# An Open-label Study Evaluating the Long-term Efficacy, Quality of Life, and Safety of ABSORICA® (isotretinoin) Capsules Administered Without Food in Patients with Severe Recalcitrant Nodular Acne

NCT number: NCT02457520

Date: 19 December 2014

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| **Study Title:** | An Open-label Study Evaluating the Long-term Efficacy, Quality of Life, and Safety of ABSORICA® (isotretinoin) Capsules Administered Without Food in Patients With Severe Recalcitrant Nodular Acne |
| **Drug Name:** | ABSORICA® (isotretinoin) capsules |
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Sponsor:

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## SIGNATURE PAGE

**Product:** ABSORICA® (isotretinoin) capsules

**Protocol number:** ABS1517LT

The signatures of the representatives below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol, including all statements as to confidentiality. It is also agreed that that the study will not be initiated without the approval of an appropriate Institutional Review Board (IRB) or Ethics Review Committee (IEC).

[redacted]

[redacted]

[redacted]

## SIGNATURE PAGE FOR INVESTIGATOR(S)

**Product:** ABSORICA® (isotretinoin) capsules

**Protocol number:** ABS1517LT

**Protocol title:** An Open-label Study Evaluating the Long-term Efficacy, Quality of Life, and Safety of ABSORICA® (isotretinoin) Capsules Administered Without Food in Patients With Severe Recalcitrant Nodular Acne

I have carefully read this protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA), and any local regulatory requirements and will endeavor to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by the sponsor to all personnel responsible to me and who will participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information in accordance with Food and Drug Administration regulations.

_____
Principal Investigator's printed name

_____ _____
Principal Investigator's signature Date

## 1.0 SYNOPSIS

| | |
|---|---|
| Study Title: | An Open-label Study Evaluating the Long-term Efficacy, Quality of Life, and Safety of ABSORICA® (isotretinoin) Capsules Administered Without Food in Patients With Severe Recalcitrant Nodular Acne |
| Protocol Number: | ABS1517LT |
| Sponsor: | RANBAXY LABORATORIES Inc<br>600 College Road East<br>Princeton, NJ 08540 |
| Development Phase: | 4 |
| Study Objectives: | **20-Week Active Treatment Period (ATP)**<br>The primary objective during the 20-week ATP of the study will be to investigate the quality of life (QOL) of subjects who are taking Absorica® (isotretinoin) capsules twice daily (bid) without food for the treatment of severe recalcitrant nodular acne.<br>The secondary objective during the 20-week treatment period will be to investigate the efficacy and safety of Absorica® (isotretinoin) taken bid without food during the ATP.<br>**104-Week Post-treatment Period (PTP)**<br>The primary objective during the 104-week PTP of the study is to determine both the time to retreatment and the proportion of subjects who require retreatment with oral isotretinoin during a 2-year PTP.<br><br>The secondary objectives during the PTP are:<br>• To investigate the QOL at the end of the 2-year PTP;<br>• To investigate the severity of the acne over time, as measured by the Investigator's Global Assessment (IGA) and lesion counts;<br>• To document any acne treatment (prescription and/or over-the-counter [OTC]) used by those subjects;<br>• To evaluate the long-term safety during the 2-year PTP. |
| Study Design: | Uncontrolled open-label. |
| Planned Sample Size: | 200 enrolled subjects |
| Study Population: | Eligible subjects will include healthy males and non-pregnant, non-nursing females, age 12 to 45 years, with severe recalcitrant nodular acne. |
| Investigational Product(s): | ABSORICA® (isotretinoin) capsules 0.5 mg/kg/day for 4 weeks followed by 1.0 mg/kg/day for 16 weeks. Female subjects must consent to 2 forms of birth control or abstinence. |
| Reference Product(s): | Not applicable |
| Control Product(s): | Not applicable |
| Evaluation Criteria: | The primary endpoint during the ATP will be the change from Baseline to the end of ATP (Week 20/Visit 8) in the acne-specific quality of life (acne-QOL) questionnaire score for those subjects who complete the 20-week ATP and are at least 75% compliant with the treatment regimen.<br><br>Secondary endpoints for the ATP will be:<br>• The change from Baseline in the lesion count (nodules and inflammatory lesions) at the end of the ATP; |

| | |
|---|---|
| | • The change from Baseline in the acne-QOL score at Weeks 4, 8, 12, and 16 weeks;<br>• The change from Baseline in the IGA at the end of the ATP in subjects who complete the 20-week ATP;<br>• Treatment safety, as determined by the frequency and severity of adverse events (AEs) and local skin irritation.<br><br>Primary endpoints for the PTP will be to determine:<br>• The proportion of subjects who require retreatment with oral isotretinoin at any time during the PTP; and<br>• The time at which retreatment is required.<br>Secondary endpoints for the PTP will be to determine:<br>• The proportion of subjects who require treatment with a prescription anti-acne medication other than oral isotretinoin at any time during the PTP;<br>• The proportion of subjects who use an over-the-counter (OTC) anti-acne medication at any time during the PTP;<br>• The severity of acne (lesion count and IGA) at the time of retreatment in subjects treated with a prescription or OTC anti-acne treatment;<br>• The severity of acne (lesion count and IGA) at each visit;<br>• The time to retreatment with a prescription or over-the-counter (OTC) anti-acne medication at any time during the PTP;<br>• The acne-QOL at the end of the PTP;<br>• Safety as assessed through the monitoring of AEs, laboratory test results, vital signs, and physical examinations. |
| Pharmacokinetics Evaluation Criteria: | Not applicable |
| Safety Evaluation Criteria: | During the ATP: adverse event (AE) incidence and severity, laboratory test results (hematology, serum biochemistry, lipid profile), pregnancy tests, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate)<br>During the PTP: Serious AEs related to study drug. |
| Statistical Methods: | Efficacy will be evaluated descriptively.<br>Adverse events will be presented in data listings and summarized by frequency and severity. Laboratory and vital sign data will be presented in data listings. Abnormal laboratory findings will be presented. Results from the acne-QOL will be summarized. |
| Study Sites: | Approximately 20 study sites in the United States (US) |
| Planned Dates of Study: | January 2015 – April 2018 |

**Table 1-1 Visit Schedule and Assessments – Active Treatment Phase (ATP)**

| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8 EOT |
|---|---|---|---|---|---|---|---|---|
| | Screening ≤30 days of Baseline[a] | Baseline | Week 2 ± 4 days | Week 4 ± 4 days | Week 8 ± 4 days | Week 12 ± 4 days | Week 16 ± 4 days | Week 20 ± 4 days |
| | | 0.5 mg/kg/day | | 1.0 mg/kg/day | | | | |
| Informed consent[b] including photographic consent | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | |
| Demographics and medical history | X | | | | | | | |
| Physical examination | X | | | | | | | X |
| Vital signs and weight | X | | | | | | | X |
| Prior and concomitant medication assessment | X | X | X | X | X | X | X | X |
| Childbearing potential (female subjects only)[c] | X | X | | | | | | |
| Clinical laboratory assessment[d]<br>Hematology<br>Serum chemistry | X | X | X | X | X | X | X | X |
| Pregnancy test[e] | X | X | X | X | X | X | X | X |
| Contraceptive counseling | X | X | | X | X | X | X | X |
| Photography[f] | | X | | X | X | X | X | X |
| Quality of Life Questionnaire | | X | | X | X | X | X | X |
| Investigator's Global Assessment (IGA) | | X | | X | X | X | X | X |
| Lesion count[g] (nodules and inflammatory lesions) | X | X | | X | X | X | X | X |
| Adverse event assessment | | X | X | X | X | X | X | X |
| Issue 30-day supply of study medication | | X | | X | X | X | X | |
| Reconcile medication use and counsel as required | | | | X | X | X | X | X |

EOT = end of treatment

a. Females of childbearing potential must undergo a mandatory 30-day waiting period before receiving isotretinoin.

b. Subjects under 18 years of age must sign and assent to participate in the study as well has having written informed consent from a parent or guardian. The parent or guardian must also give permission for a minor to receive contraceptive counseling.

c. Childbearing potential includes dates of menstruation and forms of contraceptives currently used and to be used during the study.

d. Laboratory assessments at Screening and EOT will include a complete blood count, fasting clinical chemistry, and fasting lipid profile. Laboratory assessments at all other visits will include only fasting clinical chemistry and fasting lipid profile.

e. Females of childbearing potential must have a second, confirmatory pregnancy test with negative results that occurs after the 30-day waiting period.

f. Specified sites will perform photography using equipment supplied by the photography vendor; other sites will use on-site photography equipment.

g. Only nodules will be counted at Screening.

