Patient-reported Outcomes for Sarecycline Effectiveness and Safety (PROSES)

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AVANT HEALTH

almirall

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LIST OF ABBREVIATIONS

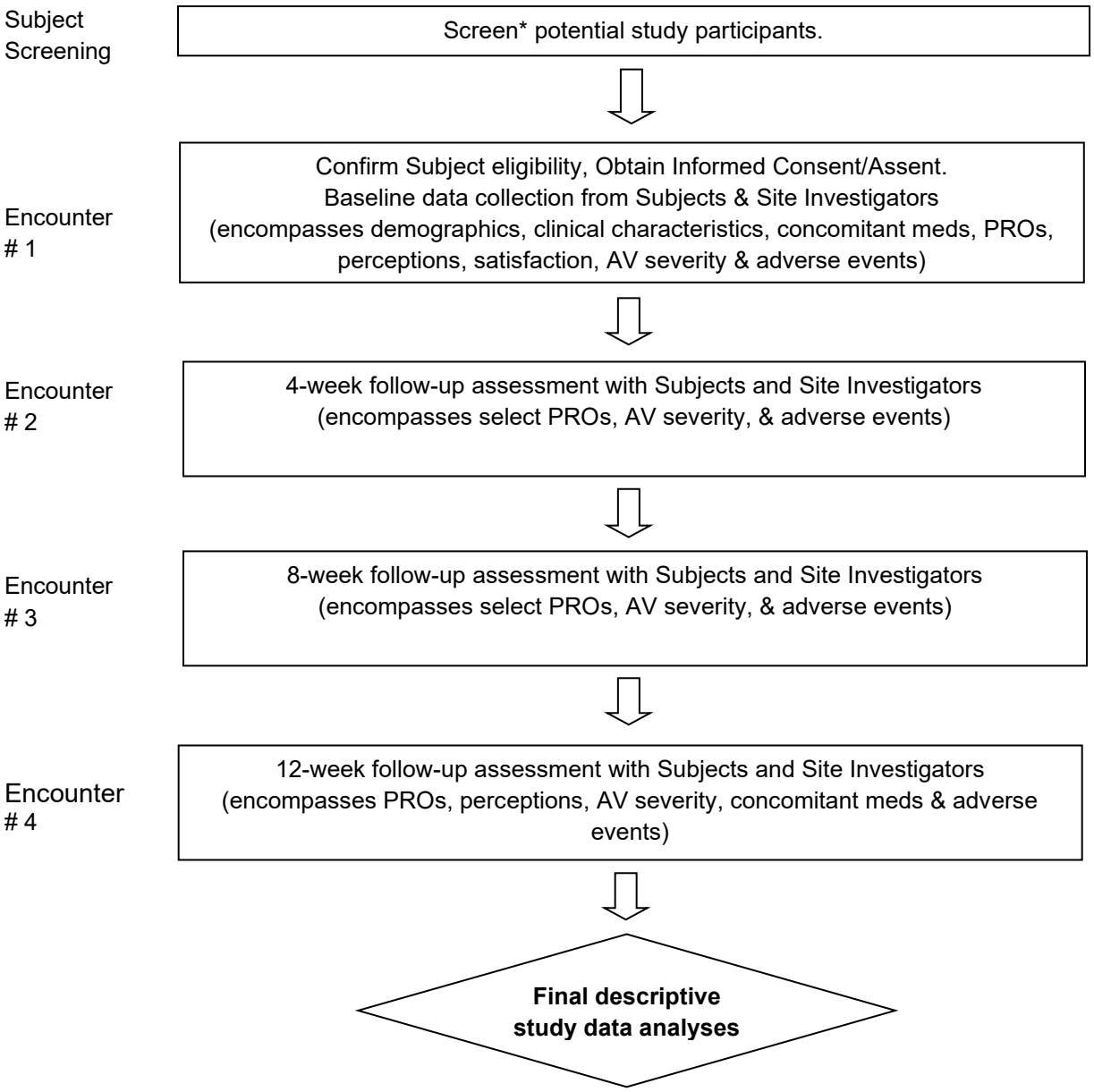
ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Experience
App	Application / Mobile Application
Approx.	Approximately
ASIS	Acne Symptom and Impact Scale
AV	Acne Vulgaris
CASRO	Council of American Survey Research Organizations
CFB	Change From Baseline
CIRQ	The CASRO Institute for Research Quality
ClinRO	Clinician Reported Outcome
CRO	Clinical Research Organization
DCF	Data Collection Form
EC	Ethics Committee
EDC	Electronic Data Collection
EU	European Union
eDCF	Electronic Data Collection Form
FAS	Full Analysis Set
FDA	The U.S Food and Drug Administration
GEP	Good Epidemiology Practices
HCP	Healthcare Provider
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IRB	Institutional/Independent Review Board
Med	Medication
N	Number (typically refers to participants)
PI	Principal Investigator
PRO	Patient Reported Outcome
PROMS	Patient Reported Outcome Measures
PtGA	Patient Global Assessment
QoL	Quality of Life
Qr	Questionnaire

RCT	Randomized Controlled Trial
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard Deviation
SEM	Standard Error of Mean
SOP	Standard Operating Procedure
TBD	To Be Decided
US	United States

PROTOCOL SUMMARY

Title:	Patient-reported Outcomes for Sarecycline Effectiveness and Safety (PROSES).
Précis:	A prospective cohort study of patients with acne vulgaris (AV) treated with sarecycline and followed for 12 weeks post treatment-initiation. Patient Reported Outcomes (PROs) and clinical profile of patients will be gathered for descriptive analyses of patient outcomes over the 12 week study observation period.
Objectives:	Evaluate PROs and clinician reported outcomes among patients with moderate to severe non-nodular AV who are prescribed sarecycline in clinical practice settings in the U.S. Primary: Evaluate PROs related to Acne symptoms and impact. Secondary: Evaluate sarecycline treatment effectiveness, in terms of IGA of AV severity on the face. Additional: Evaluate clinician satisfaction with sarecycline treatment, sarecycline safety/tolerability, and concordance in perception of facial AV severity among clinicians and patients.
Population:	Three hundred (300) patients of age ≥9 years at the time of initiation of treatment with sarecycline from clinical practices across the U.S. For pediatric patients, their parents/primary caregivers will also be recruited.
Number of Sites:	Maximum of fifty sites will be recruited.
Duration of Treatment	12 weeks.
Study Drug & Mode of Administration	Seysara® tablets; 60 mg, 100 mg, 150 mg, providing a dose of approx. 1.5mg/kg/day; oral. Commercial supply of medication may be supplied to clinical sites/Subjects for the duration of the study.
Study Duration:	Approximately eighteen months of study duration, including study set-up, 12 weeks of subject observation period and study close out followed by study data analyses.

Schematic of Study Design



**Subject screening could be done via phone, prior to Subject's visit to the clinic; or it could be combined with Encounter # 1 (baseline data collection).*

*Clinicians shall prescribe sarecycline (*Seysara®*) to eligible Subjects per own clinical judgement and manage them as they normally would, in clinical practice.*

1 KEY PERSONNELL AND CONTACT INFORMATION

Principal Investigators:

PPD MD
Ph PPD
PPD

PPD MD, MBA
Ph PPD
PPD

Other Key Personnel

PPD MS, MHS, MPhil (PhD)
Ph PPD
PPD

PPD MD, MHA
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PPD

PPD MD
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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Acne Vulgaris (AV), hereinafter referred to as acne, affects up to 50 million Americans and is the most common skin condition in the United States (US) (Bickers et al, 2006). Acne affects both adolescents and young adults. Approximately 85 percent of people between the ages of 12 and 24 experience at least minor acne (Bhate & Williams, 2013). Since patients may have acne over a long duration of time, and may also experience recurrence and relapse, and manifestations such as acute outbreaks or slow onset, acne may be classified as a chronic disease (Cherynshov et al, 2018).

Core outcomes in acne studies often focus on clinical assessment of acne severity, in terms of investigator global assessment (IGA) or lesion counts. Patient reported outcome measures (PROMs) have been sporadically used, but the increased recognition of their importance to patients has resulted in a proliferation of studies depicting the impact of acne on patient's health-related QoL (HRQoL) (Thiboutot et al, 2019). Acne has been shown to negatively affect QoL resulting in low self-esteem, increased social and emotional anxiety (Timms, 2013; Revol et al, 2015). Patients with acne report more effects of their skin condition on their functioning, emotions, and symptoms than do patients with isolated benign skin lesions or those in the normative sample (Lasek & Chren, 1998). Acne has been associated with considerable psychosocial impact, causing significant negative effects on self-image leading to feelings of isolation and loneliness, and a significantly lower self-attitude, uselessness feeling, sense of pride and self-worth, and body satisfaction (Gieler, 2015).

