Clinical Study Report SYM 2016-02 Appendix Table of Contents

Appendix 16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan Amendment #1

Protocol No.:   SYM 2016-02

Title: A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra + (with Lidocaine) versus Revanesse® Ultra for the Correction of Nasolabial Folds

Previous SAP (v1.0) Date: October 07, 2016

Amendment 01 Date: March 17, 2017

Sponsor: Prollenium Medical Technologies Inc.
138 Industrial Parkway North
Aurora Ontario
L4G 4C3
Canada

Amendments:

1. Original text and location

5.3 Demographics and Baseline Characteristics

Baseline and demographic characteristic variables (including date of birth, sex, race, ethnicity, and Fitzpatrick skin type) will be tabulated using descriptive statistics. For each continuous variable, the summary will include the mean, standard deviation (SD), median, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages.

Revised text and location

5.3 Demographics and Baseline Characteristics

Baseline and demographic characteristic variables (including date of birth, sex, race, ethnicity, and Fitzpatrick skin type) will be tabulated using descriptive statistics. For each continuous variable, the summary will include the mean, standard deviation (SD), median, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages.

Poolability of the data across study sites for key demographic and baseline characteristics (age, sex, Fitzpatrick skin type, Body Mass Index) will be assessed for the ITT population. For age and Body Mass Index, one-way analysis of variance (ANOVA) was performed with study site as the main factor. For Fitzpatrick Skin Type Classification (I-VI), nonparametric

Kruskal Wallis test was conducted with study site as the class variable. For sex, Pearson's Chi-square test, or exact test if more appropriate, will be performed.

Reason for the amendment
To incorporate the responses to the FDA request for the Prollenium SYM 2014-02 study regarding assessment of multi-center poolability for demographic and baseline characteristics.

2. Original text and location

5.6.1   Adverse Events

All adverse events (AEs) occurring during the study will be recorded and coded in the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1 or higher. TEAEs are defined as events that appear subsequent to the first injection or that were present prior to the first injection but worsened in intensity after the first injection. TEAEs may include, but are not limited to, injection site bruising, injection site discoloration, injection site edema, injection site erythema, injection site inflammation, injection site pain, and injection site swelling.

Frequency and percent of subjects reporting TEAEs of injection site reactions will be tabulated for each treatment by preferred terms, and further by severity. In summaries of severity, subjects who reported more than one event in a treatment arm that are mapped to the same preferred term will be counted only once in that treatment arm under the strongest severity.

Revised text and location

5.6.1   Adverse Events

All adverse events (AEs) occurring during the study will be recorded and coded in the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1 or higher. TEAEs are defined as events that appear subsequent to the first injection or that were present prior to the first injection but worsened in intensity after the first injection. TEAEs may include, but are not limited to, injection site bruising, injection site discoloration, injection site edema, injection site erythema, injection site inflammation, injection site pain, and injection site swelling.

Frequency and percent of subjects reporting TEAEs of injection site reactions will be tabulated for each treatment by preferred terms, and further by severity. In summaries of severity, subjects who reported more than one event in a treatment arm that are mapped to the same preferred term will be counted only once in that treatment arm under the strongest severity. **Frequency and percent of subjects reporting injection-site TEAEs by severity will also be tabulated separately for subjects of Fitzpatrick Skin Type I-IV and for subjects of Fitzpatrick Skin Type V and VI.**

Reason for the amendment

To incorporate the responses to the FDA request for the Prollenium SYM 2014-02 study regarding TEAE incidence rate between subjects with Fitzpatrick Skin Type I-IV versus those with V-VI.

3. Original text and location

Table 14.2.1.2 – Primary Efficacy by Study Site: Proportion of Responders Immediately After Injection at Visit 1/Day 1

Site Number	N	n (%) of Responders (MI)	n (%) of Responders (WCS)	n (%) of Responders (BCS)	N	n (%) of Responders
1	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)
2						
3						
4						
5						
Total	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0 (0.0%)

*Responder (to Revanesse Ultra+) is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra+) in VAS pain score of at least 10 mm on a 100-mm scale.
For mITT analyses, MI (Multiple Imputation): Subjects with missing VAS scores are defined as responder or non-responder based on their VAS values through MI; WCS (Worst Case Scenario): Subjects with missing VAS scores are considered non-responders; BCS (Best Case Scenario): Subjects with missing VAS scores are considered responders.
Source: Listing 16.2.6.2.1, 16.2.6.3.1
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Revised text and location

Table 14.2.1.2 – Primary Efficacy by Study Site: Proportion of Responders Immediately After Injection at Visit 1/Day 1

Site Number	Modified Intent-to-Treat (mITT)		Per-Protocol	
	N	n (%) of Responders	N	n (%) of Responders
1	0	0 (0.0%)	0	0 (0.0%)
2				
3				
4				
Total	0	0 (0.0%)	0	0 (0.0%)

*Responder (to Revanesse Ultra+) is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra+) in VAS pain score of at least 10 mm on a 100-mm scale.
Source: Listing 16.2.6.2.1, 16.2.6.3.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month, Day, Year.

Reason for the amendment

To remove reference to MI, WCS and BCS for mITT due to the fact, per the definition, there is no missing data for the primary efficacy variable.

4. Newly added summary table on poolability

Table 14.1.5.4 – Key Demographic and Baseline Characteristics by Site for Intent-to-Treat Subjects

Parameter	Category	Site 1 (N=xx)	Site 2 (N=xx)	Site 3 (N=xx)	Site 4 (N=xx)	p-value
Gender	Female	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.xxx[1]
	Male	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Age (years)	N	0	0	0	0	
	Mean ± SD	00.0 ± 00.00	00.0 ± 00.00	00.0 ± 00.00	00.0 ± 00.00	0.xxx[2]
	Median	0.0	0.0	0.0	0.0	
	Min, Max	0, 0	0, 0	0, 0	0, 0	
Body Mass Index (BMI)	N	0	0	0	0	
	Mean ± SD	00.0 ± 00.00	00.0 ± 00.00	00.0 ± 00.00	00.0 ± 00.00	0.xxx[2]
	Median	0.0	0.0	0.0	0.0	
	Min, Max	0, 0	0, 0	0, 0	0, 0	
Fitzpatrick Skin Type Classification	I	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.xxx[3]
	II	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	III	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	IV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	V	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	VI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

[1]P-value from Pearson's Chi-square test or exact test if appropriate.
[2]P-value from one-way analysis of variance (ANOVA) with study site as the main factor.
[3]P-value from nonparametric Kruskal Wallis test with study site as the class variable.

Reason for the amendment
To present added poolability analysis for demographic and baseline characteristics for the ITT population.

5. Newly added summary table of TEAE by subject Fitzpatrick Skin Type

(After Table 14.3.3.4 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Causality for Intent-to-Treat (ITT) Population)

Note:
Table 14.3.2.2 will be used as the shell for the following tables:

Table 14.3.4.1 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Subjects of Fitzpatrick Skin Type I to IV

Table 14.3.4.2 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Subjects of Fitzpatrick Skin Type V and VI

Reason for the amendment
To present added tabulations for TEAE incidence rate for subjects with Fitzpatrick Skin Type I-IV and for subjects with Fitzpatrick Skin Type V-VI.

6. Original text and location

Listing 16.2.6.2.1 – Primary and Secondary Efficacy Responses for Modified Intent-to-Treat Population

| Site-Subject | Study Visit | Time Point | Revanesse Ultra | | Revanesse Ultra+ | | Ultra minus Ultra+ in VAS | Responder* | | |
			Observed or MI	VAS Score	Observed or MI	VAS Score		MI	WSC	BCS
xx-xxxx	Visit 1/Day 1	Immediately after injection	Observed	50	Observed	42	8	No	No	No
		15 minutes post injection	Observed	46	MI	34.4	11.6	Yes	No	Yes
		30 minutes post injection	Observed	31	MI	25.5	5.5	No	No	Yes

Missing VAS scores for the mITT analysis will be replaced using the multiple imputation (MI) method. The average values from the MI copies of VAS are present and used for analysis.

*Responder (to Revanesse Ultra+) is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra+) in VAS pain score of at least 10 mm on a 100-mm scale. MI (Multiple Imputation): Subjects with missing VAS scores are defined as responder or non-responder based on their VAS values through MI; WCS (Worst Case Scenario): Subjects with missing VAS scores are considered non-responders; BCS (Best Case Scenario): Subjects with missing VAS scores are considered responders.

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Revised text and location

Listing 16.2.6.2.1 – Primary and Secondary Efficacy Responses for Modified Intent-to-Treat Population

| Site-Subject | Study Visit | Time Point | Revanesse Ultra | | Revanesse Ultra+ | | Ultra minus Ultra+ in VAS | Responder* | | | |
			Observed or MI	VAS Score	Observed or MI	VAS Score		**Observed**	MI	WSC	BCS
xx-xxxx	Visit 1/Day 1	Immediately after injection	Observed	50	Observed	42	8	**No**			
		15 minutes post injection	Observed	46	MI	34.4	11.6		Yes	No	Yes
		30 minutes post injection	Observed	31	MI	25.5	5.5		No	No	Yes

Missing VAS scores for the mITT analysis will be replaced using the multiple imputation (MI) method. The average values from the MI copies of VAS are present and used for analysis.

*Responder (to Revanesse Ultra+) is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra+) in VAS pain score of at least 10 mm on a 100-mm scale. **Observed: Subjects are defined as responder or non-responder based on the non-missing values;** MI (Multiple Imputation): Subjects with missing VAS scores are defined as responder or non-responder based on their VAS values through MI; WCS (Worst Case Scenario): Subjects with missing VAS scores are considered non-responders; BCS (Best Case Scenario): Subjects with missing VAS scores are considered responders.

O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Reason for the amendment

To add "Observed" Responder which will be filled for all subjects "Immediately after injection" due to the fact, per the definition, there is no missing data for the primary efficacy variable.

Statistical Analysis Plan Amendment #2

Protocol No.:   SYM 2016-02

Title: A Multicenter, Double-Blind, Randomized, Split-Face
Study to Evaluate the Safety and Efficacy of Revanesse®
Ultra + (with Lidocaine) versus Revanesse® Ultra for the
Correction of Nasolabial Folds

Previous SAP (v2.0) Date: April 03, 2017

Amendment 02 Date: July 21, 2017

Sponsor: Prollenium Medical Technologies Inc.
138 Industrial Parkway North
Aurora Ontario
L4G 4C3
Canada

Amendments:

1. Original text and location

5.1 Methodological Considerations

SAS software (version 9.1.3 or higher) will be used for all data analyses and tabulations.

Revised text and location

5.1 Methodological Considerations

SAS software (version 9.1.3 **or higher**) will be used for all data analyses and tabulations.

Reason for the amendment
SAS software is being updated.

2. Original text and location

5.3   Demographics and Baseline Characteristics

Baseline and demographic characteristic variables (including date of birth, sex, race, ethnicity, and Fitzpatrick skin type) will be tabulated using descriptive statistics. For each continuous variable, the summary will include the mean, standard deviation (SD), median, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages.

Poolability of the data across study sites for key demographic and baseline characteristics (age, sex, Fitzpatrick skin type, Body Mass Index) will be assessed for the ITT population. For age and Body Mass Index, one-way analysis of variance (ANOVA) was performed with study site as the main factor. For Fitzpatrick Skin Type Classification (I-VI), nonparametric Kruskal Wallis test was conducted with study site as the class variable. For sex, Pearson's Chi-square test, or exact test if more appropriate, will be performed.

Revised text and location

5.3 Demographics and Baseline Characteristics

Baseline and demographic characteristic variables (including date of birth, sex, race, ethnicity, and Fitzpatrick skin type) will be tabulated using descriptive statistics. For each continuous variable, the summary will include the mean, standard deviation (SD), median, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages.

Poolability of the data across study sites for key demographic and baseline characteristics (age, sex, Fitzpatrick skin type, Body Mass Index) will be assessed for the ITT population. For age and Body Mass Index, one-way analysis of variance (ANOVA) was performed with study site as the main factor. For Fitzpatrick Skin Type Classification (I-VI), nonparametric Kruskal Wallis test was conducted with study site as the class variable. For sex, Pearson's Chi-square test, or exact test if more appropriate, will be performed.

Demographic and baseline characteristics will be summarized and compared for PP subjects versus non-PP subjects. For categorical variables, comparison will be performed using the Cochran-Mantel-Haenszel (CMH) test for general association adjusted for site. For continuous variables, comparison will be conducted using two-way analysis of variance model (ANOVA) with fixed factors of group and site, with respect to the original values if normality assumption is satisfied, or with respect to ranked values if otherwise.

