An Open Label Phase 1b Study of Secukinumab in Patients With Moderate to Severe Papulopustular Rosacea

Study Protocol and Statistical Analysis Plan

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An open label phase 1b study of secukinumab in patients with moderate to severe papulopustular rosacea

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I. Background

Rosacea is a common inflammatory skin disease affecting up to 10% of adults. Despite this, the etiology of rosacea is unclear, although there may be a genetic predisposition (Chang *et al.,* 2015). Currently, there is no cure. Rosacea can lead to scarring, itching, burning, and is associated with anxiety and depression (Moustafa *et al.,* 2015), significantly affecting quality of life.

II. Study Rationale

Rosacea is a common inflammatory skin disease affecting up to 10% of adults. Despite this, the etiology of rosacea is unclear, although there may be a genetic predisposition (Chang *et al.,* 2015). Currently, there is no cure. Rosacea can lead to scarring, itching, burning, and is associated with anxiety and depression (Moustafa *et al.,* 2015), significantly affecting quality of life.

Secukinumab is an antibody that binds to a protein (interleukin (IL)-17A) that is involved in inflammation. When IL-17A is bound to secukinumab, it cannot bind to its receptor, thereby inhibiting its ability to feed the inflammatory response. In clinical trials, secukinumab has been effective for moderate to severe psoriasis (Blauvelt *et al*., 2015). Recently, human data from all types of rosacea have shown Th1/Th17 polarization profile of the T-cell response, suggesting that anti-IL-17 therapy may be beneficial for rosacea (Buhl *et al*., 2015). Hence, secukinumab could be effective against rosacea. This proposal is a proof-of-concept study to use secukinumab in open label design for moderate to severe papulopustular rosacea.

III. Objective and endpoints

Primary objective:

To assess whether secukinumab can reduce the number of papules and/or pustules in moderate to severe papulopustular rosacea after 16 weeks of use.

Secondary objective 1: To assess whether secukinumab can reduce the number of papules and/or pustules in moderate to severe papulopustular rosacea after 12 weeks of use.

Secondary objective 2: To assess whether secukinumab can reduce the overall severity of rosacea by global assessment combining patient reported symptoms and clinical inspection.

Secondary objective 3: To assess whether secukinumab can reduce on erythema in patients with moderate to severe papulopustular rosacea after 16 weeks of use.

Secondary objective 4: To assess whether secukinumab can significantly improve quality of life measures in patients with moderate to severe papulopustular rosacea after 16 weeks of usage.

Secondary objective 5: To assess whether secukinumab leads to any adverse events ≥ grade 3 in rosacea patients during the 16 weeks of the study.

Secondary objective 6: To assess whether secukinumab leads to any changes in immune infiltrate in papulopustular rosacea lesions after 16 weeks.

Secondary endpoint 1: Change in the number of papulopustular lesion count on the face due to rosacea before and after 12 weeks of secukinumab.

Secondary endpoint 2: Change in composite global assessment of rosacea using the clinical scorecard measures as shown in Appendix 2.

Secondary endpoint 3: Change in the area of involvement of erythema on the face due to rosacea before and after 16 weeks of secukinumab, as assessed by blinded and independent

photographic assessor using the visual scale in Appendix 3.

Secondary endpoint 4: Change in any of the quality of life scores before and after 16 weeks of secukinumab using the questionnaire in Appendix 4.

Secondary endpoint 5: Describe the incidence and severity of adverse events while on secukinumab for rosacea from baseline to week 16.

Secondary endpoint 6: Describe and quantitate changes in the level and composition of the peri-follicular immune infiltrate in rosacea lesions before and after 16 weeks of secukinumab.