**Table 1-2 Visit Schedule and Assessments – Post-Treatment Phase (PTP)**

| | Visit 9 | Visit 10 | Visit 11 | Visit 12 | Visit 13 | Visit14/EOS |
|---|---|---|---|---|---|---|
| | **Week 24 ± 4 days** | **Week 32 ± 2 weeks** | **Week 46 ± 2 weeks** | **Week 72 ± 2 weeks** | **Week 98 ± 2 weeks** | **Week 124 ± 2 weeks** |
| Vital signs and weight | X | | | | | |
| Clinical laboratory assessment[a] Serum chemistry | X | | | | | |
| Pregnancy test | X | | | | | |
| Prior and concomitant medication assessment | X | X | X | X | X | X |
| Photography[b] | | X | X | X | X | X |
| Quality of Life Questionnaire | | X | X | X | X | X |
| Investigator's Global Assessment (IGA) | | X | X | X | X | X |
| Lesion count (nodules and inflammatory lesions) | | X | X | X | X | X |
| Adverse event assessment[c] | X | X | X | X | X | X |

a. Laboratory assessments at Visit 9 will include fasting clinical chemistry and fasting lipid profile.

b. Specified sites will perform photography using equipment supplied by the photography vendor; other sites will use on-site photography equipment.

c. Only serious adverse events related to study treatment will be collected.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation | Definition |
|---|---|
| Acne-QOL | Acne-specific Quality Of Life Questionnaire |
| AE | Adverse event |
| ALT | Alanine transaminase |
| AR | Adverse reaction |
| AST | Aspartate transaminase |
| ATP | Active treatment period |
| bid | *Bis in die* (twice daily) |
| BUN | Blood urea nitrogen |
| CFR | Code of Federal Regulations |
| CLIA | Clinical Laboratory Improvement Amendments |
| eCRF | Electronic case report form |
| CRO | Contract Research Organization |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| EOS | End of study |
| EOT | End of treatment |
| FDA | Food and Drug Administration |
| GGT | Gamma glutamyl transferase |
| HDL | High density lipoproteins |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed consent form |
| ICH-GCP | International Conference on Harmonisation-Good Clinical Practice |
| IGA | Investigator's Global Assessment |
| IRB | Institutional Review Board |
| ITT | Intent to treat |
| LDL | Low density lipoproteins |
| MDMA | 3,4-methylenedioxymethamphetamine |
| OTC | Over the counter |
| *P acnes* | *Propionibacterium acnes* |
| PCOS | Polycystic ovarian syndrome |
| PCP | Phencyclidine |
| PTP | Post-treatment period |
| QOL | Quality of Life |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |

| Abbreviation | Definition |
|---|---|
| SAR | Suspected adverse reaction |
| SCID-CT | Structured Clinical Interview DSM-IV clinical trials |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reaction |
| UPT | Urine pregnancy test |
| US | United States |
| WBC | White blood cell |

# 2.0 INTRODUCTION

## 2.1 Background

Acne is a common skin condition, affecting a large portion of the general population, particularly adolescents. The prevalence of acne amongst adolescents is estimated between 70% and 87%,[1] with approximately 95% to 100% of boys and 83% to 85% of girls aged 16 to 17 years[2] affected by this condition. Cystic acne is estimated to affect approximately 17 million people in the United States (US), which includes 80% of all persons between the ages of 11 and 30 years, regardless of race, ethnicity, or gender.[3]

Acne lesions occur primarily on the face, neck, upper back, and chest. Noninflammatory lesions include open or closed comedones (blackheads and whiteheads, respectively). Inflammatory lesions include papules, pustules, and nodules/nodular cystic lesions, with the type of inflammatory lesions depending on the severity and location of the inflammation within the dermis. Nodules are defined as inflammatory lesions that are greater than 5 mm in diameter. Severe nodular acne, defined as grade 4 or 5 acne on the Investigator's Global Assessment (IGA) scale, is a skin condition characterized by intense erythema, inflammation, nodules, cysts, and scarring. Variants of nodular acne include acne conglobata, acne fulminans, and pyoderma faciale.

Acne can have an important and potentially lasting impact on quality of life and self-image, especially during the emotionally critical period of adolescence. Persons with acne may think of themselves as unworthy and socially unacceptable. Severe acne may lead to scarring and disfigurement, aggravating the already present psychosocial aspects of this condition. Acne also has a significant economic and social impact on doctor visits, medications, and absenteeism.[3] Patients with acne report levels of social, psychological, and emotional problems as great as those reported by patients with chronic disabling asthma, epilepsy, diabetes, back pain, or arthritis.[4]

Isotretinoin (13-cis-retinoic acid) is an oral retinoid that has been approved in the US since 1982 for patients with recalcitrant, severe nodular or scarring acne, acne conglobata, and acne fulminans.[5] Isotretinoin has also been used off-label as an effective treatment of acne that is either treatment-resistant or is producing physical or psychological scarring. Isotretinoin is the only agent that targets all pathophysiological processes of acne; it reduces the secretion of sebum, decreases the size of the sebaceous glands, prevents the development of comedones, and decreases the colonization with *Propionibacterium acnes* (*P acnes*), the prevalent bacterium in acne. It also possesses anti-inflammatory properties, and reduces the levels of metalloproteinases in sebum.[3,5] The approved dosage of 0.5 to 1.0 mg/kg/day[6] is typically given over a 20-week course, to a total cumulative dose of 120 to 150 mg/kg.[4,5,7] Beyond this maximal dosing, no further benefit has been reported. However, if this dosage range has not been achieved, patients

are more likely to relapse and require subsequent courses of therapy.[5] Patients often require only a single course of treatment with isotretinoin and improvement continues even after the drug has been stopped.[3]

In one study, 69% of patients (61/88) were still virtually clear of disease an average of 9 years after completing treatment with isotretinoin, whereas of the remaining patients, 16% required further treatment with conventional antibiotics and 23% required a second course of isotretinoin.[8] Relapses have been reported to occur in approximately 23% of patients (primarily during the first 2 years after treatment discontinuation) even in patients who received a full course of 150 mg/kg of isotretinoin.[9] Recent studies examining risk factors for relapse in patients treated with isotretinoin emphasize the importance of the total cumulative dose rather than the daily dose used during treatment. Patients treated with a lower cumulative dose (less than 120 mg/kg) have a significantly higher recurrence rate than patients treated with a higher cumulative dose.[4] One study found a significant association between acne relapse and the following factors: male gender, age under 16 years, living in an urban area, isotretinoin cumulative doses above 2,450 mg, and isotretinoin treatment longer than 121 days.[10]

The current study will be conducted to evaluate the safety and efficacy of Absorica® (isotretinoin), a modified formulation of isotretinoin. Although isotretinoin is the most effective drug for the treatment of severe recalcitrant nodular acne, the molecule is quite lipophilic. Because of this lipophilicity, isotretinoin products such as Amnesteem® and Claravis®, etc.[11-15] must be taken with a high-fat meal to achieve optimal absorption. When these formulations are administered without food, fasted plasma levels of the active drug can be nearly 60% lower than fed levels. Noncompliance with the food intake results in large fluctuations in drug plasma levels (up to approximately three times between fasting and fed conditions) and can compromise the efficacy of isotretinoin. Absorica® (isotretinoin) has been developed as a formulation for which absorption is less dependent on the amount and/or type of food intake, thus providing a more reliable isotretinoin blood concentration.

### 2.2 Rationale of the Study

Previous studies with isotretinoin products, including Absorica® (isotretinoin), have been performed with the subject in a fed state. This study is designed to provide efficacy, safety, and quality of life (QOL) data on subjects who receive Absorica® without food. The study will investigate the efficacy of the treatment, the frequency of relapse once the treatment has been discontinued, the quality of life during the active treatment and during a 2-year period after treatment has been completed, and the overall safety of treatment with Absorica®.

### 2.3 Benefit-Risk Assessment

Isotretinoin is currently regarded as the most effective treatment option for severe nodular or nodular cystic acne, due to the ability of this compound to induce complete and prolonged remission, with an expected cure rate of 80% to 85%.[4] The duration of suffering is shortened,

and the amount of scarring is typically reduced. The current study offers subjects with severe acne the opportunity to receive a highly effective treatment with a 2-year follow-up period, during which re-treatment with Absorica® (isotretinoin) or another anti-acne medication will be offered if a relapse occurs.

More than 12 million subjects have been treated with isotretinoin since its approval in 1982.[4] Side effects include those of the mucocutaneous, musculoskeletal, and ophthalmic systems, as well as headaches and central nervous system effects. Most of the adverse effects are reversible after the drug is discontinued.[8]

Isotretinoin is a known teratogen, with the overall risk of birth defects estimated to be about 30%.[5] Female subjects of childbearing potential must participate in a risk management program such as iPLEDGE™ to minimize pregnancy risk.

## 3.0 TRIAL OBJECTIVES AND PURPOSE

### 3.1 20-Week Active Treatment Period (ATP)

The primary objective during the 20-week ATP of the study will be to investigate the quality of life (QOL) of subjects who are taking Absorica® (isotretinoin) capsules twice daily (bid) without food for the treatment of severe recalcitrant nodular acne.

The secondary objective during the 20-week treatment period will be to investigate the efficacy and safety of Absorica® (isotretinoin) taken bid without food during the ATP.

