Q-Med AB, part of the Galderma Group

A Prospective, Non-interventional Study to Collect Subject and Physician Satisfaction During Long Term Treatment of Glabellar Lines with Dysport® in Subjects of Chinese Origin in Real Clinical Practice

05PF2009

Statistical Analysis Plan

Version: 2.0

Date: 15Mar2024

APPROVAL PAGE

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MODIFICATION HISTORY

VERSION	*VERSION DATE*	*AUTHOR*	*DESCRIPTION*
1.0	2024.02.19	PPD	FINAL VERSION
2.0	2024.03.15		All adverse reactions were revised to adverse events; TFL is updated according to the ICH-E3 standard

TABLE OF CONTENTS

ABBREVIATION

Abbreviation	Specification
AE	Adverse Event
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BoNT	Botulinum toxin
BoNT-A	Botulinum toxin serotype A
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
GCP	Good Clinical Practice
GL	Glabellar lines
FAS	Full Analysis Set
ICH	International Council for Harmonization
IP	Investigational Product
MedDRA	Medical Dictionary For Regulatory Activities
NA	Not Applicable
NMPA	National Medical Products Administration
PPS	Per Protocol Set
PT	Preferred Term
Q1	25% quartile
Q3	75% quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Statistical Analysis Report
SAS	Statistical Application Software
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
SS	Safety Set
SS Event	Special Situation Event
UAE	Unexpected Adverse Drug Reaction
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used in summarizing and analyzing the efficacy and safety data that will be collected in this study 05PF2009 and aims to support the clinical study report (CSR). This statistical analysis plan will be finalized prior to database lock.

This document is developed based on the protocol version 2.0 (28 Jun 2021) and electronic Case Report Form (eCRF) version 1.1 (01 Jan2023) and compliances with the recommendations of the International Conference on Harmonization (ICH) E9 guidelines "Statistical Principles for Clinical Trials" [1] and the ICH E3 guidelines "Structure and Content of Clinical Study Reports" [2].

2. STUDY OBJECTIVE

To collect subject and physician satisfaction, and treatment experience with Dysport in real clinical practice in subjects of Chinese origin.

3. STUDY DESIGN

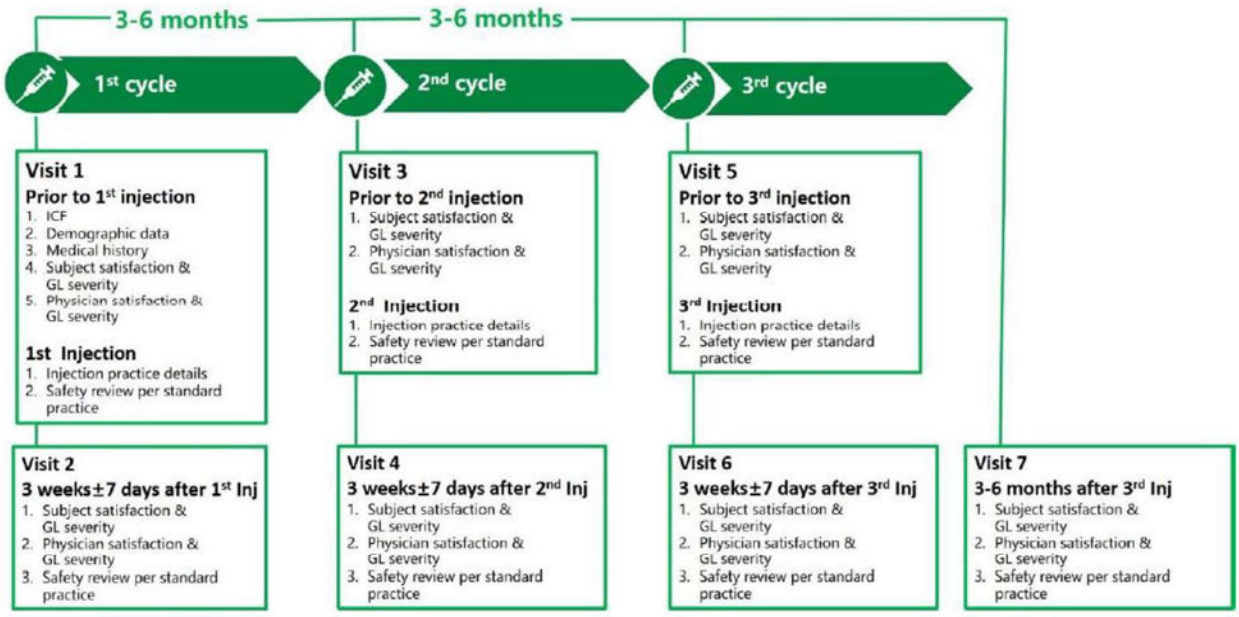
This is a prospective, longitudinal, non-interventional, multi-center study.

