Clinical Study Protocol

Protocol Title:	A phase 2b randomized, double-blind, placebo controlled, multi-center 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.
Protocol Number:	AV002
Compound Number:	M1095
Short Title:	M1095 phase 2b psoriasis study
Sponsor Name:	Bond Avillion 2 Development LP
Legal Registered Address:	Nerine House, St. George's Place, St. Peter Port, Guernsey, GY1 3ZG.
Clinical Development Company:	Avillion LLP, Central Working, Eccleston Yards, 25 Eccleston Place, London, SW1W 9NF, United Kingdom
Regulatory Agency Identifying Numbers:	IND 135169 EudraCT 2017-004611-38 ClinicalTrials.gov NCT03384745
Version Number & Approval Date:	Version 3.0, incorporating CZE-1, dated 16th October 2018

Signatory:

[redacted]

[redacted] Date

Chief Medical Officer, Avillion LLP

Medical Monitor Name and Contact Information will be provided separately.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor:	Bond Avillion 2 Development LP
Name of Finished Product:	M1095
Name of Active Ingredient:	M1095
Title of Study:	A phase 2b randomized, double-blind, placebo controlled, multi-center 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.
Protocol No:	AV002
Co-ordinating Investigators:	**North America**: [redacted] **Europe**: [redacted]
Study centers:	Approximately 60 sites, in Europe and North America
Study duration: 52 weeks	**Phase:** 2b

Objectives:

Primary:

- 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.

Secondary:

- To evaluate the efficacy of four dose regimens of M1095 compared to placebo during a 12-week treatment period on secondary endpoints: Psoriasis Area Severity Index (PASI) 75, PASI 90, PASI 100, change in PASI and shift in IGA.
- 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.

Exploratory:

- 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 anti-drug 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 efficacy after being withheld in subjects with an IGA score of 0 at Week 24.

Study Design:

This is a multi-center 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. The study will consist of a 4-week screening period (Week -4 to Week 0), a 12 week treatment period which is placebo-controlled (Week 0 to Week 12), a 12 week maintenance/ escalation period where all subjects are on active treatment (Week 12 to Week 24), a 24 week response assessment/dose hold period where active treatment is withheld if subjects being treated with M1095 have an IGA score of 0 at the beginning of the period (Week 24 to Week 48) and a final assessment period for safety follow up (Week 48 to Week 52). The study will be double-blind up to Week 24, with subject- and investigator-blind maintained throughout.

Subjects will be randomized 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. Placebo wk 0, 1, 2, 3, 4, 6, 8, 10 / M1095 120mg wk 12, 14, 16 and q4w.
2. M1095 30mg wk 0, 2, 4, 8, 12 and q4w.
3. M1095 60mg wk 0, 2, 4, 8, 12 and q4w.
4. M1095 120mg wk 0, 2, 4, 8, 12 and q8w.
5. M1095 120mg wk 0, 2, 4, 6, 8, 10, 12 and q4w.
6. Secukinumab 300mg wk 0, 1, 2, 3, 4, 8, 12 and q4w.

<u>Prior to Week 24:</u>
M1095 subjects in Arms 2 and 3 will receive placebo at Weeks 1, 3, 6, 10 and 14.
M1095 subjects in Arm 4 will receive placebo at Weeks 1, 3, 6, 10, 14 and 16.
M1095 subjects in Arm 5 will receive placebo at Weeks 1, 3 and 14.
Secukinumab subjects in Arm 6 will receive placebo at Weeks 6, 10 and 14.

Subjects randomized to 30mg or 60mg M1095 who do not achieve an IGA score of 0 or 1 at Week 12 will be dose escalated to 120mg q4w starting at Week 12.

Any subjects on M1095 who did not undergo dose escalation at Week 12 and who achieve an IGA score of 0 at Week 24 will have study drug withheld and will receive placebo q4w. Subsequently, if IGA score is 1 or more, these subjects will re-commence M1095 at the dose they received prior to

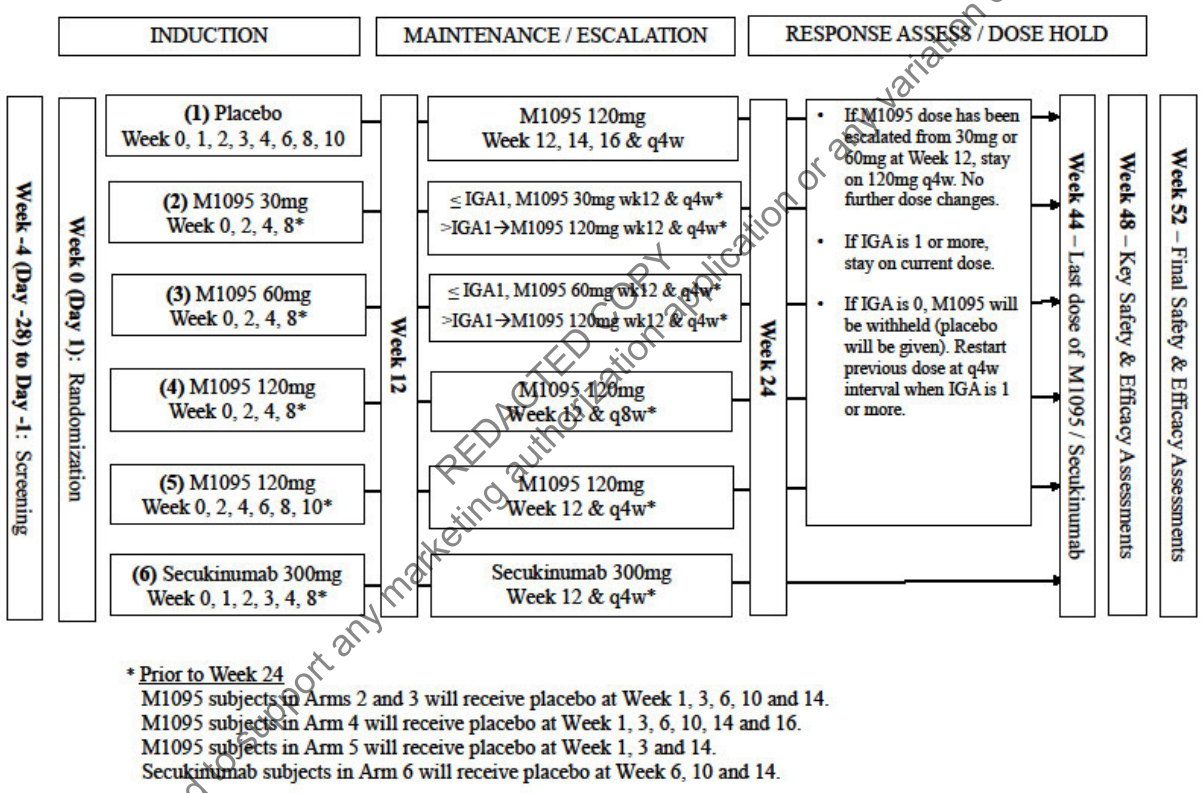
Week 24 on a q4w regimen at the visits scheduled by the protocol until the end of the treatment period. Dose will not be withheld for a second time, irrespective of subsequent IGA scores.

Subjects receiving secukinumab will continue to receive 300mg q4w throughout the study.

The subject blind will be maintained by the use of M1095 and matched placebo. The syringes used for all M1095 and placebo doses will be identical. All subjects will receive two injections of 1mL at each visit. There is also physical protection of the blind. Subjects will be asked to wear an eye-mask for all injections.

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

Figure 1 Flow chart / 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.

The last study drug injection is at Week 44, with key safety and efficacy evaluations at Week 48 and final safety and efficacy assessments at Week 52.

Planned number of subjects:	300
Diagnosis and main criteria for inclusion:	Inclusion Criteria: 1. Ambulatory male and female subjects between 18 and 75 years of age at time of consent.

	2. Subject has had stable moderate to severe plaque-type psoriasis for at least 6 months prior to randomization (e.g., no morphology changes or significant flares of disease activity in the opinion of the investigator). 3. Subject must be considered, in the opinion of the investigator, not adequately controlled by photo, topical or previous systemic treatments and a candidate for systemic biologic therapy. 4. Subject has IGA ≥3, involved body surface area (BSA) ≥10%, and PASI ≥12 at screening and at baseline. 5. Subject is in the opinion of the investigator able to comply with the study procedures. 6. Following verbal and written information about the study, subject must provide signed and dated informed consent before any study related activity is carried out. <u>Exclusion Criteria</u>: 1. Subject diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, or other skin conditions at the time of the screening visit (e.g., eczema) that would interfere with evaluations of psoriasis (Note: psoriatic arthritis is NOT exclusionary). 2. Subject has drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium). 3. Other medical conditions: a. At the time of consent, subject has a planned in-patient surgical intervention between baseline and the Week 52 evaluation. b. Subject has an active infection or history of infections as follows: i. Any active infection for which systemic anti-infectives were used within 28 days prior to randomization. ii. A serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to randomization. iii. Any history of bone infection requiring surgical intervention and/or intravenous antibiotics. iv. Recurrent or chronic infections or other active infection that, in the opinion of the investigator,

	might cause this study to be detrimental to the subject. c. Subject has active tuberculosis. d. Subject has a positive QuantiFERON®-TB Gold test for tuberculosis at screening, or the first test and a repeat test are both indeterminate, unless (i) subject has a known history of latent TB and has completed a course of treatment or (ii) subject has received sufficient treatment for latent TB to allow concomitant treatment with a biological therapy as per local guidelines (note these subjects must continue their concomitant latent TB treatment to completion while participating in the study). If these subjects are outside of the screening window (>28 days since consent) when they become eligible to participate, they should be fully re-screened for the study. e. Subject has an underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator places the subject at unacceptable risk for receiving an immunomodulatory therapy. f. Subject has known history of inflammatory bowel disease. g. Subject with known chronic liver disease or tests positive for hepatitis B virus (HBV) infection or has antibodies to hepatitis C virus (HCV) at screening (see Section 10.5, Appendix 5 in the protocol main text). h. Subject has antibodies to human immunodeficiency virus (HIV) at screening (see Section 10.5, Appendix 5 in the protocol main text). i. Subject has history of heart failure, myocardial infarction or unstable angina pectoris within the 12 months prior to randomization. j. Subject has uncontrolled hypertension characterized by two blood pressure measurements separated by at least 15 minutes with systolic >160mmHg or diastolic >100mmHg. k. Subject has clinically significant electrocardiogram (ECG) abnormalities on centrally read ECG.

	l. Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma. m. Subject has history of malignancy within 5 years EXCEPT cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma which has been treated and considered cured. n. Subject has any concurrent medical condition that, in the opinion of the investigator, could cause this study to be detrimental to the subject. 4. Subject has laboratory abnormalities at screening, including any of the following: a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x the upper limit of normal (one retest is allowed for aminotransferase abnormalities). b. Serum direct bilirubin >1.5 mg/dL. c. White blood cell (WBC) count <3.00 x 10^3/µL. d. Absolute neutrophil count <1.50 x 10^3/µL. e. Absolute lymphocyte count <0.50 x 10^3/µL. f. Platelet count <100,000/µL. g. Creatinine clearance of <30mL/min (calculated via Cockcroft Gault). A subsequent 24-hour urine collection may be performed with the prior approval of the Medical Monitor, and if via urine collection the creatinine clearance is >30mL/min the subject is eligible for the study. AMENDMENT FOR CZECH REPUBLIC Creatinine clearance of <60 mL/min (calculated via Cockcroft Gault). A subsequent 24-hour urine collection may be performed with the prior approval of the Medical Monitor, and if via urine collection the creatinine clearance is >60mL/min the subject is eligible for the study. h. Any other laboratory abnormality, which, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.

	5. Subject has used topical therapy as follows: a. Topical psoriasis treatment within 14 days of randomization, including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, topical calcineurin inhibitors, retinoids, tazarotene, as well as emollients and other non-prescription topical products that contain urea, >3% salicylic acid, or alpha- or beta-hydroxyl acids, and medicated shampoos (e.g. those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues). **Exceptions:** mild/least potent topical steroids are permitted during **screening** for use limited to the face, axillae, and/or genitalia but **must be discontinued 24 hours prior to the baseline visit (randomization)**. b. Bland emollients (without alpha or beta hydroxy acids) within 24 hours of baseline visit (randomization). Note that as per Section 6.5 **bland emollients (without alpha or beta hydroxy acids) may be used during the study but MAY NOT be used within 24 hours prior to any study visit**. 6. Subject has used the following within 28 days of randomization: ultraviolet A (UVA) light therapy (with or without psoralen); ultraviolet B (UVB) light therapy; excimer laser; oral retinoids; methotrexate; cyclosporine; systemically administered calcineurin inhibitors; azathioprine; thioguanine; hydroxyurea; cyclophosphamide; fumarates; apremilast; or oral or parenteral corticosteroids including intramuscular or intraarticular administration (exception: otic, nasal, ophthalmic, or inhaled corticosteroids within recommended doses is permitted); other non-biologic systemic therapy for psoriasis. 7. Subject is not willing to limit ultraviolet (UV) light exposure (e.g. sunbathing and/or the use of tanning devices) during the study. 8. Subject has received live vaccine(s) within 6 weeks of randomization. 9. Subject has received prior treatment at any time before screening with any compound (marketed or investigational) targeting IL-17 (i.e. direct inhibitor, receptor blocker, etc.).

	10. Subject has received prior treatment at any time before screening with more than 2 biologic therapies (ustekinumab, tumour necrosis factor (TNF) targeting therapies, or investigational therapies). 11. Subject has received TNF targeting therapies in the 12 weeks prior to randomization, ustekinumab in the 6 months prior to randomization, or investigational biological therapies within 12 weeks, or 5 half lives of randomization, whichever is the longer. 12. Subject has known sensitivity to any of the products or components to be administered during dosing. 13. Subject has a history or evidence of suicidal ideation or behavior within the 12 months prior to randomization or evidence of severe depression at screening or baseline [i.e. severity level 3, 4 or 5 based on an assessment with the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)]. 14. Subject has a history of chronic alcohol abuse or chronic drug abuse, or has used intravenous (IV) drugs in the past 2 years. 15. Women of child bearing potential who are not willing to use highly effective methods of birth control during treatment and for 12 weeks after the last dose of study drug. See Section 10.4, Appendix 4 in the main protocol text for the definition of child bearing potential and guidance on highly effective methods of birth control. 16. Subject has a positive serum pregnancy test during screening or a positive urine pregnancy test at baseline (Week 0, randomization visit), except those surgically sterile or at least 1 year postmenopausal. 17. Subject is pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 12 weeks after the last dose of study drug. 18. Male subjects who are not willing to use contraception during treatment and for 12 weeks after the last dose of study drug. See Section 10.4, Appendix 4 for definition of permitted methods of contraception in male subjects. 19. Subject will not be available for protocol required study visits or procedures, (e.g. venepuncture) to the best of the subject's and investigator's knowledge. 20. Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give

	informed consent and/or to comply with all required study procedures. 21. Subject is either a. Currently enrolled in another interventional, investigational device or drug study. b. Has been in another investigational device or drug study(s) in the 30 days prior to consent. 22. Subject or subject's immediate family is an employee of the study sponsor (Bond Avillion 2 Development LP), Avillion LLP, EMD Serono, Merck KGaA or any contract research organization (CRO) associated with the study. 23. Subject or subject's immediate family is working for or employed by the investigator.
Reference therapy, dose, and mode of administration:	1. Placebo, in 2 x 1mL subcutaneous injections, given at Week 0, 1, 2, 3, 4, 6, 8 and 10. (These subjects will then receive study drug: M1095, 120mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1mL placebo, given at Week 12, 14, 16, and q4w).
Active therapy, dose and mode of administration:	2. M1095, 30 mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1mL placebo, given at Week 0, 2, 4, 8, 12 and q4w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 1, 3, 6, 10 and 14). 3. M1095, 60 mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1mL placebo, given at Week 0, 2, 4, 8, 12 and q4w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 1, 3, 6, 10 and 14). 4. M1095, 120 mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1mL placebo, given at Week 0, 2, 4, 8, 12 and q8w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 1, 3, 6, 10, 14, 16, 24, 32 and 40). 5. M1095, 120 mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1mL placebo, given at Week 0, 2, 4, 6, 8, 10, 12 and q4w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 1, 3 and 14). 6. Secukinumab, 300mg, in 2 x 1mL (150mg/mL) subcutaneous injections, given at Week 0, 1, 2, 3, 4, 8, 12 and q4w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 6, 10 and 14).

