and prior use of biologic therapy stratum, the assessment at baseline and the assessments at all visits. If step 1.c. was skipped, the *n* datasets will be generated at that stage.

No rounding or range restrictions will be applied to imputed values during Steps 1.c and 1.d (Horton et al., 2003). The imputation (Steps 1.c and/or 1.d) will be run multiple times with different random seeds to ensure that the imputation model convergence was reached.

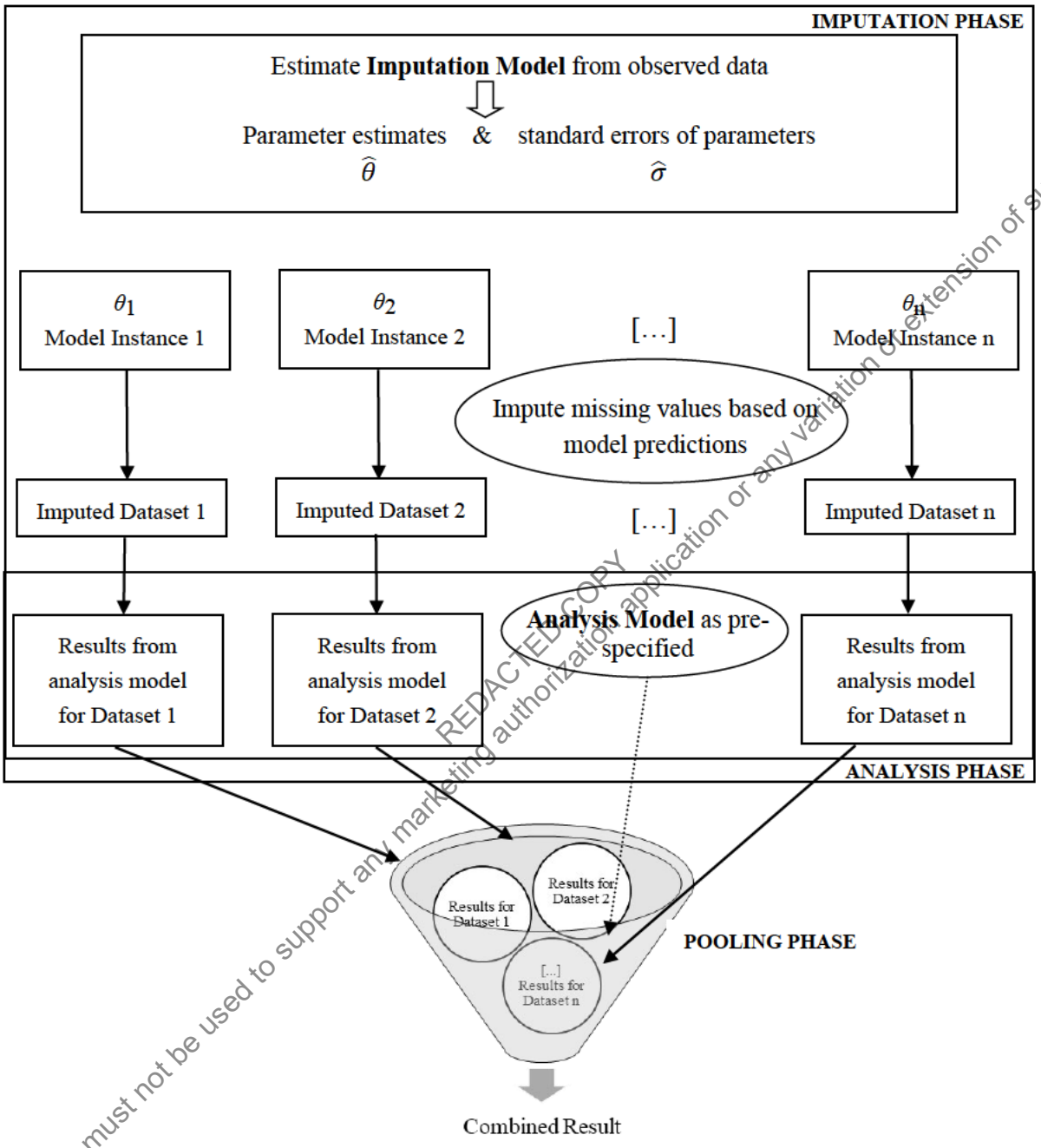


Figure 4.1: Multiple Imputation Process when Imputing *n* Datasets

4.1.1.4.2 Step 2: Analysis Phase

Analyze the *n* imputed datasets separately using a Cochran-Mantel-Haenszel (CMH) analysis for the binary variables and an ANCOVA for the continuous variables.

2.a. Binary Variables

The analysis model and the displayed statistics will be identical to those described for the primary or secondary analyses (refer to Sections 4.2.1.3 and 4.2.2.2.1 for further details). Briefly, a CMH analysis with the actual weight category and prior use of biologic therapy stratum as the stratification factors will be performed for each imputed dataset yielding *n* common CMH ORs with their 95% CI and *n* p-values for each pairwise treatment comparison at a given visit where applicable.

2.b. Continuous Variables

Treatment comparisons will be made for each imputed dataset using an ANCOVA model including planned treatment group, actual weight category and prior use of biologic therapy stratum as factors and the baseline value as a covariate in the model as described in Section 4.2.2.2.3. The Least-Squares Means (LSM) along with the SE and 95% CI for each treatment group and the differences in LSM for each pairwise treatment comparison, their associated SE, 95% CI and p-value will be computed for the *n* datasets at the specified visits.

4.1.1.4.3 Step 3: Pooling Phase

The analysis results from the *n* imputed datasets will be combined into an overall result for each treatment comparison and visit using SAS® PROC MIANALYZE.

3.a. Binary Variables

Rubin's rules for combining results from multiple imputed datasets are based on the assumption that the statistics estimated from each imputed dataset are normally distributed (Rubin D., 1976). Therefore, estimates of ORs that follow a log normal distribution will be pooled after using a log transformation. Similarly, a Wilson-Hilferty transformation will be applied before combining the p-values given that the CMH test is based on a chi-square distributed statistic (Ratitch, B., Lipkovich, I. & O'Kelly, M., 2013).

3.b. Continuous Variables

The LSM along with the SE and 95% CI and the differences in LSM, their associated SE, 95% CI and p-value for each treatment comparison will be combined using Rubin's rule (Rubin D., 1976).

4.1.1.5 Tipping Point Analysis

The tipping point analysis will only be performed on the primary analysis. It will test the null hypotheses of no treatment effect vs. placebo at Week 12 for the primary endpoint (IGA score of 0 or 1 at Week 12, with an IGA reduction from baseline of at least 2 points) as specified in Section 4.2.1.3 for a range of deviations from Missing At Random (MAR) assumption for the control group and the active treatment groups independently. It will include scenarios where the dropout on active treatment has worse outcomes than dropouts on the placebo group.

The purpose of the tipping point analysis is to assess how severe a departure from MAR has to be to overturn the conclusions drawn from the primary analysis. If the departures from MAR assumption to change the statistical significance (evidence of treatment effect) to statistical insignificance (no evidence of treatment effect) are deemed implausible, the tipping point analysis will give supportive evidence to the primary objective under Missing Not At Random (MNAR) assumption (Liublinska, V. and Rubin, D.B., 2014).

4.1.1.5.1 Step 1: Imputation Phase

1.a. Initialization

Create *n* copies of the analysis dataset and combine these datasets. The analysis dataset should be identical in structure and content to the dataset created for MI (refer to Section 4.1.1.4.1).

1.b. Imputation

For any active or control treatment group, different response probabilities (e.g. 0%, 20%, 40% 60%, 80% and 100%) will be applied successively to impute the missing values of IGA response at Week 12 and similarly for the placebo group. Missing IGA responses at Week 12 will be randomly imputed with 0 (i.e. non-responder) and 1 (i.e. responder) with the chosen response probabilities. The different steps below will be described with the aforementioned response probabilities provided as an example: 0%, 20%, 40% 60%, 80% and 100%.

This imputation will be performed by generating random numbers from a Bernoulli distribution to perform the imputation on the missing IGA responses at Week 12 in two steps:

i. Impute the missing values of the placebo group by generating random numbers from a Bernoulli distribution using a response probability of 0% for example.
ii. Impute the active/control treatment groups with the same methodology using a response probability of 20% for example.

4.1.1.5.2 Step 2: Analysis Phase

Analyze the *n* imputed datasets separately using a CMH analysis as described in Section 4.1.1.4.2.

4.1.1.5.3 Step 3: Pooling Phase

The analysis results from the *n* imputed datasets will be combined into an overall result for each treatment comparison and visit using SAS® PROC MIANALYZE as described in Section 4.1.1.4.3 - binary variables.

4.1.1.5.4 Step 4: Repetition Phase

Return to Step 1 using the next combination of response probability for the missing IGA response at Week 12: 0% for the placebo group and 40% for the active/control treatment group (0/0.4) and so forth.

For the following response probability combinations 0/0, 0/1, 1/0, 1/1, missing data will be imputed using one single dataset and analyzed as described in Section 4.1.1.4.2.

4.2 Efficacy

4.2.1 Primary Analysis

The primary objective is to assess the efficacy of four dose regimens of M1095 versus placebo on IGA score in subjects with moderate to severe chronic plaque-type psoriasis at Week 12.

All subjects within the ITT population will be included in the primary efficacy analysis.

4.2.1.1 Variable

The primary variable is the response rate for the IGA score at Week 12, which is defined as the proportion of subjects who achieve an IGA score of 0 or 1 at Week 12 and with an IGA reduction from baseline of 2 points or more at Week 12. This variable will be denoted by "IGA response" in subsequent sections.

Baseline IGA score is defined as the last non-missing IGA score prior to the first dose of study medication.

IGA response for subjects with missing baseline and/or Week 12 IGA score will be imputed using NRI approach. NRI consists in imputing any missing IGA score response as a non-response (see Section 4.1.1.2 for further information).