Several QoL instruments have been used in acne studies, with varying level of focus on patient attributes impacted by acne (Alexis et al, 2014; Cherynshov et al, 2018). An expert panel of dermatologists was recently convened (in December 2020) to review the existing QoL instruments and identify key patient-centric elements that reflects the day-to-day concerns of their adult and pediatric acne patients. An existing 17-item validated instrument, namely, Acne Symptom and Impact Scale (ASIS) that asks patients about the acne signs and impact of acne on emotional and social wellbeing, was used as the anchor for further panel deliberations on

complimentary PROMs. Using a qualitative modified delphi method, the expert panel agreed on 10 specific items that relate to how acne impacts the patient's mood (anger/sadness), social interactions, general thoughts/worries about acne and one's future goals, and impact on daily activities, including sleep. These recommendations are aligned with research on factors impacting young acne patients (Seite et al, 2012; Timms, 2013; Lafrance & Carey, 2018). The panel also suggested comparing the perceptions of acne severity of patients with those of their treating clinicians, and the perceptions of pediatric patients with those of their parents; and suggested the utility of comparing the parent/caregiver perceptions of acne severity and impact to that of their children. The 10 main patient-centric questions constituting the Expert Panel Questionnaire along with ASIS questionnaire was identified as an optimal tool to use in community-based real world research involving acne patients.

Besides QoL, fear/concerns of side effects to existing treatments are in the minds of acne patients (Tuchayi, 2016). Newer treatments, such as sarecycline (Seysara®), an oral tetracycline class narrow-spectrum antibiotic indicated as first line therapy for the treatment of moderate to severe AV, may be viable options to acne patients, owing to the proven safety profile, in addition to the efficacy (Moore et al, 2018; Deeks, 2019). As antibiotic resistance remains a concern for clinicians and patients alike (Kircik, 2010; Farrah & Tan, 2016; Del Rosso et al, 2019), the narrow-spectrum antibiotic attribute of sarecycline with a lower propensity for antibiotic resistance may be appealing to these stakeholders (Zhanel et al, 2019).

In two pivotal RCTs, after 12 weeks of treatment, statistically significantly more recipients of once-daily sarecycline 1.5 mg/kg (as tablets) than of placebo achieved treatment success on the face; for those affected, acne on the chest and back also improved statistically significantly with sarecycline (Moore et al, 2018; Deeks, 2019). Sarecycline was generally well tolerated; other broad-spectrum tetracycline-class antibiotics are often associated with certain gastrointestinal, vestibular and phototoxic adverse effects and, in females, vaginal yeast infections, although these treatment-emergent adverse events were generally uncommon with sarecycline. As importantly, sarecycline was associated with HRQoL benefits, depicted by more favorable outcomes measured using Skindex-16 questionnaire (Moore et al, 2018; Deeks, 2019).

The clinical trial results of sarecycline highlight the clinical and QoL benefits derived by the acne patients. The demonstration of sarecycline-related benefits, including its impact on patient HRQoL in real world community practice settings is warranted to highlight sarecycline value proposition to patients, clinicians and payers alike. The ASIS questionnaire, along with the complimentary novel Expert Panel Questionnaire on patient HRQoL could be beneficial to use for research in community practice settings.

2.2 Rationale

General understanding of acne impact on different aspects of patient HRQoL is still evolving. A real-world study leveraging validated HRQoL instruments such as ASIS questionnaire and the complimentary novel Expert Panel Questionnaire (developed using modified delphi method) could help portray a broader picture of impact of acne on pediatric and adult patient HRQoL. Further, assessing the impact of sarecycline treatment on acne patient outcomes, including patient HRQoL, in real-world community practice settings could highlight the humanistic and clinical benefits associated this narrow-spectrum antibiotic treatment option.

3 OBJECTIVES

3.1 Study Objectives

The primary objective of the study is to evaluate PROs in terms of health related quality of life (HRQoL) among patients with moderate to severe non-nodular AV who are administered sarecycline in real-world community practice settings in the U.S. The secondary objective is to evaluate effectiveness of sarecycline treatment, measured by Investigator Global Assessment (IGA) of AV severity on the face.

The additional study objectives include the following evaluations among study Subjects and Site Investigators*:

- Investigator satisfaction with their sarecycline treatment outcomes.
- Safety and tolerability of sarecycline.

- Comparison of Investigator and Subject perceptions of AV severity.

Note: Dermatologists are expected to predominantly constitute the Site Investigator category, while a few physician assistants and nurse practitioners may be included in the study, reflecting the routine care management of acne in community practice settings.

3.2 Study End Points

The primary endpoint of the study will be the PROs, in terms of self-perceived acne symptoms and impact of acne on emotional functioning, social functioning and activities of daily living, at Week 12.

The secondary endpoint will be the proportion of Subjects with Facial IGA success at Week 12, defined as a 2-point decrease in IGA score from baseline and a score of 0 (clear) or 1 (almost clear).

Additional endpoints of the study will include:

- Proportion of Subjects for whom Site Investigator reported 'very satisfied' or 'satisfied' in the question on global satisfaction with sarecycline treatment, at Week 12.
- Description of changes in PROs from baseline, at Week 12.
- Frequency of documented adverse events (AEs) and severe adverse events (SAEs) during the 12-week study observation period.
- Comparison of Subject perception and Site Investigator perception of AV severity, at Week 12.

4 STUDY DESIGN

This is a single-arm, prospective cohort study which will enroll patients with moderate to severe acne vulgaris (AV) who are prescribed sarecycline in real-world community practices in the U.S. Caregivers will also enroll in the study, in case of pediatric patients. Study Subjects will be followed for up to 12 weeks post-index date (with the 'index-date' defined as the date of initiation

of sarecycline). Study Site Investigators and Subjects will complete online surveys at baseline (at time of study enrollment) and at weeks 4, 8 and 12, post-index date.

This study will entail provision of sarecycline treatment to study participants. Site Investigators will decide on who to prescribe sarecycline as part of usual care, based on their best clinical judgment, prior to subject recruitment. The study is sponsored by Almirall, hereinafter referred to as the Sponsor. The study will be managed by Avant Health, hereinafter referred to as the Contract Research Organization (CRO).

5 STUDY MEDICATION

The study protocol will require identification and selection of patients considered as candidates for a specific medication, namely, sarecycline (Seysara®), as part of usual care. In this context, the study medication will be sarecycline (Seysara®). Site Investigators shall provide the commercial supply of sarecycline (Seysara®) to eligible study Subjects.

Sarecycline has a restricted market access in the U.S, with payers reimbursing for the commercial prescriptions on a restricted basis. Selection of only the patients who are able to fill the prescription for reimbursed sarecycline may not be representative of individuals who might be candidates for sarecycline in the U.S; this may impact the generalization of the study results. To avoid this potential selection bias and improve the prospect of generalization of study results, the commercial supply of sarecycline (Seysara®) will be supplied to Site Investigators for the study duration of 12 weeks.

Per FDA prescribing information, the recommended dosage of sarecycline is once daily with or without food:

- 60 mg for patients who weigh 33-54 kg,
- 100 mg for patients who weigh 55-84 kg,
- 150 mg for patients who weigh 85-136 kg. approximately 1.5 mg/kg once daily

The Site Investigators will prescribe relevant sarecycline dose to patients per their clinical judgement. Correspondingly, sarecycline prescribed dose at the start of the study and any subsequent modifications to dose during the study observation period will be captured as part of study data collection.

6 STUDY ENROLLMENT AND WITHDRAWAL

A total of three hundred (300) Subjects will be enrolled in the study, from a maximum of fifty (50) community practices (sites) from across the U.S. During the study enrollment window, study-eligible clinical sites will be sequentially screened, consented for study participation and completion of all study procedures, including enrollment of study eligible Subjects.

The study Subjects will be patients with moderate to severe non-nodular AV who are candidates for sarecycline, and caregivers of pediatric patients (age <18 yrs) within this cohort. The study cohort will be drawn from dermatology clinics from across the U.S.

