Official Title: STEVIE—A SINGLE-ARM, OPEN-LABEL, PHASE II, MULTICENTER STUDY TO ASSESS THE SAFETY OF VISMODEGIB (GDC-0449) IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC BASAL CELL CARCINOMA

NCT Number: NCT01367665

Document Date: Statistical Analysis Plan: 14-Sep-15

Output Specification

Study title:	**STEVIE - A single-arm, open-label, phase II, multicenter study to assess the safety of Vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma**
Protocol number:	**MO25616/ NCT01367665**

Author: [redacted]

SPA: [redacted]

Biostatistician: [redacted]

General Considerations

Disease Status

Outputs are split by disease status, unless otherwise specified. This means that outputs should be summarized by the following cohorts: Locally Advanced BCC and Metastatic BCC (disease status is collected on the CRF).

Definition of First Dose

Earliest date of drug dispensed when the amount of drug taken is greater than 0 and the doses are not missed on this date, in case the dose is missed on this date then take the date of the day after the last dose missed amongst the first group of missed doses. A drug is considered 'taken' if there is a non-zero, non-missing 'Taken' record in the subject's Drug Accountability CRF page.

Definition of Last Dose

Latest date of drug returned where amount taken is greater than 0 and the doses are not missed on this date, in case the dose is missed on this date then take the date of the day before the first dose missed amongst the last group of missed doses.

Reference Date (Study Day 1)

Where derivations refer to reference date please use date of first dose as there is no randomization date available.

Baseline

Baseline is considered as the most recent time prior to treatment. If a record is collected on the day of first dose, then that record is considered as baseline.

Age

Age is collected on the CRF, but the Age used is the calculated Age. This is defined from the patient's birth date and the patient's consent to the study (both captured on the CRF).

Visit Windowing

Visits are windowed in this study, and all outputs should use the analysis windowed visit as

opposed to the collected visit unless otherwise specified. The definition of windowing is stored in the DAP M3 (Visit Windowing Spec tab).

Unscheduled Visits

Visits will be windowed, so any unscheduled visits will be assigned to a visit based upon the collection date. The information about visit windowing is discussed in the Visit Windowing section.

Deaths

Date of Death can be found on the following pages of the eCRF:

- End of study treatment
- Death page
- Adverse event – end date of AE with grade 5 severity or AE outcome is death
- Serious adverse event – SAE outcome end date; date of death
- End of follow-up page
- Survival follow-up page
- ECOG performance status – status is Grade 5: death

Take the date as defined on the Death page if the sources have different dates, as well as the reason defined on the Death page.

Measurable/Non-Measurable Disease

A patient is considered to have measurable disease if they have a target lesion at baseline according to the tumour CRF page. This is a 'Yes'/'No' box, but it is not a mandatory field, so some subjects can have a 'missing' result, and such subjects are not considered to have either measurable or non-measurable disease. Measurable/non-measurable disease information is also collected on the CRF disease history page as a tick box, but this information will not be used as the target lesion assessment page is felt to be more accurate.

Histologically Confirmed Disease

A patient is considered to have histologically confirmed disease if they have no record in their PDMS data that suggests that they did not have histologically confirmed disease. Science considered that the protocol deviation of 'non-histologically confirmed disease' stored in PDMS was more accurate than the tick box on the CRF, as the CRF page is the histological status at the time of collection, but the PDMS system collects information more often. As mentioned, histological disease confirmation information is also collected on the CRF as a tick box, but this information will not be used in the outputs. The reason for using

the PDMS system is that the information on whether a patient had histologically confirmed disease contained in the PDMS system is directly assessed and reviewed by Clinical Science.

Data Cut Derivation

The input data will have a data-cut applied prior to being stored in a VAD, but will not be stored anywhere as ‘cut’ raw data. The definition of the data cut is stored in the DAP M3 (Data Cut Spec tab).

Populations:

All Subject Population (AP)

The "All Subjects" population is any patient in the study for which their disease status (Locally Advanced or Metastatic, based on the disease history CRF page) is known.

Enrolled Population (ENR)

The "Enrolled" population is any patient in the study with a recorded Disease status and for whom actual treatment is not recorded as Screen Failure.

Safety Population (SE)

The "Safety" population is any patient who took at least one dose of study medication according to the dose accountability CRF page. A patient was considered dosed if they had a ‘number of capsules taken’ record according to the exposure CRF page that wasn’t zero or missing.

Protocol Populations

Protocol Version 4 Population (PV4ANY)

The "Protocol Version 4" population is any patient who consented to Protocol version 4 (or higher) at any point in the study. The protocol version is taken from the Protocol CRF page.

Last Protocol Consented to: 1 or 2 (PV1N2)

The "Last Protocol Consented to: 1 or 2" population includes any patient who consented to Protocol version 1 or 2 as their most recent version. The protocol version is taken from the Protocol CRF page.

Last Protocol Consented to: 3 or higher (PV3PLUS)

The "Last Protocol Consented to: 3 or higher" population includes any patient who consented to Protocol version 3 or higher as their most recent version. The protocol version is taken from the Protocol CRF page.

Last Protocol Consented to: 5 or higher (PV5PLUS)

The "Last Protocol Consented to: 5 or higher" population includes any patient who consented to Protocol version 5 or higher as their most recent version. The protocol version is taken from the Protocol CRF page.

Protocol Version 3 (+) 12 Month Follow-up Completion (PV3COMP)

The "Protocol Version 3 (+) 12 Month Follow-up Completion" population includes any patient who consented to Protocol version 3 or higher at any time (according to the Protocol CRF page) and completed the study according the their 12 month FU record from the DS CRF.

Efficacy Populations

Outputs will be repeated by given populations combinations as defined in the LoPO and in this document.

Intent-to-Treat Population (IT)

The "Intent-to-Treat" population is any patient who took at least one dose of study medication according to the dose accountability CRF page. A patient was considered dosed if they had a ‘number of capsules taken’ record according to the exposure CRF page that wasn’t zero or missing.

mBCC Protocol 4 (+) Population (MBCC)

The "mBCC Protocol 4 (+)" population was any patient who had all of the following criteria:
- Consented to Protocol version 4 or Higher as a first version according to the CRF.
- Had a metastatic disease status according to the CRF.

8 Weekly Tumour Assessment Population (TU8)

The "8 Weekly Tumour Assessment" population was any patient who had all of the following criteria:
- Tumour assessments every 8 weeks (+/- 10 days of the expected date of the next assessment) since consenting Protocol version 4. Protocol signing date taken from CRF page defining consent. Tumour assessment visits taken from the CRF page defining tumour information.
- Did not miss ANY tumour assessments since consenting to Protocol version 4.

The population also includes all patients from the MBCC population, regardless of whether they meet the aforementioned criteria.

Symptomatic Patients (SYMP)

Clinical Science manually reviewed all Metastatic patients to determine which subjects had symptoms of the disease. This was completed by looking at numerous data including medical history information. The “Symptomatic Patients” population were the patients who were considered symptomatic by Clinical Science Review.

Non-Symptomatic Patients (NSYMP)

Clinical Science manually reviewed all Metastatic patients to determine which subjects had symptoms of the disease. This was completed by looking at numerous data including medical history information. The “Non-Symptomatic Patients” population were the patients who were considered non-symptomatic by Clinical Science Review.

Measurable Disease Patients

Some outputs require the subset of Measurable Disease Patients only. This subset would consist of patients with a target measurable disease at Baseline. This is identified within the titles and footnotes of the relevant outputs.

Histologically Confirmed Disease Patients

Some outputs require the subset of Histologically Confirmed Disease Patients only. This subset would consist of patients with histologically confirmed disease as per PDMS. This is identified within the titles and footnotes of the relevant outputs.

Measurable and Histologically Confirmed Disease Patients

Some outputs require the subset of Measurable and Histologically Confirmed Disease Patients. This subset would consist of patients with a target measurable disease at Baseline as well as histologically confirmed disease as per PDMS. This is identified within the titles and footnotes of the relevant outputs.

Other Populations

Potentially Reversible AE Population (PV3DSC6M)

The “Potentially Reversible AE” population is defined as the patients who consented to protocol version 3 or higher at any point during the study (from the CRF), excluding:
- Patients who discontinued treatment within 6 months of the cut (discontinue date from the CRF).
- Patients who were lost to follow-up within 6 months of treatment discontinuation (both from CRF).
- Patients who died within 6 months of treatment discontinuation (both from CRF).

The reason for inclusion of only patients who consented to version 3 or higher is due to the fact that patients consenting to earlier versions were only subject to a 1 month follow up period.

Output Specifications: Demography Outputs

Patient Populations:

	Locally Advanced (N=xxxx)	Metastatic (N=xxxx)	Total (N=xxxx)
Number of patients screened	xxxx	xx	xxxx
Screening failure	x	x	x
Safety Evaluable Population	xxxx	xx	xxxx
Total Exclusions	xx	x	xx
Intent to Treat Population	xxxx	xx	xxxx
Total Exclusions	xx	x	xx
mBCC Protocol 4(+) Patients (1)	x	xx	xx
8-Weekly Tumour Assessment (2)	xxx	xx	xxx
First Consented Protocol Version: 1	xxx	xx	xxx
First Consented Protocol Version: 2	xxx	xx	xxx
First Consented Protocol Version: 3	xxx	xx	xxx
First Consented Protocol Version: 4	xx	x	xx
First Consented Protocol Version: 5	x	xx	xx
Last Consented Protocol Version: 1	xx	x	xx
Last Consented Protocol Version: 2	xxx	xx	xxx
Last Consented Protocol Version: 3	xxx	xx	xxx
Last Consented Protocol Version: 4	xxx	xx	xxx
Last Consented Protocol Version: 5	xxx	xx	xxx
Last Consented Protocol Version: 6	xx	x	xx

Programming Note:

- N is Number of Patients present in each of Disease status category i.e. Locally Advanced or Metastatic.
- Number of Patients screened and screen failure information comes from the CRF.
- Number of Subjects Excluded from Safety/Intent to Treat population are the Patients excluded from Safety/Intent to Treat population other than screen failures.
- See Patient Population section for information about populations.
- Patient's First and Last protocol consent information comes from the CRF.

Listing of Patients Populations

Disease Status: Locally Advanced

Center/ Patient ID	All Subjects	Screening Failure	Safety Population	ITT Population	mBCC Protocol 4(+) Patients	8- Weekly Tumour Assessment	First Consented Protocol Version	Last Consented Protocol Version
xxxxxx/xxx	Yes	No	Yes	Yes	No	No	x	x
xxxxxx/xxx	Yes	No	Yes	Yes	No	No	x	x
xxxxxx/xxx	Yes	No	Yes	Yes	No	No	x	x
xxxxxx/xxx	Yes	No	Yes	Yes	No	No	x	x

Programming Note:

- Listing will display whether the Patients are included or excluded from the Population.
- See Patient Population section for information about populations.
- Patient First/last consented to protocol version information comes from CRF page.
- All Patients with non-missing disease status are included in the listing.

Listing of Patients excluded from the Safety Population

Disease Status: Locally Advanced

Center/ Patient ID	Drug Dispensed	MedDRA Preferred Term	Start Date of Adverse Event	End Date of Adverse Event	Serious	Most Extreme Intensity
xxxxxx/xxx	Y					
xxxxxx/xxx	Y					
xxxxxx/xxx	Y	ACUTE MYOCARDIAL INFARCTION	[redacted]		Yes	Death
xxxxxx/xxx	Y	CARDIAC FAILURE			No	Mild
		CYSTITIS			No	Moderate
		DEHYDRATION			Yes	Severe
		DIABETES MELLITUS			No	Moderate
		GENERAL PHYSICAL HEALTH DETERIORATION			Yes	Severe
		HYPERCALCAEMIA			No	Severe
		HYPERTHYROIDISM			No	Moderate
		HYPOPARATHYROIDISM			No	Moderate

Programming Note:

- Only include patients who are excluded from Safety Population and are not screen failures.

Disposition:

Patients will be considered to have completed the study if they have discontinued or completed treatment, and have completed their follow-up period (1 month for subjects who enrolled to protocol version 1 or 2, or 12 months for subjects who were enrolled to protocol 3 or later).

The reason for discontinuation of the study comes from the End of Follow Up CRF Page and should be listed under reasons for Study Discontinuation based on Safety and Non-safety categories.

Patients discontinued from treatment for a variety of reasons (recorded in the End of Study Treatment CRF page), and these should be listed under reasons for treatment discontinuation based on Safety and Non-safety categories.

Note: under the treatment discontinuation category, those who recorded “withdrew from treatment” in the CRF were assumed to have also left the study (as the investigators were additionally asked for study withdrawal information). As a result, patients who discontinued treatment but remained in follow-up were counted in the “Other” category. A footnote to the discontinuation table should be added to explain this idiosyncrasy.

1. Patient Disposition

DST01	Output ID: t_ds_* ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** Disease status (Locally Advanced, Metastatic) ● **Column Totals:** Total of non-missing Disease status ● **Analysis Variables:** Number of Patients Completed study ○ Follow-up of 1 month ○ Follow-up of 12 months, Number of Patients discontinued from Study , ○ Safety ○ Non-Safety Number of Patients Ongoing in Study ○ In Follow-Up ○ On Treatment, Number of Patients discontinued from Treatment ○ Safety ○ Non-Safety ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

1. Patients are considered as completers (i.e. included in the row *Number of Patients Completed Study*) if an End of Follow-Up (EOFU) page is present, or (for patients whose EOFU page was missing due to a known database issue where the EOFU page was not available), one of the following conditions is met:
    a. for subjects whose latest protocol version consented to was 1 or 2, they were alive at the date of their 30 day FU visit.
    b. for subjects whose latest protocol version consented to was 3 or higher, they were alive at the date of their 12 month FU visit.
2. Patients who completed (as per point 1) were sub-categorised as having completed "Follow-up of 1 month" if their latest protocol consented to was version 1 or 2, or having completed "Follow-up of 12 months" if their latest protocol consented to was version 3 or a subsequent version.
3. For the sub-categories of *Number of patients discontinued from treatment*: reasons of "Adverse Event" and "Death" are classified as *Safety*; any other reasons are classified as *Non-Safety*.
4. For the sub-categories of *Number of patients ongoing in study*: patients categorised as *in Follow up* include the patients who have discontinued from treatment (but are still in the study); patients categorised as *On Treatment* include patients still receiving treatment.
5. If the reason for Study Discontinuation is the same as the reason for Treatment Discontinuation then the record should be included in both sections of the display.