IV. Study design

This is an open label single arm study whose primary objective is to assess whether secukinumab can significantly reduce the number of papule/pustules after 16 weeks of use. After Stanford Human Subjects Panel approval and written Informed Consent, study participants will use secukinumab 300 mg weekly x 5 weeks (Dose at Week 0, 1, 2, 3, and 4) followed by 2 additional monthly injections (a total of seven 300mg doses), according to the Visit Table. Adverse events will be graded and recorded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. To avoid investigator bias, a board certified dermatologist blinded to the before or after status of the participant will assess the facial photographs for papulopustule count and erythema. As this is not a crossover study, participants are certainly at risk for reporting bias, however, future larger studies may address this issue. (Because rosacea takes at least 16 weeks to reach maximal clinical response, a crossover study with washout between treatment intervals would be estimated to take 28 weeks, which is a long duration for an exploratory study.) Study participants will follow the procedures as outlined in the Visit Table. Our team has experience administering rosacea quality of life surveys (Chang *et al.,* 2012).

Biomarkers for response such as type and degree of inflammatory infiltrate before and after treatment (16 weeks) will be assessed from 4 mm Keyes punch biopsies of rosacea papules. The tissue will be fixed in formalin and embedded in paraffin for staining with hematoxylin and eosin. Histological assessments will be made by a dermatopathologist blinded to the before or after treatment status of the tissue assessed. Severity of inflammation will be assessed using a 5 point Likert scale, and the numbers of neutrophils, lymphocytes and Langerhans cells will be assess be high powered field.

V. Patient population

Adults (N=24) with moderate or severe papulopustular rosacea who meet the eligibility criteria as outlined below.

Key inclusion criteria

1) *Moderate to severe papulopustular rosacea defined clinically using the grading system of Wilkin et al. (2004) as having at least ten lesions (either papules or pustules) on face at time of enrollment*
2) *Age 18 years or greater*
3) *Willing and able to understand and sign informed consent form*

Key exclusion criteria

1) *Known hypersensitivity to secukinumab*

2) *Topical or oral anti-rosacea medication usage for 28 days prior to enrollment*

3) *Active Crohn's disease, as secukinumab may exacerbate this disease*

4) *Active infection including tuberculosis, hepatitis B or C, human immunodeficiency virus*

5) *Participants with latent tuberculosis will need to have treatment initiated prior to starting study drug*

6) *Pregnant or lactating*

7) *Active and/or uncontrolled medical conditions that may interfere with study procedures or obscure rosacea assessment such as cutaneous lupus*

8) *Use of retinoids within past 4 weeks of enrollment.*

    a. *Use of topical retinoids within past 3 months of enrollment is allowed if the regimen is stable for 1 month prior to enrollment and subject agrees to keep regimen unchanged for duration of study*

9) *Use of antibiotics within 4 weeks of enrollment*

10) *Use of light based or laser treatment to face within 8 weeks of enrollment*

11) *Use of systemic steroids within 4 weeks of enrollment*

    a. *Use of topical steroids is allowed if the regimen is unchanged for 2 weeks prior to enrollment and is unchanged for the duration of the study*

12) *Acne conglobate, acne fulminans, chloracne, severe acne requiring systemic treatment*

VI. Treatment

This is an open label study using secukinumab 300 mg subcutaneously weekly x5 weeks (Dose at Week 0, 1, 2, 3, and 4) then monthly x2 months (a total of seven doses of 300mg).

VII. Drug administration

Subcutaneous injection

VIII. Dosing guidelines

This study will use a flat dose that is the FDA approved dose for psoriasis (see Package Insert)

IX. Visit schedule and Assessments

<u>Visit 1 (Week -4 to Baseline)</u>

Following written informed consent, a past medical history, concomitant medications, and physical examination will be performed. Vitals signs will be taken and peripheral blood draw will be performed to assess for blood counts, kidney function, and tuberculosis exposure (See Study Calendar).

Visit 2 Week 0 (Baseline)

After verification of eligibility, participants will undergo vital signs, physical examination, adverse event determination, concomitant medication review, photography, skin biopsy and questionnaire administration. Biopsy will be sent for histology and immunohistochemistry. Study drug will be dispensed with a study diary and instructions on self administration.