Descriptive summary of racial distribution within Fitzpatrick Skin Type will provided for the ITT subjects.

Reason for the amendment
To incorporate the responses to the FDA request for the Prollenium SYM 2014-02 study regarding similarity in demographic and baseline characteristics between the PP and non-PP subjects. Also to incorporated a summary of race by skin type from the interim analysis done for SYM 2016-02.

3. **Original text and location**

5.6.1 Adverse Events

All adverse events (AEs) occurring during the study will be recorded and coded in the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1 or higher. TEAEs are defined as events that appear subsequent to the first injection or that were present prior to the first injection but worsened in intensity after the first

injection. TEAEs may include, but are not limited to, injection site bruising, injection site discoloration, injection site edema, injection site erythema, injection site inflammation, injection site pain, and injection site swelling.

Frequency and percent of subjects reporting TEAEs of injection site reactions will be tabulated for each treatment by preferred terms, and further by severity. In summaries of severity, subjects who reported more than one event in a treatment arm that are mapped to the same preferred term will be counted only once in that treatment arm under the strongest severity. Frequency and percent of subjects reporting injection-site TEAEs by severity will also be tabulated separately for subjects of Fitzpatrick Skin Type I-IV and for subjects of Fitzpatrick Skin Type V and VI.

For other AEs where an association with either treatment may not be clearly identified, including systemic TEAEs, frequency and percent of subjects will be tabulated to treated subjects as one group by system organ class and preferred terms, and further by severity and relationship to study device. In summaries of severity and relationship, subjects who reported more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship.

Treatment-Emergent Serious Adverse Events (TESAEs) will be discussed within the clinical study report. TESAEs and TEAEs that led to treatment interruption or discontinuation will be presented in data listings.

Revised text and location

5.6.1   Adverse Events

All adverse events (AEs) occurring during the study will be recorded and coded in the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1 or higher. TEAEs are defined as events that appear subsequent to the first injection or that were present prior to the first injection but worsened in intensity after the first injection. TEAEs may include, but are not limited to, injection site bruising, injection site discoloration, injection site edema, injection site erythema, injection site inflammation, injection site pain, and injection site swelling.

Frequency and percent of subjects reporting TEAEs of injection site reactions will be tabulated for each treatment by **system organ class and** preferred terms, and further by severity. In summaries of severity, subjects who reported more than one event in a treatment arm that are mapped to the same preferred term will be counted only once in that treatment arm under the strongest severity.

For other AEs where an association with either treatment may not be clearly identified, including systemic TEAEs, frequency and percent of subjects will be tabulated to treated subjects as one group by system organ class and preferred terms, and further by severity and relationship to study device. In summaries of severity

and relationship, subjects who reported more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship.

Injection-site TEAEs and non-injection site TEAEs will also be tabulated by subject Fitzpatrick Skin Type (I-IV vs. V-VI) and by number of injections subjects received. Summary by preferred term will further be provided for TEAEs that are reported by subject and for TEAEs that are reported by Investigator separately. Most frequently occurring injection site TEAEs will also be summarized by event's severity and duration.

Treatment-Emergent Serious Adverse Events (TESAEs) will be discussed within the clinical study report. TESAEs and TEAEs that led to treatment interruption or discontinuation will be presented in data listings.

<u>Reason for the amendment</u>

To incorporate the responses to the FDA request for the Prollenium SYM 2014-02 study regarding TEAE incidence rate between subjects with Fitzpatrick Skin Type I-IV versus those with V-VI, and by number of injections subjects received, and further separated for TEAEs reported by subject and for TEAEs reported by investigator.

4. **Newly added summary table on demographics and baseline characteristics**

Table 14.1.5.5 – Summary of Racial Distribution within Fitzpatrick Skin Type for Intent-to-Treat Population

| Race | Skin Type | | | | Total I-IV (N=xx) | Skin Type | | Total V-VI (N=xx) | Overall Total (N=xx) |
	I (N=xx)	II (N=xx)	III (N=xx)	IV (N=xx)		V (N=xx)	VI (N=xx)		
White	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black or African American	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 14.1.5.6 –Demographic and Baseline Characteristics for PP Subjects and Subjects Excluded from the PP Population

Parameter	Category	PP Subjects (N=xx)	Non-PP Subjects (N=xx)	p-value
Gender	Female	0 (0%)	0 (0%)	0.xxx[1]
	Male	0 (0%)	0 (0%)	
Ethnicity	Hispanic or Latino	0 (0%)	0 (0%)	0.xxx[1]
	Not Hispanic or Latino	0 (0%)	0 (0%)	
	Not Willing to Provide	0 (0%)	0 (0%)	
Race	White	0 (0%)	0 (0%)	NA
	Asian	0 (0%)	0 (0%)	
	Native Hawaiian or Other Pacific-Islander	0 (0%)	0 (0%)	
	Black or African American	0 (0%)	0 (0%)	
	American Indian or Alaska Native	0 (0%)	0 (0%)	
	Other	0 (0%)	0 (0%)	
Age (years)	N	0	0	
	Mean ± SD	00.0 ± 00.00	00.0 ± 00.00	0.xxx[2]
	Median	0.0	0.0	
	Min, Max	0, 0	0, 0	
-- Age Groups	18 to <40	0 (0%)	0 (0%)	
	40 to <64	0 (0%)	0 (0%)	
	64 to <75	0 (0%)	0 (0%)	
	>=75	0 (0%)	0 (0%)	
BMI	N	0	0	
	Mean ± SD	00.0 ± 00.00	00.0 ± 00.00	0.xxx[2]
	Median	0.0	0.0	
	Min, Max	0, 0	0, 0	
FST Classification	I	0 (0%)	0 (0%)	0.xxx[1]
	II	0 (0%)	0 (0%)	
	III	0 (0%)	0 (0%)	

Parameter	Category	PP Subjects (N=xx)	Non-PP Subjects (N=xx)	p-value
	IV	0 (0%)	0 (0%)	
	V	0 (0%)	0 (0%)	
	VI	0 (0%)	0 (0%)	

PP = Per-Protocol. FST = Fitzpatrick Skin Type. BMI = weight (lbs) / height^2 (in) x 703

[1] P-values for group comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.

[2] P-value for group comparisons from nonparametric ranked two-way analysis of variance with fixed factors of group and site.

Source: Listing 16.2.4.1, 16.2.8.1

Reason for the amendment

Table 14.1.5.5 to present race by FST as done for the interim analysis for the study.

Table 14.1.5.6 to present comparisons of demographic and baseline characteristics between the PP and non-PP subjects per FDA request for the SYM 2014-02 study.

5. Original text and location

Table 14.3.2.1 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	Revanesse Ultra (N=xx)	Revanesse Ultra+ (N=xx)
Subjects with at Least One Injection Site TEAE	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)

…

Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one injection site TEAE are counted only once.
Source: Listing 16.2.7.1
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Revised text and location

Table 14.3.2.1 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	All TEAEs		Reported by Subject		Reported by Investigator	
	Revanesse Ultra (N=xx)	Revanesse Ultra+ (N=xx)	**Revanesse Ultra (N=xx)**	**Revanesse Ultra+ (N=xx)**	**Revanesse Ultra (N=xx)**	**Revanesse Ultra+ (N=xx)**
Subjects with at Least One Injection Site TEAE	0 (0%)	0 (0%)	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Class 1	0 (0%)	0 (0%)	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Term 1	0 (0%)	0 (0%)	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Term 2	0 (0%)	0 (0%)	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Class 2	0 (0%)	0 (0%)	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Term 1	0 (0%)	0 (0%)	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**

…

Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Reason for the amendment
To incorporate FDA's request for the SYM 2014-02 study to look at the TEAEs separately for those reported by subject vs. those reported by Investigator.

6. Newly added summary table of Injection Site TEAE by subject Fitzpatrick Skin Type and by number of injections

Table 14.3.2.4 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

Table 14.3.2.4a – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

Table 14.3.2.4b – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Investigator by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

Table 14.3.2.5 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

Table 14.3.2.5a – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

Table 14.3.2.5b – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Investigator by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

Reason for the amendment
To incorporate FDA's request for the SYM 2014-02 study to tabulate TEAE incidence by subject Fitzpatrick Skin Type (individual type and pooled I-IV vs. V-VI), and by number of injections.

7. Newly added summary table of Injection Site TEAE by severity and by duration

Table 14.3.2.6 – Overall Summary of Injection Site Treatment-Emergent Adverse Events (TEAEs) for Intent-to-Treat Population

	Revanesse Ultra		Revanesse Ultra+	
	Subjects[1] (N=xx)	Events[2] (N=xx)	Subjects[1] (N=xx)	Events[2] (N=xx)
Overall				
	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Duration				
Less than 1 week	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Between 1 week and 1 month (30 days)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
More than 1 month (30 days)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severity				
Mild	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Causality				
Treatment-related*	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not treatment-related	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Outcome				
Resolved	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Improved	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stabilized	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Worsened	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unchanged	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment Required (Action Taken)				
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Study treatment interrupted/discontinued	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-drug therapy	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	Revanesse Ultra		Revanesse Ultra+	
	Subjects[1] (N=xx)	Events[2] (N=xx)	Subjects[1] (N=xx)	Events[2] (N=xx)
New OTC or Rx drug added	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hospitalized (includes ER visits)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[1] Denominator is the number of subjects who received the corresponding treatment.

[2] Denominator is the number of adverse events reported by subjects who received the corresponding treatment.

*Treatment-related includes Possibly and Probably Related.

For Severity and Causality, subjects reporting more than one injection site TEAE associated with a treatment arm are counted only once for the treatment arm under the greatest reported severity and most likely causality, respectively.

For Duration, Outcome and Treatment Required (Action Taken), at each level of the categories, subjects reporting more than one injection site TEAE associated with a treatment arm are counted only once for the treatment arm at that category level.

Source: Listing 16.2.7.1

O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.2.7 – Severity of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

Adverse Event	Revanesse Ultra				Revanesse Ultra+			
	Events % (n/N)[1]	Mild % (n/N)[2]	Moderate % (n/N)[2]	Severe % (n/N)[2]	Events % (n/N)[1]	Mild % (n/N)[2]	Moderate % (n/N)[2]	Severe % (n/N)[2]
Preferred Term 1	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)
Preferred Term 2	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)

Most frequently occurring injection site TEAEs are those that were reported by 5% or more subjects of any treatment group.

[1] Denominator is the number of injection site TEAEs reported by all ITT subjects who received the corresponding treatment.

[2] Denominator for percentages by severity is the number of subjects with respective TEAEs after receiving the corresponding treatment. Numerator (count of subjects) is based on the rule that subjects reporting more than one same incidence associated with a treatment arm are counted only once for the treatment arm under the greatest reported severity.

Source: Listing 16.2.7.1

O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.2.8 – Duration of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

Adverse Event	Revanesse Ultra				Revanesse Ultra+			
	Events % (n/N)[1]	<7 Days % (n/N)[2]	7-30 Days % (n/N)[2]	>30 Days % (n/N)[2]	Events % (n/N)[1]	<7 Days % (n/N)[2]	7-30 Days % (n/N)[2]	>30 Days % (n/N)[2]
Preferred Term 1	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)
Preferred Term 2	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)

Most frequently occurring injection site TEAEs are those that were reported by 5% or more subjects of any treatment group.

[1] Denominator is the number of injection site TEAEs reported by all ITT subjects who received the corresponding treatment.

[2] Denominator for percentages by duration is the number of subjects with respective TEAEs after receiving the corresponding treatment. Numerator (count of subjects) is based on the rule that subjects reporting more than one same incidence associated with a treatment arm are counted only once for the treatment arm under the longest duration.

Source: Listing 16.2.7.1

O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Reason for the amendment

To incorporate FDA's request for the SYM 2014-02 study regarding labeling.

8. **Original text and location**

Note:
Tables 14.3.2.1-14.3.2.3 will be used as the shell for the following tables with only one group as "All ITT Subjects" (since association to either treatment was not identified):

Table 14.3.3.1 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population

Table 14.3.3.2 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Population

Table 14.3.3.3 – Most Frequently Occurring Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

With the phrase "injection site TEAE" changed to read "non-injection site TEAE".

