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TITLE PAGE

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Product:	**Tildrakizumab**
Short Title:	**Efficacy and Safety Profile of Tildrakizumab in Subjects with Moderate to Severe Plaque Psoriasis of the Scalp.**
Study Phase:	**3b**
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TABLE OF CONTENTS

SUMMARY OF CHANGES **3**
LIST OF APPENDICES **11**
LIST OF TABLES **12**
LIST OF FIGURES **12**
1.0 PROTOCOL SUMMARY **13**
1.1 Synopsis 13
[redacted]
2.0 INTRODUCTION **25**
2.1 Background 25
2.2 Study Rationale 25
2.3 Benefit/Risk Assessment 26
3.0 OBJECTIVES AND ENDPOINTS **27**
4.0 STUDY DESIGN **30**
4.1 Overall Design 30
4.2 Scientific Rationale for Study Design 31
4.3 Justification for Dose 31
4.4 End of Study Definition 32
5.0 STUDY POPULATION **33**
5.1 Inclusion Criteria 33
5.2 Exclusion Criteria 34
5.3 Lifestyle Considerations 35
5.4 Screen Failures 36
6.0 STUDY TREATMENT **37**
[redacted]
6.2 Preparation/Handling/Storage/Accountability 38
6.3 Measures to Minimize Bias: Randomization and Blinding 38
6.4 Study Treatment Compliance 39
6.5 Concomitant Therapy 39
6.5.1 Rescue Medicine 40
[redacted]
6.6 Dose Modification 40
6.7 Treatment after the End of the Study 40

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL 41
7.1 Discontinuation of Study Treatment 41
7.1.1 Temporary Discontinuation 41
7.2 Subject Discontinuation/Withdrawal from the Study 42
7.3 Lost to Follow-up 42
8.0 STUDY ASSESSMENTS AND PROCEDURES 44
8.1 Efficacy Assessments 44
8.1.1 Assessments for Scalp: 45
8.1.2 Assessments for Whole Body: 45
8.1.3 Dermatology Life Quality Index 46
8.2 Safety Assessments 46
8.2.1 Physical Examinations 47
8.2.2 Vital Signs 47
8.2.3 Assessment of Suicidal Ideation and Behavior 47
8.2.4 Electrocardiograms 48
8.2.5 Tuberculosis Testing 48
8.2.6 Chest X-ray 48
8.2.7 Clinical Safety Laboratory Assessments 48
8.3 Adverse Events 49
8.3.1 Time Period and Frequency for Collecting AE and SAE Information 49
8.3.2 Method of Detecting AEs and SAEs 50
8.3.3 Follow-up of AEs and SAEs 50
8.3.4 Regulatory Reporting Requirements for SAEs 50
8.3.5 Pregnancy 51
8.3.6 Adverse Events of Special Interest 52
8.3.7 Events of Clinical Interest 52
8.4 Treatment of Overdose 52
8.5 Pharmacokinetics 53
8.6 Pharmacodynamics 53
8.7 Genetics 53
8.8 Biomarkers 53
8.9 Health Economics or Medical Resource Utilization and Health Economics 53
9.0 STATISTICAL CONSIDERATIONS 54
9.1 Statistical Hypotheses 54
9.2 Sample Size Determination 54

9.3 Populations for Analyses 55
9.4 Statistical Analyses 56
9.4.1 Efficacy Analyses 57
9.4.2 Safety Analyses 59
9.4.3 Other Analyses 61
9.5 Interim Analyses 61
9.6 Monitoring Committee 61

LIST OF APPENDICES

Appendix 2: Regulatory, Ethical and study oversight considerations 66
Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 77
Appendix 5: Anaphylaxis 83
Appendix 6: Excluded Medications/Therapy 84
Appendix 7: Contraceptive guidance and collection of pregnancy 85
Appendix 19: Columbia-Suicide Severity Rating Scale 100

LIST OF TABLES

Table 1 .....Study Objectives and Endpoints 27
Table 2 .....Study Treatment Details 37
Table 3 .....Analysis Sets 56
Table 4 .....Efficacy Analyses 57
Table 5 .....Study Administrative Structure 68
Table 6 .....Protocol-required Safety Laboratory Assessments 74
Table 7 .....Excluded Medications 84

LIST OF FIGURES

Figure 1:.....Study Schema 21

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multicenter, Randomized, Double-blind, Placebo-Controlled Clinical Study to Assess the Efficacy and Safety of Tildrakizumab in the Treatment of Moderate to Severe Plaque Psoriasis of the Scalp

Short Title: Efficacy and Safety Profile of Tildrakizumab in Subjects with Moderate to Severe Plaque Psoriasis of the Scalp.

Rationale:

Psoriasis is a chronic inflammatory skin disorder and affects approximately 1% to 2% of people worldwide. Scalp psoriasis occurs in about 50% to 80% of patients in the United States and Western Europe and is associated with itching and discomfort causing significant burden to quality of life (QoL) and work function. Currently approved biological treatments for moderate to severe plaque psoriasis include tumor necrosis factor (TNF) antagonist agents, a p40 (interleukin [IL]-12 and IL-23) antagonist, p19 (IL-23) antagonists, and IL-17 antagonist agents. Despite the availability of treatment options for plaque psoriasis, scalp lesions remain difficult to treat. Thus, there remains an unmet need for effective therapeutic options for scalp psoriasis. Recent studies have demonstrated that IL-23-dependent T-helper (Th)17 cells control much of the inflammatory damage that is observed in psoriasis. Based on this rationale, several therapeutic anti-IL-23 antibodies were developed and entered into clinical studies. Tildrakizumab, [redacted] demonstrates comparable efficacy in psoriasis [redacted] Tildrakizumab was approved as ILUMYA™ in the United States on 20 March 2018 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy and in Australia on 06 September 2018 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.

This study is planned to be a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of tildrakizumab in the treatment of moderate to severe scalp psoriasis.

Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy Objective	**Primary Efficacy Endpoint**
• To assess the efficacy of tildrakizumab in subjects with moderate to severe scalp psoriasis, as measured by the proportion of subjects who achieve Investigator Global Assessment (IGA) mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16.	• The proportion of subjects with IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16
Primary Safety Objective	**Primary Safety Endpoint**
• To assess the safety and tolerability of tildrakizumab in subjects with moderate to severe plaque psoriasis of the scalp [redacted]	• The percentage of subjects with incidence, seriousness and severity of all adverse events. • The percentage of subjects with severe infections [redacted] whether or not reported as a serious event as per the regulatory definition. • The percentage of subjects with malignancies (excluding carcinoma in situ of the cervix). • The percentage of subjects with non-melanoma skin cancer. • The percentage of subjects with melanoma skin cancer. • The percentage of subjects with Major Adverse Cardiovascular Events. • The percentage of subjects with study treatment-related hypersensitivity reactions (eg, anaphylaxis, urticaria, angioedema, etc.). • The percentage of subjects with injection site reactions (eg, pain, erythema, edema etc).
Secondary Objectives	**Secondary Endpoints**

Objectives	**Endpoints**
• To assess the efficacy of tildrakizumab in subjects with moderate to severe plaque psoriasis of the scalp, as measured by the proportion of subjects who achieve at least 90% improvement from Baseline in the Psoriasis Scalp Severity Index (PSSI) response at Week 16 compared with placebo. • To assess the efficacy of tildrakizumab in subjects with moderate to severe scalp psoriasis, as measured by the proportion of subjects who achieve IGA (Scalp only) of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16. • To assess the efficacy of tildrakizumab in subjects with moderate to severe scalp psoriasis, as measured by the proportion of subjects who achieve Investigator Global Assessment (IGA) mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 12. • To assess the efficacy of tildrakizumab in subjects with moderate to severe plaque psoriasis of the scalp, as measured by the proportion of subjects who achieve at least 90% improvement from Baseline in the Psoriasis Scalp Severity Index (PSSI) response at Week 12 compared with placebo. To assess the efficacy of tildrakizumab in the treatment of moderate to severe plaque psoriasis of the scalp compared with placebo as measured by scalp surface area involvement at Week 16.	• The proportion of subjects with at least 90% improvement from Baseline in the PSSI at Week 16. (Key secondary endpoint). • The proportion of subjects with IGA (scalp only) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16. (Key secondary endpoint). • The proportion of subjects with IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 12 (key secondary endpoint) • The proportion of subjects with at least 90% improvement from Baseline in the PSSI at Week 12. (Key secondary endpoint). • Mean percentage change in PSSI score from Baseline to Week 16. • The proportion of subjects achieving PSSI 75 at Week 16. • The proportion of subjects achieving PSSI 100 at Week 16. • Mean percentage change in scalp surface area involvement from Baseline to Week 16.
• To assess the effect of Tildrakizumab on IGA mod 2011 (scalp) and PSSI at other measured time points through week 52. • To assess the effect of tildrakizumab on, IGA (scalp only), Scalp Itch NRS, PASI, PGA-S (whole body), IGA mod 2011 (whole body) at week 12 and other measured time points through Week 52.	• Change from baseline in IGA mod 2011 (scalp) and PSSI at other measured time points through Week 52. • Change from Baseline in IGA (scalp only), Scalp Itch NRS, PASI, PGA-S (whole body), and IGA mod 2011 (whole body) at week 12 and other measured time points through Week 52.