	The 30mg and 60mg M1095 doses (in arms 2 and 3) will be escalated at Week 12 in subjects who have not achieved an IGA score of 0 or 1, as described in Section 6.6.1. M1095 doses (in arms 1 to 5) may be replaced by placebo at Week 24 as described in Section 6.6.2 of the main protocol text.

Criteria for evaluation:

Primary Endpoint:

- IGA score of 0 or 1 at Week 12, with an IGA reduction of at least 2 points from baseline.

Secondary Endpoints:

- Efficacy:
  - PASI 75 at Week 12.
  - PASI 90 at Week 12.
  - PASI 100 at Week 12.
  - PASI 75, PASI 90 and PASI 100 beyond Week 12.
  - Change from baseline in PASI score and in total BSA affected by plaque-type psoriasis.
  - Shift from baseline in IGA score category.
- Safety: Adverse events, skin evaluation, laboratory assessments, vital signs, ECGs, drug discontinuations, and instruments to assess depression and suicidality [electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and Personal Health Questionnaire Depression Scale (PHQ-8)].

Exploratory Endpoints:

- Dermatology Life Quality Index (DLQI), Short Form 36 (SF-36) and Euro-Quality of Life Questionnaire for Psoriasis (EQ-PSO).
- Population PK evaluation.
- Anti-drug antibodies: determination of binding and neutralizing antibodies defined by percentage of subjects with antibodies and titers of antibody.
- Monitoring of pre-existing antibodies against M1095.
- IGA and PASI endpoints in subjects who dose escalate to 120mg M1095 q4w at Week 12.
- IGA and PASI endpoints in subjects with an IGA score of 0 for whom M1095 is withheld at Week 24.

Statistical Methods

Sample size:

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 responder 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 regimens 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 approximately 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.

Analysis sets:
The Intent to Treat (ITT) population includes all subjects randomly allocated to a treatment. The Modified Intent to Treat (MITT) population includes all subjects in the ITT Analysis Set who receive at least one dose of study drug, have a baseline, and at least one post baseline efficacy assessments. The Per-Protocol (PP) population includes all subjects in the MITT Analysis Set who have no important protocol deviations affecting the assessment of efficacy. Membership of the PP Analysis Set will be confirmed prior to unblinding the data. The ITT, MITT and PP populations will be analyzed per planned treatment.

The Safety population is all subjects who receive at least one dose of study treatment. The Safety population will be analyzed per the actual treatment received.

Primary analysis:
The primary endpoint is achievement of an IGA score of 0 or 1 at 12 weeks. The response rate for the IGA score of 0 or 1 at Week 12 is defined as the proportion of subjects at Week 12 with an IGA score of 0 or 1 and with a reduction from baseline IGA of 2 points or more. Baseline IGA score is the last score prior to the first dose of study medication. Any missing IGA score of 0 or 1 response will be imputed as a non-response.

The primary analysis will be based on the ITT Analysis Set. The primary treatment comparisons will be made using the two-sided Cochran-Mantel-Haenszel (CMH) test stratified by prior biologic use (yes/no) and body weight stratum (≤90kg, >90kg.)

Sensitivity analyses:
The primary analysis will be repeated on the MITT and PP Analysis Sets. Furthermore, selected sensitivity analyses will be performed on the ITT Analysis Set, including multiple imputation and last-observation carried forward.

Secondary analyses:
Secondary efficacy and QoL endpoints will be compared between treatments at each visit up to Week 48 using the CMH test for binary endpoints and an Analysis of Covariance (ANCOVA) model for changes from baseline.

Safety data will be summarized in the Safety Analysis Set by treatment and over time, for each treatment period separately and overall.

Exploratory analyses:
Exploratory analyses of efficacy will be made for (i) all subjects who were dose-escalated at Week 12, and (ii) all subjects who had active treatment withheld following an IGA score of 0 at Week 24.

Subgroup analyses:
Subgroup analyses of key efficacy and safety data will be performed as appropriate by geographical region, prior biological use, weight category, gender and geriatric status.

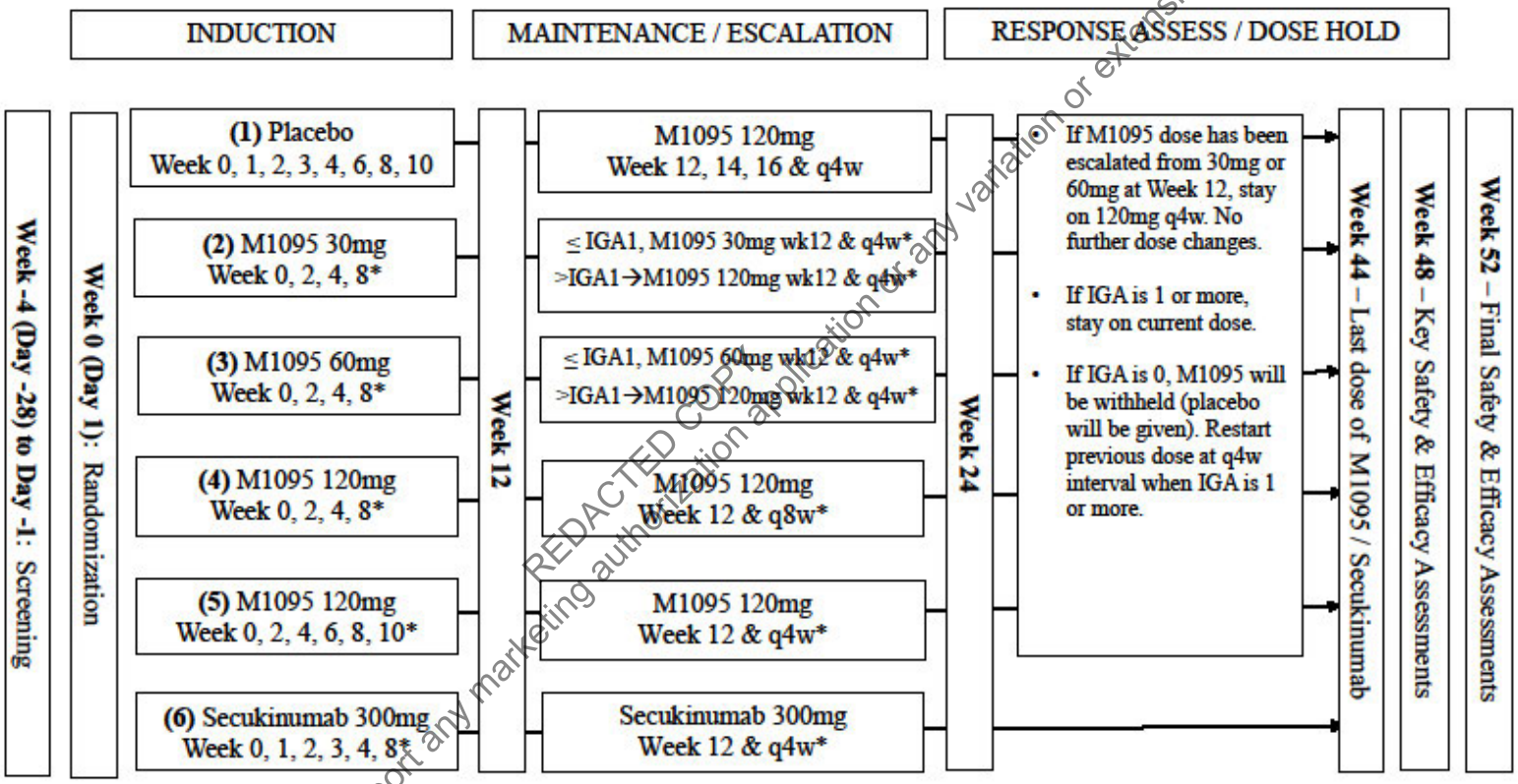
Interim analyses:
An independent Data Monitoring Committee (DMC) will be established to perform and review interim analyses during the study. The DMC will be operational prior to enrolment of the first subject into the study. The composition and operation of the DMC will be described in a DMC charter. 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 DMC will closely monitor the safety and tolerability data throughout the trial. No formal analysis of efficacy is planned during the double-blind, placebo-controlled 12-week induction phase.

An unblinded interim analysis of 12-week data will occur at the completion of the Week 12 period, while the study is still ongoing. These data will be shared with firewalled individuals who are not directly involved in the conduct of the study.

A second interim analysis will occur at the completion of the Week 24 period. All investigators and subjects will remain blinded to treatment assignments until the last subject completes the study and the final database lock occurs. Once the second interim database lock has occurred after Week 24, the sponsor study team will be unblinded.

1.2 Schema



* 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.

1.3 Schedule of Activities (SoA)

Visit	Screening	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Early D/C[A]
Week	N/A	0	1	2	3	4	6	8	10	12	14	16	20	24	28	32	36	40	44	48	52	N/A
Day	-28 to -1	1	8	15	22	29	43	57	71	85	99	113	141	169	197	225	253	281	309	337	365	N/A
Visit Window (in days)	N/A	N/A	±1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±5	±5	±5	±5	±5	±5	±5	N/A
Informed Consent	X																					
Demographics	X																					
Inc/Exc Criteria	X	X																				
Psoriasis Medical History	X																					
Prior Psoriasis Treatments	X																					
Other Medical History	X																					
Adverse Events	X[B]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[A]
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[A]
Skin Evaluation[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X[A C]
Physical Examination	X[D]	X				X				X				X			X			X		X[A]
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[A]
Laboratory Analysis Chemistry and Haematology (central)	X			X		X		X			X	X	X		X	X		X	X		X	X[A]
Laboratory Analysis Chemistry and Haematology (central, fasting)		X								X				X			X			X		
Urinalysis (local)	X	X								X				X			X			X		X[A]
Serum Pregnancy Test (central)	X																					
Urine Pregnancy Test (local)		X[E]				X[E]		X[E]		X[E]		X[E]	X[E]	X[E]	X[E]	X[E]	X[E]	X[E]	X[E]	X[E]	X[E]	X[A,E]
QuantiFERON®-TB Gold Test	X[F]																					
HBV, HCV, HIV Test (central)	X																					

Visit	Screening	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Early D/C[A]
Week	**N/A**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**N/A**
Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**N/A**
Visit Window (in days)	**N/A**	**N/A**	**±1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**N/A**
ECG standard 12 lead (central)	X									X				X			X			X		X[A]
Blood sample for Immunogenicity (pre-dose)		X		X		X		X		X				X			X		X	X	X[G]	X[A,G]
Blood sample for Pharmacokinetics (pre-dose)		X		X		X		X		X				X			X		X	X	X	X[A]
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X[L]	X	X	X	X	X	X	X	X[A]
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X[L]	X	X	X	X	X	X	X	X[A]
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X[L]	X	X	X	X	X	X	X	X[A]
DLQI[H]		X								X				X			X			X		X[A]
EQ-PSO[H]		X								X				X			X			X		X[A]
SF-36[H]		X								X				X			X			X		X[A]
PHQ-8[H]		X				X		X		X		X	X	X	X	X	X	X	X	X	X	X[A]
eC-SSRS[H]		X				X		X		X		X	X	X	X	X	X	X	X	X	X	X[A]
Chest X-Ray	X[I]																					
Randomization (via IRT)		X																				
Study Treatment (allocated via IRT)		X	X	X	X	X	X	X	X	X[J]	X	X	X	X[K]	X	X	X	X	X			

A. See Section 8.1.11 - Early Discontinuation Visit should be performed as close as possible to 28 days after the last dose of study drug, and prior to the initiation of any other biological therapy. The reason for discontinuation should be discussed with the Medical Monitor. All subjects should have further follow up by telephone, or if they have ongoing SAEs or AEs, by attending the study site approximately 8 weeks (56 days) after the last dose of study drug to report any new, and follow up any existing AEs. Subjects that have completed Early Discontinuation from study treatment will continue to be contacted by telephone as per the q4w study schedule up to Week 52.

B. AEs to be collected from the time of consent.

C. On skin evaluation, if a subject develops a cutaneous rash that is not typical of a psoriatic picture, the following evaluations should be conducted – photograph, skin biopsy, and skin culture for microbiological assessment. Any such rash should be discussed with the Medical Monitor (see Section 8.4.2 for details).

D. Physical examination includes subject's weight. Subject's height is measured only within the physical examination at Screening.

E. If a urine pregnancy test is positive, study treatment must be withheld. A serum pregnancy test (central) should be performed. See Section 10.4, Appendix 4 for details.
F. Quantiferon TB test must be study specific and can be performed either by the central or local laboratory. If a Quantiferon TB test result is 'indeterminate' the test must be repeated during the Screening period. If any Quantiferon TB test is 'positive' or if the first test and the repeat test are both 'indeterminate', the subject must be referred for tuberculosis workup per local guidelines. The subject is eligible for randomization if (i) they have a known history of latent TB and have completed a course of treatment or (ii) they have received sufficient treatment for latent TB to allow concomitant treatment with a biological therapy as per local guidelines (note these subjects must continue their concomitant latent TB treatment to completion while participating in the study, and if these subjects are outside of the screening window (>28 days since consent) when they become eligible to participate, they should be fully re-screened for the study). The subject is not eligible for randomization if either 'active tuberculosis is present' or if 'latent tuberculosis is present and is untreated per local guidelines.'
G. Subjects that test positive for anti-drug antibodies at the last study visit (either Week 52 or Early Discontinuation) may be requested to provide another sample approximately 6 to 12 months after study completion.
H. Patient Reported Outcomes should be conducted at the start of each visit, before other assessments.
I. Chest X-ray within 3 months of consent is considered acceptable. When performed as part of the Screening visit, the chest X-ray should be the last study procedure to be completed, as this will prevent unnecessary exposure to radiation if the subject is found to be ineligible following an earlier procedure. Investigator should follow up the results of the chest X-ray with the Medical Monitor if clinically indicated.
J. Subjects randomized to M1095 30mg or 60mg who do not achieve an IGA score of 0 or 1 at Week 12 will be dose escalated to 120mg q4w. All study drug is allocated via IRT.
K. Any subjects randomized to M1095 who did not undergo dose escalation at Week 12 and who achieve an IGA score of 0 at Week 24 will have study drug withheld and will receive placebo q4w. Subsequently, if IGA score is 1 or more, these subjects will re-commence M1095 at the dose they received prior to Week 24 on a q4w regimen at the visits scheduled by the protocol until the end of the treatment period. Dose will not be withheld for a second time, irrespective of subsequent IGA scores. All study drug is allocated via the IRT.
L. The investigator should carefully consider the subject's response at Week 24 and if there has been a worsening of psoriasis compared to baseline then the investigator should consider discontinuing the subject from the study if they are not receiving adequate benefit from their participation.

2.0 INTRODUCTION

M1095 is a trivalent monomeric nanobody® that neutralizes interleukins IL-17A, IL-17F, and IL-17A/F. A strong scientific and medical rationale exists for the use of M1095 in the treatment of autoimmune disease, including psoriasis.

2.1 Study Rationale

Despite several biologic treatment options, the development of new psoriasis therapies is important. M1095 is a viable investigational treatment of psoriasis with the potential for a similar or improved risk/benefit profile compared to available therapies. This is a phase 2b study to evaluate the safety and efficacy of M1095 for the treatment of moderate to severe plaque-type psoriasis.

