Protocol No. DMVT-505-3003
IQVIA Biotech Study No. GZA92798

A LONG-TERM, OPEN-LABEL, EXTENSION STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TAPINAROF CREAM, 1% FOR THE TREATMENT OF PLAQUE PSORIASIS IN ADULTS

Statistical Analysis Plan Amendment 2, version 3.0

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Revision History

Date	Reason for update	Section Updated
21FEB2020	Original Version 1.0	NA
15JUN2020	Amendment 1 Version 2.0	• Section 11.4 Study Medication and Exposure Compliance o Updated the calculation for average grams of study drug administered per doses administered. • Section 11.7 Efficacy endpoint o Added PASI-50, PASI-75, PASI-90 analysis • Added Section 11.12 Additional Analyses – COVID-19 • Removed Section 11.11.5 Physical Examination • Section 12 Change from the protocol and planned analyses o Clarified additional analyses added due to COVID-19
16NOV2020	Amendment 2 Version 3.0	• Section 8 Handling of missing data o Clarified Visit 1 date instead of first dose date will be used in imputation rule of AE dates • Section 10.4 Baseline and change from baseline o Updated baseline definition • Section 11.1 Subject disposition o Updated definition of number of days in the study • Section 11.4 Study medication exposure and compliance o Updated exposure parameter definition • Section 11.7 Efficacy endpoints o Updated definition of time to achieving PGA score of 0, duration of treatment episodes, duration of treatment successes • Section 11.11.1 Adverse events o Updated treatment-emergent AE definition o Added a listing for AEs resolved prior to the Visit 1 date o Added additional TEAE summaries

Table of Contents

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADaM	Analysis dataset model
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body mass index
BSA	Body surface area
COVID-19	Coronavirus Disease 2019
DLQI	Dermatology Life Quality Index
eCRF	Electronic Case Report Form
EOS	End of study
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LTS	Local Tolerability Scale
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed Cases
ODS	Output Delivery System
PASI	Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
PT	Preferred Term
QoL	Quality of Life
RTF	Rich-text-formatted
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study data tabulation model
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization – Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP), based on the study Protocol Amendment 1 (Version 1.0) dated December 16, 2019, provides additional details concerning the statistical analyses outlined in the protocol and will reflect all changes to the protocol from all amendments. This plan will not repeat all the definitions given in the protocol but will provide further details of the summaries and analyses planned therein.

2. STUDY OBJECTIVES

The objectives of this study are as follows:

- To evaluate the safety and tolerability of tapinarof cream, 1% in adults with plaque psoriasis
- To describe the efficacy of tapinarof cream, 1% over an extended period of time in adults with plaque psoriasis
- To describe the effect of tapinarof cream, 1% on psoriasis symptom severity and the associated impact on daily activities and attitudes in adults with plaque psoriasis

3. STUDY DESIGN

This is a long-term, open-label, multicenter, study to evaluate the safety and efficacy of topical tapinarof cream, 1% in adults with plaque psoriasis. Subjects in this study completed treatment with tapinarof or vehicle in 1 of 2 pivotal Phase 3 efficacy and safety studies (Study DMVT-505-3001 or Study DMVT-505-3002). The study consists of up to 40 weeks of treatment and a 4-week safety follow-up period.

At the completion of the Week-12 Visit of the pivotal study (Visit 1, Baseline [Day 1] in this study), eligibility of the subjects opting to enroll in this extension study is confirmed. Study visits during the treatment period occur every 4 weeks (±3 days). A Phone Call is performed at Week 2 (Day 15). Unscheduled visits occur, as needed. Subjects who withdraw from the study before Week 40 return to the study center for an Early Termination Visit. The total duration of study participation is approximately 44 weeks.

At the start of the study, subjects entering with a PGA ≥ 1 receive treatment with tapinarof cream, 1% until they achieve a PGA score of 0, at which time treatment is discontinued and subjects are monitored for durability of response. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed.