Revised text and location

Table 14.3.3.1 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	All TEAEs All ITT Subjects (N=xx)	Reported by Subject All ITT Subjects (N=xx)	Reported by Investigator All ITT Subjects (N=xx)
Subjects with at Least One Non-Injection Site TEAE	0 (0%)	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)

…

Counts reflect numbers of subjects reporting one or more non-injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one non-injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.3.2 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Population

System Organ Class Preferred Term	All ITT Subjects (N=xx)		
	Mild	Moderate	Severe
Subjects with at Least One Non-Injection Site TEAE	0 (0%)	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)

…

Counts reflect numbers of subjects reporting one or more non-injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one non-injection site TEAE are counted only once (under the greatest reported severity).
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.3.3 – Most Frequently Occurring Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	All ITT Subjects (N=xx)
Class 1	
Term 1	0 (0%)
Term 2	0 (0%)
Class 2	
Term 1	0 (0%)
…	

Most frequently occurring non-injection site TEAEs are those that were reported by 5% or more subjects.

Counts reflect numbers of subjects reporting one or more non-injection site TEAEs that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (preferred term) subjects reporting more than one non-injection site TEAE are only counted once.

Source: Listing 16.2.7.1

O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

<u>Reason for the amendment</u>
Listing 14.3.3.1 to provide template and incorporate FDA's post hoc request for the SYM 2014-02 study to look at the TEAEs separately for those reported by subject vs. those reported by Investigator.
Listings 14.3.3.2-14.3.3.3 to provide template.

9. Original text and location

Note:
Table 14.3.2.2 will be used as the shell for the following tables:

Table 14.3.4.1 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Subjects of Fitzpatrick Skin Type I to IV

Table 14.3.4.2 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Subjects of Fitzpatrick Skin Type V and VI

Revised text and location

Table 14.3.3.5 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

System Organ Class Preferred Term	FST I (N=xx)	FST II (N=xx)	FST III (N=xx)	FST IV (N=xx)	Pooled FST I-IV (N=xx)	FST V (N=xx)	FST VI (N=xx)	Pooled FST V-VI (N=xx)
Subjects with at Least One Non-Injection Site TEAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
…								
…								
Class 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
…								
…								

Counts reflect numbers of subjects reporting one or more non-injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one non-injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.5 will be used as the shell for the following table:

Table 14.3.3.5a – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

Table 14.3.3.5b – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Investigator by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

Table 14.3.3.6 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

System Organ Class Preferred Term	Ultra[1]Ultra+[1] (N=xx)	Ultra[1]Ultra+[2] (N=xx)	Ultra[2]Ultra+[1] (N=xx)	Ultra[2]Ultra+[2] (N=xx)
Class 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)

…

TEAEs are grouped by number of injection(s) a subject received up to when the events started.

Ultra[i]Ultra+[j] = AFTER Revanesse Ultra injection #i and Revanesse Ultra+ injection #j AND BEFORE any other injections if applicable.
Note: The denominator for a grouping includes all the subjects who went through the indicated period regardless if they reported any TEAEs during the period.
Counts reflect numbers of subjects reporting one or more non-injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one non-injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.3.6 will be used as the shell for the following table:

Table 14.3.3.6a – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

Table 14.3.3.6b – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Investigator by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

Reason for the amendment
To incorporate FDA's request for the SYM 2014-02 study to tabulate TEAE incidence by subject Fitzpatrick Skin Type (individual type, pooled I-IV vs. V-VI), and by number of injections.

10. Original text and location

Listing 16.2.7.1 – Adverse Events

Site-Subject	Analyses	System Organ Class// Preferred Term// Verbatim Term	Start Date [Day #]	Stop Date [Day #]	Severity	Causality	Action Taken[1]	Out[2]	Serious?
Treatment: Revanesse Ultra									
…									
…									
…									
Treatment: Revanesse Ultra+									
…									
…									
…									
Treatment: Unidentified (not on face)									
…									
…									

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.

Day # is calculated from baseline (Visit 1) date. Day 1 is the baseline date while Day -1 is the day prior to the baseline visit.

[1] Action Taken: 1=None, 2=Study treatment interrupted/discontinued, 3=Non-drug therapy, 4=New OTC or Rx drug added, 4=Hospitalized

[2] Out (outcome): 1= Resolved, 2=Improved, 3=Stabilized, 4=Worsened, 5=Unchanged, 6=Lost to Follow-up/Unknown, 7=Fatal

O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Revised text and location

Listing 16.2.7.1 – Adverse Events

Site-Subject	Analy	Skin Type	AE Reported by	System Organ Class// Preferred Term// Verbatim Term	Start Date [Day #]	Stop Date [Day #]	Severity	Causality	Action Taken[1]	Out[2]	Serious?
Treatment: Revanesse Ultra											
…											
…											
…											
Treatment: Revanesse Ultra+											
…											
…											
…											
Treatment: Unidentified (not on face)											
…											
…											

Analy (Analyses): I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.

Day # is calculated from baseline (Visit 1) date. Day 1 is the baseline date while Day -1 is the day prior to the baseline visit.

[1] Action Taken: 1=None, 2=Study treatment interrupted/discontinued, 3=Non-drug therapy, 4=New OTC or Rx drug added, 4=Hospitalized

[2] Out (outcome): 1= Resolved, 2=Improved, 3=Stabilized, 4=Worsened, 5=Unchanged, 6=Lost to Follow-up/Unknown, 7=Fatal

O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Reason for the amendment

To add "Skin Type" and "AE Reported by" which will help refer to the appropriate AE records when reviewing the newly added summary tables.

11. <u>Original text and location</u>

Note:
Repeat Listing16.2.7.1 for AEs that led to study treatment interrupted/Discontinued and Serious AEs –

Listing 16.2.7.2 – Adverse Events Leading to Study Treatment Interrupted/Discontinued

Listing 16.2.7.3 – Serious Adverse Events

<u>Revised text and location</u>

Note:
Repeat Listing16.2.7.1 for AEs that led to study treatment interrupted/Discontinued and Serious AEs –

Listing 16.2.7.2 – Adverse Events Leading to Study Treatment Interrupted/Discontinued

Listing 16.2.7.3 – Serious Adverse Events

Listing 16.2.7.4 – Injection Site Adverse Events Lasted More Than 30 Days

<u>Reason for the amendment</u>
To add Listing 16.2.7.4 per Sponsor request

12. Newly added summary table and data listings for the 17 subjects who rolled over from SYM 2014-02 into SYM 2016-02

Subject Subgroup Summary Tables
1) Subgroup Table s14.1.1 – Analysis Population for Subset of Rollover subjects
2) Subgroup Table s14.1.2 – Subject Discontinuations by Reason for Subset of Rollover Subjects
3) Subgroup Table s14.1.3 – Subject Enrollment by Study Site for Subset of Rollover Subjects
4) Subgroup Table s14.1.4 – Significant Protocol Violations for Subset of Rollover Subjects
5) Subgroup Table s14.1.5.1 – Demographic and Baseline Characteristics for Intent-to-Treat Population - Subset of Rollover Subjects
6) Subgroup Table s14.1.5.2 - Demographic and Baseline Characteristics for Modified Intent-to-Treat Population - Subset of Rollover Subjects
7) Subgroup Table s14.1.5.3 - Demographic and Baseline Characteristics for Per-Protocol Population - Subset of Rollover Subjects
8) Subgroup Table s14.1.5.4 – Key Demographic and Baseline Characteristics by Site for Intent-to-Treat Population - Subset of Rollover Subjects
9) Subgroup Table s14.1.5.5 – Summary of Racial Distribution within Fitzpatrick Skin Type for Intent-to-Treat Population - Subset of Rollover Subjects
10) Subgroup Table s14.2.1.1 – Primary Efficacy: Proportion of Responders Immediately After Injection at Visit 1/Day 1 for Subset of Rollover Subjects
11) Subgroup Table s14.2.1.2 – Primary Efficacy by Study Site: Proportion of Responders Immediately After Injection at Visit 1/Day 1 for Subset of Rollover Subjects
12) Subgroup Table s14.2.2.4 – Secondary Efficacy: Proportion of Responders at 60 Minutes Post Injection at Visit 1/Day 1 for Subset of Rollover Subjects
13) Subgroup Table s14.2.2.5 – Secondary Efficacy: Proportion of Responders at 2 Weeks Post Injection at Visit 2/Week 2 for Subset of Rollover Subjects
14) Subgroup Table s14.2.3.1 – Other Efficacy: Wrinkle Severity Rating Scale (WSRS) by Visit for Modified Intent-to-Treat Population - Subset of Rollover Subjects
15) Subgroup Table s14.2.3.2 – Other Efficacy: Wrinkle Severity Rating Scale (WSRS) by Visit for Per-Protocol Population - Subset of Rollover Subjects
16) Subgroup Table s14.2.4.1 – Other Efficacy: Patient Global Aesthetic Improvement (pGAI) by Visit for Modified Intent-to-Treat Population - Subset of Rollover Subjects

30) Subgroup Table s14.3.2.8 – Duration of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population - Subset of Rollover Subjects
31) Subgroup Table s14.3.3.2 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Population - Subset of Rollover Subjects
32) Subgroup Table s14.3.3.3 – Most Frequently Occurring Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population - Subset of Rollover Subjects
33) Subgroup Table s14.3.3.4 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Causality for Intent-to-Treat Population - Subset of Rollover Subjects
34) Subgroup Table s14.3.3.5 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population - Subset of Rollover Subjects
35) Subgroup Table s14.3.3.6 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population - Subset of Rollover Subjects

Subject Subgroup Listings
1) Subgroup Listing s16.2.1.1 – Subject Analysis Status for Subset of Rollover Subjects
2) Subgroup Listing s16.2.1.2 – Subject Disposition for Subset of Rollover Subjects
3) Subgroup Listing s16.2.2.3 – Significant Protocol Violations for Subset of Rollover Subjects
4) Subgroup Listing s16.2.2.4 – Comments for Subset of Rollover Subjects
5) Subgroup Listing s16.2.4.1 – Demographics for Subset of Rollover Subjects
6) Subgroup Listing s16.2.4.3 – Medical History Findings for Subset of Rollover Subjects
7) Subgroup Listing s16.2.5.1 – Treatment Administration at Visit 1/Day 1 for Subset of Rollover Subjects
8) Subgroup Listing s16.2.5.2 – Touch-Up Treatment Administration at Visit 2/Week 2 for Subset of Rollover Subjects
9) Subgroup Listing s16.2.6.1.1 – Efficacy Evaluations of Visual Analog Scale (VAS) for Pain for Subset of Rollover Subjects
10) Subgroup Listing s16.2.6.1.2 – Efficacy Evaluations (WSRS, pGAI, iGAI) for Subset of Rollover Subjects
11) Subgroup Listing s16.2.6.2.1 – Primary and Secondary Efficacy Responses for Modified Intent-to-Treat Population - Subset of Rollover Subjects
12) Subgroup Listing s16.2.6.2.2 – Other Efficacy Responses for Modified Intent-to-Treat Population - Subset of Rollover Subjects
13) Subgroup Listing s16.2.6.3.1 – Primary and Secondary Efficacy Responses for Per-Protocol Population - Subset of Rollover Subjects
14) Subgroup Listing s16.2.6.3.2 – Other Efficacy Responses for Per-Protocol Population - Subset of Rollover Subjects

15) Subgroup Listing s16.2.7.1 – Adverse Events for Subset of Rollover Subjects
16) Subgroup Listing s16.2.7.2 – Adverse Events Leading to Study Treatment Interrupted/Discontinued for Subset of Rollover Subjects
17) Subgroup Listing s16.2.7.3 – Serious Adverse Events for Subset of Rollover Subjects

<u>Reason for the amendment</u>
To add TLs for the subject of rollover subjects per Sponsor request

STATISTICAL ANALYSIS PLAN

Protocol SYM 2016-02

Version 3.0
July 21, 2017

A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra + (with Lidocaine) versus Revanesse® Ultra for the Correction of Nasolabial Folds

Prollenium Medical Technologies Inc.

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Written By: Ye Wang, PhD
Project Statistician
Symbio LLC

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Ye Wang, PhD   Date
Director of Statistics
Symbio LLC

_____   _____
Ario Khoshbin   Date
President
Prollenium Medical Technologies Inc.

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

Protocol SYM 2016-02

Version 3.0
July 21, 2017

A Multicenter, Double-Blind, Randomized, Split-Face Study to Evaluate the Safety and Efficacy of Revanesse® Ultra + (with Lidocaine) versus Revanesse® Ultra for the Correction of Nasolabial Folds

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Approved By:

_____   7/21/2017
Ye Wang, PhD   Date
Director of Statistics
Symbio LLC

_____   _____
Ario Khoshbin   Date
President
Prollenium Medical Technologies Inc.

Table of Contents

Statistical Analysis Plan

1   Purpose of Statistical Analysis Plan

The purpose of the statistical analysis plan is to describe in detail all the data, statistical methods, and summary tables required to implement the statistical analysis of Clinical Study Protocol SYM 2016-02 (Section 9 in the study protocol version 1.0, dated July 08, 2016).