2.2 Background

Psoriasis is a skin condition estimated to affect about 2-4% of the population in western countries with a higher prevalence in Caucasians and approximately equal frequency in males and females.[1] The most common form is psoriasis vulgaris (plaque-type psoriasis) which is characterized by lesions which often itch and burn and manifest as raised, inflamed, red skin covered with silvery, white scales. The disease can appear anywhere although it is most common on extensor surfaces such as elbows and knees, plus the scalp and lower back. Mild severity disease can often be managed with topical treatments. As the disease severity increases, phototherapy or systemic therapies such as retinoids, methotrexate, cyclosporine, apremilast, or biologic immune modifying agents are required for disease control.

The understanding of the pathophysiology behind psoriatic plaques has expanded markedly during the past twenty years leading to an expansion in the armamentarium for disease treatment. Cytokines which are known to play a role in psoriasis include, but are not limited to, TNF-α, IL-12, IL-23, and IL-17.[2] Since 2004, several biologic therapies targeting these cytokines have been developed and approved for the treatment of moderate to severe psoriasis. The first therapy targeting TNF-α was approved in 2004, a therapy targeting IL-12/IL-23 was approved in 2009, the first therapy targeting IL-17 was approved in 2015, and a therapy targeting only IL-23 was approved in 2017. While these therapies have significantly improved on prior treatments there are still significant unmet needs in psoriasis which drive continued development of new therapies.

IL-17 is a known target for psoriasis treatment and three drugs that target this mechanism are currently available. Secukinumab is a human immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds IL-17A, ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds IL-17A, and brodalumab is a human monoclonal IgG2 antibody that selectively binds to the IL-17 receptor inhibiting interactions with IL-17A, IL-17F, IL-17C, IL-17A/F and IL-25.[3]

M1095 differs from the approved therapies in several important ways which could provide a therapeutic advantage. First, it is a nanobody vs. an antibody. Nanobodies are a novel class of proteins that are based on single-domain antibody fragments and therefore are smaller and more robust than conventional antibodies.[4] Second, M1095 specifically targets IL-17A and IL-17F. Secukinumab and ixekizumab only interact with IL-17A and it has been reported that IL-17F also plays a role in psoriasis pathophysiology. Brodalumab does target both IL-17A and IL-17F; however, it also blocks the IL-17 receptor from interacting with several other cytokines (IL-17C and IL-25) which may account for additional untoward effects that are not related to its ability to treat psoriasis.

M1095 has been evaluated in subjects with psoriasis in study EMR200574-003, "A Multicenter, Phase 1, Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Safety, Tolerability, Immunogenicity, Pharmacokinetics, Pharmacodynamics and Efficacy of Multiple Ascending Doses of Subcutaneous M1095 (Anti-IL17A/F Nanobody) in Male and Female Subjects with Moderate to Severe Psoriasis." The phase 1 study demonstrated that M1095 was generally well tolerated with robust efficacy and a pharmacokinetic (PK) profile suitable for long-term dosing on a 4 weekly or 8 weekly schedule. Furthermore, the efficacy results were suggestive that M1095 at the proposed doses may be able to deliver an improvement in Psoriasis Area and Severity Index (PASI) 90 and PASI 100 responses compared to what has been described with currently approved IL-17 modulating therapies. A full description of the results for this study can be found in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

Despite several biologic treatment options, new psoriasis therapies are needed. M1095 is a viable candidate treatment with the potential for a similar or improved risk/benefit profile compared to available therapies. All subjects in this study will receive M1095 or secukinumab as those randomized to placebo will switch to M1095 at Week 12.

In EMR200574-003, subjects received three doses of M1095 at 2-week intervals over one month. Dose levels of 30mg through 240mg were tested. The study demonstrated that

- M1095 administered up to a dose of 240mg q2w x 3 was generally well tolerated in a group of 33 subjects with moderate to severe psoriasis.
- AUC and Cmax were dose proportional from 30mg to 240mg with a terminal half life of 11-12 days.
- A dose-response relationship was observed with PASI 75/90/100 responses.

The most common AEs (occurring in 2 or more of the 33 subjects treated with M1095) were pruritus, headache, hypertension, nasopharyngitis, somnolence and bronchitis. Two subjects discontinued due to AEs (an injection site reaction in a subject receiving 120mg and an elevation in aminotransferases in a subject receiving 240mg) and one SAE occurred (acute vestibular syndrome, in a subject receiving 30mg, which was deemed unrelated to study drug).

Subjects in the study were between 18 and 70 years old with moderate to severe psoriasis of at least 6 months duration, a static Physician's Global Assessment (sPGA) of ≥3, ≥10% body surface area and a PASI score of ≥12. PASI 75/90/100 responses at Week 12 (8 weeks after the last M1095 injection) ranged from 88%/50%/13% to 100%/100%/56%. Achievement of sPGA scores of 0 and 1 at week 12 ranged from 88% to 100%. A full description of the safety and efficacy data from this study can be found in the Investigator's Brochure.

Secukinumab is an IL-17 antagonist that was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2015 and is indicated for moderate to severe plaque-type psoriasis in adult subjects who are candidates for systemic therapy or phototherapy, the same population that will be enrolled in this study. The most common adverse reactions (>1%) are nasopharyngitis, diarrhea, and upper respiratory tract infection. Warnings and precautions include infections, tuberculosis, inflammatory bowel disease, and hypersensitivity reactions. In the pivotal phase 3 studies ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis), at the 300mg secukinumab dose PASI 75 responses ranged from 76 to 82% and PASI 90 responses ranged from 54 to 59%.[5] A full description of the safety and efficacy data for secukinumab can be found in the Prescribing Information[6] or Summary of Product Characteristics (SmPC).[7]

All subjects in this 52-week study will receive active therapy, 1/6 will be exposed to placebo for 12 weeks followed by M1095, 4/6 will be randomized to M1095 from the outset and 1/6 will receive secukinumab at the approved dose. Based on currently available data subjects should experience some improvement in their psoriasis with either M1095 or secukinumab. Of note, subjects on the lower doses of M1095 who do not achieve an IGA score of 0 or 1 at Week 12 will be increased to the highest dose.

The most likely predicted AEs based on the clinical studies conducted to date are infections, injection site reactions, and gastrointestinal upset. Less common, but more severe AEs which have been reported with other IL-17 modulating agents such as hypersensitivity reactions, more severe infections, and suicidality will be managed via inclusion/exclusion criteria, careful and frequent monitoring, and administration of all study drug in the clinic.

In cynomolgus monkeys, non-clinical toxicology studies lasting 26-weeks and 39-weeks minimal to mild reddish discoloration of the skin in the axillary and inguinal regions, associated with a histopathological diagnosis of superficial perivascular dermatitis, was observed. These findings improved but did not completely recover during the recovery period in these studies. The overall risk associated with these findings in human study subjects is low. If similar findings occur they will be observable on skin evaluation and managed appropriately.

Subjects will be followed closely (weekly during the first month, biweekly for the second and third month and then at least monthly for the remainder of the study) and observed via standard assessments including queries about AEs, periodic examinations, and laboratory assessments. Subjects who experience notable study drug related AEs or lab abnormalities will be discontinued (see Section 7.1).

In addition to the assessment of an individual's benefit-risk there will be an independent Data Monitoring Committee (DMC) that will evaluate study data periodically to ensure there are no new risks that emerge from the accumulating data.

3.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of four dose regimens of M1095 compared to placebo on achievement of an IGA score of 0 or 1 after 12 weeks of treatment in subjects with moderate to severe chronic plaque-type psoriasis.	• IGA score of 0 or 1 at Week 12, with an IGA reduction from baseline of at least 2 points.
Secondary	

• To evaluate the efficacy of M1095 compared to placebo during a 12-week treatment period on secondary endpoints: PASI 75, PASI 90, PASI 100, change in PASI and shift in IGA.
• 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.
	• Efficacy:
	  • PASI 75 at Week 12.
	  • PASI 90 at Week 12.
	  • PASI 100 at Week 12.
	  • PASI 75, PASI 90 and PASI 100 beyond Week 12.
	  • Change from baseline in PASI score and in total BSA affected by plaque-type psoriasis.
	  • Shift from baseline in IGA score category.
	• Safety:
	  • Adverse events, skin evaluation, laboratory assessments, vital signs, ECGs, drug discontinuations, and instruments to assess depression and suicidality [electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and Personal Health Questionnaire Depression Scale (PHQ-8)].

Exploratory	
• 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 PK of various doses and dose regimens of M1095. • Assessment of the development of anti-drug antibodies for various doses and dose regimens of M1095.	• Dermatology Life Quality Index (DLQI), Short Form 36 (SF-36), and EuroQuality of Life Questionnaire for Psoriasis (EQ-PSO). • Population PK evaluation. • Anti-drug antibodies: determination of binding and neutralizing antibodies defined by percentage of subjects with antibodies and titers of antibody. • Monitoring of pre-existing antibodies against M1095.

Objectives	Endpoints
• 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.	• IGA and PASI endpoints in subjects who dose escalate to 120mg M1095 q4w at Week 12. • IGA and PASI endpoints in subjects with an IGA score at 0 for whom M1095 is withheld at Week 24.

4.0 STUDY DESIGN

4.1 Overall Design

This is a multi-center 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. The study will consist of a 4-week screening period (Week -4 to Week 0), a 12 week treatment period which is placebo-controlled (Week 0 to Week 12), a 12 week maintenance/escalation period where all subjects are on active treatment (Week 12 to Week 24), a 24 week response assessment/dose hold period where active treatment is withheld if subjects being treated with M1095 have an IGA score of 0 at the beginning of the period (Week 24 to Week 48) and a final assessment period for safety follow up (Week 48 to Week 52). The study will be double-blind up to Week 24, with subject- and investigator-blind maintained throughout.

Subjects will be randomized 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. Placebo wk 0, 1, 2, 3, 4, 6, 8, 10 / M1095 120mg wk 12, 14, 16 and q4w.
2. M1095 30mg wk 0, 2, 4, 8, 12 and q4w.
3. M1095 60mg wk 0, 2, 4, 8, 12 and q4w.
4. M1095 120mg wk 0, 2, 4, 8, 12 and q8w.
5. M1095 120mg wk 0, 2, 4, 6, 8, 10, 12 and q4w.
6. Secukinumab 300mg wk 0, 1, 2, 3, 4, 8, 12 and q4w.

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

Subjects randomized to 30mg or 60mg M1095 who do not achieve an IGA score of 0 or 1 at Week 12 will be dose escalated to 120mg q4w starting at Week 12.

Any subjects randomized to M1095 who did not undergo dose escalation at Week 12 and who achieve an IGA score of 0 at Week 24 will have study drug withheld and will receive placebo q4w. Subsequently, if IGA score is 1 or more, these subjects will re-commence M1095 at the dose they received prior to Week 24 on a q4w regimen at the visits scheduled by the protocol until the end of the treatment period. Dose will not be withheld for a second time, irrespective of subsequent IGA scores.

Subjects receiving secukinumab will continue to receive 300mg q4w throughout the study.

The subject blind will be maintained by the use of M1095 and matched placebo. The syringes used for all M1095 and placebo doses will be identical. All subjects will receive two injections of 1mL at each visit. There is also physical protection of the blind. Subjects will be asked to wear an eye-mask for all injections.

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

4.2 Scientific Rationale for Study Design

The study design is similar to that utilized by several biologics in psoriasis for phase 2 and phase 3 studies. The evaluation of M1095 versus placebo at Week 12 is consistent with regulatory precedents and guidance.[8] The overall duration of 52 weeks will enable assessment of long term efficacy and safety as well as the effect of treatment withdrawal in subjects with an IGA score of 0. All subjects will be eligible for at least 36 weeks of active therapy with placebo subjects converting from placebo to M1095 at Week 12.

As described in the background and thoroughly covered in the Investigator's Brochure, IL-17 is a validated target in psoriasis. Furthermore, proof of concept has been obtained via the phase 1 multiple dose study in subjects with psoriasis. Secukinumab is an approved drug that also targets IL-17.

Inclusion and exclusion criteria described in Sections 5.1 and 5.2 have been developed to ensure a well-defined population where efficacy can be determined without introducing any unacceptable risks. The study design incorporates frequent visits and evaluations to optimize assessment of endpoints and collection of safety data.

4.3 Justification for Dose

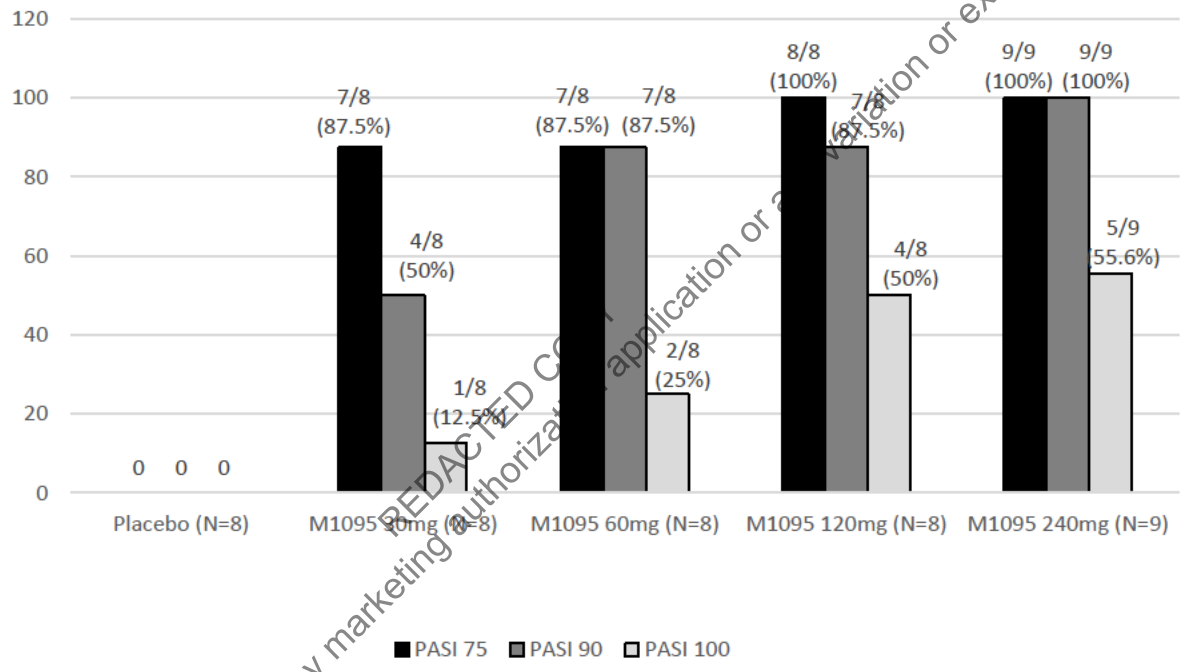
The M1095 doses selected for the study (30mg, 60mg, 120mg) are based on the results from the phase 1 multiple dose study EMR200574-003 in subjects with moderate to severe psoriasis (Figure 2). All doses in study EMR200574-003 showed efficacy based on PASI response, however, the lowest dose of 30 mg was less efficacious than the highest dose planned for this study, 120mg. This suggests that the doses selected are differentiated and will allow an understanding of the dose/exposure response relationship. It is notable that the dosing regimen employed in the phase 1 study was administered at Week 0, 2, and 4 followed by endpoint evaluation at Week 12.

In the current phase 2b study, q2w, q4w and q8w regimens will be evaluated. Simulations using the efficacy-exposure data from phase 1 suggest that PASI 100 scores at Week 12 will vary between approximately 45% to 60% in subjects receiving 30mg M1095 administered at Week 0, 2, 4, 8 and 12, and 72% to 85% in subjects receiving 120mg M1095 administered at Week 0, 2, 4, 6, 8, 10 and 12. While comparison between each treatment arm will not necessarily reveal statistically significant differences, exploratory comparisons between the various dose arms will enable exploration of several questions: (1) does the amount of drug significantly affect Week 12 response? (comparison of 30 mg, 60mg and 120 mg where drug is administered on an identical schedule); (2) does duration and schedule of loading affect Week 12 response? (comparison of 120mg administered as q2w x 7 and q2w x 3 followed by q4w x 2); (3) does frequency of administration affect longer term results? (comparison of Week 24 response for the different 120mg dose regimens).