2. Patient Disposition within 24 weeks of first dose

DST01	Output ID: t_ds_24wkdisc_* ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** Disease status (Locally Advanced, Metastatic) ● **Column Totals:** Total of non-missing Disease status ● **Analysis Variables:** Number of Patients Completed study Number of Patients discontinued from Treatment ○ Safety ○ Non-Safety ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

1. Only include Patients whose overall Duration of study treatment is less than or equal to 24 weeks i.e. less than equal to 168 days from first valid dose.
2. Patients are considered as completers (i.e. included in the row *Number of Patients Completed Study*) if an End of Follow-Up (EOFU) page is present, or (for patients whose EOFU page was missing due to issues with the system), one of the following conditions is met:
    a. for subjects whose latest protocol version consented to was 1 or 2, they were alive at the date of their 30 day FU visit.
    b. for subjects whose latest protocol version consented to was 3 or higher, they were alive at the date of their 12 month FU visit.
3. For the sub-categories of *Number of patients discontinued from treatment*: reasons of “Adverse Event” and “Death” are classified as *Safety*; any other reasons are classified as *Non-Safety*.

3. Patient Disposition within 52 weeks of first dose

Output ID: t_ds_52wkdisc_*

Repeat t_ds_24wkdisc_* output for Patients whose overall Duration of study treatment is less than equal to 52 weeks i.e. less than equal to 364 days from first valid dose.

4. Listing of Primary Reason for Patients Prematurely Discontinuing Treatment

Disease Status: Locally Advanced

Center/ Patient ID	Age/Sex/Race	Date of First Study Drug Administration	Day of Last Study Drug Administration	Day of Treatment Discontinuation	Reason for Treatment Discontinuation	Other Reason for Treatment Discontinuation
xxxxxx/xxx	xx [redacted]	xxxx-xx-xx	xxx	xxx	ADVERSE EVENT	
xxxxxx/xxx	xx	xxxx-xx-xx	xx	xx	ADVERSE EVENT	
xxxxxx/xxx	xx	xxxx-xx-xx	xxx	xxx	PROGRESSIVE DISEASE	
xxxxxx/xxx	xx	xxxx-xx-xx	xx	xx	ADVERSE EVENT	
xxxxxx/xxx	xx	xxxx-xx-xx	xx	xx	ADVERSE EVENT	
xxxxxx/xxx	xx	xxxx-xx-xx	xxx	xxx	ADVERSE EVENT	
xxxxxx/xxx	xx	xxxx-xx-xx	xxx	xxx	PROGRESSIVE DISEASE	
xxxxxx/xxx	xx	xxxx-xx-xx	xxxx	xxxx	WITHDRAWAL BY SUBJECT	
xxxxxx/xxx	xx	xxxx-xx-xx	xxx	xxx	ADVERSE EVENT	
xxxxxx/xxx	xx	xxxx-xx-xx	xxx	xxx	OTHER	'Patient requested to discontinue treatment but agreed to continue in follow up'

Programming note:

- Include safety evaluable patients who discontinued from study drug treatment.
- Variables to include: Centre, Subject, Age, Sex, Race, Date of Treatment Start, Day of Last Treatment, Study Day of Treatment Discontinuation, Reason and Other Reason for Treatment Discontinuation.
- Please see programming notes for the l_ds* output.
- Please see information for the output ID: DSL02.

Demographic:

1. Demographic and Baseline Characteristics

DMT01	Output ID: t_dm_* • **Analysis Population:** Intent-to-Treat Patients • **Column Variables:** Disease status (Locally Advanced, Metastatic) • **Column Totals:** Total of non-missing Disease status • **Analysis Variables:** Age (Years), Age group (years), Sex, Race, Height (cm) at at baseline, Weight (kg) at baseline, BMI (kg/m^2), Temparature (C), Years from First BCC Diagnosis to Dose, Baseline ECOG Performance Status, Gorlin Syndrome, Child Bearing Potential (Females), Number of Target Lesions at Baseline. • **Statistics and Calculation Methods:** Use Proc means for Summary Statistics and Proc freq for Frequency Counts. Summary Statistics should be displayed for following analysis variables. Age(Years), Height (cm) at baseline, Weight (kg) at baseline, Years from First BCC Diagnosis to Dose, Number of Target Lesions at Baseline Frequency counts should be displayed for following analysis variables: Age group (years), Sex, Race, Baseline ECOG Performance Status, Gorlin Syndrome, Child Bearing Potential (Females) • **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

1. N is Number of Patients present in each *Disease Status* category i.e. Locally Advanced or Metastatic.
2. The variable *Baseline Age (varname BAGE)* should be used for Age information (in Age (years) and Age group (years) section). Baseline Age is the Patient's age (years)

at the informed consent (to study) date and it is derived from Informed consent date and Imputed Birth date (ASL.BAGE):
(Set to integer part of (Informed consent date – Imputed Birth Date +1)/365.25).

If Birth date of subject is partial (at least year of Birth date is present) then use the following Missing Data Handling Rule:

- If the day part of the birth date is missing, impute it with 15.
- If the month part of the birth date is missing, impute it with June.

Age categories should be derived on the basis of Baseline Age.

3. Sex, Height, Weight, and Temperature information come from the Demography and Vital Signs CRF page. BMI is derived using the common formula defined in the DAP M3.

4. Race information comes from the Demography CRF page and as per SDTM controlled terminology
"Black" should be mapped as "Black or African American".
Race was recorded as "Not applicable" in France.

5. Years from First BCC Diagnosis to Dose should derived as difference between First Treatment start Date and Date of First BCC Diagnosis comes from CRF page divided by year i.e. 365.25 days.

If First BCC Diagnosis date is partial then
a) Impute to the first day of the month if the day is missing.
b) Impute to the first month of the year if the month is missing.

6. Baseline ECOG Performance Status, Gorlin Syndrome, Child Bearing Potential information comes from CRF.

7. Number of Target Lesion at Baseline should be calculated as total number of target Lesions collected on last Tumor assessment date which is on or prior to First Dosing date having non missing Tumor Location and Tumor assessment date.

2. Listing of Demographic and Baseline Characteristics

Output ID: l_dm_IT

Center/ Patient ID	Age/Sex/Race	Height [cm]	Weight [kg]	BMI [kg/mx]	Temperature [C]	Years from First BCC Diagnosis to Dose	Baseline ECOG Performance Status	Gorlin Syndrome	Child Bearing Potential (Females)	Number of Target Lesions at Baseline
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No		x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xxx.x	xx.x	xx.x	xx.x	Grade x	Yes		x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No	No	x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No	No	x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No	Yes	x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	xx.xx	Grade x	No	No	x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No	No	x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No	No	x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No		x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.x	Grade x	No		x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No	No	x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xxx.x	xx.x	xx.x	xx.xx	Grade x	Yes		x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No	No	x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xxx.x	xx.x	xx.x	xx.xx	Grade x	No		x
xxxxxx/xxx	xx [redacted] Not Applicable	xxx	xx.x	xx.x	xx.x	x.xx	Grade x	No	No	x

Note: Race was recorded as Not applicable in France.

Programming Note:

- The listing should include patients in the Intent-to-Treat population.
- Please refer to the programming notes for table t_dm_* for definitions of the variables to be displayed in this listing.
- One row per subject.

3. Listing of Centers and Countries

Output ID: l_dm_inv_SE

Center	Country
xxxxxx	UNITED KINGDOM
xxxxxx	GREECE
xxxxxx	SLOVAKIA
xxxxxx	CZECH REPUBLIC

Programming Note:

- Centers for Safety-Evaluable Patients are included in the Listing.
- Center and Country information comes from Demographic data.
- One row per centre and country.

Medical History:

1. Medical History at Baseline

MHT01	Output ID: t_mh_* ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:**Disease status (Locally Advanced, Metastatic) ● **Column Totals:** Total of non-missing Disease status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

Only display General Medical History (other than BCC) collected on MEDHX CRF page .

2. Medical History at Baseline for Patients with an Abnormal ECG Result

MHT01	Output ID: t_mh_ecgabn_* ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** Disease status (Locally Advanced, Metastatic) ● **Column Totals:** Total of non-missing Disease status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** Patients with abnormal ECG results at baseline

Programming Note:

Only include patients who had an abnormal ECG result at baseline, according to the ECG CRF page.

Only display General Medical History (other than BCC) collected on MEDHX CRF page.

3. Medical History Glossary

AEL01_NOLLT	Output ID: l_mh_gloss_SE ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** MedDRA System Organ Class, MedDRA Preferred Term, Lowest Level Term and Reported Term for the Medical History. ● **Column Totals:** NA ● **Analysis Variables: None** ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- A glossary of all previous and current medical conditions other than BCC history will be provided.
- Data will be ordered alphabetically by MedDRA System Organ Class, MedDRA Preferred Term, Lowest Level Term and Reported Term for the Medical History.

4. Disease History of Advanced or Metastatic Basal Cell Carcinoma

DMT01	Output ID: t_dm_dishis* • **Analysis Population**: Safety-Evaluable Patients • **Column Variables**: Disease status (Locally Advanced, Metastatic) • **Column Totals:** Total of non-missing Disease status • **Analysis Variables:** 1.Diagnosis histologically confirmed - Yes - No 2.Current disease status - Metastatic - Locally Advanced a) Inoperable b) Surgery Medically Contraindicated i) Substantial morbidity and / or deformity ii) Unlikely to be curatively resected iii) Other 3.Previously administered radiotherapy - Yes - No a) Contraindicated b) Inappropriate 4.Measurable Disease Status - Yes - No 5. Current sites of locally advanced or metastatic disease - Any Site - Different Disease sites collected on CRF page. • **Numeric Precision and Formatting of Statistics**: Use standard display in the mockup

Programming Note:

Refer to CRF Page "Disease History of advanced or metastatic BCC".

5. Disease History Glossary

AEL01_NOLLT	Output ID: l_ds_gloss_SE ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** Current Disease Status, Current Site and Other Specify. ● **Column Totals:** NA ● **Analysis Variables: None** ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- Investigator text will be used from 'Disease History of advanced or metastatic BCC' CRF page.
- Data will be ordered alphabetically by Current Disease Status, Current Site and Other Specify.

Concomitant Medication:

1. Surgery and Procedures History

1a. Surgery and Procedures History: Non-Cancer Related

CMT01	Output ID: t_cm_NCANRELSUR_* • **Analysis Population:** Safety-Evaluable Patients • **Column Variables:** Disease status (Locally Advanced, Metastatic) • **Column Totals:** Total of non-missing Disease status • **Analysis Variables:** Coded INN Class Name Standardized Medication Name • **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup • **Optional Subsetting:** Select General (Non-Cancer Related) Surgical Procedure History

Programming Note:

- Only include records where patient had General (Non-Cancer Related) Surgical Procedure History collected on CRF page “Surgery and Procedures History”.

1b. Surgery and Procedures History: Cancer Related

Output ID: t_cm_CANRELSURG_*

Repeat Output t_cm_NCANRELSUR_* for Cancer Related Surgery and Procedures History.

Programming Note:

- Only include records where patient had Cancer Related Surgical Procedure History collected on CRF page “Surgery and Procedures History”.

1c. Prior Medication and Therapies

Output ID: t_cm_PRIOR_*

Repeat Output t_cm_NCANRELSUR_* for prior Prior Medication and therapies.

Programming Note:

- Only include records where patient had Prior Medication and therapies (concomitant medication started and ended before actual study treatment start) collected on CRF page “Concomitant Medications and Therapies”.

1d. Concomitant Medication and Therapies

Output ID: t_cm_CONMED_*

Repeat Output t_cm_NCANRELSUR_* for Concomitant Medication and Therapies.

Programming Note:

- Only select records where patient had Concomitant Medication and therapies (ongoing medication during study treatment) collected on CRF page “Concomitant Medications and Therapies”.

2. Prior Therapies

2a. Prior Systemic Cancer Therapy Other Than Basal Cell Carcinoma

CMT01	Output ID: t_cm_SYSNBCC _* • **Analysis Population:** Safety-Evaluable Patients • **Column Variables:** Disease status (Locally Advanced, Metastatic) • **Column Totals:** Total of non-missing Disease status • **Analysis Variables:** Cancer Therapy, Reason for Discontinuation • **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup • **Optional Subsetting:** Select Prior Cancer Therapy

Programming Note:

- Only include records where patients had Prior Cancer Therapy collected on CRF page "Previous Systemic cancer therapy other than BCC cancer therapy".
- Cancer Therapy and Reason for Discontinuation comes from the Previous Cancer Therapy CRF Page.

2b. Prior Cancer Therapy for Metastatic Basal Cell Carcinoma

CMT01	Output ID: t_cm_prior_mbcc_* • **Analysis Population**: Safety-Evaluable Patients, Protocol 4 Subset • **Column Variables:** Disease status (Locally Advanced, Metastatic) • **Column Totals:** Total of non-missing Disease status • **Analysis Variables:** Treatment Agent, Reason for Discontinuation • **Numeric Precision and Formatting of Statistics**: Use standard display in the mockup • **Optional Subsetting:** Select Prior cancer therapy for

	Metastatic BCC

Programming Note:

- Only include records where Patients had Prior cancer therapy for Metastatic BCC collected on CRF page "Previous Systemic cancer therapy for Metastatic BCC".
- Treatment Agent and Reason for Discontinuation information comes from Prior Cancer Therapy CRF page.

2c. Prior Radiotherapy for Metastatic Basal Cell Carcinoma

CMT01	Output ID: t_cm_rad _mbcc* • **Analysis Population:** Safety-Evaluable Patients, Protocol 4 Subset • **Column Variables:** Disease status (Locally Advanced, Metastatic) • **Column Totals:** Total of non-missing Disease status • **Analysis Variables:** Site,Reason for Administration • **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup • **Optional Subsetting:** Select Prior radiotherapy for Metastatic BCC

Programming Note:

- Only include records where patients had Prior radiotherapy for Metastatic BCC collected on CRF page "Previous Radiotherapy for advanced or Metastatic BCC".
- Site and Reason for Administration information comes from CRF.

3. Listing of Concomitant Medication Glossary

AEL01_NOLLT	Output ID: l_cm_gloss_SE • **Analysis Population:** Safety-Evaluable Patients • **Column Variables:** Class Term, Standardized Medication and Reported Name of Drug, Med or Therapy. • **Column Totals:** NA

	• **Analysis Variables: None** • **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- A glossary of all Concomitant Medications will be provided.
- Data will be ordered by Class Term, Standardized Medication and Reported Name of Drug, Med or Therapy.