6.1 Subject Inclusion Criteria

Patient Inclusion Criteria: In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Male or female, aged 9 years and above at the time of study recruitment.
- Has facial non-nodular AV with IGA score of moderate (3) or severe (4).
- Considered as a potential candidate for sarecycline treatment to manage their AV, per clinician's judgment.
- Able to read and write English.
- Provide consent (in case of adult patients) or assent (in case of pediatric patients) to participate in the study.
- Willing to comply with all study procedures and be available for the duration of the study.

Caregiver Inclusion Criteria: In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Male or female, aged 18 years and above.
- Able to read and write English.
- Primary caregiver of the study-eligible patient.
- Provide consent to participate in the study.
- Willing to comply with all study procedures and be available for the duration of the study.

6.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Patients with any dermatological or physical condition of the face that could interfere with the AV clinical evaluations.
- Patients with any history of allergy to tetracycline-class antibiotics, pseudomembranous colitis or antibiotic-associated colitis.
- Patients with any known resistance to other tetracyclines.
- Patients currently treated with any of the following: penicillin, oral retinoids (incl. Isotretinoin and acitretin).
- Among female Subjects: Currently pregnant, lactating, or is planning a pregnancy during the study period.
- Patients or their caregivers are unable to comply with the requirements of the study or patients who in the opinion of the Site Investigator should not participate in the study.
- Patients for whom medical chart is inaccessible to Site Investigators to complete baseline data collection.

6.3 Strategies for Screening, Recruitment and Retention

6.3.1 Site Investigators

Screening of potential study sites/investigators will take place by reaching out directly to sites and sharing study synopsis and soliciting their interest. If a site expresses interest in the study, they will be asked to consent for study participation. Subsequently, additional information will be shared for contracting and site initiation for subject screening.

All Site Investigators will be nominally compensated (per fair market value) for the study activities they undertake, encompassing subject screening/recruitment, data collection using online electronic data collection forms (eDCFs) at baseline (at time of enrollment), and at weeks 4, 8 and 12 post-index date. Periodic follow-up with the study sites will take place throughout the study observation period to ensure engagement and retention.

6.3.2 Study Subjects

Upon successful recruitment of the study sites, the respective Site Investigators may identify a study coordinator at their clinics. Site Investigators and/or the study coordinator will approach, screen and consent up to ten (10) study-eligible Subjects sequentially within the study enrollment window. The approach may take place during the routine patient visit or via email or phone; upon establishing contact with study Subjects, they will be provided with a description of study objectives and procedures.

In the case of in-person recruitment of study Subjects, Subjects will be screened for study eligibility using the study screener. The Subjects deemed eligible for the study will then be provided with a study informed consent form. The study coordinator or Site Investigator will ensure that Subjects can read the consent form and ask questions, and be given adequate time to consider the benefits/risks associated with participation in the study. An informed consent (with an accompanying assent, if applicable, for pediatric patients) will be obtained from each subject (and parent(s) or legal guardian(s), if applicable) in accordance with applicable regulations prior to participating in any study procedures. Subjects under the age of 18 will assent.

In the case of recruitment of study Subjects via email or phone, study coordinator or Site Investigator will pre-screen the Subjects for study eligibility, and will then contact the subject to describe the study to each subject (and parent(s) or legal guardian(s), if applicable) and give them adequate time to consider the risks associated with participation in the study. The eligible Subjects will be then provided with a weblink to an online screener and electronic consent (e-consent) form. If a Mobile App is used for the purpose of the study data collection from the Subjects, recruited study Subjects will be asked to download the Mobile App; as they log-in an e-consent form may be presented via the App. Subjects will be able to quickly read and provide informed consent (and assent if applicable, for pediatric patients) prior to participating in any study procedures by checking a box next to the statement, "I have read the above statement and I consent to participate in this study" and signing their name(s) along with dating the online form (using their web browser or the study Mobile App).

Site Investigator or the study coordinator will assign subject IDs to Subjects sequentially, as they are recruited. Site coordinator will maintain a recruitment log that will identify the subject ID number to their name/contact info. For study follow-up reminders, the study subject will be consented to share their contact details with study research staff; such information will be kept strictly confidential and not shared with the study sponsor, and this administrative information will not be part of the research study data thereby preserving the anonymity of study Subjects.

Only positively-screened and consenting patients will be allowed to participate in the study and proceed with the study steps. Study subjects will be compensated nominally (per fair market value) for survey completion at baseline (at recruitment) and at weeks 4, 8 and 12 post-index date. Study coordinators and/or their Site Investigators will serve as the main point of contact for participants/Subjects at their site for questions and ensure subject retention during the study observation period. Reminders for eDCF completion may be sent to study Subjects via email, phone or via the Mobile App.

6.4 Subject Withdrawal

This is a real-world study and the study participation is completely voluntary. Subjects may withdraw voluntarily from the study at any juncture during the study observation period following the enrollment, for any reason.

Site Investigator may terminate a subject's participation in the study at any juncture, in specific scenarios, as outlined below.

6.4.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

A Site Investigator may terminate a study subject's participation in the study if:

- Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the subject. This may include pregnancy among female subjects.
- In the event Subjects are unable to swallow the sarecycline tablets after enrollment, they will be discontinued from the study and the reason for study discontinuation will be recorded as the inability to swallow tablet.
- The subject meets a study exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

6.4.2 Handling of Subject Withdrawals

If a subject requests withdrawal from the study voluntarily for any reason, the Site Investigators or site coordinator will follow-up with the patient to solicit and document the reason for withdrawal. If the Site Investigator determines that the withdrawal is related to a severe adverse event (SAE) associated with sarecycline, he/she will gather necessary information concerning the SAE. The Site Investigator may follow-up with the subject subsequently to ensure resolution of SAE episode and close out the study documentation for the concerned Subject.

There will be no replacement of Subjects who withdraw or discontinue early from the study.

7 STUDY SCHEDULE & PROCEDURES

Study eligible patients who are considered as candidates for sarecycline treatment as part of usual care Acne management will be screened, consented and recruited into the study, followed for up to 12 weeks post-index date, encompassing four distinct data collection encounters. With 'T' being the index date of sarecycline treatment initiation, the baseline data collection may transpire anytime between T= -2 weeks post-index date and T= +4 days post-index date; the 4-week follow-up data collection will happen at T=4 weeks post-index date ± 4 days; the 8-week follow-up data collection will happen at T=8 weeks post-index date ± 4 days, and 12-week follow-up data collection will happen at T=12 weeks post-index date ± 4 days. Index date is the date of initiation of sarecycline treatment, when the subject took the first sarecycline dose.

Different data elements will be collected from Site Investigators and from study Subjects at these data collection encounters, as outlined below. For patients of age 12yrs and older, acne patients themselves will complete relevant PRO elements pertinent to study endpoints, at all encounters; for patients of age 9-11yrs, parents/caregivers of pediatric patients will complete the PRO elements at all encounters, serving as a proxy, upon consulting with their child on question responses.

The schedule of events is summarized in Appendix A.

7.1 Enrollment/Baseline (Encounter # 1)

Baseline data collection will take place at the time of subject enrollment into the study or within a few days of recruitment. The subject encounters are expected to take place during in-person subject visits to the clinic, but remote/virtual visits will be allowed where Covid-related protocols prevent in-person visits. The recruited Site Investigators and study Subjects will be sent a weblink to the eDCFs and survey respectively for their completion. Subjects will be able to access the surveys on their mobile phone, using a study-specific Mobile App.

The following data elements will be collected at baseline, from patient medical charts and/or per Site Investigator's best clinical judgement based on their recent encounter with the study subject

while prescribing sarecycline as part of usual care and based on subject's recent past medical history:

- Demographics (e.g., age, gender).
- General clinical characteristics, as documented in medical charts (incl. blood pressure, waist circumference, height/weight measurements, comorbidities).
- AV disease characteristics (AV history; current IGA of AV severity in face).
- Past AV treatment history (used ever, and those used within the past 6 months).
- Sarecycline treatment characteristics (dose, frequency, date of recommendation).
- Concomitant medications (for AV and comorbidities).
- Perceptions about antibiotics/antibiotic resistance.

The following data elements will be collected at baseline, from study Subjects, via online survey portal or a mobile app:

- Demographics (e.g., gender, race/ethnicity, education, employment/school status, living status).
- Perceptions of AV-related symptoms and impact of AV on emotional functioning, social functioning and activities of daily living.
- Perceptions about antibiotics/antibiotic resistance (asked in only Adult Subjects).