Objectives	Endpoints
• To assess the time to response.	• Time to 75% reduction in PSSI during the 16-week placebo-controlled treatment period. • Time to IGA mod 2011 (scalp) response during the 16-week placebo-controlled treatment period.
• To assess the efficacy of tildrakizumab in the improvement of scalp itch as measured by the proportion of subjects achieving a 4-point reduction in Scalp Itch Numeric Rating Scale (NRS) score from Baseline at Week 16 compared with placebo.	• The proportion of subjects achieving a 4-point reduction in Scalp Itch NRS score from Baseline to Week 16.
• To assess the efficacy of tildrakizumab in the treatment of moderate to severe psoriasis (entire body including scalp) compared with placebo as measured by Psoriasis Area and Severity Index (PASI), IGA mod 2011(whole body), Physician Global Assessment for skin (PGA-S) score (whole body), and total body surface area (BSA) involvement at Week 16.	• The proportion of subjects achieving PASI 75, PASI 90, and PASI 100 at Week 16. • The proportion of subjects with IGA mod 2011 score (whole body) and PGA-S (whole body) score of "clear" or "almost clear" with at least a 2-point reduction from Baseline to Week 16. • Mean percentage change in total BSA involvement from Baseline to Week 16.
Exploratory Objectives	**Exploratory Endpoints**
• To assess the effect of tildrakizumab on Quality of Life measured by: o Dermatology Life Quality Index (DLQI).	• Change from Baseline in DLQI score (total and 6 domain scores) at [redacted] Week 52.

Overall Design:

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tildrakizumab in the treatment of moderate to severe psoriasis of the scalp.

Subjects with a clinical diagnosis of chronic plaque psoriasis for at least 6 months, having moderate to severe plaque psoriasis of the scalp at Screening and at Baseline (Investigator Global Assessment [IGA mod 2011 (Scalp)]) of ≥3, Psoriasis Scalp Severity Index [PSSI] score of ≥12, and 30% or higher of scalp surface area affected) as well as moderate to severe plaque psoriasis at Screening and Baseline (IGA Mod 2011 (whole body) of ≥3, Psoriasis Area and Severity Index [PASI] score ≥12 and Body Surface Area [BSA] involvement of ≥10%) and who are considered candidates for systemic therapy will be enrolled in the study.

After a Screening Period of 28 days, all eligible subjects will be randomly allocated on Day 1 to receive either tildrakizumab 100 mg or placebo by subcutaneous (SC) injection subjects initially randomized to placebo will be switched over to receive tildrakizumab 100 mg and subjects initially randomized to tildrakizumab 100 mg will continue to receive tildrakizumab In order to maintain the blind, subjects in both treatment arms will receive matching placebo injections at specified time points as described in the Schedule of Activities (SoA).

After Week 52 (or early termination of study treatment prior to Week 52), the study treatment should be stopped, and the subjects will enter the Observational Safety Follow-up Period following the last dose of study treatment. During the follow-up period, subjects should continue on study-approved concomitant medications only, however may be placed on other appropriate therapies for safety concerns or significant worsening of psoriasis based on the judgment of the Investigator. The subjects will not receive study treatment during the follow-up period.

The subject's disease activity (response to study treatment) will be evaluated using the IGA Mod 2011 (scalp), PSSI, PASI, IGA (scalp only), PGA-S (whole body), IGA Mod 2011 (whole body), Scalp Itch Numeric Rating Scale (NRS), BSA, and Dermatology Life Quality Index (DLQI) scores.

Safety assessments including adverse event (AE)/serious adverse event (SAE) monitoring, vital signs, physical examinations, electrocardiogram, and laboratory measurements will be performed during the study.

Number of Investigators and Study Centers:

Up to Investigators and study centers (in United States and Australia) are expected to participate in this study.

Number of Subjects:

The study will randomize approximately 107 subjects per treatment arm (Total N=214) randomization to either tildrakizumab 100 mg arm or placebo arm.

Treatment Groups

The study consists of a Screening Period treatment period (double-blind placebo-controlled treatment period followed by double-blind active treatment period), and Observational Safety Follow-up Period.

Part 1: Double-blind placebo-controlled, where subjects will receive either tildrakizumab (Arm A) or placebo (Arm B)

Part 2: At Week 16, subjects initially randomized to placebo will be switched over to receive tildrakizumab 100 mg Subjects initially randomized to tildrakizumab 100 mg will continue to receive active drug In order to maintain the blind, subjects in both treatment arms will receive matching placebo injections at specified time points as described in the SoA.

Part 3: After Week 52 (or early termination of study treatment prior to Week 52), subjects will enter the Observational Safety Follow-up Period where tildrakizumab treatment will be stopped.

Statistical methods:

The primary efficacy endpoint for this study is the proportion of subjects with IGA mod 2011(scalp) score of "clear" and "almost clear" with at least 2-point reduction from baseline at Week 16. The key secondary efficacy endpoints are the proportion of subjects with at least 90% improvement in the PSSI (PSSI90) from baseline at Week 16, the proportion of subjects with IGA (scalp only) score of "clear" and "almost clear" with at least 2-point reduction from baseline at Week 16, the proportion of subjects with IGA mod 2011(scalp) score of "clear" and "almost clear" with at least 2-point reduction from baseline at Week 12 and the proportion of subjects with at least 90% improvement in the PSSI (PSSI90) from baseline at Week 12. For each endpoint, the tildrakizumab 100 mg dose will be compared with placebo Both the primary and key secondary efficacy endpoints will be analyzed with Cochran-Mantel-Haenszel test using the Intent-to-treat (ITT) population.

Secondary efficacy and exploratory endpoints that are dichotomous will be analyzed in the same manner as the primary efficacy endpoint using the ITT population. Continuous secondary efficacy and exploratory endpoints will be analyzed using an MMRM procedure

Safety endpoints will be analyzed descriptively based on the Safety Analysis Set (SAS) Subjects will be summarized based on the actual treatment they received.

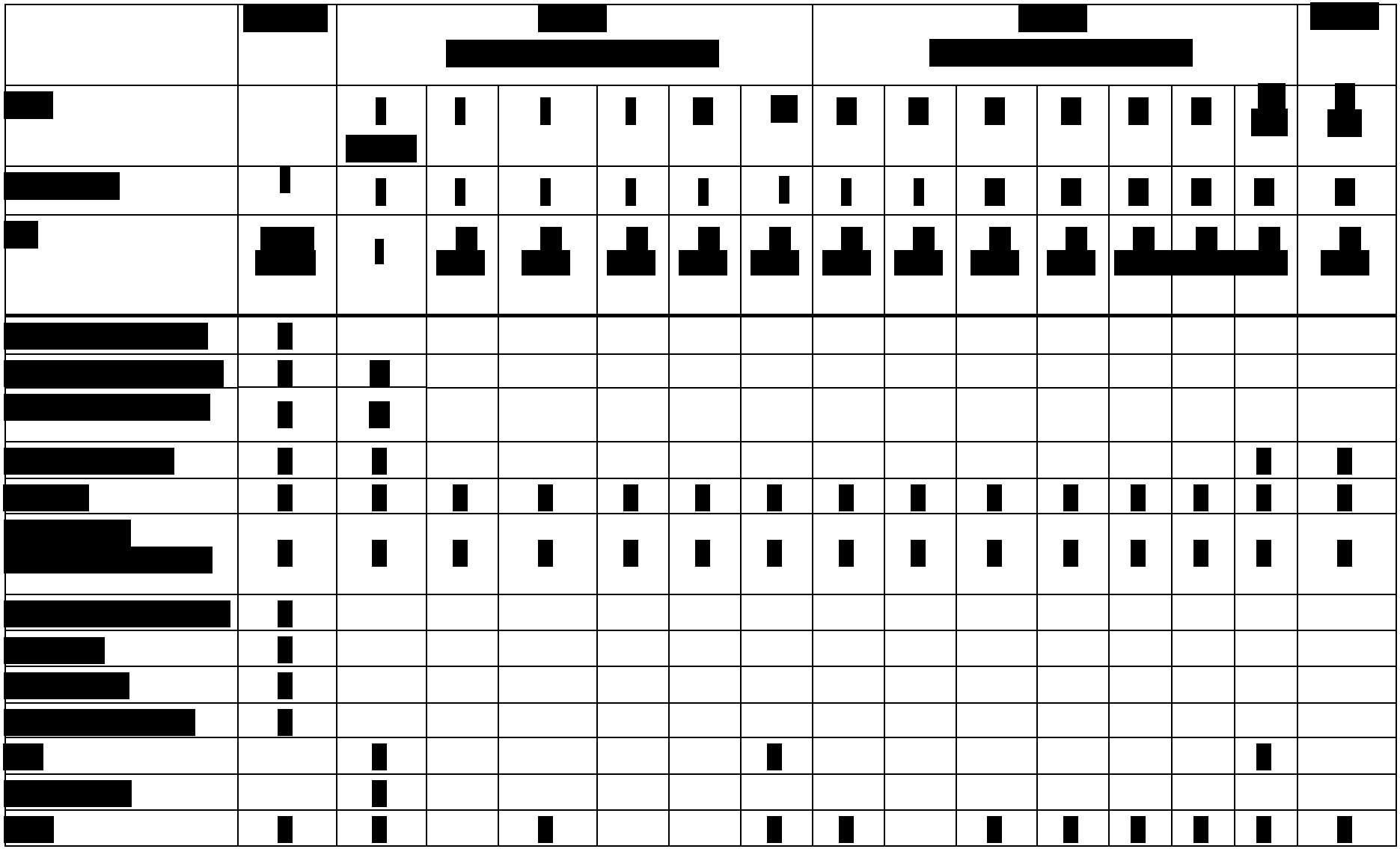
Intent-to-Treat (ITT): All randomized subjects who have received at least one dose of study treatment The primary efficacy population will be the ITT. Subjects will be summarized based on their planned treatment assignment