Subjects entering with a PGA of 0 will have treatment discontinued and they will be monitored for durability of response. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment is re-initiated and continued until a PGA of 0 is observed.

The pattern of treatment, suspension and re-treatment is continued until the Week 40 visit.

Study drug dispensed to subjects during the clinic visits is applied once daily to all affected areas, including newly appearing lesions and lesions that improve during the study. Subjects

apply sufficient study drug to cover completely each lesion with a thin layer of study drug and record the time of study drug application in a daily diary provided by the study site. Subjects may treat fingernails, toenails, palms, soles, and scalp lesions with study drug; however, improvement of psoriasis is not assessed in these areas.

Safety assessments include AEs, local (application site) tolerability, clinical laboratory tests, vital signs, physical examinations, and investigator-assessed LTS. Efficacy assessments include a 5-point static PGA (0-4 scale), %BSA affected, the PASI, and subject-reported DLQI.

A subject is considered to have completed the study when he/she completes all required procedures/visits for the 40-week (Visit 11) treatment period. The end of the study is defined as when the last active subject has completed the Follow-up Visit.

4. HARDWARE AND SOFTWARE

Statistical analysis will be performed following IQVIA Biotech standard operating procedures and on the IQVIA Biotech computer network. All statistical analysis will be performed using SAS Version 9.4 or greater with program code prepared specifically for the project by qualified IQVIA Biotech statisticians and SAS programmers.

The SAS programs will generate rich-text-formatted (RTF) output with the "RTF" extension using the SAS (ODS). Datasets will be created and taken as input to validated SAS programs to generate the report-ready tables, listings, and figures. Each output display will show the names of the data sets and SAS program used to produce it.

5. DATABASE CLOSURE

After completion of all data review procedures, validation of the project database, and approval of the data review document by the study sponsor, the clinical database will be closed. Any change to the clinical database after this time will require written authorization, with explanation, by the Sponsor and the Biostatistician.

6. SAMPLE SIZE DETERMINATION

The sample size of this study is based on the ICH E1 guideline on extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. An estimated 850 subjects who complete Study DMVT-505-3001 or Study DMVT-505-3002 will be enrolled in this study at approximately 100 to 120 study sites in the US and Canada. A high discontinuation rate is anticipated in this long-term extension study. Approximately 300 subjects are expected to complete the study (40 weeks of treatment).

7. ANALYSIS POPULATIONS

Intent-To-Treat (ITT) Analysis Set: includes all subjects enrolled into the study. All subjects who signed the informed consent will have enrolled in the study. All efficacy and safety analysis will be performed over ITT analysis set.

Subjects will be analyzed overall and by the original treatment assigned in pivotal studies (DMVT-505-3001 and DMVT-505-3002). This will be referred to below as DB (double-blind) treatment group.

8. HANDLING OF MISSING DATA

Efficacy endpoints will be summarized by visit using observed cases (OC) and last observation carried forward (LOCF) methods as appropriate. Baseline values will not be carried forward.

Imputation of Start and End Dates of Adverse Event (AE)

To calculate duration of Adverse Events, the following rules will be used where applicable to impute partial or completely missing start dates or end dates:

- If only the day is missing for a start date, the 1st of the month will be imputed. If the new estimated date falls before the Visit 1 date, while the known month and year match the month and year of the Visit 1 date, the date of Visit 1 will be used as the new estimated date.

- If only the day is missing for an end date, the last day of the month will be imputed. If the new estimated date falls after the date of last study visit, the date of last study visit will be used as the new estimated date.

- If both the day and the month are missing for a start date or end date, no imputation will be used, and the duration will not be calculated.

- If the start date or end date is completely missing, duration will not be calculated.

For AEs ongoing at the end of pivotal studies, duration will be computed using the DMVT-505-3003 visit 1 date as the AE start date.

If relationship of AE to treatment is missing, the event will be conservatively considered as being related to study drug. Missing AE severity will be imputed to the highest severity level (most severe). Through the data cleaning process, all attempts will be made to avoid missing values for relationship and severity.