Safety will be assessed through the monitoring of AEs, laboratory test results, vital signs, and physical examinations.

### 3.2 104-Week Post-Treatment Period (PTP)

The primary objective during the 104-week PTP of the study is to determine both the time to retreatment and the proportion of subjects who require retreatment with oral isotretinoin during a 2-year PTP.

The secondary objectives during the PTP are:

- To investigate the QOL at the end of the 2-year PTP;
- To investigate the severity of the acne over time, as measured by the Investigator's Global Assessment (IGA) and lesion counts;
- To document any acne treatment (prescription and/or over-the-counter [OTC]) used by those subjects;
- To evaluate the long-term safety during the 2-year PTP.

## 4.0 STUDY DESIGN

### 4.1 Overall Study Design

This is a single-arm, open-label study consisting of 2 phases: a 20-week (5-month) open-label ATP and a 104-week (2-year) PTP. The total study duration is to be 124 weeks, excluding a screening period. During the ATP, after a Week 2 visit, visits will be scheduled at 4-week intervals for a total of 8 visits (1 screening visit, 1 baseline visit, and 6 on-study visits). During the PTP, the first visit will be 4 weeks after End of Treatment (EOT), the second visit will be 12 weeks after EOT, and subsequent visits will be scheduled at 26-week (± 2 weeks) intervals for a total of 6 visits.

Subjects will provide written informed consent, including mandatory photographic consent, on an informed consent form (ICF). Subjects who are under the age of 18 years will sign an assent form and their parent or guardian will sign the ICF. Subjects will then undergo a complete physical examination and will provide blood samples for hematology and fasting clinical chemistry, including liver function tests and a lipid profile with triglyceride levels. Female subjects of childbearing potential will be required to comply with mandatory pregnancy testing (see Section 7.4.5) and contraception specifications (see Section 6.6) before receiving study medication.

Subjects who meet the entry criteria will enter a 20-week ATP, during which they will receive Absorica® (isotretinoin) capsules. Dosing will be at an initial titration dose of approximately 0.5 mg/kg/day divided into 2 daily doses for the first 4 weeks, followed by 16 weeks of dosing with approximately 1 mg/kg/day divided into 2 daily doses. Study medication is to be taken

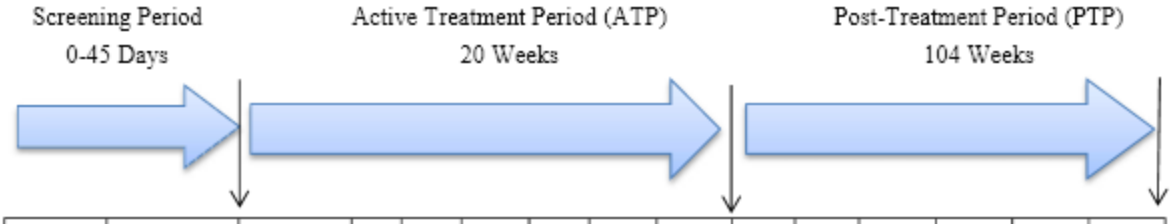
without food (ie, 1 hour before or at least 2 hours after the ingestion of food or beverages other than water).

Beginning at Visit 2 (Baseline) and continuing throughout the ATP and PTP (excluding Visits 3 and 9), subjects will be asked to complete an acne-specific quality of life (acne-QOL) questionnaire and photographs will be taken of the subject's face. Safety during the ATP will be assessed by adverse event (AE) monitoring and laboratory test results. Efficacy will be assessed by lesion counts (nodules, inflammatory lesions) and an IGA.

Subjects who are prescribed a second course of treatment Absorica® or any other formulation of isotretinoin during the PTP will be withdrawn from the study after their lesion count and IGA are recorded. Subjects who use OTC or oral non-isotretinoin acne treatment can remain in the study, but their medication use is to be recorded.

The study design is summarized in Figure 4-1.

**Figure 4-1 Study Design**




| | Screening | Baseline | | | | | | EOT | | | | | | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| Weeks: | ≤30 days of Baseline[a] | 0 | 2[b] | 4 | 8 | 12 | 16 | 20 | 24[c] | 32 | 46 | 72 | 98 | 124 |

Note: EOT = end of treatment; EOS = end of study

a. A mandatory, confirmatory pregnancy test for female subjects of childbearing potential must be conducted according to the iPLEDGE guidelines.

b. Week 2 safety laboratory tests.

c. 4 Week post treatment safety follow-up

## 4.2 Study Endpoints

### 4.2.1 Active Treatment Period

#### 4.2.1.1 Primary Endpoint for the ATP

The primary endpoint during the ATP will be the change from Baseline to the end of ATP (Week 20/Visit 8) in the acne-specific quality of life (acne-QOL) questionnaire score for those subjects who complete the 20-week ATP and are at least 75% adherent with the dosage regimen during study visits.

#### 4.2.1.2 Secondary Endpoints for the ATP

Secondary endpoints will be:

- The change from Baseline in the lesion count (nodules and inflammatory lesions) at the end of the ATP;
- The change from Baseline in the acne-QOL score at Weeks 4, 8, 12, and 16 weeks;
- The change from Baseline in the IGA at the end of the ATP in subjects who complete the 20-week ATP;
- Treatment safety, as determined by the frequency and severity of AEs and local skin irritation.

### 4.2.2 Post-Treatment Period

#### 4.2.2.1 Primary Endpoints for the PTP

Primary endpoints for the PTP will be:

- The proportion of subjects who require retreatment with oral isotretinoin at any time during the PTP; and
- The time at which retreatment is required.

#### 4.2.2.2 Secondary Endpoints for the PTP

Secondary endpoints for the PTP will be:

- The proportion of subjects who require treatment with a prescription anti-acne medication other than oral isotretinoin at any time during the PTP;
- The proportion of subjects who use an over-the-counter (OTC) anti-acne medication at any time during the PTP;
- The severity of acne (lesion count and IGA) at the time of retreatment in subjects treated with a prescription or OTC anti-acne treatment;
- The severity of acne (lesion count and IGA) at each visit;
- The time to retreatment with a prescription or over-the-counter (OTC) anti-acne medication at any time during the PTP;
- The acne-QOL at the end of the PTP;
- Safety as assessed through the monitoring of AEs, laboratory test results, vital signs, and physical examinations.

# 5.0 SELECTION OF STUDY POPULATION

## 5.1 Subject Population

It is planned to enroll approximately 200 subjects at approximately 20 sites in the US in order to provide approximately 140 subjects who complete the ATP. An individual subject will be allowed to participate in the study one time only. A rationale for the choice of sample size is provided in Section 8.2 of this protocol.

## 5.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for participation in the study:

### 5.2.1 General Inclusion Criteria

Subjects must meet the following mandatory inclusion criteria at the time of screening to be eligible to enter the study and must agree to conform to the requirements of the study and the iPLEDGE program.

1. Subjects must provide written informed consent, including mandatory photographic consent, on a gender-specific informed consent form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) authorization prior to the performance of any study-related procedures. Because the study presents different risks with regard to pregnancy for men and women, the ICFs are different for male and female subjects.
2. Subjects will be male or non-pregnant, non-lactating female subjects age 12 to 45 years.
3. Isotretinoin is teratogenic. Female subjects are prohibited from entering the study if pregnant and they are not to become pregnant during the ATP phase of the trial and for 30 days after receiving their last dose of study drug.
4. Female subjects of childbearing potential must use 2 forms of effective contraception simultaneously for 1 month before starting Absorica® (isotretinoin), while taking Absorica®, and for 1 month after Absorica® has been stopped, unless they commit to continuous abstinence from heterosexual intercourse. Female subjects who choose abstinence will also have to wait the mandatory 30-day waiting period per the study Pregnancy Prevention Program requirements. The screening visit may be repeated for a subject if, in the opinion of the investigator, the subject requires re screening.
5. Male subjects and female subjects of non-childbearing potential must be able to satisfy all inclusion/exclusion criteria within 30 days prior to first drug administration. Female subjects of childbearing potential must meet the requirements of the iPLEDGE program.

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### 5.2.2 Specific Inclusion Criteria

1. Severe recalcitrant nodular acne, which in the opinion of the investigator is compatible with isotretinoin treatment;
2. Five (5) or more nodule lesions on the face;

3. Treatment-naïve without any prior exposure to systemic isotretinoin or other systemic retinoids (ie, acitretin, etretinate);
4. Age between 12 and 45 years;
5. Weight between 40 and 110 kg;
6. Female subjects of childbearing potential only: Negative results from serum pregnancy tests with a sensitivity of at least 25 mIU/mL. Pregnancy tests are to be performed according to the iPLEDGE specifications.
7. Good general health as determined by the investigator based on the subject's medical history, physical examination, vital signs measurements, and laboratory test results;
8. Subjects who present with stable and controlled diabetes mellitus (Types I and II) may be included in the study. However, subjects may not been hospitalized for any diabetes-related complications in the last 12 months, and have to have been on stable medication for the preceding 6 months.