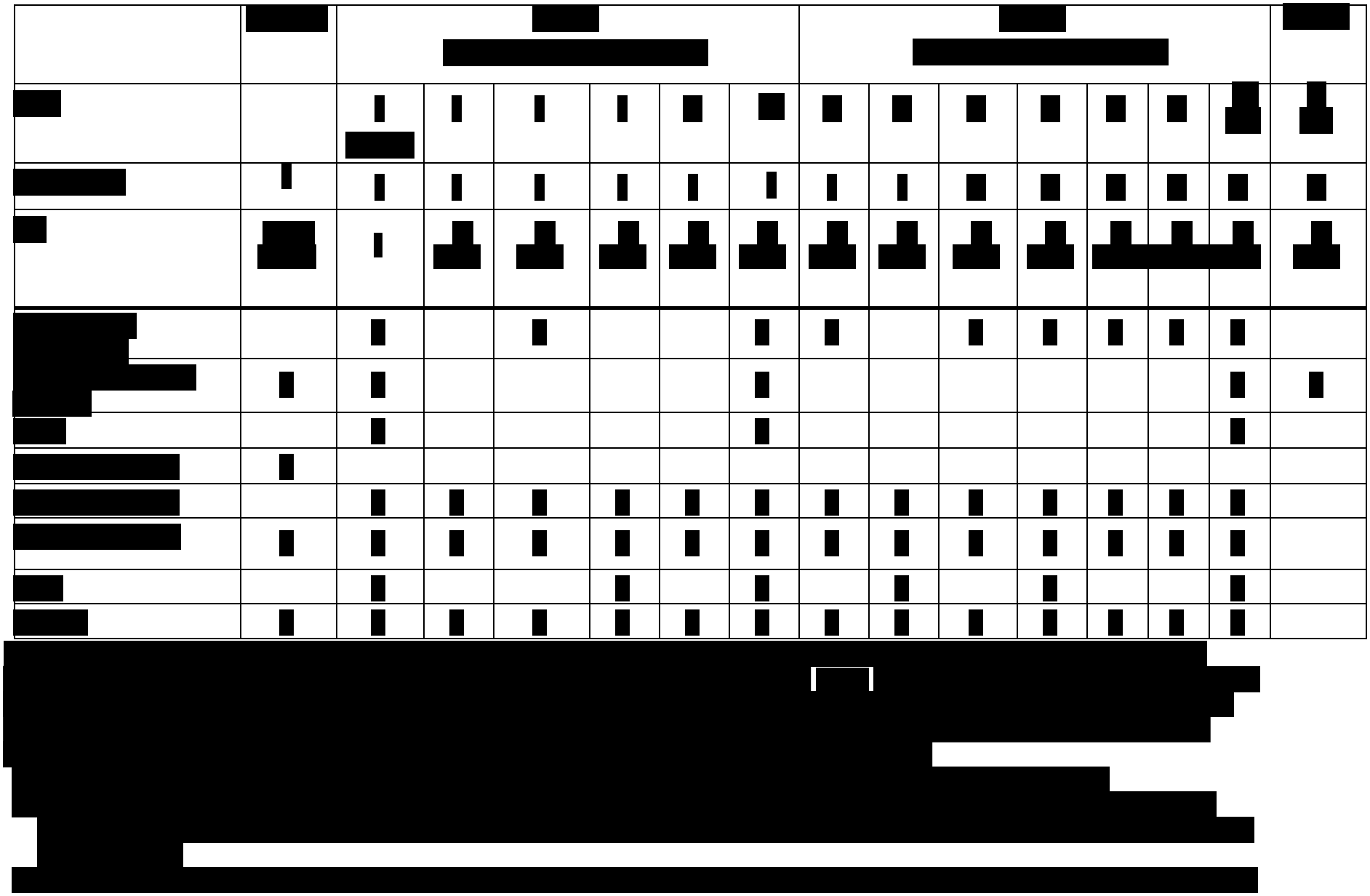
Sample Size:

The study will randomize to either tildrakizumab 100 mg arm or placebo

This sample size calculation is based on an assumed PSSI90 response for the tildrakizumab 100 mg arm and for the placebo arm.

[redacted]





2.0 INTRODUCTION

2.1 Background

Psoriasis is a chronic, immune-mediated inflammatory disease characterized by the hyper-proliferation of keratinocytes and skin-infiltrating T-lymphocytes that overexpress pro-inflammatory mediators. The disease has a lifelong remitting and relapsing course with varying factors that trigger exacerbations in susceptible individuals. Psoriasis affects approximately 1% to 2% of people worldwide, with plaque psoriasis being the most common form that affects 80% to 90% of patients.

Of those affected by psoriasis, up to 80% will have involvement of the scalp. Scalp psoriasis may occur in isolation or in conjunction with other forms of psoriasis and is characterized by red, thickened plaques with silver-white scale, either contained within the hairline, or extending onto the forehead, ears, and posterior neck. Psoriasis of scalp can be a cause of great physical and social distress, with up to 97% of affected individuals reporting that the condition interferes in their daily life. In many cases, it is associated with intense pruritus, scale is commonly shed as dandruff creating significant social embarrassment for affected individuals and can result in alopecia. In a recent multinational survey, 43% of respondents to a telephone survey identified itch as the most bothersome symptom of their psoriasis[redacted]

2.2 Study Rationale

Biological therapies are indicated for the treatment of subjects with moderate to severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. Currently approved biological treatments include tumor necrosis factor (TNF) antagonist agents, a p40 (interleukin [IL]-12 and IL-23) antagonist, p19 (IL-23) antagonists, and IL-17 antagonists. Despite the availability of treatment options for psoriasis, scalp psoriasis lesions remain difficult to treat. The use of topical therapy, typically the first-line of treatment, is often challenging because of the inaccessibility of scalp lesions due to the presence of hair [redacted] Patient satisfaction and compliance with topical therapy is known to be low [redacted]. Thus, there remains an unmet need for effective therapeutic options for scalp psoriasis.

In recent years, accumulating data has implicated the IL-23/T-helper (Th)-17 pathway in psoriasis pathogenesis. Recent genome-wide association studies have identified psoriasis risk alleles around gene regions that encode IL-23 (IL23A, IL12B) and the IL-23 receptor (IL-23R) [redacted]

Tildrakizumab is a high-affinity (297 pM), humanized immunoglobulin (Ig)-G1/κ antibod . Tildrakizumab has demonstrated efficacy in the treatment of patients with moderate to severe plaque psoriasis who are candidates for systemic therapy and phototherapy. Tildrakizumab 100 mg has recently been approved by the Food and Drug Administration for the treatment of moderate to severe chronic plaque psoriasis.

Study TILD-18-20 is planned to be a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of the approved dose of tildrakizumab (100 mg by subcutaneous [SC] injection) in the treatment of moderate to severe psoriasis of the scalp.

2.3 Benefit/Risk Assessment

Details about specific benefits and risks for subjects in this clinical study can be found in the IB and informed consent form (ICF).

Given that efficacy benefits were reported in the completed Phase 2b study Phase 3 studies in psoriasis, there is an expectation that subjects treated with tildrakizumab will demonstrate improvement in scalp psoriasis disease activity and quality of life.

The study has also been designed to minimize potential risks to subjects; all subjects will undergo screening procedures aimed at reducing the likelihood and impact of any such risks. In addition, regular safety monitoring during the treatment period for all subjects will ensure that any unanticipated effects of study participation are identified promptly and managed appropriately. In view of the long half-life ($t_{1/2}$) of tildrakizumab at doses previously studied, subjects will continue to be monitored throughout wash-out period following the end of treatment (EoT) visit, during which no active study treatment will be administered.

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH), Good Clinical Practice (GCP), and applicable regulatory requirements.

3.0 OBJECTIVES AND ENDPOINTS

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy Objective	**Primary Efficacy Endpoint**
• To assess the efficacy of tildrakizumab in subjects with moderate to severe scalp psoriasis, as measured by the proportion of subjects who achieve Investigator Global Assessment (IGA) mod 2011(scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16.	• The proportion of subjects with IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16.
Primary Safety Objective	**Primary Safety Endpoint**
• To assess the safety and tolerability of tildrakizumab in subjects with moderate to severe plaque psoriasis of the scalp [redacted] 52 weeks.	• The percentage of subjects with incidence, seriousness and severity of all adverse events. • The percentage of subjects with severe infections, [redacted] whether or not reported as a serious event as per the regulatory definition. • The percentage of subjects with malignancies (excluding carcinoma in situ of the cervix). • The percentage of subjects with non-melanoma skin cancer. • The percentage of subjects with melanoma skin cancer. • The percentage of subjects with Major Adverse Cardiovascular Events (MACE). • The percentage of subjects with study treatment-related hypersensitivity reactions (eg, anaphylaxis, urticaria, angioedema, etc.). • The percentage of subjects with injection site reactions (eg, pain, erythema, edema etc).
Secondary Objectives	**Secondary Endpoints**
• To assess the efficacy of tildrakizumab in subjects with moderate to severe plaque psoriasis of the scalp, as measured by the proportion of subjects who achieve at least 90% improvement from Baseline in the Psoriasis Scalp Severity Index (PSSI) response at Week 16 compared with placebo.	• The proportion of subjects with at least 90% improvement from Baseline in the PSSI at Week 16. (Key secondary endpoint). • The proportion of subjects with IGA (scalp only) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16. (Key secondary endpoint).