4. Listing of Anti-Cancer Treatment for Subjects with AEs Ongoing at Treatment Discontinuation, and Still Ongoing at 12 Months after Treatment Discontinuation, Population : Safety-Evaluable Patients, Protocol 3 (+) Subset, Excluding Patients who Discontinued Treatment within 6 Months of Cut, or Lost to Follow-Up or Died Within 6 Months of Treatment Discontinuation

Output ID: l_cm_anticancer_SE_PV3DSC6M

Subject / Age / Sex / Disease Status / Treatment Discont. Date/ Study Discont. Date / Study Discont. Reason	INN Name	Treatment Start Date	Treatment End Date
[redacted]xxxxxx-xxx / xx / [redacted] Locally Advanced / xxxx-xx-xx /	IMIQUIMOD	xxxx-xx-xx	
[redacted]-xxxxxx-xxx / xx / [redacted] / Locally Advanced / xxxx-xx-xx / xxxx-xx-xx / LOST TO FOLLOW-UP	SKIN NEOPLASM EXCISION	xxxx-xx-xx	xxxx-xx-xx
	TUMOUR EXCISION	xxxx-xx-xx	xxxx-xx-xx
[redacted]-xxxxxx-xxx / xx / [redacted] Locally Advanced / xxxx-xx-xx / xxxx-xx-xx / DEATH	VISMODEGIB	xxxx-xx-xx	
[redacted]-xxxxxx-xxx / xx / [redacted] Locally Advanced / xxxx-xx-xx / xxxx-xx-xx / DEATH	ELECTROCHEMOTHERAPY	xxxx-xx-xx	
		xxxx-xx-xx	

Programming Note:

- Output includes anti-cancer therapy for subjects with any of the following AE preferred terms ongoing at treatment discontinuation and still ongoing 12 months after treatment discontinuation: Muscle Spasm; Ageusia; Dysgeusia; Alopecia; Weight Decrease.

5. Listing of Anti-Cancer Treatment for Subjects with AEs Ongoing at Treatment Discontinuation, and Still Ongoing at 12 Months after

Treatment Discontinuation, Population : Safety-Evaluable Patients, 12 Months FU Complete Subset

Output ID: l_cm_anticancer2_SE_PV3COMP

Subject / Age / Sex / Disease Status / Treatment Discont. Date/ Study Discont. Date / Study Discont. Reason	INN Name	Treatment Start Date	Treatment End Date
MOxxxxx-xxxxxx-xxx / xx / [redacted] Locally Advanced / xxxx-xx-xx / xxxx-xx-xx / COMPLETE	RADIOTHERAPY	xxxx-xx-xx	xxxx-xx-xx
	RADIOTHERAPY	xxxx-xx-xx	xxxx-xx-xx
	CRYOTHERAPY	xxxx-xx-xx	xxxx-xx-xx
MOxxxxx-xxxxxx-xxx / xx / [redacted] Locally Advanced / xxxx-xx-xx / xxxx-xx-xx / COMPLETE	VISMODEGIB	xxxx-xx-xx	
	VISMODEGIB	xxxx-xx-xx	
	VISMODEGIB	xxxx-xx-xx	xxxx-xx-xx

Programming Note:

- Output includes anti-cancer therapy for subjects with any of the following AE preferred terms ongoing at treatment discontinuation and still ongoing at last assessment: Muscle Spasm; Ageusia; Dysgeusia; Alopecia; Weight Decrease.

Histology:

Output ID: t_histol_SE

	Locally Advanced (N=xxxx)	Metastatic (N=xxxx)	Total (N=xxxx)
Histologically confirmed Disease			
Yes	xxxx (xx.x%)	xx (xx.x%)	xxxx (xx.x%)
No	x (x.x%)	x (x.x%)	xx (x.x%)

Programming Note:

- N = Number of patients present in each disease status category i.e. Locally Advanced or Metastatic.
- Histology confirmation comes from PDMS system - i.e. Subjects included in the PDMS system for a deviation of ‘Non-histologically confirmed disease’ will be included in the ‘No’ category.
- Include Safety Evaluable Patients.

Disease Progression prior to Study:

Output ID: t_di_prog_IT_PV4ANY

	Locally Advanced (N=xxx)	Metastatic (N=xx)	Total (N=xxx)
Documentation of Disease Progression			
Radiographic	xx (xx.x%)	xx (xx.x%)	xx (x.x%)
Clinical	x (x.x%)	x (x.x%)	x (x.x%)
Histological	x (x.x%)	x (x.x%)	x (x.x%)
Newly Diagnosed mBCC			
Yes	xx (xx.x%)	xx (xx.x%)	xx (x.x%)

Programming Note:

- N is Number of Patients in the Intent-to-Treat population with Protocol 4 Subset (consented to Protocol version 4 or higher at any time).
- Percentages should be based upon N.
- Documentation of Disease Progression and Newly Diagnosed mBCC information comes from 'Documentation of Progression prior to Enrolment' CRF page.

.

Symptom Status of Metastatic Patients:

Summary of Symptom Status of Metastatic Patients:

STREAM Template	Description
N/A	Output ID: t_mbcc_symp_* ● **Analysis Populations:** Safety, Excluding Patients with Baseline MDASI Score ● **Column Variables:** Disease Status (Metastatic) ● **Column Totals:** None ● **Analysis Variables:** n, Symptomatic, Non-Symptomatic ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** N/A ● **Optional Subsetting:** None.

Summary of Symptom Status of Metastatic Patients, Population : Safety-Evaluable Patients
Protocol: MO25616
Snapshot Date: 03 August 2015. Clinical Cut-Off Date: 16 March 2015.
File: t_mbcc_symp_SE.

	Metastatic (N=96)
n	96
Symptomatic	31 (32.3%)
Non-Symptomatic	65 (67.7%)

Note: Symptom Status was adjudicated by the Sponsor following medical review of baseline symptom data.

Programming Note:

- Symptom status was defined via Sponsor (Clinical Science) manual review of the data as to whether the subject was symptomatic or not. Details of this are in the DAP M3.

Protocol Violations:

Protocol Violations (PVs) will be taken from the PDMS (Protocol Deviation Management System) and reviewed by Clinical Science. All major Protocol Violations will be summarised and Listed. At the request of the Science team, the Cut-off date should not be used with Violations as the date of the Violations according to the system are the dates that the violation was input, not the date that the violation occurred. Clinical Science reviewed the file to ensure that all correct violations are included and reported.

STREAM Template	**Description**
MHT01	Output ID: t_pv* ● **Analysis Population:** Safety ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Total Patients with at least one Deviation, Total number of Inclusion Criteria Violations, Total number of Procedural Violations, Total number of Medication Violations, Total number of Exclusion Criteria Violations ● **Statistics and Calculation Methods:** Use proq freq for individual violations or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each Category of Violations, include the counts for each individual Violation.
PDL01	Output ID: l_pv* ● **Analysis Population:** Safety ● **Column Variables:** Use Standard STREAM columns ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Output Specifications: Safety Outputs

Exposure:

Capsules are dispensed to each subject at the time of each visit and are recorded on the CRF. Subjects take a dose of 150 mg daily and fill in any missed dose dates on the Patient Diary, in case of dose missed for any reason. The investigator completes the number of capsules taken between visits on the basis of number of capsules returned by the subject at the next visit.

It is possible for a subject to have taken all the dispensed capsules between two visits and still have a missed dose if there is a delay in scheduling or attending the next visit. Consider the total number of capsules dispensed, taken, and the missed dosing date for daily dose calculation (ie, consider the sum of all dispensed/taken doses).

1. Overall Summary of Exposure to Study Medication (Vismodegib)

EXT01	Output ID: t_ex_SE ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Summary Statistics o Number of days missed dose o Cumulative dose of Vismodegib o Duration on treatment (in days) o Dose intensity o Total doses ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- The number of days of missed dose (and so the number of missed doses) will be calculated as follows: The number of days between the first and last dose, minus the sum of the number of capsules taken according to the Dose Accountability CRF page. i.e. If first dose was the 1st Jan, and the last dose

as the 28th Feb, and the subject had taken 55 capsules (according to their 'taken' records, then there would be 4 (59-55) missed doses.

- Cumulative dose of Vismodegib will be calculated as the sum of the total number of capsules taken (recorded on the Dose Accountability CRF page) at each visit multiplied by 150 mg.
- Duration on treatment will be calculated as time from first dose date to last dose date (last dose date minus first dose date + 1), measured in days.
- Dose intensity will be calculated as the sum of the total number of capsules taken (recorded on the Dose Accountability CRF page) at each visit / sum of the total number of capsules dispensed (recorded on the Dose Accountability CRF page) at each visit x 100.

2. Summary of Duration of Exposure to Vismodegib as a Monotherapy

Output ID: t_ex_dur_bymon_SE

Vismodegib Exposure	Safety Population (N=xxxx)	Person-Years
1 month or more	xxxx (xx.x%)	xxxx.xx
3 months or more	xxxx (xx.x%)	xxxx.xx
6 months or more	xxx (xx.x%)	xxx.xx
12 months or more	xxx (xx.x%)	xxx.xx
24 months or more	xx (x.x%)	xxx.xx
36 months or more	xx (x.x%)	xx.xx

Programming Note:

- N is number of Patients in the Safety Population.
- Vismodegib Exposure Duration categories derived as Total duration of Exposure in months which is calculated using (difference between first and last administration of Vismodegib) divided by 30.4375 (last dose date minus first dose date + 1)/30.4375.
- Patients with exposure of 1 month or more will be included in the summary frequencies (numerator). The denominator for percentages will be the subjects in the Safety Population.
- Person-years should be calculated as sum of exposure duration (in days) of patients in each category divided by 365.25.

3. Summary of Exposure to Vismodegib as a Monotherapy by Dose.

Output ID: t_ex_bydose_SE

Vismodegib Daily Exposure (mg)	Safety Population (N=xxxx)	Person-Years
150	xxxx (xxx.x%)	xxxx.xx

Programming Note:

- N is number of patients in the Safety population.
- Vismodegib Daily Exposure is the total daily dose taken by patient. This is constant at 150 mg as per protocol; no daily dose variations are permitted.
- Person-years should be calculated as sum of exposure duration in all patients in the safety population divided by 365.25.

4. Summary of Exposure to Vismodegib as a Monotherapy by Age Group and Gender

Output ID: t_ex_byage_bysex_SE

Age Group (Years)	Patients n (%)		Person-Years	
	Male (N=xxx)	Female (N=xxx)	Male (N=xxx)	Female (N=xxx)
<65	xxx (xx.x%)	xxx (xx.x%)	xxx.xx	xxx.xx
>=65	xxx (xx.x%)	xxx (xx.x%)	xxx.xx	xxx.xx
<75	xxx (xx.x%)	xxx (xx.x%)	xxx.xx	xxx.xx
>=75	xxx (xx.x%)	xxx (xx.x%)	xxx.xx	xxx.xx

Programming note:

- N is number of patients in each sex category (in the safety population).
- Age Groups derived on the basis of Baseline Age.
- Person-years should be calculated as sum of exposure duration of Patients for each category of gender and age group divided by 365.25.

5. Summary of Exposure to Vismodegib as a Monotherapy by Ethnicity

Output ID: t_ex_byrace_SE

Race	Safety Population (N=xxxx)	Person-Years
n	xxxx	
WHITE	xxx (xx.x%)	xxx.xx
NOT APPLICABLE	xxx (xx.x%)	xxx.xx
OTHER	xx (x.x%)	xx.xx
BLACK OR AFRICAN AMERICAN	x (x.x%)	x.xx
ASIAN	x (x.x%)	x.xx

Programming note:

- N is number of patients in safety population.
- n is number of patients with non-missing race information.
- Race information comes from the Demography CRF page and as per SDTM controlled terminology "Black" should be mapped as "Black or African American".
- Race was recorded as "Not applicable" in France (hence the need for this category).
- Person-years should be calculated as sum of exposure duration of Patients in each race category divided by 365.25.

6. Summary of Exposure to Vismodegib as a Monotherapy by Gorlin Status

Output ID: t_ex_bygorlin_SE

Disease Status		Safety Population (N=xxxx)	Person-Years
Locally Advanced	n	xxxx	
	Non-Gorlin Syndrome	xxx (xx.x%)	xxx.xx
	Gorlin Syndrome	xxx (xx.x%)	xxx.xx
Metastatic	n	xxxx	
	Non-Gorlin Syndrome	xxx (xx.x%)	xxx.xx
	Gorlin Syndrome	xxx (xx.x%)	xxx.xx

Programming note:

- N is number of patients in safety population.
- n is number of patients with non-missing Gorlin Syndrome information in each of disease status.
- *Gorlin Syndrome* information comes from "Gorlin Syndrome" CRF page.
- Person-years should be calculated as sum of exposure duration of patients in each Syndrome category and disease status category divided by 365.25.

7. Reason for Breaks in Treatment, Population : Safety-Evaluable Patients

Output ID: l_ex_trtbrk_SE

Disease Status: Metastatic

Center/Patient ID	Cycle	Period Start Date	Reason for Treatment Break	Specify if Other
xxxxxx/xxx	CxDx	xxxxxxxxx	OTHER REASON (AFTER DISCUSSION WITH MEDICAL ADVISOR)	Adverse Event
xxxxxx/xxx	CxDx	xxxxxxxxx	OTHER REASON (AFTER DISCUSSION WITH MEDICAL ADVISOR)	SAE: Facial paralysis of unknown etiology
xxxxxx/xxx	CxDx	xxxxxxxxx	OTHER REASON (AFTER DISCUSSION WITH MEDICAL ADVISOR)	Missed dose
	CxxDx	xxxxxxxxx	OTHER REASON (AFTER DISCUSSION WITH MEDICAL ADVISOR)	Missed dose
	CxxDx	xxxxxxxxx	OTHER REASON (AFTER DISCUSSION WITH MEDICAL ADVISOR)	Patient can interrupt treatment for a maximum of x weeks (break xxxx-xx-xx)
xxxxxx/xxx	CxDx	xxxxxxxxx	OTHER REASON (AFTER DISCUSSION WITH MEDICAL ADVISOR)	Ended capsules
xxxxxx/xxx	END OF STUDY	xxxxxxxxx	OTHER REASON (AFTER DISCUSSION WITH MEDICAL ADVISOR)	ae/side effects
xxxxxx/xxx	CxDx	xxxxxxxxx	OTHER REASON (AFTER DISCUSSION WITH MEDICAL ADVISOR)	Patient forgot to take two doses of medication

Programming note:

- *Cycle* and *Period Start Date* will be derived based on visit windowing algorithm.
- Information on *Reason for Treatment Break* and *Specify if Other* will come from the “Reason for breaks in treatment” CRF page.