9. INTERIM ANALYSIS

A data-cut will be made at the time of preparation of the marketing application to present interim results, Guidance ICH-E1A suggests that at such time, 100 tapinarof subjects should have completed 52 weeks of treatment and 300 tapinarof subjects should have completed 26 weeks of treatment exposure combined over the pivotal studies and the current study. The final analysis will be conducted after study completion (e.g., the last participant's last visit).

10.DATA CONVENTIONS FOR ANALYSIS

10.1 General Statistical Principles

The study efficacy and safety results will be summarized descriptively. There will be no statistical testing.

All observed and derived variables (e.g., change from baseline, percentage change from baseline, and response status) that are summarized will be presented in by-subject listings. Unless otherwise noted, the data will be sorted by DB treatment group and subject number and then by date within subject number.

For categorical parameters, the number and percentage of subjects in each category will be presented. The denominators for percentages will be the number of subjects appropriate for the purpose. For continuous parameters, descriptive statistics will include number of subjects, mean, standard deviation (SD), median, minimum, and maximum.

10.2 Pooling of Study Sites

No by-site summaries are planned.

10.3 Study Day

Day 1 is the date of Visit 1 (which is also the last visit in pivotal studies). Study day is calculated relative to the date of Day 1.

10.4 Baseline and Change from Baseline

For PGA score and % BSA Affected, baseline is defined as the assessment collected at Visit 1 in the extension study. If Visit 1 measurement is missing, the baseline value will be considered as missing.

For all other efficacy and safety assessments (PASI, DLQI, vital signs and laboratory results), baseline is defined as the last available measurement on or after Week 12 visit date in pivotal studies and on or before the Visit 1 visit date in the extension study. If there's no measurement available during this time period, the baseline value will be considered as missing. Change from baseline is the post-baseline value minus baseline unless otherwise specified. Percent change from baseline is (Change from baseline / baseline) * 100%.

10.5 Analysis Visit Window

Efficacy and safety endpoints will be summarized according to the nominal visit as assigned by the investigator except for assessments collected on early termination visits. Early termination visit will be re-numbered to the last nominal visit number + 1. For example, if a subject attended Visit 1, Visit 2 (Week 4), Visit 3 (Week 8) and then early terminated, the early termination visit will be re-numbered and analyzed as Visit 4 (Week 12).

Unscheduled visits will not be re-numbered and will not be included in table summaries. They will only be listed.

10.6 Multiple Comparisons

Does not apply.

11.STATISTICAL EVALUATION

11.1 Subject Disposition

Subjects who enroll (ITT population), who apply any study medication, who complete the study and who withdraw from the study (together with the reasons for withdrawal) will be summarized by counts and percentages. Subjects for whom drug was permanently withdrawn or interrupted due to AE, PGA score or other reasons will also be summarized by counts and percentages, over the entire study and by visit.

Counts will be presented overall and by DB treatment group. Listings by subject will document enrollment and disposition.

The number of days in the study, defined as date of study completion / discontinuation (or date of last visit if the study completion/discontinuation date is missing) minus date of Visit 1 plus 1, will be summarized using descriptive statistics overall and by DB treatment group. A figure with Kaplan-Meier curves will also be generated to illustrate this information.

11.2 Protocol Deviation

Protocol deviations will be listed by subject. Protocol deviation categories will be summarized overall and by DB treatment group.

11.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized overall and by DB treatment group over the ITT population. The following demographic (as collected in pivotal studies) and baseline variables will be included:

- Age (years)
- Gender
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Baseline PGA – current study and pivotal study
- Baseline PASI score – current study and pivotal study
- Baseline %BSA Affected – current study and pivotal study

11.4 Study Medication Exposure and Compliance

Subjects will be characterized by a series of treatment episodes as defined in Section 11.7. These treatment episode definitions are based on attainment of specified PGA values.