2   Study Objectives

To compare the safety and efficacy profiles of Revanesse® Ultra + (with lidocaine, hereafter referred to as Revanesse Ultra +) to Revanesse Ultra for subjects undergoing correction of nasolabial folds (NLFs).

3   Study Design and Sample Size Determination

3.1   Study Design

For the purpose of exploring the above objectives, the study will be conducted as a multicenter, double-blind, randomized, split-face study in subjects seeking nasolabial fold correction. Subjects will be treated with Revanesse Ultra + in the NLF on one side of the face and Revanesse Ultra in the NLF on the other side of the face. The side of the face for each study product will be randomly assigned. The investigator and the subject will be blinded to the treatment; injections of the study product will be performed by an unblinded injecting investigator.

At each visit, investigator and subject evaluations of the treated areas will be performed and recorded. Visits will occur at:
Visit 1/Week 0 (Day 1) – baseline and treatment
Visit 2/Week 2 – interim visit, touch-up if the iGAI score = 3 or 4
Visit 3/Week 4 – interim visit
Visit 4/Week 12 – interim visit
Visit 5/ Week 24 –End of Study

Evaluations include:
Pain assessment using a visual analog scale (VAS)
Wrinkle Severity Rating Scale (WSRS)
Patient Global Aesthetic Improvement (pGAI)
Investigator Global Aesthetic Improvement (iGAI)
Safety will be assessed by monitoring adverse events (AEs) at all study visits.
Other evaluations include Investigator Ease of Use Assessment.

3.2   Sample Size Determination

Restylane-L Injectable Gel was approved in supplement P040024/S039 on January 29, 2010 for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds such as NLFs. For the supplement study (MA-1100-001), the primary endpoint was the proportion of subjects who had a within-subject difference in VAS (Restylane minus Restylane-L) pain assessment of at least 10 mm at injection. The objective was to show that the 95% confidence interval for the within-subject difference lay above 50%. The key study results are shown in Table 1 (Source: Summary of Safety and Effectiveness Data (SSED), for Restylane-L Injectable Gel).

Table 1 Subjects with at Least a 10 mm Difference in VAS (*Restylane – Restylane-L*)

Timepoint	No. of subjects with assessments**	Number of subjects with Δ ≥ 10 mm			
		n	%	95% LCL	95% UCL
Treatment*	60	43	71.7	58.6	82.5
15 Minutes	60	28	46.7	33.7	60.0
30 Minutes	60	17	28.3	17.5	41.4
45 Minutes	60	10	16.7	8.3	28.5
60 Minutes	60	4	6.7	1.8	16.2

Source: Statistical Report Appendix 16.1.9, Table 1.23, Appendix 16.2.6.1
*Primary endpoint
**Denominator (N), % = 100*n/N
UCL=upper confidence limit; LCL=lower confidence limit

The following sample size is calculated based on the data from the above Restylane-L study, assuming that similar statistics and the same criterion will be applicable for Revanesse Ultra + vs Revanesse Ultra.

Table 2 Sample Size Calculations

Proportion of Responders	Power by N (Number of mITT subjects)	
	N=90	N=80
70%	97.2%	94.1%
68%	93.3%	87.8%

To detect the difference between the null hypothesis proportion of responders of 50% and the alternative proportion of responders of 70% via a two-sided exact binomial test with a 0.05 significance level, 80 mITT subjects will supply a power of 94.1%. For the alternative proportion of responders of 68%, 80 mITT subjects will supply a power of 87.8%.

A total of 100 subjects will be randomized to obtain 80 mITT subjects and to provide adequate data for monitoring safety of the study product.

4 Populations To Be Analyzed

Three subject populations are defined as follows:

(1) Intent-to-treat (ITT) (safety population): All randomized subjects who received study product.

(2) Modified intent-to-treat (mITT): All randomized subjects who met the inclusion/exclusion criteria, were randomized, received both study products, and returned for at least 1 post-injection assessment of pain score immediately post injection from both sides of the face.

(3) Per-protocol (PP): All randomized subjects who met all inclusion/exclusion criteria; received both study products; completed Visit 5/Week 24 within the specified window; had data on pain score from both sides of the face immediately post injection and at 15, 30, 45, and 60 minutes post injection at Visit 1/Day1; had data on pain score at 2 weeks post injection (prior to touch-up); and had no significant protocol violations that would affect the treatment evaluation.

For the purpose of determining the PP status of the subject, "significant protocol violations" are any unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy.

Efficacy analyses will be performed on the mITT and PP populations. Analyses of safety and other evaluations will be performed on the ITT population.

5   Planned Analyses

5.1   Methodological Considerations

SAS software (version 9.1.3 or higher) will be used for all data analyses and tabulations.

Two-sided hypothesis testing will be conducted for all inferential analyses. Resulting p-values less than 0.05 will be considered statistically significant. To control the overall error rate, a hierarchical approach will be applied. Upon the significance of the primary efficacy outcome, secondary endpoints will be analyzed sequentially. If success is achieved at 15 minutes, 30 minutes will be evaluated; if success is achieved at 30 minutes, 45 minutes will be evaluated; if success is achieved at 45 minutes, 60 minutes will be evaluated; and if success is achieved at 60 minutes, 2 weeks post-injection will be evaluated.

All the data points will be presented in subject data listings.

5.2   Handling of Dropouts or Missing Data

For demographics, baseline characteristics, safety profile and other evaluations, each variable will be analyzed using the existing data. Subjects with missing data will be excluded only from the analyses for which data are not available.

There will not be missing data for the primary efficacy endpoint for the mITT and PP based on the definitions of these analysis populations (Section 4).

For the mITT analysis of the secondary efficacy endpoints, missing VAS scores will be replaced using the multiple imputation (MI) approach. Depending on the pattern of missingness, a two-step process may be employed. If missing data occur for an intermediate visit or time point, they will be imputed first via a Markov Chain Monte Carlo (MCMC) method. As a result, a monotone missingness pattern will be obtained for the data to be fully imputed. The subsequent imputation will use Monotone Regression to produce 5 imputed datasets where the remaining missing data are filled in using 5 different sets of values. The average value of the 5 copies of the VAS scores from MI will be used for each missing data point in the mITT analysis.

To prepare for MI, for subjects who are early discontinued from the study, their VAS scores captured at the termination visit will be assigned to the nearest corresponding scheduled visit. VAS scores to be imputed include those at 15, 30, 45, and 60 minutes post injection and at 2 weeks post injection (prior to touch-up). Other variables that go into the imputation models include treatment, site, and key baseline characteristics such as age, gender, race and Fitzpatrick skin type. When missing VAS score at a given visit or time point is imputed, the values from all its previous visits or time points will be included as predictor in the imputation

model. For example, for a subject with missing VAS at 45 minutes post injection on Day 1, the VAS scores from immediately after injection, 15 minutes and 30 minutes post injection for the subjects will be included in the imputation model.

Other efficacy endpoints will be tabulated using the observed data; no missing values will be replaced in the analyses.

5.3   Demographics and Baseline Characteristics

Baseline and demographic characteristic variables (including date of birth, sex, race, ethnicity, and Fitzpatrick skin type) will be tabulated using descriptive statistics. For each continuous variable, the summary will include the mean, standard deviation (SD), median, minimum and maximum.   For each categorical variable, the summary will include frequencies and percentages.

Poolability of the data across study sites for key demographic and baseline characteristics (age, sex, Fitzpatrick skin type, Body Mass Index) will be assessed for the ITT population. For age and Body Mass Index, one-way analysis of variance (ANOVA) was performed with study site as the main factor. For Fitzpatrick Skin Type Classification (I-VI), nonparametric Kruskal Wallis test was conducted with study site as the class variable. For sex, Pearson's Chi-square test, or exact test if more appropriate, will be performed.

Demographic and baseline characteristics will be summarized and compared for PP subjects versus non-PP subjects. For categorical variables, comparison will be performed using the Cochran-Mantel-Haenszel (CMH) test for general association adjusted for site. For continuous variables, comparison will be conducted using two-way analysis of variance model (ANOVA) with fixed factors of group and site, with respect to the original values if normality assumption is satisfied, or with respect to ranked values if otherwise.

Descriptive summary of racial distribution within Fitzpatrick Skin Type will provided for the ITT subjects.

5.4   Subject Accountability

A summary of subject disposition will be provided for all subjects descriptively, including reason for discontinuation and analysis populations. Disposition of analysis populations will also be tabulated by study site.

5.5   Efficacy Variables

Key efficacy assessments include the following:

- Pain assessment using a visual analog scale (VAS) on a 100-mm scale
- Wrinkle Severity Rating Scale (WSRS): 1=Absent, 2=Mild, 3=Moderate, 4=Severe, 5=Extreme
- Patient Global Aesthetic Improvement (pGAI) Score: 1=Worse, 2=No change, 3=Improved, 4=Much improved, 5=Very much improved
- Investigator Global Aesthetic Improvement (iGAI) Score: 1=Worse, 2=No change, 3=Improved, 4=Much improved, 5=Very much improved

All efficacy analyses will be performed for both the PP and mITT populations. For the primary endpoint, the results from mITT are considered definitive and those from PP supportive.

5.5.1   Primary Efficacy Analysis

The primary efficacy variable is the proportion of responders (to Revanesse Ultra +) immediately after injection, where a responder is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra +) in VAS pain score of at least 10 mm on a 100-mm scale. The VAS score will be summarized for each treatment and for the within-subject difference with mean, standard deviation (SD), minimum, median, and maximum. The proportion of responders will be summarized with frequency and percentage. A 95% CI for proportion of responders will be constructed using a one-sample binomial exact test. If the lower bound of this 95% CI is greater than 50%, the test product will be claimed to be superior to the comparator product. The primary endpoint will also be summarized by site descriptively.

To assess consistency of treatment effect across study sites, a Pearson's Chi-square test will be performed with respect to the proportion of responders for the mITT population. Due to the low power of the interaction test, a significance level of 0.15 will be used for determining poolability. If the p-value from the Chi-square test is less than 0.15, possible site outlier(s) will be identified and examined. To investigate the impact of these potential site outlier(s), the primary analysis will be performed separately for the site outlier(s) and for the other sites.

5.5.2   Secondary Efficacy Analysis

The secondary efficacy endpoints are the proportion of responders at 15, 30, 45, and 60 minutes post injection and at 2 weeks post injection (prior to touch-up). Similar method used for the primary efficacy endpoint will be used to analyze the secondary variables.

Missing VAS scores for the mITT analysis will be replaced using the multiple imputation (MI) method. To evaluate the robustness of MI method, subjects with missing VAS scores for the mITT analysis will also be considered in two different ways: (1) as non-responders to the test product (worst case scenario), and (2) as responders to the test product (best case scenario).

5.5.3   Other Efficacy Analysis

Other efficacy variables include change in WSRS score from baseline, pGAI, and iGAI at each scheduled post-baseline visit. Descriptive summaries will be provided for each treatment and for within-subject difference.

5.5.4   Interim Analysis

One interim analysis is planned after all subjects have completed Visit 3 or discontinued prior to Visit 3. The purpose is to determine the safety and pain relief of Revanesse Ultra + to support regulatory submissions outside the US that are currently under review for products containing lidocaine. The sponsor does not plan to change the protocol or stop the study based on the results of the interim analysis.

To maintain the integrity of the study, there will be a separate Statistical Analysis Plan for the interim analysis. The interim analysis will be performed by an independent group that is not

involved in the day-to-day trial activities. Access to the interim analysis results will be strictly limited to people who are not directly involved in the study conduct.

Because no change in the study conduct is planned based on the results of the interim analysis, the Haybittle-Peto method will be used to guard the overall Type 1 error rate, with a 0.001 level of significance for the interim analysis and a 0.05 level of significance for the final analysis.

5.6 Safety Variables

Key safety variables include incidence rate of treatment-emergent adverse events and the exposure to the study product. They will be summarized using the ITT population.