Adverse Events:

General AE Reporting

Listings will include all AEs unless otherwise specified. A Treatment Emergent AE (TEAE) is defined as an AE that starts on or after the first day of study treatment and within 30 days of last dose (please see General Considerations for definition). Unless otherwise specified, AE and SAE summary tables will be restricted to TEAEs.

In STEVIE, the data collection guidelines require that the same AE is entered multiple times into the database, with a separate record for each change in toxicity grade or Lower Level Term. AEs can be reported using this or a “collapsed” Adverse Events analysis dataset.

The Collapsed Adverse Events dataset is derived by combining records that can be reasonably considered to be referring to a single AE term but with changes in toxicity grade (or lower level term). Records from the original AE dataset are grouped, and each group is represented in the collapsed dataset by a single record. The groups are built up by “chaining” records from the original dataset as follows:

- if the Subject ID, System Organ Class and Preferred Term are the same, and
- either the periods defined by the two AEs’ start and end dates overlap, or the Start Date of the later AE is <=2 days after the End Date of the earlier one.

In the single record representing the “collapsed” AE:

- Subject ID, System Organ Class and Preferred Term are copied across from any of the records in the group (these are identical so it doesn’t matter which record these variables come from)
- Severity (i.e. toxicity grade) is taken as the most severe grade in the group
- Start Date is taken as the earliest start date in the group
- End Date, Lower Level Term and Outcome are taken from the record with the latest end date in the group

Examples are given on the next page.

Example of derivation of “collapsed” AEs:

Example 1:

SUBJID	System Organ Class	Preferred Term	Lower Level Term	Severity	Outcome	Start Date	End Date
[redacted]	GASTROINTESTINAL DISORDERS	DYSPEPSI	DYSPEPSIA	GRADE 2 / MODERATE	RESOLVED	[redacted]	
	GASTROINTESTINAL DISORDERS	DYSPEPSIA	HEART BURN	GRADE 3 / SEVERE	RESOLVED		

Collapsed to:

[redacted]	GASTROINTESTINAL DISORDERS	DYSPEPSIA	HEART BURN	GRADE 3 / SEVERE	RESOLVED	[redacted]	

Example 2:

SUBJID	System Organ Class	Preferred Term	Lower Level Term	Severity	Outcome	Start Date	End Date
[redacted]	MUSCULOSKELETAL	MUSCLE SPASMS	CRAMPS OF LOWER EXTREMITIES	GRADE 2 / MODERATE	RESOLVED	[redacted]	
	MUSCULOSKELETAL	MUSCLE SPASMS	CRAMP IN HAND	GRADE 2 / MODERATE	RESOLVED		
	MUSCULOSKELETAL	MUSCLE SPASMS	CRAMPS OF LOWER EXTREMITIES	GRADE 1 / MILD	RESOLVED		

Collapsed to:

[redacted]	MUSCULOSKELETAL	MUSCLE SPASMS	CRAMP IN HAND	GRADE 2 / MODERATE	RESOLVED	[redacted]	

Additional Note:

Summaries of amenorrhea are based upon the sub-population of patients who are at risk of this AE, including women of child-bearing potential or having menses at baseline. The demography CRF page captures whether patients are of child-bearing potential but there is nowhere to indicate whether patients have menses, and so all patients who experienced the AE of interest (Amenorrhea/ Irregular Menses) were also included in the denominator.

Overall summary of AEs:

STREAM Template	Description
AET01	Output ID: t_ae_o_* ● **Analysis Population:** Safety ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Total Patients with at least one AE, Total number of events, Total number of deaths, Total number of patients withdrawn from study due to an AE, Total number of patients with at least one: AE with Fatal outcome, Serious AE, Serious AE leading to treatment withdrawal, Serious AE leading to dose modification/interruption, AE leading to treatment withdrawal, AE leading to dose modification/interruption ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Number of patients reporting AEs:

STREAM Template	Description
AET02	Output ID: t_ae_* ● **Analysis Populations:** Safety Output will be repeated for different population combinations - please see the LoPO for details of these combinations ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include Total number of patients with at least one AE, Overall total number of events

Number of patients reporting AEs by Sub-group:

STREAM Template	Description
AET02	Output ID: t_ae_bysubgp_* ● **Analysis Populations:** Safety ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include sub-grouping for: o Age (see General Considerations) i.e. <65, >= 65, <75, >= 75. o Race where Race is taken from the CRF and grouped i.e. White, Non-White, Missing. o Sex where sex is taken from CRF i.e. Male, Female. o Baseline (see General Considerations) ECOG Score i.e. 0, 1, >=2, Missing

Number of patients reporting AEs by Severity:

STREAM Template	Description
AET02	Output ID: t_ae_bysev_* ● **Analysis Populations:** Safety Output will be repeated for different population combinations - please see the LoPO for details of these combinations ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include sub-grouping for: o Any Grade o Grades 1 through 5 o Missing Grade

Number of patients reporting AEs by Drug Relationship:

STREAM Template	Description
AET02	Output ID: t_ae_byrel_* ● **Analysis Populations:** Safety ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include sub-grouping for: o Related o Not Related o Not Applicable

Number of patients reporting AEs by Exposure Duration:

STREAM Template	Description
AET02	Output ID: t_ae_byexp_* ● **Analysis Populations:** Safety Output will be repeated for different population combinations - please see the LoPO for details of these combinations ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include sub-grouping for: o < 12 months exposure o >= 12 months exposure

Number of patients reporting AEs by Outcome:

STREAM Template	Description
AET02	Output ID: t_ae_byout_* ● **Analysis Populations:** Safety Output will be repeated for different population combinations - please see the LoPO for details of these combinations ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include sub-grouping for: o Recovered / Resolved o Not Recovered / Not Resolved o Recovered / Resolved with SequelAE o Fatal

Resolution of Collapsed AEs Ongoing by Outcome:

STREAM Template	Description
AET02	Output ID: t_ae_out_c_* ● **Analysis Populations:** Safety Output will be repeated for different population combinations - please see the LoPO for details of these combinations ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include sub-grouping for: o Resolved o Resolved with SequelAE o Ongoing o Fatal o Unknown o Missing

Summary of Muscle Spasm AEs Ongoing at the Time of Discontinuation (Collapsed AEs), and Still Ongoing at Last Assessment by Preferred Term, Excluding Patients with Commercial Vismodegib

AET02	Output ID: t_ae_out_ongo_AEMUS_* ● **Analysis Population:** Safety-Evaluable Patients, 12 Months FU Complete Subset ● **Column Variables:** Disease status (Locally Advanced, Metastatic) ● **Column Totals:** Total of non-missing Disease status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include sub-grouping for: ○ Resolved ○ Resolved with SequelAE ○ Ongoing ○ Fatal ○ Unknown ○ Missing

Programming Notes:

- Only ongoing "Muscle Spasm" Adverse Events at the time of discontinuation are included.
- Patients, who took commercial Vismodegib (according to the Concomitant Medication CRF page) between treatment discontinuation and 12 months after treatment and had ongoing Adverse Events at treatment discontinuation, have been excluded.

Summary of Alopecia AEs Ongoing at the Time of Discontinuation (Collapsed AEs), and Still Ongoing at Last Assessment by Preferred Term, Excluding Patients with Commercial Vismodegib

Output Id : t_ae_out_ongo_AEAL_*

Repeat output t_ae_out_ongo_AEMUS_* for “Alopecia” adverse event.

Summary of Ageusia AEs Ongoing at the Time of Discontinuation (Collapsed AEs), and Still Ongoing at Last Assessment by Preferred Term, Excluding Patients with Commercial Vismodegib

Output Id : t_ae_out_ongo_AEAG_*

Repeat output t_ae_out_ongo_AEMUS_* for “Ageusia” adverse event.

Summary of Dysgeusia AEs Ongoing at the Time of Discontinuation (Collapsed AEs), and Still Ongoing at Last Assessment by Preferred Term, Excluding Patients with Commercial Vismodegib

Output Id : t_ae_out_ongo_AEDY_*

Repeat output t_ae_out_ongo_AEMUS_* for “Dysgeusia” adverse event.

Summary of Weight Decreased AEs Ongoing at the Time of Discontinuation (Collapsed AEs), and Still Ongoing at Last Assessment by Preferred Term, Excluding Patients with Commercial Vismodegib

Output Id : t_ae_out_ongo_AEWG_*

Repeat output t_ae_out_ongo_AEMUS_* for “Weight Decreased” adverse event.

Number of Patients reporting TEAEs (Enrolled Population):

STREAM Template	Description
AET02	Output ID: t_ae2_* ● **Analysis Populations:** Enrolled Population Output will be repeated for different population combinations - please see the LoPO for details of these combinations ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include Total number of patients with at least one AE, Overall total number of events

Programming Notes:

- Table to repeated for TEAEs leading to Death, Serious TEAEs, TEAEs of Grades 3 to 5 and TEAEs Leading to Study Drug Discontinuation.

- Rate of AEs per 100 Patient Years by Exposure Duration:

STREAM Template	Description
AET02	Output ID: t_ae_byptyrs_* ● **Analysis Populations:** Safety Output will be repeated for different population combinations - please see the LoPO for details of these combinations ● **Column Variables:** Exposure Duration Categories (< 12 Months Exposure, >= 12 Months Exposure) ● **Column Totals:** None ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include Total number of patients with at least one AE, Overall total number of events

Disposition of patients with an AE ongoing at treatment discontinuation:

STREAM Template	Description
N/A	Output ID: t_ae_ds_persae_* ● **Analysis Populations:** Safety Output will be repeated for different population combinations - please see the LoPO for details of these combinations ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Total number of Patients with an Ongoing AE at discontinuation, Reason for Discontinuation from Treatment, Patient Died after Discontinuation from Treatment, Patient was Lost to Follow-Up After Discontinuation from Treatment, Latest Protocol Version Consented to ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use AET02 standard template in the mockup ● **Optional Subsetting:** Reason for Discontinuation i.e. Death, Lost To Follow-Up. Patient Died After Discontinuation from Treatment i.e. 0-3 months, 0-6 months, >6 months after discontinuation.

Summary of Disposition of Patients with an AE ongoing at the time of Discontinuation (Latest Protocol Version consented to: 1 or 2) (Safety Population)

	Locally Advanced (N=282)	Metastatic (N=16)	Total (N=298)
Total number of patients with an ongoing AE at discontinuation	110 (39.0%)	12 (75.0%)	122 (40.9%)
Reason for Discontinuation from Treatment			
n	5 (1.8%)	1 (6.3%)	6 (2.0%)
Death	4 (1.4%)	1 (6.3%)	5 (1.7%)
Lost To Follow-Up	1 (0.4%)	0	1 (0.3%)
Patient Died After Discontinuation from Treatment			
n	4 (1.4%)	0	4 (1.3%)
0-3 months after discontinuation	3 (1.1%)	0	3 (1.0%)
0-6 months after discontinuation	1 (0.4%)	0	1 (0.3%)
Patient was Lost to Follow-Up After Discontinuation from Treatment			
n	12 (4.3%)	5 (31.3%)	17 (5.7%)
0-3 months after discontinuation	12 (4.3%)	5 (31.3%)	17 (5.7%)
Date of Treatment Discontinuation < 3 Months Before 6th November 2013			
n	6 (2.1%)	0	6 (2.0%)
Patients	6 (2.1%)	0	6 (2.0%)
Protocol Version Consented (Latest)			
n	110 (39.0%)	12 (75.0%)	122 (40.9%)
Version 1	21 (7.4%)	3 (18.8%)	24 (8.1%)
Version 2	89 (31.6%)	9 (56.3%)	98 (32.9%)

Programming Notes:

- Only include the AEs which were ongoing at the time of treatment discontinuation.

Number of Patients Reporting AEs by age group:

STREAM Template	Description
AET02	Output ID: t_ae_byagegp_* ● **Analysis Populations:** Safety Output will be repeated for different population combinations - please see the LoPO for details of these combinations ● **Column Variables:** Age Groups (< 65 and >= 65, < 75 and >= 75) ● **Column Totals:** None ● **Analysis Variables:** MedDRA System Organ Class, MedDRA Preferred Term. ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use AET02 as standard display but with above columns ● **Optional Subsetting:** For each System Organ Class and Preferred Term, include Total number of patients with at least one AE, Overall total number of events

Listing of Ongoing Adverse Events for Patients who Discontinued Treatment (Latest Protocol Version Consented to: 1 or 2)

AEL02	Output ID: l_ae_ds_PV1N2_AEPERS* ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:**Disease status (Locally Advanced, Metastatic), Center/Patient ID - Age/Sex/Race, MedDRA Preferred Term, Date of First/ Last Study Drug Admin., Date of Adverse Event, Date of Treatment Disc., Date of Last Known Alive, Reason for Treatment Disc.,Related to Study Drug, Serious ● **Column Totals:** NA ● **Analysis Variables: None** ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming notes:

1. Listing includes patients who had an AE ongoing at time of treatment discontinuation, and still ongoing at the time of analysis and patients who latest consented to protocol version 1 and 2.
2. Patients who died or were lost to follow-up within 6 months after treatment discontinuation are excluded.

Listing of Ongoing Adverse Events for Patients who Discontinued Treatment (Latest Protocol Version Consented to: 3 or Higher)

Output ID: l_ae_ds_PV3PLUS_AEPERS*

Repeat l_ae_ds_PV1N2_AEPERS_* output for Patients who latest consented to Protocol version 3 or higher.

Listing of Adverse Events for Patients with Primary Reason of Death for Treatment Discontinuation

AEL02	Output ID: l_ae_ds_dth* ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** Disease status (Locally Advanced, Metastatic), Center/Patient ID/Cause of Death-Other Reason, Date of First Study Drug Administration, Adverse Event MedDRA Preferred Term, Study Day of Onset, AE Duration in Days, Most Extreme Intensity, Caused by Study Drug, Treatment for SAE, Action taken with Study Drug ● **Column Totals:** NA ● **Analysis Variables: None** ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

Only include patients who discontinued from Treatment due to Death.

Listing of All Adverse Events

AEL02	Output ID: l_ae_SE ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** Disease status (Locally Advanced, Metastatic), Center/Patient ID - Age/Sex/Race, Date of First Study Drug Administration, Adverse Event MedDRA Preferred Term, Study Day of Onset, AE Duration in Days, Serious, Most Extreme Intensity, Caused by Study Drug, Outcome, , Treatment for SAE, Action taken with Study Drug ● **Column Totals:** NA ● **Analysis Variables: None** ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Listing of Cause of Death On Study

AEL04	Output ID: l_ae_dth_SE ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** Disease status (Locally Advanced, Metastatic), Center/Patient ID, Age/Sex/Race, Date of First Study Drug Administration, Date of Last Study Drug Administration, Day of Death, Cause of Death, Autopsy Performed? ● **Column Totals:** NA ● **Analysis Variables: None** ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Listing of Adverse Event Glossary

AEL01_NOLLT	Output ID: l_ae_gloss_SE ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** MedDRA System Organ Class, MedDRA Preferred Term and Investigator-Specified Adverse Event Term. ● **Column Totals:** NA ● **Analysis Variables: None** ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- A glossary of all Adverse Events will be provided.
- Data will be ordered by MedDRA System Organ Class, MedDRA Preferred Term and Investigator-Specified Adverse Event Term.