   Subjects with previously diagnosed polycystic ovarian syndrome (PCOS) can be included in the study if in the opinion of the investigator they do not have any other clinically significant abnormality (eg, metabolic syndrome or elevated lipids

### 5.3 Exclusion Criteria

Subjects who fulfill any of the criteria listed below will be ineligible to participate in the study.

#### 5.3.1 General Exclusion Criteria

1. Presence of any clinically significant physical examination finding, vital signs measurement, or abnormal laboratory value;
2. Presence of a beard or other facial hair that could interfere with the study assessments;
3. Participated in another clinical trial or received an investigational product within 3 months prior to screening;
4. History of excessive or suspected abuse of alcohol (based on the clinical judgment of the investigator), recreational drugs, and/or drugs of abuse, eg, club drugs, cocaine, ecstasy/MDMA (3,4-methylenedioxymethamphetamine), heroin, inhalants, marijuana, methamphetamine, phencyclidine (PCP), prescription medications, anabolic steroids, etc., which, in the opinion of the investigator, would interfere with participation in the study;
5. Use of prohibited or restricted prior or concomitant medications (see Section 5.3.5).

#### 5.3.2 Female Specific Exclusion Criteria

1. Are pregnant;
2. Are at a high risk for becoming pregnant or likely to become pregnant during treatment;
3. Are breast-feeding or considering breast-feeding during the course of the study;
4. Have a known history of PCOS with another clinically significant abnormality (eg, metabolic syndrome or elevated lipids);

5. Are unable or unwilling to maintain compliance with birth control measures.

### 5.3.3 Concurrent Disease Exclusion Criteria

1. Have a known history or presence of any clinically significant unstable medical condition(s) which, in the opinion of the investigator, may pose a risk to the safety of the subject including any previous history of gastrointestinal disease (eg, Crohn's disease, ulcerative colitis, pancreatitis, etc) or a history of bone disease;
2. Have any skin disease or other condition that may interfere with the evaluation of recalcitrant nodular acne;
3. Have a lifetime history of major depressive, manic, hypomanic, or mixed episodes, or are receiving lithium;
4. Have reported past or current psychotic symptoms (assessed with the Psychosis Module of the Structured Clinical Interview DSM-IV clinical trials [SCID-CT]);
5. Reported of any suicidal behavior (including attempts, interrupted attempts, aborted attempts, or other preparatory behaviors) within the past year or serious suicidal ideation (defined as any suicidal ideation of Type 4 or 5 on the Columbia Suicide Severity Rating Scale [C-SSRS]) in the past year;
6. Have a known history or suspected carcinoma;
7. Have a known history of liver or kidney disorders (hepatic and renal insufficiency);
8. Have a known history or current pseudotumor cerebri (benign intracranial hypertension).

### 5.3.4 Hypersensitivity/Allergy Exclusion Criteria

1. Hypersensitivity or idiosyncratic reaction to isotretinoin, vitamin A and/or any other drug substances with similar activity;
2. Allergy to soybeans, soybean oil, or any other ingredients in the study.

### 5.3.5 Prohibited Medication Before and/or During the Study

#### 5.3.5.1 Medication Prohibited Before or During the ATP

1. Tegison (etretinate) or Soriatane (acitretin): any previous treatment at any time;
2. Vitamin A supplements: Subjects with known daily intake of >1000 pg for males and >800 pg females will be excluded from the study. During the course of the study, subjects are to limit their intake of vitamin A supplements to <1000 pg for males and <800 pg for females;
3. Systemic corticosteroids (within 30 days prior to Baseline). Very low dose inhaled corticosteroids are allowed;
4. Topical corticosteroids applied to the face within 7 days prior to Baseline;
5. Spironolactone and its derivatives used within 30 days prior to Baseline and during both phases of the study;

6. Phenytoin;
7. Antimicrobials:
    a. Oral antibiotics or topical antibiotics (on the face) within 14 days of Baseline and throughout the ATP.
        i. Short courses of antibiotics may be administered during the ATP for purposes other than acne therapy at the discretion of the investigator.
        ii. (Note: some antibiotics, eg, rifampin and penicillin derivatives, have the potential to decrease the effectiveness of birth control pills. This needs to be taken into consideration by the study investigator).
    b. Tetracyclines: Isotretinoin use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Therefore, concomitant treatment with tetracyclines should be avoided.
        i. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. An ophthalmologist should evaluate subjects for papilledema if these suggestive symptoms develop.
        ii. Also, if these symptoms occur or if the investigator and/or ophthalmologist judge this to be appropriate, tell the subjects to discontinue isotretinoin immediately and refer them to a neurologist for further evaluation and care. Such cases should be reported to the designated Medical Monitor.
8. Any other medication used to treat acne, including over-the-counter and prescription topical therapies and systemic medications. These should not be used within 14 days of Baseline or during either phase of the study;
9. Microdose progesterone preparations for contraception in female subjects. The subject must stop using the microdose preparations and switch to an iPLEDGE acceptable form of oral contraceptive under the direction of her primary physician or gynecologist;

    Note: Female subjects using combined oral contraceptives are eligible for the study and will be allowed to continue using them if they have been on the contraceptive for at least the last 3 months prior to Screening and there has been no improvement in the status of their acne.

10. Medications that may decrease the effectiveness of birth control products when used concomitantly with hormonal contraceptives. The study investigators are advised to EXERCISE CAUTION and consult the package insert of the medications prior to administering them to females of childbearing ability. Drugs that are known to decrease the effectiveness of hormonal contraceptives should not be used concomitantly with the study medication;
11. Any other medication that the investigator judges to have an adverse effect when given with isotretinoin or any medication disallowed in the protocol;

12. Any physical therapies (ie, PDT, laser, lights, peels, microdermabrasion, etc) within 1 month prior to Baseline and during both phases of the study;
13. Over-the-counter products that may worsen acne, eg, products that contain high iodine levels, such as kelp;
14. Herbal products (St. John's Wort, red clover, milk thistle, etc).

#### 5.3.5.2 Medication Prohibited During the PTP

1. Tegison (etretinate) or Soriatane (acitretin);
2. Vitamin A supplements: Subjects with known daily intake of >1000 pg for males and >800 pg females will be excluded from the study during both phases of the study (29 months). During the course of the study, subjects are to limit their intake of vitamin A supplements to <1000 pg for males and <800 pg for females;
3. Systemic corticosteroids or topical corticosteroids applied to face. Very low dose inhaled corticosteroids are allowed;
4. Over-the-counter products that may worsen acne, eg, products that contain high iodine levels, such as kelp.
5. Note: During the PTP, any antibiotic therapy given for intercurrent illness (ie, upper respiratory infection, urinary tract infection) must be documented with the name of the antibiotic, dose, and duration of treatment.
6. Note: the contraception methods used by female subjects of childbearing potential during the PTP should be documented.

### 5.4 Discontinuation of Treatment

In accordance with legal requirements and International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) guidelines, every subject has the right to refuse further participation in this study at any time and without providing reasons. A subject's participation is to be terminated immediately upon his/her request. The Investigator should seek to obtain the reason and record this on the electronic case report form (eCRF), whenever possible.

If, at the time of refusal, a study product has already been administered, the subject should be advised on follow-up safety investigations.

In the case of significant disease or intolerance of study medication, the decision to stop treatment for a given subject can be made by the investigator alone. If such a treatment discontinuation occurs, the investigator will notify the sponsor and provide medical justification.

A subject may be withdrawn from the study at any time at the discretion of the investigator for medical reasons and/or due to non-adherence to the treatment scheme and other duties stipulated in the study protocol. The reasons for early termination are to be fully documented on the eCRF.

In addition, the sponsor reserves the right to end or suspend the study at any time (see Section 9.2).

If a subject withdraws from the study, all efforts will be made to complete the final evaluation procedures at the time of termination if possible. Protocol-specified withdrawal procedures are the same as those to be performed at the End of Treatment (EOT) visit (if withdrawal occurs during the ATP) or at the End of Study (EOS) visit (if withdrawal occurs during the PTP).

Subjects discontinued for an AE will be monitored until the AE is resolved, a reasonable explanation is provided for the event, or the subject is referred to his/her own primary medical doctor. The specific AE in question will be recorded on the appropriate CRF.

Subjects who prematurely discontinue the study will not be replaced.

## 6.0 STUDY TREATMENTS

### 6.1 Investigational Products and Controls

Absorica® (isotretinoin) will be provided in a capsule form for oral consumption. The capsules should be swallowed whole. In this study, Absorica® will be taken twice daily for a total daily dose of approximately 1 mg/kg/day, to attain a target cumulative dose of 120 to 150 mg/kg during the active 20-week course of therapy.

During the first 4 weeks of the treatment period, subjects will receive doses of 0.5 mg/kg/day divided into 2 daily doses of 0.25 mg/kg. During the remaining 16 weeks of the study, subjects will receive approximately 1 mg/kg/day divided into 2 daily doses of approximately 0.5 mg/kg/day. The subject will be instructed to take each dose without food, specifically, at least 2 hours after the previous meal or at least 1 hour before the next meal.