In case of pediatric patients, Caregivers will also complete a battery of questions related to their own perceptions of antibiotics/antibiotic resistance, their child's current acne severity, and impact of acne on their child.

In a small subset of sites, Site Investigators may utilize Canfield® photography equipment to take photographs of patient's face to document the baseline AV severity of acne patients in the study, during in-person patient visits.

7.2 Shipment of Study medication

Following the Site Investigator's decision to prescribe sarecycline (Seysara®) to study eligible patients, a commercial supply of the appropriate dose and quantity of study medication will be shipped to the attention of Site Investigator at their clinic/site. The study Subjects will be asked to record the first day of administration of sarecycline via the mobile app, and this date will constitute the study 'index date', upon which the follow-up encounter timepoints (at weeks 4, 8 & 12) will be determined.

7.3 First Follow-up Encounter (Encounter # 2)

At the completion of 4 weeks (± 4 days) post-index date, the Site Investigator and Subjects will be asked to complete the first follow-up data collection, conducted via in-person or virtual/remote visits.

The patients will be advised to visit their site/clinician's offices to do the following:

- Drop off the first tablet/pill bottle of Seysara® (bottle # 1) supplied to them at study start, be it empty or with left-over pills.
    - This may be done as curb-side interaction, without entering clinician's offices.
- Pick-up the second bottle of Seysara® supply (bottle # 2) for the next four weeks of use.
    - This may be done as curb-side interaction, without entering clinician's offices.
- Undergo AV clinical evaluation inside clinician's office, if feasible.

The Site Investigators will complete the following, based on the information documented in patient medical charts and per clinical judgment guided by observing study subject via in-person or virtual/remote visit:

- IGA of current AV severity on the face.
- Patient treatment compliance, per sarecycline pill/tablets left over in the subject-returned bottle.

- Modifications to sarecycline treatment characteristics (e.g,, change in dose, discontinuation), in the past 4 weeks, if any.
- AEs (incl. SAEs) related to or possibly related to sarecycline, observed in the past 4 weeks, as documented in the medical charts.
- Information on withdrawal from study (if occurred within the past 4 weeks).

The study Subjects will provide the following information via online survey portal or a mobile app: perceptions of current AV-related signs/severity. In case of pediatric patients, this information will be obtained from parents/caregivers as well.

7.4 Second Follow-up Encounter (Encounter # 3)

At the completion of 8 weeks (± 4 days) post-index date, the Site Investigators and Subjects will be asked to complete the second follow-up data collection, conducted via in-person or virtual/remote visits.

The patients will be advised to visit their site/clinician's offices to do the following:

- Drop off the second tablet/pill bottle of Seysara® (bottle # 2) supplied to them at the Wk-4 visit, be it empty or with left-over pills.
    - This may be done as curb-side interaction, without entering clinician's offices.
- Pick-up the third bottle of Seysara® supply (bottle # 3) for the next four weeks of use.
    - This may be done as curb-side interaction, without entering clinician's offices.
- Undergo AV clinical evaluation inside clinician's office, if feasible.

The Site Investigator will complete the following, based on the information documented in patient medical charts and per clinical judgment guided by observing study subject via in-person or virtual/remote visit:

- IGA of current AV severity on the face.

- Patient treatment compliance, per sarecycline pill/tablets left over in the subject-returned bottle.
- Modifications to sarecycline treatment characteristics (e.g,, change in dose, discontinuation), in the past 4 weeks, if any.
- AEs (incl. SAEs) related to or possibly related to sarecycline, observed in the past 4 weeks, as documented in the medical charts.
- Information on withdrawal from study (if occurred within the past 4 weeks).

The study Subjects will provide the following information via online survey portal or a mobile app: perceptions of current AV-related signs/severity. In case of pediatric patients, this information will be obtained from parents/caregivers as well.

7.5 Third Follow-up & Study Close-out Encounter (Encounter # 4)

At the completion of 12 weeks (± 4 days) post-index date, the Site Investigators and Subjects will be asked to complete the third and final follow-up data collection to close out the study. The subject encounters are expected to take place during in-person subject visits to the clinic, but remote/virtual visits will be allowed where Covid-related protocols prevent in-person visits. Subjects will be asked to drop off the third tablet/pill bottle of Seysara® (bottle # 3) supplied to them at the Wk-8 visit, be it empty or with left-over pills.

The Site Investigators will complete the following, based on the information documented in the corresponding patient medical charts and per clinical judgment guided by observing study subject via in-person or remote/virtual visit:

- Current IGA of current AV severity on the face.
- Patient treatment compliance, per sarecycline pill/tablets left over in the subject-returned bottle.
- Modifications to sarecycline treatment characteristics (e.g,, change in dose, discontinuation), in the past 4 weeks, if any.

- Perceptions of sarecycline overall treatment satisfaction.
- AEs (incl. SAEs) related to or possibly related to sarecycline, observed in the past 4 weeks, as documented in the medical charts.
- Information on withdrawal from study (if occurred within the past 4 weeks).
- Newly documented changes to patient clinical characteristics, as documented in medical charts in past 12 weeks since the baseline encounter (incl. blood pressure, weight, comorbidities).
- Modifications made to concomitant medications (for AV and comorbidities) in the past 12 weeks since the baseline encounter.

In the instances when in-person subject visits take place at Week 12, for those patients for whom baseline photographic data collection was completed, corresponding Site Investigators will take photographs of patient's face to document current acne severity at Week 12.

The study Subjects will provide the following information via online survey portal or a mobile app: Perceptions of AV-related symptoms and impact of AV on emotional functioning, social functioning and activities of daily living. In a small subset of sites, clinicians will request Subjects to provide a 1–3 minute audio recording of Subject's perception of sarecycline treatment benefits experienced during the study period.

In case of pediatric patients, Caregivers will also complete a battery of questions related to their perceptions of child's current acne severity, and impact of acne on their child.

Both the Site Investigators and Subjects will be thanked for their participation in the study. No specific study close-out tasks are expected of the study Subjects. Site Investigators will be asked to submit any outstanding data queries to the research team and then close out the study records at their respective sites.

7.6 Early Termination Encounter (Encounter # x)

Site Investigators will attempt to follow the progress of every subject admitted to the study through to study completion. If a subject fails to complete requested study procedures (i.e, completion of online surveys), a reasonable effort will be made to contact the subject and ascertain the reason(s) for non-compliance with study procedures.

If a subject does not complete the study for any reason (including Investigator discretion), the reason and circumstances for the subject's early termination will be fully documented; if possible, the assessments specified for the forthcoming (next) study encounter will be performed.

8 STUDY ASSESSMENTS

PROs will be assessed with study Subjects. Sarecycline treatment effectiveness will be assessed by treating Site Investigator using IGA scores and lesion counts. Safety will be evaluated in terms of adverse events and ADRs during the treatment period.

8.1 PRO Assessments

A combination of a validated questionnaire and an ad hoc questionnaire prepared via modified delphi panel consensus method involving dermatologists, will be used for PRO assessments.

ASIS Questionnaire:

The ASIS is a 17-item questionnaire that asks patients about the signs and impact of AV (Appendix B); responses are reported as two scales: Signs (9 items), and Impact (8 items). Impact domain has two subscales, pertinent to Emotional (6 items) and Social impact (2 items). The following questions (items) correspond to each scale:

Scale	Items
Signs	1-9
Impact	10-17

All items are scored on a five-point adjectival response scale, with a potential score of 0 to 4, even though the individual item responses are different for certain question clusters. A domain score is determined by the average of scores in each scale within the domain. A total score is the average of all 17 items. Higher scores on the ASIS Sign domain, comprised of all items that assess symptoms (items 1-9), indicate the presence of more severe symptoms, whereas higher scores on the ASIS Impact domain, comprised of all of the items that assess impacts (items 10-17), indicate a greater negative impact of acne on HRQoL and appearance. The questionnaire will be administered in entirety, at baseline and at Week 12 post-index date.

At Weeks 4 & 8 post-index date, Subjects will be asked to complete ASIS Item # 9 (how is your acne on your face right now) and ASIS Item # 10 (rate how your face looked because of your acne).

Expert Panel Questionnaire:

Ten (10) ad hoc questions related to patient perception of impact of Acne on their social functioning, emotional functioning and activities of daily living were formulated based on an expert consensus involving a panel of dermatologists using modified delphi method. The items relate to how Acne impact patient's mood (anger), social interactions, general thoughts/worries about Acne and one's future goals, and impact on daily activities, including sleep (Appendix B).