Listing of Ongoing Adverse Events Ongoing at Treatment Discontinuation and still Ongoing 12 Months after Treatment Discontinuation:

STREAM Template	Description
N/A	Output ID: l_ae_ongo_pt* ● **Analysis Populations:** Safety-Evaluable Patients with Protocol 3+ Subset, Excluding Patients who Discontinued Treatment within 6 months Output will be repeated for different AE Groups: Muscle Spasms, Alopecia, Ageusia, Dysgeusia and Weight Decreased ● **Column Variables:** Subject ID, Age, Sex, Disease Status, Treatment Discontinuation Date, Study Discontinuation Date and Reason, MedDRA Preferred Term, AE Start Date, Relativity to Treatment Discontinuation, AE End Date, AE Toxicity Grade and AE Outcome.

Programming Note:

- Data will be ordered by Subject ID, AE Start Date and AE End Date within each AE Group.

Listing of Ongoing Adverse Events Ongoing at Treatment Discontinuation and still Ongoing at Last Assessment (12 Months Follow Up):

STREAM Template	Description
N/A	Output ID: l_ae_ongo_pt2* ● **Analysis Populations:** Safety-Evaluable Patients with Protocol Version 3 or more and who completed the 12 Months Follow Up Visit Output will be repeated for different AE Groups: Muscle Spasms, Alopecia, Ageusia, Dysgeusia and Weight Decreased ● **Column Variables:** Subject ID, Age, Sex, Disease Status, Treatment Discontinuation Date, Study Discontinuation Date and Reason, MedDRA Preferred Term, AE Start Date, Relativity to Treatment Discontinuation, AE End Date, AE Toxicity Grade and AE Outcome.

Programming Note:

- Complete for Patients who completed the study and their 12 month Follow Up Assessment
- Data will be ordered by Subject ID, AE Start Date and AE End Date within each AE Group.

Listing of Ongoing Adverse Events Ongoing at Treatment Discontinuation and still Ongoing at Last Assessment (12 Months Follow Up), Excluding Patients with Commercial Vismodegib:

STREAM Template	Description
N/A	Output ID: l_ae_ongo_pt3* ● **Analysis Populations:** Safety-Evaluable Patients with Protocol Version 3 or more and who completed the 12 Months Follow Up Visit, but exclude any Patients who took commercial Vismodegib Output will be repeated for different AE Groups: Muscle Spasms, Alopecia, Ageusia, Dysgeusia and Weight Decreased ● **Column Variables:** Subject ID, Age, Sex, Disease Status, Treatment Discontinuation Date, Study Discontinuation Date and Reason, MedDRA Preferred Term, AE Start Date, Relativity to Treatment Discontinuation, AE End Date, AE Toxicity Grade and AE Outcome.

Programming Note:

- Exclude Patients who took commercial Vismodegib between treatment discontinuation and 12 months after treatment discontinuation.
- Data will be ordered by Subject ID, AE Start Date and AE End Date within each AE Group.

Deaths:

Summary of Deaths:

STREAM Template	Description
N/A	Output ID: t_dd_* ● **Analysis Populations:** Safety ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Number of Patients Died, Primary Reason for Death ● **Statistics and Calculation Methods:** Use proq freq for events or proc sql for patient counts. ● **Numeric Precision and Formatting of Statistics:** Use DST01 standard template in the mockup ● **Optional Subsetting:** Primary Reason for Death: Adverse Event, Disease Progression, Other.

Summary of Deaths, Population : Safety-Evaluable Patients
Protocol: MO25616
Snapshot Date: 03 August 2015. Clinical Cut-Off Date: 16 March 2015.
File: t_dd_SE.

Status	Locally Advanced (N=1119)	Metastatic (N=96)	Total (N=1215)
Number of Patients who Died	92 (8.2%)	18 (18.8%)	110 (9.1%)
Primary Reason for Death	92 (8.2%)	18 (18.8%)	110 (9.1%)
Adverse Event	65 (5.8%)	6 (6.3%)	71 (5.8%)
Disease Progression	15 (1.3%)	12 (12.5%)	27 (2.2%)
Other	12 (1.1%)	0	12 (1.0%)

Program: /opt/BIOSTAT/prod/cdpt3616/mo25616/t_dd.sas
Output: /opt/BIOSTAT/prod/cdpt3616/i25616f/reports/t_dd_SE.out
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Laboratory Assessments:

Laboratory data that have been obtained using the Site's Local Ranges will be converted to System International (SI) units. The vendor will supply Roche with the Conversion factors to convert the results and local ranges to SI Units. All local units should be incorporated within the Conversion Factors document.

These Conversion Factors will then be reviewed by the Medical Review Team. The conversion factors will be applied directly to the raw data and reported as is; i.e. no adjustment for seemingly incorrect conversions will be performed.

Grading system NCI-CTC version 4 will be used to Grade the relevant tests.

Hematology and Chemistry Laboratory Data:

Listings will be produced for the hematology and chemistry laboratory parameters (LBCAT=HEMATOLOGY, LBCAT=CHEMISTRY).

Shift tables will also be presented for the laboratory parameters that have NCI CTC grade ranges available from baseline to worst CTC Grade on-treatment, split by High and Low Parameters where applicable.

A Listing of Patients with a CTC Grade 3 at Baseline moving to a CTC Grade 4 will be created, showing the Patient's CTC Grade 4 results.

Pregnancy:

Pregnancy results will be listed for all women of childbearing potential.

Serum Hormone:

Serum hormone evaluation tests and results will be listed for all women of childbearing potential.

Ultrasound:

Ultrasound results will be listed for all women of childbearing potential.

Creatine Kinase (CPK):

As part of the exploratory analysis, outputs will be produced with Creatine Kinase status (any Abnormal and No Abnormality) versus Treatment Emergent Muscle Spasm status (any Muscle Spasm Adverse Event and No Muscle Spasms).

A Listing of CPK Results and Adverse Events of Muscle Spasms will be created.

A table of CPK Elevations by maximum CTC Grade will be created.

A table of CPK Elevations with the maximum CTC Grade and relative to onset of first Treatment Emergent Muscle Spasm will be created.

A Listing of CPK results and any Adverse Events linked to specific elevated Lab Tests levels which will include CPK, ALT or AST and Renal Insufficiency will be created.

For Patients who consented to Protocol Version 4 and above, a shift table of maximum NCI CTC Grade of CPK Tests, before and after first recorded Treatment Emergent Muscle Spasm will be created.

A graph of CPK Results, together with 95% Confidence Intervals will be created.

Shift from Baseline to Worst NCI CTCAE Grade During Treatment:

STREAM Template	Description
N/A	Output ID: t_lb_shift_wrstctc_* ● **Analysis Population:** Safety Output will be repeated for each Lab Category. ● **Column Variables:** Baseline CTC Grades 0 to 4 ● **Column Totals:** Totals of non-missing Grades, Missing column ● **Analysis Variables:** For each Parameter (in either direction) and Disease Status (Locally Advanced, Metastatic), Worst Post-Baseline CTC Grades 0 to 4, Total of non-missing Grades, Missing row. ● **Statistics and Calculation Methods:** Use proc freq. ● **Numeric Precision and Formatting of Statistics:** Display whole numbers for patient counts and 1 decimal point for percentages.

Parameter: Alkaline Phosphatase (High)

Worst NCI-CTC Grade During Treatment Period	Baseline NCI-CTC Grade						
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Missing
Locally Advanced (N=1119)							
Grade 0	787 (70.3%)	29 (2.6%)	1 (<0.1%)	0	0	817 (73.0%)	14 (1.3%)
Grade 1	138 (12.3%)	83 (7.4%)	0	0	0	221 (19.7%)	7 (0.6%)
Grade 2	20 (1.8%)	12 (1.1%)	2 (0.2%)	0	0	34 (3.0%)	0
Grade 3	5 (0.4%)	2 (0.2%)	0	0	0	7 (0.6%)	0
Grade 4	0	0	0	0	0	0	0
Total	950 (84.9%)	126 (11.3%)	3 (0.3%)	0	0	1079 (96.4%)	21 (1.9%)
Missing	0	0	0	0	0	0	0
Metastatic (N=96)							
Grade 0	48 (50.0%)	8 (8.3%)	0	0	0	56 (58.3%)	1 (1.0%)
Grade 1	16 (16.7%)	14 (14.6%)	0	0	0	30 (31.3%)	1 (1.0%)
Grade 2	0	3 (3.1%)	2 (2.1%)	0	0	5 (5.2%)	0
Grade 3	0	0	0	1 (1.0%)	0	1 (1.0%)	0
Grade 4	0	0	0	0	0	0	0
Total	64 (66.7%)	25 (26.0%)	2 (2.1%)	1 (1.0%)	0	92 (95.8%)	2 (2.1%)
Missing	0	0	0	0	0	0	0

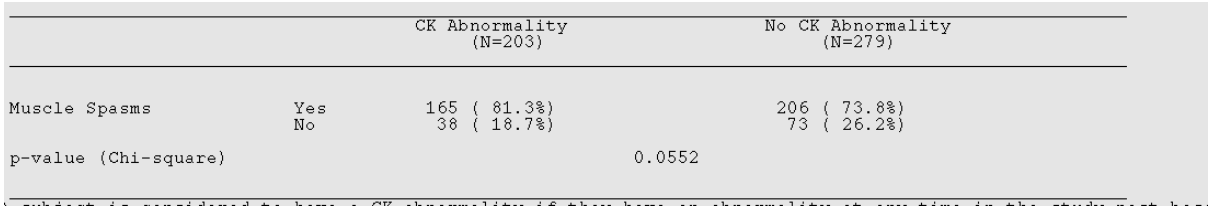
Baseline is the patient's last observation prior to initiation of study drug.
Note: Collected values have been converted using a Sponsor validated conversion file.

Programming Notes:

- Only include tests which occurred during Treatment.
- Select Worst Post-Baseline Grade for each Parameter and NCI CTC Grade Direction

Summary of CPK Abnormality Status versus Muscle Spasm Status:

STREAM Template	Description
N/A	Output ID: t_lb_chi_ck_* ● **Analysis Population:** Safety ● **Column Variables:** CK Abnormality, No CK Abnormality ● **Column Totals:** None ● **Analysis Variables:** Muscle Spasm status, p-value (Chi-square). ● **Statistics and Calculation Methods:** Use proc freq with Chi-square test. ● **Numeric Precision and Formatting of Statistics:** Display whole numbers for patient counts and 1 decimal point for percentages. ● **Optional Subsetting:** For Muscle Spasm status, split by Yes and No



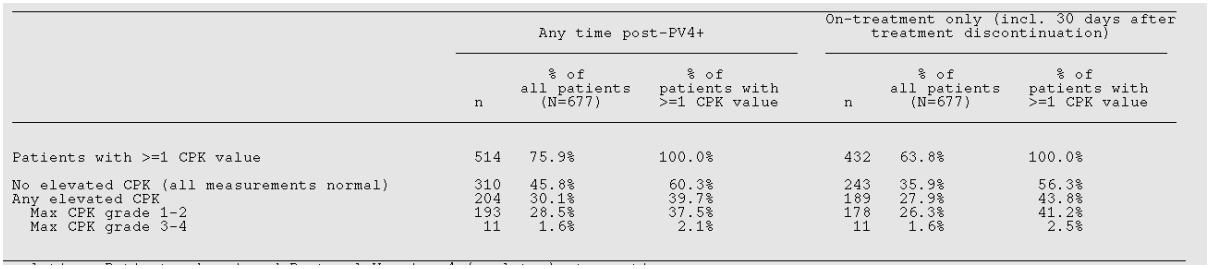
		CK Abnormality (N=203)	No CK Abnormality (N=279)
Muscle Spasms	Yes	165 (81.3%)	206 (73.8%)
	No	38 (18.7%)	73 (26.2%)
p-value (Chi-square)		0.0552	

Programming Notes:

- A Patient is considered to have a CK Abnormality if they have a CTC Grade 1 or above any time Post-baseline
- A Patient is considered to have a Muscle Spasm if they have a Treatment Emergent Adverse Event of Muscle Spasm.