The highest dose planned in this phase 2b study, 120mg, has shown adequate safety when administered q2w for three doses in the phase 1 study and appears to be toward the top of the

dose response curve at 12 weeks compared to a higher 240mg dose. A full description of the safety and efficacy from the phase 1 study can be found in the Investigator's Brochure.

Figure 2 – Proportion of Subjects with PASI 75/90/100 at Day 85 (Week 12) in Study EMR200574-003



4.4 End of Study Definition

The end of study participation for each subject will be after 52 weeks. The end of the overall study is defined as the date of the last subject's last visit globally across all countries.

At the time of the last subject's last visit, any SAEs or AESI that are unresolved will be considered ongoing.

5.0 STUDY POPULATION

Prospective approvals of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1. Ambulatory male and female subjects between 18 and 75 years of age at time of consent.

2. Subject has had stable moderate to severe plaque-type psoriasis for at least 6 months prior to randomization (e.g., no morphology changes or significant flares of disease activity in the opinion of the investigator).

3. Subject must be considered, in the opinion of the investigator, not adequately controlled by photo, topical or previous systemic treatments and a candidate for systemic biologic therapy.

4. Subject has Investigator's Global Assessment (IGA) ≥3, involved body surface area (BSA) ≥10% and PASI ≥12 at screening and at baseline.

5. Subject is in the opinion of the investigator able to comply with the study procedures.

6. Following verbal and written information about the study, subject must provide signed and dated informed consent before any study related activity is carried out.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Subject diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, or other skin conditions at the time of the screening visit (e.g., eczema) that would interfere with evaluations of psoriasis (Note: psoriatic arthritis is NOT exclusionary.)

2. Subject has drug-induced psoriasis (i.e. new onset or current exacerbation from beta-blockers, calcium channel inhibitors or lithium)

3. Other medical conditions:

    a. At the time of consent, subject has a planned in-patient surgical intervention between baseline and the Week 52 evaluation.

    b. Subject has an active infection or history of infections as follows:

i. Any active infection for which systemic anti-infectives were used within 28 days prior to randomization.

ii. A serious infection, defined as requiring hospitalization or intravenous anti-infectives within 8 weeks prior to randomization.

iii. Any history of bone infection requiring surgical intervention and/or intravenous antibiotics.

iv. Recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this study to be detrimental to the subject.

c. Subject has active tuberculosis.

d. Subject has a positive QuantiFERON®-TB Gold test for tuberculosis at screening, or if the first test and a repeat test are both indeterminate, unless (i) subject has a known history of latent TB and has completed a course of treatment or (ii) subject has received sufficient treatment for latent TB to allow concomitant treatment with a biological therapy as per local guidelines (note these subjects must continue their concomitant latent TB treatment to completion while participating in the study). If these subjects are outside of the screening window (>28 days since consent) when they become eligible to participate, they should be fully re-screened for the study.

e. Subject has an underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator places the subject at unacceptable risk for receiving an immunomodulatory therapy.

f. Subject has known history of inflammatory bowel disease.

g. Subject with known chronic liver disease or tests positive for hepatitis B virus (HBV) infection or has antibodies to hepatitis C virus (HCV) at screening. See Section 10.5 Appendix 5.

h. Subject has antibodies to human immunodeficiency virus (HIV) at screening. See Section 10.5, Appendix 5.

i. Subject has history of heart failure, myocardial infarction or unstable angina pectoris within the past 12 months prior to randomization.

j. Subject has uncontrolled hypertension characterized by two blood pressure measurements separated by at least 15 minutes with systolic >160mmHg or diastolic >100mmHg.

k. Subject has clinically significant electrocardiogram (ECG) abnormalities on centrally read ECG.

l. Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.

m. Subject has history of malignancy within 5 years EXCEPT cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma which has been treated and considered cured.

n. Subject has any concurrent medical condition that, in the opinion of the investigator, could cause this study to be detrimental to the subject.

4. Subject has laboratory abnormalities at screening, including any of the following:

a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x the upper limit of normal (one retest is allowed for aminotransferase abnormalities.)

b. Serum direct bilirubin >1.5 mg/dL.

c. White blood cell (WBC) count <3.00 x 10^3/µL.

d. Absolute neutrophil count <1.50 x 10^3/µL.

e. Absolute lymphocyte count <0.50 x 10^3/µL.

f. Platelet count <100,000/µL.

g. Creatinine clearance of <30mL/min (calculated via Cockcroft Gault). A subsequent 24-hour urine collection may be performed with the prior approval of the Medical Monitor, and if via urine collection the creatinine clearance is >30mL/min the subject is eligible for the study.

AMENDMENT FOR CZECH REPUBLIC
Creatinine clearance of <60 mL/min (calculated via Cockcroft Gault). A subsequent 24-hour urine collection may be performed with the prior approval of the Medical Monitor, and if via urine collection the creatinine clearance is >60mL/min the subject is eligible for the study.

h. Any other laboratory abnormality, which, in the opinion of the investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results.

5. Subject has used topical therapy as follows:

a. Topical psoriasis treatment within 14 days of randomization, including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, topical calcineurin inhibitors, retinoids, tazarotene, as well as emollients and other non-prescription topical products that contain urea, >3% salicylic acid, or alpha- or beta-hydroxyl acids, and medicated shampoos (e.g. those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues).

   Exceptions: mild/least potent topical steroids are permitted during **screening** for use limited to the face, axillae, and/or genitalia but **must be discontinued 24 hours prior to the baseline visit (randomization).**

b. Bland emollients (without alpha or beta hydroxy acids) within 24 hours of baseline visit randomization. Note that as per Section 6.5 **bland emollients (without alpha or beta hydroxy acids) may be used during the study but MAY NOT be used within 24 hours prior to any study visit.**

6. Subject has used the following within 28 days of randomization: ultraviolet A (UVA) light therapy (with or without psoralen); ultraviolet B (UVB) light therapy; excimer laser; oral retinoids; methotrexate; cyclosporine; systemically administered calcineurin inhibitors; azathioprine; thioguanine; hydroxyurea; cyclophosphamide; fumarates; apremilast; or oral or parenteral corticosteroids including intramuscular or intraarticular administration (exception: otic, nasal, ophthalmic, or inhaled corticosteroids within recommended doses is permitted); other non-biologic systemic therapy for psoriasis.

7. Subject is not willing to limit ultraviolet (UV) light exposure (e.g. sunbathing and/or the use of tanning devices) during the study.

8. Subject has received live vaccine(s) within 6 weeks of randomization.

9. Subject has received prior treatment at any time before screening with any compound (marketed or investigational) targeting IL-17 (i.e. direct inhibitor, receptor blocker, etc.).

10. Subject has received prior treatment at any time before screening with more than 2 biologic therapies (ustekinumab, tumour necrosis factor (TNF) targeting therapies, or investigational therapies).

11. Subject has received TNF targeting therapies in the 12 weeks prior to randomization, ustekinumab in the 6 months prior to randomization, or investigational biological therapies within 12 weeks, or within 5 half lives of randomization, whichever is the longer.

12. Subject has known sensitivity to any of the products or components to be administered during dosing

13. Subject has a history or evidence of suicidal ideation or behavior within the 12 months prior to randomization or evidence of severe depression at screening or baseline [i.e. severity level 3, 4 or 5 based on an assessment with the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)].

14. Subject has a history of chronic alcohol abuse or chronic drug abuse, or has used intravenous (IV) drugs in the past 2 years.

15. Women of child bearing potential who are not willing to use highly effective methods of birth control during treatment and for 12 weeks after the last dose of study drug. See Section 10.4, Appendix 4 for definition of child bearing potential and guidance on highly effective methods of birth control.

16. Subject has a positive serum pregnancy test during screening or a positive urine pregnancy test at baseline (Week 0, randomization visit) except those surgically sterile or at least 1 year postmenopausal.

17. Subject is pregnant or breast feeding, or planning to become pregnant while enrolled in the study and for 12 weeks after the last dose of study drug.

18. Male subjects who are not willing to use contraception during treatment and for 12 weeks after the last dose of study drug. See Section 10.4, Appendix 4 for definition of permitted methods of contraception in male subjects.

19. Subject will not be available for protocol required study visits or procedures, (e.g. venepuncture) to the best of the subject's and investigator's knowledge.

20. Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give informed consent and/or to comply with all required study procedures.

21. Subject is either

    a. currently enrolled in another interventional, investigational device or drug study.

    b. has been in another investigational device or drug study(s) in the 30 days prior to consent.

22. Subject is an employee of the study sponsor (Bond Avillion 2 Development LP), Avillion LLP, EMD Serono, Merck KGaA or any contract research organization (CRO) associated with the study.

23. Subject or subject's immediate family is working for or employed by the investigator.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Subjects should be fasting when they attend for the baseline (randomization) visit, and for Weeks 12, 24, 36 and 48. These visits should be conducted in the morning and the subject should not have had breakfast.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabis/Marijuana

There no specific restrictions on caffeine, alcohol, tobacco, or cannabis/marijuana, all of which can be used in moderation during the study. Non-smokers should not start smoking during the study.

5.3.3 Activity

UV light exposure (e.g. sunbathing and/or the use of tanning devices) must be limited for the course of the study.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the study but are not randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements[9] and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened. One central laboratory re-test for ALT and AST is permitted within the 28-day screening period. If treatment of latent tuberculosis is instigated and the use of biological therapy is permitted per local guidelines the subject may be enrolled into the study. In such cases, if the study screening period has extended beyond 28 days since consent, the subject should be fully re-consented and re-screened to check they remain eligible for the study.

6.0 STUDY DRUGS

Study drug is defined as any investigational product, marketed product or placebo, intended to be administered to a study subject according to the study protocol. All study drugs in this study are considered Investigational Medicinal Products (IMP).

Study drugs must NOT be used for any purpose other than as described in this protocol, and this includes other human studies, animal investigations and in vitro testing.

Only subjects enrolled in the study may receive study drugs and only authorised site staff may prepare, supply or administer study drugs.

6.1 Study Drugs Administered

Study drugs will be administered by subcutaneous injection. Before all injections, the appropriate personnel and requirements to treat severe allergic reactions should be available. A physician must be available at the time of each injection.

Treatment Groups

1. Placebo, in 2 x 1mL subcutaneous injections, given at Week 0, 1, 2, 3, 4, 6, 8 and 10. (These subjects will then receive study drug: M1095, 120mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1 mL placebo, given at Week 12, 14, 16, and q4w).

2. M1095, 30 mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1mL placebo, given at Week 0, 2, 4, 8, 12 and q4w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 1, 3, 6, 10 and 14).

3. M1095, 60 mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1mL placebo, given at Week 0, 2, 4, 8, 12 and q4w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 1, 3, 6, 10 and 14).

4. M1095, 120 mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1mL placebo, given at Week 0, 2, 4, 8, 12 and q8w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 1, 3, 6, 10, 14, 16, 24, 32 and 40).

5. M1095, 120 mg, in 2 x 1mL subcutaneous injections, i.e. 1mL study drug, 1mL placebo, given at Week 0, 2, 4, 6, 8, 10, 12 and q4w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 1, 3 and 14).

6. Secukinumab, 300mg, in 2 x 1mL (150mg/mL) subcutaneous injections, given at Week 0, 1, 2, 3, 4, 8, 12 and q4w. (These subjects will also receive placebo, in 2 x 1mL subcutaneous injections, at Week 6, 10 and 14).

The 30mg and 60mg M1095 doses (in Arms 2 and 3) will be escalated at Week 12 in subjects who have not achieved an IGA score of 0 or 1, as described in Section 6.6.1.

M1095 doses (in Arms 1 to 5) may be replaced by placebo at Week 24 as described in Section 6.6.2.

6.2 Preparation/Handling/Storage/Accountability

Further guidance and information can be found in the Study Drug Manual provided for the study.

The investigator is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Study drug storage and accountability will be reviewed by the unblinded monitor during routine monitoring visits.

Study drug will be provided as subject kits each containing 2 vials (A and B) of M1095 of the appropriate strength (60mg or 120mg) to reconstitute the randomized dose and/or matching placebo, and subject kits containing commercial secukinumab 2 x 150mg pre-filled syringes.

M1095 and placebo will be supplied as a lyophilized powder in glass vials. The 30mg dose will be reconstituted from a 60mg vial with 1mL placebo and 1mL sterile water for injection (WFI), the 60mg dose will be reconstituted from a 60mg vial with 1mL sterile WFI, and the 120mg dose will be reconstituted from a 120mg vial with 1mL sterile WFI. Secukinumab will be supplied as commercial pre-filled syringes, over-labelled and packaged for the study.

All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions (2 to 8ºC, 36 to 46ºF) with access limited to the investigator and authorized site staff.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies must be reported and resolved before the study drug is used.

Investigators and site staff are reminded to check temperatures daily (i.e., manually or by using alarm systems to alert of any excursions) and ensure that temperature monitoring device(s) is (are) working correctly as required for proper storage of study drug. Any temperature excursions should be documented and reported to the sponsor, noting any actions taken. Once a deviation is identified, study drug must be quarantined and not used until the sponsor provides documentation of permission that the study drug can be used.

All study drugs will be prepared for injection by an unblinded preparer in syringes with 1mL volume. The syringes for injection will be provided to the site approved study drug administrator, who is also unblinded (see Section 6.3 for further details). The unblinded preparer and the unblinded administrator may be the same person.

Study drug will be administered via subcutaneous injection. All doses are comprised of two injections, each of 1mL, which should be administered at least 5 centimetres apart on any quadrant of the abdomen or the upper thigh. The body location for injections should not be repeated at consecutive study visits. Injections should not be given in areas where the skin is

tender, bruised, erythematous, or indurated. Areas of the skin affected by psoriasis should be avoided as injection sites.

For subjects assigned to M1095 or placebo, the site approved unblinded administrator will be instructed to inject the subject with 1ml of solution from vial A and 1ml of solution from vial B. Subjects assigned to secukinumab will be dosed with 2 x 150mg/mL pre-filled syringes, as directed. Blinded study personnel should not be in attendance while study drug is being prepared or administered. Used syringes should be placed immediately out of sight in a sealed sharps container.

Subjects should be observed for approximately 2 hours after the first dose of study drug and 1 hour for subsequent doses. At Week 12 all subjects should be observed for approximately 2 hours. If a subject experiences symptoms indicative of an acute hypersensitivity reaction after an injection, this should be discussed with the Medical Monitor before the next study visit/injection.

Regulatory agencies require accounting for the disposition of all study drugs received by each clinical site. The investigator is responsible for maintaining information related to drug disposition which at minimum consists of the date received, date dispensed, quantity dispensed and the subject to whom the drug was dispensed.

At the end of the study, the investigator should return unused study drug and packaging to the sponsor's representative. Local destruction may be permitted with the sponsor's approval.

6.3 Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally assigned to randomized study drug using an Interactive Response Technology System (IRT). Before the study is initiated, the log in information and directions for the IRT (including the process for emergency unblinding) will be provided to each site, plus a back up telephone number and call-in directions.

Study drug will be dispensed at the study visits as summarized in the SoA (Section 1.3).

Any study drug that is prepared but not administered to a subject should not be re-dispensed.

Unblinding will only occur during the study in the case of subject emergencies where it is necessary to determine the subject's treatment assignment to ensure the best course of medical management is taken. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if the unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. While not required, it is recommended that the investigator should contact the Medical Monitor prior to unblinding unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, the sponsor must be notified within 24 hours of breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case record form (eCRF), as applicable.