4.2.1.2 Descriptive Analyses

Descriptive summary of the proportion of subjects achieving the primary endpoint will be tabulated by treatment group and also by treatment group and actual stratum (≤ 90 kg and prior biologic use, ≤ 90 kg and no prior biologic use, > 90 kg and prior biologic use, > 90 kg and no prior biologic use) i.e. derived from the observed values of body weight and prior biologic use for all visits up to Week 12. Summary statistics will include the number and percentage of subjects achieving an IGA response for all visits up to Week 12.

The 95% confidence intervals of the binomial proportions will be estimated using the Clopper-Pearson exact interval.

The primary variable will also be listed by treatment group, subject and visit.

Bar plots of IGA responder rates (95% CI) by treatment group overall and for each stratum will be created.

4.2.1.3 Inferential Analyses

The IGA responder rates at Week 12 will be compared between treatment groups using CMH test stratified by actual prior use of biologic therapy (yes/no) and body weight stratum (≤ 90 kg, > 90 kg) as observed at baseline. The following four null hypotheses will be individually tested at the unadjusted two-sided 5% significance level:

- H_1: M1095 30 mg Q2W × 3, followed by 30 mg Q4W × 1, is not different from placebo with respect to achievement of IGA response,
- H_2: M1095 60 mg Q2W × 3, followed by 60 mg Q4W × 1, is not different from placebo with respect to achievement of IGA response,
- H_3: M1095 120 mg Q2W × 3, followed by 120 mg Q4W × 1, is not different from placebo with respect to achievement of IGA response,
- H_4: M1095 120 mg Q2W × 6 is not different from placebo with respect to achievement of IGA response

resulting in the following comparisons at Week 12 between the treatment groups/regimens:

- M1095 30 mg wk 0, 2, 4, 8
- M1095 60 mg wk 0, 2, 4, 8
- M1095 120 mg wk 0, 2, 4, 8
- M1095 120 mg wk 0, 2, 4, 6, 8, 10

} vs. placebo wk 0, 1, 2, 3, 4, 6, 8, 10.

The CMH Odds Ratio (OR) for the comparison of each M1095 treatment arm to placebo will be presented along with its 95% CI and associated p-value.

4.2.1.4 Sensitivity Analyses

Several sensitivity analyses may be performed to assess the robustness of the primary analysis to changes among stratification factors as randomized, analysis population, missing data and definition of the primary endpoint (refer to Table 4.4 and Section 4.1.1).

4.2.1.4.1 Sensitivity Analysis to Stratification Factors

The assumption of homogeneity of the OR over the actual strata will be tested by the Breslow-Day statistic at a 10% significance level for each pairwise comparison to placebo.

In the event of non-homogeneity of the OR for a particular test, the corresponding treatment OR will be calculated separately with its 95% confidence interval for each stratum. Owing to the limited sample size in each stratum, no p-value will be reported, the main purpose of this assessment being to evaluate the relative magnitude of the treatment difference in each stratum.

In case of a large number of stratification errors, the primary analysis may be repeated as described in Section 4.2.1.3 but using the per randomized stratum i.e. as entered by the sites into the IRT system at the randomization.

4.2.1.4.2 Sensitivity Analyses to Analysis Population

Sensitivity analyses will be performed identically to the primary analysis but using the following populations: MITT12 and PP12.

4.2.1.4.3 Sensitivity Analyses to Missing Data

The primary analysis may be replicated using the ITT population:

- with missing data being imputed with:
  - LOCF (see Section 4.1.1.3),
  - MI (see Section 4.1.1.4)
  - Tipping point analysis (see Section 4.1.1.5)
- on complete cases (see Section 4.1.1.1)

(refer to Table 4.4 for further details about the pre-planned analyses).

In addition, the extent of missing IGA data will be summarized by visit and treatment group.

Figures of individual raw IGA as well as mean raw IGA may be provided for the subgroups of complete cases and cases with missing IGA assessment at Week 12, by treatment group and over time up to Week 12.

4.2.1.4.4 Sensitivity Analysis to Endpoint Definition

To assess the robustness of inferences to the definition of the primary endpoint, the same analysis as in Section 4.2.1.3 will be repeated by considering a different definition for an IGA responder: "complete IGA response" where a complete IGA response is defined as an IGA score of 0 and with an IGA reduction from baseline of 3 points or more.

4.2.2 Secondary Analyses

All subjects in the ITT population will be included in the secondary efficacy analyses.

The main estimands of the secondary objectives of longer-term efficacy after Week 12:

- for the binary endpoint IGA (and the key secondary endpoints PASI 75 / PASI 90 / PASI 100) is the difference in response proportions between treatment conditions at:
  - Week 24,
  - Week 36,
  - Week 48
- for the continuous endpoint PASI score (and the other secondary endpoint percentage of total BSA affected by plaque-type psoriasis) is the difference in means between treatment conditions in the change from baseline to:
  - Week 24,
  - Week 36,
  - Week 48

in the ITT population regardless of whether or not escalating to the M1095 120 mg from Week 12 or having dose held at Week 24 had occurred.

4.2.2.1 Variables

The secondary efficacy variables will include:

- IGA-derived endpoints,
- PASI-derived endpoints

as defined in Table 4.5 below.

Table 4.5: Secondary Efficacy Endpoints and Variables

Endpoints	Type of Variables	Secondary Variables
IGA-derived endpoints	Binary	• IGA response: proportion of subjects achieving an IGA score ≤ 1 and with an IGA reduction from baseline of 2 points or more at all visits up to Week 48.
	Categorical	• shift from baseline in IGA score category at all visits up to Week 48.
	Time-to-event	• time to first IGA response from baseline. • time to first complete IGA response from baseline.
PASI& BSA-derived endpoints	Binary	• proportion of subjects achieving PASI 75/PASI 90/PASI 100 at all visits up to Week 48 (key secondary variables).
	Continuous	• absolute change and percent change from baseline in PASI score at all visits up to Week 48. • absolute change from baseline in percentage of total BSA affected by plaque-type psoriasis.

The proportion of subjects in the eight categories of IGA (see below) will be determined for the shift analysis from baseline in IGA score category at each post-baseline visit from considering the individual IGA score at baseline in order to assess:

- worsening/stability in IGA score from baseline,
- improvement in IGA score from baseline.

	IGA Score at each post-Baseline Visit				
IGA Score at Baseline	0	1	2	3	4
3	Improvement				Worsening/ Stability
4					

PASI 75/PASI 90/PASI 100 response will be derived from the overall PASI score ranging from 0 for no signs of psoriasis up to 72 for the most severe form of the disease.
A PASI 75, PASI 90 responder is defined as a subject achieving an improvement (i.e. a reduction) of at least 75% and 90% respectively in PASI score compared to baseline. A PASI

100 responder will be a subject achieving a complete clearing of psoriasis at a post-baseline visit that is a PASI score of 0.

An improvement in PASI is represented by a decrease in PASI score from baseline. Percent change in PASI from baseline will be computed by dividing the change from baseline in PASI by the baseline PASI score and multiplying this result by 100.

The methods to handle missing binary, shift and continuous secondary efficacy variables are summarized in Table 4.4.

In the next subsections, the analysis of the secondary variables will be handled according to the type of variables: binary for proportions, categorical for shift from baseline, or continuous for change from baseline and/or percent change variables.

4.2.2.2 Descriptive and Inferential Analyses

4.2.2.2.1 Binary and Categorical Variables

The proportions of the binary variables will be summarized by treatment group at each visit up to Week 52. Pairwise comparisons vs. placebo and pairwise comparisons across M1095 treatment arms will be made at each visit up to Week 12 and at Weeks 24, 36 and 48 using the CMH test of 2-by-2 tables stratified by actual prior use of biologics (yes/no) and body weight stratum (≤ 90 kg, > 90 kg) in the same way as for the primary analysis (please refer to Section 4.2.1.3). No formal statistical testing will be performed between M1095 treatment arms and Secukinumab as the Secukinumab arm is for reference only. However, Secukinumab will be compared to placebo using the same methodology. In case of a large number of stratification errors, the key secondary analyses might be repeated as described in Section 4.2.1.3 but using the per randomized stratum as entered into the IRT system by the sites.

The assumption of homogeneity of association between treatment and the binary variables in the different actual strata will be tested at Weeks 12, 24, 36 and 48 for all pairwise comparisons M1095 vs. placebo at 10% significance level using the Breslow-Day test as explained in Section 4.2.1.4.

For the categorical analyses, the proportion and number of subjects in each IGA category at a given visit from baseline will be presented by treatment group and over time at each visit up to Week 12 for the induction period, from Week 12 to Week 24 for the maintenance/escalation period and from Week 24 to Week 48 for the response assessment/dose hold period.

Bar plots and line plots of the responder rates with 95% CI will be provided by treatment group and over time up to Week 48 overall.

The binary secondary efficacy variables will be listed by treatment group and over time.

4.2.2.2.2 Time-to-event Variables

Time-to-event variables will be presented by treatment group with tables of Kaplan-Meier (KM) estimates as well as KM curves. For KM curves, the number of subjects that are still at risk (Pocock et al, 2012) will also be displayed under the time axis. In addition, the following descriptive statistics will be presented by treatment group: the number and percentage of IGA response, complete IGA response and censored data at each visit and the median time (or other estimable percentile (say 75%) if median is not estimable) to IGA response or complete IGA response along with its 95% confidence interval.

4.2.2.2.3 Continuous Variables

The raw PASI score, absolute change and percent change from baseline in PASI score will be presented by treatment group and over time for all visits up to Week 52 using summary statistics and listings. Mean of change from baseline in PASI and its associated standard error will be displayed graphically over time by treatment group.

For the percent change in PASI, treatment comparisons vs. placebo and between M1095 treatment groups will be tested at each specified visit up to Week 48. The treatment LSM along with the corresponding SE, 95% CI and the LSM differences along with its SE, 95% CI and p-value will be obtained at each visit separately using an analysis of covariance (ANCOVA) model. The ANCOVA will include the planned treatment group, actual prior biologic and weight stratum as factors and the baseline value as a covariate. The residuals from the ANCOVA model will be examined to check that the assumptions of normality, independence and homoscedasticity hold.