3.1.Investigational Product (IP)

Commercially available Dysport, a BoNT-A product, strength: 300U per vial, produced and supplied by Q-Med AB, part of the Galderma Group.

3.2.Study Flow Chart

Study Flow Chart is shown below.



3.3.Schedule of Assessments

Schedule of Assessments of the study is shown below.

	Injection Cycle 1		Injection Cycle 2		Injection Cycle 3		
Visit Number	Visit 1[1]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Visit Name	Screening Baseline/ Injection 1[1]	Follow up 1	Injection 2	Follow up 2	Injection 3	Follow up 3	Follow up 4
Visit Window	≤ 30 days of Baseline/Injection 1	3 weeks (± 7 days) from Injection 1	3-6 months from Injection 1	3 weeks (± 7 days) from Injection 2	3-6 months from Injection 2	3 weeks (± 7 days) from Injection 3	3-6 months from Injection 3
Informed Consent	X						
Demographic Data	X						
Medical History	X						
Safety Review	X	X	X	X	X	X	X
Injection Practice Details	X		X		X		
Physician GL Severity Assessment	X[2]	X	X[2]	X	X[2]	X	X
Physician Satisfaction Questionnaire	X[2]	X	X[2]	X	X[2]	X	X
Subject assessments							
Subject GL Severity Assessment	X[2]	X	X[2]	X	X[2]	X	X
Subject Satisfaction Questionnaire	X[2]	X	X[2]	X	X[2]	X	X

Definitions:

- 1 month = 4 weeks

1. Screening and Baseline/Visit 1 (i.e., Injection 1) may be performed on the same day. If performed as separate visits, informed consent, demographic data, and medical history should be complete at Screening, and all other remaining visit procedures and confirmation of subject medical history should be performed at Baseline /Visit 1 (i.e., Injection 1).
2. Prior to injection.

3.4.Randomization Design and Execution

Not applicable. This is a non-interventional study.

3.5.Blinding Design and Execution

Not applicable. This is a non-interventional study.

3.6.Sample Size Consideration

The sample size of approximately 250 subjects is not based on a statistical calculation. The selected number of subjects is regarded as sufficient for an evaluation of the studied endpoints by using descriptive statistics.

4. ENDPOINTS

4.1.Efficacy Endpoints

4.1.1. Primary Efficacy Endpoints

The primary efficacy endpoint is subject satisfaction after three injection cycles with Dysport with GL. At Visit 6 subjects will be asked “What is your overall satisfaction after three treatments cycles with Dysport?” Response options are: very satisfied, satisfied, dissatisfied, and very dissatisfied. The primary endpoint will evaluate the proportion of subjects in each response category.

4.1.2. Secondary Efficacy Variables

① Physician satisfaction after three injection cycles with Dysport in the GL. The proportion of subjects in each response category for the physician's overall satisfaction with Dysport at Visit 6.

② a. Proportions of subjects in each response category per question answered on the Subject Satisfaction Questionnaire complete at all visits.