Visit 3 Week 4
Adverse events and concomitant medication changes will be ascertained. Drug diary will be reviewed for correct study agent usage. Unused drug and sharps containers will be collected. Vitals signs and physical examination will be performed and photographs taken. Rosacea Questionnaire will be administered. Study drug will be dispensed.

Visit 4 Week 12
Adverse events and concomitant medication changes will be ascertained. Drug diary will be reviewed for correct study agent usage. Unused drug and sharps containers will be collected. Vitals signs and physical examination will be performed and photographs taken. Rosacea Questionnaire will be administered. Study drug will be dispensed.

Visit 5 Week 16 (End of treatment)

Adverse events and concomitant medication changes will be ascertained. Drug diary will be reviewed for correct study agent usage. Unused drug and sharps containers will be collected. Vitals signs and physical examination will be performed and photographs taken. Rosacea Questionnaire will be administered. Biopsy will be performed and sent for histology and immunohistochemistry.

Evaluation schedule:

TABLE OF VISITS

Visit number	**1**	**2**	**3**	**4**	**5**
Time of Visit	**Week -4 to BL**	**W0 (BL)**	**W4**	**W12¥**	**W16¥**
Inclusion/Exclusion criteria	x	x			
Information & Informed consent	x				
Vital signs	x	x	x	x	x
Physical examination	x	x	x	x	x
Lab test: CBC, MetC, UA	x	x**			x
Quantiferon	x				
Dispense study medication		x	x	x	
Self-administration of study drug		x*	x	x	
Adverse events		x	x	x	x
Concomitant medications evaluation	x	x	x	x	x
Rosacea clinical assessment (Appendix 1-3)	x	x	x	x	x
Facial photography		x	x	x	x
RoseQOL questionnaire (Appendix 4)		x	x	x	x
Skin Biopsy		x			x
Histology & immunohistochemistry		x			x

*In addition to self-administration at the study site at baseline (BL) under study staff supervision, study participants will be provided with three additional doses and a sharps container for weekly self-administration at home. Study participants will be asked to fill out a study diary to assess for compliance and adverse events.

¥Week 16 time point was selected to compare the primary endpoint of papule and pustule count with baseline due to previous studies suggesting this time point is needed to achieve significant differences in papule and pustule count using systemic anti-inflammatory treatment with doxycycline (Theobald *et al.,* 2007) and the 16 week time period observed for maximal therapeutic impact for secukinumab in psoriasis. (Langley *et al.,* 2014) We also include a 12 week time point to assess for therapeutic benefit as another study (Sanchez et al., 2005) indicated that this time period is sufficient to detect therapeutic benefit using another systemic agent for rosacea, doxycycline.

** If screening labs within 7 days of baseline, can use screening labs as baseline labs

APPENDIX 1. Severity grading of papulopustular rosacea, adapted from Sanchez *et al.*, 2005.

Severity	Papules/Pustules	Study Score
Mild	1-9	1
Moderate	10-14	2
Severe	15+	3

APPENDIX 2. Clinical score for assessing rosacea severity, reproduced from Sanchez *et al.*, 2005.

Table I. Clinician's Global Severity Score*

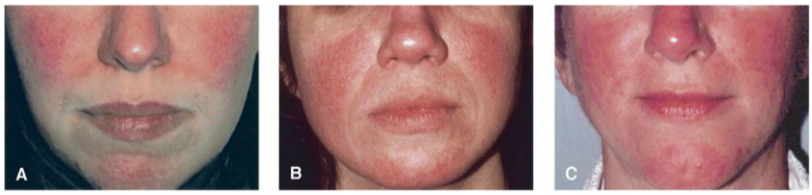
Score/Grade	Definition	Guideline
(0) None to very mild	No signs or symptoms present; at most, mild erythema	0-3 papules/pustules Erythema Assessment Score Total score <1; Area-specific score: 0 or 1
(1) Mild	Mild erythema present; none to few papules/pustules	4-9 papules/pustules Erythema Assessment Score Total score <5; Area-specific score: 0 or 1
(2) Moderate	Moderate erythema; moderate number of papules/pustules	10-14 papules/pustules Erythema Assessment Score Total score 6-10; Area-specific score: 2 or 3
(3) Severe	Severe erythema; papules/pustules common	15-19 papules/pustules Erythema Assessment Score Total score 16-20; Area-specific score: 3 or 4
(4) Very severe	Fiery red erythema; numerous papules/pustules	>20 papules/pustules Erythema Assessment Score Total score 16-20; Area-specific score: 3 or 4