4.2.3 Exploratory Analyses

The exploratory analyses are planned:

- **After Week 12**: to evaluate the change in efficacy from Week 12 to Week 24 in subjects who undergo dose escalation or maintenance at Week 12 in the MITT population who enter the maintenance/escalation period (MITT24),
- **After Week 24**: to explore the effect of withholding M1095 at Week 24 in IGA score of 0 responders in the MITT population who enter the response assessment/dose hold period (MITT48).

Sensitivity analyses for the exploratory analyses after Week 12 and Week 24 will not be performed unless deemed necessary.

4.2.3.1 Exploratory Analyses after Escalation at Week 12

At Week 12, subjects randomized to M1095 30 mg or M1095 60 mg are planned to undergo a dose escalation to M1095 120 mg if they fail to achieve an IGA response i.e. if they have an IGA > 1.

The assessment of change in efficacy from Week 12 to Week 24 will be investigated in the subgroup of subjects who were randomized to 30 mg and 60 mg M1095 at Week 0 and who

underwent dose escalation at Week 12 due to IGA > 1 during the period starting from Week 12 to Week 24 by treatment sequence of the induction and maintenance/escalation periods (the treatment sequence will be the combination of the initial randomized treatment and the administered treatment at Week 12). In addition, the change in longer term efficacy to Week 48 in this subgroup of subjects will be explored.

The exploratory analyses after Week 12 will be conducted in the MITT24 population.

4.2.3.1.1 Variables

The post-Week 12 exploratory objective will be examined with the help of these variables:

Endpoints	Type of Variables	Exploratory Variables
IGA-derived endpoints	Binary	• proportion of subjects with an IGA response at all visits from Week 12. • proportion of subjects with a complete IGA response at all visits from Week 12.
	Categorical	• shift from Week 12 in IGA score category at all post-Week 12 visits.
	Time-to-Event	• time to first IGA response from Week 12. • time to first complete IGA response from Week 12.
PASI-derived endpoints	Binary	• proportion of subjects achieving PASI 75/PASI 90/PASI 100 response at all visits from Week 12.
	Continuous	• raw PASI score at all visits from Week 12. • absolute change and percent change from baseline in PASI score at all visits from Week 12. • absolute change and percent change from Week 12 in PASI score at all visits from Week 12.

Table 4.6: Exploratory Endpoints and Variables Related to Post-Week 12 Dose Escalation/Maintenance Analyses

The shift from Week 12 in IGA score category at each post-Week 12 visit will be determined from considering the individual IGA score at Week 12 in order to assess:

- worsening/stability in IGA score from baseline,
- improvement in IGA score from baseline.

	IGA Score at each post-Week 12 Visit				
IGA Score at Week 12	0	1	2	3	4
0		Worsening			
1			Worsening		
2		Improvement	Stable	Worsening	
3				Response	
4					

The two time-to-event endpoints will measure the planned time interval in weeks between the Week 12 assessment and the first assessment from Week 12 with an IGA response, or a complete IGA response, respectively. Data will be censored at the last assessment visit if the event had not occurred up to that point.

The continuous variables will be imputed with LOCF whereas the categorical variables will be imputed with NRI. No other imputations will be implemented for these exploratory variables unless indicated otherwise.

4.2.3.1.2 Descriptive Analyses

Data will be summarized over time according to the assigned treatment sequence for both induction (Week 0-12) and maintenance/escalation (Week 12-24) periods (refer to Table 4.7) in the subgroup of subjects randomized to M1095 30 and 60 mg at Week 0 who dose escalated:

(2b) 30mg (x4), Q4/Esc to 120mg

(3b) 60mg (x4), Q4/Esc to 120mg.

		Treatment Label	
	Dose Escalation due to IGA > 1 at Week 12?	**Maintenance/ Escalation Period**	**Response Assessment/ Dose Hold Period**
Planned Treatment Group with Dose Escalation		**12 2 4 52 (in weeks)**	
(1) - Placebo at Week 0, 1, 2, 3, 4, 6, 8 (and /M1095 120 mg at Week 12, 14, 16 and Q4W)	N/A	Plac/ 120mg (x4), Q4	
(6) - Secukinumab 300 mg at Week 0, 1, 2, 3, 4, 8 (and 12 and Q4W)	N/A	Secukinumab	
(2) - M1095 30 mg at Week 0, 2, 4, 8 (and: (2a) Q4W if no escalation at Week 12)	No	30mg (x4), Q4/ No Esc	
(2b) M1095 120 mg Q4W if escalation at Week 12)	**Yes**	**30mg (x4), Q4/ Esc to 120mg**	**30mg (x4), Q4/ Esc to 120mg**
(3) - M1095 60 mg at Week 0, 2, 4, 8 (and: (3a) Q4W if no escalation at Week 12)	No	60mg (x4), Q4/ No Esc	
(3b) M1095 120 mg Q4W if escalation at Week 12)	**Yes**	**60mg (x4), Q4/ Esc to 120mg**	**60mg (x4), Q4/ Esc to 120mg**
(4) - M1095 120 mg at Week 0, 2, 4, 8 (and 12 and Q8W)	N/A	120mg (x4), Q8	
(5) - M1095 120 mg Q2W at Week 0, 2, 4, 6, 8, 10 (and 12 and Q4W)	N/A	120mg (x6), Q4	

Note: The only treatment groups displayed in all exploratory analyses after Escalation at Week 12 are the treatment groups displayed in bold in the table. The other treatment groups (identified by rows in grey) are only displayed for completeness and information.

Table 4.7: Planned Treatment Groups with Dose Escalation and their Labels for each Treatment Period for Exploratory Analyses after Week 12.

The variables in Table 4.6 will be presented per treatment group for the Maintenance/ Escalation Period: at Weeks 12, 14, 16, 20 and 24 and the Response Assessment/Dose Hold Period.

No formal inferential analyses will be conducted. Comparisons of treatment groups (1), (4), (5) and (6) will be presented elsewhere. For treatment groups (2) and (3) after Week 12, comparisons will be biased due to the Week 12 treatment change being based on post-randomization unfavorable event of lack of efficacy. Comparisons after Week 12 based on descriptive statistics will be made between treatment groups of subjects who dose escalated in subjects who were initially randomized to M1095 30 mg and M1095 60 mg at Week 0.

4.2.3.1.3 Binary and Categorical Variables

The number and proportion of subjects for each binary variable of Table 4.6 will be described in a tabulated and graphical manner per treatment group for each visit with the time in weeks since Week 12. The 95 % exact CI of the proportion will also be presented.

Line plots will present the responder proportions (and its 95% CI) by treatment group and over time from Week 12 and possibly, from Week 0.

For the shift analyses, the proportion and number of subjects in each category will be presented by treatment group and over time.

4.2.3.1.4 Continuous Variables

The raw PASI score, absolute and percent change from baseline will be described for all visits in the same tabular and graphical way as in Section 4.2.2.2.3 per treatment group.

Means of absolute change from baseline in PASI and their associated standard error will be displayed graphically over time by treatment group.

These descriptive statistics above will also be produced for change and percent change from Week 12 in PASI.

A mean/SE plot of improvement in PASI over time will also be created, showing the effect of dose escalation from Week 12.

4.2.3.1.5 Time-to-event Variables

Time-to-event variables will be graphically presented by treatment group using Kaplan-Meier curves. The number of subjects that are still at risk (Pocock et al, 2012) will also be displayed under the time axis. In addition, the following descriptive statistics will be presented by treatment group:

- The number and percentage of IGA response, complete IGA response and censored data at each visit,
- The median time (or other percentile) to IGA response or complete IGA response along with its 95% confidence interval.

4.2.3.1.6 Subset Analyses

The exploratory post-Week 12 analyses will be repeated to assess the longer-term efficacy in the MITT48 population that includes the MITT subjects who completed the maintenance/ escalation period and who entered the dose assessment/dose hold period.

Given the study design that allows subjects to dose escalate to the highest dose of M1095 at Week 12 following post-randomization efficacy assessments, selected exploratory analyses may be performed in a subset of subjects with similar post-baseline efficacy characteristics. The purpose of this population is to investigate the differences in a descriptive manner between subjects with similar post-baseline efficacy characteristics at the start of the considered period who had a dose change and those who did not have a dose change. Therefore, an additional population may be derived for this purpose:

Population	Description
Week 12 IGA Non-Responder Population	Week 12 IGA non-Responder Population is a subset of MITT12 population. This population includes all MITT12 subjects who are classified as IGA non-responders at Week 12 (i.e. with IGA > 1). Subjects will be analyzed according to planned treatment in the maintenance/escalation period (from Week 12 to Week 24).

Table 4.8: Definition of Additional Analysis Population for Exploratory Analyses

The exploratory post-Week 12 analyses may be repeated in the Week 12 IGA non-Responder Population. The aim is to compare all treatment groups from Week 12 to Week 24 in the MITT subjects who enter the maintenance/escalation period but who had an unfavorable efficacy event at Week 12 (all treatment groups will be included except for (2a) and (3a) – refer to Table 4.7).

4.2.3.2 Exploratory Analyses after Withholding/Restarting M1095 from Week 24

From Week 24, subjects receiving M1095 who were not escalated from M1095 30 mg or M1095 60 mg at Week 12 will have their M1095 treatment withheld (placebo will be given) if their IGA score equals 0 at Week 24. If their IGA score is 1 or more at Week 24, these subjects will stay on current dose.

Then, withheld subjects will restart M1095 at the previous dose level (Q4W) at the first visit post-Week 24 when their IGA is 1 or more.

The exploratory analyses after Week 24 will be conducted in the MITT48.