All items are scored on a five-point adjectival response scale, with a potential score of 0 to 4, even though the individual item responses are different for certain question clusters. The questions will be administered in entirety, at baseline and at Week 12 post-index date.

8.2 Treatment Satisfaction Assessments

Investigator's global satisfaction with sarecycline treatment will be assessed at Week 12 using a single question: "how satisfied are you with sarecycline treatment outcomes", with response options ranging from 'Very Satisfied' to 'Very Dissatisfied'.

8.3 Treatment Effectiveness Assessments

The effectiveness of sarecycline treatment will be assessed from the perspective of Site Investigators as well the Subjects.

8.3.1 Investigator Assessments

An IGA scale of 0 (Clear) to 4 (Severe) will be used by the Site Investigators to assess the severity of a subject's facial acne at the time of study encounters. The IGA should be representative of the investigator's overall general assessment of the subject's Acne and take into account the quality, as well as the quantity, of lesions. These assessments will be done at baseline encounter to document AV severity before initiation of sarecycline treatment; the assessments will be repeated by the Site Investigators at study subject follow-up encounters at Weeks 4, 8 & 12, post-index date. The comparison of follow-up assessments to the baseline assessment will help determine treatment effectiveness. It is expected that the Investigator assessments will be conducted via in-person visits/encounters at baseline and week-12, and when in-person assessments are not feasible (owing to COVID-related travel restrictions), the assessments maybe done via virtual/remote visits. The same evaluator shall perform all evaluations for a subject during the study, as feasible.

8.3.2 Study Subject Assessments - Quantitative

The study Subjects will undertake multiple assessments to report their self-perceived severity of AV in general. These assessments will be done at baseline encounter to document the perception of AV severity corresponding to the time of initiation of sarecycline. They are then repeated by the Subjects at ensuing encounters at Weeks 4, 8 & 12, post-index date.

Patient Global Assessment (PtGA)

This is based on the global acne severity question within ASIS (Item # 9), where the question asks the Subjects to assess the severity of acne, with a response ranging from 'Clear' to 'Severe', scored on a scale of 0 to 4. See Section 8.1 for general details on questionnaire scoring and administration.

Patient Rating of Appearance

ASIS Item # 10 asks the Subjects to rate how their face looked because of their Acne, with a response ranging from 'Excellent' to 'Bad', scored on a scale of 0 to 4. See Section 8.1 for general details on questionnaire scoring and administration.

Parent/Caregiver Rating of AV Severity

Parents/caregivers of children of age 12-17yrs will report their own perceived severity of children's AV, in addition to the children providing their perceptions. This will be accomplished via a single item "Overall, how is your child's acne on his/her face right now?", with the 5-point likert response scales mimicking the Item # 9 in ASIS. This will be scored in the same way as the corresponding ASIS item.

8.3.3 Study Subject Assessments - Qualitative

Subjects from a small subset of study sites will be asked to record a 1-3 minute audio (using the Mobile App) narrating their perceptions of treatment benefits associated with the sarecycline, at the end of their study participation or at Week 12, whichever comes earlier. This qualitative data will be used to ascertain attributes that study Subjects associate with sarecycline treatment in an un-prompted manner.

8.3.4 Study Subject Photographic Assessments

Site Investigators from a subset of study sites will take photographs of facial acne of patients at baseline encounter and at Week 12, during the in-person visits. This photographic data will be used to document and depict the changes in acne severity that may be associated with sarecycline treatment in the study.

8.4 Additional Subject Assessments

Parent/Caregiver Worries about Acne

The parents/caregivers of pediatric patients with AV will be asked - how worried they are about their child's acne, with a response option of 'not at all' to 'extremely', and how concerned they are about their child's ability to accomplish future goals and reach full potential due to acne, with a 5-point likert response scale of 'not at all' to 'extremely'. These questions will be asked at baseline and Week 12.

Concern about Antibiotics and Antibiotic Resistance

Parents/caregivers and adult patients will be asked about their concerns about (themselves or their child) using antibiotics, or concerns about antibiotic resistance, with a 5-point likert response scale of 'not at all' to 'extremely'. These questions will be assessed at baseline and at Week 12.

Understanding of Acne-related Concerns

Pediatric patients (of age 12-17) will be asked whether their parents understand their acne-related concerns, and correspondingly, the parents/caregivers will be asked whether they understand their child's acne-related concerns. This pair of questions will have a response item on a 5-point likert scale of 'not at all' to 'very much'. These questions will be asked at baseline and Week 12.

8.5 Compliance to Treatment

Compliance with the assigned treatment regimen will be assessed by comparing the number of doses/tablets expected to be used, based on the total number of treatment days, with the actual number used (expressed as a percentage of used/expected) at each encounter and for the study overall. The actual consumption/use of study pills/tablets will be evaluated by assessing the left-over pills/tablets in the medication bottles returned to sites/investigators by the Subjects.

8.6 Safety Assessments

8.6.1 Definition of Adverse Events & Adverse Drug Reactions

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

The Site Investigator will use the following terms to assess the severity of each AE:

- Mild: Awareness of symptoms or signs, but easily tolerated (acceptable).
- Moderate: Enough discomfort to interfere with usual activity (disturbing).
- Severe: Interferes significantly with ability to do work or usual activity (unacceptable).

A Serious Adverse Event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. With respect to human clinical experience, this includes any event which:

- results in death,
- is life-threatening,
- requires inpatient hospitalization* or prolongation of hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug.
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
    - social reasons and respite care in the absence of any deterioration in the subject's general condition.
- results in persistent of significant disability / incapacity, or

- is a congenital anomaly / birth defect,
- is a significant or important medical event that, based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

* Hospitalization is defined as an overnight (in-patient) stay at the hospital or emergency room.

For all AEs (either related or not related to study medication), information about the outcome (resolved or ongoing) and the action taken with the study treatment (drug withdrawn, dose reduced, dose increased, dose not changed, not applicable) will be documented.

Each AE, either serious or non-serious for which a causal relationship to sarecycline cannot be excluded, will be considered as an ADR. An ADR is an injury caused by taking medication. ADRs may occur following a single dose or prolonged administration of a medicinal product or result from the combination of two or more medicinal products.

The determination of whether an AE is related to study treatment (sarecycline) will be based on information regarding the degree to which the study treatment had caused or contributed to the event and will be categorized per the following criteria:

- Related: There were good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal relationship with the study medication in the sense that it is plausible, conceivable or likely.

- Not Related: There were good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with the study medication.

8.6.2 Documentation and Reporting of ADRs, Events with Fatal Outcome and Other Reportable Events

The Site Investigator is responsible for assessing and documenting (in subject medical charts, as part of usual care) all AEs that occur at any time during the study. The Site Investigator will determine the relatedness, seriousness, and severity for each AE, which is then recorded in the

Adverse Events page of the eDCF, per study schedule of events (Appendix A). Following each subject encounter (be it, via in-person or remote encounters), the Site Investigator will evaluate the last 4-weeks of documentation (in subject medical charts) to report AEs and indicate whether those events resulted in stoppage or changes to dose of study medication.

Each AE that meets the definition of ADR will be recorded in the Adverse Events page of the eDCF and comprehensively documented on the "Adverse Drug Reaction" form to be reported within 1 working day (24 hours) of learning of the event and proactively reported to the Almirall LLC, CRO Safety Team via email or fax. ADR reporting details will be included in the Safety Reporting Plan.

For the purpose of this study, all AEs that meet the aforementioned definition of an SAE (in Section 8.6.1) that occurred during the treatment period will be reported to the sponsor as SAEs. Upon receipt of SAE data by the study CRO (collected as part of eDCF), they will be reported within 1 working day (24 hours) of learning of the event to the sponsor regardless of its relationship to the study treatment. If any additional information is needed to adequately document the SAEs, the study CRO will follow-up with the Site Investigators to ensure data completeness and will report the updated information back to the study sponsor. If an SAE results in modification of study medication dose or discontinuation of study medication and/or withdrawal of subject from the study, such information will be documented as part of eDCF and reported to the study sponsor.

As part of usual care, Site Investigator will follow Subjects concerning all SAEs and ADRs until adequate resolution or stabilization. If the SAE/ADR has not resolved or stabilized by the time the subject completed the final study visit, the Site Investigator may gather the status of the subject's SAE/ADR within 30 days beyond the subject's final study visit, if required.