5.6.1 Adverse Events

All adverse events (AEs) occurring during the study will be recorded and coded in the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1 or higher. TEAEs are defined as events that appear subsequent to the first injection or that were present prior to the first injection but worsened in intensity after the first injection. TEAEs may include, but are not limited to, injection site bruising, injection site discoloration, injection site edema, injection site erythema, injection site inflammation, injection site pain, and injection site swelling.

Frequency and percent of subjects reporting TEAEs of injection site reactions will be tabulated for each treatment by system organ class and preferred terms, and further by severity. In summaries of severity, subjects who reported more than one event in a treatment arm that are mapped to the same preferred term will be counted only once in that treatment arm under the strongest severity.

For other AEs where an association with either treatment may not be clearly identified, including systemic TEAEs, frequency and percent of subjects will be tabulated to treated subjects as one group by system organ class and preferred terms, and further by severity and relationship to study device. In summaries of severity and relationship, subjects who reported more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship.

Injection-site TEAEs and non-injection site TEAEs will also be tabulated by subject Fitzpatrick Skin Type (I-IV vs. V-VI) and by number of injections subjects received. Summary by preferred term will further be provided for TEAEs that are reported by subject and for TEAEs that are reported by Investigator separately. Most frequently occurring injection site TEAEs will also be summarized by event's severity and duration.

Treatment-Emergent Serious Adverse Events (TESAEs) will be discussed within the clinical study report. TESAEs and TEAEs that led to treatment interruption or discontinuation will be presented in data listings.

5.6.2 Exposure to Study Product

Amount of syringe used will be summarized using descriptive statistics (mean, SD, minimum, median, maximum) at Visit 1 for all the ITT subjects and at Visit 2/Week 2 for those who received a touch-up treatment.

5.6.3 Other Variables

<u>Investigator Ease of Use Assessment</u>: overall ease of use of the device will be evaluated by the investigator using the NRS from 0 being not easy to 10 being most easy at Visit 1/Day. It will be summarized for the ITT subjects descriptively with mean, SD, minimum, median, and maximum.

<u>Concomitant Medications</u>
Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, Version March 2013, and will be presented in data listings.

6   Tables and Listings

The following is an example of tables and listings that will be included in the clinical study report. Tables and listings may be modified as needed during the data analyses.

7   Appendices

7.1   Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

<u>Adverse Events</u>
Handling of partial dates is only considered for the start date. An adverse event with a partial start date is considered treatment emergent if:

- only the day is missing and the start month/year is the same or after the month/year of the first injection
- the day and month are missing and the start year is the same or greater than the year of the first injection date
- the start date is completely missing

<u>Concomitant Medications</u>
Handling of partial dates is only considered for the stop date. A medication with a partial stop date is considered concomitant if:

- only the day is missing and the stop month/year is the same or after the month/year of the first injection
- the day and month are missing and the stop year is the same or greater than the year of the first injection date
- the stop date is completely missing or the medication is ongoing.

7.2   Summary of Assessments

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	
Scheduled Day (Week)	Day 1 (Week 0)	Day 14 (Week 2)	Day 28 (Week 4)	Day 84 (Week 12)	Day 168 (Week 24)	Unsched Visit
Scheduling Window	none	± 2 days	± 2 days	± 4 days	± 7 days	
Informed consent	X					
Medical history/ demographics	X					
Physical examination (including vital signs)	X					
Concomitant medication/treatment	X	X	X	X	X	X
Inclusion/exclusion criteria review	X					
Urine pregnancy test[a]	X					
Wrinkle Severity Rating Scale (WSRS)	X	X	X	X	X	X[b]
Randomization	X					
Treatment with study products	X	X[c]				
Pain score (VAS)	0, 15, 30, 45, 60 min[d]	X[e]	X[c]			
Investigator Ease of Use	X					
Evaluation for touch-up		X				
Patient GAI (pGAI)		X	X	X	X	X[b]
Investigator GAI (iGAI)		X	X	X	X	X[b]
Adverse event assessment	X	X	X	X	X	X
Subject Diary	Dispense	Review/ Dispense[b]	Collect	Collect[b]		
Schedule/confirm next visit	X	X	X	X	X	X[b]

a   For women of childbearing potential, to be completed prior to enrollment.

b   If applicable.

c   For subjects who receive a touch-up treatment (iGAI = 3 or 4)

d   To be administered to the subject immediately after injection and 15, 30, 45, and 60 minutes post injection.

e   To be administered to subjects who will receive a touch-up treatment prior to touch-up, immediately after injection and 15, 30, 45, and 60 minutes post injection, and to be administered during the visit to subjects who do not receive a touch-up treatment.

Summary Tables

Table 14.1.1 – Analysis Population

	Total
Subjects Randomized	0
Subjects Included in the Intent-to-Treat (ITT) Population	0 (0%)
Subjects Included in the Modified Intent-to-Treat (mITT) Population	0 (0%)
Subjects Included in the Per-Protocol (PP) Population	0 (0%)

Source: Listings 16.2.1.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.1.1 will be used as the shell for the following table:

Table s14.1.1 – Analysis Population – Subset of Rollover Subjects

Table 14.1.2 – Subject Discontinuations by Reason for All Randomized Subjects

	Total
Subjects Randomized	0
Number Completed Study	0 (0%)
Total Discontinued	0 (0%)
Reason Discontinued	
-- Subject or legal representative withdrew consent	0 (0%)
-- Subject's product code was unblinded	0 (0%)
-- Significant protocol violation	0 (0%)
-- Subject became pregnant	
-- An AE occurs for which the subject or the investigator determines that it is in the subject's best interest to be discontinued	0 (0%)
-- Lost to follow-up	0 (0%)
-- Investigator discretion	0 (0%)
-- Other	0 (0%)

Source: Listing 16.2.1.2
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month, Day, Year.

Note:

Table 14.1.2 will be used as the shell for the following table:

Table s14.1.2 – Subject Discontinuations by Reason for Subset of Rollover Subjects

Table 14.1.3 – Subject Enrollment by Study Site

Site Number	Randomized	ITT	mITT	PP	Completed	Discontinued
1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2						
3						
4						
5						
Total	XX	XX	XX	XX	XX	XX

ITT: Intent-to-treat; mITT: modified ITT; PP: Per-protocol.
Percentages are based on the total number of subjects in each column.
Source: Listing 16.2.1.1, 16.2.1.2
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month, Day, Year.

Note:

Table 14.1.3 will be used as the shell for the following table:

Table s14.1.3 – Subject Enrollment by Study Site for Subset of Rollover Subjects

Table 14.1.4 – Significant Protocol Violations

Significant Protocol Violation	Total
Did not use any study product	0 (0%)
Violation of inclusion/exclusion criteria	0 (0%)
Did not complete Visit 5 within the specified window	0 (0%)
Use of prohibited medications	0 (0%)
…	

Significant protocol violations (SPVs) are those events that exclude subjects from any of the analysis populations.
Subjects with multiple SPVs are presented under each category as appropriate (e.g., Subjects who had no post-baseline visit are not counted under SPVs related to Visit 5).
Source: Listing 16.2.1.1, 16.2.2.3
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.1.4 will be used as the shell for the following table:

Table s14.1.4 – Significant Protocol Violations for Subset of Rollover Subjects

Table 14.1.5.1 – Demographic and Baseline Characteristics for Intent-to-Treat Population

Parameter	Category	Total (N=xx)
Gender	Female	0 (0%)
	Male	0 (0%)
Ethnicity	Hispanic or Latino	0 (0%)
	Not Hispanic or Latino	0 (0%)
	Not Willing to Provide	0 (0%)
Race	White	0 (0%)
	Asian	0 (0%)
	Native Hawaiian or Other Pacific-Islander	0 (0%)
	Black or African American	0 (0%)
	American Indian or Alaska Native	0 (0%)
	Other	0 (0%)
	Mixed*	0 (0%)
Age (years)	N	0
	Mean ± SD	00.0 ± 00.00
	Median	0.0
	Min, Max	0, 0
Age Groups	18 to < 40	0 (0%)
	40 to < 64	0 (0%)
	64 to <75	0 (0%)
	>= 75	0 (0%)
Body Mass Index (BMI)**	N	0
	Mean ± SD	00.0 ± 00.00
	Median	0.0
	Min, Max	0.0, 0.0
Fitzpatrick Skin Type Classification	I	0 (0%)
	II	0 (0%)
	III	0 (0%)
	IV	0 (0%)
	V	0 (0%)
	VI	0 (0%)

*Subjects who reported more than one race are categorized as Mixed race.
** BMI = weight (lbs) / height² (in) x 703
Source: Listing 16.2.4.1, 16.2.8.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.1.5.1 will be used as the shell for the following tables:

Table s14.1.5.1 – Demographic and Baseline Characteristics for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.1.5.2 - Demographic and Baseline Characteristics for Modified Intent-to-Treat Population

Table s14.1.5.2 – Demographic and Baseline Characteristics for Modified Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.1.5.3 - Demographic and Baseline Characteristics for Per-Protocol Population

Table s14.1.5.3 – Demographic and Baseline Characteristics for Per-Protocol Population – Subset of Rollover Subjects

Table 14.1.5.4 – Key Demographic and Baseline Characteristics by Site for Intent-to-Treat Population

Parameter	Category	Site 1 (N=xx)	Site 2 (N=xx)	Site 3 (N=xx)	Site 4 (N=xx)	p-value
Gender	Female	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.xxx[1]
	Male	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Age (years)	N	0	0	0	0	
	Mean ± SD	00.0 ± 00.00	00.0 ± 00.00	00.0 ± 00.00	00.0 ± 00.00	0.xxx[2]
	Median	0.0	0.0	0.0	0.0	
	Min, Max	0, 0	0, 0	0, 0	0, 0	
Body Mass Index (BMI)	N	0	0	0	0	
	Mean ± SD	00.0 ± 00.00	00.0 ± 00.00	00.0 ± 00.00	00.0 ± 00.00	0.xxx[2]
	Median	0.0	0.0	0.0	0.0	
	Min, Max	0, 0	0, 0	0, 0	0, 0	
Fitzpatrick Skin Type Classification	I	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.xxx[3]
	II	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	III	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	IV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	V	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	VI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

[1]P-value from Pearson's Chi-square test or exact test if appropriate.
[2]P-value from one-way analysis of variance (ANOVA) with study site as the main factor.
[3]P-value from nonparametric Kruskal Wallis test with study site as the class variable.

Note:

Table 14.1.5.4 will be used as the shell for the following table:

Table s14.1.5.4 – Key Demographic and Baseline Characteristics by Site for Intent-to-Treat Population - Subset of Rollover Subjects

Table 14.1.5.5 – Summary of Racial Distribution within Fitzpatrick Skin Type for Intent-to-Treat Population

| | Skin Type | | | | Total I-IV | Skin Type | | Total V-VI | Overall Total |
Race	I (N=xx)	II (N=xx)	III (N=xx)	IV (N=xx)	(N=xx)	V (N=xx)	VI (N=xx)	(N=xx)	(N=xx)
White	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black or African American	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Note:

Table 14.1.5.5 will be used as the shell for the following table:

Table s14.1.5.5 – Summary of Racial Distribution within Fitzpatrick Skin Type for Intent-to-Treat Population - Subset of Rollover Subjects

Table 14.1.5.6 –Demographic and Baseline Characteristics for PP Subjects and Subjects Excluded from the PP
Population

Parameter	Category	PP Subjects (N=xx)	Non-PP Subjects (N=xx)	p-value
Gender	Female	0 (0%)	0 (0%)	0.xxx[1]
	Male	0 (0%)	0 (0%)	
Ethnicity	Hispanic or Latino	0 (0%)	0 (0%)	0.xxx[1]
	Not Hispanic or Latino	0 (0%)	0 (0%)	
	Not Willing to Provide	0 (0%)	0 (0%)	
Race	White	0 (0%)	0 (0%)	NA
	Asian	0 (0%)	0 (0%)	
	Native Hawaiian or Other Pacific-Islander	0 (0%)	0 (0%)	
	Black or African American	0 (0%)	0 (0%)	
	American Indian or Alaska Native	0 (0%)	0 (0%)	
	Other	0 (0%)	0 (0%)	
Age (years)	N	0	0	
	Mean ± SD	00.0 ± 00.00	00.0 ± 00.00	0.xxx[2]
	Median	0.0	0.0	
	Min, Max	0, 0	0, 0	
-- Age Groups	18 to <40	0 (0%)	0 (0%)	
	40 to <64	0 (0%)	0 (0%)	
	64 to <75	0 (0%)	0 (0%)	
	>=75	0 (0%)	0 (0%)	
BMI	N	0	0	
	Mean ± SD	00.0 ± 00.00	00.0 ± 00.00	0.xxx[2]
	Median	0.0	0.0	
	Min, Max	0, 0	0, 0	
FST Classification	I	0 (0%)	0 (0%)	0.xxx[1]
	II	0 (0%)	0 (0%)	
	III	0 (0%)	0 (0%)	
	IV	0 (0%)	0 (0%)	
	V	0 (0%)	0 (0%)	
	VI	0 (0%)	0 (0%)	