The dose will be delivered as 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, or 40 mg capsules, with the number of capsules dependent upon the body mass of the subject as shown in Table 6-1. To decrease the risk of esophageal irritation, subjects will be instructed to swallow the capsules with a full glass of liquid.

### 6.2 Dosing Justification and Regimen

The dosage range recommended in the Absorica® (isotretinoin) package insert is 0.5 mg/kg/day to 1 mg/kg/day given in 2 divided doses without regard to meals for 15 to 20 weeks.

The dosing regimen selected for this study is consistent with approved labeling for isotretinoin in both the US and Canada. The overall goal is to standardize the dosing and assure a uniform cumulative drug exposure in order to uniformly assess any emergent adverse events (AEs), yet to remain within the dosages approved in the labeling.

In trials comparing 0.1, 0.5, and 1 mg/kg/day, it was found that all dosages provided initial clearing of disease, but that retreatment was more likely to be necessary if lower dosages were used. Therefore subjects will be titrated up to a maximum dose of 1 mg/kg. Higher dosages (ie,

2 mg/kg/day) are recommended only in adults with particularly recalcitrant acne and should not be given in this study.

[redacted]

[redacted]

### 6.3 Packaging and Labeling

[redacted]

Study medication will be stored in a locked cabinet at the study site in accordance with the site procedures for storage of investigational products. Study medication should be stored at controlled room temperature (68°F to 77°F or 20°C to 25°C) with excursions permitted to 59°F to 86°F (15°C to 30°C).

Subjects who qualify for study entry will receive a 30-day supply of study medication at each visit during the ATP beginning at Baseline (Visit 2).

## 6.4 Assignment to Treatment

### 6.4.1 Randomization

Not applicable. All subjects will receive treatment according to the same regimen. There will be no randomization or stratification.

### 6.4.2 Blinding

Not applicable. This is an open-label study.

## 6.5 Prior and Concomitant Therapy

All medications, including OTC drugs, taken within 30 days prior to the start of the study will be recorded at Screening. Thereafter, a record of all medications and supportive therapy taken during the course of the study will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be recorded on the subject's eCRF.

Restricted or prohibited medications and treatments are listed in the Exclusion Criteria (Section 5.3.5).

## 6.6 Contraception

Female subjects of childbearing potential must follow the iPLEDGE requirements regarding contraception. Both a primary and a secondary form must be used while in the ATP phase of the study.

| Primary forms | Secondary forms |
|---|---|
| • Tubal sterilization<br>• Partner's vasectomy<br>• Intrauterine device<br>• Hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring) | *Barrier forms (always used with spermicide)*<br>• Diaphragm<br>• Cervical cap<br>*Barrier forms (used with or without spermicide)*<br>• Male latex condom<br>*Others:*<br>• Vaginal sponge (contains spermicide) |

Unacceptable Forms of Contraception include:

- Progesterone-only "mini-pills," eg:
    - Ortho Micronor® Tablets
- IUD Progesterone T
- Female condoms
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield* (* A cervical shield shold not be confused with a cervical cap, which is an effective secondary form of contraception. See page 20 of iPLEDGE).

Some medications used concomitantly with hormonal contraceptives may decrease the effectiveness of the birth control products. The study investigators are advised to EXERCISE CAUTION and consult the package insert of the medications prior to administering them to females of childbearing ability. Drugs that are known to decrease the effectiveness of hormonal contraceptives should not be used concomitantly with the study medication.

### 6.7 Allowed Medications

The following medications, preparations, and treatments are acceptable to use during the study:

- Simple analgesics or cold preparations (ie, Tylenol) taken for headache, cough and/or common cold, etc;
- Low dose inhaled corticosteroids;
- Lip balms, skin moisturizers and mild skin cleansers, nasal lubricant gel, natural tears;
- Medicines prescribed under a doctor's care that are taken on a regular basis for at least 3 months and at doses that have not changed more than 25% in the last 60 days, unless disallowed in the study protocol;
- Medications that are prescribed by primary care providers to the subject during the course of the trial. If the subject is prescribed a medication for a medical condition during the trial, the investigator is to evaluate the medication and medical condition to ensure the subject can safely continue to participate in the trial.

### 6.8 Disallowed Medications

Subjects who had used the following medications at any time are to be excluded from the study:

- Tegison® (etretinate).

- Soriatane® (acitretin).

Use of the following medications, preparations, and treatments is disallowed as noted below.

- 30 days prior to Baseline and throughout the study (both ATP and PTP):
  - Systemic corticosteroids.
  - Spironolactone and its derivatives.
- 14 days prior to Baseline and throughout the study:
  - Antibiotics. Tetracyclines are prohibited during the study. Short courses of other antibiotics can be administered during the study at the discretion of the investigator. [Note: Per Section 5.3.5, antibiotics and tetracyclines are prohibited during ATP but allowed during the PTP]
  - Phenytoin (eg, Dilantin);
  - Any other medication used to treat acne (both ATP and PTP).
- 7 days prior to Baseline:
  - Topical corticosteroids.
- During the study (both ATP and PTP):
  - Vitamin A supplements > 1000 µg for males and >800 µg for females (ATP and PTP)
  - Herbal products (St. John's Wort, red clover, milk thistle, etc).
  - Microdose progesterone preparations (see Section 6.6).
  - Oral contraceptives with approved anti-acne indication for nodular acne (eg, Ortho Tri-Cyclen®, Yaz®, and Estrostep®). Females using oral contraceptives with anti-acne activity are allowed to continue using them if they had been on the contraceptive for at least the last 3 months prior to screening and there was no improvement in the status of their acne. For subjects who remain on an oral contraceptive during the PTP, it is preferred that they continue on the same medication as in the ATP; if any change is required, it is preferred that the medications named above be avoided. All medications taken should be documented.

### 6.9 Adherence to Dosing Regimen

Records of study product used and dosages administered will be kept during the study. Subjects will be issued a diary in which they are to record the date and time they take each dose of study medication. Subjects will be instructed to bring the diary, all unused study medication, and all packaging from used study medication to each post-Baseline study visit in the ATP. Use of study drug will be reconciled, and the number of missed doses as noted in the diary will be recorded.

Subjects who are consistently noncompliant (ie, **<75%** of required doses) will be counseled and may be withdrawn from the study.

After reconciliation of study medication use, all study medication packaging and unused study medication will be returned to the subject.

## 7.0 VISIT SCHEDULE AND ASSESSMENTS

### 7.1 Study Procedures

The visit schedule and assessments are summarized in Table 1-1.

### 7.2 Study Visits and Assessments

#### 7.2.1 Visit 1 – Screening (Visit 1, Day –30 to Day 1)

Screening procedures should be completed no more than 30 days prior to the baseline visit (Day 1), except when required to meet the contraception and pregnancy test requirements for women of childbearing potential. The following screening procedures are to be performed:

- Review study information with the subject or with his/her legal guardian and obtain written informed consent, including photographic consent.
- Count the acne nodules on the subject's face.
- Review inclusion and exclusion criteria with the subject to determine the subject's eligibility.
- Collect medical history and demographic information.
- Review and record prior medication (used within the previous 30 days) and concomitant medication (medications currently used).
- Perform a physical examination, including height and weight.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position.
- For females of childbearing potential, obtain the date of the subject's last menstrual period and information on her contraceptive use.
- Perform a serum pregnancy test in all female subjects of childbearing potential (a urine pregnancy test may also be performed if the site holds the appropriate certifications). Counsel all female subjects on the use of at least 2 approved form(s) of contraception and provide pregnancy prevention information. Register for the iPLEDGE program. Female subjects of childbearing potential must comply with the mandatory contraception and pregnancy testing requirements of the iPLEDGE program (see also Section 6.6 and Section 7.4.5).
- Obtain blood samples for a laboratory profile including hematology, fasting clinical chemistry, and a fasting lipid profile.

- If subject meets the inclusion/exclusion criteria, schedule Visit 2. Instruct the subject on fasting prior to the visit.

### 7.2.2 Active Treatment Period – Visit 2 – Baseline (Day 1)

**Reminder:** Before receiving study medication, female subjects of childbearing potential must have completed a 30-day waiting period during which they use two effective forms of contraception; had a negative screening pregnancy test at the end of the 30-day period, and then a second, confirmatory negative pregnancy test conducted at least 19 days after the first pregnancy and during the first 5 days of the menstrual period. If subjects do not have regular menstrual periods, eg, due to contraception choice, then they must still have two negative pregnancy tests.

- Review inclusion and exclusion criteria to ensure that the subject is qualified for study participation.
- Review and record medication used since Screening and update medical history.
- Obtain blood samples for a laboratory profile including fasting clinical chemistry and a fasting lipid profile.
- For females of childbearing potential, obtain the date of the subject's last menstrual period and information on her contraceptive use.
- Perform a UPT for females of childbearing potential. Ensure that female subjects of childbearing potential meet the iPLEDGE requirements.
- Take baseline photographs of the subject's face (see Section 7.2.13).
- Have the subject complete the acne-QOL questionnaire.
- Complete the baseline lesion count and IGA.
- Record any AEs.
- Prescribe the 30-day supply of study medication.
- Schedule the next study visit. Remind subject not to eat prior to the visit and to bring any unused capsules and used packaging with them to the visit.