The outer packaging of study kits will appear identical, but as the M1095 and placebo doses require reconstitution, and secukinumab is provided as commercially available pre-filled syringes (PFS), it is not possible to blind the study completely. An unblinded study drug preparer will be responsible for the reconstitution and dispensation of study drug and will endeavor to ensure that there are no differences in the time taken to dispense each arm of the study.

Once syringes for injection have been prepared, they will be provided to the study drug administrator, who will also be unblinded.

The study drug preparer and the study drug administrator may be the same person.

Other than the study drug preparer and administrator, the study team (including the IGA and PASI assessors) will be completely blinded throughout the study and will be kept physically separate from the preparation and administration of study medication.

The subject blind will be maintained by the use of M1095 and matched placebo. The syringes used for all M1095 and placebo doses will be identical. All subjects will receive two injections of 1mL at each visit. There is also physical protection of the blind. Subjects will be asked to wear an eye-mask for all injections.

An unblinded interim analysis of 12-week data will occur at the completion of the 12-week period, while the study is still ongoing. This will be managed by an independent DMC and statistical analysis group to preserve the blinding. This data will be shared with firewalled individuals who are not directly involved in the conduct of the study.

All members of the sponsor's study team will be blinded to subject treatment assignments until all subjects complete 24 weeks and the database is locked, with all queries through Week 24 resolved. After Week 24 data has been cleaned and locked, the study statistician and designated sponsor team members will be unblinded to perform analysis of key study endpoints. All other members of the sponsor's study team, site staff (except the unblinded preparer) and subjects will remain blinded until the end of study.

An unblinded study monitor will be assigned by the CRO to visit site and check the documentation maintained by the unblinded study preparer and administrator and all drug accountability records. The unblinded study monitor will not reveal any study details that could unblind the study to the blinded study monitor. In the event of a Quality Assurance audit, the auditor(s) will also be allowed access to unblinded study drug records at the site(s) to verify that randomization/dispensing has been performed accurately.

Laboratory personnel performing the bioanalytical PK sample analysis may receive an open randomization list to enable analysis of relevant samples. 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.

6.4 Study Drug Compliance

Site personnel will document the use of study drug appropriately. Compliance for all treatment groups will be reviewed by the sponsor's unblinded study monitor utilizing source documents, dispensing and inventory records, the Accountability Log, and study drug eCRFs. Study drug syringes will be disposed of immediately after administration in sealed sharps containers and cannot be checked. Accountability will be performed on the packaging and kits utilized for administration before destruction.

6.5 Previous and Concomitant Therapy, and Prohibited Medications

Any medication or vaccine (including over-the-counter or prescription medicines, cannabis/marijuana for medicinal use, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Therapies taken at/from the time of consent, but stopped prior to randomization, will be considered previous therapies.

Therapies taken from the time of randomization will be considered concomitant therapies.

The Medical Monitor should be contacted if there are any questions regarding previous or concomitant therapy.

Concomitant therapies that are prohibited throughout the course of the study are described in Table 1.

Table 1 Prohibited Concomitant Medications

Treatment [A, B]	Washout or minimum period since previous exposure (before randomization)
Any compound (marketed or investigational) targeting IL-17 (i.e. direct inhibitor, receptor blocker, etc.)	Subject is excluded from the study
Ustekinumab	6 months
Biological immunomodulating agents other than ustekinumab (e.g., adalimumab, etanercept, infliximab)	12 weeks
Investigational biological therapies	12 weeks or 5 half lives, whichever is the longer
Other systemic immunomodulating treatments and systemic treatments for psoriasis (e.g., oral retinoids, methotrexate, cyclosporine, systemically administered calcineurin inhibitors, azathioprine, thioguanine, hydroxyurea, cyclophosphamide, fumarates, apremilast,	4 weeks

Treatment [A, B]	Washout or minimum period since previous exposure (before randomization)
or oral or parenteral corticosteroids [CS][C] including intramuscular or intraarticular administration)	
Photochemotherapy (e.g., PUVA)	4 weeks
Phototherapy (e.g., UVA with or without psoralen, UVB)	4 weeks
Excimer laser	4 weeks
Topical psoriasis treatment, including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, topical calcineurin inhibitors, retinoids, tazarotene, as well as emollients and other non-prescription topical products that contain urea, >3% salicylic acid, or alpha- or beta-hydroxyl acids, and medicated shampoos (e.g. those that contain >3% salicylic acid, corticosteroids, coal tar, or vitamin D3 analogues)[D]	2 weeks
Live vaccinations	6 weeks
Non-biological investigational treatment or participation in any interventional trial	4 weeks or 5 half lives, whichever is the longer

A If a prohibited treatment is used during the study, the subject must discontinue the prohibited medication to continue in the study.

B In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator, and in consultation with the Medical Monitor. If the subject receives a live vaccination during the study, the subject must discontinue study treatment.

C Otic, nasal, ophthalmic, or inhaled CS (e.g., to treat asthma) are not considered "systemic immunomodulating treatments" and are therefore acceptable as co-medication.

D Mild/least potent topical steroids are permitted during screening for use limited to the face, axillae, and/or genitalia. These topical steroids must be stopped 24 hours prior to the baseline (randomization visit).

Bland emollients (without alpha or beta hydroxy acids) may be used during the study but may not be used within 24 hours of any study visit.

6.5.1 Rescue Medicine

Rescue medication is not permitted in this study.

6.6 Dose Modification

6.6.1 Week 12

Subjects randomized to placebo will receive M1095 120mg at Week 12, 14, 16 and then q4w.

Subjects randomized to M1095 30mg or 60mg and who do not achieve an IGA score of 0 or 1 at Week 12 will be dose escalated to receive M1095 120mg q4w.

Site personnel will enter the IGA score into the IRT prior to the study drug kit being assigned at Week 12.

6.6.2 Week 24

Any subjects on M1095 who did not undergo dose escalation at Week 12 and who achieve an IGA score of 0 at Week 24 will have study drug withheld and will receive placebo q4w.

Subsequently, if IGA score is 1 or more, these subjects will re-commence M1095 at the dose they received prior to Week 24 on a q4w regimen at the visits scheduled by the protocol until the end of the treatment period. Dose will not be withheld for a second time, irrespective of subsequent IGA scores.

At Week 24, subjects on secukinumab will continue to be treated q4w.

Site personnel will enter the IGA score into the IRT prior to the study drug kit being assigned at Week 24, 28, 32, 36, 40 and 44.

At Week 24, the investigator should carefully consider the subject's response and if there has been a worsening of psoriasis compared to baseline then the investigator should consider discontinuing the subject from the study if they are not receiving adequate benefit from their participation.

6.7 Treatment after the End of the Study

The final dose of study drug will be administered at the Week 44 visit with the final study visit occurring at Week 52.

Subjects that discontinue study treatment during the study should complete Early Discontinuation, with visits approximately 4 weeks (28 days) and 8 weeks (56 days) after the last dose of study drug (see the SoA, Section 1.3, and Sections 7.2 and 8.1.11). Once the Early Discontinuation visits have been completed, subjects will be contacted by telephone as per the q4w study schedule.

After study completion at Week 52, or after completion of the Early Discontinuation visits, subjects should be treated as per local guidance and physician recommendation.

7.0 DISCONTINUATION OF STUDY DRUG AND SUBJECT DISCONTINUATION/WITHDRAWAL

Subjects should be discontinued from study drug if any of the criteria described in Section 7.1 are met. Such subjects will continue to be followed for safety assessments as described in the SoA, Section 1.3, and Section 8.1.11.

Subjects may voluntarily withdraw from the study for any reason at any time, or be withdrawn by the investigator or the sponsor as per Section 7.2. The investigator should strongly recommend that withdrawn subjects return for follow-up visits approximately 28 days and 56 days after the last dose of study drug to assess their safety and, if willing, to assess duration of effect (e.g. rebound assessments). The information to be collected is identical to the Early Discontinuation visit, as described in the SoA (Section 1.3) and Section 8.1.11.

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Such subjects will be considered to have discontinued the study.

Subjects who are prematurely discontinued from study treatment, or who have chosen to withdraw from the study, or who are lost to follow up, will not be replaced.

7.1 Discontinuation of Study Drug

See the SoA (Section 1.3) and Section 8.1.11 for data to be collected at the time of study drug discontinuation, plus follow-up and for evaluations that need to be completed.

Study treatment must be discontinued under the following circumstances (all cases should be discussed with the Medical Monitor):

- Withdrawal of consent
- Emergence of the following:
    - AE considered related to study treatment including:
        - Clinically significant systemic hypersensitivity reaction following administration of study drug that does not respond to symptomatic treatment.
        - Severe (grade 3 or higher Common Terminology Criteria for AEs (CTCAE) Version 5.0) anaphylaxis (symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema / angioedema; hypotension).
        - Severe (grade 3 or higher CTCAE Version 5.0) serum sickness (severe arthralgia or arthritis; extensive rash, with steroids or intravenous fluids indicated).
            - Note that if a subject experiences symptoms consistent with a grade 2 serum sickness (moderate arthralgia, fever, rash, or urticaria, with antihistamine treatment indicated), and causality

by the study drug cannot be ruled out, the subject should return to site for an unscheduled visit. There should be a documented assessment and physical examination concurrent with the event. Grade 2 serum sickness does not require discontinuation of study drug, however the Medical Monitor should be informed.

- Any other severe (grade 3 CTCAE Version 5.0) event that does not resolve with supportive care.
- Any life threatening (grade 4 CTCAE Version 5.0) event.

- Any other AE that in the judgment of the investigator, and considering the subject's overall status, prevent the subject from continuing to participate in the study (for example, sepsis or serious infection).
- Laboratory findings as follows regardless of CTCAE Version 5.0 grade:
  - Total WBC count $<2.00 \times 10^3/\mu L$.
  - Total ANC $<1.00 \times 10^3/\mu L$.
  - Platelet count $<50{,}000/\mu L$.
  - Elevated transaminases (ALT or AST) >3 x upper limit of normal (ULN) and associated with total bilirubin >2 x ULN (without accompanying alkaline phosphatase elevation >2 x ULN suggestive of cholestasis) – i.e. subject meets Hy's Law criteria.
  - Elevated transaminases (ALT or AST) >5 x ULN without clear alternative etiology (tests should be repeated within 72 hours to verify the result prior to discontinuation.)
  - Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.
- Pregnancy (see Sections 8.5.5 and 10.4, Appendix 4).
- The subject develops a malignancy. (Exception: Subjects may be allowed to continue if they develop no more than 2 non-melanoma skin cancers (NMSC) during the study)
- Use of prohibited treatment as per recommendations in Section 6.5.

- Any other protocol deviation that results in a significant risk to the subject's safety.
- Administrative decision by the investigator, the sponsor or it's designee to stop the subject's study treatment for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Subject noncompliance (significant violation of protocol requirements or missing two consecutive visits).

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given subject if, on balance, continuation would be detrimental to the subject's well-being. The investigator should carefully consider the subject's response at Week 24 and if there has been a worsening of psoriasis compared to baseline then the investigator should consider discontinuing the subject from the study if they are not receiving adequate benefit from their participation.

The appropriate personnel from the study site and the sponsor or it's designee will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

Subjects who discontinue study treatment should NOT be considered withdrawn from the study. They will continue to be followed up for assessments. See the SoA, Section 1.3 and Section 8.1.11 for the required assessments of these subjects after study treatment discontinuation.

Subjects should be considered to still be on study unless any of the criteria for study withdrawal are met (see Section 7.2).

7.1.1 Temporary Discontinuation

Temporary discontinuations are not permitted in this study. Any missed doses should be discussed with the Medical Monitor.

7.1.2 Rechallenge

Rechallenge is defined as the re-introduction of study drug following a temporary withdrawal/ dose hold for safety related reasons.

Rechallenge is not permitted for any reason including after study drug being withheld due to related/possibly related AEs; in these circumstances the Medical Monitors should be consulted prior to withholding study drug and the subject considered for permanent discontinuation.

7.2 Subject Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator or the sponsor for safety, behavioral, compliance, or administrative reasons.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the applicable eCRF. The withdrawn subjects must return for a follow-up visit approximately 28 days after the last dose of study drug to assess their efficacy, safety, quality of life (QoL), report any AEs and assess duration of effect (e.g. rebound assessments). A further visit/telephone call should be conducted approximately 56 days after the last dose of

study drug to follow up on AEs. The information to be collected is identical to the Early Discontinuation visit 1 and visit 2, as described in the SoA (Section 1.3) and Section 8.1.11.

7.3 Lost to Follow Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

For subjects who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible. The subject should be counselled on the importance of maintaining the assigned visit schedule and it should be ascertained whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have discontinued from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Study visit dates are scheduled relative to Week 0.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Patient Reported Outcomes (PROs) during any visit should be conducted before other tests, procedures, or consultations.
- IGA, BSA and PASI during any visit should be conducted after the PROs (if applicable) and before other tests, procedures and consultations. As far as possible, the same evaluator should perform the IGA, BSA and PASI at all visits for a particular subject, especially at Week 0 (randomization), Week 12, and Week 24.
- The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 565mL, with a maximum 50mL taken at any visit. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Study Procedures

8.1.1 Screening

Subjects will attend for a Screening Visit during the 4 weeks (28 days) prior to Week 0/randomization. This is designed to assess the inclusion/exclusion criteria and establish baseline characteristics.

The approved consent form must be signed and dated by the subject and the consenting investigator prior to any study related procedures being conducted. AEs will be collected from the time that consent is signed.

IGA, BSA and PASI should be performed before any other study procedures, assessments or consultations. The following assessments will be performed and information collected:-

- Demographics
- Inclusion/Exclusion Criteria
- Psoriasis Medical History
- Prior Psoriasis Treatments
- Other Medical History

- IGA
- BSA
- PASI
- Adverse events are to be recorded from the time of consent
- Concomitant Medications
- Skin Evaluation
- Physical Examination
- Vital Signs
- Laboratory Analysis Chemistry and Haematology (Central Laboratory)
- Urinalysis (Local)
- Serum Pregnancy Test (Central Laboratory)
- ECG (Standard 12 Lead, Central ECG Laboratory)
- QuantiFERON®-TB Gold Test (Local or Central Laboratory)
    - If a local or central Quantiferon TB test result is 'indeterminate' the test must be repeated during the screening period.
    - If any Quantiferon TB test is 'positive' or if the first test and the repeat test are both 'indeterminate', the subject must be referred for tuberculosis workup per local guidelines.
    - If any Quantiferon TB test is 'positive' or if the first test and the repeat test are both 'indeterminate', the subject is eligible for randomization if (i) they have a known history of latent TB and have completed a course of treatment or (ii) they have has received sufficient treatment for latent TB to allow concomitant treatment with a biological therapy as per local guidelines (note these subjects must continue their concomitant latent TB treatment to completion while participating in the study, and if these subjects are outside of the screening window (>28 days since consent) when they become eligible to participate, they should be fully re-screened for the study).
    - If any Quantiferon TB test is 'positive' or if the first test and the repeat test are both 'indeterminate', the subject is not eligible for randomization if either 'active tuberculosis is present' or if 'latent tuberculosis is present and is untreated per local guidelines.'
- HBV, HCV and HIV Testing (Central Laboratory), Section 10.5, Appendix 5

- Chest X-Ray (CXR) – CXR within 3 months of consent is considered acceptable. When performed as part of the Screening visit, the chest X-ray should be the last study procedure to be completed, as this will prevent unnecessary exposure to radiation if the subject is found to be ineligible following an earlier procedure. Investigator should follow up the results of the chest X-ray with the Medical Monitor if clinically indicated.

8.1.2 Week 0 / Randomization

At Week 0, subjects who meet the inclusion/exclusion criteria will be randomized.

Fasting blood samples should be obtained, so the visit should be conducted in the morning and the subject should not have had breakfast.

Patient reported outcomes (PRO) i.e. DLQI, EQ-PSO, SF-36, PHQ-8, and eC-SSRS should be performed before any other study procedures, assessments or consultations.