The following exposure and compliance parameters will be summarized descriptively over the overall span of treatment episodes, overall and by DB treatment group:

- Total expected number of days exposed, calculated as the sum of number of days over all treatment episodes.
- Total number of doses administered within treatment episodes, calculated from the subject dose diary and summed over all treatment episodes. If a subject does not return diary or returns the diary with missing dosing record, the number of doses taken during that period is assumed to be 0.
- Grams (g) of study drug administered within treatment episodes, total will be summed over all treatment episodes. Drug administered is calculated as the summation of the difference between dispensed weight and returned weight for all returned tubes. Unreturned tubes will be assumed unused and will be included as 0 gram in amount drug used calculation. Average grams of study drug administered per expected day exposed and per doses administered will be calculated as the total grams / total number of days exposure (or total number of doses administered). Subjects with more than 1-day exposure but had no diaries returned will not have average grams per doses administered reported.
- Percent compliance will be calculated as the total number of doses administered within treatment episodes over the total expected number of days exposed.
- Subject compliance, defined as ≥80% compliance over the entire duration of study. If the percentage of study medication compliance is unknown, the subject is assumed to be non-compliant with study medication.

In addition, the following exposure parameters will be summarized descriptively for the entire study (regardless of PGA status) overall and by DB treatment group:

- Total number of doses administered, calculated from the subject dose diary and in-clinic dosing. If a subject does not return diary or returns the diary with missing dosing record, the number of doses taken during that period is assumed to be 0.
- Grams (g) of study drug administered. Drug administered is calculated as the summation of the difference between dispensed weight and returned weight for all returned tubes. Unreturned tubes will be assumed unused and will be included as 0 gram in amount drug used calculation. Average grams of study drug administered per doses administered will

be calculated as the total grams / total number of doses administered. Subjects that had no diaries returned will not have average grams per doses administered reported.

11.5 Prior and Concomitant Medications

Prior (within 30 days before Visit 1 and with stop dates prior to Visit 1) medications would have been captured in the pivotal studies and will not be presented in this study.

Concomitant (ongoing or with stop dates on or after Visit 1) medications will be listed by subject. If the medication is ongoing or the stop year is missing, the medication will be considered as received for the entire duration of the study. Concomitant medications that are ongoing as of the end of the pivotal studies will be displayed in a separate listing.

Medications will be coded using WHO-DD terminology. Concomitant medications will be summarized by WHO-DD Anatomical-Therapeutic-Chemical (ATC) classification and preferred term (PT), overall and by DB treatment group.

11.6 Medical History and Concurrent Procedures

Medical history (including previous and ongoing medical conditions) collected during the pivotal studies will be coded using MedDRA and listed by subject. Medical history will be summarized by system organ class (SOC) and PT, overall and by DB treatment group.

11.7 Efficacy Endpoints

Efficacy endpoints are as follows:

For subjects entering the study with a PGA score of clear (0):

- Proportion of subjects who experience PGA ≥ 2 at least 1 time during the study.
- Proportion of subjects who never experience PGA ≥ 2 throughout the study.
- Time to first worsening (PGA ≥ 2), defined as days from date of Visit 1 date to the date of first occurrence of PGA ≥ 2. Subjects who never experience PGA ≥ 2 throughout the study will be censored at the date of their last PGA assessment.

For subjects entering the study with a PGA score ≥ 1:

- Proportions of subjects who achieve PGA = 0 at least 1 time during the study
- [redacted]
- [redacted]

For subjects entering the study with a PGA score ≥ 2:

- Proportions of subjects who achieved PGA = 0 or 1 at least 1 time during the study.
- Proportions of subjects who never achieve PGA = 0 or 1 throughout the study.

The following endpoints will be summarized over subjects in ITT population:

- Duration (days) of treatment episodes, defined as time (days) from the date of each PGA ≥2 (or PGA ≥ 1 for the first episode) to 1 day before each subsequent treatment success (PGA = 0). The date of the last PGA assessment will be used as the end date for episodes ongoing at the end of the study.