### 7.2.3 Active Treatment Period – Visit 3 (Week 2 ± 4 days)

- Reconcile the medication use and record the number of missed doses as indicated in the diary
- Review any concomitant medication used since the previous study visit.
- Review laboratory test results from the Visit 2 assessment.
- Query the subject regarding consumption of food around the time of dosing.

- Obtain blood samples for a laboratory profile including fasting clinical chemistry, and a fasting lipid profile.
- Perform a serum pregnancy test for females of childbearing potential. Ensure that female subjects of childbearing potential are following the iPLEDGE requirements.
- Record any AEs.
- Schedule the next study visit. Remind subject not to eat prior to the visit and to bring any unused capsules and used capsule packaging with them to the visit.

### 7.2.4 Active Treatment Period – Visits 4, 5, 6, and 7 (Weeks 4, 8, 12, and 16 ± 4 days)

- Reconcile the medication use and record the number of missed doses per the diary.
- Review any concomitant medication used since the previous study visit.
- Query the subject regarding consumption of food around the time of dosing and remind subject that dosing should be at least one hour before a meal or at least two hours after a meal.
- Obtain blood samples for a laboratory profile including fasting clinical chemistry and a fasting lipid profile.
- Perform a serum pregnancy test for females of childbearing potential. Ensure that female subjects of childbearing potential are using 2 approved method(s) of contraception.
- Have the subject complete the acne-QOL questionnaire.
- Complete the lesion count and IGA.
- Record any AEs.
- Obtain photographs of the subject's face.
- Prescribe a 30-day supply of study medication.
- Schedule the next study visit. Remind subject not to eat prior to the visit and to bring any unused capsules and used capsule packaging with them to the visit.

### 7.2.5 Active Treatment Period – Visit 8/End of Treatment Visit (Week 20 ± 4 days)

- Reconcile the medication use and record the number of missed doses per the diary.
- Review any concomitant medication used since the previous study visit.
- Query the subject regarding consumption of food around the time of dosing.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position and record weight.
- Obtain blood samples for a laboratory profile including fasting clinical chemistry, and a fasting lipid profile.
- Perform a serum pregnancy test for females of childbearing potential. Ensure that female subjects of childbearing potential are using 2 approved method(s) of contraception.

- Take EOT photographs of the subject's face (see Section 7.2.13).
- Have the subject complete the acne-QOL questionnaire.
- Complete the lesion count and IGA.
- Record any AEs.
- Schedule the next study visit.

### 7.2.6 Post Treatment Period – Visit 9 (Week 24 ± 4 days 4 weeks post treatment safety visit)

- Review any concomitant medications that affect acne (including all antibiotics) used since the previous study visit.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) with subject in a seated position and record weight.
- Obtain blood samples for a laboratory profile including fasting clinical chemistry and a fasting lipid profile.
- Perform a serum pregnancy test for females of childbearing potential and counsel on any continued birth control needs (iPLEDGE does not require birth control to continue for more than 30 days post last dose)
- Record any AEs.
- Schedule the next study visit.

### 7.2.7 Post Treatment Period – Visits 10 to 14 (Weeks 32, 46, 72, 98, and 124 ± 2 Weeks)

- Review any concomitant medications that affect acne (including all antibiotics) used since the previous study visit.
- Take photographs as specified for the site (see Section 7.2.13).
- Have the subject complete the acne-QOL questionnaire.
- Complete the lesion count and IGA.
- Record any SAEs related to study medication.
- At Visits 10, 11, 12, and 13, schedule the next study visit.
- If an acne flare occurs during the PTP, the subject is to notify the site and report for an unscheduled visit at which acne severity will be assessed and treatment options will be considered. If the subject refuses to return, the investigator is to attempt to determine the acne severity and type of retreatment through discussion with the subject and with the subject's prescribing physician.

### 7.2.8 Early Termination

If a subject withdraws from the study during the ATP and prior to Week 20/Visit 8, the subject is to return to the site. All EOT procedures should be performed, including the administration of

the acne-QOL questionnaire, the lesion count, the IGA, and a pregnancy test (if applicable). The photography should be performed using the method assigned to the site.

If a subject withdraws from the study during the PTP and prior to Visit 14, the subject is to return to the site for an early termination visit. All EOS procedures should be performed, including the acne QOL, lesion count, the IGA, and photography. Subjects who require an additional course of isotretinoin therapy are to be discontinued after the EOS procedures are performed.

### 7.2.10 Quality of Life Assessment

Beginning at Baseline, subjects will be asked to complete an acne-QOL at each visit, except Visit 3 and 9.

### 7.2.11 Lesion Count

Lesion counts will be performed at every visit, except Visits 3 and 9. Qualified trained medical practitioners will make counts of nodules and inflammatory lesions (papules and pustules) on the face and record the counts separately. Where possible, the same individual will perform all lesion counts for a subject.

### 7.2.12 Investigator's Global Assessment (IGA)

The IGA is a static assessment that is independent of the baseline score. A qualified trained medical practitioner will perform the IGA at every visit beginning at Visit 2, except Visits 3 and 9. The evaluator should make the assessments without referring to the baseline value. It is preferred that the same evaluator performs all assessments for a subject to the extent possible. The grading system for the IGA is shown in Table 7-1.

**Table 7-1 Investigator's Global Assessment**

| Grade | Description | Acne Disease Status |
|---|---|---|
| 0 | Clear | No papules/ pustules present; no nodules present; no comedones present; residual hyperpigmentation and/or erythema may be present; acne scars may be present. |
| 1 | Almost clear | A few scattered small papules/pustules may be present; no nodules present; a few scattered comedones may be present. |
| 2 | Mild | Some papules/pustules present; no nodules present; some comedones may be present. |
| 3 | Moderate | Many papules/pustules present; up to 2 nodules may be present; some or many comedones may be present. |
| 4 | Severe | Several papules/pustules and many nodules (>2) present, some to several comedones may be present. |
| 5 | Very severe | Highly inflammatory acne with several papules/pustules covering the face with several nodules present; some to several comedones may be present. |

Source: Tan et al[16]

### 7.2.13 Photography

Subjects will consent to photography prior to enrollment in the study; consent for photography is mandatory for participation in the study. Facial photographs will be taken at every visit except Visits 3 and 9.

At selected sites, photographs of the face will be recorded using the photography equipment supplied by the photography vendor. At all other sites, photographs will be taken using on-site equipment.

### 7.3 Assessment of Pharmacokinetics (not applicable)

No pharmacokinetics determinations will be assessed during this study.

### 7.4 Assessment of Safety

#### 7.4.1 Adverse Events

##### 7.4.1.1 General Considerations

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

In this study, information about all AEs, whether volunteered by the subject, discovered by the investigator through questioning, or detected through physical examination, laboratory tests, or other means, will be collected and recorded on the Adverse Event page of the CRF. Abnormal laboratory values or test results will be recorded as AEs only if (1) they induce clinical signs or symptoms, (2) require therapy, or (3) are considered by the investigator to be of clinical significance. Prior medical conditions/diseases will be considered AEs only if they worsen after the start of protocol-specified study procedures. For each AE, the AE record will include start and stop dates, severity (mild, moderate, or severe), relationship to the study treatment (definite, probably, possibly, unlikely, or not related), actions taken, and outcome.

Adverse events are collected beginning after the first administration of study medication. Adverse events occurring before starting study treatment but after signing the informed consent form are to be recorded on the Medical History page of the CRF. In the PTP, information will be collected only for serious adverse events (SAE) related to study medication.

##### 7.4.1.2 Severity of Adverse Events

The investigator is to classify the severity (intensity) of an AE according to the definitions outlined in Table 7-2.

**Table 7-2 Terms for Defining Adverse Event Severity**

| Severity | Definition |
|---|---|
| Mild | The event is readily tolerable - no interference with the state of the subject |
| Moderate | The discomfort is enough to cause interference with usual activities - uncomfortable event |
| Severe | There is significant interference with the state of the subject and the subject's usual activities |

The maximum intensity of an AE (mild, moderate, or severe) will be assessed taking into account the possible range of intensity of the symptom(s).

#### 7.4.1.3 Relationship of an Adverse Event to Study Treatment

An adverse reaction (AR) is any AE caused by a drug. A suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE, ie, there is evidence to suggest a causal relationship between the drug and the AE. Thus, an AR is a SAR for which there is reason to conclude that the drug caused the event.

The determination of the causal relationship between the drug and the AE will be based in part on the investigator's assessment of the relationship of the AE to the investigational treatment. An AE considered by the investigator to be probably or definitely related to the study treatment is to be considered an AR, and an AE considered by the investigator to be possibly related to the study treatment is an SAR, but not an AR. An AE considered by the investigator unlikely to be related, or to be unrelated, to the study treatment, is not an SAR, unless the sponsor determines otherwise based on other evidence.