Summary of CPK Elevations, by Maximum CTC Grade:

STREAM Template	Description
N/A	Output ID: t_lb_ck_* ● **Analysis Population:** Safety and consented to Protocol Version 4 and above ● **Column Variables:** Any time post-PV4+, On-treatment only (including 30 days after treatment discontinuation) ● **Column Totals:** None ● **Analysis Variables:** Patients with at least 1 CPK result, No Elevated CPK result, Any Elevated CPK Result. ● **Statistics and Calculation Methods:** Use proc freq. ● **Numeric Precision and Formatting of Statistics:** Display whole numbers for patient counts and 1 decimal point for percentages. ● **Optional Subsetting:** For Any Elevated CPK result, split by Max CPK Grade 1-2 and Max CPK Grade 3-4



	Any time post-PV4+			On-treatment only (incl. 30 days after treatment discontinuation)		
	n	% of all patients (N=677)	% of patients with >=1 CPK value	n	% of all patients (N=677)	% of patients with >=1 CPK value
Patients with >=1 CPK value	514	75.9%	100.0%	432	63.8%	100.0%
No elevated CPK (all measurements normal)	310	45.8%	60.3%	243	35.9%	56.3%
Any elevated CPK	204	30.1%	39.7%	189	27.9%	43.8%
Max CPK grade 1-2	193	28.5%	37.5%	178	26.3%	41.2%
Max CPK grade 3-4	11	1.6%	2.1%	11	1.6%	2.5%

Programming Notes:

- Only include Patients that have consented to Protocol Version 4 and above
- Select Worst Post-Baseline Grade for CPK tests within each Patient and group by Grades 1-2 and 3-4

Summary of CPK Elevations and Muscle Spasm AEs including Relative Timing of CPK Elevations with onset of First Muscle Spasm:

STREAM Template	Description
N/A	Output ID: t_ck_ms_* ● **Analysis Population:** Safety and consented to Protocol Version 4 and above ● **Column Variables:** No Muscle Spasm, With Muscle Spasm at any time, Prior to onset of 1st Muscle Spasm, After onset of 1st Muscle Spasm ● **Column Totals:** None ● **Analysis Variables:** Patients with at least 1 CPK result, No Elevated CPK result, Any Elevated CPK Result. ● **Statistics and Calculation Methods:** Use proc freq. ● **Numeric Precision and Formatting of Statistics:** Display whole numbers for patient counts and 1 decimal point for percentages. ● **Optional Subsetting:** For Any Elevated CPK result, split by Max CPK Grade 1, 2, 3 and 4

		With muscle spasm		
	No muscle spasm	At any time	Prior to onset of 1st muscle spasm	After onset of 1st muscle spasm
Patients with >=1 CPK value	120	62	43	60
No CPK elevation	76 (63.3%)	35 (56.5%)	31 (72.1%)	35 (58.3%)
Any CPK elevation	44 (36.7%)	27 (43.5%)	12 (27.9%)	25 (41.7%)
Max grade 1	36 (30.0%)	19 (30.6%)	10 (23.3%)	18 (30.0%)
Max grade 2	4 (3.3%)	5 (8.1%)	1 (2.3%)	5 (8.3%)
Max grade 3	3 (2.5%)	2 (3.2%)	1 (2.3%)	1 (1.7%)
Max grade 4	1 (0.8%)	1 (1.6%)	0	1 (1.7%)

Programming Notes:

- Only include Patients that have consented to Protocol Version 4 and above
- Select Worst Post-Baseline Grade for CPK tests within each Patient
- First Muscle Spasm refers to the first occurrence of Muscle Spasm after Protocol Version 4 consent date

Shift Table of Maximum CPK CTC Grade before and after onset of First Muscle Spasm:

STREAM Template	Description
N/A	Output ID: t_ck_ms_shift_* ● **Analysis Population:** Safety and consented to Protocol Version 4 and above ● **Column Variables:** Max CTC grade after onset of 1st Muscle Spasm ● **Column Totals:** None but include Missing column ● **Analysis Variables:** Max CTC Grade prior to onset of 1st Muscle Spasm, include Missing row ● **Statistics and Calculation Methods:** Use proc freq. ● **Numeric Precision and Formatting of Statistics:** Display whole numbers for patient counts and 1 decimal point for percentages. ● **Optional Subsetting:** For Max CTC Grade, split by Max CPK Grade 0, 1, 2, 3 and 4

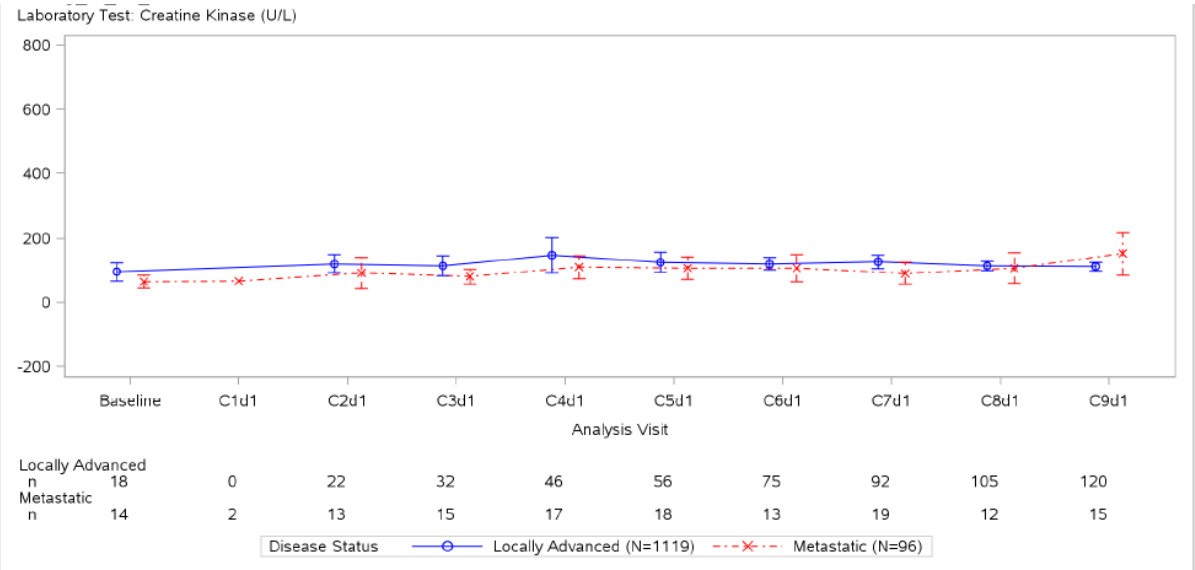
Max. CPK grade prior to onset of 1st muscle spasm	Max. CPK grade after onset of 1st muscle spasm					
	0	1	2	3	4	Missing
0	23	4	0	1	1	2
1	1	7	2	0	0	0
2	1	0	0	0	0	0
3	0	0	1	0	0	0
4	0	0	0	0	0	0
Missing	10	7	2	0	0	1

Programming Notes:

- Only include Patients that have consented to Protocol Version 4 and above
- Select Worst Post-Baseline Grade for CPK tests within each Patient
- First Muscle Spasm refers to the first occurrence of Muscle Spasm after Protocol Version 4 consent date

Plot of Mean and 95% CI of CPK over Time:

STREAM Template	Description
MNG01	Output ID: g_lb_ck_* • **Analysis Population:** Safety • **Plot:** 1 Line per Disease Status (Locally Advanced and Metastatic) • **Y Axis:** CPK Result • **X Axis:** Analysis Visits (use tick-marks for each Visit) • **Methods:** Use Standard STREAM method. • **Numeric Precision and Formatting of Statistics:** Display whole numbers for Y Axis and Visit descriptions for X Axis. • **Optional Additions:** Include N counts underneath each Visit for each Disease Status. Include Safety Population N count for each Disease Status in Legend.



Programming Notes:

- Include all visits from Baseline

Listing of CPK Results and Adverse Events of Muscle Spasm:

STREAM Template	Description
N/A	Output ID: l_ck_ae_* • **Analysis Population:** Safety • **Column Variables:** For Lab Data include Visit, Sample Date(with study Day), CPK Standard Result and CTC Grade. For Adverse Events of Muscle Spasm, include Reported Term, Start and End Date and CTC Grade

Disease Status: Locally Advanced

	Lab Data				AE Data			
Center/ Patient ID	Visit of CK Sample	Date of Lab Sample (day)	CK Value (U/L)	CTC Grade	Reported term of AE	Date of AE Start (day)	Date of AE End (day)	CTC Grade
[redacted]	C23D1	[redacted]		1	MUSCLE CRAMPS	[redacted]		1
	C25D1			0				
	C26D1			0				
	C27D1			0				
	C28D1			0				
	C29D1			0				
	C31D1			0				
	C32D1			0				
	C33D1			0				
	C34D1			0				
	C35D1			0				
	END OF STUDY			1				
	BASELINE			1				
					KRAMPS MUSCLE OF LEGS			3
					KRAMPS MUSCLE OF LEG			2
					NIGHT CRAMPS			1
					CRAMPS LEG			1
	FU 12 MONTHS			0				
	FU 6 MONTHS			0				
	FU 9 MONTHS			0				
	FU 12 MONTHS			0				

Programming Notes:

- Where possible, merge Lab CPK Samples Dates with AE Start Date of Muscle Spasms and display on same line

Listing of Creatine Kinase and Adverse Events Linked with [* (See below)].

Disease Status: Metastatic

	Lab Data				AE Data			
Center/ Patient ID	Visit of CK Sample	Date of Lab Sample (day)	CK Value (U/L)	CTC Grade	Reported term of AE	Date of AE Start (day)	Date of AE End (day)	CTC Grade
xxxxxx/xxx	CxxDx	xxxx-xx-xx (xxx)	xx	x	CREATININE SERUM HIGH	xxxx-xx-xx (xxx)	Ongoing	x
	FU xx DAYS	xxxx-xx-xx (xxx)	xx	x	CREATININE SERUM HIGH	xxxx-xx-xx (xxx)	Ongoing	x
	FU x MONTHS	xxxx-xx-xx (xxx)	xx	x	CREATININE SERUM HIGH	xxxx-xx-xx (xxx)	Ongoing	x
xxxxxx/xxx	FU xx DAYS	xxxx-xx-xx (xxx)	xx	x	CREATININE SERUM HIGH	xxxx-xx-xx (xxx)	xxxx-xx-xx (xxx)	x
xxxxxx/xxx	FU x MONTHS	xxxx-xx-xx (xxx)	xx.x	x				
xxxxxx/xxx	FU x MONTHS	xxxx-xx-xx (xxx)	xxx	x				
xxxxxx/xxx	CxDx	xxxx-xx-xx (xx)	xx	x				
	CxDx	xxxx-xx-xx (xx)	xx	x				
	END OF STUDY	xxxx-xx-xx (xxx)	xx	x				
	FU xx DAYS	xxxx-xx-xx (xxx)	xx	x				
	FU xx DAYS	xxxx-xx-xx (xxx)	xx	x				
	FU xx DAYS	xxxx-xx-xx (xxx)	xx	x				

Investigator text for AEs encoded using MedDRA version xx.x.
Listing shows Windowed Visits.
PRE-BASELINE Visits can include Screening or other visits collected prior to Dosing.
For some patients, Screening and Baseline visits were done on the same day and results were duplicated.

Programming Notes:

- Safety-Evaluable patients are included in the listing.
- * would be Creatine Kinase and Adverse Events of Linked to AE with Muscle Spasms, Elevated Creatinine, Renal Insufficiency, Elevant Transaminase (ALT or AST). (ie, Listing of Creatine Kinase and Adverse Events Linked with Muscle Spasms).
- Create a separate listing for Creatine Kinase and Adverse Events of Linked to AE with Muscle Spasms, Elevated Creatinine, Renal Insufficiency, Elevant Transaminase (ALT or AST).
- Where possible, merge Lab Creatine Kinase Samples Dates with AE Start Date of XXX AE and display on same line.
- Display all the records of lab Creatine Kinase which include Visit, Sample Date(with study Day), CPK Standard Result and CTC Grade. For Adverse Events include Reported Term, Start and End Date and CTC Grade.

Listing of Lab Data:

STREAM Template	Description
N/A	Output ID: l_lb_* ● **Analysis Population:** Safety Evaluable ● **Column Variables:** Center, Patient ID, Windowed Visit, relevant Lab test (within Lab Category) and results in SI Units.

Programming Note:

- Create Table for Lab Categories: Hematology and Biochemistry. Also repeat for all tests within Hematology and Biochemistry with a Shift from Grades 3 to 4.

Listing of Hormone Results for Subjects with Amenorrhea or Irregular Menses:

A subject is considered to have Amenorrhea or Irregular Menses if they have a record of either according the the AE CRF page.

STREAM Template	Description
N/A	Output ID: l_lb_hrm_* ● **Analysis Population:** Safety Evaluable ● **Column Variables:** Center, Patient ID, Parameter with SI Unit, Windowed Visit, Date of Sample Collection, Result in SI Units and High / Low Range indicator

Listing of Serum Pregnancy Results for Subjects with Amenorrhea or Irregular Menses:

A subject is considered to have Amenorrhea or Irregular Menses if they have a record of either according the the AE CRF page.

STREAM Template	Description
N/A	Output ID: l_lb_preg_* ● **Analysis Population:** Safety Evaluable ● **Column Variables:** Center, Patient ID, Windowed Visit, Date of Sample Collection, Character Result and Specimen Type

Listing of Ultrasound Results for Subjects with Amenorrhea or Irregular Menses:

A subject is considered to have Amenorrhea or Irregular Menses if they have a record of either according the the AE CRF page.

STREAM Template	Description
N/A	Output ID: l_lb_ult_* ● **Analysis Population:** Safety Evaluable ● **Column Variables:** Center, Patient ID, Windowed Visit, Date of Examination, Character Result, Abnormality Specified, Is Abnormality Significant? and Method of Test or Examination

ECG:

Statistical Summary of Electrocardiogram

DMT01	Output ID: t_eg_* • **Analysis Population:** Safety-Evaluable Patients • **Column Variables:** Disease status (Locally Advanced, Metastatic) • **Column Totals:** Total of non-missing Disease status • **Analysis Variables:** Number of Patients in each Visit with ECG results Number of Patients with ECG Normal Result in each Visit Number of Patients with Abnormal, not clinically relevant in each Visit Number of Patients with Abnormal, not clinically relevant in each Visit • **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- Summary will be displayed by Visit.
- Baseline is the patient's last observation prior to initiation of study drug.
- If multiple records were collected during the same cycle, then the worst record within that cycle is used for the analysis.

Listing of Electrocardiogram

ECG data will be listed. Displayed columns will be: Subject ID; Disease Status; Age; Sex; Race; Windowed Visit; Date of ECG; ECG Status; ECG Result.

Vitals:

Statistical Summary of Vital Signs, Population

VST01	Output ID: t_vs_* ● **Analysis Population:** Safety-Evaluable Patients ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Following parameters are to be summarized. o Diastolic Blood Pressure o Systolic Blood Pressure o Heart Rate o Temperature o Weight ● **Statistics and Calculation Methods:** Use proc means or proc univariate. o n, mean (SD), median, 25th-75th Percentiles and min-max statistics are to be included in the table. o N in the column heading is the number of patients in a disease status in the analysis population. n in the rows is the number of patients with available data at the visit. o Change from baseline at Visit X is defined as (Visit X value – baseline value). Only patients with non-missing values at both baseline and Visit X are included in calculating change from baseline at Visit X. o All Visit after Windowing would be displayed in this table. With repeat Vital sign measurements in a same Visit, the last non-missing value is reported. o Vital sign measurements collected 30 days after the last dose of study drug should be excluded from summaries of actual values and changes from baseline. ● **Numeric Precision and Formatting of Statistics:** Level of precision for means, SDs, and medians is one digit more than the level of precision

	of the vital sign measurement (e.g. pulse reported to a single place after the decimal point). Present the minimum and maximum to the level of precision of the measurement.