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4.2.Safety Endpoints

4.2.1. Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory

finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Thus, any new sign, symptom or disease, or any clinically significant worsening of an existing sign, symptom or disease (including new episodes of a chronic disease) compared to the condition at the first visit, should be considered as an AE.

4.2.2. Unexpected Adverse Event (UAE)

An unexpected AE is defined as an adverse event, the nature or severity of which is not consistent with the applicable study product information (e.g., medicinal package insert/summary of product characteristics for an approved study product).

4.2.3. Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose:

(1) Results in death

(2) Is life-threatening

(3) Requires inpatient hospitalization or prolongation of existing hospitalization

(4) Results in persistent or significant disability/incapacity

(5) Is a congenital anomaly/birth defect

4.2.4. Special Situation (SS) Events

SS Event is an incidence of overdose, off-label use, medication error, occupational exposure, abuse, misuse, or lack of therapeutic efficacy while using the medicinal product, or any instance of drug exposure during pregnancy or breast-feeding.

4.2.5. Severity

(1) Mild: Awareness of signs or symptom, but easily tolerated.

(2) Moderate: Discomfort, enough to cause interference with usual activity.

(3) Severe: Incapacitating with inability to work or perform usual activity.

4.3.Demographics and Disease Characters

4.3.1. Demographics

The demographics including age, sex, and nation will be recorded in CRF.

4.3.2. Medical History

The information of medical history including disease name, start date, end date and ongoing will be recorded in CRF.

4.3.3. Surgery History

The name and date of surgery prior to screening will be recorded in CRF.

4.3.4. Allergy History

The information of allergy history will be recorded in CRF.

4.4.Prior/Concomitant Medication

The information of prior/concomitant medication including drug name, dose, unit, frequency, route of administration, start date, end date, ongoing, and reason for usage will be recorded in CRF.

4.5.Prior/Concomitant Treatment

The information of prior/concomitant treatment including name of treatment, start date, end date, ongoing, and treatment reason will be recorded in CRF during the study.

4.6.Protocol Deviation

Clinical operation team shall record the cause, date and severity of all protocol deviations in the file Protocol Deviation Tracking Log.

5. STATISTICAL HYPOTHESIS

Not applicable. This is a non-interventional study.

6. ANALYSIS SETS

6.1.Full Analysis Set (FAS)

All subjects screened, enrolled in the study treated at least once with Dysport.

6.2.Per Protocol Set (PPS)

A subset of FAS that include subjects who have evaluable primary efficacy endpoints, have overall good compliance, and have no major protocol deviations during the study. Subjects excluded from PPS will be determined in Data Review Meeting before Data Base Lock.

6.3.Safety Set (SS)

The set of subjects who have received at least one dose of study treatment and for whom actual data on safety endpoints are available.

7. STATISITICAL METHODS

7.1.General Statistical Consideration

Demographics and disease characteristics data, efficacy data, and safety data will be analyzed. The annotated or explanatory transcript will only be listed. The following rules apply to general situations unless otherwise stated.

7.1.1. Application of Analysis Sets

Baseline analyses will be based on FAS and PPS; efficacy analyses will be primarily based on PPS, and on FAS as reference; safety analyses will be based on SS.

7.1.2. Descriptive Statistics

For continuous data, descriptive statistics include number of non-missing patients, number of missing patients (nmiss), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum.

For categorical data, the frequency and percentage of patients in each category will be presented. Counts that are zero will be displayed as "0". Percentages will be based on non-missing data unless otherwise specified. Two-sided 95% confidence interval will be calculated for the estimated incidence wherever appropriate.

7.1.3. Decimals

The minimum and maximum will keep the same decimal place with the raw data, while mean, median, Q1 and Q3 will keep 1 more decimal place, and SD will keep 2 more decimal places. The decimal place of above statistics will not exceed 4 regardless of the decimal place of raw data.