Objectives	Endpoints
• To assess the efficacy of tildrakizumab in subjects with moderate to severe scalp psoriasis, as measured by the proportion of subjects who achieve IGA (scalp only) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16. • To assess the efficacy of tildrakizumab in subjects with moderate to severe scalp psoriasis, as measured by the proportion of subjects who achieve Investigator Global Assessment (IGA) mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 12. • To assess the efficacy of tildrakizumab in subjects with moderate to severe plaque psoriasis of the scalp, as measured by the proportion of subjects who achieve at least 90% improvement from Baseline in the Psoriasis Scalp Severity Index (PSSI) response at Week 12 compared with placebo.To assess the efficacy of tildrakizumab in the treatment of moderate to severe plaque psoriasis of the scalp compared with placebo as measured by scalp surface area involvement at Week 16.	• The proportion of subjects with IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 12 (key secondary endpoint) • The proportion of subjects with at least 90% improvement from Baseline in the PSSI at Week 12. (Key secondary endpoint). • Mean percentage change in PSSI score from Baseline to Week 16. • The proportion of subjects achieving PSSI 75 at Week 16. • The proportion of subjects achieving PSSI 100 at Week 16. • Mean percentage change in scalp surface area involvement from Baseline to Week 16.
• To assess the effect of Tildrakizumab on IGA mod 2011 (scalp) and PSSI at other measured time points through week 52. • To assess the effect of tildrakizumab on IGA (scalp only), Scalp Itch NRS, PASI, PGA-S (whole body), and IGA mod 2011 (whole body), at week 12 and other measured time points through Week 52.	• Change from baseline in IGA mod 2011 (scalp) and PSSI at other measured time points through Week 52. • Change from Baseline in IGA (scalp only), Scalp Itch NRS, PASI, PGA-S (whole body) and IGA mod 2011 (whole body), at week 12 and other measured time points through Week 52.
• To assess the time to response.	• Time to 75% reduction in PSSI during the 16-week placebo-controlled treatment period. • Time to IGA mod 2011 (scalp) response during the 16-week placebo-controlled treatment period.
• To assess the efficacy of tildrakizumab in the improvement of scalp itch as measured by the proportion of subjects achieving a 4-point reduction in Scalp Itch Numeric Rating Scale (NRS) score from Baseline at Week 16 compared with placebo.	• Proportion of subjects achieving a 4-point reduction in Scalp Itch NRS score from Baseline to Week 16.
• To assess the efficacy of tildrakizumab in the treatment of moderate to severe psoriasis	• The proportion of subjects achieving PASI 75,

Objectives	Endpoints
compared with placebo as measured by Psoriasis Area and Severity Index (PASI), IGA mod 2011(whole body), Physician's Global Assessment for Skin (PGA-S) (whole body), and total body surface area (BSA) involvement at Week 16	PASI 90, and PASI 100 at Week 16. • The proportion of subjects with IGA mod 2011 (whole body) and PGA-S (whole body) of "clear" or "almost clear" with at least a 2-point reduction from Baseline to Week 16. • Mean percentage change in total BSA involvement from Baseline to Week 16.
Exploratory Objectives	**Exploratory Endpoints**
• To assess the effect of tildrakizumab on Quality of Life measured by: o Dermatology Life Quality Index (DLQI).	• Change from Baseline in DLQI score (total and 6 domain scores) at [redacted] Week 52.

4.0 STUDY DESIGN

4.1 Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tildrakizumab in the treatment of moderate to severe psoriasis of the scalp. The study will be conducted in up to 35 study centers across the United States and Australi

Approximately 214 subjects (approximately 107 per arm) with moderate to severe psoriasis of the scalp will be enrolled in the study. Eligible subjects will be randomized to 1 of the 2 arms Arm A: Tildrakizumab 100 mg, SC (n=107) and Arm B: Placebo, SC (n=107).

The study will comprise of 3 parts:

PART 1: Double-blind Placebo-controlled (Day 1 to Week 16)

After a Screening Period of up to 28 days and on Day 1, all eligible subjects will be randomized to receive either tildrakizumab 100 mg or placebo Subjects should receive the first dose of study treatment within 24 hours of randomization.

PART 2: Double-blind Active Treatment Extension (Week 16 to Week 52)

subjects initially randomized to placebo will be switched over to receive tildrakizumab while subjects initially randomized to tildrakizumab 100 mg will continue to receive tildrakizumab In order to maintain the blind, subjects in both treatment arms will receive matching placebo injections at specified time points as described in the Schedule of Activities (SoA)

PART 3: Observational Safety Follow-up (Week 52 to Week 72)

After Week 52 (or early termination of study treatment prior to Week 52), the study treatment should be stopped and all subjects, including those who terminated early from Part 1 and 2 will enter the Observational Safety Follow-up Period to monitor safety and tolerability following last dose of study treatment. During the follow-up period, subjects should continue on study-approved concomitant medications only, however may be placed on appropriate

therapies for safety concerns or significant worsening of psoriasis based on the judgment of the Investigator. The subjects will not receive study treatment during the follow-up period.

4.2 Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of tildrakizumab administered by SC injection in subjects with moderate to severe scalp psoriasis. The study has been developed based on design features used in the completed Phase 2b protocol for subjects with psoriasis as well as ongoing Phase 3 studies for subjects with psoriasis. In this study, tildrakizumab will be compared with placebo. Placebo-controlled studies are the best way to ensure the accurate assessment (in absolute terms) of the safety and tolerability of a new molecular entity.

The study has been designed with 4 distinct phases (Screening, Double-Blind Placebo-Controlled Period, Double-blind Active Treatment Period, and an Observational Safety Follow-up Period). This enables scientific evaluation of efficacy . The 52-week treatment duration is expected to provide adequate time to assess the safety and efficacy of tildrakizumab in subjects with scalp psoriasis.

4.3 Justification for Dose

The dose of tildrakizumab was selected based on the results of the Phase 2 dose-ranging study, and two Phase 3 studies in addition to an exposure-response model that was developed using these results.

[redacted]

[redacted]

[redacted]

[redacted]

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all parts of the study including the last visit [redacted]

The EoS is defined as the date of the last visit of the last subject in the study globally.

5.0 STUDY POPULATION

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

5.1 Inclusion Criteria

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

1. Subjects should be 18 years or older at the time of signing the informed consent during the Screening visit.
2. Subjects with a clinical diagnosis of chronic plaque psoriasis of at least 6 months (as determined by-subject interview and confirmation of diagnosis through physical examination by Investigator).
3. Subjects must have moderate to severe plaque psoriasis of the scalp at Screening and at Baseline, defined by:
    - Scalp Investigator Global Assessment (IGA mod 2011 (scalp) of ⩾3
    - Psoriasis Scalp Severity Index (PSSI) score of ⩾12
    - ⩾30% or scalp surface area affected.
4. Subject must have moderate to severe plaque psoriasis at Screening and Baseline defined by
    - IGA mod 2011 (whole body) of at least moderate severity (score of ≥3 on a 5-pointer scale)
    - PASI score of ≥12
    - Body Surface Area (BSA) involvement of ≥10%
5. Subjects must be considered candidates for systemic therapy, meaning scalp psoriasis inadequately controlled by topical treatments (corticosteroids), and/or phototherapy, and/or previous systemic therapy.
6. Subjects has a negative evaluation for tuberculosis (TB) within 4 weeks before initiating study treatment, defined as a negative QuantiFERON® test. Subjects with a positive or 2 successive indeterminate. QuantiFERON® tests are allowed if they have all of the following:
    - No history of active TB or symptoms of TB.
    - A posterior-anterior chest radiogram (with associated report available at study center) performed within 3 months of Screening with no evidence of active TB (or of any other pulmonary infectious diseases).
    - If prior latent TB infection (LTBI), must have history of adequate prophylaxis (per local standard of care).
    - If presence of LTBI is established, then treatment according to local country guidelines must have been followed for 4 weeks prior to inclusion in the study.

    A maximum of 2 QuantiFERON® tests are allowed. A re-test is only permitted if the first is indeterminate; the result of the second test will then be used.