Output Specifications: Questionnaires

ECOG:

Patients will be graded according to the Eastern Cooperative Oncology Group performance status scale and criteria as described below at each scheduled Visit mentioned in the Protocol:

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Shift Table from Baseline: Eastern Cooperative Oncology Group Performance Score

Visit: C1D1

	Status at Baseline							
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Missing	Total
Locally Advanced (N=xxxx)								
Grade 0	x (x.x%)	x	x	x	x	x	x	x (x.x%)
Grade 1	x (x.x%)	x (x.x%)	x	x	x	x	x	x (x.x%)
Grade 2	x	x (<x.x%)	x	x	x	x	x	x (<x.x%)
Grade 3	x	x	x	x	x	x	x (<x.x%)	x (<x.x%)
Grade 4	x	x	x	x	x	x	x	x
Grade 5	x	x	x	x	x	x	x	x
Missing	x	x	x	x	x	x	x	x
Total	x (x.x%)	x (x.x%)	x	x	x	x	x (<x.x%)	xx (x.x%)
Metastatic (N=xxxx)								
Grade x	x (x.x%)	x	x	x	x	x	x	x (x.x%)
Grade x	x	x	x	x	x	x	x	x
Grade x	x	x	x	x	x	x	x	x
Grade x	x	x	x	x	x	x	x	x
Grade x	x	x	x	x	x	x	x	x
Grade x	x	x	x	x	x	x	x	x
Missing	x	x	x	x	x	x	x	x
Total	x (x.x%)	x	x	x	x	x	x	x (x.x%)

Programming Note:

- N is Number of Patients in each Disease Status.
- Shift of ECOG Grade for each Visit from Baseline will be summarised.
- Percentages will be calculated based on N in each Disease status.
- If multiple records were collected during the same cycle, then the last record within that cycle is used for the analysis.
- Population : Intent to treat Population

Skindex-16 QoL Questionnaire:

Skindex-16 (Appendix 1) is a 16-question instrument that has been validated to accurately measure the extent patients are bothered by certain skin conditions. Each question asks the degree to which a patient has been concerned by their specific skin condition in the week prior to administration of the questionnaire. Patients answer every question with a number ranging from 0 ("never bothered") to 6 ("always bothered"). In terms of scoring algorithm, responses to each item are transformed to a linear scale of 100, varying from 0 ("never bothered") to 100 ("always bothered"). Thus, each item has a minimum score of 0 and a maximum score of 100. With the exception of the 16 individual scores, three domain scores (symptom [items 1 – 4], emotion [items 5 – 11], and function [items 12 – 16] are grouped and calculated as their means ranging from 0 to 100).

Below Table summarizes the Skindex-16 scoring algorithm.

Table: Skindex-16 Scoring Algorithm

Question	Response Option and Score Algorithm[1]
During the past week, how often have you been bothered by:	If Q(i) = "never bothered," then single item original score Q(i)=0 if Q(i)="always bothered," then single item original score Q(i) = 6
Question 1 - 4: 1) Itching, 2) Burning/stinging 3) Hurting 4) Being irritated	Individual Skindex-16 Q1 to Q4 = (original item score)*100/6
	Symptom Domain Score = [(sum of original item scores of Q1 to Q4)*100/6]/4
Question 5 - 11: 5) Persistence/reoccurrence 6) Worry 7) Appearance 8) Frustration 9) Embarrassment	Individual Skindex-16 Q5 to Q11 = (original item score)*100/6
	Emotion Domain Score = [(sum of original item scores of Q5 to

10) Being annoyed 11) Feeling depressed	Q11)*100/6]/7
Question 12 - 16: 12) Interaction with others, 13) Desire to be with people, 14) Show affection 15) Daily activities 16) Work or do what you enjoy	Individual Skindex-16 Q12 to Q16 = (original item score)*100/6
	Function Domain Score = [(sum of original item scores of Q12 to Q16)*100/6]/5

Note: Q = question item

[1] The “50% missing rule” which is commonly cited and used in patient-reported outcome analysis is used. If more than 2 items for the symptom domain, more than 4 items for the emotion domain, or more than 3 items for the function domain are missing, their respective domain values should be regarded as missing. Otherwise, the sum of the nonmissing item scores should be calculated as the domain score by using the formula stated in the table and denominator should be total no. item with non-missing score.

Skindex-16 Analysis of Composite Domains Scores and Individual Item Scores:

VST01	Output ID: t_sk_* ● **Analysis Population:** Intent-to-Treat Patients with measurable disease at baseline. Outputs will be repeated for Change from Baseline for Composite Domains Scores and Individual Item Scores. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Following parameters are to be summarized. o Composite Domain (Emotion, Function and Symptom) o Individual Item (Itching, Burning Or Stinging, Hurting, Being Irritated, Persistence/Reoccurrence, Worry, Appearance, Frustration, Embarrassment, Being Annoyed, Feeling Depressed, Interaction With Others, Desire To Be With People, Show Affection, Daily Activities, Work Or Do What You Enjoy) ● **Statistics and Calculation Methods:** Use proc means or proc univariate. o n, mean (SD), median, and min-max statistics are to be included in the table. o N in the column heading is the number of patients in a disease status in the analysis population. n in the rows is the number of patients with available data at the visit. o Change from baseline at Visit X is defined as (Visit X value – baseline value). Only patients with non-missing values at both baseline and Visit X are included in calculating change from baseline at Visit X. o All Visit after Windowing would be displayed in this table. With repeat Individual Item Score or Domain Score in a same Visit, the last non-missing Score is reported. o Individual Item Score or Domain Score collected 30 days after the last dose of study

	drug should be excluded from summaries of actual values and changes from baseline. ● **Numeric Precision and Formatting of Statistics:** Display 1 decimal point for Min-Max and 2 decimal points for Mean, SD and Median.

Skindex-16 Analysis of Composite Domains Scores and Individual Item Scores:

VST01	Output ID: t_sk2_* ● **Analysis Population:** Intent-to-Treat Patients with Excludes patients with non-histologically confirmed disease. Outputs will be repeated for Change from Baseline for Composite Domains Scores and Individual Item Scores. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Following parameters are to be summarized. o Composite Domain (Emotion, Function and Symptom) o Individual Item (Itching, Burning Or Stinging, Hurting, Being Irritated, Persistence/Reoccurrence, Worry, Appearance, Frustration, Embarrassment, Being Annoyed, Feeling Depressed, Interaction With Others, Desire To Be With People, Show Affection, Daily Activities, Work Or Do What You Enjoy) ● **Statistics and Calculation Methods:** Use proc means or proc univariate. o n, mean (SD), median, and min-max statistics are to be included in the table. o N in the column heading is the number of patients in a disease status in the analysis population. n in the rows is the number of patients with available data at the visit. o Change from baseline at Visit X is defined as (Visit X value – baseline value). Only patients with non-missing values at both baseline and Visit X are included in calculating change from baseline at Visit X. o All Visit after Windowing would be displayed in this table. With repeat Individual Item Score or Domain Score in a same Visit, the last non-missing Score is reported. o Individual Item Score or Domain Score

	collected 30 days after the last dose of study drug should be excluded from summaries of actual values and changes from baseline. ● **Numeric Precision and Formatting of Statistics:** Display 1 decimal point for Min-Max and 2 decimal points for Mean, SD and Median.

M.D. Anderson Symptom Inventory (MDASI):

MDASI contains 20 questions aimed to measure symptom severity. These questions are split across two sections.

The first section contains 14 questions. Each question asks the severity that patients feel for specific symptoms at that visit. Patients answer every question with a number ranging from 0 (“Not Present”) to 10 (“As Bad As You Can Imagine”). The 14 questions are outlined on the eCRF.

The second section contains 6 questions. Each question asks how much specific symptoms affect subjects’ lives in general. Patients answer every question with a number ranging from 0 (“Did Not Interfere”) to 10 (“Interfered entirely”). The 6 questions are outlined on the eCRF.

Disease Related Symptoms:

The study has some specific items which are considered to be ‘Disease Related Symptoms’. These items are as follows:

Item 1: Pain

Item 2: Fatigue

Item 6: Shortness of Breath

Item 8: Lack of Appetite

Item 10: Dry Mouth

Item 14: Coughing

MDASI Individual Item Scores:

VST01	Output ID: t_md_* ● **Analysis Population:** Intent-to-Treat Patients with measurable disease at baseline. Outputs will be repeated for Change from Baseline for Individual Item Scores. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Following parameters are to be summarized. o Individual Items ● **Statistics and Calculation Methods:** Use proc means or proc univariate. o n, mean (SD), median, and min-max statistics are to be included in the table. o N in the column heading is the number of patients in a disease status in the analysis population. n in the rows is the number of patients with available data at the visit. o Change from baseline at Visit X is defined as (Visit X value – baseline value). Only patients with non-missing values at both baseline and Visit X are included in calculating change from baseline at Visit X. o All Visit after Windowing would be displayed in this table. With repeat Individual Item Score or Domain Score in a same Visit, the last non-missing Score is reported. o Individual Item Score collected 30 days after the last dose of study drug should be excluded from summaries of actual values and changes from baseline. ● **Numeric Precision and Formatting of Statistics:** Display 1 decimal point for Min-Max and 2 decimal points for Mean, SD and Median.

MDASI Reductions for Patients with Disease Related Symptoms:

The protocol suggests that the MDASI reduction in disease related symptoms should only be considered for patients who had four (or more) MDASI points at baseline, in order to obtain a meaningful assessment of reduction in severity from baseline. It is unclear whether this 4 points would be a patient's average baseline score, or baseline score from any domain. The following output, therefore, was created for all patients with a baseline MDASI, patients with any score of 4 or higher at baseline, and patients with an average baseline score of 4 or higher.

	Metastatic (N=XX)	Total (N=XX)
30% Reduction in Disease Related Symptoms		
n	xx	xx
Yes	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)

Programming Note:

1. This output will be repeated for different subsets of patients.
2. MDASI was only collected for Metastatic patients, so only display the Metastatic column.
3. Percentages should be based upon the small n.
4. 30% reductions is any 30% reduction in a given analysis variable. See titles and footnotes in the lopo for these different reduction criteria.
5. N is the number of patients within the specific population.
6. Only include the questions for Disease Related Symptoms.
7. If a subject has had a reduction for the given criteria (see 30% reduction note) then they would appear in 'yes' and not in 'no'.

Output Specifications: Efficacy Tables

Best Response:

1) Best Confirmed overall response.

RSPT01	Output ID: t_rs_best_* ● **Analysis Population:** Patients with measurable disease at baseline, excluding patients without histologically confirmed BCC. Outputs will be repeated for different population combinations - please see the LoPO for details of these combinations, and the Efficacy Population section for details on populations. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Response variable is the Best Overall Response: Complete Response, Partial Response, Stable Disease, Progressive Disease, Not evaluable, or Missing. ● **Statistics and Calculation Methods:** Use proq freq. o Display Patients with histologically-confirmed measurable disease at baseline o CIs for Best Overall Response Rate presented in the table are displayed as percentages, i.e. the actual values multiplied by 100. o α level for CIs is 2-sided 5%. o Method of Clopper-Pearson is to be used to derive 95% CI for proportion. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup ● **Optional Subsetting:** Display Response categories i.e. Complete Response, Partial Response, Stable Disease, Progressive Disease, Missing, or Not evaluable, are displayed with percentage.

Programming Notes:

- Best Overall Response (BOR) would be Complete Response (CR) if subject had CR on each of two tumor assessments which are greater than or equal to 23 days apart (with either no other tumor assessments in between or the tumor response between these two assessments is CR or Not Evaluable (NE)).

- Best Overall Response would be Partial Response (PR) if subject's best overall response is not CR and the subject had two tumor assessments greater than or equal to 23 days apart with the response of the first assessment being PR and the second being PR or CR (with either no other tumor assessments in between or the tumor response between these two assessments being CR, PR, or NE).
- Best Overall Response would be Stable Disease (SD) if subject's best overall response is not CR or PR, and there is at least one response assessment of CR, PR or SD with minimum of 51 days after First Dose Date without any Progressive Disease (PD) in between.
- Best Overall Response would be Progression Disease (PD) if subject's best overall response is not CR, PR, or SD, and if there is at least one response assessment of PD.
- Best Overall Response would be Not Evaluable (NE) if subject's best overall response is not CR, PR, SD, or PD, and there is at least one response assessment of NE.
- BOR would be PD if PD occurred before satisfying any of the above criteria of Best Overall Response.
- Patients who achieve best overall response of CR or PR are considered a responder.
- Best overall response rate is defined as the number of patients with a CR or PR observed at two consecutive assessments >=4 weeks apart (>= 23 days) divided by the total number of patients with histologically confirmed measurable disease at baseline.
- N in column headings is the number of patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC. Percentages are calculated based on the number of patients with a measurable disease at baseline and histologically confirmed BCC.
- Display only Responder and 95%CI for Best Overall Response Rate.

2) Best Confirmed Overall Response (Measurable Disease at Baseline) by Location of Metastatic Disease

Output ID: t_rs_best_byloc*

Repeat t_rs_best* output by Location of Metastatic Disease as on the “Disease History of advanced or metastatic BCC” CRF page.

3) Best Confirmed Overall Response (Non-Measurable Disease at Baseline)

Output ID: t_rs_nonm*

Repeat t_rs_best* output for patients with non-measurable disease at baseline.

Programming Note:

- Percentages are calculated based on the number of patients with a non-measurable disease at baseline and histologically confirmed BCC.
- Only patients with non-measurable disease at baseline and histologically confirmed BCC should be included in the table.

Duration of Response:

TTET01	Output ID: t_tte_OBJRDR_* ● **Analysis Population:** Intent-to-Treat Patients with measurable disease at baseline, excluding patients without histologically confirmed BCC. Outputs will be repeated for different population combinations - please see the LoPO for details of these combinations, and the Efficacy Population section for details on populations. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Duration of response in Months ● **Statistics and Calculation Methods:** Use proc freq and proc lifetest. o α level for CIs is 2-sided 5%. o Use proc lifetest to obtain time to event (Median, Percentiles) information. The 95% confidence interval for the median is calculated using the Brookmeyer & Crowley method. o Range, 25th and 75th Percentiles are displayed. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- Duration of response will be calculated only for patients whose confirmed best response is CR or PR.
- Duration of response is the interval between the Date of First Response and the Date of Progressive Disease or Death, and is calculated only for patients with confirmed best response of CR or PR at two consecutive assessments >= 23 days.
- Patients without Progression of Disease or Death will be censored at the date of last tumour assessment and the duration of response is calculated using the interval between Date of First Response and the date of last tumour assessment.
- N would be the number of patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC.
- Percentages are based on the number of patients with a measurable disease at baseline and histologically confirmed BCC, and who had a CR or PR.
- Duration of response will be calculated in Months.