Percentages and 95% confidence interval (CI) will keep 1 decimal place.

P value will be rounded to 4 decimal places. '<.0001' will be displayed when the P value is lesser than 0.0001 and '>.9999' will be displayed when the P value is greater than 0.9999.

7.1.4. General Statistical Test Methods

For continuous data, parametric or non-parametric method will be used according to the result of Shapiro-Wilk test with 5% significance level.

For within-group comparison, paired t-test will be performed if the assumption of normality is satisfied, otherwise Wilcoxon signed rank test will be performed.

For between-group comparison, two sample t-test will be performed if the assumption of normality is satisfied, otherwise Wilcoxon rank sum test will be performed.

For between-group comparison of categorical data, chi-square test will be basically performed and the Wald asymptotic 95% confidence interval will be calculated.

But in case of more than 20% of the number of cells with an expected frequency of less than 5, Fisher's exact test will be performed and the exact 95% confidence intervals will be calculated.

7.1.5. Significance Level

Statistical analysis will be performed with a two-sided test at a significance level of 5% whenever required.

7.1.6. Software for Statistical Analysis

Statistical programming will use SAS® 9.4 or higher version.

7.1.7. Definition of Baseline

The baseline values for all variables (if applicable) are defined as the latest measurement or examine result before injection.

7.1.8. Scheduled and Unscheduled Visit

Generally, statistical description by visits will be performed on the scheduled visits unless it is specified otherwise. For shift table of clinical evaluation of safety data, the data on scheduled and unscheduled visits will be all included in the analyses.

7.1.9. Subject Identifier

For the data listing, screening number (USUBJID) will be used as a unique identifier.

7.2.Data Handling

Data will be analyzed as observed without imputation for missing values.

7.3.Subjects in Study

7.3.1. Subjects Disposition

The following summaries will be tabulated:

- No. and percentage of subjects screened and reasons for screening failure
- No. and percentage of subjects who are treated and not treated.
- No. and percentage of subjects who completed the study.
- No. and percentage of subjects who prematurely discontinued study and reasons of early termination

The above analysis will be summarized for each site.

Detailed information regarding disposition of each subject will be listed.

7.3.2. Protocol Deviation

For all enrolled subjects, all major protocol deviations recorded by clinical operation team will be summarized according to predefined categories. All the protocol deviations will be recorded in the file Protocol Deviation Tracking Log.

Major protocol deviations will be summarized for each site.

All protocol deviations recorded by clinical operation team of each subject will be listed.

7.3.3. Analysis Sets

For all enrolled subjects, the number of subjects in each analysis set will be summarized together with the number of subjects excluded from each analysis set and the corresponding reasons.

The above analysis will be summarized for each site.

Detailed information of analysis sets will be listed.

7.3.4. Demographics and Baseline Characters

- Demographics

The demographics including age, sex, and nation will be summarized using descriptive statistics.

Detailed information of demographics will be listed by subject.

- Medical/ Surgery History

Number of events, number and percentage of subjects who had at least one medical history will be summarized using descriptive statistics. All medical history will also be summarized by System Organ Class (SOC) and preferred term (PT) that will be coded using the MedDRA version 25.1.

Detailed information of medical/surgery history will be listed by subject.

7.3.5. Allergy History

Number of events, number and percentage of subjects who had at least one allergy history will be summarized using descriptive statistics. The number of events will also be presented.

Detailed information of allergy history will be listed by subject.

7.3.6. Prior/Concomitant Medication

Prior medication and concomitant medication analyses will be based on FAS and PPS.

Prior medication and concomitant medications will be coded by the World Health Organization Drug Dictionary (WHO DD) Global (B3) E [V2022SEP]. Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification (including Anatomy group, Therapeutic group and Chemical group) and WHO preferred drug name, respectively. The summary will be sorted in decreasing order of percentage of ATC class firstly and then sorted in decreasing order of percentage of preferred drug term within the ATC class.