The relationship between an AE and the study medication is determined by the Investigator on the basis of his or her clinical judgment and the definitions outlined in Table 7-3.

**Table 7-3 Terms for Defining Relationship of Adverse Event to Study Product**

| Association | Definition |
|---|---|
| Not related | There is no temporal relationship to trial medication administration (too early, too late or trial medication not administered), or there is a reasonable causal relationship between another treatment, concurrent disease or circumstance and the AE. |
| Unlikely related | A clinical event, including laboratory test abnormality (if applicable), with an improbable time sequence to product administration and in which other drugs, chemicals for underlying disease provide plausible explanations. |
| Possibly related | There is a reasonable causal relationship between the trial medication and the AE. The reaction follows a reasonable temporal sequence from drug administration. Dechallenge information is lacking or unclear. |
| Probably related | There is a reasonable causal relationship between the study medication and the AE. The reaction follows a reasonable temporal sequence from drug administration and cannot be reasonably explained by the known characteristics of the subject's clinical state, by toxic or environmental agents, or by concomitant medications. The event responds to dechallenge. Rechallenge is not required. |
| Definitely Related | There is a reasonable causal relationship between the clinical trial therapy and the AE. The event responds to withdrawal of the trial medication and recurs with rechallenge when clinically feasible. The reaction is associated with a foreseeable event of the administered drug. |

#### 7.4.1.4 Serious Adverse Event

An AE or SAR is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death;
- is life-threatening;
- inpatient hospitalization or a prolongation of an existing hospitalization;
- a persistent or significant disability/incapacity;
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. An AE or SAR is considered "life-threatening" if, in the view of either the investigator or the sponsor, its occurrence places the subject or patient at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe

form, might have caused death. As with the definition of "serious," the determination of whether an AE is life-threatening can be based on the opinion of either the investigator or sponsor. Thus, if either believes that an AE meets the definition of life-threatening, it must be considered life-threatening, and therefore serious, for reporting purposes. An AE can be severe without being serious.

Serious adverse events (SAEs) which occur during clinical trials are subject to legal reporting requirements. Therefore, in this study, the occurrence of any SAE from the time of informed consent until 4 weeks after the last subject visit will be reported to the Sponsor within 24 hours of its having come to the attention of the Investigator. The SAE will be recorded using the designated Serious Adverse Event Report form, which includes all legally required data (and must include an assessment of whether there is a reasonable possibility that the drug caused the event). The SAE will also be reported to the responsible Institutional Review Board (IRB) according to that IRB's reporting requirements. Study endpoints that are SAEs (eg, mortality) are to be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (eg, death from anaphylaxis); in that case, the Investigator must immediately report the event to the Sponsor.

Clinical safety personnel will be available for SAE reporting on a 24-hour basis. Reports will be reviewed during normal business hours. Investigator instructions for reporting Serious Adverse Events are provided in Section 13.2.

#### 7.4.1.5 Unexpected Adverse Events

An AE or SAR is considered "unexpected" if it is not listed in the product labeling or Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected" as used in this definition, also refers to AEs or SARs that are mentioned in the investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

### 7.4.2 Serious Adverse Event Reporting by Investigator

Any SAE, whether or not deemed drug related or expected, must be reported immediately to the sponsor as soon as it becomes known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of an SAE. The investigator will document such events in the best possible detail on the SAE Report Form to be transmitted to the sponsor.

### 7.4.3 Expedited Reporting by the Sponsor

The IRB will be informed of Suspected Unexpected Serious Adverse Reactions (SUSARS) according to local requirements. All investigators participating in the trial will also be notified of unexpected SAEs.

### 7.4.4 Safety Laboratory Assessments

Laboratory testing will be done as specified in Table 1-1. Subjects will be instructed to fast for at least 2 hours prior to Visits 1 through 7 and Visit 9. Blood will be collected for routine safety laboratory tests (hematology and serum biochemistry) at Visit 1 (Screening) and Visit 8 (Week 20/EOT) or at early termination from the study and for serum biochemistry at all other visits (Visits 2 through 7 and Visit 9) during the ATP. Clinical laboratory specimens will be analyzed by a licensed and accredited central laboratory facility according to the laboratory's standard operating procedures. The following tests will be performed:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelet count;
- Fasting serum chemistry: glucose (non-fasting), blood urea nitrogen (BUN), creatinine, cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transferase (GGT), total bilirubin;
- Fasting lipid panel: cholesterol, triglycerides, high density lipoproteins (HDLs), low density lipoproteins (LDLs);
- Pregnancy testing: all female subjects of childbearing potential will undergo serum pregnancy testing at all visits during the ATP beginning with Screening and continuing through Visit 9 (Week 24, 4 weeks after EOT) or early termination as specified in Section 7.4.5.

The investigator may collect additional blood samples to repeat any laboratory test that is abnormal post-dosing, is within normal limits at Baseline, and is considered clinically significant. Abnormal laboratory results at EOT may require additional collection of samples on an "as needed" basis until: a) the values return to the baseline value, b) the values are within normal limits, c) the values are clinically stable, or d) the investigator determines that further follow-up is unnecessary. The investigator will record the date and time of all additional samples collected. If the investigator establishes a clear explanation for the laboratory abnormality, he or she will record this explanation in the CRFs.

### 7.4.5 Pregnancy Testing

Female subjects of childbearing potential will undergo a pregnancy test (urine or serum) at Visit 1 (Screening) before any study-specific procedures are performed. If the pregnancy test is positive, the subject will not be permitted to enroll in the study. Female subjects who test negative for pregnancy must use two approved methods of contraception for a mandatory one-month waiting period. These subjects must have a second pregnancy test conducted at least 19 days after the initial pregnancy test; and, if enrolled into the ATP, throughout the ATP and for 1 month after their last dose as specified in iPLEDGE.

Should a subject become pregnant during the study, treatment must be discontinued. Subjects should continue with non-treatment and/or follow-up visits.

All pregnancies should be immediately reported to the medical monitor and followed through to resolution (ie, delivery, miscarriage, or abortion). The report should be submitted within the same timelines as an SAE (within 24 hours of knowledge), although a pregnancy per se is not considered an SAE.

### 7.4.6 Vital Signs

Measurements of vital signs, including blood pressure, pulse rate, and respiratory rate, will be taken at Screening and at the end of treatment visit with the subject seated.

### 7.4.7 Physical Examination

At Visit 1 (Screening) and at the end of treatment visit, the investigator or designee will complete an abbreviated general physical examination including measurements of weight and height.

## 7.5 Appropriateness of Measurements

Lesion counts and IGA are the standardized and most widely accepted methods for evaluating efficacy in studies of acne. The safety determinations, including liver function tests and a lipid panel, address safety concerns with the use of isotretinoin. As isotretinoin is known to cause birth defects, female subjects of childbearing potential are required to undergo pregnancy testing at every visit.

# 8.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE STATISTICAL AND ANALYTICAL PLANS

## 8.1 General Considerations for Data Analysis

The methodology presented below is a summary of the more detailed analysis plan that will be presented in the Statistical Analysis Plan (SAP). The SAP will be finalized before the database is locked. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

It is planned that the data from all centers that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

All statistical analysis will be performed using SAS statistical software.

## 8.2 Sample Size and Power Considerations

The sample size of 200 subjects was selected to provide adequate estimates of probable events in the population. Estimates of the endpoints of interest will be calculated with 95% 2-sided confidence intervals wherever possible. No statistical hypothesis tests are planned.

### 8.3 Analysis Populations

Efficacy will be investigated in 2 populations. The PP population will be defined as including all randomized subjects who are at least 75% compliant with their assigned treatment, have no major study protocol violations, have a Week 20 count of total nodular lesions, and do not use any disallowed medications during the 20 weeks of treatment. The ITT population will be defined as including all subjects who are randomized and receive study medication.

The safety population will comprise all subjects who have consumed at least 1 dose of study medication, including those for whom dosing information is unknown.

### 8.4 Analysis of Efficacy

Lesion count and IGA data will be summarized as descriptive statistics. No inferential tests will be performed.

### 8.5 Analysis of Safety

Adverse events will be presented in data listings and summarized by frequency and severity. Laboratory and vital sign data will be presented in data listings. Abnormal laboratory findings will be presented. The analysis of safety will be described in the SAP.

### 8.6 Quality of Life Analysis

The primary endpoint during the ATP will be the change from Baseline to the end of the ATP (Week 20/Visit 8) in the acne-specific quality of life questionnaire (acne-QOL) in those subjects who complete the 20-week ATP and are at least 75% compliant with the dosage regimen.

## 9.0 CHANGES IN THE PLANNED STUDY

### 9.1 Protocol Amendments

With the exception of administrative changes, any changes or additions to this clinical study protocol require a written protocol amendment that must be approved by the sponsor and the investigators before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study, require additional approval by the Institutional Review Board (IRB) for each study center.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or the sponsor in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons, the sponsor should be notified and the IRB should be informed according to their reporting requirements.