7. Subjects are unlikely to conceive, as indicated by at least one "Yes" answer to the following questions:
    - Subject is a male.
    - Subject is a female and agrees to abstain from heterosexual activity OR use a highly effective method of contraception as per Appendix 7.
    - Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (eg, condom) if not surgically sterile (ie, vasectomy).
    - Subject is a surgically sterilized female or is documented to be postmenopausal. For contraceptive guidance see Appendix 7
8. For women of childbearing potential, a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to Day 1 and on subsequent visits at which study treatment doses are scheduled.
9. Subjects must have results of a physical examination within normal limits or clinically acceptable limits to the Investigator prior to Day 1. The Investigator is encouraged to consult with the Medical Monitor (or appropriate designee) if there are questions regarding the significance of any out-of-range values.
10. Subjects must be capable of giving signed informed consent as described in Appendix 2, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

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

1. Subjects who have laboratory abnormalities at Screening including any of the following:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 × the upper limit of normal (ULN)
    - Creatinine ≥2 × the ULN
    - Serum direct bilirubin ≥1.5 mg/dL
    - White blood cell count $<3.0\times10^3/\mu L$
    - 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.
2. Subjects who have predominantly non-plaque forms of psoriasis specifically erythrodermic psoriasis, predominantly pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new-onset guttate psoriasis.
3. Women of childbearing potential who are pregnant, intend to become pregnant (within 6 months of completing the study), or are lactating.
4. Subjects with any infection or history of recurrent infection requiring treatment with systemic antibiotics within 2 weeks prior to Screening, or severe infection (eg, pneumonia, cellulitis, bone or joint infections) requiring hospitalization or treatment with intravenous (IV) antibiotics within 6 weeks prior to Screening.

5. Subjects with any previous use of tildrakizumab or other IL-23/Th-17 pathway inhibitors, including p40, p19 and IL-17 antagonists for psoriasis.
    - Prior use of TNF-alpha inhibitors with a wash-out period of 12 weeks would be allowed. However, the number of subjects with prior use of TNF-alpha inhibitors would be capped at 40% and the analysis will be stratified based on prior use of these biologics.
6. Subjects with a positive human immunodeficiency virus test result, hepatitis B surface antigen, or hepatitis C virus test result.
7. Subjects with a prior malignancy or concurrent malignancy (excluding successfully treated basal cell carcinoma, squamous cell carcinoma of the skin in situ, squamous cell carcinoma of skin with no evidence of recurrence within 5 years or carcinoma in situ of the cervix that has been adequately treated).
8. Subjects who have received live viral or bacterial vaccination within 4-weeks prior to Baseline or who intend to receive live viral or bacterial vaccination during the study.
9. Subjects who are currently participating in another interventional clinical study or has participated in an interventional clinical study within 5-half-lives (of the drug) to wash-out prior to randomization (Subjects participating in observational studies or non-interventional registry studies may be included in the study).
10. Subjects or a family member is among the personnel of the study center or Sponsor/designee staff directly involved with this study.
11. Subjects who have any concomitant medical condition which in the opinion of the Investigator could affect the study outcome or present an unacceptable risk.
12. Subjects who were hospitalized due to an acute cardiovascular event (such as myocardial infarction, cerebrovascular accident, cardiovascular illness [eg, angina pectoris], or cardiovascular surgery [such as coronary artery bypass grafting (CABG)]) within 6 months before Screening.
13. Subjects who, in the opinion of the Investigator, will not be a reliable participant in the study and those who can confound the results of the study.
14. Subjects who have a history of alcohol or drug abuse in the previous year.
15. Subjects who have high risk of suicidality at the Screening assessment based on Investigator's judgment or, if appropriate, as indicated by a response of "yes" within the last 12 months to Questions 4 or 5 in the suicidal ideation section, or any positive response in the behavioral section of the C-SSRS.
16. Subjects with any other clinically significant 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.

5.3 Lifestyle Considerations

Excessive exposure to sunlight should be avoided during the study. Subjects should avoid use of tanning booths or other ultraviolet light sources for the duration of the study.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. 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 publishing requirements and to respond to queries from regulatory authorities. The minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at the discretion of the Investigator for up to 2 additional times, with a minimum of 2 weeks between each rescreening. When a subject is rescreened, all Screening procedures will be repeated.

Note: If the original ICF was signed within 30 days of the rescreening visit, a new ICF does not need to be completed.

Rescreened subjects should not be assigned the same subject number as for the initial Screening. Any subject who is started on prophylactic treatment for latent TB during the Screening Period may be randomized 4 weeks after initiation of treatment without need for rescreening.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a subject according to the study protocol.

The study treatment in this study is tildrakizumab and placebo. The study arms will receive study treatment during the course of the study as follows:

Arm A:
- Tildrakizumab 100 mg SC injections
- Placebo injections

Arm B:
- Placebo injections
- Tildrakizumab 100 mg SC injections

Study Treatment Name:	**Tildrakizumab**	**Placebo**
Unit Dose Strength/Dosage Level:	100 mg	-
Route of Administration	Subcutaneous (SC)	SC

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only subjects enrolled in the study may receive study treatment and only authorized study center staff may supply or administer the study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
3. Study treatment experiencing temperature excursions outside this temperature should be quarantined and can only be released for subject use after consultation with the Sponsor.
4. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study treatment will be provided by the study center monitor.

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Form.

6.3 Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally assigned to receive either tildrakizumab 100 mg or placebo using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each study center.

This is a double-blind study with limited access to the randomization code. Tildrakizumab and placebo will be identical in physical appearance.

Study treatment will be dispensed at the study visits summarized in the SoA

Returned study treatment should not be re-dispensed to the subjects.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a subject's treatment assignment 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 after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

A designated member of the Sponsor's safety team will be unblinded for any Suspected Unexpected Serious Adverse Reactions, for regulatory reporting purposes. Unblinding is for regulatory reporting purpose only

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

Study treatment accountability and subject compliance will be documented throughout the treatment periods using study-specific study treatment dispensing record forms. If a subject does not receive the scheduled dose, every effort should be made to administer the dose as soon as possible.

6.5 Concomitant Therapy

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

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

In addition, all prior medications used to treat the disease conditions and any other medications taken within 6 months prior to enrollment must be recorded in the eCRF.

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

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor if required.

6.5.1 Rescue Medicine

Not applicable.

6.6 Dose Modification

No dose modification is allowed in this study. Study treatment can be interrupted temporarily or permanently if deemed necessary as per the Investigator's discretion.

6.7 Treatment after the End of the Study

The Sponsor will not provide any study treatment to the subjects during the Observational Safety Follow-up Period. Patient care should not differ from what is normally expected for subjects with psoriasis.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Subjects may voluntarily discontinue study treatment for any reason at any time and enter the [redacted] wash-out period, or completely withdraw from the study[redacted] Subjects who consent to enter the wash-out period will undergo the Week 52 (EoT) assessment a minimum of 4-weeks after administration of the last dose of study treatment.

At any time during Part 1 or Part 2 of the study, the Investigator should discontinue study treatment of a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

The study treatment must be discontinued under the following circumstances and the further steps need to be discussed with the Medical Monitor:

- An SAE, drug reaction or complication, or an unacceptable AE, whether attributed to study treatment or not, that precludes continuation of treatment with study treatment. This includes the development of allergic reactions or the development of other potentially serious drug reactions to medication required by the protocol
- Diagnosis of malignancy (except basal or squamous cell carcinoma of skin) during study (at discretion of the subject and Investigator)
- Subjects who develop suicidal behavior
- Evidence of pregnancy
- Withdrawal of informed consent
- Lost to follow-up
- Significant non-compliance of the subject with study procedures
- Decision of the Sponsor to terminate the subject, study center, or the study.

[redacted]

Subjects who withdraw from the study at any part will undergo the Week 52 (EoT) assessments. Patient related outcome (PRO) measurement should be obtained immediately after subject withdrawal. Week 52 (EoT) assessments should be conducted a minimum of 4-weeks after administration of the last dose of study treatment.

See the SoA [redacted] for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Study treatment can be interrupted temporarily in case of:

- Clinically important laboratory abnormalities.
- Subjects who develop suicidal ideation.
- Other intercurrent illnesses or major surgery.
- Use of prohibited treatment.
- Any other protocol deviation that results in a significant risk to the subject's safety.
- Sponsor decision.

The Medical Monitor should be informed. Re-starting of study treatment at the next scheduled administration study visits can be done after discussion with the Medical Monitor.

7.2 Subject Discontinuation/Withdrawal from the Study

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

Withdrawal of consent occurs when a subject does not want to participate in the study anymore and does not want to attend any further visits or assessments, have further study-related contact, or allow analysis of already obtained biologic material.

If a subject withdraws consent, the Investigator must make every effort to determine the primary reason for this decision and record this information on the treatment disposition eCRF page. If the subject decides to completely withdraw from the study (refuses any further study participation or contact), all study participation for that subject will cease and data to be collected at subsequent visits will be considered missing. The study treatment must be discontinued, and no further assessments conducted. Further attempts to contact the subject are not allowed unless safety findings require communication or follow-up.

However, for safety reasons, Week 52 (EoT) assessments should be conducted for subjects withdrawing during Part 1 or 2, if the withdrawn subject is willing to undergo the assessments. For subjects withdrawing during Part 3 and willing to undergo final assessments, the Week 72 (EoS) assessments should be conducted at least 4 weeks after their last visit.

The appropriate personnel from the study center and CRO will assess whether the study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

The Investigator must also contact the IWRS to register the subject's discontinuation from the study treatment.

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 center.