4.2.3.2.1 Variables

The post-Week 24 exploratory objectives will be explored with these variables:

Endpoints	Type of Variables	Exploratory Variables
IGA-derived endpoints	Binary	• proportion of subjects with an IGA response at all visits from Week 24. • proportion of subjects with a complete IGA response at all visits from Week 24. • proportion of subjects requiring M1095 restart after withholding study drug at each visit from Week 24. • cumulative proportion of subjects with M1095 restarted after withholding study drug at each visit from Week 24.
	Categorical	• shift from Week 24 in IGA score category at all post-Week 24 visits.
	Time-to-Event	• time to first IGA ≥ 1. • time from M1095 restart to first complete IGA response during Week 24-48 interval.
PASI-derived endpoints	Binary	• proportion of subjects achieving PASI 75/PASI 90/PASI 100 response at all visits from Week 24. • proportion of subjects achieving PASI 75/PASI 90/PASI 100 response by visit during the M1095 dose hold interval. • proportion of subjects achieving PASI 75/PASI 90/PASI 100 response at all visits after M1095 restart.
	Continuous	• raw PASI score at all visits from Week 24. • absolute change and percent change from baseline in PASI score at all visits from Week 24. • absolute change and percent change from Week 24 in PASI score at all visits from Week 24. • raw PASI score by visit during the M1095 dose hold interval. • raw PASI score at all visits after M1095 restart. • raw PASI score after M1095 restart as a function of time in weeks.

Table 4.9: Exploratory Endpoints and Variables Related to Post-Week 24 Dose Hold/Restart Analyses

Missing continuous or categorical variables will not be imputed. Time-to event data will be censored at the last assessment visit if the event had not occurred up to that point.

4.2.3.2.2 Descriptive Analyses

Data will be summarized according to the assigned treatment sequence for both maintenance/escalation (Week 12-24) and response assessment/dose hold (Week 24-48) periods (see Table 4.10):

(1.i) Plac/120mg (x4), Q4/Hold

(1.j) Plac/120mg (x4), Q4/No Hold

(2a.i) 30mg (x4), Q4/No Esc/Hold

(2a.j) 30mg (x4), Q4/No Esc/No Hold

(3a.i) 60mg (x4), Q4/No Esc/Hold

(3a.j) 60mg (x4), Q4/No Esc/No Hold

(4.i) 120mg (x4), Q8/Hold

(4.j)120mg (x4), Q8/No Hold

(5.i) 120mg (x4), Q4/Hold

(5.j) 120mg (x4), Q4/No Hold.

As treatment assignment is based on post-randomization efficacy results, only descriptive treatment summaries will be reported. No inferential analyses are planned. More specifically, the descriptive comparisons with exploratory nature will be made:

- between treatment group of subjects who had their dose hold from Week 24
- between treatment group of subjects who had not their dose hold from Week 24

in the MITT48 population who were initially randomized to any of the M1095 at Week 0 and who did not dose escalated.

Binary, continuous and time-to-event data will be reported in a way similar to the corresponding endpoints for the post-Week 12 exploratory analyses (refer to Sections 4.2.3.1.3, 4.2.3.1.4 and 4.2.3.1.5 for further information).

		Treatment Label
	IGA = 0 at Week 24?	**Response Assessment/Dose Hold Period**
Planned Treatment Group and Dose Escalation/Hold		**(Week 24-52)**
(1) - Placebo at Week 0, 1, 2, 3, 4, 6, 8 (and (1.i) M1095 120 mg at Week 12, 14, 16, 20 and dose hold from Week 24)	**Yes**	**Plac/120mg (x4), Q4/Hold**
(1.j) M1095 120 mg at Week 12, 14, 16 and Q4W	No	Plac/120mg (x4), Q4/No Hold
(6) - Secukinumab 300 mg at Week 0, 1, 2, 3, 4, 8 (and 12 and Q4W)	N/A	
(2) - M1095 30 mg at Week 0, 2, 4, 8 (and (2a.i) Q4W and dose hold from Week 24)	**Yes**	**30mg (x4), Q4/No Esc/Hold**
(2a.j) Q4W)	No	30mg (x4), Q4/No Esc/No Hold
(2b) M1095 120 mg Q4W if escalation at Week 12)	N/A	
(3) - M1095 60 mg at Week 0, 2, 4, 8 (and (3a.i) Q4W and dose hold from Week 24)	**Yes**	**60mg (x4), Q4/No Esc/Hold**
(3a.j) Q4W)	No	60mg (x4), Q4/No Esc/No Hold
(3b) M1095 120 mg Q4W if escalation at Week 12)	N/A	
(4) - M1095 120 mg at Week 0, 2, 4, 8 (and (4.i) 12 and Q8W)	**Yes**	**120mg (x4), Q8/Hold**
(4.j) 12 and Q8W and dose hold from Week 24)	No	120mg (x4), Q8/No Hold
(5) - M1095 120 mg Q2W at Week 0, 2, 4, 6, 8, 10 (5.i) 12 and Q4W and dose hold from Week 24)	**Yes**	**120mg (x6), Q4/Hold**
(5.j) 12 and Q4W	No	120mg (x6), Q4/No Hold

Note: The only treatment groups displayed in all exploratory analyses after M1095 dose hold/restart from Week 24 are the treatment groups identified by rows in white in the table. The other treatment groups identified by rows in grey are only displayed for completeness and information and will be presented in other tables. The descriptive comparisons will be made between treatment group of subjects who had their dose hold from Week 24 (in bold) and separately between treatment group of subjects who had no dose hold from Week 24.

Table 4.10: Planned Treatment Groups with Dose Escalation/Hold and their Labels for each Treatment Period for Exploratory Analyses after Week 24.

4.3 Quality of Life

All subjects in the ITT population will be selected for the analyses of Quality of Life (QoL) variables.

4.3.1 Variables

The QoL variables are:

- Change from baseline in Dermatology Life Quality Index (DLQI) total score and in DLQI subscales,
- Achievement of DLQI of 0 or 1 (binary variable),
- Change from baseline in the norm-based Short Form 36 (SF-36) scores for the eight sections and for the physical and mental summary components,
- Change from baseline in EuroQuality of Life Questionnaire for Psoriasis (EQ-PSO) as measured by VAS and EQ-PSO score for the 7 dimensions.

The derivations of QoL scores are described in the Appendices on page 68.

LOCF will be used to impute any missing values for the continuous variables and NRI for the binary variable (refer to Section 4.1.1.3).

4.3.2 Descriptive Analyses and Inferential Analyses

The raw continuous QoL variables at baseline and post-baseline visits as well as their change from baseline will be presented by randomized treatment group at each visit up to Week 48 using summary statistics, listings and appropriate graphical methods.

Treatment comparisons of continuous QoL variables will be assessed at all visits up to Week 12 by an ANCOVA including planned treatment group, actual prior biologic and weight stratum as factors and the baseline value as a covariate in the model. The treatment LSM, the corresponding SE and 95% CI and the pairwise LSM difference, the corresponding SE, 95% CI and p-value will be presented. This analysis will be replicated at Weeks 24, 36 and 48.

The proportions of the binary variable will be examined and reported as described in Section 4.2.2.2.1.

The analyses of QoL variables may be replicated using complete cases. Additional exploratory analyses of QoL may be performed.

4.4 Subject Demographics/Other Baseline Characteristics

The subject demographics and other baseline characteristics will be reported in the analysis populations specified in Table 4.11.

4.4.1 Variables

The variables are the demographics of subjects plus all data for background and other baseline characteristics such as relevant medical history, results of laboratory screens, drug tests and any other relevant information.

The demographics of subjects include:

- continuous age (in years) along with categorical age (< 45, ≥ 45 - < 65, ≥ 65), gender, race and ethnicity,
- country, geographical region (Europe, North America),
- height (in cm) at screening, continuous weight (in kg) as well as categorical weight (≤ 90 kg, > 90 kg) and Body Mass Index (BMI) (in kg/m²) at baseline. BMI will be calculated by dividing weight in kilograms by height in meters squared.
- randomized prior biologic use and weight stratum (as entered into IRT system by the sites).

Other baseline characteristics consist of:

- psoriasis medical history i.e. the number of significant flares of disease activity in the last 6 months, the time since diagnosis and the actual prior biologic use,
- results of laboratory screens, drug tests at baseline,
- IGA score, PASI score and percentage of BSA affected by psoriasis at baseline,
- DLQI total score, EQ-PSO total score (VAS), SF-36 physical and mental component summaries at baseline,
- PHQ-8 and eC-SSRS total score at baseline.

The variables of subject demographics and other baseline characteristics will be performed in the ITT population. Besides, these variables will be reported in other analysis populations to evaluate the differences between non-randomized treatment groups that are assigned on the basis of post-randomization efficacy results in the exploratory analyses after Week 12 and Week 24. All subjects within the ITT population and/or safety population will be included in the analysis of the results of laboratory screens, drug tests, PHQ-8 and eC-SSRS total score (refer to Table 4.11 for further details).

4.4.2 Descriptive Analyses

All data for background and demographic variables, psoriasis medical history, results of laboratory screens and drug tests, IGA score, PASI score and percentage of BSA as well as QoL and Patient Reported Outcomes (PRO) data will be summarized by treatment group as specified in Table 4.11 at screening and/or baseline visit. No treatment comparisons will be performed. This data will also be listed by treatment group and subject.

Table 4.11: Analysis Populations in Function of Demography Variables

Demography Variables	Analysis Population
• Demographics • Psoriasis medical history • IGA score, PASI total score and percentage of BSA affected by psoriasis at baseline	• ITT Population • MITT24 Population by assigned treatment sequence for both induction and maintenance/escalation periods. • MITT48 by assigned treatment sequence for both maintenance/escalation and response assessment/dose hold. • Week 12 IGA non-Responder Population by assigned treatment sequence for both induction and maintenance/escalation periods (optional)
• DLQI total score, EQ-PSO total score, SF-36 physical and mental component summaries at baseline	• ITT Population
• Results of laboratory screens, drug tests at baseline, PHQ-8 and eC-SSRS total score at baseline	• ITT Population/Safety Population

4.5 Analysis Populations

4.5.1 Variables

The analysis populations will be summarized in the enrolled population with the following variables:

- number and percentage of subjects who are enrolled but are not randomized overall and by reasons for exclusion,
- number and percentage of subjects who are:
  - randomized
  - in the ITT population,
  - in the MITT populations,
  - in the PP populations,
  - in the safety population.