PP = Per-Protocol. FST = Fitzpatrick Skin Type. BMI = weight (lbs) / height² (in) x 703
[1] P-values for group comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.
[2] P-value for group comparisons from nonparametric ranked two-way analysis of variance with fixed factors of group and site.
Source: Listing 16.2.4.1, 16.2.8.1

Table 14.2.1.1 – Primary Efficacy: Proportion of Responders Immediately After Injection at Visit 1/Day 1

Population Endpoint	Statistics	Revanesse Ultra	Revanesse Ultra+	Difference: Ultra minus Ultra+
Modified Intent-to-Treat (mITT)				
VAS Score	N	0	0	0
	Mean ± SD	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
	Median	0.0	0.0	0.0
	Min, Max	0, 0	0, 0	0, 0
Proportion of Responders	n (%)			0 (0.0%)
	95% Confidence Interval			(0.0%, 0.0%)[1]
	P-value for Interaction			0.xxx[2]
Per-Protocol (PP)				
VAS Score	N	0	0	0
	Mean ± SD	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
	Median	0.0	0.0	0.0
	Min, Max	0, 0	0, 0	0, 0
Proportion of Responders	n (%)			0 (0.0%)
	95% Confidence Interval			(0.0%, 0.0%)[1]

Note: The results from mITT are considered definitive and those from PP supportive.
Responder (to Revanesse Ultra+) is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra+) in VAS pain score of at least 10 mm on a 100-mm scale.
[1]The 95% confidence intervals are constructed using a one-sample binomial exact test.
[2]P-value for testing treatment effect by site interaction is from Pearson's Chi-square test.
Source: Listing 16.2.6.2.1, 16.2.6.3.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month, Day, Year.

Note:

Table 14.2.1.1 will be used as the shell for the following table:

Table s14.2.1.1 – Primary Efficacy: Proportion of Responders Immediately After Injection at Visit 1/Day 1 for Subset of Rollover Subjects

Table 14.2.1.2 – Primary Efficacy by Study Site: Proportion of Responders Immediately After Injection at Visit 1/Day 1

Site Number	Modified Intent-to-Treat (mITT)		Per-Protocol	
	N	n (%) of Responders	N	n (%) of Responders
1	0	0 (0.0%)	0	0 (0.0%)
2				
3				
4				
Total	0	0 (0.0%)	0	0 (0.0%)

*Responder (to Revanesse Ultra+) is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra+) in VAS pain score of at least 10 mm on a 100-mm scale.
Source: Listing 16.2.6.2.1, 16.2.6.3.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month, Day, Year.

Note:

Table 14.2.1.2 will be used as the shell for the following table:

Table s14.2.1.2 – Primary Efficacy by Study Site: Proportion of Responders Immediately After Injection at Visit 1/Day 1 for Subset of Rollover Subjects

Table 14.2.2.1 – Secondary Efficacy: Proportion of Responders at 15 Minutes Post Injection at Visit 1/Day 1

Population Endpoint	Statistics	Revanesse Ultra	Revanesse Ultra+	Difference: Ultra minus Ultra+
Modified Intent-to-Treat (mITT)				
VAS Score	N	0	0	0
	Mean ± SD	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
	Median	0.0	0.0	0.0
	Min, Max	0, 0	0, 0	0, 0
Responders (MI)*	n (%)			0 (0.0%)
	95% Confidence Interval			(0.0%, 0.0%)[1]
Responders (WCS)*	n (%)			0 (0.0%)
	95% Confidence Interval			(0.0%, 0.0%)[1]
Responders (BCS)*	n (%)			0 (0.0%)
	95% Confidence Interval			(0.0%, 0.0%)[1]
Per-Protocol (PP)				
VAS Score	N	0	0	0
	Mean ± SD	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
	Median	0.0	0.0	0.0
	Min, Max	0, 0	0, 0	0, 0
Responders	n (%)			0 (0.0%)
	95% Confidence Interval			(0.0%, 0.0%)[1]

Responder (to Revanesse Ultra+) is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra+) in VAS pain score of at least 10 mm on a 100-mm scale.
Missing VAS scores for the mITT analysis will be replaced using the multiple imputation (MI) method.
*MI (Multiple Imputation): Subjects with missing VAS scores are defined as responder or non-responder based on their VAS values through MI; WCS (Worst Case Scenario): Subjects with missing VAS scores are considered non-responders; BCS (Best Case Scenario): Subjects with missing VAS scores are considered responders.
[1]The 95% confidence intervals are constructed using a one-sample binomial exact test.
Source: Listing 16.2.6.2.1, 16.2.6.3.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month, Day, Year.

Note:

Table 14.2.2.1 will be used as the shell for the following tables:

Table 14.2.2.2 – Secondary Efficacy: Proportion of Responders at 30 Minutes Post Injection at Visit 1/Day 1

Table 14.2.2.3 – Secondary Efficacy: Proportion of Responders at 45 Minutes Post Injection at Visit 1/Day 1

Table 14.2.2.4 – Secondary Efficacy: Proportion of Responders at 60 Minutes Post Injection at Visit 1/Day 1

Table s14.2.2.4 – Secondary Efficacy: Proportion of Responders at 60 Minutes Post Injection at Visit 1/Day 1 for Subset of Rollover Subjects

Table 14.2.2.5 – Secondary Efficacy: Proportion of Responders at 2 Weeks Post Injection at Visit 2/Week 2

Table s14.2.2.5 – Secondary Efficacy: Proportion of Responders at 2 Weeks Post Injection at Visit 2/Week 2 for Subset of Rollover Subjects

Table 14.2.3.1 – Other Efficacy: Wrinkle Severity Rating Scale (WSRS) by Visit for Modified Intent-to-Treat Population

Study Visit	Category	Revanesse Ultra	Revanesse Ultra+	Difference: Ultra minus Ultra+
Visit 1/Day 1	N	0	0	
	1 = Absent	0 (0%)	0 (0%)	
	2 = Mild	0 (0%)	0 (0%)	
	3 = Moderate	0 (0%)	0 (0%)	
	4 = Severe	0 (0%)	0 (0%)	
	5 = Extreme	0 (0%)	0 (0%)	
	N of subjects with data from both sides			0
	Mean ± SD			0.0 ± 0.00
Visit 2/Week 2	…			
…	…			
	…			
Visit 5/Week 24	N	0	0	0
	1 = Absent	0 (0%)	0 (0%)	
	2 = Mild	0 (0%)	0 (0%)	
	3 = Moderate	0 (0%)	0 (0%)	
	4 = Severe	0 (0%)	0 (0%)	
	5 = Extreme	0 (0%)	0 (0%)	
	N of subjects with data from both sides			0
	Mean ± SD			0.0 ± 0.00

Missing values are not imputed for the summary. A positive mean value in difference is in favor of Revanesse Ultra+.
Source: Listing 16.2.6.2.1, 16.2.6.3.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month, Day, Year.

Note:

.1 will be used as the shell for the following table:

Table s14.2.3.1 – Other Efficacy: Wrinkle Severity Rating Scale (WSRS) by Visit for Modified Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.2.3.2 – Other Efficacy: Wrinkle Severity Rating Scale (WSRS) by Visit for Per-Protocol Population

Table s14.2.3.2 – Other Efficacy: Wrinkle Severity Rating Scale (WSRS) by Visit for Per-Protocol Population – Subset of Rollover Subjects

Table 14.2.4.1 – Other Efficacy: Patient Global Aesthetic Improvement (pGAI) by Visit for Modified Intent-to-Treat Population

Study Visit	Category	Revanesse Ultra	Revanesse Ultra+	Difference: Ultra minus Ultra+
Visit 2/Week 2	N	0	0	
	1 = Worse	0 (0%)	0 (0%)	
	2 = No Change	0 (0%)	0 (0%)	
	3 = Improved	0 (0%)	0 (0%)	
	4 = Much Improved	0 (0%)	0 (0%)	
	5 = Very Much Improved	0 (0%)	0 (0%)	
	N of subjects with data from both sides			0
	Mean ± SD			0.0 ± 0.00
Visit 3/Week 4	…			
…	…			
	…			
Visit 5/Week 24	N	0	0	
	1 = Worse	0 (0%)	0 (0%)	
	2 = No Change	0 (0%)	0 (0%)	
	3 = Improved	0 (0%)	0 (0%)	
	4 = Much Improved	0 (0%)	0 (0%)	
	5 = Very Much Improved	0 (0%)	0 (0%)	
	N of subjects with data from both sides			0
	Mean ± SD			0.0 ± 0.00

Missing values are not imputed for the summary. A negative mean value in difference is in favor of Revanesse Ultra+.
Source: Listing 16.2.6.2.1, 16.2.6.3.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month, Day, Year.

Note 1:

Table 14.2.4.1 will be used as the shell for the following table:

Table s14.2.4.1 – Other Efficacy: Patient Global Aesthetic Improvement (pGAI) by Visit for Modified Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.2.4.2 – Other Efficacy: Patient Global Aesthetic Improvement (pGAI) by Visit for Per-Protocol Population

Table s14.2.4.2 – Other Efficacy: Patient Global Aesthetic Improvement (pGAI) by Visit for Per-Protocol Population – Subset of Rollover Subjects

Note 2:

Tables 14.2.4.1 and 14.2.4.2 will be used as the shell for the following tables:

Table 14.2.5.1 – Other Efficacy: Investigator Global Aesthetic Improvement (iGAI) by Visit for Modified Intent-to-Treat Population

Table s14.2.5.1 – Other Efficacy: Investigator Global Aesthetic Improvement (iGAI) by Visit for Modified Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.2.5.2 – Other Efficacy: Investigator Global Aesthetic Improvement (iGAI) by Visit for Per-Protocol Population

Table s14.2.5.2 – Other Efficacy: Investigator Global Aesthetic Improvement (iGAI) by Visit for Per-Protocol Population – Subset of Rollover Subjects

Table 14.3.1 – Exposure to Study Product, Investigator Ease of Use Assessment and Patient Comfort Rating for Intent-to-Treat Population

	Statistics	Revanesse Ultra	Revanesse Ultra+
Amount of Syringe Used (ml) at Visit 1/Day 1	N	0	0
	Mean ± SD	0.0 ± 0.00	0.0 ± 0.00
	Median	0.0	0.0
	Min, Max	0, 0	0, 0
Investigator Ease of Use Assessment at Visit 1/Day 1	Mean ± SD	0.0 ± 0.00	0.0 ± 0.00
	Median	0.0	0.0
	Min, Max	0, 0	0, 0
Subject Received a Touch-Up at Visit 2/Week 2	N (%)	0 (0.0%)	0 (0.0%)
Amount of Syringe Used for Touch-Up (ml)	Mean ± SD	0.0 ± 0.00	0.0 ± 0.00
	Median	0.0	0.0
	Min, Max	0, 0	0, 0

Investigator Ease of Use Assessment based on the Numerical Rating Scale (NRS): 0 (Not Easy) to 10 (Most Easy).
Source: Listing 16.2.5.1, 16.2.5.2
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month, Day, Year.