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

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not 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, 3 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 withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- [redacted] Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue the study treatment.
- Adherence to the study design requirements [redacted] is essential and required for the 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.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame [redacted].
- 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 more than 150 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- The efficacy assessments, IGA mod 2011 (scalp), PSSI, IGA (scalp only), scalp surface area, PASI, PGA-S (whole body), IGA mod 2011 (whole body), BSA will be assessed at each visit during the study. At all visits where efficacy assessments are made, the Patient reported Outcomes (PROs) (in particular Dermatology Life Quality Index [DLQI] and Scalp Itch NRS) must be completed by the subject prior to other efficacy assessments performed by the Investigator or designee. The order of the efficacy assessments evaluated by Investigator should be primary endpoint, key secondary endpoint followed by other secondary/exploratory endpoints.
- To ensure consistency of efficacy assessments over the study duration, it is preferred that the same person perform the same assessment on the same subject across all visits.
- [redacted] All doses of study treatment will be administered at the study center; at home administration is not permitted.
- All unscheduled visits and assessments performed during the visits will be recorded in the subject's eCRF. During any unscheduled visits the Investigator will record any AEs and concomitant medications as well as performing any assessments or collecting samples deemed necessary at the discretion of the Investigator.

[redacted]

8.1.1 Assessments for Scalp:

8.1.1.1 Investigator Global Assessment (IGA) mod 2011 rating scale (Scalp)

The IGA mod 2011 is a scale that is static This scale met the evidence standard for pivotal trials, and has supported previous product labeling claims

8.1.1.2 Investigator Global Assessment (Scalp only)

The IGA score is a useful clinician assessment of scalp lesions based on thickness, erythema, and scaling that is here retained as a secondary endpoint

8.1.1.5 Psoriasis Scalp Severity Index (PSSI)

The PSSI is a modification of the PASI to specifically assess severity of scalp disease. The PSSI use a scale to grade the 3 clinical parameters in the same way as the PASI, but for scalp only.

8.1.2 Assessments for Whole Body:

8.1.2.1 Investigator Global Assessment (IGA) mod 2011 rating scale (whole body)

The IGA mod 2011 is a scale

[redacted] This scale met the evidence standard for pivotal trials, and has supported previous product labeling claims [redacted]

[redacted]

8.1.2.2 Physician Global Assessment of Skin (Whole body)

The PGA-S is a [redacted] useful clinician assessment of psoriasis lesions on the skin based on degree of erythema, thickness, and scale averaged over the entire body. [redacted]

8.1.2.3 Psoriasis Area and Severity Index

Psoriasis Area and Severity Index will be used to determine the treatment response (PASI 75, PASI 90, and PASI 100) in subjects with scalp psoriasis. [redacted]

8.1.2.4 Body Surface Area

Body Surface Area is a commonly used measure of severity of skin disease. It is defined as the percentage of the total BSA affected by psoriasis, it represents the area of affected scalp. [redacted]

8.1.3 Dermatology Life Quality Index

The DLQI questionnaire will be used to assess treatment response on the subject's quality of life. The aim of this questionnaire is to measure how much the skin condition has affected the subject's life during the previous week.

[redacted] The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation [redacted]

8.2 Safety Assessments

[redacted]

8.2.1 Physical Examinations

- A complete physical examination will include assessments of general appearance; skin; head/neck
- A detailed examination of the skin should be performed for the efficacy assessments
- Height and weight will also be measured and recorded at Baseline before administration of study treatment.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Oral body temperature, pulse rate, blood pressure, and respiratory rate will be assessed at the time points
- Blood pressure and pulse measurements will be assessed in the supine position.
- Blood pressure and pulse measurements should be preceded by approximately 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute) using a validated device. The average of the 3 blood pressure readings will be recorded on the eCRF.

8.2.3 Assessment of Suicidal Ideation and Behavior

- The subjects will be assessed for suicidal ideation and behavior at Screening
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- Those subjects who develop suicidal ideation during the study rated as high risk according to the above classification must be temporarily discontinued from receiving study treatment and referred promptly for psychiatric evaluation.
- Subjects rated as displaying the intermediate level of suicidal ideation should receive psychological support and be assessed on an individual basis.
- All individuals assessed as exhibiting suicidal behavior, except preparatory acts, must discontinue study treatment permanently. The presence of non-suicidal self-injurious behavior should be assessed on an individual basis.

8.2.4 Electrocardiograms

- Single 12-lead electrocardiogram (ECG) will be obtained [redacted] using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, RR and QTc intervals.
- The ECG will be reviewed by an ECG vendor and the instructions and guidelines for collection (eg, equipment), transmission, and archiving of ECG data will be provided in the ECG Manual.

8.2.5 Tuberculosis Testing

- During the Screening Period, it must be determined and documented that a subject does not show evidence of active infection with TB.
- The subject must have a negative evaluation for TB within 4 weeks before initiating study treatment, defined as a negative QuantiFERON® test.
- Subjects with a positive or 2 successive indeterminate QuantiFERON® tests are allowed to enter the study if they have no history of active TB or symptoms of TB, and a PA chest radiogram performed (and with a report available at the study center) within 3 months of Screening with no evidence of TB (or of any other pulmonary infectious diseases).
- If there is evidence of prior LTBI, subjects must have history of adequate prophylaxis per local standard of care. If presence of LTBI is established, treatment according to local country guidelines must have been followed for at least 4 weeks prior to inclusion in the study.

8.2.6 Chest X-ray

- A chest X-ray will be performed at Screening if the subject has a positive or 2 indeterminate QuantiFERON results unless it has been taken and documented within the 3 months prior to Screening (the X-ray and associated report must be available at the study center). There must be no evidence of active TB or any other pulmonary infectious diseases for the subject to be considered eligible for the study.

8.2.7 Clinical Safety Laboratory Assessments

- [redacted]

- A central laboratory will be used to perform all laboratory tests except urine pregnancy dipstick which will be assessed by the center staff. However, local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately and the Investigator needs to take an immediate decision for any safety concerns based on the laboratory results.
- 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. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that 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 including the subject's last EoS visit should be repeated until the values return to normal or Baseline or until stabilized or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, if possible and the Sponsor notified.

All protocol-required laboratory assessments,[redacted] must be conducted in accordance with the Laboratory Manual[redacted]

8.3 Adverse Events

The safety and tolerability of subjects will be assessed by the incidence of treatment-emergent adverse events (TEAEs), laboratory test results, vital signs, ECGs, and physical examination findings.

The definitions of an AE or SAE can be found in Appendix 4.

The Investigator will document all AEs in the subject's source document and eCRF. All entries should contain an event term, date of onset, date of resolution, severity, action taken, outcome, relationship to study treatment, and a seriousness assessment.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Any relevant observations made before the end of the Screening and Baseline visit (prior to first dose of study treatment) are to be recorded on the AE eCRF, but will not be considered TEAEs and will be reported separately from TEAEs. Any relevant observations made after the first dose of study treatment will be recorded as an AE in the subject's AE eCRF[redacted]

[redacted]For the purposes of this study, any detrimental change in the subject's condition, after the first dose of study treatment and up to completion of the EoS visit, should be considered

an AE. For those subjects who may withdraw during the Observational Safety Follow-up Period or wash-out period, at least 2 attempts should be made to collect the AEs.

A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the study, it must be reported as an AE.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the AE section of the eCRF, however will not be considered as TEAEs.

All SAEs will be recorded and reported to the CRO within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the CRO within 24 hours of it being available. The Investigator is responsible for informing the Ethics Committee of the SAE as per local requirements. All AEs/SAEs have to be reported to the Sponsor, whether or not considered causally related to the study treatment or to the study procedures.

Investigators are not obligated to actively seek AE or SAE after conclusion of the 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 treatment or study participation, the Investigator must promptly notify the CRO.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 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.

8.3.3 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. All SAEs, and non-serious AEs of special interest (as defined in Section 8.3.6), 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). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. The report will contain as much available information concerning the SAE to enable the Sponsor's designated pharmacovigilance personnel/ CRO to file a report,

which satisfies regulatory reporting requirements. The SAE report will be notified by Investigator within 24-hours of his/her awareness to the Sponsor's designated pharmacovigilance personnel/CRO. These timelines apply to initial reports of SAEs and to all follow-up reports.

All SAEs will be recorded on the SAE report form in the eCRF and source documents.

The following minimum information must be included in the SAE form:

- Name, address and telephone number of the reporting Investigator
- Study treatment details
- Subject identification number, initials, sex and date of birth
- Description of the SAE, measures taken and outcome

Relevant pages from the eCRF may be provided in parallel (eg, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (eg, laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (eg, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor's designated pharmacovigilance personnel/CRO may have on the SAE. This is necessary to ensure prompt assessment of the event by the Sponsor's designated pharmacovigilance personnel to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

8.3.5 Pregnancy

Pregnancy itself is not regarded as an AE unless there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication. If a pregnancy is reported for a subject, no further study treatment will be administered to this subject and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented. Follow-up should be performed up to delivery and examination of the newborn, after which a follow-up report should be sent with any new information regarding the pregnancy and the outcome of the birth.

The pregnancy shall be followed every 3 months during pregnancy until its outcome and 1 month post-delivery. If there are abnormalities present at delivery, the newborn will be followed for an appropriate period, or up to 3 months, to assess the functional and health status of the child.

All congenital abnormalities/birth defects should be classified as SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs but should be reported as a follow-up report for the pregnancy. All outcomes of pregnancy must be reported to the Sponsor on a Pregnancy Outcomes Report Form.

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

Pregnancies must be reported to Novella Clinical Pharmacovigilance and Safety Services using the reporting details provided in Appendix 4 within 24 hours of becoming aware of the pregnancy.