4.5.2 Descriptive Analyses

The incidence in the various analysis populations will be presented by treatment group and overall if applicable for each treatment period. In addition, a listing of subjects excluded from

each analysis population with the primary reason for exclusion whenever available will be produced.

4.6 Subject Disposition

Subject disposition will be analyzed in the enrolled population unless stated otherwise.

4.6.1 Variables

Subject disposition will be described by:

- the number and percentages of subjects who are screened, randomized, treated, who completed the treatment period and/or study, who discontinued along with the primary reason for early discontinuation for the study overall as well as for each treatment period separately.
- the number and percentages of subjects who dose escalated from Week 12 or of subjects who had dose withheld from Week 24 for the maintenance/escalation period and the response assessment/dose hold period respectively,
- the number and percentage of subjects with important protocol deviations in the ITT population overall and grouped into categories for the study overall as well as for each treatment period separately,
- the number and percentages of subjects in analysis populations and excluded from the analysis populations,
- the time in weeks to study drug discontinuation due to any reasons and due to an AE for the induction period.

To assess the exploratory analyses after Week 12 and 24, the disposition of subjects after the post-randomization treatment assignment at Week 12 or Week 24 will be explored in the MITT24 or MITT48 populations and by assigned treatment sequence for the maintenance/escalation period or dose assessment/response hold period respectively using these variables:

- the number and percentage of subjects completing the maintenance/escalation period or dose assessment/response hold period,
- discontinuing the treatment during the maintenance/escalation period or dose assessment/response hold period and by primary discontinuation reason.

4.6.2 Descriptive Analyses

Subject disposition variables will be summarized by treatment group.

In addition, a listing of important protocol deviations will be presented by subject and treatment broken down by center.

4.6.3 Graphical Presentation

The time in weeks to study drug discontinuation due to any reasons and due to an AE will be represented graphically with Kaplan-Meier plots by treatment groups for the ITT population during the induction period.

The time to subject discontinuation in days for the induction period will be defined as the difference in days between the withdrawal date if occurring in the induction period and the date of first dose of study drug plus an additional day. The subject who will complete the induction period will be censored at the completion date of the induction period i.e. at the date of Week 12. For other subjects who did not withdraw during the induction period and did not complete the period, they will be censored at the date of the last known study visit during this period when they last received study treatment.

This graphical presentation and descriptive statistics will be repeated overall.

4.7 Treatment Compliance

All subjects within the safety population will be included in the data analysis.

4.7.1 Variables

Treatment exposure will be characterized by the following variables:

- the duration of study exposure that corresponds to the period from the date of the first dose of study drug to either the date of last study visit (Week 52) for the subjects who completed the study or the date of discontinuation for subjects who discontinued during the study,
- the duration of treatment exposure in days and in subject-years including the duration of dose hold in days for the response assessment/dose hold period (subject-years is calculated by adding the number of subjects in the group and multiplying that number by the years that subjects were on treatment),
- the frequency of treatment exposure determined by the number of injections received,
- the actual amount/dose in mg received by the subjects as well as the percentage of the scheduled dose that was actually received,

Treatment compliance will also be described with:

- the number and proportion of subjects receiving the complete dose as scheduled,
- the number and proportion of subjects that are compliant and non-compliant in each treatment group.

For the induction and maintenance/escalation periods, the duration of treatment exposure is the difference in days between the date of last study visit in the considered treatment period unless subjects have discontinued during this period and the date/time of the first dose of study drug in the same period.

Exposure $_{[period\ x]}$ = last study visit date $_{[period\ x]}$ – 1st study drug dose date/time $_{[period\ x]}$.

For subjects who have discontinued from placebo at or prior to the last visit of the induction period, the duration of exposure will be the sum of the number of days between the date/time of the first dose and the date of treatment discontinuation.

For subjects who have discontinued from M1095/Secukinumab treatment at or prior to the last visit of the induction or maintenance/escalation periods, the duration of exposure will be the sum of the number of days between the date/time of the first dose in the considered period and the date of the last dose before discontinuation and 56 days that correspond to the longest period of washout for M1095/Secukinumab. If the study discontinuation occurred within the 56 days after the last dose received, the duration of exposure will be defined as the difference in days between the date of study discontinuation and the date of first dose of study drug.

Exposure $_{[period\ x]}$ = last dose date/time $_{[period\ x]}$ – 1st study drug dose date/time $_{[period\ x]}$ + 56 days.

The treatment exposure of response assessment/dose hold period will be described by several variables:

- the number of subjects who have dose of study drug being withheld at Week 24,
- the duration in days of the dose being withheld during the period i.e. the difference in days between the date of the visit at Week 24 and the date/time of M1095 re-commencement,
- the total duration in days of the dose being withheld since the last dose of M1095 i.e. the difference in days between the date of the last dose of study drug before dose of Week 24 being withheld i.e. at Week 20 and the date/time of M1095 re-commencement (see Table 4.12).

The duration of exposure to M1095/secukinumab treatment overall during the combined induction, maintenance/escalation and response assessment/dose hold periods be calculated as follows:

Secukinumab: Exposure $_{[overall]}$ = date/time of last dose – date/time of 1st dose + 56 days.

M1095: Exposure $_{[overall]}$ = date/time of last dose – date/time of 1st dose – d_1 + 56 days.

with the date/time of the first dose as described in Table 4.12 for the different treatment groups and subtracting the dose hold duration for the overall period while considering the 5 half lives of the M1095 treatment (d_1) as explained in Table 4.12. This duration will also be expressed in subject-years by adding the amount of times in days that subjects spent on treatment for all subjects divided by the total number of days in a year i.e. 365.25.

A subject being administered the complete dose at a given visit is a subject who received the planned number of injections and the planned dosage in mg per injection. A subject being administered the complete dose overall is a subject who received the cumulative number of injections and the cumulative dosage in mg as planned.

A subject will be considered overall compliant for each study period or overall if this subject is missing no more than 20% of the planned treatment and not missing two or more consecutive planned dosing occasions of the considered period or overall. Although subjects will receive two injections at each visit, the two injections at the same visit will be regarded

as a single dosing occasion. If a subject misses two injections at a visit, this subject will be reported as missing the dosing occasion at this visit.

Table 4.12: First M1095 Dose and Calculation of Dose Hold Duration Depending on Treatment Group

Actual Treatment Group	First Dose	Total Dose Hold Duration (d) since last dose of study drug (in days)	Dose Hold Duration for Overall Period (d_1) (in days) If d–56 <0, d_1=0
(1) – Placebo at Week 0, 1, 2, 3, 4, 6, 8 (and (1.i) M1095 120 mg at Week 12, 14, 16, 20 and dose hold from Week 24)	Week 12	d = M1095 Restart – Week 20*	$d_1 = d - 56$
(1.j) M1095 120 mg at Week 12, 14, 16 and Q4W	Week 12	N/A	$d_1 = 0$
(2) - M1095 30 mg at Week 0, 2, 4, 8 (and (2b) M1095 120 mg Q4W if escalation at Week 12)	Week 0	N/A	$d_1 = 0$
(2a.i) Q4W and dose hold from Week 24)	Week 0	d = M1095 Restart – Week 20*	$d_1 = d - 56$
(2a.j) Q4W)	Week 0	N/A	$d_1 = 0$
(3) - M1095 60 mg at Week 0, 2, 4, 8 (and (3b) M1095 120 mg Q4W if escalation at Week 12)	Week 0	N/A	$d_1 = 0$
(3a.i) Q4W and dose hold from Week 24)	Week 0	d = M1095 Restart – Week 20*	$d_1 = d - 56$
(3a.j) Q4W)	Week 0	N/A	$d_1 = 0$
(4) - M1095 120 mg at Week 0, 2, 4, 8 (and (4.i) 12 and Q8W and dose hold from Week 24)	Week 0	d = M1095 Restart – Week 20*	$d_1 = d - 56$
(4.j) 12 and Q8W	Week 0	N/A	$d_1 = 0$
(5) - M1095 120 mg Q2W at Week 0, 2, 4, 6, 8, 10 (5.i) 12 and Q4W and dose hold from Week 24)	Week 0	d = M1095 Restart – Week 20*	$d_1 = d - 56$
(5.j) 12 and Q4W	Week 0	N/A	$d_1 = 0$
(6) - Secukinumab 300 mg at Week 0, 1, 2, 3, 4, 8 (and 12 and Q4W)	Week 0	N/A	N/A

*If a subject missed the dose of Week 20, the last visit of the maintenance/escalation period when the subjects were injected the study drug will be considered instead of Week 20.

4.7.2 Descriptive Analyses

The duration of study exposure will be summarized. Summary statistics of the duration of treatment exposure in days and in subject-years will be reported by treatment group for the induction, maintenance/escalation and overall periods. The treatment exposure of the response assessment/dose hold period will be described with the number of subjects who have dose withheld and with summary statistics of the duration of the dose being withheld and of the total duration of the dose being withheld since the last dose of M1095.

The frequency of treatment exposure and the amount/dose of treatment will be provided at each visit and overall for each treatment period. The percentage of the scheduled dose will be reported for the induction, maintenance/escalation and overall periods.

All descriptive analyses on treatment compliance will be also summarized for the three treatment periods and for the overall study. The number and proportion of subjects having received the complete dose administered will be presented by each dose administered and overall by treatment group. Proportions of subjects compliant and non-compliant with study drug will be summarized by treatment group.

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

4.8 Previous and Concomitant Therapy

Data of previous and concomitant therapies will be summarized in the ITT Population.

Prior and concomitant therapies will be coded according to World Health Organization Drug Dictionary (WHO-DD version of March 2018). Prior therapies are defined as all therapies that ended prior to randomization at Week 0. Concomitant therapies are all medications:

- that started or continued on the day of or after randomization for the induction period and the overall period (from Week 0 to 52),
- or that started or continued on the day of or after the first dose of study drug of the considered period i.e.:
    - at Week 12 for the maintenance/escalation period,
    - at Week 24 for the response assessment/dose hold period.