Time to Response:

TTET01	Output ID: t_tte_TMTRS_* ● **Analysis Population:** Intent-to-Treat Patients with measurable disease at baseline, excluding patients without histologically confirmed BCC. Outputs will be repeated for different population combinations - please see the LoPO for details of these combinations, and the Efficacy Population section for details on populations. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Time to response in patients with Best Overall Response (BOR) and patients without BOR in Months ● **Statistics and Calculation Methods:** Use proq freq and proc lifetest. o α level for CIs is 2-sided 5%. o Use proc lifetest to obtain time to event (Median, Percentiles) information. The 95% confidence interval for the median is calculated using the Brookmeyer & Crowley method. o Range, 25th and 75th Percentiles are displayed. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- Time to response is defined as the interval between the date of first treatment and the date of first documentation of confirmed CR or PR (whichever occurs first).
- Patients without CR or PR will be censored at the date of last tumour assessment.
- N would be the number of patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC.
- Percentages are based on the number of patients with a measurable disease at baseline and histologically confirmed BCC.

Progression Free Survival:

TTET01	Output ID: t_tte_PFS_* ● **Analysis Population:** Intent-to-Treat Patients, excluding patients without histologically confirmed BCC. Outputs will be repeated for different population combinations - please see the LoPO for details of these combinations, and the Efficacy Population section for details on populations. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Progression Free Survival in Months ● **Statistics and Calculation Methods:** Use proq freq and proc lifetest. o α level for CIs is 2-sided 5%. o Use proc lifetest to obtain time to event (Median, Percentiles) information. The 95% confidence interval for the median is calculated using the Brookmeyer & Crowley method. o Range, 25th and 75th Percentiles are displayed. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- Progression-Free Survival is defined as the interval between the date of first treatment and the date of Progressive Disease or Death.
- Patients without disease progression or death will be censored at the date of last tumour assessment.
- N would be the number of patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC.
- Percentages are based on N.
- Patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC are included in the analysis.

Overall Survival:

TTET01	Output ID: t_tte_OS_* ● **Analysis Population:** Intent-to-Treat Patients, excluding patients without histologically confirmed BCC. Outputs will be repeated for different population combinations - please see the LoPO for details of these combinations, and the Efficacy Population section for details on populations. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** Totals of non-missing Disease Status ● **Analysis Variables:** Overall Survival in Months ● **Statistics and Calculation Methods:** Use proq freq and proc lifetest. o α level for CIs is 2-sided 5%. o Use proc lifetest to obtain time to event (Median, Percentiles) information. The 95% confidence interval for the median is calculated using the Brookmeyer & Crowley method. o Range, 25th and 75th Percentiles are displayed. ● **Numeric Precision and Formatting of Statistics:** Use standard display in the mockup

Programming Note:

- Overall Survival is defined as the interval between the date of first treatment and the date of Death (see above for derivation of date of death).
- Patients who remain alive will be censored at the last date known to be alive.
- N would be the number of patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC.
- Percentages are based on N.
- Patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC are included in the analysis.

For deriving the Date Last Known Alive, please use the standard STREAM default derivation, excluding lab dates.

Kaplan Meier Plot of Duration of Response:

KMG01	Output ID: g_rs_km_OBJRDR_IT ● **Analysis Population:** Intent-to-Treat Patients with measurable disease at baseline, excluding patients without histologically confirmed BCC. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** NA ● **Analysis Variables:** Plot Survival Distribution Function ● **Statistics and Calculation Methods:** Kaplan-Meier using PROC LIFETEST. o α level is 2-sided 5%. o Use proc lifetest to obtain time to event information in months. ● **Numeric Precision and Formatting of Statistics:** o Display censored values by flagging with cross "+" marks. o Label of X axis should be "Time" and Y axis should be "Survival Distribution Function".

Programming Note:

- Duration of response will be calculated only for patients whose confirmed best response is CR or PR.
- Duration of response is interval between the Date of First Response and the Date of Progressive Disease or Death, and is calculated only for patients with confirmed best response of CR or PR at two consecutive assessments >= 23 days.
- Patients without disease progression or death will be censored at the date of last tumour assessment and the duration is calculated using the interval between the Date of First Response and the date of last tumour assessment.
- Legend should display the number of patients with measurable disease at baseline and histologically confirmed BCC for each Disease Status.
- Patients with measurable disease at baseline and histologically confirmed BCC should only be included in the analysis.
- Display No. of Subject at Risk for each Disease Status.

Kaplan Meier Plot of Progression-Free Survival:

KMG01	Output ID: g_rs_km_PFS_IT ● **Analysis Population:** Intent-to-Treat Patients, excluding patients without histologically confirmed BCC. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** NA ● **Analysis Variables:** Plot Survival Distribution Function ● **Statistics and Calculation Methods:** Kaplan-Meier using PROC LIFETEST. o α level is 2-sided 5%. o Use proc lifetest to obtain time to event information in months. ● **Numeric Precision and Formatting of Statistics:** o Display censored values by flagging with cross "+" marks. o Label of X axis should be "Time" and Y axis should be "Survival Distribution Function".

Programming Note:

- Progression-Free Survival is defined as the interval between the date of first treatment and the date of Progressive Disease or Death.
- Patients without disease progression or death will be censored at the date of last tumour assessment.
- Legend should display the number of patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC for each Disease Status.
- Patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC are included in the analysis.
- Display No. of Subject at Risk for each Disease Status.

Kaplan Meier Plot of Overall Survival:

KMG01	Output ID: g_rs_km_OS_IT ● **Analysis Population:** Intent-to-Treat Patients, excluding patients without histologically confirmed BCC. ● **Column Variables:** Disease Status (Locally Advanced, Metastatic) ● **Column Totals:** NA ● **Analysis Variables:** Plot Survival Distribution Function ● **Statistics and Calculation Methods:** Kaplan-Meier using PROC LIFETEST. o α level is 2-sided 5%. o Use proc lifetest to obtain time to event information in months. ● **Numeric Precision and Formatting of Statistics:** o Display censored values by flagging with cross "+" marks. o Label of X axis should be "Time" and Y axis should be "Survival Distribution Function".

Programming Note:

- Overall Survival is defined as the interval between the date of first treatment and the date of Death.
- Patients who remain alive will be censored at the last date known to be alive.
- see above output ID for t_tte_OS_* for derivation of date of death & last date known to be alive
- Legend should display the number of patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC for each Disease Status.
- Patients with a measurable or non-measurable disease at baseline and histologically confirmed BCC are included in the analysis.
- Display No. of Subject at Risk for each Disease Status

Overall Lesion Assessment:

output ID: l_tu_lsass_IT

Disease Status: Locally Advanced

Center/ Patient ID	Date of Assessment	Response of Target Lesions	Response of Non-Target Lesions	Overall Response at Visit	Date of Progression	Post-progression Management	Any New Lesions
xxxxxx/xxx	xxxx-xx-xx	SD	NON CR/PD	SD			No
	xxxx-xx-xx	PR	NON CR/PD	PR			No
	xxxx-xx-xx	PR	NON CR/PD	PR			No
	xxxx-xx-xx	CR	CR	CR*			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
	xxxx-xx-xx	CR	CR	CR			No
xxxxxx/xxx	xxxx-xx-xx	SD		SD*			No
	xxxx-xx-xx	SD		SD			No
	xxxx-xx-xx	SD		SD			No
	xxxx-xx-xx	SD		SD			No
	xxxx-xx-xx			PD	xxxxxxxxx	END OF TREATMENT	Yes
xxxxxx/xxx	xxxx-xx-xx	SD	NON CR/PD	SD			No
	xxxx-xx-xx	SD	NON CR/PD	SD*			No
xxxxxx/xxx	xxxx-xx-xx	SD	NON CR/PD	SD			No
	xxxx-xx-xx	PR	NON CR/PD	PR*			No
	xxxx-xx-xx	CR	NON CR/PD	PR			No

*Best overall response.

Programming Note:

- There can be multiple rows per subject: one row for each tumor assessment . Best overall response will be flagged (asterisk). See ‘Best Overall Response’ section for details on this derivation.
- Patients with non-histologically confirmed disease are excluded from the listing.
- Refer to CRF page ‘Overall Lesion Assessment’ for reporting.
- Population: Intent-to-Treat Patients.

Listing of Overall Lesion Assessment: New Lesions:

output ID: l_tu_lsass_newls_IT

Disease Status: Locally Advanced

Center/ Patient ID	Date New Lesion Identified	Organ Site	Specific Location	Method of Assessment	Was Photo taken
xxxxxx/xxx	xxxx-xx-xx	OTHER	left orbital region	SPIRAL CT SCAN	Yes
xxxxxx/xxx	xxxx-xx-xx	OTHER	ethmoid	SPIRAL CT SCAN	Yes
xxxxxx/xxx	xxxx-xx-xx	NOSE	nasal cavity		Yes
xxxxxx/xxx	xxxx-xx-xx	BONE	Lesion growing from orbitabone	SPIRAL CT SCAN	No
xxxxxx/xxx	xxxx-xx-xx	SKIN/SOFT TISSUE	left ala of the nose		Yes
xxxxxx/xxx	xxxx-xx-xx	FOREHEAD	left side of the face on the wall of the sinus amillaris sin.	SPIRAL CT SCAN	No
xxxxxx/xxx	xxxx-xx-xx	SKIN/SOFT TISSUE	zigomatic region (left)		No
xxxxxx/xxx	xxxx-xx-xx	SKIN/SOFT TISSUE	left inferior eyelid		No
xxxxxx/xxx	xxxx-xx-xx	SKIN/SOFT TISSUE	peritumoral nodules on right shoulder		Yes
	xxxx-xx-xx	SKIN/SOFT TISSUE	peritumoral nodules on right shoulder		Yes
	xxxx-xx-xx	SKIN/SOFT TISSUE	peritumoral nodules on right shoulder		Yes
	xxxx-xx-xx	SKIN/SOFT TISSUE	peritumoral nodules on right shoulder		Yes
xxxxxx/xxx	xxxx-xx-xx	CHEEK	right side		Yes
	xxxx-xx-xx	OTHER	right temple		Yes
xxxxxx/xxx	xxxx-xx-xx	EAR	left auricle		Yes
xxxxxx/xxx	xxxx-xx-xx	FOREHEAD	middle of the forehead		Yes

Programming Note:

- Patients with non-histologically confirmed disease are excluded from the listing.
- Refer to the “Overall Lesion Assessment” CRF page (‘New Lesion details Entry’ section) for reporting.
- Population: Intent-to-Treat Patients.

Target Lesion Assessment:

output ID: l_tu_lsass_tgt_IT

Disease Status: Locally Advanced

Center/ Patient ID	Date of Assessment	Response of Target Lesion	Organ Site	Specific Location	Method of Assessment	Diameter (mm)	Sum of Diameters (mm)	Any Non-target Lesions Identified
xxxxxx/xxx	xxxx-xx-xx	NE	SKIN/SOFT TISSUE	Scalp forehead	CLINICAL EXAMINATION WITH PHOTOGRAPHY			Yes
	xxxx-xx-xx	NE	SKIN/SOFT TISSUE	Scalp Left side.	CLINICAL EXAMINATION WITH PHOTOGRAPHY			Yes
		NE	SKIN/SOFT TISSUE	Scalp forehead	CLINICAL EXAMINATION WITH PHOTOGRAPHY			Yes
	xxxx-xx-xx	NE	SKIN/SOFT TISSUE	Scalp Left side.	CLINICAL EXAMINATION WITH PHOTOGRAPHY			Yes
		NE	SKIN/SOFT TISSUE	Scalp forehead	CLINICAL EXAMINATION WITH PHOTOGRAPHY			Yes
	xxxx-xx-xx	PR	SKIN/SOFT TISSUE	Scalp forehead	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes
		PR	SKIN/SOFT TISSUE	Scalp Left side.	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes
	xxxx-xx-xx	CR	SKIN/SOFT TISSUE	Scalp Left side.	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes
		CR	SKIN/SOFT TISSUE	Scalp forehead	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes
	xxxx-xx-xx	CR	SKIN/SOFT TISSUE	Scalp Left side.	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes
		CR	SKIN/SOFT TISSUE	Scalp forehead	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes
	xxxx-xx-xx	CR	SKIN/SOFT TISSUE	Scalp Left side.	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes
		CR	SKIN/SOFT TISSUE	Scalp forehead	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes
	xxxx-xx-xx	CR	SKIN/SOFT TISSUE	Scalp Left side.	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes
		CR	SKIN/SOFT TISSUE	Scalp forehead	CLINICAL EXAMINATION WITH PHOTOGRAPHY	x	x	Yes

BML = Below measurable limit.

Programming Note:

- Patients with non-histologically confirmed disease are excluded from the listing.
- Refer to the “Target Lesion Assessment” CRF page for reporting.
- Population: Intent-to-Treat Patients.

Non-Target Lesion Assessment:

output ID: l_tu_lsass_ntgt_IT

Disease Status: Locally Advanced

					Follow-up Entry			
Center/ Patient ID	Date of Assessment	Organ Site	Specific Location	Method of Assessment	Date of Examination	Response of Non-target Lesion	Method of Assessment	Status of Lesion
xxxxxx/xxx	xxxx-xx-xx	SKIN/SOFT TISSUE	chest	CLINICAL EXAMINATION WITH PHOTOGRAPHY	xxxx-xx-xx	CR	CLINICAL EXAMINATION WITH PHOTOGRAPHY	ABSENT
		SKIN/SOFT TISSUE	chest	CLINICAL EXAMINATION WITH PHOTOGRAPHY	xxxx-xx-xx	CR	CLINICAL EXAMINATION WITH PHOTOGRAPHY	ABSENT
		SKIN/SOFT TISSUE	chest	CLINICAL EXAMINATION WITH PHOTOGRAPHY	xxxx-xx-xx	NON CR/PD	CLINICAL EXAMINATION WITH PHOTOGRAPHY	PRESENT
		SKIN/SOFT TISSUE	chest	CLINICAL EXAMINATION WITH PHOTOGRAPHY	xxxx-xx-xx	NON CR/PD	CLINICAL EXAMINATION WITH PHOTOGRAPHY	PRESENT
		SKIN/SOFT TISSUE	chest	CLINICAL EXAMINATION WITH PHOTOGRAPHY	xxxx-xx-xx	NON CR/PD	CLINICAL EXAMINATION WITH PHOTOGRAPHY	PRESENT
		SKIN/SOFT TISSUE	chest	CLINICAL EXAMINATION WITH PHOTOGRAPHY	xxxx-xx-xx	NON CR/PD	CLINICAL EXAMINATION WITH PHOTOGRAPHY	PRESENT
		SKIN/SOFT TISSUE	chest	CLINICAL EXAMINATION WITH PHOTOGRAPHY	xxxx-xx-xx	NON CR/PD	CLINICAL EXAMINATION WITH PHOTOGRAPHY	PRESENT

Programming Note:

- Patients with non-histologically confirmed disease are excluded from the listing.
- Refer to the “Non-Target Lesion Assessment” CRF page for reporting.
- Population: Intent-to-Treat Patients.