*One score to be selected for each patient at each evaluation.

APPENDIX 3. Visual scoring system for erythematotelangiectatic rosacea, a secondary endpoint. 0=none, 1=mild (panel A), 2=moderate (panel B), and 3=severe (panel C). Top table reproduced from Sanchez *et al*., 2005; bottom figure reproduced from Wilkin *et al.,* 2004.

Table II. Clinician's Erythema Assessment Scale*

Score/Grade	Definition
(0) None	No redness present
(1) Mild	Slight pinkness
(2) Moderate	Definite redness
(3) Significant	Marked erythema



Appendix 4. Rosacea quality of life survey derived from Nicholson *et al*., 2007. The response choices for the questions below are as follows: 1=never, 2=rarely, 3=sometimes, 4=often, 5=all the time. The items below are reliable and have good discriminant ability.

RosaQoL items
1. I worry that my rosacea may be serious
2. My rosacea burns or stings
3. I worry about getting scars from my rosacea
4. I worry that my rosacea may get worse
5. I worry about side effects from rosacea medications
6. My rosacea is irritated
7. I am embarrassed by my rosacea
8. I am frustrated by my rosacea
9. My rosacea makes my skin sensitive
10. I am annoyed by my rosacea
11. I am bothered by the appearance of my skin (redness, blotchiness)
12. My rosacea makes me feel self-conscious
13. I try to cover up my rosacea (with makeup)
14. I am bothered by persistence/reoccurrence of my rosacea
15. I avoid certain foods or drinks because of my rosacea
16. My skin feels bumpy (uneven, not smooth, irregular)
17. My skin flushes
18. My skin gets irritated easily (cosmetics, aftershaves, cleansers)
19. My eyes bother me (feel dry or gritty)
20. I think about my rosacea
21. I avoid certain environments (heat, humidity, cold) because of my rosacea

10. Safety monitoring and reporting

Serious adverse events, drug misuse or abuse, reports of drug exposure during pregnancy, and any other information that may suggest a change in the benefit-risk profile of secukinumab, and where required, copes of the Investigator Notifications for suspected unexpected serious adverse events (SUSAR) and copies of the Development Safety Update Report, as appropriate.

We will perform an adverse event reconciliation between the Sponsor's trial database and an output from the Novartis safety database periodically throughout the trial.

11. Statistical methods and Data analysis

This study is powered for the primary endpoint of significant reduction of papule/pustule count at baseline versus week 16.

The null hypothesis is that there will be no difference in papule/pustule count at baseline and after 16 weeks of secukinumab due to known chronic and incurable nature of rosacea and that when used for psoriasis, maximum therapeutic effect is seen at 16 weeks. Because of the risk profile of the study medication in suppressing the immune system, we estimate that any reduction in papule/pustule count less than 20% would not be clinically meaningful. Since 10 papules/pustules are required to enroll, the difference in papule/pustule count would have to be at least 2 (assuming a standard deviation of 3). Using an alpha=0.05 and power=0.80 (two sided test), sample size needed is 20.

Assuming a dropout rate of 20% from 20 patients, we would need to enroll **24** patients to achieve sufficient sample size. This is consistent with a study by Sanchez *et al.,* 2005 for oral doxycycline in which 20 individuals were enrolled and achieved statistical significance. (Calculation by Shufeng Li, MS, Stanford Dermatology biostatistician)