In case of missing start and end dates, the medication will be considered as concomitant medication for the whole duration of study. If either the start date or the end date is missing or both dates are incomplete, the available information about the data will be used to infer from the randomization date/time if the therapy was taken prior to randomization or concomitantly:

- If the end date is missing and:
    - the start date is available and complete and:
        - after or on the day of randomization, the medication will be considered as concomitant,
        - prior to randomization, the medication will be regarded as concomitant therapy.
    - the start date is partial and:
        - the partial part of the start date is after the randomization date, the medication will be inferred as concomitant,

          the partial part of the start date is prior to or the same as the comparable part of the randomization date, the medication will be concomitant medication.
- If the start date is missing and:

- the end date is available and complete and:
  - on the day of or after randomization, the medication will be considered as concomitant,
  - prior to randomization, the medication will be inferred as a prior therapy.
- the end date is partial and:
  - the partial part of the end date is the same as or after the comparable part of the randomization date, the medication will be concomitant,
  - the partial part of the end date is prior to the comparable part of the randomization date, this medication will be regarded as previous.

- If both start and end dates are incomplete,
  - If the partial part of the end date is before randomization, the medication will be classified as prior,
  - If the partial part of the start date is the same as or after the comparable part of the randomization date, the medication will be classified as concomitant.

The same rules will apply for the other treatment periods but using the first dose of study drug of the considered period as the reference date.

The number and percentage of subjects taking previous medications and previous psoriasis medications will be summarized by treatment group, Anatomical Therapeutic Class (ATC) and preferred name. Similarly, the concomitant medications will be summarized by treatment group, by ATC and preferred name for the induction period separately and for the study overall.

Previous and concomitant therapies will be listed by treatment group and subject. The therapies will be listed with dose, unit, frequency, route of administration (if applicable), indication, start and end dates and the ongoing status.

A listing of any new treatments for psoriasis in subjects who early discontinued will be produced by treatment group and subject.

4.9 Safety and Tolerability Data

Safety data will be summarized in the Safety Population by actual treatment group.

Unless indicated otherwise, safety variables will be summarized separately for the induction period (Week 0 to 12) and the overall study (Week 0 to Week 52) per actual treatment group (refer to Table 4.2 and Table 4.3 for details about defining actual treatment groups). Overall study corresponds to the time interval from Week 0 to Week 52 for the subjects who completed the study or from Week 0 to the last follow-up for subjects who discontinued. Please note that for the overall safety analyses, the baseline for subjects who were randomized to placebo will be the last non-missing assessment before the first dose of M1095.

No formal statistical treatment comparisons of the safety data are planned.

Further safety analyses may be conducted for the overall period, maintenance/escalation and response assessment/dose hold periods as described in

Table 4.13, Table 4.14 and Table 4.15 after assessment of safety data and if deemed necessary or if indicated otherwise in this section.

Table 4.13: Actual Treatment Groups and their Labels for Pooled Safety Analyses of the Overall Period

Actual Treatment Group*	Treatment Label Overall (Week 0-52) Per actual received doses
(1) - (Placebo at Week 0, 1, 2, 3, 4, 6, 8 and) M1095 120 mg at Week 12, 14, 16 and Q4W	Plac/120mg (x4), Q4[a]
(6) - Secukinumab 300 mg at Week 0, 1, 2, 3, 4, 8 (and 12 and Q4W)	Secukinumab
(2a) - M1095 30 mg at Week 0, 2, 4, 8 and Q4W if no escalation at Week 12	30mg (x4), Q4[b]
(2b) - M1095 120 mg Q4W from Week 12 if escalation at Week 12	Presented separately
(3a) - M1095 60 mg at Week 0, 2, 4, 8 and Q4W if no escalation at Week 12	60mg (x4), Q4[c]
(3b) - M1095 120 mg Q4W from Week 12 if escalation at Week 12	Presented separately
(4) - M1095 120 mg at Week 0, 2, 4, 8 (and 12 and Q8W)	120mg (x4), Q8
(5) - M1095 120 mg Q2W at Week 0, 2, 4, 6, 8, 10 (and 12 and Q4W)	120mg (x6), Q4
	Total 120 mg[d]
	Total M1095[e]

*: For (2a), (3a), (4), (5) and (6), subjects will be assigned to a treatment group based on the actual treatment they received most.

a: Plac/120mg (x4), Q4 include all subjects who were mostly administered M1095 120 mg from Week 12 to Week 44 having received placebo during the induction period. The data will only be presented from Week 12 for this treatment group.

b: 30mg (x4), Q4 include the data of:

- all subjects who did not escalate and who were mostly administered M1095 30 mg during the overall period
- all subjects who escalated at Week 12 from Week 0 to Week 12 only and who mostly received M1095 30 mg during the induction period.

c: 60mg (x4), Q4 include the data of:

- all subjects who did not escalate and who were mostly administered M1095 60 mg during the overall period
- all subjects who escalated at Week 12 from Week 0 to Week 12 only and who mostly received M1095 60 mg during the induction period.

d: Total 120 mg will include the subjects who mostly received M1095 120 mg i.e. the following treatments: (1), (4), (5), (2b) and (3b). For (1), (2b) and (3b), only data from Week 12 of subjects who escalated to M1095 120 mg from Week 12 after receiving placebo, M1095 30 mg or 60 mg in the induction period will be included.

e: Total M1095 will include all subjects who received M1095 at any time during the study i.e. (1), (2a), (2b), (3), (4) and (5).

Table 4.14: Actual Treatment Groups and their Labels for Safety Analyses of the Maintenance/Escalation Period

		Treatment Label	
	Dose Escalation due to IGA > 1 at Week 12?	**Maintenance/ Escalation Period**	**Response Assessment/ Dose Hold Period**
Actual Treatment Group*		**12 2 → (in weeks)**	**4 52**
(2) - M1095 30 mg at Week 0, 2, 4, 8 (and: (2a) Q4W if no escalation at Week 12)	No		
(2b) M1095 120 mg Q4W if escalation at Week 12)	**Yes**	**30mg (x4), Q4/ Esc to 120mg**	**30mg (x4), Q4/ Esc to 120mg**
(3) - M1095 60 mg at Week 0, 2, 4, 8 (and: (3a) Q4W if no escalation at Week 12)	No		
(3b) M1095 120 mg Q4W if escalation at Week 12)	**Yes**	**60mg (x4), Q4/ Esc to 120mg**	**60mg (x4), Q4/ Esc to 120mg**

*: Subjects will be assigned to a treatment group based on the actual treatment they received most during the induction and maintenance/escalation periods.
Note: Rows in grey will not be presented in tables.

Table 4.15: Actual Treatment Groups and their Labels for Safety Analyses of the Response Assessment/Dose Hold Period

		Treatment Label
	IGA = 0 at Week 24?	**Response Assessment/ Dose Hold Period**
Actual Treatment Group*		**(Week 24-52)**
(1) - Placebo at Week 0, 1, 2, 3, 4, 6, 8 (and: (1.i) M1095 120 mg at Week 12, 14, 16, 20 and dose hold from Week 24)	**Yes**	**Plac/120mg (x4), Q4/Hold**
(1.j) M1095 120 mg at Week 12, 14, 16 and Q4W	No	Plac/120mg (x4), Q4/No Hold
(6) - Secukinumab 300 mg at Week 0, 1, 2, 3, 4, 8 (and 12 and Q4W)	N/A	
(2) - M1095 30 mg at Week 0, 2, 4, 8 (and: (2a.i) Q4W and dose hold from Week 24)	**Yes**	**30mg (x4), Q4/No Esc/Hold**
(2a.j) Q4W)	No	30mg (x4), Q4/No Esc/No Hold
(2b) M1095 120 mg Q4W if escalation at Week 12)	N/A	
(3) - M1095 60 mg at Week 0, 2, 4, 8 (and: (3a.i) Q4W and dose hold from Week 24)	**Yes**	**60mg (x4), Q4/No Esc/Hold**
(3a.j) Q4W)	No	60mg (x4), Q4/No Esc/No Hold
(3b) M1095 120 mg Q4W if escalation at Week 12)	N/A	
(4) - M1095 120 mg at Week 0, 2, 4, 8 (and: (4.i) 12 and Q8W)	**Yes**	**120mg (x4), Q8/Hold**
(4.j) 12 and Q8W and dose hold from Week 24)	No	120mg (x4), Q8/No Hold
(5) - M1095 120 mg Q2W at Week 0, 2, 4, 6, 8, 10: (5.i) 12 and Q4W and dose hold from Week 24)	**Yes**	**120mg (x6), Q4/Hold**
(5.j) 12 and Q4W	No	120mg (x6), Q4/No Hold

*: Subjects will be assigned to a treatment group based on the actual treatment they received most during the induction, maintenance/escalation and response assessment/dose hold periods.
Note: Rows in grey will not be presented in tables.

4.9.1 Variables

Safety and tolerability data encompass vital signs, skin evaluations, ECGs, laboratory values, number and severity of adverse events, instruments to assess depression and suicidality such as electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and Personal Health Questionnaire Depression Scale (PHQ-8).

4.9.2 Descriptive Analyses

4.9.2.1 Vital Signs

All vital signs data (systolic and diastolic Blood Pressure (BP), Heart Rate (HR), weight) will be listed up to Week 52 by treatment group, subject, and visit/time and when reference ranges are available, abnormalities will be flagged. Summary statistics for absolute values and change from baseline, will be provided by treatment group and visit/time. The number and percentage of subjects within each baseline category (low, normal, high and missing) versus the post-baseline category (low, normal, high and missing) of vital signs will also be summarized at all post-baseline visits (the low, normal and high categories will be defined as follows for these parameters: heart rate: <60 beats/min, 60-100 beats/min, >100 beats/min, systolic blood pressure: <90 mmHg, 90-139 mmHg, >139 mmHg, diastolic blood pressure: <60 mmHg, 60-89 mmHg, >89 mmHg and temperature: <36.5°C, 36.5-37.3°C, >37.3°C).

4.9.2.2 Skin Evaluations

All skin evaluation data including any findings not typical of psoriasis, conduction of further skin assessments such as biopsy will be listed by treatment group, subject and visit up to Week 52.