If a study subject (in case of female) becomes pregnant during the study period, the Site Investigator may withdraw the patient from the study (i.e., early termination) for safety reasons. In this scenario, the Site Investigator will document the reasons for withdrawal in the eDCF and

may conduct necessary follow-ups with the patient to ensure safety, as part of usual care. Occurrence of this (pregnancy) event will be reported to the study sponsor within 1 working day (24 hours) of learning of the event.

In addition, all events with a fatal outcome and all other reportable events (lack of effectiveness of sarecycline, overdose, off-label use, misuse, abuse, medication error or occupational exposure) – even in the absence of an ADR – will be documented on the "Adverse Drug Reaction" form and reported to the study sponsor within 1 working day (24 hours) of learning of the event.

Early terminated patients will be evaluated for safety assessments at the time of next scheduled encounter, as feasible. This will be documented in the eDCF.

9 STUDY OVERSIGHT

The overall study principal investigators (PIs) along with the principal investigator (Program Lead) at CRO will be responsible for this real-world study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. The Program Lead within the CRO will review the data for safety concerns and data trends at regular intervals, and will promptly report to the study PIs, the central IRB (and any local IRBs, if applicable) and to the study Sponsor any ADRs, protocol deviation, or any other significant event that arises during the conduct of the study.

10 SITE MONITORING, QUALITY CONTROL AND ASSURANCE

Study site monitoring is conducted to ensure that the rights of human Subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Site monitoring for this minimal-risk, real-world study will be performed by the CRO. The CRO will

routinely evaluate study processes and documentation based on the protocol and other applicable requirements, if any.

All site monitoring activities will be performed remotely for this study, with occasional visits to select sites to check on study procedures. Site Investigators or the assigned study coordinators will be contacted routinely by phone and email to ensure that study procedures are followed per protocol and study subject follow-ups happen as planned. Study data review will be undertaken by the CRO staff following the baseline and follow-up encounters for data collection from Site Investigators and study Subjects. Data inquiries will be shared with the Site Investigators for clarification and/or fill missing data elements, or gather additional information, as it may pertain to reported AEs/SAEs.

11 DATA MANAGEMENT

The study data portal will comprise of two distinct, linked data sources, one being the traditional EDC containing eDCF to gather data from Site Investigators; another being the mobile App that gathers data directly from study Subjects. The back-end EDC platform will be programmed with edit checks to ensure that the incoming data from Site Investigators and Subjects are routinely checked for data quality, any systematic missing data, trends in select outcome measures and safety events.

A centralized data review strategy will ensure consistency, integrity, logical completeness, and coding of collected data. Queries will be generated for study sites to solicit additional required information, as needed. Any necessary data corrections in the EDC portal at the back-end will be made by the central research staff, and ratified by the CRO Program Lead for appropriateness and correctness.

Incoming AE data will be routinely checked to flag SAEs and other pertinent high-priority safety events, gather additional information from the sites (as/if needed), and additionally collected information will be integrated back with the master study dataset, while the safety data is processed for expedited reporting to study sponsor.

Any additional quality assessment(s) will be carried out for the study per the study specific data management plan. Following completion of all data review activities for all patients, records within the master dataset will be locked, followed by completion of medical coding for concomitant medications and adverse events and preparation of dataset for statistical analyses.

12 STATISTICAL CONSIDERATIONS

Detailed plans for the statistical methods will be provided in a Statistical Analysis Plan (SAP) which will be finalized prior to database lock.

12.1 Sample Size Considerations

No formal sample size and power calculations were undertaken. Considering the descriptive nature of the study and the feasibility of recruiting the study population, approximately 300 study Subjects from across a maximum of 50 clinical sites for the entire study has been identified as a sample to guide the planned analysis addressing the study objectives.

12.2 Analysis Populations and Datasets

Statistical analysis and data tabulation will be performed using the following analysis populations unless specified otherwise:

- Safety Population: All patients who received at least one dose of sarecycline during the study observation period, as part of usual care.
- Full Analysis Set (FAS): All patients within the Safety Population that had at least some data pertaining to study primary research objective.

There is a likelihood that the Safety population and FAS may be the same in certain scenarios, including when no patient discontinues sarecycline following study enrollment and prior to 3-month follow-up data collection. In such scenarios, FAS will be the main dataset for all analyses. In the event that the safety population and FAS differ, all safety evaluations (part of additional

objectives) will be conducted among the safety population, while FAS will be used to conduct analyses addressing rest of the study objectives, including the primary objective.

12.3 General Statistical Procedures

12.3.1 Overview

Data from Site Investigators and study Subjects will be combined into one dataset. No site-specific analyses will be conducted. Validated instruments will be scored according to developer guidelines, reporting domain scores and overall summary scores, as appropriate. Home-grown questions/items will be analyzed and reported individually, based on the respective response scales.

Statistical differences in discrete variables will be assessed using a $\chi 2$ test. Continuous measures will be assessed using the appropriate parametric or nonparametric test. P values ≤ 0.05 will be considered significant in all analyses. All statistical analyses will be based on all available data assuming that all missing data are uninformative and will be conducted using appropriate statistical software, such as SAS.

The final study analyses will be conducted after the completion of 12 weeks of data collection for all study Subjects.

12.3.1 Summary Statistics

The descriptive statistics for all the continuous variables will include the mean, median, 25th percentile, 75th percentile, standard deviation (SD), standard error of mean (SEM), minimum, maximum, and number of Subjects. Descriptive summaries will be provided for raw, CFB, and %CFB values for relevant endpoints, where applicable. Frequency distributions for all the categorical variables will be presented as counts and percentages. Summaries will be provided by encounters, as appropriate. Results from the descriptive analyses will be presented as summary tables and figures.

12.3.2 Subgroup Analysis

Primary and additional outcome measures may be summarized and repeated for the following subgroups, only if sample size allows by study visit using FAS:

- Gender: male and female
- Age groups: 9 to 17 years and ≥ 18 years
- Race: white, African-American/Black, other
- Body mass index: < 25 kg/m^2 and ≥ 25 kg/m^2
- Baseline facial IGA score: moderate and severe
- Oral contraceptive use in females: female Subjects who use oral contraceptives versus female Subjects who do not (if sample size permits)

12.3.3 Multivariate Analyses

CFB in key study outcome measures at Week 12 post-index date, and at Weeks 4 and 8 (if applicable) post-index date will be assessed using relevant multivariate analyses, adjusting for subject baseline characteristics and other variables (such as medication adherence) to discern the factors influencing these outcomes, as feasible. Repeated measures analyses with covariates may be used to statistically test the changes/trends for relevant outcome measures over time.

Pearson correlation coefficients may be used to assess the correlation between key outcome measures; this may also inform the consideration of covariates in select multivariate analyses (to reduce multicollinearity).

12.4 Primary Endpoint Analysis

The primary endpoint of PROs at Week 12 will be assessed descriptively, using the FAS dataset.

For ASIS questionnaire, the individual item and domain/subscale scores will be created per instrument developer instructions, analyzed descriptively for the baseline and Week 12 encounters,

treating the responses as categorical variables and/or continuous variable, as appropriate. For the overall questionnaire data evaluation, no missing data imputation will be applied to compute domain/subscale scores.

The Patient Global Assessment (PtGA) of acne severity based on the single ASIS item (# 9) will be analyzed separately using descriptive statistics and reported for Week 12. Specifically, proportion of Subjects who reported clear (0) and almost clear (1) on the item scale at Week 12 will be assessed. Last Observation Carried Forward (LOCF) data imputation method will be used to impute responses to ASIS item # 9 at Week 12 for the Subjects with missing data at Week 12.

Patient self-rating of their appearance based on the single ASIS Item (# 10) will be analyzed separately using descriptive statistics and reported for Week 12. Specifically, proportion of Subjects reporting "very good" or "excellent" at Week 12 will be assessed. LOCF data imputation method will be used to impute responses to ASIS item # 10 at Week 12 for the Subjects with missing data at Week 12.

For Expert Panel Questionnaire, the items will be analyzed individually, using descriptive statistics and reported for Week 12.

For all PRO elements, descriptive statistics will be computed, stratified by age and other relevant subgroups, to explore the relationship between these HRQoL items and subject characteristics.