IGA, BSA and PASI should be conducted after the PROs and before other tests, procedures and consultations.

The first dose of study drug should be administered **after** completion of all other study procedures.

The following assessments will be performed and information collected:-

- Repeat check of Inclusion/Exclusion Criteria
- AEs
- Concomitant Medications
- DLQI
- EQ-PSO
- SF-36
- PHQ-8
- eC-SSRS
- IGA
- BSA
- PASI
- Skin Evaluation
- Physical Examination
- Vital Signs

- Laboratory Analysis Chemistry and Haematology (Fasting, Central Laboratory)
- Urinalysis (Local)
- Urine Pregnancy Test (Local) – if positive, study drug must be withheld and a Serum Pregnancy Test (Central Laboratory) performed
- Blood Sample for Immunogenicity (must be pre-dose)
- Blood Sample for Pharmacokinetics (must be pre-dose)
- Randomization (via IRT)
- Study Treatment (allocated via IRT)

8.1.3 Weeks 1, 3, 6, 10

There is a visit window of ±1 day for Weeks 1 and 3, and ±2 days for Weeks 6 and 10.

IGA, BSA and PASI should be performed before any other study procedures, assessments or consultations.

Study drug should be administered **after** completion of all other study procedures.

The following assessments will be performed and information collected:-

- IGA
- BSA
- PASI
- AEs
- Concomitant Medications
- Skin Evaluation
- Vital Signs
- Study Treatment (allocated via IRT)

8.1.4 Week 2

There is a visit window of ±1 day for the Week 2 visit.

IGA, BSA and PASI should be performed before any other study procedures, assessments or consultations.

Study drug should be administered **after** completion of all other study procedures.

The following assessments will be performed and information collected:

- IGA

- BSA
- PASI
- AEs
- Concomitant Medications
- Skin Evaluation
- Vital Signs
- Laboratory Analysis Chemistry and Haematology (Central Laboratory)
- Blood Sample for Immunogenicity (must be pre-dose)
- Blood Sample for Pharmacokinetics (must be pre-dose)
- Study Treatment (allocated via IRT)

8.1.5 Week 4

There is a visit window of ±1 day for the Week 4 visit.

Patient reported outcomes (PRO) i.e. PHQ-8, and eC-SSRS should be performed before any other study procedures, assessments or consultations.

IGA, BSA and PASI should be conducted after the PROs and before other tests, procedures and consultations.

Study drug should be administered **after** completion of all other study procedures.

The following assessments will be performed and information collected:

- PHQ-8
- eC-SSRS
- IGA
- BSA
- PASI
- AEs
- Concomitant Medications
- Skin Evaluation
- Physical Examination
- Vital Signs
- Laboratory Analysis Chemistry and Haematology (Central Laboratory)
- Urine Pregnancy Test (Local) – if positive, study drug must be withheld and a Serum Pregnancy Test (Central Laboratory) performed

- Blood Sample for Immunogenicity (must be pre-dose)
- Blood Sample for Pharmacokinetics (must be pre-dose)
- Study Treatment (allocated via IRT)

8.1.6 Weeks 8, 44, 52

There is a visit window of ±2 days for Week 8, and ±5 days for Weeks 44 and 52.

Patient reported outcomes (PRO) i.e. PHQ-8, and eC-SSRS should be performed before any other study procedures, assessments or consultations.

IGA, BSA and PASI should be conducted after the PROs and before other tests, procedures and consultations.

Study drug should be administered **after** completion of all other study procedures.

The following assessments will be performed and information collected:

- PHQ-8
- eC-SSRS
- IGA
- BSA
- PASI
- AEs - SAEs and AEs will be followed until resolution, stabilization or the event is otherwise explained or the subject is lost to follow up (see Section 7.3). AEs not considered serious or as an AESI will be considered ongoing if they have not resolved by Week 52.
- Concomitant Medications
- Skin Evaluation
- Vital Signs
- Laboratory Analysis Chemistry and Haematology (Central Laboratory)
- Urine Pregnancy Test (Local) – if positive, study drug must be withheld and a Serum Pregnancy Test (Central Laboratory) performed
- Blood Sample for Immunogenicity (must be pre-dose) – subjects testing positive at Week 52 may be requested to provide another sample 6 to 12 months after study completion
- Blood Sample for Pharmacokinetics (must be pre-dose)
- Study Treatment (allocated via IRT) with the exception of Week 52

- At Week 52, male and female subjects of child bearing potential should be reminded that they must use highly effective contraception for a further 4 weeks

8.1.7 Weeks 12, 24, 36, 48

There is a visit window of ±2 days for Weeks 12 and 24, and ±5 days for Weeks 36 and 48.

Fasting blood samples should be obtained, so the visit should be conducted in the morning and the subject should not have had breakfast.

Patient reported outcomes (PRO) i.e. DLQI, EQ-PSO, SF-36, PHQ-8, and eC-SSRS should be performed before any other study procedures, assessments or consultations.

IGA, BSA and PASI should be conducted after the PROs and before other tests, procedures and consultations.

Study drug should be administered **after** completion of all other study procedures.

The following assessments will be performed and information collected:-

- DLQI
- EQ-PSO
- SF-36
- PHQ-8
- eC-SSRS
- IGA
- BSA
- PASI
- AEs
- Concomitant Medications
- Skin Evaluation
- Physical Examination
- Vital Signs
- Laboratory Analysis Chemistry and Haematology (Fasting, Central Laboratory)
- Urinalysis (Local)
- Urine Pregnancy Test (Local) – if positive, study drug must be withheld and a Serum Pregnancy Test (Central Laboratory) performed
- ECG (Standard 12 Lead, Central ECG Laboratory)

- Blood Sample for Immunogenicity (must be pre-dose)
- Blood Sample for Pharmacokinetics (must be pre-dose)
- Study Treatment (allocated via IRT) with the exception of Week 48
- At Week 24, the investigator should carefully consider the subject's response and if there has been a worsening of psoriasis compared to baseline then the investigator should consider discontinuing the subject from the study if they are not receiving adequate benefit from their participation.

8.1.8 Week 14

There is a visit window of ±2 days for the Week 14 visit.

IGA, BSA and PASI should be performed before any other study procedures, assessments or consultations.

Study drug should be administered **after** completion of all other study procedures.

The following assessments will be performed and information collected:-

- IGA
- BSA
- PASI
- AEs
- Concomitant Medications
- Skin Evaluation
- Vital Signs
- Laboratory Analysis Chemistry and Haematology (Central Laboratory)
- Study Treatment (allocated via IRT)

8.1.9 Week 16, 20, 28, 32, 40

There is a visit window of ±2 days for Weeks 16 and 20, and ±5 days for Weeks 28, 32 and 40.

Patient reported outcomes (PRO) i.e. PHQ-8, and eC-SSRS should be performed before any other study procedures, assessments or consultations.

IGA, BSA and PASI should be conducted after the PROs and before other tests, procedures and consultations.

Study drug should be administered **after** completion of all other study procedures.

The following assessments will be performed and information collected:

- PHQ-8
- eC-SSRS
- IGA
- BSA
- PASI
- AEs
- Concomitant Medications
- Skin Evaluation
- Vital Signs
- Laboratory Analysis Chemistry and Haematology (Central Laboratory)
- Urine Pregnancy Test (Local) – if positive, study drug must be withheld and a Serum Pregnancy Test (Central Laboratory) performed
- Study Treatment (allocated via IRT)

8.1.10 Unscheduled Visit

Subjects may return to site for an Unscheduled Visit as clinically indicated. Laboratory assessments performed at an Unscheduled Visit should be sent to the central laboratory.

All assessments should be documented in the medical record and entered in the eCRF.

8.1.11 Early Discontinuation

The Early Discontinuation Visit involves two contacts with the subjects. The subject should attend the study site as close to possible to 4 weeks (28 days) after the last dose of study drug, and prior to the initiation of any other biological therapy. The reason for discontinuation should be discussed with the Medical Monitor. All subjects should then have further follow up either by telephone, or if they have ongoing SAEs or AEs, by attending the study site approximately 8 weeks (56 days) after the last dose of study drug to report any new, and follow up any existing AEs.

Patient reported outcomes (PRO) i.e. DLQI, EQ-PSO, SF-36, PHQ-8, and eC-SSRS should be performed before any other study procedures, assessments or consultations.

IGA, BSA and PASI should be conducted after the PROs and before other tests, procedures and consultations.

The following assessments will be performed and information collected:-

Visit 1 – As close as possible to 4 weeks (28 days) after the last dose of study drug, and prior to the initiation of any other biological therapy.

- DLQI
- EQ-PSO
- SF-36
- PHQ-8
- eC-SSRS
- IGA
- BSA
- PASI
- AEs
- Concomitant Medications
- Skin Evaluation
- Physical Examination
- Vital Signs
- Laboratory Analysis Chemistry and Haematology (Central Laboratory)
- Urinalysis (Local)
- Urine Pregnancy Test (Local)
- ECG (Standard 12 Lead, Central ECG Laboratory)
- Blood Sample for Immunogenicity – subjects testing positive may be requested to provide another sample six to twelve months after study completion
- Blood Sample for Pharmacokinetics

Visit 2 / Telephone Call – As close as possible to 8 weeks (56 days) after the last dose of study drug

- AEs
- Concomitant medication
- Male and female subjects of child bearing potential should be reminded that they must use highly effective contraception for a further 4 weeks

Following completion of the Early Discontinuation visits, subjects will continue to be contacted by telephone q4w as per the study schedule up to Week 52. The following information will be collected.

- AEs
- Concomitant medication
- Any new treatments for psoriasis

8.2 Efficacy Assessments

Efficacy evaluations selected for this study are consistent with those used to evaluate other therapies for psoriasis.

The IGA and PASI will be administered by site personnel according to the SoA (Section 1.3). All assessors of IGA and PASI must be qualified, experienced in evaluating subjects with psoriasis in clinical trials, and have completed study specific training in IGA and PASI rating. It is recommended that the same assessor conducts the IGA and PASI at all visits for a particular subject, but especially at Week 0 (randomization), Week 12, and Week 24.

8.2.1 Investigator's Global Assessment (IGA mod 2011)

IGA will be conducted for overall psoriatic disease as indicated in the SoA (Section 1.3).

The IGA rating scale for overall psoriatic disease is shown in Section 10.6.1, Appendix 6.

The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points.[10] The IGA mod 2011 is thought to better correlate with PASI 90 responses.

The IGA mod 2011 used in this study is static, i.e. it refers exclusively to the subject's disease state at the time of the assessments, and does not attempt a comparison with any of the subject's previous disease states, whether at baseline or at a previous visit.

The IGA mod 2011 score will initially be recorded on paper, and then entered in the IRT/eCRF.

8.2.2 Assessment of Total Body Surface Area (BSA) and Psoriasis Area and Severity Index (PASI)

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see Section 10.6.2, Appendix 6).

The PASI combines assessments of the extent of body-surface area involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no psoriasis to 72.0 for the most severe disease.[11, 12] See Section 10.6.2, Appendix 6 for details.

Subjects achieving PASI 75, PASI 90, or PASI 100 are defined as having an improvement of at least 75%, 90%, or 100%, respectively, in PASI score from baseline.

The site will initially record assessments on paper, and will then enter the data into the eCRF, which will auto-calculate the PASI score (no manual PASI calculations will be performed by the site).

8.3 Quality of Life Instruments

8.3.1 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts.[13] The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in 55 languages. The recall period is the last week and the instrument requires 1 to 2 minutes for completion. Each item has four response categories, ranging from 0 (not at all) to 3 (very much). "Not relevant" is also a valid response and is scored as 0. The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30, and higher scores indicate greater health-related quality-of-life impairment. Additionally, each subscale of the DLQI may be analyzed separately.

The DLQI questionnaire will be completed by the subject as indicated in the SoA (Section 1.3). It will be completed using an electronic tablet device.

8.3.2 Short-Form 36 (SF-36)

The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section.[14, 15] Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score the less disability.

The eight sections are:

[redacted]

The SF-36 questionnaire will be completed by the subject as indicated in the SoA (Section 1.3). It will be completed using an electronic tablet device.

8.3.3 Euro-Quality of Life Questionnaire for Psoriasis (EQ-PSO)

EQ-5D is a generic instrument to assess a subject's health status. It provides a simple descriptive profile and a single index value for health status.[16]

The instrument essentially consists of 2 pages – the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 response levels: no problems, some problems, severe problems. The subject is asked to indicate their health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. In the EQ-PSO two additional dimensions, skin irritation and self confidence, have been added to make the questionnaire more disease specific for psoriasis.[17]

The VAS records the subject's self-rated health on a vertical, VAS where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable helath state.' This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

The EQ-PSO questionnaire will be completed by the subject as indicated in the SoA (Section 1.3). It will be completed using an electronic tablet device.

8.4 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will include collection of AEs, skin evaluation, laboratory values, vital signs, ECGs, drug discontinuations, and instruments to assess depression and suicidality [electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and Personal Health Questionnaire Depression Scale (PHQ-8)]. Blinded data will be reviewed during the study. An independent Data Monitoring Committee (DMC) will have access to unblinded information and will conduct periodic scheduled reviews as well as ad hoc reviews as needed.

8.4.1 Physical Examination

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Weight will also be measured and recorded.

Height will be measured at screening only.

8.4.2 Skin Evaluation

Subjects are expected to manifest skin findings associated with psoriasis which may include stable disease, worsening disease, or improving disease.

If a subject develops a clinically significant cutaneous rash that is not typical of a psoriatic picture, then the following evaluations should be conducted:

- Photographs

  - Upper and lower body, front and back, 4 pictures in total. Further close up pictures (15cm x 15cm, 6 inches x 6 inches) should be taken of any areas of interest.

- Skin biopsy
  - Two ≥4mm punch biopsies, one of normal skin, one within the rash.
- Skin culture

Detailed instructions for these evaluations will be provided as Skin Evaluation Instructions for the study.

The Medical Monitor should be notified if photographs/skin biopsy/skin culture are being conducted and the subject should be treated as indicated while he/she continues study therapy.

8.4.3 Vital Signs

Vital signs will be measured after at least 5 minutes rest, and will include temperature (oral, axillary, core, temporal, or tympanic), sitting or supine blood pressure and heart rate.

8.4.4 Electrocardiograms

12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

At each time point, triplicate ECGs are required. Three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

ECG should also be performed at any time in the study if clinically indicated.

Digital ECGs will be transmitted to a central vendor who will assess ECG measurements for screening requirements prior to randomization.

The investigator is to assess ECG measurements for safety and should report any clinically significant findings as adverse events.

8.4.5 Clinical Safety Laboratory Assessments

See Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed by the central laboratory and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within eight weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor.

- All protocol-required laboratory assessments, as defined in Section 10.2, Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory assessments performed at the study site's local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the values must be recorded in the eCRF.

8.4.6 Depression and Suicidal Risk Monitoring

In studies of brodalumab, there have been reports of suicidal ideation or behavior. The sponsor considers it important to monitor for such events before and during this clinical study.

Subjects being treated in this study should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing study drug in subjects who experience signs of suicidal ideation or behavior.

Families and caregivers of study subjects should be instructed to monitor for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be assessed during the study using the electronic Columbia Suicide Severity Rating Scale (e-C-SSRS). Depression will be assessed using the Patient Health Questionnaire-8 (PHQ-8).

8.4.6.1 Electronic Self Rated Version, Columbia-Suicide Severity Rating Scale (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.[18, 19, 20] Subjects respond to standardized clinical questions that are presented in a uniform fashion. The eC-SSRS defines five subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The eC-SSRS takes approximately 3 to 10 minutes to complete.

The eC-SSRS questionnaire will be completed by the subject as indicated in the SoA (Section 1.3). It will be completed using an electronic tablet device.