8.3.6 Adverse Events of Special Interest

The events of severe infections, injection site reactions (e.g. pain, edema, erythema), malignancies (including non-melanoma and melanoma skin cancer), Major Adverse Cardiovascular Events, and study treatment -related hypersensitivity reactions (see Appendix 5) will be identified as adverse events of special interest (AESIs) for summarizing in this study. Major Adverse Cardiovascular Events include non-fatal stroke, non-fatal myocardial infarction and cardiovascular death. An AESI must be reported as if it were an SAE.

8.3.7 Events of Clinical Interest

An Event of Clinical Interest (ECI) is a non-serious AE or occurrence that is designated to be of special interest and must be reported to the Sponsor as though it were an SAE.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

8.4 Treatment of Overdose

A drug overdose is defined as the accidental or intentional use of a drug or medicine or an administration error in an amount that is higher than is normally used. [redacted]

Overdose in this study is specifically defined as any dose greater than the intended protocol dose [redacted] In case of overdose, it is recommended that the subject be monitored for any signs

or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health Economics or Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy endpoint for this study is proportion of subjects with IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least a 2-point reduction from Baseline at Week 16. The key secondary efficacy endpoints are the proportion of subjects with at least 90% improvement in the PSSI (PSSI90) response from baseline at Week 16, the proportion of subjects with IGA (scalp) score of "clear" and "almost clear" with at least a 2-point reduction from baseline at Week 16, the proportion of subjects with IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least a 2-point reduction from Baseline at Week 12 and the proportion of subjects with at least 90% improvement in the PSSI (PSSI90) response from baseline at Week 12. For each endpoint, the tildrakizumab 100 mg dose will be compared with placebo.

9.2 Sample Size Determination

The study will randomize to either tildrakizumab 100 mg arm or placebo arm

tests

[redacted]

9.3 Populations for Analyses

For purposes of analysis, the analysis sets in Table 3 are defined.

Table 3 Analysis Sets

Analysis Set	Description
Intent-to-Treat (ITT)	All randomized subjects who have received dose of study treatment Subjects will be analyzed according to their planned treatment assignment.
Per Protocol Set (PPS)	All subjects in the ITT population who complete the placebo-controlled treatment
Safety Analysis Set (SAS)	All randomized subjects who receive dose of study treatment. Subjects will be analyzed according to the treatment they actually received. Safety endpoints will be analyzed descriptively based on the SAS.

9.4 Statistical Analyses

The statistical analysis will be performed using statistical analysis system (SAS®) Version 9.3 or higher if available. All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the Statistical Analysis Plan (SAP). The SAP will be developed and finalized before database lock after the completion of the placebo-controlled treatment period. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

The following descriptive statistics will be used as applicable to summarize the study data unless otherwise specified:

- Continuous variables: sample size (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).
- Categorical variables: frequencies and percentages.

Unless otherwise specified, "Baseline" is defined as the last observed value of the parameter of interest prior to the first intake of study treatment (this includes unscheduled visits).

Statistical comparisons for the primary and key secondary endpoints will be performed for inferential purpose following the testing approached other statistical comparisons will be performed for descriptive purpose.

Individual subject data will be presented in listings.

9.4.1 Efficacy Analyses

Table 4 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	
Primary Efficacy Endpoint	
The proportion of subjects with IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16.	The primary efficacy variable will be analyzed using with Cochran-Mantel- Haenszel (CMH) test The Mantel-Haenszel common risk (response rate) difference between tildrakizumab 100 mg and placebo
Key Secondary endpoints	
• The proportion of subjects with at least 90% improvement in the PSSI at Week 16. • The proportion of subjects with IGA	The key secondary efficacy endpoints will be analyzed using the same statistical methods as for the primary efficacy endpoint

Endpoint	Statistical Analysis Methods
(scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 16. • The proportion of subjects with IGA mod 2011 (scalp) score of "clear" and "almost clear" with at least 2-point reduction from Baseline at Week 12. • The proportion of subjects with at least 90% improvement in the PSSI at Week 12.	including all subsequent secondary analyses, subset analyses, and missing value imputations.
Other Secondary Endpoints	
• Mean percentage change in PSSI score from Baseline to Week 16. • Mean percentage change in scalp surface area involvement from Baseline to Week 16. • Mean percentage change in total BSA involvement from Baseline to Week 16.	Continuous secondary efficacy endpoints will be analyzed using a mixed model repeated measures procedure (MMRM) [redacted]
• The proportion of subjects achieving PSSI 75 at Week 16. • The proportion of subjects achieving PSSI 100 at Week 16. • Proportion of subjects achieving a 4-point reduction in Scalp Itch NRS score from Baseline to Week 16 compared with placebo. • The proportion of subjects achieving PASI 75, PASI 90, and PASI 100 at Week 16. • The proportion of subjects PGA-S score (whole body) of "clear" or "almost clear" with at least a 2-point reduction from Baseline to Week 16. • Time (days) to IGA mod 2011 (whole body) response during the 16-week placebo-controlled treatment period. • IGA (scalp only), Scalp Itch NRS, PASI, PGA-S (whole body), and IGA mod 2011 (whole body), at week 12 and	[redacted] secondary efficacy endpoints will be analyzed using the same method as for the primary efficacy endpoint [redacted] All efficacy endpoints obtained from Week 1 [redacted]

Endpoint	Statistical Analysis Methods
other measured time points through Week 52. • IGA mod 2011 (scalp), PSSI measured at other time points through Week 52.	
• Time (days) to 75% reduction in PSSI during the 16-week placebo-controlled treatment period. • Time to IGA mod 2011 (scalp) response during the 16-week placebo-controlled treatment period.	[redacted] Time to PSSI-75 or IGA mod 2011 (scalp), response will be analyzed using the Kaplan-Meier method. [redacted]
Exploratory Endpoints	
• Change from Baseline in DLQI score (total and 6 domain scores) at measured time points through Week 52.	All efficacy endpoints obtained [redacted] will be summarized using descriptive statistics.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set based on the actual treatment they received. All the safety will be summarized by-treatment arm and by-subject listings will be provided.

9.4.2.1 Adverse events and Serious Adverse Events

Treatment-emergent adverse events are defined as AEs that first occurred or worsened in severity after the first administration of study treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. For each study treatment, numbers of TEAEs and incidence rates will be tabulated by preferred term and system organ class.

Treatment-emergent AEs by maximum severity, TEAEs by relationship to study treatment, SAEs, TEAEs leading to death, and TEAEs leading to discontinuation of study treatment will be

tabulated for each treatment arm. Commonly occurring TEAEs, in either treatment arm, will be summarized using descriptive statistics.

The safety of tildrakizumab will be evaluated by and reported as the percentage of subjects for the following TEAEs:

- Incidence, seriousness and severity of all AEs, death cases and discontinuations from the study.
- Percentage of subjects with severe infections, defined as any infection meeting the regulatory definition of a serious adverse event, or any infection requiring IV antibiotics whether or not reported as a serious event as per the regulatory definition.
- Percentage of subjects with malignancies (excluding carcinoma in situ of the cervix).
- Percentage of subjects with non-melanoma skin cancer.
- Percentage of subjects with melanoma skin cancer.
- Percentage of subjects with MACE
- Percentage of subjects with study treatment-related hypersensitivity reactions (eg, anaphylaxis, urticaria, angioedema, etc).
- Percentage of subjects with injection site reactions (eg, pain, erythema, edema, etc).

9.4.2.2 Physical Examinations, 12-Lead ECG, Vital Signs and Clinical Safety Laboratory Tests (Hematology, Biochemistry, and Urinalysis)

Summaries and listings of data for physical examination findings, vital signs, hematology, biochemistry, and urinalysis laboratory tests will be presented. Appropriate descriptive statistics will be summarized for the observed value at each scheduled assessment and for the corresponding change from Baseline.

For hematology and biochemistry tests, listings of subject data will also flag up any abnormal or out-of-range values. Clinically significant changes in the laboratory test parameters will be summarized and listed. Hematology and clinical laboratory data will be reported in System International units.

Descriptive statistics will be used to present the safety outcomes including, physical examination results, weight, body mass index, 12-Lead ECG, vital signs measurements, and clinical laboratory test results.

Change from Baseline will also be summarized for vital signs measurements and clinical laboratory test results.

All ECG data results (normal/abnormal) will be summarized using frequency and percentages. Clinically significant abnormalities will be presented in by-subject listings.

The incidence of treatment-emergent abnormal laboratory, vital sign, and ECG values will also be summarized using descriptive statistics.

9.4.3 Other Analyses

No other analyses are planned for this study.

[redacted]

9.5 Interim Analyses

Following the last subject's Week 16 visit, the IA (primary analysis) will be conducted on available data to evaluate efficacy and safety.

[redacted]

The SAP will describe the planned IA (primary analysis) in greater detail.

9.6 Monitoring Committee

No external data monitoring committee is constituted for this study.

[redacted]

[redacted]

APPENDIX 2: REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

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 International Ethical Guidelines.
  - Applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to 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 serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
  - After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (see Appendix 20).
  - The study will not start at any study center at which the Investigator has not signed the protocol.

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 course of the study and for 1 year after completion of the study.

Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

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 center.
- The medical record must include a statement that written informed consent was obtained before the subject was entered 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.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

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 Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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Quality Control and Quality Assurance

[redacted]

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Central laboratories for clinical laboratory parameters.
- Study center Initiation visit.
- Early study center visits post-enrollment.
- Routine study center monitoring.
- Ongoing study center communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report (CSR).