Note:

Table 14.3.1 will be used as the shell for the following table:

Table s14.3.1 – Exposure to Study Product, Investigator Ease of Use Assessment and Patient Comfort Rating for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.2.1 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	All TEAEs		Reported by Subject		Reported by Investigator	
	Revanesse Ultra (N=xx)	Revanesse Ultra+ (N=xx)	Revanesse Ultra (N=xx)	Revanesse Ultra+ (N=xx)	Revanesse Ultra (N=xx)	Revanesse Ultra+ (N=xx)
Subjects with at Least One Injection Site TEAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

…

Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.1 will be used as the shell for the following table:

Table s14.3.2.1 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.2.2 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Population

System Organ Class Preferred Term	Revanesse Ultra (N=xx)			Revanesse Ultra+ (N=xx)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Subjects with at Least One Injection Site TEAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

…

Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one injection site TEAE are counted only once (under the greatest reported severity).
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.2 will be used as the shell for the following table:

Table s14.3.2.2 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Population - Subset of Rollover Subjects

Table 14.3.2.3 – Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	Revanesse Ultra (N=xx)	Revanesse Ultra+ (N=xx)
Class 1		
Term 1	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)
Class 2		
Term 1	0 (0%)	0 (0%)
…		

Most frequently occurring injection site TEAEs are those that were reported by 5% or more subjects of any treatment group.
Counts reflect numbers of subjects reporting one or more injection site TEAEs that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (preferred term) subjects reporting more than one injection site TEAE are only counted once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.3 will be used as the shell for the following table:

Table s14.3.2.3 – Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.2.4 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

System Organ Class Preferred Term	Treatment Group	FST I (N=xx)	FST II (N=xx)	FST III (N=xx)	FST IV (N=xx)	Pooled FST I-IV (N=xx)	FST V (N=xx)	FST VI (N=xx)	Pooled FST V-VI (N=xx)
Subjects with at Least One Injection Site TEAE	Revanesse Ultra	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Revanesse Ultra+	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 1	Revanesse Ultra	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Revanesse Ultra+	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	Revanesse Ultra	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Revanesse Ultra+	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
…									
…									
Class 2	Revanesse Ultra	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Revanesse Ultra+	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	Revanesse Ultra	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Revanesse Ultra+	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
…									
…									

Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.4 will be used as the shell for the following table:

Table s14.3.2.4 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.2.4a – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

Table 14.3.2.4b – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Investigator by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

Table 14.3.2.5 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

System Organ Class Preferred Term	Revanesse Ultra		Revanesse Ultra+	
	1 Injection (N=xx)	2 Injections (N=xx)	1 Injection (N=xx)	2 Injections (N=xx)
Class 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)

…

TEAEs are grouped by number of injection(s) a subject received up to when the events started.
1 Injection = ON or AFTER the injection on Day 1 AND BEFORE the touch up. 2 Injections = ON or AFTER the touch up.
Note: The denominator for a grouping includes all the subjects who went through the indicated period regardless if they reported any TEAEs during the period.
Counts reflect numbers of subjects reporting one or more injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.5 will be used as the shell for the following table:

Table 14.3.2.5a – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

Table 14.3.2.5b – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Investigator by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

Table s14.3.2.5 – Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population – Subset of Rollover Subjects

Table s14.3.2.5a – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population – Subset of Rollover Subjects

Table s14.3.2.5b – Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Investigator by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.2.6 – Overall Summary of Injection Site Treatment-Emergent Adverse Events (TEAEs) for Intent-to-Treat Population

	Revanesse Ultra		Revanesse Ultra+	
	Subjects[1] (N=xx)	Events[2] (N=xx)	Subjects[1] (N=xx)	Events[2] (N=xx)
Overall	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Duration				
Less than 1 week	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Between 1 week and 1 month (30 days)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
More than 1 month (30 days)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severity				
Mild	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Causality				
Treatment-related*	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not treatment-related	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Outcome				
Resolved	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Improved	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stabilized	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Worsened	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unchanged	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment Required (Action Taken)				
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Study treatment interrupted/discontinued	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-drug therapy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New OTC or Rx drug added	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hospitalized (includes ER visits)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[1] Denominator is the number of subjects who received the corresponding treatment.
[2] Denominator is the number of adverse events reported by subjects who received the corresponding treatment.
*Treatment-related includes Possibly and Probably Related.
For Severity and Causality, subjects reporting more than one injection site TEAE associated with a treatment arm are counted only once for the treatment arm under the greatest reported severity and most likely causality, respectively.

For Duration, Outcome and Treatment Required (Action Taken), at each level of the categories, subjects reporting more than one injection site TEAE associated with a treatment arm are counted only once for the treatment arm at that category level.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.6 will be used as the shell for the following table:

Table s14.3.2.6 – Overall Summary of Injection Site Treatment-Emergent Adverse Events (TEAEs) for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.2.7 – Severity of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

Adverse Event	Revanesse Ultra				Revanesse Ultra+			
	Events % (n/N)[1]	Mild % (n/N)[2]	Moderate % (n/N)[2]	Severe % (n/N)[2]	Events % (n/N)[1]	Mild % (n/N)[2]	Moderate % (n/N)[2]	Severe % (n/N)[2]
Preferred Term 1	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)
Preferred Term 2	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)

Most frequently occurring injection site TEAEs are those that were reported by 5% or more subjects of any treatment group.

[1] Denominator is the number of injection site TEAEs reported by all ITT subjects who received the corresponding treatment.

[2] Denominator for percentages by severity is the number of subjects with respective TEAEs after receiving the corresponding treatment. Numerator (count of subjects) is based on the rule that subjects reporting more than one same incidence associated with a treatment arm are counted only once for the treatment arm under the greatest reported severity.

Source: Listing 16.2.7.1

O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.7 will be used as the shell for the following table:

Table s14.3.2.7 – Severity of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.2.8 – Duration of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population

Adverse Event	Revanesse Ultra				Revanesse Ultra+			
	Events % (n/N)[1]	<7 Days % (n/N)[2]	7-30 Days % (n/N)[2]	>30 Days % (n/N)[2]	Events % (n/N)[1]	<7 Days % (n/N)[2]	7-30 Days % (n/N)[2]	>30 Days % (n/N)[2]
Preferred Term 1	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)
Preferred Term 2	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)

Most frequently occurring injection site TEAEs are those that were reported by 5% or more subjects of any treatment group.
[1] Denominator is the number of injection site TEAEs reported by all ITT subjects who received the corresponding treatment.
[2] Denominator for percentages by duration is the number of subjects with respective TEAEs after receiving the corresponding treatment. Numerator (count of subjects) is based on the rule that subjects reporting more than one same incidence associated with a treatment arm are counted only once for the treatment arm under the longest duration.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.8 will be used as the shell for the following table:

Table s14.3.2.8 – Duration of Most Frequently Occurring Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.3.1 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term for Intent-to-Treat Population

System Organ Class Preferred Term	All TEAEs All ITT Subjects (N=xx)	Reported by Subject All ITT Subjects (N=xx)	Reported by Investigator All ITT Subjects (N=xx)
Subjects with at Least One Non-Injection Site TEAE	0 (0%)	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)

…

Counts reflect numbers of subjects reporting one or more non-injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one non-injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Table 14.3.3.2 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Population

System Organ Class Preferred Term	All ITT Subjects (N=xx)		
	Mild	Moderate	Severe
Subjects with at Least One Non-Injection Site TEAE	0 (0%)	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)

…

Counts reflect numbers of subjects reporting one or more non-injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one non-injection site TEAE are counted only once (under the greatest reported severity).
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.3.2 will be used as the shell for the following table:

Table s14.3.3.2 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.3.3 – Most Frequently Occurring Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat
Population

System Organ Class Preferred Term	All ITT Subjects (N=xx)
Class 1	
Term 1	0 (0%)
Term 2	0 (0%)
Class 2	
Term 1	0 (0%)
…	

Most frequently occurring non-injection site TEAEs are those that were reported by 5% or more subjects.
Counts reflect numbers of subjects reporting one or more non-injection site TEAEs that map to the MedDRA (version x.x) system organ class/preferred term. At each level of
summarization (preferred term) subjects reporting more than one non-injection site TEAE are only counted once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.3.3 will be used as the shell for the following table:

Table s14.3.3.3 – Most Frequently Occurring Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term for Intent-to-Treat
Population – Subset of Rollover Subjects

Table 14.3.3.4 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Causality for Intent-to-Treat Population

| System Organ Class | All ITT Subjects (N=xx) | |
Preferred Term	Unlikely	Related*
Subjects with at Least One Non-Injection Site TEAE	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)

…

*Related category includes Possibly and Probably Related.
Counts reflect numbers of subjects reporting one or more non-injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term) subjects reporting more than one non-injection site TEAE are only counted once (under the most likely relationship to study medication).
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.3.4 will be used as the shell for the following table:

Table s14.3.3.4 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Causality for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.3.5 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

System Organ Class Preferred Term	FST I (N=xx)	FST II (N=xx)	FST III (N=xx)	FST IV (N=xx)	Pooled FST I-IV (N=xx)	FST V (N=xx)	FST VI (N=xx)	Pooled FST V-VI (N=xx)
Subjects with at Least One Non-Injection Site TEAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
…								
…								
Class 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
…								
…								

Counts reflect numbers of subjects reporting one or more non-injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one non-injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.2.5 will be used as the shell for the following table:

Table s14.3.3.5 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.3.5a – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

Table 14.3.3.5b – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Investigator by MedDRA System Organ Class, Preferred Term, and Fitzpatrick Skin Type (FST) for Intent-to-Treat Population

Table 14.3.3.6 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

System Organ Class Preferred Term	Ultra[1]Ultra+[1] (N=xx)	Ultra[1]Ultra+[2] (N=xx)	Ultra[2]Ultra+[1] (N=xx)	Ultra[2]Ultra+[2] (N=xx)
Class 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Class 2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Term 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)

…

TEAEs are grouped by number of injection(s) a subject received up to when the events started.
Ultra[i]Ultra+[j] = AFTER Revanesse Ultra injection #i and Revanesse Ultra+ injection #j AND BEFORE any other injections if applicable.
Note: The denominator for a grouping includes all the subjects who went through the indicated period regardless if they reported any TEAEs during the period.
Counts reflect numbers of subjects reporting one or more non-injection site TEAE that map to the MedDRA (version x.x) system organ class/preferred term. At each level of summarization (system organ class or preferred term), subjects reporting more than one non-injection site TEAE are counted only once.
Source: Listing 16.2.7.1
O:\Studies\Prollenium\SYM 2016-02\Biometrics\Programs\Tables\xxx.sas ran on Month Day, Year at hh:mm on data from Month Day, Year.

Note:

Table 14.3.3.6 will be used as the shell for the following table:

Table s14.3.3.6 – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population – Subset of Rollover Subjects

Table 14.3.3.6a – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Subject by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

Table 14.3.3.6b – Non-Injection Site Treatment-Emergent Adverse Events (TEAEs) Reported by Investigator by MedDRA System Organ Class, Preferred Term, and Number of Injection for Intent-to-Treat Population

Subject Listings

Listing 16.2.1.1 – Subject Analysis Status

Site-Subject	Participated in SYM 2014-02	Site-Subject from SYM 2014-02	Intent-to-Treat (ITT)		Modified Intent-to-Treat (mITT)		Per-Protocol (PP)	
			Included?	Reason for Not Included	Included?	Reason for Not Included	Included?	Reason for Not Included

O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Note:

Listing 16.2.1.1 will be used as the shell for the following listing:

Listing s16.2.1.1 – Subject Analysis Status for Subset of Rollover Subjects

Listing 16.2.1.2 – Subject Disposition

Site-Subject	Analyses	Subject Disposition	Date Completed or Discontinued	Reason, if Discontinued	Diary cards collected?	Used prohibited meds?

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Note:

Listing 16.2.1.2 will be used as the shell for the following listing:

Listing s16.2.1.2 – Subject Disposition for Subset of Rollover Subjects

Listing 16.2.1.3 – Dates of Visits

Site-Subject	Analyses	Visit 1/ Day 1 (Baseline)	Visit 2/ Week 2 Day 14 (±2 days) [Day #]	Visit 3/ Week 4 Day 28 (±2 days) [Day #]	Visit 4/ Week 12 Day 84 (±4 days) [Day #]	Visit 5/ Week 24 Day 168 (±7 days) [Day #]	No. of UVs: Unscheduled Visit(s) [Day #]

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses
Day # (Study Days) = Visit Date - Baseline (Visit 1) Date +1.
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Listing 16.2.2.1 – Violation of Inclusion Criteria

Site-Subject	Analyses	1	2	3	4	5	6

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
*Please see section 8.3.1 of study protocol for description of the inclusion criteria.
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Listing 16.2.2.2 – Violation of Exclusion Criteria

Site-Subject	Analy.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

Analy. (Analyses): I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
*Please see section 8.3.2 of study protocol for description of the exclusion criteria.
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Listing 16.2.2.3 – Significant Protocol Violations

Site-Subject	Analyses	Significant Protocol Violation

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
Significant protocol violations are those events that exclude subjects from any analysis population.
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Note:

Listing 16.2.2.3 will be used as the shell for the following listing:

Listing s16.2.2.3 – Significant Protocol Violations for Subset of Rollover Subjects

Listing 16.2.2.4 – Comments

Site-Subject	Analyses	Date of Comments	CRF Page Number	Comment(s)	Initials

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses

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Note:

Listing 16.2.2.4 will be used as the shell for the following listing:

Listing s16.2.2.4 – Comments for Subset of Rollover Subjects

Listing 16.2.4.1 – Demographics

Site-Subject	Subject Initials	Analyses	Age (yrs)	Sex	Race	Ethnicity	Fitzpatrick Skin Type	Informed Consent	
								Signed?	Date

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Note:

Listing 16.2.4.1 will be used as the shell for the following listing:

Listing s16.2.4.1 – Demographics for Subset of Rollover Subjects

Listing 16.2.4.2 – Brief Physical Examination at Baseline

| | | | | Physical Examination | | |
Site-Subject	Analyses	Height (inches)	Weight (lbs)	Heart	Lungs	Abdomen

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Listing 16.2.4.3 – Medical History Findings

Site-Subject	Analyses	Medical System	Diagnosis/Procedure	Onset Date	Stop Date	Concomitant Medication?
		xxx	xxxx	-----2002	Ongoing	Yes
		xxxxxxx	xxxxxxxxxxxx	-----1997	Ongoing	No

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
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Note:

Listing 16.2.4.3 will be used as the shell for the following listing:

Listing s16.2.4.3 – Medical History Findings for Subset of Rollover Subjects

Listing 16.2.5.1 – Treatment Administration at Visit 1/Day 1

| | | | Injection placed | Time of Injection and Amount of Syringe Used (hh:mm/ml) | | | Investigator Ease of Use Assessment | | | Diary card |
Site-Subject	Analy.	Random Number	successfully in both side?	Revanesse Ultra	Revanesse Ultra+	Injected By	Revanesse Ultra	Revanesse Ultra+	Assessed By	reviewed and dispensed?