### 9.2 Termination or Suspension of the Study

The sponsor reserves the right to terminate or suspend the study at any time. In case of premature termination or suspension of the study, the project manager will promptly inform the investigators, regulatory authorities, and IRBs about the premature termination or suspension, including the reason for it. In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

## 10.0 DATA HANDLING AND RECORD KEEPING

### 10.1 Recording of Data

#### 10.1.1 General Principles

Study data will be collected as required by the protocol through a combination of electronic and paper-based tools. Procedures for data collection and data management will be designed to ensure that each data element may be traced with a high level of confidence from its originator or recorder to its representation in the study database and then to its place in the analysis and report of study results. At each stage in the data collection process, the data must be accessible for review by authorized parties, such as the study monitor, a designated auditor, and a Food and Drug Administration (FDA) inspector. Once recorded, the study data must be protected from unauthorized modification or deletion, and all authorized modifications and deletions must be securely linked in the permanent record with their author, time of change, and reason for change (ie, the audit trail must be maintained). The primary data collection tool for the study is a CRF designed specifically for the study.

#### 10.1.2 Source Documents

Source documents comprise all the original source records, either paper-based or electronic, of the study data. Source data may be written or typed by authorized and qualified study personnel directly from clinical observation, or they may be generated, on paper or electronically, by an automated measurement device or system of devices. In order to ensure the integrity of the study data, procedures must be in place to allow every element of the study data to be traced to its source. In some instances, the eCRF is itself the source document. It is the responsibility of the study monitor to verify that data recorded on the eCRF are an accurate transcription of the source data. The source documents are typically the property of the study site itself, and may include data that are not relevant to the study database and are therefore not subject to study-related quality control procedures. Source documents may include, for example, subject medical records, enrollment logs, laboratory reports, electrocardiograms, subject diaries, drug dispensing and collection records, drug accounting logs, study notes, and study-related correspondence.

#### 10.1.3 Case Report Forms

The primary data collection tool for the study is an electronic case report form (eCRF) designed specifically for the study. In some instances, the eCRF is itself the source document. For each

subject enrolled in the study, an eCRF will be completed by the study coordinator and signed by the investigator or his/her designate.

The investigator will be responsible for ensuring the accuracy of all data entered in the eCRFs. All eCRFs are to be completed in a timely manner.

Errors occurring in the eCRFs will be queried. Queries raised by data reviewers must be addressed by site personnel.

On request, the investigator will provide the sponsor with additional data relating to the study, or copies of relevant source records, duly anonymized (ie, subject's name is redacted).

### 10.2 Data Management Plan

Procedures and specifications for management of the study data will be described in detail in a separate Data Management Plan to be approved by the sponsor. This document will include definitions of the data sets and variables based on applicable CDISC standards (www.cdisc.org), definitions of programmed edit checks, references to prevailing standard operating procedures (SOPs), and descriptions of the following procedures:

- Procedures for data management review and query processing;
- Procedures for assignment and medical review of standard preferred-term coding of adverse events, concomitant medications, or other terminology collected in the study data;
- Procedures for electronic data transfer of study data elements from external non-CRF data sources, such as analytical, imaging, or other specialized laboratory services;
- Procedures for certification and closure of the database.

#### 10.2.1 Retention of Documents

The site will maintain an Investigator Site File/Binder with essential documentation. The file/binder will contain tabbed sections for study documents, including, but not limited to, the following: study personnel identification and responsibilities signature list, subject screening records, protocol and amendments or administrative changes, , study staff curricula vitae, IRB documentation, an approved sample ICF, drug accountability records, correspondence, lab accreditations, and lab normal values. The site must keep this file/binder current and available for review by the Sponsor or its designee, the IRB, and the Food and Drug Administration (FDA).

To comply with FDA/ICH requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the sponsor, or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms received from the sponsor.

Such documentation is subject to inspection by the sponsor or its agents, the FDA and/or other regulatory agencies.

## 11.0 QUALITY CONTROL AND QUALITY ASSURANCE

### 11.1 Direct Access to Source Documents

As specified in the investigator's agreement, the investigator agrees to allow the sponsor's (or designated CRO's) study monitor, quality assurance auditor, health authority inspector, and/or the IRB's inspector direct access to all relevant source documents, and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Such source documents include any documentation, either on paper or electronic, from which study data elements have been derived. Computer systems and devices, which are used to produce electronic source documents, must conform to the principles described in relevant regulatory guidances (eg, the FDA's Draft Guidance [December 2010] on Electronic Source Documentation in Clinical Investigations, and references therein), which are designed to ensure the security and integrity of those data sources.

### 11.2 Monitoring Procedures

During the study, the study monitor may visit the study site periodically to verify the completeness of subject records, the accuracy of entries on the CRFs, and the progress of enrollment; to ensure adherence to the protocol and to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines; and to confirm that study product is stored, dispensed, and accounted for according to legal requirements. Key study personnel must be available to assist the study monitor during these visits. Monitoring visits will be conducted in accordance with the clinical monitoring plan.

The data required by the protocol must be recorded on the appropriate eCRFs. The eCRFs and any source documents will be available to the study monitor who will monitor the data as specified in the data monitoring plan. The eCRFs and source data must also be available for audit by the sponsor and regulatory authorities at any time.

No information in these records about the identity of the subjects will leave the study site. Specific data verification procedures may be described in a study-specific monitoring plan. Original source documents and other study related materials will be maintained in archive at the study site or designated off-site archive for at least 5 years after the study close-out monitoring visit or as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval).

### 11.3 Auditing Procedures

In addition to the routine monitoring procedures, the study site may be audited in depth for study quality assurance by the sponsor, an external auditor on behalf of the sponsor, an IRB, and/or regulatory authorities. This audit may include a review of all source documents, drug records, and eCRFs at some or all of the study sites used in the study. The investigator is to notify the Sponsor/CRO immediately of any inspection by regulatory authorities or IRBs.

## 12.0 ETHICS

### 12.1 Ethical Conduct of the Study

This study must be carried out in compliance with the protocol and the applicable laws and regulatory requirements of the FDA. The study must be conducted in accordance with the ethical principles originating from the Declaration of Helsinki and amendments and the ICH-GCP guidelines.

### 12.2 Institutional Review Board (IRB)

This protocol, the proposed informed consent form, and other information for subjects must be reviewed and approved by an IRB, before the start of the trial, in compliance with local regulations. This committee must also approve any amendments to the protocol, other than administrative ones, before initiation of the amendment procedures.

### 12.3 Subject Information and Consent

Before participation in the study, each subject or his/her parent or guardian is required to provide written consent to participate in the study. Subjects under the age of 18 years are required to sign an assent form. As the study presents different risks with regard to pregnancy for men and women, the informed consent forms are different for male and female subjects. No study-specific procedures will be performed before a subject's informed consent/assent is obtained. Subjects will provide HIPAA authorization to participate in the study.

### 12.4 Disclosure and Confidentiality

#### 12.4.1 Confidentiality of Study Documentation

By signing the protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the study sponsor (ie, protocols, Investigators' Brochures, eCRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the Investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

### 12.4.2 Privacy of Individual Health Information

The investigator will undertake to protect the privacy of all individually identifiable health information except as specifically authorized by each individual subject through the written informed consent. The Informed Consent document will include a request of the subject's consent to release the collected data for research purposes in such a way that the individual's identity remains masked. While all data records will be identified by the corresponding subject number, the identity of the subject will be held in confidential source documents at the study site. All study personnel with access to this information are legally bound not to disclose it.

## 13.0 EMERGENCY PROCEDURES

### 13.1 Emergency Unblinding

This is an open-label study.

### 13.2 Reporting of Serious Adverse Events and Pregnancies

### 13.2.1 Contact Person(s) and Number(s)

Serious adverse events and pregnancies must be reported immediately (ie, not later than 24 hours after first knowledge) to the designated person, who then forwards the information to the Medical Monitor and the sponsor.

The telephone and fax numbers of the study personnel to be contacted in the event of an SAE are listed in the investigator site files provided to each site.

### 13.2.2 Reporting Procedures

**Serious Adverse Events**

For each SAE, the Investigator will complete a Serious Adverse Event Report Form and assess the relationship of each SAE to study treatment. The completed form(s) should be sent electronically to the CRO within 24 hours of first knowledge of the SAE.

Follow-up reports regarding the status of the SAE and the subject's subsequent course should be submitted until the SAE has subsided, the condition stabilized (in the case of persistent impairment), the subject receives alternative therapy, or the subject dies. The form and fax confirmation will be retained. Contacts for reporting SAEs and other safety concerns are provided in the Investigator site files provided to each site.

## 14.0 PUBLICATION POLICY

The data collected during this study are the property of Ranbaxy Laboratories, Inc. Individual center results or the results of the study may not be published at any time without written permission from Ranbaxy.

## 15.0 REFERENCE LIST

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