4.9.2.3 ECG Evaluations

The ECG evaluations will be reported by treatment group for the induction period and the overall study. The number and proportions of subjects with a normal, abnormal, abnormal clinically significant or unevaluable overall 12-lead ECG evaluation will be reported by treatment group. In addition, summary statistics for the absolute values and change from baseline for ECG parameters will be provided by treatment group and visit/time. ECG parameters comprise HR, PR interval, QRS, QT interval and the corrected QT intervals i.e. QTcB using Bazett's correction and QTcF using Fridericia's correction QTcB is calculated by dividing the QT interval by the square root of the preceding R-R interval while QTcF is calculated by dividing the QT interval by the cube root of the preceding R-R interval.

A shift analysis from baseline will be implemented for PR, QRS, QT, QTcB and QTcF intervals and HR describing the change from baseline (normal, abnormal) to end of period/study (normal, abnormal, abnormal clinically significant or unevaluable) in ECG parameters.

The number and proportion of subjects with abnormal elevated QT, QTcB and QTcF intervals i.e. exceeding the upper limit value of 450 ms, 480 ms and 500 ms will be summarized by treatment group. The number and proportion of subjects who experience an increase from baseline in QT, QTcB and QTcF interval greater than 30 ms and 60 ms will also be reported by treatment group.

All ECG data will be listed by treatment, subject and visit/time up to Week 48, abnormalities will be flagged.

4.9.2.4 Clinical Laboratory Evaluations

All laboratory data up to Week 52 including serology tests (at screening only), pregnancy tests (women only) and urinalyses will be listed by treatment, subject, and visit/time. If reference normal ranges are available, laboratory abnormalities will be flagged and the CTCAE grade included.

Summary statistics of hematology, chemistry and urinalysis data and their change from baseline in SI units will be provided by treatment group and visit/time. Unscheduled measurements e.g. laboratory re-test due to abnormal laboratory results or unplanned visits due to safety concerns will be excluded from this analysis.

In addition, the number and percentage of subjects with abnormal, high or low, hematology, chemistry and urinalysis values will be summarized by treatment group.

Individual subject changes from baseline to worst post-baseline assessment in laboratory parameters graded using CTCAE will be summarized using shift tables by treatment group for the induction and overall period. The worst post-baseline laboratory assessment will correspond to the worst post-baseline CTCAE grade observed on-treatment over all visits (including scheduled and unscheduled measurements).

For non-graded laboratory parameters, shift tables will present the number and percentages of subjects within each baseline category (low, normal, high and missing) versus the post-baseline category (low, normal, high and missing). The categories will be defined by using the minimum and maximum values. Minimum/maximum baseline value will be the lowest/highest non-missing value observed during the baseline period i.e. before the first dose of study treatment. The minimum/maximum post-baseline laboratory assessment will be determined relative to the reference normal ranges i.e. to on-treatment lowest decrease and highest increase from minimum/maximum baseline over all visits (including scheduled and unscheduled measurements) for the considered period. In addition, a shift table from normal/high baseline category to low post-baseline category will be produced using the minimum value. Similarly, a shift table from low/normal baseline category to high post-baseline category will be produced using the maximum value.

Scatterplots of minimum/maximum absolute laboratory values during baseline vs. minimum/maximum absolute laboratory values during the treatment period will be presented with lines indicating the reference limits (Lower Limit Normal, Upper Limit Normal and absence of change from baseline).

4.9.2.5 Adverse Events

Treatment-Emergent AEs (TEAEs) per treatment period are AEs that emerge while on study treatment during a given treatment period (e.g. induction period), having been absent pre-treatment, or that worsen during the considered period (e.g. induction period) relative to the pre-treatment state i.e. after baseline and on or prior to the date of the last visit of the considered period (e.g. Week 12 for the induction period). On study treatment during a treatment period is defined as the period from the first study treatment administration at the start of period (e.g. Week 0 for the induction period) up to the last visit of the treatment period for subjects who did not discontinue treatment during the considered period (e.g. Week 12 for the induction period) or for subjects who discontinued during the considered period, up to the end of the considered period or up to 8 weeks after the last dose of study treatment, whichever occurs first. TEAEs will be assigned to the actual treatment period to which they are considered treatment-emergent.

When considering the study overall, treatment-Emergent AEs (TEAEs) are AEs that emerge while on study treatment i.e. from the first study treatment administration up to 8 weeks after the last dose of study treatment, having been absent pre-treatment, or that worsen during study treatment relative to the pre-treatment state i.e. after baseline.

If the classification of an AE cannot be clearly established because of missing or incomplete date/time of AE, the AE will be classified as treatment-emergent. No imputation of missing or partial AE start and end dates will be performed.

To determine whether an AE is pre-treatment, on-treatment or post-treatment in case of partial or missing AE dates, the rules below will be followed:

- If the start date is incomplete and either the end date is incomplete or available:
    - if the non-missing part of the start date infers that the AE occurred post-treatment, the AE will be considered as post-treatment.
    - If the partial or complete end date indicates that the AE occurred prior to the first dose of study drug, the AE will be considered as pre-treatment.
    - If the partial start date does not give any evidence as to when the AE occurred during the study, and the end date infers that the AE stopped after the first dose of study drug, the AE will be flagged as on-treatment for all periods for which the first dose of study drug was started before the end of the AE.
    - If the partial or complete start and end dates do not indicate as to when the AE started and ended compared to the first dose of study drug of any period, the AE will be flagged on-treatment for all periods.
- If both start and end dates are both missing: the AE will be considered on-treatment and therefore a TEAE for all periods.

To determine the worsening of an AE during study treatment, the maximum severity for each AE during the baseline period will be considered. In case of missing severity, the conservative approach below will be followed:

- If an AE has a missing severity during the study treatment, it will be defined as treatment-emergent.

- If the severity of an AE is missing at baseline and this event continues during the study treatment, this AE will be considered as treatment-emergent.

Adverse events of Special Interest (AESI) include cytopenias, liver function test changes/enzyme elevations, infections, injection-site reactions, allergic/hypersensitivity reactions, cerebrocardiovascular events, malignancies, depression, Crohn's disease and ulcerative colitis. Additional adverse events may be identified as being of special interest during the study and prior to first unblinding.

An overview table will present the number and percentage of subjects experiencing these types of AEs below by treatment:

- TEAEs,
- TEAEs by relationship to investigational product,
- serious TEAEs including deaths,
- TEAEs by maximum severity,
- deaths,
- and TEAEs leading to study treatment discontinuation.

This table will be produced for all separate treatment periods and the overall periods (refer to Table 4.3, Table 4.13, Table 4.14 and Table 4.15).

For the overall period, the exposure-adjusted incidence per 100 subject-years will also be presented. The exposure-adjusted incidence will be calculated by dividing the number of subjects with AEs by the total person years of exposure during the treatment period (refer to Section 4.7). This result will be multiplied by 100 to obtain the exposure-adjusted incidence per 100 subject-years.

The AESI will also be displayed with an overview table by treatment for each treatment period and the overall periods.

The incidence of subjects with TEAEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ class (SOC) and Preferred Term (PT) and by treatment group. A subject with multiple AEs in the same SOC (or with the same PT) will only be counted once for that SOC (or PT). The PTs will be presented in decreasing order of frequency over all treatment groups within the SOC. Similarly, incidence tables will be produced for treatment-related TEAEs, for serious TEAEs, for TEAEs by maximum severity, for TEAEs leading to deaths and study drug discontinuations. In addition, the number and percentage of subjects with AESI will be presented by treatment group classed by SOC and PT. An additional summary table will be created to include the relatively common TEAEs i.e. with an incidence greater than 5%. All information obtained on adverse events will be listed by treatment group and subject. A listing of deaths will be also provided by indicating the study period in which the deaths occurred in the enrolled population.

4.9.2.6 Depression and Suicidality/Self-Injurious Behavior

Suicide-related thoughts and behaviors and self-injurious behavior with no suicidal intent based on the eC-SSRS, and depression based on the PHQ-8 will be listed by subject and visit up to Week 52.

In addition, the frequency and percentage of subjects with at least one post-baseline eC-SSRS assessment with suicidal ideation, suicidal behavior, suicidal ideation or behavior, treatment-emergent suicidal ideation and emergence of suicidal behavior will be summarized by treatment group (see Section 7.5 – Appendix E: Derivation of eC-SSRS for further information). The total PHQ-8 score and absolute change from baseline will be described by a by-treatment summary table for each visit (see Section 7.4 – Appendix D: Scoring of PHQ-8).

4.9.3 Graphical Presentation

Boxplots to visualize trends and data distributions in longitudinal continuous safety data (vital signs, ECG parameters, laboratory parameters) will be produced by treatment group and visit.

4.10 Pharmacokinetic (PK) Parameters

All subjects within the pharmacokinetic population will be included in the PK parameter analysis and may be reported in a separate report.

4.10.1 Variables

M1095 serum concentrations in ng/mL will be assessed at the following visits: Weeks 0, 2, 4, 8, 12, 24, 36, 44, 48 and 52.

4.10.2 Descriptive Analyses

Descriptive summary statistics of serum concentration will be provided for each treatment period by treatment sequence of the considered period and visit/sampling time point (the induction period summaries will present all treatment groups of Table 4.2 except for Secukinumab (6), Placebo (1) and total M1095, the maintenance/escalation period summaries will present all treatment groups of Table 4.14 in addition to Plac/120mg (x4), Q4, 30mg (x4), Q4/No Esc, 60mg (x4), Q4/No Esc, 120mg (x4), Q8, 120mg (x6), Q4, the response assessment/dose hold period summaries will present all treatment groups of Table 4.14 and Table 4.15). The summary statistics will include arithmetic and geometric means, SD, arithmetic and geometric CV, minimum, median, and maximum and the frequency (number of subjects and percentage) of concentrations below the LLOQ. All concentrations below LLOQ will be treated as zero in summary statistics for concentration data. The geometric mean will not be reported if the data include zero values. Serum concentrations will also be listed by treatment group, subject and visit/sampling time point. Graphical methods will be

employed to show the mean concentration-time plot and the individual concentration-time profiles by actual treatment group, with time defined as visit and actual day respectively.