12.5 Secondary Endpoint Analysis

The secondary endpoint of the study is the proportion of patients with Facial IGA success at Week 12, defined as a 2-point decrease in IGA score from baseline and a score of 0 (clear) or 1 (almost clear). The analyses of IGA success will be conducted for the overall cohort (using FAS), as well as stratified by age and other relevant subgroups. Relationship between this endpoint and subject characteristics will be explored using descriptive analyses. LOCF data imputation method will be used to impute responses at Week 12 for the Subjects with missing data at Week 12.

12.6 Additional Analysis

12.6.1 Treatment Satisfaction Analyses

Investigator's global satisfaction with sarecycline treatment will be analyzed using data at Week 12 from a single question: "how satisfied are you with sarecycline treatment outcomes", with response options ranging from 'Very Satisfied' to 'Very Dissatisfied'. Frequency of responses will be tallied for all Subjects. Proportion of Subjects for whom Investigators indicated 'Very Satisfied' or 'Satisfied' will be reported.

The analyses will be done for the overall cohort, using FAS, and stratified by age and other relevant subgroups. Relationship between Investigator satisfaction and subject characteristics will be explored using descriptive analyses.

12.6.2 Treatment Compliance

Compliance will be assessed by comparing the expected number of doses taken, based on the total number of treatment days between the encounters/surveys and within the entire treatment period of the study, with the number of unused doses/tablets identified/returned at each encounter/visit. Treatment compliance will be calculated for each subject/visit and over all visits for the Safety population. Compliance values that are less than 0% will be set to 0%. Summaries will be presented using descriptive statistics for the Safety population.

Compliance = [# Expected to be used - # Unused] / [# Expected to be used]

12.6.3 Comparison of Investigator and Subject Assessment of AV Severity

The IGA and Subject perception of AV severity at Week 12 will be compared and reported using descriptive statistics, to portray the level of concordance/discordance in stakeholder perceptions. This analysis will be conducted for the entire cohort and for select subgroups. Correspondingly, the Investigator and Subject responses to the questions related to AV severity at baseline will also be compared and reported using descriptive statistics. The baseline level of

concordance/discordance between the stakeholders may be used to further stratify the Week 12 data analyses.

12.6.4 CFB in PROs

CFB in ASIS domain scores and subscale scores at Week 12 will be assessed. CFB will be first analyzed descriptively for the entire cohort and select subgroups. Analyses will be provided for FAS. For this analysis, the domain scores will be considered as continuous variables. No missing data imputation will be used. Scoring, scaling, and the handling of missing data will be handled in accordance with the recommendations accompanying the ASIS documentation and will be described in more detail in the SAP.

CFB in select individual items of ASIS, most specifically, items # 9 & 10, will be conducted by treating these variables as continuous variables. Based on data availability, CFB at Weeks 4 & 8 will be assessed in addition to Week 12. CFB will be first analyzed descriptively for the entire cohort and select subgroups. LOCF data imputation method will be used to impute responses to ASIS items # 9 & 10 for respective encounters for the Subjects with missing data at those encounters, prior to analyses.

Items from Expert Panel Questionnaire will be analyzed individually and CFB in individual questions/items will be reported for relevant categories of responses (depending on the response scales) descriptively. More detailed portrayal of this planned analysis will be outlined in the study SAP. No missing data imputation will be undertaken for these items.

12.6.5 Comparison of Parent/Caregiver and Patient Perceptions of AV Severity and Impact

Parent/caregiver and pediatric patient responses to the questions related to AV severity at Week 12 will be compared and reported using descriptive statistics, to portray the level of concordance/discordance in stakeholder perceptions, within the Subject age group of 12-17 yrs. This analysis will be conducted for the entire relevant cohort and for select subgroups, if sample size permits.

Responses to select Expert Panel Questionnaire items at Week 12 related to worries about Acne and impact of acne on child's lives will be compared to corresponding questions to parents/caregivers to portray the level of concordance/discordance in stakeholder perceptions, within the Subject age group of 12-17 yrs. This analysis will be conducted for the entire relevant cohort and for select subgroups, if sample size permits.

Parent/caregiver and pediatric patient responses to the questions at Week 12 related to the parents' understanding of child's concerns will be compared and reported using descriptive statistics, to portray the level of concordance/discordance in stakeholder perceptions, within the Subject age group of 12-17 yrs. This analysis will be conducted for the entire relevant cohort and for select subgroups, if sample size permits.

No missing data imputation will be undertaken for these items.

12.6.6 Safety Assessments

The safety data will be analyzed descriptively using Safety Population dataset (if it is different from FAS), to report the frequency of occurrences of AEs/ADRs and SAEs. These will be reported at individual item level as well in aggregate at specific category level (e.g., GI effects, vestibular effects) for each of the subject encounter timepoints (4, 8 & 12 weeks post-index date). The number of patients discontinuing treatment within the 3-month post-index date, and number of patients discontinuing the study within the entire study observation window (of 12 weeks) because of AEs/ADRs will be reported, as documented in patient medical charts.

12.7 Missing Data Handling

The missing data pertinent to the validated instrument ASIS will be handled per instrument owner instructions / scoring manual. For effectiveness measures obtained from Site Investigators and Subjects, namely, IGA, PtGA (from ASIS item # 9) and Patient appearance rating scale (from ASIS item # 10), LOCF data imputation method will be used to impute responses for Week 12 for the Subjects with missing data at Week 12. LOCF may also be used to impute responses for Weeks 4 & 8 for the Subjects with missing data at those encounters for

these select measures, as feasible. For all other study variables and endpoints, no missing data imputation is planned.

12.8 Sensitivity Analyses

Sensitivity analyses will explore the impact of missing data on the robustness of the results. Reasons for missing data and time to drop-out will be explored in a descriptive fashion. The key study outcomes will be explored for Subjects that completed the study versus those that discontinued the study, using descriptive statistics and multivariate regression models, as appropriate. If some Subject visits are conducted via remote visits instead of in-person visits, the nature of visit (remote vs. in-person) may be used to stratify the analysis of secondary endpoint involving IGA. The dataset with LOCF imputed values will be used to repeat only the select outcomes analyses as outlined in Section 12.7 and the results will be shown along with the results from analyses without LOCF data imputation.

Details of the sensitivity analyses will be described in SAP prior to database lock.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study for the integrity of research and protection of confidentiality of Subjects. Study staff will permit authorized representatives of the IRB and study CRO to examine research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

The eDCFs represent a record of the subject's experience in the study, therefore, the eDCF data will be supported by original (or source) medical records, where feasible. Prior to enrolling a subject in the study, the s Site Investigator or site staff will document his/her review of subject eligibility criteria in the source records for the subject. Current or changes in clinical characteristics of the AV patients, including current or changes to disease severity and medications will be documented in patient medical charts as part of routine clinical practice, and these may constitute source records for the Subjects. Data recorded directly into the eDCF (via online portal) is also considered source data when there are no other written or electronic records

preceding the eDCF entry; data from online surveys completed by study Subjects will be considered as source data, with no back-up records (or data copies) in patient medical charts.

No study monitoring visits will be conducted by the CRO as part of the study, as the sites and Subjects will be managed remotely, and all data will be collected using eDCFs. Occasional visits to select sites may be conducted (only as feasible) to monitor the progress of the study.

The electronically collected data will be periodically reviewed to evaluate the progress of the study; to verify the accuracy and completeness of eDCFs; to ensure that all protocol requirements, and Investigator's obligations are being fulfilled; and to resolve any inquiries related to the study data.

The Site Investigators agrees that the Study CRO or the IRB will have reasonable access to study source documentation (albeit, in de-identified manner) for purposes of audit both during and after completion of the study.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigators will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2 Institutional Review Board

The protocol, informed consent form(s), and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study. A progress report will

be submitted by the Study CRO Program Lead to the IRB at intervals specified by the IRB, but not less than annually.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

The participating Site Investigator will ensure that written informed consent (and/or assent, if applicable) is obtained from each subject (and parent(s) or legal guardian(s), if applicable) in accordance with applicable regulations. Subjects under the age of 18 must sign the Assent Form. The subject and their parent(s) or legal guardian(s), if applicable, will be given adequate time to consider the risks associated with participation in the study. Study Subjects may provide consent/asset using online data collection portal, in case of virtual study visits/encounters in the absence of in-person visits/encounters. Each subject will provide informed consent (and/or assent if applicable and according to IRB regulations) prior to participating in any study procedures, as outlined in Section 6.3.2 of this protocol. As an addendum to the main consent form, the Subjects from a small subset of sites will be consented (with necessary assent) to allow facial photographs taken at baseline and Week 12 by their clinician at the privacy of the clinician's office and will be consented (with necessary assent) to provide a 1-3 minute testimonial of Subject's experience with sarecycline (Seysara®) at Week 12.