In addition, Sponsor may conduct periodic audits of the study processes, including, but not limited to study center, central laboratories, vendors, clinical database, and final CSR. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

Monitoring

Sponsor has engaged the services of a contract research organization, to perform all monitoring functions within this clinical study. monitors will work in accordance with SOPs. The monitor will establish and maintain regular contact between the Investigator and Sponsor.

The monitor will evaluate the competence of the study center, informing Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, the monitor will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. The monitor is also entitled to compare entries in the eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. The monitor will also assess and control adherence to the protocol and ICH/GCP guidelines at the study center. The monitor will arrange for the supply of study treatment, ensure proper study treatment dispensing/accountability, and appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each center while subjects are enrolled in the study.

During monitoring visits, all entries in the eCRFs will be compared with the original source documents (source data verification). For the following and all other items, this check will be 100%:

- Subject identification number.
- Subject consent obtained.
- Subject eligibility criteria (inclusion and exclusion criteria).
- Efficacy variables (not directly entered into PRO).
- Safety variables.
- Medical record of AE.

Quality Management

A system should be implemented to manage quality throughout all stages of the study process with the focus on study activities essential to ensuring human subject protection and the reliability of study results. The methods used to assure and control the quality of the clinical study should be proportionate to the risks inherent in the trial and the importance of the information collected. All aspects of the study should be operationally feasible and should avoid unnecessary complexity, procedures, and data collection.

During protocol development, processes and data that are critical to ensure human subject protection and the reliability of trial results should be identified. Risks should be considered at both the system level (eg, standard operating procedures, computerized systems, personnel) and clinical trial level (eg, trial design, data collection, informed consent process). The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Quality management activities should be documented and communicated to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

Data Management/Coding

[redacted]

Electronic data capture will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study centers. Data collection will be completed by authorized study center staff designated by the Investigator. Appropriate training and security measures will be

completed with the Investigator and all designated study center staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial Baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data when all the data is clean prior to database lock.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. The monitor cannot enter data in the eCRFs. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study center staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time, and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include but are not limited to laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Any changes to the source documents or cancellations should be signed and initialed with date. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who is screened and enrolled in the study regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

User Roles and Responsibilities:

Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center staff responsible for entering the clinical data into the eCRF will be determined in advance.

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature.

Data Handling and Record Keeping

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation). The study center should plan on retaining such documents for approximately 15 years after study completion. The study center should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the study treatment. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to Sponsor. The Investigator must contact Sponsor prior to disposing of any study records.

Direct Access to Source Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each subject randomized into the study.

The Investigator will allow Sponsor, [redacted] and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual subject medical records, as appropriate. Such information must be kept confidential and must have locked facilities that allow for this. Subject identification number will be recorded on all documents related to the study.

Study and Study Center Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center 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 center 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 treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

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APPENDIX 4: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • 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 treatment.
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 treatment 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 treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "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 fulfill 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. • Pregnancy itself is not regarded as an AE unless there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication. If a pregnancy is reported for a subject, no further study treatment will be administered to this subject and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented. Follow-up should be performed up to delivery and examination of the newborn, after which a follow-up report should be sent with any new information regarding the pregnancy and the outcome of the birth. • All congenital abnormalities/birth defects should be classified as SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs but should be reported as a follow-up report for the pregnancy. All outcomes of pregnancy must be reported to the Sponsor on a Pregnancy Outcomes Report Form. • Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner. • The pregnancy shall be followed every 3 months during pregnancy till its outcome and 1 month post-delivery. If there are abnormalities present at delivery, the newborn will be followed for an appropriate period, or up to 3 months, to assess the functional and health status of the child. • Pregnancies must be reported to [redacted] using the reporting details provided in Section 8.3.4within 24 hours of awareness.

Definition of SAE

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, death due to progression of disease).

An SAE is defined as, but is not limited to, an event that:
a) Results in death Death is not an AE in itself, but an outcome. The cause of the death is the AE which resulted in death.
b) Is life-threatening Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it had been more severe. .

c) Requires inpatient hospitalization or prolongation of existing hospitalization

Hospitalization is defined as at least 1 overnight formal admission into hospital, usually in order to perform additional tests, provide treatment which it is not possible to provide at home and/or due to an unstable medical condition which requires specific monitoring of the subject. Pre-planned hospitalizations (known already prior to signing the ICF) for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health or if the hospitalization is clearly not associated with an AE (eg, social hospitalization) will not be considered an SAE, unless any of the above criteria are fulfilled over the course of the hospitalization due to unplanned complications. Any Hospitalization due to logistic reason will not be considered as SAE" "Social" hospitalization whereby it is administratively impossible to release the subject home is not necessarily an SAE. Complications that occur during hospitalizations are AEs unless they would qualify as an SAE for any of the above criteria. If the complication delays subject release from hospital, then the AE becomes an SAE. Hospitalizations which are not performed due to an AE are not regarded as SAEs.

d) Results in persistent or significant disability/incapacity

The term significant disability refers to any condition that impairs physical/physiological well-being to the extent that the subject is unable to function normally. Physical disability may include, but is not limited to, permanent disability of locomotion or motility, but also systemic permanent dysfunction including heart failure, liver insufficiency or pulmonary fibrosis.

e) Is a congenital anomaly/birth defect

f) Is an important medical event:

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered as an SAE when, based on appropriate medical judgment, they may jeopardize the subject, or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Recording and Follow-up of AE and/or SAE

Definition of the Adverse Event Reporting Period

The AE/ SAE reporting period for safety surveillance begins after subject signs ICF. The safety surveillance continues until 20 weeks from last dose of study treatment administration. Any AE/-SAE occurred post 20 weeks from last dose of study treatment administration will be reported if it is considered related to study treatment by the Investigator.

Unexpected Adverse Event

Any adverse event that is not identified in nature, severity, frequency or outcome in Investigator Brochure (IB) will be considered as unexpected. Most recent version of IB will serve as reference safety information for assessment of expectedness of SAEs.

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 eCRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to [redacted] in lieu of completion of the/AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by [redacted]. 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 to [redacted].
- 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 for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as certainly/definitely related, unrelated, unlikely to be related, possibly related, or probably related.
    - "Certainly/definitely related" suggests that a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
    - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
    - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
    - "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
    - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
- 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 treatment administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her 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 [redacted]. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to [redacted].
- 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.

Action Taken with respect to study treatment

Action taken is categorized as "none", "study treatment discontinued permanently", "study treatment discontinued temporarily and restarted", or unknown.

Event Outcome

Event outcome recorded and categorized as "Fatal", "Resolved", "Resolved with sequelae", "Resolving", "Not Resolved", or "Unknown".

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 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 or during a recognized follow-up period, the Investigator will provide with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE data to the within 24 hours of receipt of the information.
Follow-up of unresolved AEs and SAEs
Any AE/ SAE unresolved at end of study visit will be followed until resolution/ stabilization or as per medical judgment of the Investigator.

Reporting of SAEs

SAE Reporting to via Paper Case Report Form (CRF)
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
Safety Reporting to Sponsor
• will forward the SAE and Pregnancy report to the Sponsor's safety representatives within 1 business day or 3 calendar days (whichever is earlier) of becoming aware of it.

APPENDIX 5: ANAPHYLAXIS

The clinical criteria for diagnosing anaphylaxis are as follows:

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
• Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula). AND AT LEAST ONE OF THE FOLLOWING o Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) o Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
• Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours): o Involvement of the skin-mucosal tissue (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) o Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) o Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) o Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
• Reduced BP after exposure *to known allergen for that patient* (minutes to several hours): o Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP o Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

[redacted]

APPENDIX 6: EXCLUDED MEDICATIONS/THERAPY

Excluded medications/therapy is listed below. The concomitant use of an excluded medication/therapy with study treatment is not in compliance with the study protocol and must be recorded in the eCRF.

APPENDIX 7: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

6. Premenarchal
7. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
8. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the study and for 6 months after the last dose of study treatment:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
    - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- In addition, male subjects must refrain from donating sperm for the duration of the study and for 6 months after the last dose of study treatment.
- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study and for 6 months after the last dose of the study treatment.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 6 months, after the last dose of study treatment.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at Screening and urine pregnancy test on Day 1 (prior to study treatment administration).
- Additional pregnancy testing should be performed as mentioned in SoA (see Section 1.3)
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Positive urine pregnancy test result should be confirmed with serum test.

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. This applies only to male subjects who receive the study treatment.
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 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. The pregnancy shall be followed every 3 months during pregnancy until its outcome and 1 month post-delivery. 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. The pregnancy shall be followed every 3 months during pregnancy until its outcome and 1 month post-delivery. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. The method of reporting pregnancy will be similar to SAE reporting as mentioned in Appendix 4.
- 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 treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the

Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

- Any female subject who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.
- The pregnancy shall be followed every 3 months during pregnancy till its outcome and one month post-delivery. If there are abnormalities present at delivery, the newborn will be followed for an appropriate period, or up to 3 months, to assess the functional and health status of the child.

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APPENDIX 19: COLUMBIA-SUICIDE SEVERITY RATING SCALE

1) C-SSRS Screening

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS-Screening - United States/English - Mapi.
ID040351 / C-SSRS-Screening_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Past X Months

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Past X Years or Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

 C-SSRS—Screening (Version 1/14/09)

2) C-SSRS Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even f the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

3) C-SSRS Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
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[redacted]