Prior medications: if the end date of the medication is before the date of injection in this study. Concomitant medications: if the end date of the medication is on or after the date of injection in this study or still ongoing.

Detailed information of prior and concomitant medications will be listed by subject.

7.3.7. Prior/Concomitant Treatment

Prior and concomitant treatment analyses will be based on FAS and PPS.

Number of events, number and percentage of subjects who had at least one treatment will be summarized using descriptive statistics.

All prior/concomitant treatment will be coded by MedDRA version 25.1 and summarized by SOC and PT.

Detailed information of prior/concomitant treatment will be listed by subject.

7.4.Efficacy Analysis

7.4.1. Analysis on Primary Efficacy Endpoints

Analysis on primary efficacy endpoints will be performed on PPS and FAS.

At Visit 6 proportion of subjects in each response category from subject satisfaction will be evaluated and its exact 95% CI will be calculated.

7.4.2. Analysis on Secondary Efficacy Endpoints

Analysis on secondary efficacy endpoints will be performed on PPS and FAS.

① At Visit 6 proportion of subjects in each response category from physician overall satisfaction will be evaluated and its exact 95% CI will be calculated.

② a. At all visits proportion of subjects in each response category per question from subject satisfaction will be evaluated and its exact 95% CI will be calculated.

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7.5.Safety Analysis

AEs will be coded by MedDRA version 25.1. SOC and PT will be presented in summary tables of AE. All summary table will be based on Treatment Emergent AE (TEAE).

TEAE defines as all AEs that occur after the first treatment.

Overall TEAEs, UAEs, SAEs, SS Events, AEs leading to discontinuation from study, AEs leading to death and whether these AEs are possibly caused by the product and/or injection procedure, will be summarized by number of events, number of subjects, percentage and 95% CI.

The number of events, number of subjects and percentage with AEs and product and/or injection procedure related AEs will be summarized for each category by SOC, PT and severity. If multiple

AEs in the same SOC (PT) have occurred in the same subject when summarizing the number of subjects, the subject will be counted only once for this SOC (PT). When summarizing the number of subjects by severity, if multiple AEs in the same SOC (PT) have occurred in the same subject, the event with the highest severity of this SOC (PT) will be used for analysis. When summarizing the number of events, all the AEs will be accounted.

Detailed information of AEs, UAEs, SAEs, SS Events, AEs possibly caused by the product and/or injection procedure, AEs leading to discontinuation, and AEs leading to death will be listed by subject.

7.6.Interim Analyses

Two interim analyses will be performed before the final analysis. The first interim analysis will be performed after Visit 2. The second interim analysis will be performed after Visit 4. Only applicable tables and listings will be generated for interim analyses.

7.7.Change from the Analysis Plan in Protocol

Two interim analyses are added after the first two injection cycles before the final analysis.

Section	Description in protocol	Description in SAP
4.2.1	Adverse Drug Reaction (ADR) For marketed medicinal products, an ADR is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modifications of physiological function.	delete
4.2.2	Unexpected Adverse Drug Reaction (UADR) An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study product information (e.g.,medicinal packageinsert/summary of product characteristics for an approved study product).	Unexpected Adverse Event (UAE) An unexpected AE is defined as an adverse event, the nature or severity of which is not consistent with the applicable study product information (e.g., medicinal package insert/summary of product characteristics for an approved study product).

8. REFERENCE

[1] ICH E9: Statistical Principles for Clinical Trials (1998).

[2] ICH E3: Structure and Content of Clinical Study Reports (1995).

9. TFL SHELL

Refer to the attached document of SAP.

PPD

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	3/18/2024 6:03:48 PM
Certified Delivered	Security Checked	3/19/2024 10:06:29 AM
Signing Complete	Security Checked	3/19/2024 10:06:42 AM
Completed	Security Checked	3/19/2024 10:06:42 AM

Payment Events	Status	Timestamps

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