[redacted]

- [redacted] ≥ [redacted]

[redacted]

- [redacted]
- [redacted] change and percent change from baseline in %BSA affected by visit (OC and LOCF).
- [redacted] change and percent change from baseline in PASI score by visit (OC and LOCF)
- [redacted] ≥ [redacted]
- [redacted] ≥ [redacted]
- [redacted] ≥ [redacted]

11.8 Efficacy Analyses

All efficacy parameters will be summarized over the ITT analysis set overall and by DB treatment group. Summaries of efficacy endpoints by visit will be performed using OC and LOCF methods.

Time to event parameters, such as the time from treatment success to subsequent worsening (PGA ≥ 2) or duration of treatment episode, will be summarized by the Kaplan-Meier product limit method using OC. Median time to event will be estimated. If the median time is not determined, other percentiles will be estimated.

The remaining efficacy endpoints will be summarized descriptively as follows: continuous data will include the mean, SD, minimum, maximum, median, and number of observations; descriptive summary statistics for categorical data will include frequency counts and percentages.

For the following efficacy outcomes:

1. Proportions of subjects who achieve PGA = 0 at least 1 time during the study (for subjects entering the study with a PGA score ≥ 1):
2. Proportions of subjects who experienced PGA ≥ 2 at least 1 time during the study (for subjects entering the study with a PGA score = 0):
3. PGA scores at Week 40 (LOCF)
4. BSA [redacted] change from baseline to Week 40 (LOCF)
5. PASI [redacted] change from baseline to Week 40 (LOCF)

subgroup analyses will be generated for the following groupings:

- Baseline PGA
- Age (<65 and >= 65 years old)
- Sex
- Race (White, Other)
- Baseline % BSA affected – (<10%, ≥10%)
- Duration of disease (<5 years, 5-10 years, >10 years)
- Country (USA and Canada)

11.9 Health-related Quality of Life

The DLQI was assessed at 4-week intervals to measure the impact of tapinarof cream, 1% on quality of life in adults with plaque psoriasis.:

The DLQI is a 10-item PRO measure that assesses the extent to which the skin condition has affected the subject's quality of life over the past week, including 6 domains (daily activities, personal relationships, symptoms and feelings, leisure, work/school, and treatment). The total score (0-30) is the sum of 10 questions with each ranging from 0 to 3. The scoring of each question (for Question 7 see below) is as follows:

Response	Score
Very much	3
A lot	2
A little	1
Not at all	0
Not relevant	0
Question unanswered	0

Question 7: Over the last week, has your skin prevented you from working or studying?	Question 7A: If "No", over the last week how much has your skin been a problem at work or studying?	Score
Yes	Any response	3
No	A lot	2
No	A little	1
No	Not at all	0
Not relevant	Any response	0

If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30. If two or more questions are left unanswered the total DLQI score is missing.

When summarizing the domain scores, if a domain contains two questions and the answer to one of the questions is missing, that domain will be scored as the answer to the non-missing question. If all the answers to questions in a domain are missing, the domain will not be scored.

DLQI total score and subscores on DLQI domains and their changes from baseline as well as percent change from baseline values will be summarized descriptively. The following table identifies the DLQI domains and the questions that are summed in order to calculate them.

Domain	Questions
Symptoms and feelings	1 and 2
Daily activities	3 and 4
Leisure	5 and 6
Work and school	7
Personal relationships	8 and 9
Treatment	10

11.10 Patient Satisfaction Questionnaire

[redacted].

11.11 Safety Analysis

All safety parameters will be summarized over the ITT population of all enrolled subjects, overall and by DB treatment group.

11.11.1 Adverse Events

AE terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary. All AEs reported in current study are considered as treatment-emergent AE (TEAE) except for those AEs ongoing at the end of pivotal studies but resolved prior to the Visit 1 date in the extension study.

All TEAEs will be listed by subject, detailing the verbatim term given by the investigator, the preferred term (PT), system organ class (SOC), onset date and time, end date and time, ongoing at the end of pivotal studies (Y/N), duration (days), CTCAE grade, outcome, relationship to study drug, action taken with study drug, other action taken to treat the event, AE of special interest (Y/N), seriousness and criteria for seriousness.