14.4 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. The final research data will constitute only **de-identified** data, for research analyses and reporting. Participants will be identified by a unique study ID number assigned by the site coordinator and/or study CRO, which will be listed on the paper-based consent forms or online e-consent forms and on each of the online e-DCFs. The site coordinator and the CRO project team may review the e-DCFs for any missing data periodically. Access to

the online e-DCFs will be restricted to the patient/caregiver, the site coordinator/Investigator, and the relevant representatives from the CRO.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. Site Investigator and study subject contact information will be collected strictly for administrative purposes, such as processing of incentives and to share study follow-up reminders. This personally identifiable information will remain separate from research data.

Photographs to document baseline clinical status and Week 12 outcomes (of acne severity) associated with the use of study medication will be obtained from a small subset of study Subjects. Audio testimonials depicting Subject's experience with sarecycline may be obtained from a subset of study Subjects at Week 12. All of these data will be stored electronically and anonymized (using appropriate digital technology) before using this data for further analyses and/or publications.

No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor or the study CRO. The study CRO or other authorized representatives of the sponsor may inspect all study documents and records, but at no juncture will study subject identifiable information will be collected or disclosed.

15 OTHER INFORMATION

15.1 Publication and Disclosure Policy

Publication and disclosure policy is addressed in a separate agreement.

15.2 Termination of the Study

If the study is terminated prematurely or suspended, the appropriate IRB will be promptly informed of the termination or suspension and will be provided the reason(s) for the termination or suspension. All obligations and responsibilities of the Sponsor and the Investigator will remain in force if the study is terminated prematurely.

16 LITERATURE REFERENCES

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17 APPENDICES

Appendix A: Study Schedule of Events

Appendix B: Select Study Questionnaires

Appendix C: Signature Page

17.1 APPENDIX A: Study Schedule of Events

Study Encounter (physical or virtual)	**Baseline E1**	**E2**	**E3**	**End of Study E4**	**Early Termination Visit**
Week†		Wk 4 (± 4 d)	Wk 8 (± 4 d)	Wk 12 (± 4 d)	-
Informed consent	X				
Selection criteria	X				
Demographics & baseline clinical characteristics[1]	X				
Physical examination[2]	X			X	X
AV medical history and relevant comorbidites[3]	X			X	X
Seysara dose[4]	X	X	X	X	X
Dispensing and return of study medication	X	X	X	X	X
Prior acne medication (since diagnosis & past 6 months)	X				
Concomitant general medication	X			X	X
Concomitant anti acne medication	X			X	X
Site Investigator's clinical assessment of acne[5]	X	X	X	X	X
Study subject questionnaires[6]	X	X	X	X	X
AEs/SAEs[7]	X	X	X	X	X
Reasons for premature study withdrawal					X

† Expected in-person or virtual encounter/visit schedule, in relation to the index date (date of first administration of sarecycline).

[1] Clinical characteristics data assessed retrospectively based on what is documented in patient medical charts.

[2] Routine physical examination conducted as part of usual care alone and as documented in patient medical charts; such data may include - blood pressure, waist circumference, height/weight measurements.

[3] May include AV date of diagnosis, baseline severity, relevant comorbidities, per clinician judgment and/or as documented in patient medical charts immediately before the index date; new emerging comorbidities during the study period will be recorded, based on the documentation in patient medical charts.

[4] Expected usage is once daily, every day during the duration of the trial.

[5] Site Investigator assessments of AV severity of Subjects may be conducted during subject visit to clinician offices, or via remote/virtual (telehealth) visits owing to Covid-related travel restrictions.

[6] Subject self-assessments will include PtGA of acne severity; various HRQOL assessments will be conducted at baseline and Week 12.

[7] In the case of premature study discontinuation due to an AE, the Investigator should make every effort to collect the AE duration and outcome. Any SAE that is ongoing at the End of the Study or at the time of premature withdrawal will be followed up until the SAE is resolved or at least up to 4 weeks. AE follow-up information will be reported in the eDCF.

Note: AE, adverse event; eDCF, electronic Data Collection Form; E, encounter; W, week.

17.2 Appendix B: Select Study Questionnaires

ASIS

Please read and answer each of the following questions about **acne signs and symptoms**. Before answering each question, **look in the mirror and think about the acne on your face**. Select one answer for each question that best describes your experience with acne **right now**. There are no right or wrong answers.

1. How oily is your face right now?

Not at all	A little	Somewhat	Quite a bit	Very
☐	☐	☐	☐	☐

2. How many pimples do you have on your face right now?

None	A few	Some	Quite a bit	A lot
☐	☐	☐	☐	☐

3. How many acne scars (holes or indents) do you have on your face right now?

None	A few	Some	Quite a bit	A lot
☐	☐	☐	☐	☐

4. How many scabs from acne do you have on your face right now?

None	A few	Some	Quite a bit	A lot
☐	☐	☐	☐	☐

5. How many dark marks from acne do you have on your face right now?

None	A few	Some	Quite a bit	A lot
☐	☐	☐	☐	☐

6. How many blackheads do you have on your face right now?

None	A few	Some	Quite a bit	A lot
☐	☐	☐	☐	☐

7. How many whiteheads do you have on your face right now?

None	A few	Some	Quite a bit	A lot
☐	☐	☐	☐	☐

8. How much redness do you have on your face right now?

None	A few	Some	Quite a bit	A lot
☐	☐	☐	☐	☐

9. Overall, how is the acne on your face right now?

Clear	Almost clear	Mild	Moderate	Severe
☐	☐	☐	☐	☐

Please read and answer each of the following questions about how **acne impact your quality of life**. Before answering each question, look in the mirror and think about the acne on your face. Select one answer for each question that best describes your experience with acne in the past 7 days. There are no right or wrong answers.

10. Over the past 7 days, rate how your face looked because of your acne.

Excellent	Very good	Good	Fair	Bad
☐	☐	☐	☐	☐

11. Over the past 7 days, how often did you feel sad because of the acne on your face?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

12. Over the past 7 days, how often did you feel embarrassed because of the acne on your face?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

13. Over the past 7 days, how often did you feel self-conscious because of the acne on your face?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

14. Over the past 7 days, how often did you feel annoyed because of the acne on your face?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

15. Over the past 7 days, how often did you feel not confident because of the acne on your face?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

16. Over the past 7 days, how often did you choose not to be around other people because of the acne on your face?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

17. Over the past 7 days, how often did someone make bad comments about the acne on your face?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

Expert Panel Questionnaire

Please read and answer each of the following questions about how **acne affect your emotional wellbeing, social interactions, and other daily activities**. Before answering each question, look in the mirror and think about the acne on your face. Select one answer for each question that best describes your experience with acne over the past 7 days. There are no right or wrong answers.

1. Over the past 7 days, how often has your acne made you feel angry (mad/sad)?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

2. How worried are you about how long your acne will last and how bad it will get?

Not at all	Slightly	Somewhat	Moderately	Extremely
☐	☐	☐	☐	☐

3. How often do you think about your acne?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

4. Over the past 7 days, how worried have you been about your acne?

Not at all	Slightly	Somewhat	Moderately	Extremely
☐	☐	☐	☐	☐

5. How often do you change, edit, or filter your social media photo or selfie because of your acne?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

6. How often does acne impact your “in real-life” plans (IRL) (like dating or social engagements, playing sports, swimming or hanging out)?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

7. How often are you doing something to hide your acne (like mess with, squeeze/pop, or use makeup, concealer, hairstyle, clothes to cover up)?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

8. How often do you feel picked on or judged because of your acne?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

9. How concerned are you that your acne will affect your ability to reach your future goals (in school or work) and be the best you can be?

Not at all	Slightly	Somewhat	Moderately	Extremely
☐	☐	☐	☐	☐

10. Over the past 7 days, how often has worrying about or discomfort (itching/hurting) from acne affected your sleep?

Never	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

17.3 APPENDIX-C: Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to relevant legal and regulatory requirements.

Study PIs (for Central IRB Purposes):

PPD

Name | Signature | Date

PPD

Name | Signature | Date

Almirall Approvals:

PPD MD

PPD | Signature | Date

Global Medical Affairs

PPD

PPD | Signature | Date

Global Development – R&D