4.11 Immunogenicity Data

Immunogenicity data analysis will be described in a separate analysis plan.

4.12 Subgroup Analyses

As possible, subgroup analysis may be performed on key efficacy and safety data to evaluate the homogeneity of the treatment effect across main subject characteristics.

The following patient characteristics and subgroups will be considered:

- geographical region (Europe, North America),
- actual prior biological use (prior biological use, no prior biological use),
- actual weight category (≤ 90 kg, > 90 kg),
- actual prior biological use and weight category stratum derived from the observed values of body weight and prior biologic use at baseline,
- gender (female, male),
- geriatric status (< 65, ≥ 65),
- PASI and/or IGA at baseline (< median of baseline PASI score, ≥ median of baseline PASI score and/or < baseline IGA score of 4, ≥ baseline IGA score of 4).

4.12.1 Variables

As feasible, subgroup analysis may be performed for the following efficacy variables in the ITT population and for the safety variables in the safety population:

Table 4.16: List of Efficacy Endpoints for Subgroup Analyses and Variables

	Endpoints	Type of Variables	Variables for Subgroup Analyses
Efficacy	IGA-derived endpoints	Binary	• proportion of subjects achieving an IGA score ≤ 1 and with an IGA reduction from baseline of 2 points or more at Weeks 12, 24, 36 and 48.
	PASI-derived endpoints	Categorical	• proportion of subjects achieving PASI 75/PASI 90/PASI 100 at Weeks 12, 24, 36 and 48.
		Continuous	• percent change from baseline in PASI score at Weeks 12, 24, 36 and 48.
Safety	Safety endpoint	Categorical	• number and percentage of subjects with AESI

In the next paragraphs, the analysis of the variables will be handled according to the type of variables or type of endpoint.

4.12.2 Descriptive and Inferential Analyses

4.12.2.1 Binary and Categorical Variables

The number and proportion of responders will be reported by treatment group and visit for each subgroup category and overall.

At each visit, proportions will be compared between treatment group using a logistic regression. The model will include the treatment and subgroup as categories as well as the treatment-by-subgroup interaction. The treatment-by-subgroup interaction will be tested at the 15% significance level. A forest plot will be produced for each endpoint and treatment comparison of interest. The following comparisons will be reported: pairwise comparison of each treatment arm to Plac/120mg (x4), Q4 at Weeks 12, 24, 36 and 48.

The forest plots will show the predicted proportions in each treatment group estimated from the models for each subgroup category and overall. Treatment comparisons will also be reported on the plots. Owing to the low sample size in the subgroups, some analyses may not be feasible. Further, no p-values will be produced, but the 95% confidence intervals on mean treatment ORs will be presented, if possible.

The calculated ORs in the forest plot for each stratum of the subgroup of combined prior biological use and weight category will also serve as the sensitivity analyses for the CMH tests of secondary efficacy analyses in case that the assumption of OR homogeneity was not met.

4.12.2.2 Continuous Variables

Each treatment comparison vs. placebo will be assessed using an ANCOVA with treatment, subgroup, the subgroup-by-treatment interaction as factors and the baseline value as a covariate in the model. Significance of the interaction will be tested at the 15% level. The LSM differences along with 95% CI for each pairwise comparison vs. placebo will be calculated at Week 12 in each category of the subgroup. This inferential analysis will be repeated for Weeks 24, 36 and 48.

The subgroup analysis of actual prior biological use and weight stratum will be used as sensitivity analyses of the secondary endpoints in case of some imbalance between the treatment groups that is solely due to chance, particularly if the imbalance is such that any M1095 groups may have a better prognosis than the control group. This will assess the robustness of the conclusions drawn from the secondary analyses based on the ANCOVA analysis. Additional analyses may be performed to adjust for other baseline covariates if deemed necessary.

A forest plot displaying the LSM differences and the 95% CI in each category of subgroups will be produced for each pairwise treatment comparison. The p-value of the treatment-by-subgroup interaction will also be displayed and tested at the 15% level.

4.12.2.3 Safety Variables

The number and percentage of subjects with AESI will be summarized by treatment group classed by SOC and PT for each category of the subgroup for the induction and overall period (refer to Section 4.9.2.5).

5 Sample Size Calculation

A sufficient number of subjects will be screened, so that a total of approximately 300 subjects will be randomized (approximately 50 per treatment group).

With this sample size, the study has > 99% power to detect a statistically significant difference between any treatment arm and placebo in the IGA score of 0 or 1 rate at Week 12, with a two-sided, unadjusted type I error of 0.05. These calculations assume IGA score of 0 or 1 rates of > 88% for study drug and ≤ 7% for placebo. As this is a phase 2 study, there will be no adjustments for multiplicity.

Exploratory analyses between the different dose levels of M1095 will also be performed. The PASI 100 response rate offers more discriminatory potential for this. Phase 1 data and response simulations give a PASI 100 response rate at Week 12 varying from 45 to 72%. With the sample size of 50 subjects per group, based on these assumed PASI 100 response rates at Week 12, the comparison between the highest and lowest M1095 doses has approximately 79% power.

Power calculations have been performed with SAS v.9.4 Proc Power using the methodology for a two-group chi square test of equal proportions.

Randomization will be stratified by prior biologic use (yes, no) and weight (≤ 90 kg, > 90 kg).

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7 Appendices

7.1 Appendix A: Scoring of DLQI

The Dermatology Life Quality Index (DLQI) includes 10 items related to general dermatology disability to assess health-related quality of life in adults with skin disease. It includes several domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school (Finlay & Khan, 1994).

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

There will be no missing items since this questionnaire is handled using an electronic tablet device.

The minimal clinically important difference of the DLQI is determined as a change in DLQI score of at least 4 points (Basra et al, 2015).

7.2 Appendix B: Derivation of EQ-PSO

EQ-PSO, based on EQ-5D-3L, is a generic instrument to assess the health status of subjects suffering from psoriasis. This instrument comprises 7 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, skin irritation and self-confidence, the last two being the two psoriasis-specific dimensions. For each dimension, there will be 3 response levels: no problems, some problems and severe problems coded as follows:

- Level 1 or "no problems": coded as 1
- Level 2 or "some problems": coded as 2
- Level 3 or "severe problems": coded as 3.

The EQ-PSO (VAS) based on vertical VAS is a score ranging from 0 to 100 (in mm), with 0 being the worst imaginable health state and 100 the best imaginable health state. An improvement in EQ-PSO will be described by a positive change from baseline since a higher score at a post-baseline visit indicates a better subject's health status.

7.3 Appendix C: Scoring of SF-36 (Version 2 Standard)

The SF-36v2® Health Survey Scoring Software (Optum® PRO CoRE Software Version 1.2) will be employed to calculate the SF-36v2® 8-domain scales and 2-component summary measures (Ware et al., 2011). The SF-36, a 36-item questionnaire completed by the subject, is designed to describe and monitor the health of subjects in terms of health domain scales: [redacted]. In addition, the Physical and Mental Component Summary (PCS and MCS) scores that aggregate all health domain scales will respectively give an assessment of the physical and mental wellbeing of subjects. Each domain scale and summary score will be directly transformed into a 0-100 scale before being standardized, with lower scores indicating more disability and higher scores less disability. In this study, the scoring will be based on the SF-36v2 standard version that has a 4-week recall period.

The process for scoring SF-36v2 health domain scales and component summary measures with the help of the scoring software is described below (Ware et al., 2011):

[redacted]

[redacted]			
[redacted]			
[redacted]			
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[redacted]			
[redacted]			

1. [redacted]

[redacted]

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7.4 Appendix D: Scoring of PHQ-8

The PHQ-8 is an eight-item version of the Patient Health Questionnaire depression scale designed to clinically assess subjects for symptoms and signs of depression (Kroenke et al., 2009).

No missing items within a questionnaire are expected since this questionnaire is handled using an electronic tablet device.

Each item will have 4 possible responses:

- Not at all: scored as 0
- Several days: scored as 1
- More than half the days: scored as 2
- Nearly every day: scored as 3.

The total PHQ-8 score will be obtained by summing the scores of all 8 items resulting in a total score between 0 and 24 points. Missing questionnaire at a scheduled visit will not be imputed. Higher the PHQ-8 score, more severe the depression is. Therefore, an improvement in PHQ-8 will be expressed by a negative change from baseline.

7.5 Appendix E: Derivation of eC-SSRS

The eC-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Mundt et al., 2010).

Each standardized clinical question below has a binary response (yes/no) and is classified into categories re-ordered from the original eC-SSRS scale:

Suicidal Ideation:

[redacted]

Suicidal Behavior:

[redacted]

The eC-SSRS defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The following variables (Nilsson et al., 2013) based on the above categories will be derived:

- Suicidal ideation: a "yes" response at any time to any of the 5 suicidal ideation questions (Categories from 1-5) during the considered visit/period,
- Suicidal behavior: a "yes" response at any time to any of the 5 suicidal behavior questions (Categories 6-10) during the considered visit/period,
- Suicidal ideation or behavior: a "yes" response at any time during treatment to any of the 10 suicidal ideation questions (Categories 1-10) during the considered visit/period,
- Suicidal ideation score that is the maximal suicidal ideation category (Categories 1-5) reported by subjects at the assessment. If no suicidal ideation is present at the assessment, a score of 0 will be assigned.

Missing eC-SSRS data will not be imputed.

Treatment-emergent suicidal ideation will be defined as an increase in the maximal suicidal ideation score after the first dose of study drug and during treatment compared to the maximal suicidal ideation score observed prior to treatment. "Lifetime" scores from the Baseline eC-SSRS scale and any "Since Last Visit" scores from the Since Last Visit C-SSRS scales will be considered to determine the maximal suicidal ideation score prior to treatment.
Emergence of suicidal behavior (Categories 6-10) will be defined as the on-treatment occurrence of suicidal behavior from not having suicidal behavior prior to treatment.