AEs resolved prior to the Visit 1 date, Serious TEAEs (STEAEs), TEAEs leading to study discontinuation and TEAEs related to study drug will also be listed separately. The following adverse events of special interest (AESIs) will be identified and listed separately: contact dermatitis, folliculitis, and headache.

The number and percent of subjects with TEAEs will be summarized as incidence rates of:

- Any TEAE
- Any TEAE Excluding Those Ongoing at the end of the Pivotal Studies
- Any TEAE Ongoing at the end of the Pivotal Studies
- Any treatment-emergent AESIs
- Any treatment-emergent AESIs Excluding Those Ongoing at the end of the Pivotal Studies
- Any treatment-emergent AESIs Ongoing at the end of the Pivotal Studies
- Any treatment-related TEAE
- Any TEAE leading to study drug discontinuation
- Any TEAE leading to study discontinuation
- Any serious TEAE

- Death
- Treatment-related Serious TEAE
- Serious TEAE leading to study drug discontinuation
- Serious TEAE leading to study discontinuation
- TEAE (COVID-19)

Individual PTs will be summarized by SOC in alphabetical order and PT in descending order of frequency for the following subsets and subgroupings:

- All TEAEs
- All TEAEs by maximum CTCAE grade
- All TEAEs by maximum causality (not related, related) to the study drug
- All TEAEs Excluding Those Ongoing at the End of the Pivotal Studies
- All TEAEs ongoing at the end of the pivotal studies
- All treatment-related TEAEs
- All TEAEs leading to study discontinuation
- All TEAEs leading to study drug discontinuation
- All serious TEAEs

All TEAEs and all serious TEAEs will also be summarized by SOC (alphabetical order) and PT (descending order) for the following subgroups:

- Age (<65 and >= 65 years old)
- Sex
- Race (White, Other)

Furthermore, TEAEs will be categorized by day of onset among the following 4 categories:

- ≤12 weeks
- >12 to ≤24 weeks
- > 24 to ≤40 weeks
- >40 weeks.

For each of these categories, TEAEs will be summarized by SOC in alphabetical order and PT in descending order of frequency. TEAEs ongoing at the end of the pivotal studies will be considered in the first category (i.e. day of onset ≤ 12 weeks).

At each level of summarization, a subject will be counted once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar

manner. For summaries of relationship to study drug, a subject will be classified according to the closest relationship. For summaries of TEAE CTCAE grade, a subject will be classified according to the worst grade.

For AESIs, summarization will be more extensive, reflecting the more detailed information collected. Information summarized will include number of events per subject, earliest onset day, duration (in days), causality, grade and seriousness of AESIs, outcome, actions taken, assorted physical characteristics of the AESIs, and demographic/baseline characteristics and PGA status of the subjects experiencing them. Each type of AESI will be summarized separately. If a subject has more than one treatment-emergent occurrence of an AESI, the subject's maximum duration, highest levels of causality and seriousness, maximum grade and generally the most extreme level of each characteristic will be summarized. If an AESI was ongoing at end of study (EOS), it will not be included in the duration summary. AESIs ongoing at the end of pivotal studies will also be included in the summary.

A Kaplan-Meier figure will be generated for each AESI of time to first event for events starting during the study. Subjects not experiencing the AESI will be censored at the date of study completion or discontinuation. AESIs ongoing at the end of pivotal studies will not be included.

11.11.2 Local Tolerability Scale (LTS)

LTS scores will be summarized by visit and DB treatment group for subject overall assessment (scores from 0=None to 4=Strong/Severe) and Investigator overall assessment (scores from 0=No irritation to 4=Very Severe) separately. .LTS scores at the sensitive areas will be summarized by visit, area and DB treatment group for Investigator overall assessment as well as listed in a by-subject and by anatomical site listing.