8.4.6.2 Patient Health Questionnaire (PHQ-8)

The PHQ-8 is a validated and widely used eight-item version of the Patient Health Questionnaire depression scale designed to clinically assess subjects for symptoms and signs of depression.[21, 22] The PHQ-8 takes approximately 3 minutes to complete and will be completed by the subject as indicated in the SoA (Section 1.3). It will be completed using an electronic tablet device.

8.5 Adverse Events (AEs) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Section 10.3, Appendix 3.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study drug.

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. These events are based on Phase 1 data and findings with other IL-17 modulating drugs. Additional adverse events may be identified as being of special interest during the study and prior to the first unblinding. Formal pre-specified evaluations beyond the discontinuation criteria in Section 7.1 are not planned at this time.

If a subject reports symptoms consistent with a grade 2 serum sickness while between study visits, and causality by the study drug cannot be ruled out, the subject should return to site for an unscheduled visit if symptoms recur after the next dose. There should be a documented assessment and physical examination concurrent with the event

8.5.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from the signing of the informed consent form (ICF).

Medical conditions that begin before the start of study drug but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section, unless related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 10.3, Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after the conclusion of a subject's study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3, Appendix 3.

8.5.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.5.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. SAEs and AEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). AEs not considered serious or as an AESI will be considered ongoing if they have not resolved by Week 52. Further information on follow-up procedures is given in Section 10.3, Appendix 3.

8.5.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study drug under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the

regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators. AEs/SAEs must be followed up and reported as appropriate for at least 8 weeks (5 terminal half lives) after the last study dose.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC if appropriate according to local requirements.

8.5.5 Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment and until at least 12 weeks (>5 terminal half lives) after the last study dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4, Appendix 4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported to the sponsor or designee within 24 hours.

8.5.6 Cardiovascular and Death Events

Cardiovascular AEs should be reported as AEs/SAEs as described in Sections 8.5 and 10.3, Appendix 3.

Any subject deaths that occur during the study should be considered SAEs and reported as per Sections 8.5 and 10.3, Appendix 3. If a death occurs, the investigator may be asked to provide a copy of any post-mortem findings including histopathology.

8.5.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

All AEs and outcomes should be reported as described in Sections 8.5 and 10.3, Appendix 3.

8.6 Overdose and Medication Errors

There is no data regarding overdose of M1095.

Secukinumab doses of up to 30 mg/kg intravenously have been administered in clinical trials without dose-limiting toxicity. In the event of overdosage, it is recommended that the subject

be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

Medication errors may result, in this study, from the administration of an unassigned treatment to the wrong subject, errors related to storage requirements, or administration of an expired product. All overdoses occurring to a study subject are to be captured on the AE page of the eCRFs and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the study drug.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error, and, if applicable, any associated AE(s) is captured on an AE eCRF page.

8.7 Pharmacokinetics

Pharmacokinetic samples will be collected at the timepoints specified on the SoA (Section 1.3).

Samples will be shipped initially to the study's central laboratory and tested by the sponsor or sponsor's designee.

Serum M1095 levels will be assessed at trough (i.e. before study drug is given) at the following visits: Weeks 0, 2, 4, 8, 12, 24, 36, 44, 48, 52 and Early Discontinuation. M1095 serum concentrations will be summarized at these timepoints.

Drug concentration information will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Details of the analysis will be provided either in the Statistical Analysis Plan (SAP), or in a separate PK Plan, prior to the analysis taking place.

8.8 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9 Genetics

Planned genetic analysis is not performed in this study. Unscheduled genomic biomarkers may be assessed as described in Section 8.10.

8.10 Biomarkers

Biomarkers are not routinely evaluated in this study. However, if a subject develops a clinically significant cutaneous rash that is not typical of psoriasis, two ≥4mm punch biopsies, one of normal skin, and one from skin within the rash will be obtained. The biopsies will be prepared and sent to a specialist laboratory for analysis of genomic biomarkers, specifically the expression of inflammatory mediators that characterize various immune reactions.

8.10.1 Immunogenicity Assessments

Antibodies to M1095 will be evaluated in serum samples collected at the timepoints specified on the SoA (Section 1.3)

Samples will be shipped initially to the study's central laboratory and tested by the sponsor or sponsor's designee.

Serum anti-drug antibodies will be assessed at trough (i.e. before study drug is given) at the following visits: Weeks 0, 2, 4, 8, 12, 24, 36, 44, 48, 52 and Early Discontinuation.

Serum samples will be screened for antibodies binding to M1095 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to M1095 and/or further characterize the immunogenicity of M1095.

The detection and characterization of antibodies to M1095 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to study drug will also be evaluated for M1095 serum concentration (see Section 8.7) to enable interpretation of the antibody data. Positive samples for anti-drug antibodies will be evaluated to determine if the antibodies are neutralizing or non-neutralizing.

If a subject's final anti-drug antibody sample is positive (i.e. sample from Week 52 or sample from an Early Discontinuation visit) then the sponsor may request an addition sample be collected approximately six to twelve months after completion of the study. Subjects will be informed of this in the consent form and will have the option to refuse this additional sample.

With a subject's consent, samples may be stored following the last subject's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to M1095.

8.11 Health Economics

This study will not collect data for Health Economics.

9.0 STATISTICAL ANALYSIS

Statistical analysis of this study will be the responsibility of the sponsor or its designee.

Continuous data will be summarized in terms of the number of observations (n); mean; standard deviation and/or standard error of the mean, if applicable; median; minimum; and maximum.

Categorical data will be summarized in terms of the number of observations (n), frequency count, and percentages.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate. Complete details of the planned analyses will be documented in the SAP.

9.1 Statistical Hypotheses

The primary endpoint is achievement of an IGA score of 0 or 1 at Week 12, with an IGA reduction of at least 2 points from baseline. The proportion of subjects in the Intent to Treat (ITT) Analysis Set with an IGA score of 0 or 1 at Week 12 will be used to compare treatment arms. The following null hypotheses will be tested at Week 12:

- H1: M1095 30mg q2w x 3, followed by 30mg q4w x 1, is not different from placebo with respect to achievement of IGA scores of 0 or 1.
- H2: M1095 60mg q2w x 3, followed by 60mg q4w x 1, is not different from placebo with respect to achievement of IGA scores of 0 or 1.
- H3: M1095 120mg q2w x 3, followed by 120mg q4w x 1, is not different from placebo with respect to achievement of IGA scores of 0 or 1.
- H4: M1095 120mg q2w x 6 is not different from placebo with respect to achievement of IGA scores of 0 or 1.

The primary analysis method will be performed on the ITT Analysis Set and the treatment arms will be compared with the Cochran-Mantel-Haenszel test stratified by prior biologic use (yes/no) and body weight stratum (≤90kg, >90kg). Significance for each hypothesis will be assessed at the 2-sided 5% level. No adjustment for multiple comparisons will be made.

9.2 Sample Size Determination

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.[6] 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 (≤90kg, >90kg).

9.3 Populations for Analyses

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.
Modified Intent To Treat (MITT)	The Modified Intent to Treat (MITT) population includes all subjects in the ITT Analysis Set who receive at least one dose of study drug, have a baseline, and at least one post baseline efficacy assessments. Subjects will be analyzed according to planned treatment.
Per-Protocol (PP)	The Per-Protocol (PP) population includes all subjects in the MITT Analysis Set who have no important clinical protocol deviations affecting the assessment of efficacy. Membership of the PP Analysis Set will be confirmed prior to unblinding the data. Subjects will be analyzed according to planned treatment.

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.
Pharmacokinetic	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 no protocol deviation with an impact on PK. The PK population will be analyzed per the actual treatment received.

The primary analysis set for efficacy data will be the ITT Analysis Set.

The primary analysis will be repeated on the MITT and PP Analysis Sets. Furthermore, selected sensitivity analyses will be performed on the ITT Analysis Set, including multiple imputation and last-observation carried forward. Safety data will be analyzed using the Safety Analysis Set.

9.4 Statistical Analyses

This section is a summary of the planned statistical analyses of the primary and secondary endpoints. A comprehensive SAP will provide full details on all planned analyses for this study prior to the first interim data analysis.

The primary analysis is at Week 12 and key secondary analyses are at Week 24.

9.4.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint is achievement of an IGA score of 0 or 1 at Week 12. Response rates of IGA score of 0 or 1 at Week 12 will be used to compare the treatment arms. The response rate of IGA score of 0 or 1 at Week 12 is defined as the proportion of subjects at Week 12 with an IGA score of 0 or 1 and with an IGA reduction from baseline of 2 points or more. Baseline IGA score is the last score prior to the first dose of study medication. Any missing IGA score of 0 or 1 response will be imputed as a non-response. The primary analysis will be based on the ITT Analysis Set. The primary treatment comparisons will be made using the two-sided Cochran-Mantel-Haenszel (CMH) test stratified by prior biologic use and body weight stratum.
Secondary	The key secondary endpoints are the PASI 75, PASI 90 and PASI 100 at Week 12. Secondary efficacy and QoL endpoints will be compared between randomized treatments in the ITT Analysis Set at each visit up to Week 12 and at Weeks 24, 36 and 48 using the CMH test for binary endpoints and for the shift from baseline in IGA and an Analysis of Covariance (ANCOVA) model

	for changes from baseline. The ANCOVA model will include treatment, prior biologic use and weight stratum as factors and the baseline value as a covariate. Descriptive summaries will be provided in tabular and graphical formats by treatment and over time. Analysis of the primary and key secondary endpoints will also be performed using the MITT and the PP populations. The impact of missing data on efficacy results will be assessed using multiple imputation, last-observation carried forward and worst-case imputation methods.
Exploratory	Exploratory analyses of efficacy will be made for subjects who (i) were dose-escalated at Week 12, and (ii) who stopped treatment following IGA score of 0 at Week 24.

For the primary and secondary endpoints, comparisons will be made to placebo (all arms), and between the M1095 treatment arms. Dose response and dosing frequency response trend testing will be performed involving selected M1095 arms and placebo. No formal statistical testing will be done between M1095 treatment arms and secukinumab as the secukinumab arm is for reference only. Secukinumab will be compared to placebo using the same methods as the primary analysis.

9.4.2 Subject Demographics/Other Baseline Characteristics

All data for background and demographic variables will be listed by treatment group and subject. For these parameters summary statistics will be provided by treatment group.

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

9.4.3 Subject Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

Subject disposition will be summarized for each treatment period and overall. Reasons for discontinuation from the study will be summarized.

9.4.4 Treatment Compliance

Treatment compliance with study drug will be summarized for each treatment period. Subject compliance with study drug will be assessed at each visit. A subject will be considered overall compliant for each study period if he/she is missing no more than 20% of the expected doses and not missing 2 consecutive doses. Proportions of subjects compliant by visit and overall compliance will be summarized by treatment groups.

9.4.5 Safety Analyses

Safety data will be summarized in the Safety Analysis Set by treatment. AEs will be summarized for each treatment period separately and overall. Treatment periods are described in Section 4.1. No statistical analyses of the safety data are planned.

9.4.5.1 Vital Signs

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

9.4.5.2 ECG Evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics, for absolute values and change from baseline, will be provided by treatment and visit/time.

9.4.5.3 Clinical Laboratory Evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

9.4.5.4 Adverse Events

All information obtained on adverse events will be displayed by treatment and subject.

Treatment-Emergent AEs (TEAEs) are AEs that emerge while on study treatment, having been absent pre-treatment, or that worsen during study treatment relative to the pre-treatment state. Serious TEAEs including deaths, TEAEs that led to investigational product discontinuation, and TEAEs by maximum severity and relationship to investigational product will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The number and percentage of subjects with TEAEs will be tabulated by body system and preferred term. A subject with multiple AEs within a body system is only counted once towards the total of the body system. A subject with multiple AEs within the same preferred term is only counted once towards the total of the preferred term.

AESI will also be presented and summarized. 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.

9.4.5.5 Suicidality and Self-Injurious Behavior

Suicide-related thoughts and behaviors and self-injurious behavior with no suicidal intent, based on the eC-SSRS, will be listed by subject.

9.4.5.6 Previous and Concomitant Therapy

Previous and concomitant therapies will be listed by treatment group and subject. Concomitant medications will be summarized by treatment.

9.4.6 Other Analyses

As possible, subgroup analyses of key efficacy and safety data will be performed by geographical region, prior biological use, weight category, gender and geriatric status.

Detailed description of the subgroup variables and detailed analysis methodology will be defined in the SAP. Additional subgroup analyses may be performed as deemed necessary.

9.4.7 PK Analyses

An exploratory population PK analysis may be performed to model M1095 pharmacokinetics. The modelling effort should provide guidance about the design of further studies in terms of dose and regimen.

Full details of the PK analysis will be provided either in the SAP, or in a separate PK plan prior to the analysis taking place. The population PK analysis will be presented separately from the main CSR.

9.4.8 Immunogenicity Analyses

Binding and neutralizing antibodies will be defined by the percentage of subjects with antibodies and the titers of antibody. These data will be summarized.

9.5 Interim Analyses

An unblinded interim analysis of complete 12-week data will occur at the end of the Week 12 period, while the study is still ongoing. This will be managed by an independent DMC and statistical analysis group to preserve the blinding. This data will be shared with firewalled individuals who are not directly involved in the conduct of the study.

A second interim analysis will occur at the completion of the Week 24 period. All investigators and subjects will remain blinded to treatment assignments until the last subject completes the study and the final database lock occurs. Once the second interim database lock has occurred after Week 24, the study statistician, statistical programmers, and designated sponsor team members will be unblinded to perform analysis of key study endpoints.

The study will not be terminated early on the basis of positive efficacy after the first or the second interim database locks.

Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded. All investigators and subjects will remain blinded to treatment assignments until the last subject completes the study and the

final database lock occurs. Once the second interim database lock has occurred after Week 24, the sponsor study team will be unblinded.

The SAP will specify the analyses to be performed and the tables, figures and listings (TFLs) to be generated at each interim analysis. The SAP will be finalized prior to the first unblinding.

9.5.1 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be established to closely monitor the safety and tolerability data throughout the study and review interim analyses during 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.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Clinical Trials Directive 2001/20/EC, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that

meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- Separate ICFs will be used to document agreement for skin evaluation (including assessments of genomic biomarkers) should this be required as per Section 8.4.2, and to document agreement to collect information from a study subject's partner in case of pregnancy.
- A separate ICF may also be used to document agreement for HIV testing, depending on local requirements.
- A separate ICF may also be used to document agreement for use of a subject expense reimbursement system, depending on local requirements.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

10.1.4 Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by study monitors, Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Study Steering Committee

A Study Steering Committee will be utilized for the study. Membership will include an overall Principal Investigator as well as regional lead investigators. The scope of the Study Steering Committee will be described in its applicable Charter.

10.1.6 Dissemination of Clinical Study Data

Key design elements of this protocol will be made publicly available via the European Clinical Trials Database (EudraCT) and www.ClinicalTrials.gov. On study completion and finalization

of the CSR, the results of this study will be either submitted for publication and/or made publicly available via the EudraCT database and www.ClinicalTrials.gov.

10.1.7 Data Quality Assurance

- All subject data relating to the study will be recorded on an eCRF (printed pages are acceptable only if the eCRF is unavailable) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Source Data Agreement agreed with each investigator prior to site initiation.

10.1.9 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

Study recruitment will be stopped at a site when the total requested number of subjects for the study has been obtained, irrespective of the specific site's inclusion number. Investigators will be informed when recruitment is to cease.

When study analyses are complete the investigators will receive information about the treatment allocation for the subjects randomised at their respective sites.

The sponsor may stop the study prematurely after consultation with the investigator, e.g., if the subject recruitment is so slow that the study cannot be completed within a reasonable time frame. Such premature termination/suspension of the study will be notified to Regulatory Authorities and IECs/IRBs as required.