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
Investigator Ease of Use Assessment assess on the Numerical Rating Scale (NRS): 0 (Not Easy) to 10 (Most Easy).
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Note:

Listing 16.2.5.1 will be used as the shell for the following listing:

Listing s16.2.5.1 – Treatment Administration at Visit 1/Day 1 for Subset of Rollover Subjects

Listing 16.2.5.2 – Touch-Up Treatment Administration at Visit 2/Week 2

			Revanesse Ultra					Revanesse Ultra+				
Site-Subject	Analyses	No Touch-up Required for Either Side	No Touch-up Required	Injection placed successfully?	Time of Injection	Amount of Syringe Used (ml)	Injected By	No Touch-up Required	Injection placed successfully?	Time of Injection	Amount of Syringe Used (ml)	Injected By

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Note:

Listing 16.2.5.2 will be used as the shell for the following listing:

Listing s16.2.5.2 – Touch-Up Treatment Administration at Visit 2/Week 2 for Subset of Rollover Subjects

Listing 16.2.6.1.1 – Efficacy Evaluations of Visual Analog Scale (VAS) for Pain

Site-Subject	Analyses	Study Visit	Time Point	Revanesse Ultra		Revanesse Ultra+	
				Time Assessed	Score	Time Assessed	Score
xx-xxxx	M	Visit 1/Day 1	Immediately After Injection	hh:mm	40	hh:mm	50

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Note:

Listing 16.2.6.1.1 will be used as the shell for the following listing:

Listing s16.2.6.1.1 – Efficacy Evaluations of Visual Analog Scale (VAS) for Pain for Subset of Rollover Subjects

Listing 16.2.6.1.2 – Efficacy Evaluations (WSRS, pGAI, iGAI)

Site-Subject	Analyses	Study Visit	Treatment Arm	Wrinkle Severity Rating Scale (WSRS)		Patient Global Aesthetic Improvement (pGAI)	Investigator Global Aesthetic Improvement (iGAI)	
				Score	Performed By		Score	Performed By
xx-xxxx	M	…						
		Visit 2/Week 2	Revanesse Ultra	5=Extreme	XXX	2=No Change	1=Worse	XXX
			Revanesse Ultra+	3=Moderate	XXX	2=No Change	3=Improved	XXX

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Note:

Listing 16.2.6.1.2 will be used as the shell for the following listing:

Listing s16.2.6.1.2 – Efficacy Evaluations (WSRS, pGAI, iGAI) for Subset of Rollover Subjects

(*Programmer note for Listing s16.2.6.1.2: Add Fitzpatrick Skin Type to the listing and present the data sorted by skin type.*)

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Listing 16.2.6.2.1 – Primary and Secondary Efficacy Responses for Modified Intent-to-Treat Population

Site-Subject		Study Visit	Time Point	Revanesse Ultra		Revanesse Ultra+		Ultra minus Ultra+ in VAS	Responder*			
				Observed or MI	VAS Score	Observed or MI	VAS Score		Observed	MI	WSC	BCS
xx-xxxx	III	Visit 1/Day 1	Immediately after injection	Observed	50	Observed	42	8	No			
			15 minutes post injection	Observed	46	MI	34.4	11.6		Yes	No	Yes
			30 minutes post injection	Observed	31	MI	25.5	5.5		No	No	Yes

Missing VAS scores for the mITT analysis will be replaced using the multiple imputation (MI) method. The average values from the MI copies of VAS are present and used for analysis.
*Responder (to Revanesse Ultra+) is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra+) in VAS pain score of at least 10 mm on a 100-mm scale. Observed: Subjects are defined as responder or non-responder based on the non-missing values; MI (Multiple Imputation): Subjects with missing VAS scores are defined as responder or non-responder based on their VAS values through MI; WCS (Worst Case Scenario): Subjects with missing VAS scores are considered non-responders; BCS (Best Case Scenario): Subjects with missing VAS scores are considered responders.
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Note:

Listing 16.2.6.2.1 will be used as the shell for the following listing:

Listing s16.2.6.2.1 – Primary and Secondary Efficacy Responses for Modified Intent-to-Treat Population – Subset of Rollover Subjects

Listing 16.2.6.2.2 – Other Efficacy Responses for Modified Intent-to-Treat Population

Site-Subject	Study Visit	Wrinkle Severity Rating Scale (WSRS)		Patient Global Aesthetic Improvement (pGAI)		Investigator Global Aesthetic Improvement (iGAI)	
		Revanesse Ultra	Revanesse Ultra+	Revanesse Ultra	Revanesse Ultra+	Revanesse Ultra	Revanesse Ultra+
…							
xx-xxxx	…						
	Visit 5/Week 12	5=Extreme	3=Moderate	3=Improved	4 =Much improved	4=Much improved	3=Improved

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Note:

Listing 16.2.6.2.2 will be used as the shell for the following listing:

Listing s16.2.6.2.2 – Other Efficacy Responses for Modified Intent-to-Treat Population – Subset of Rollover Subjects

Listing 16.2.6.3.1 – Primary and Secondary Efficacy Responses for Per-Protocol Population

| Site-Subject | Study Visit | Time Point | VAS Score | | Ultra minus Ultra+ in VAS | Responder* |
			Revanesse Ultra	Revanesse Ultra+		
xx-xxxx	Visit 1/Day 1	Immediately after injection	50	42	8	No
		15 minutes post injection	46	34	12	Yes
		30 minutes post injection	31	25	6	No

*Responder (to Revanesse Ultra+) is defined as a subject who had a within-subject difference (Revanesse Ultra minus Revanesse Ultra+) in VAS pain score of at least 10 mm on a 100-mm scale.
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Note:

Listing 16.2.6.3.1 will be used as the shell for the following listing:

Listing s16.2.6.3.1 – Primary and Secondary Efficacy Responses for Per-Protocol Population – Subset of Rollover Subjects

Listing 16.2.6.3.2 – Other Efficacy Responses for Per-Protocol Population

Site-Subject	Study Visit	Wrinkle Severity Rating Scale (WSRS)		Patient Global Aesthetic Improvement (pGAI)		Investigator Global Aesthetic Improvement (iGAI)	
		Revanesse Ultra	Revanesse Ultra+	Revanesse Ultra	Revanesse Ultra+	Revanesse Ultra	Revanesse Ultra+
… xx-xxxx	… Visit 5/Week 12	5=Extreme	3=Moderate	3=Improved	4 =Much improved	4=Much improved	3=Improved

O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Note:

Listing 16.2.6.3.2 will be used as the shell for the following listing:

Listing s16.2.6.3.2 – Other Efficacy Responses for Per-Protocol Population – Subset of Rollover Subjects

Listing 16.2.7.1 – Adverse Events

Site-Subject	Analy	Skin Type	AE Reported by	System Organ Class// Preferred Term// Verbatim Term	Start Date [Day #]	Stop Date [Day #]	Severity	Causality	Action Taken[1]	Out[2]	Serious?
Treatment: Revanesse Ultra											
…											
…											
…											
Treatment: Revanesse Ultra+											
…											
…											
…											
Treatment: Unidentified (not on face)											
…											
…											

Analy (Analyses): I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
Day # is calculated from baseline (Visit 1) date. Day 1 is the baseline date while Day -1 is the day prior to the baseline visit.
[1] Action Taken: 1=None, 2=Study treatment interrupted/discontinued, 3=Non-drug therapy, 4=New OTC or Rx drug added, 4=Hospitalized
[2] Out (outcome): 1= Resolved, 2=Improved, 3=Stabilized, 4=Worsened, 5=Unchanged, 6=Lost to Follow-up/Unknown, 7=Fatal
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Programming Note: Each AE is identified with the associated treatment arm or as a systemic event based on how the field is filled on the CRF for "If AE located on face".
- *If it is left blank, the event is considered systemic and is to be reported under the grouping for "Treatment: Unidentified (not on face)".*
- *If it is filled as on the Left Side or the Right Side, the event is to be identified with the proper treatment arm and is to be reported under the proper treatment arm.*
- *If it is filled as on Both Sides, the event is to be reported once under each treatment arm.*

Note:
Repeat Listing 16.2.7.1 for AEs that led to study treatment interrupted/Discontinued and Serious AEs –

Listing s16.2.7.1 – Adverse Events for Subsets of Rollover Subjects

Listing 16.2.7.2 – Adverse Events Leading to Study Treatment Interrupted/Discontinued

Listing s16.2.7.2 – Adverse Events Leading to Study Treatment Interrupted/Discontinued for Subsets of Rollover Subjects

Listing 16.2.7.3 – Serious Adverse Events

Listing s16.2.7.3 – Serious Adverse Events for Subset of Rollover Subjects

Listing 16.2.7.4 – Injection Site Adverse Events Lasted more than 30 Days

Listing 16.2.8.1 – Vital Signs and Urine Pregnancy Test at Baseline

Site-Subject	Analyses	Sitting Systolic BP (mmHg)	Sitting Diastolic BP (mmHg)	Heart Rate (bpm)	Oral Temperature (ºF)	Respiratory Rate (breath/min)	Urine Pregnancy Test	
							Test Results	Test Date

Analyses: I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Listing 16.2.9.1 – Prior and Concomitant Medications/Treatments

Site-Subject	Analy	Treatment Assignment	If Used on Face	WHO Class // WHO Name //Medication	Indication	Start Date [Day #]	Stop Date [Day #]	Dosage	Freq.	Route
xx-xxxx	P	L:Ultra, R:Ultra+	L, R	XXXXXXXXX // XXXXXXXXXX XXX // XXXXXXXX	XXXXXXX	01JAN05 [3]	Ongoing	xxxxx	xxxx	xxx

Analy (Analyses): I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
Note: Medications coded using the WHO Drug Dictionary, version xxx.
Day # is calculated from baseline (Visit 1) date. Day 1 is the baseline date while Day -1 is the day prior to the baseline visit. L=Left side of the face, R=Right side of the face.
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.

Listing 16.2.9.2 – Non-Pharmacological Interventions (NPIs)

Site-Subject	Analy	Treatment Assignment	If Used on Face	Non-Pharmacological Intervention	Indication	Start Date [Day #]	Stop Date [Day #]	Dosage	Freq.	Route
xx-xxxx	P	L:Ultra, R:Ultra+	L, R	XXXXXXXXXXXXXXXX	XXXXXXX	01JAN05 [3]	Ongoing	xxxxx	xxxx	xxx

Analy (Analyses): I = Intent-to-Treat (ITT) Analyses only, M = Modified Intent-to-Treat (MITT) and ITT Analyses, P = Per-Protocol, MITT, and ITT Analyses.
Day # is calculated from baseline (Visit 1) date. Day 1 is the baseline date while Day -1 is the day prior to the baseline visit. L=Left side of the face, R=Right side of the face.
O:\Studies\ Prollenium\SYM 2016-02\Biometrics\Programs\Listing\xxx.sas ran on Month Day Year at hh:mm on data from Month Day, Year.