11.11.3 Clinical Laboratory Testing

All clinical laboratory (hematology, clinical chemistry, urinalysis) values will be listed by DB treatment group and subject. The reference normal ranges and reference range indicators (e.g. high, low, normal etc.) will be supplied by the central laboratory and displayed in the data listings. For the purpose of shift table summaries, the central lab reported reference range indicators will be classified as low, normal and high accordingly based on the table below.

Reference Range Indicator in Shift Tables	Reference Range Indicator Reported by Central Lab
Low	Low, Low Level 1 Alert, Low Lever 2 Alert
Normal	Normal
High	High, High Level 1 Alert, High Level 2 Alert

Values outside the normal range will be flagged. Change from baseline in abnormality status will be summarized using shift tables. For urinalysis, only lab tests with numeric results reported are included in shift tables. Separate listings will identify subjects with markedly abnormal values. For quantitative measures, observed values and change from baseline in clinical laboratory values will be summarized descriptively by visit, overall and by DB treatment group.

11.11.4 Vital Signs

Observed values and change from baseline in vital sign parameters (systolic and diastolic blood pressure [SBP, DBP], pulse rate, and body temperature) will be summarized descriptively by visit, overall and by DB treatment group. Vital sign values will be classified as normal, low, high, based on reference ranges as per Table below. Subjects with markedly abnormal changes will be flagged in listing and tabulated separately.

	Absolute Values			**Change (Absolute) from Baseline**	
	Low	Normal	High	Abnormal Change	Markedly Abnormal Change
SBP	<90 mmHg	90-140 mmHg	>140 mmHg	≥ 20 mmHg	≥ 40 mmHg
DBP	<50 mmHg	50-90 mmHg	>90 mmHg	≥ 10 mmHg	≥ 20 mmHg
Pulse	<50 bpm	50-100 bpm	>100 bpm	≥ 10 bpm	≥ 30 bpm

11.12 Additional Analyses – COVID-19

In order to describe the impact of COVID-19 on current study, the following disposition events will be summarized in the tables separately:

- Subjects discontinued from the study as a result of a positive COVID-19 diagnosis.
- Subjects discontinued from the study due to other reasons related to COVID-19. This is excluding COVID-19 diagnosis but may include reasons such as site closure, travel restrictions, fear of infection, etc.
- Subjects with study visits altered (including modified in-clinic visit, virtual and phone visits) and missed due to COVID-19

COVID-19 related protocol deviations will be summarized separately. The impact of COVID-19 (including protocol deviation, visit alteration, treatment/study discontinuation and diagnosis of COVID-19) will also be flagged at subject-level in a data listing. Subject profile will be used to compile all COVID-19 related information for affected subjects.

Also, all COVID-19 related symptoms and confirmed cases occur during the study will be reported as AEs and included in the summaries.

12.CHANGES FROM THE PROTOCOL AND PLANNED ANALYSES

The protocol states “mean scores from the LTS will be summarized by visit”. The SAP modified it to “LTS scores will be summarized by visit”.

According to the protocol, "Responses for each question of the Patient Satisfaction Questionnaire will be summarized by visit." However, the PSQ was assessed only at the Week 40 or at ET visits. Consequently, it will be summarized overall rather than by visit.

Any additional statistical analyses to handle modifications to study conduct and/or missing data due to the COVID-19 pandemic have been documented in Section 11.12 above in this SAP and will be finalized prior to database lock.

13.HEADINGS

Each page of the analysis will show the sponsor's name, the investigational product, and the protocol number. Report tables will be embedded in the MS Word report document from SAS program output without change. The footer of each table will show the name of the SAS program module which generated it, the names of all data sets providing input data in the program and the date and time the table was generated.

14.ARCHIVING AND RETENTION OF DOCUMENTS

After finalization of the analysis, the following will be archived at IQVIA Biotech and/or with the study sponsor:

- SAP and any amendments
- All SAS code used in the project for statistical analysis, report tables generation, and analysis data set creation
- Tables, listings and figures as included in the clinical study report
- SAS study data tabulation model (SDTM) and analysis dataset model (ADaM) datasets

15.OUTLINE OF PROPOSED TABLES, LISTINGS AND FIGURES