10.1.10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the central laboratory.
- Local laboratory results are only required if central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that a sample for central analysis is obtained at the same time. Additionally, if local laboratory values are used to make either a study intervention decision or response evaluation, the values must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.0 of the protocol.
- Additional tests may be performed at any time during the study as deemed necessary by the investigator or required by local regulations.
- Review of each laboratory report must be documented by an investigator.

Table 2: Protocol-Required Safety Laboratory Assessments

Hematology	• Hemoglobin
	• Hematocrit
	• Red Blood Cell (RBC) count
	• White Blood Cell (WBC) count with differential
	  ○ Lymphocytes
	  ○ Monocytes
	  ○ Neutrophils
	  ○ Bands
	  ○ Eosinophils
	  ○ Basophils
	• Platelets
	• ESR[A]

Chemistry	• Albumin • Alkaline phosphatase • ALT • AST • Total CO_2 • Total bilirubin ○ Direct bilirubin (if Total bilirubin is out of range) • Urea • Calcium • Chloride • Creatinine • Glucose • Potassium • Total protein

	• Sodium
	• Plasma Glucose[A]
	• High sensitivity CRP[A]
	• Lipids[A]
	  ○ Total cholesterol[A]
	  ○ LDL[A]
	  ○ HDL[A]
	  ○ Total cholesterol to HDL ratio[A]
	  ○ Triglycerides[A]

Urinalysis	• Blood • White blood cells • Glucose • Protein • Ketones • pH
Serology	• Anti-HBV[B] • Anti-HCV[B] • Anti-HIV[B] • QuantiFERON®-TB Gold[C]
Pregnancy Test	• hCG (in serum)[D] • hCG (in urine)[D]

A – Additional tests performed at Weeks 0 (randomization), 12, 24, 36 and 48. This must be a FASTING blood sample. ESR will be performed at the study site using a kit provided by the central laboratory.

B – Screening only. See Section 10.5, Appendix 5 for details.

C – Screening only. Sample to be sent to central or local laboratory.

D – Pregnancy test in serum at Screening only, unless subsequent local urine pregnancy test is positive, in which case a central laboratory serum test should be repeated (See Section 10.4, Appendix 4).

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of an Adverse Event

- An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. All overdoses occurring to a study subject are to be captured on the AE page of the eCRFs and on the SAE form when appropriate. Medication errors involving the study intervention are also reportable irrespective of the presence of an associated AE/SAE and should be captured on an AE eCRF page.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of a Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study)

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or their designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by either the sponsor or their designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity as per CTCAE guidelines[23] and assign it to one of the following grades.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[A]

Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.[B]

Grade 4 - Life-threatening consequences; urgent intervention indicated.

Grade 5 - Death related to AE.

Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

Activities of Daily Living (ADL)
A - Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
B - Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The study is blinded, so the investigator will also consult the Investigator's Brochure (IB) for M1095 and the Product Information for Cosentyx in his/her causality assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor's designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of SAE data.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or their designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study, the investigator will be asked to provide a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor's designee within 24 hours of receipt of the information.
- SAEs and AEs will be followed until resolution, stabilization or the event is otherwise explained or the subject is lost to follow up (see Section 7.3). AEs not considered serious or as an AESI will be considered ongoing if they have not resolved by Week 52.

Reporting of SAEs

SAE Reporting via the eCRF

- The primary mechanism for reporting an SAE to the sponsor's designee will be the eCRF.
- If the eCRF is unavailable for more than 24 hours, then the site will use the paper SAE form (see next section).

- The site will enter the SAE data into the eCRF as soon as it becomes available.
- After the study is completed at a given site, the eCRF will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the eCRF has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor/SAE coordinator by telephone.
- Contacts for SAE reporting will be provided to each investigator and can be found in the study's Safety Management Plan.

SAE Reporting via Paper SAE Form

- Facsimile transmission of the paper SAE form is the preferred method to transmit this information to the Medical Monitor/SAE coordinator if reporting via the eCRF is unavailable.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the paper SAE form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the paper SAE form within the designated reporting time frames.
- Contacts for SAE reporting will be provided to each investigator and can be found in the study's Safety Management Plan.

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraceptive guidance is given as per the Clinical Trial Facilitation Group recommendations related to contraception and pregnancy testing in clinical trials.[24]

Women are considered not of child bearing potential if they are surgically sterile or post-menopausal defined as 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms).

Highly effective contraception must be used by all female subjects considered women of child bearing potential throughout the study and for 12 weeks following the last dose of study drug.

Highly effective contraception is defined as:

i. Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

ii. Female sterilization: have had a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

iii. Male partner sterilization (with the appropriate post-vasectomy documentation of absence of sperm in the ejaculate). (For female subjects on the study, the vasectomized male partner should be the sole partner for that subject).

iv. Use of established oral, intravaginal, transdermal, injectable or implantable hormonal methods of contraception associated with inhibition of ovulation.

v. Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).

Male subjects must also use contraception throughout the study and for 12 weeks following the last dose of study drug. The following methods of contraception are permitted for male study subjects.

i. Condom

ii. Sterilization (with the appropriate post-vasectomy documentation of absence of sperm in the ejaculate).

iii. Contraception taken by female partners if considered women of child bearing potential.

At each study visit, female and male subjects will be reminded that they must follow the study's contraceptive guidance. This includes the final study visit, either Week 52 or the Early Discontinuation – Visit 2, when subjects will be reminded that they must follow the study's contraceptive guidance for at least 4 more weeks, and that they should inform the investigator immediately should they or their partner become pregnant in this time.

Pregnancy Testing

- Women of child bearing potential should only be included in the study after a confirmed menstrual period and a negative highly sensitive serum pregnancy test, performed by the study's central laboratory as part of study screening.
- Local pregnancy testing should be performed at the baseline (randomization) visit, and at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, plus the Early Discontinuation Visit. Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. A urine dipstick test will be performed locally by the study site personnel.
- If at any stage, a local pregnancy test is positive, a highly sensitive serum pregnancy test should be performed via the study's central laboratory.

Collection of Pregnancy Information:

Male subjects with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor's designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- Any female subject who becomes pregnant while participating in the study will discontinue study drug.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.5.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

10.5 Appendix 5: HIV, Hepatitis B and Hepatitis C Virus Screening

Subjects must undergo screening for human immunodeficiency virus (HIV), hepatitis B and hepatitis C viruses. At a minimum, this includes testing for anti-HIV (HIV antibodies), HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), anti-HBc total (HBV core antibody total) and anti-HCV (HCV antibodies).

1. Subjects who test positive for either anti-HIV or anti-HCV are **NOT ELIGIBLE** for the study.

2. The following HBV test results mean the subject is **ELIGIBLE** for the study.
   - Subjects who test negative for all HBV screening tests (i.e. HBsAg, anti-HBs, anti-HBc).
   - Subjects who test negative for HBV surface antigen and anti-HBc (HBsAg -ve, anti-HBc -ve) but positive for anti-HBs (anti-HBs +ve).
   - Subjects who test negative for HBV surface antigen (HBsAg -ve) but positive for anti-HBs and anti-HBc (anti-HBs and anti-HBc +ve).

3. The following HBV test results mean the subject is **NOT ELIGIBLE** for the study.
   - Subjects who test positive for HBV surface antigen (HBsAg +ve), regardless of the results of the other HBV tests.

4. The following HBV test results must undergo **FURTHER TESTING** for HBV deoxyribonucleic acid (DNA).
   - Subjects who test positive only for anti-HBc (anti-HBc +ve).
     - If the HBV DNA test is negative, the subject is **ELIGIBLE** for the study.
     - If the HBV DNA test is positive, or cannot be performed, the subject is **NOT ELIGIBLE** for the study.

HBV tests				Eligibility
HBsAg	Anti-HBs	Anti-HBc total	HBV DNA	
-ve	-ve	-ve	N/A	Eligible
-ve	+ve	-ve	N/A	Eligible
-ve	+ve	+ve	N/A	Eligible
+ve	any result	any result	N/A	Not Eligible
-ve	-ve	+ve	-ve	Eligible
-ve	-ve	+ve	+ve or Not Done	Not Eligible

Confirmatory testing may be performed for any samples testing positive for anti-HIV, HBsAg, or anti-HCV.

10.6 Appendix 6: Measures of Psoriasis Area and Severity

The IGA and PASI will be administered by site personnel according to the SoA (Section 1.3). All assessors of IGA and PASI must be qualified, experienced in evaluating subjects with psoriasis in clinical trials, and have completed study specific training in IGA and PASI rating. It is recommended that the same assessor conducts the IGA and PASI at all visits for a particular subject, but especially at Week 0 (randomization), Week 12, and Week 24.

10.6.1 Investigator's Global Assessment (IGA mod 2011)

The IGA rating scale for overall psoriatic disease is shown in Table 3.

The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points.[10] The IGA mod 2011 is thought to better correlate with PASI 90 responses.

The IGA mod 2011 used in this study is static, i.e. it refers exclusively to the subject's disease state at the time of the assessments, and does not attempt a comparison with any of the subject's previous disease states, whether at baseline or at a previous visit.

The IGA mod 2011 score will initially be recorded on paper, and then entered in the IRT/eCRF.

Table 3: The IGA rating scale

Score	Short description	Detailed description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation maybe present.
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling.
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling.
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling.
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions. Note: Involvement of nails is not part of the assessment.

Based on this scale, a subject will be eligible to participate in the study if the subject has an IGA score at baseline of 3 or 4.

Based on this scale, a subject will be considered as an IGA 0 or 1 responder if the subject achieves a score of 0 or 1.

10.6.2 Total Body Surface Area (BSA) and Psoriasis Area and Severity Index (PASI)

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for PASI assessment).

The site will initially record assessments on paper and will then enter the data into the eCRF, which will auto-calculate the PASI score (no manual PASI calculations will be required by the site).

Rounding should occur (e.g. 9.49% = 9 and 9.5% = 10) except in any instance where the percentage is just above 0 (i.e. 0.25% should round up to 1, not down to 0).

A PASI score will be derived as indicated in Table 4.[11, 12] The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

- The neck is assessed as part of the head.
- The axillae and groin are assessed as part of the trunk.
- The buttocks are assessed as part of the lower limbs.
- When scoring the severity of erythema, scales should not be removed.

Table 4: The PASI scoring system

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A)
Head (H)†	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
Trunk (T)‡	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
Upper limbs (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
Lower limbs (L)§	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%

† Neck is assessed as part of the Head (H) body region.
‡ Axillae and groin are assessed as part of the Trunk (T) body region.
§ Buttocks are assessed as part of the Lower limbs (L) body region.

Because the head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively, the PASI score is calculated using the formula:

$$\mathbf{PASI = 0.1\,(E_H + I_H + D_H)\,A_H + 0.2\,(E_U + I_U + D_U)\,A_U + 0.3\,(E_T + I_T + D_T)\,A_T + 0.4\,(E_L + I_L + D_L)\,A_L}$$

The keys for the letters are provided in Table 4.

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0.

The investigator is only responsible for collecting the components or scoring signs and total regional area. PASI calculations, including changes over time will be calculated via the PASI Score eCRF.

Based on PASI, to be eligible a subject must have a score of 12 or more at baseline.

Based on total BSA, to be eligible, a subject must have 10% or more total BSA involved at baseline.

Definitions of efficacy variables based on PASI
The following definitions are used in this study, see Committee for Medicinal Products for Human Use (CHMP) guidelines for psoriasis.[8]

- **PASI 75 response:** subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- **PASI 90 response:** subjects achieving ≥ 90% improvement (reduction) in PASI score
- **PASI 100 response / remission:** complete clearing of psoriasis (PASI=0)
- **Relapse:** when the achieved maximal PASI improvement from baseline is reduced by >50%

10.7 Appendix 7: Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BSA	Body Surface Area
Cmax	Maximum Concentration
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
CRP	C-Reactive Protein
CS	Corticosteroids
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest X-Ray
D/C	Discontinuation
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
eC-SSRS	Electronic Columbia Suicide Severity Rating Scale
EMA	European Medicines Agency
EQ-POS	Euro-Quality of Life Questionnaire for Psoriasis
ESR	Erythrocyte Sedimentation Rate
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment

IgG	Immunoglobulin G
IL	Interleukin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intravenous
LDL	Low Density Lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
PASI	Psoriasis Area and Severity Index
PFS	Pre-Filled Syringe
PHQ-8	Patient Health Questionnaire-8
PK	Pharmacokinetics
PP	Per Protocol
PRO	Patient Reported Outcomes
PUVA	Photochemotherapy (Psoralens and UVA)
QoL	Quality of Life
q2w	Every 2 weeks
q4w	Every 4 weeks
q8w	Every 8 weeks
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	Short-Form 36
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
sPGA	Static Physician's Global Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal
UV	Ultraviolet
UVA	Ultraviolet A (longwave)
UVB	Ultraviolet B (shortwave)
VAS	Visual Analogue Scale
WBC	White Blood Cell
WFI	Water for Injection

10.8 Appendix 8: Protocol Amendment History

Amendment No.	Protocol version no.	Date issued	Details of changes made
02	3.0 inc. CZE-1	16-Oct-2018	• Change of office address for Avillion LLP • Clarification of eligibility regarding tuberculosis, and permission of re-screening if subjects become eligible after instigating treatment of latent TB • Creatinine clearance may be measured via 24-hour urine collection, in addition to calculation via Cockcroft-Gault • FOR CZECH REPUBLIC ONLY Exclusion criterion 4g amended to exclude subjects with a calculated creatinine clearance (via Cockcroft Gault) of <60mL/min • Exclusion criterion 13 amended to include suicidal behavior • Clarification of chronic drug abuse and IV drugs • Exclusion criterion 15 amended to clarify the requirement for highly effective contraceptive methods in women of child bearing potential • New exclusion criterion (18) to capture requirements for male contraception • Clarification of PASI endpoints • Addition of total BSA to secondary endpoints • Clarification of IGA endpoints • Urine pregnancy test every 4 weeks • Updates to systemic and topical prior and prohibited treatments for psoriasis

			• Consideration of subject's response at Week 24 and benefit from participating in study • Clarification that male sterilization is a permitted form of contraception in male subjects • Clarification on use of cannabis/marijuana • Clarification on release of randomization codes for PK analysis • Efficacy assessments to be recorded on paper, and clarification of who will perform assessments and rounding rules • Correction of the null hypothesis H4 and clarification of the other null hypotheses • Update to the statistical methods for the secondary endpoints • Clarification of visits for which treatment comparisons will be made • Clarification of unblinding at Week 24 to allow analysis of key study endpoints • Update to use CTCAE Version 5.0 • Addition of a separate ICF, per local requirements, to agree to the use of a subject expense reimbursement system. • Clarification at Week 52 regarding contraception for the next 4 weeks • Clarification of requirement to capture overdose/medication errors on AE eCRF • Typos and consistency in wording
CZE-1	2.0	31-Aug-2018	• Exclusion criterion 4g amended to exclude subjects with a calculated creatinine clearance (via Cockcroft Gault) of <60mL/min • Exclusion criterion 15 amended to clarify the requirement for highly

			effective contraceptive methods in women of child bearing potential • New exclusion criterion (18) to capture requirements for male contraception • Clarification that male sterilization is a permitted form of contraception in male subjects
01	2.0	03-Apr-2018	• www.ClinicalTrials.gov NCT number added • Co-ordinating Investigators added • Clarify the method used to blind injections to study subjects • ECG performed during Screening, and not at Week 0 • HIV test added at Screening • Clarify the reconstitution of 30mg dose • ESR performed at study site using a kit provided by central laboratory • Clarify that there will be separate ICFs for skin evaluation and pregnant partners, and that there may be a separate ICF for HIV testing

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12.0 SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A phase 2b randomized, double-blind, placebo controlled, multi-center 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.

PROTOCOL NO: AV002

This protocol is a confidential communication of Bond Avillion 2 Development LP. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from Bond Avillion 2 Development LP.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name/address of the center in which the study will be conducted. Return the signed copy to the CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature	Title
Printed Name	Date
Name/Address of Center	