Protocol A4091065

A Protocol to Monitor from Birth to Age 15 Months the Neurological Development of Infants with Exposure In-Utero in Tanezumab Clinical Studies at All Investigational Sites

Statistical Analysis Plan (SAP)

Version: 3.0

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study A4091065 is based on the protocol dated 26APR2016.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1.0 (13OCT2016)	Not Applicable	Not Applicable
2.0	Section 7	Added the interim summaries for submission.
3.0	Section 6.6	Added to create listing about mother's exposure in parent studies as per team discussion.

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is *italicised*.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study A4091065. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

This study will examine post-natal neurologic and cognitive development of infants who were exposed to tanezumab or placebo or comparator in-utero during the tanezumab clinical program (through maternal participation in a tanezumab clinical study) within the following protocols: A4091056, A4091057, A4091058, A4091059, A4091061 and A4091063. The specific objective is:

- *Evaluate physical development, neurological development (including the autonomic nervous system) and cognitive development through the age of 15 months of infants (and possibly beyond until the infant is considered stable in the judgment of the pediatric neurologist, developmental psychologist or pediatrician) exposed to tanezumab, placebo or comparator in-utero due to maternal participation in a tanezumab clinical study. All observed or volunteerd SAEs and non-serious neurological or neuro-developmental adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported.*

2.2. Study Design

This study is a multicenter, prospective, cohort study with enhanced physical and neurodevelopmental surveillance to characterize the outcomes related to the development of infants up to the age of 15 months, who were exposed to tanezumab, placebo or comparator

via maternal exposure at conception or in-utero in any tanezumab clinical study at any investigational site. The postnatal monitoring will include assessments at birth, (0-2 months), approximately 8 months and approximately 15 months of age up to a maximum of 36 months of age as needed.

This is an observational study, using enhanced surveillance of infants with potential exposure in-utero whose mother participated in a tanezumab clinical study. There is no active study treatment in this observational study. However, the neonatal/pediatric evaluations should be performed in a blinded fashion (while the mother of the infant is informed as to treatment allocation, the evaluator is not informed to the treatment the infant's mother received).

This study is designed to evaluate neurological and psychological development outcomes among infants with maternal exposure in-utero in tanezumab clinical studies. Because all tanezumab clinical studies exclude women who are currently pregnant and instruct female subjects of childbearing potential and at risk for pregnancy to use highly effective method(s) of contraception throughout the study and for 16 weeks after the last dose of subcutaneous investigational product, the total number of eligible subjects is expected to be small (fewer than 20). As such, there will not be sufficient statistical power to make use of formal statistical comparisons. Therefore, all analyses will be descriptive in nature, primarily through counts of observed outcomes.

Following is the schedule of assessments from the protocol:

Protocol Activity		**Screen**	**0-2 Months**	**8 Months**	**15 Months/ET[c,d]**
			Visit 1	**Visit 2**	**Visit 3**
Informed consent		X			
History & Physical Examination					
Occipital-frontal head circumference			X	X	X
Length			X	X	X
Weight			X	X	X
Vital Signs			X	X	X
Post-birth age (weeks)			X	X	X
Neurological Examination			X	X	X
Developmental	BINS[a]			X	X
Assessments	REEL-3[b]			X	X

a. Bayley Infant Neurodevelopmental Screener. (BINS).
b. Bzoch-League Receptive Expressive Emergent Language Test, third edition (REEL-3).
c. End of Treatment (ET)/Follow up visit: The need for further physical, neurological or developmental evaluations will be determined at the 15 month visit by the pediatrician, pediatric neurologist or a psychologist.
d. Post-study subject interview (if applicable): The need for additional post-study follow up visits will be determined subsequent to the Visit 3 (15 month) visit and may extend to a maximum of 36 months as needed (eg, should a physical or neurodevelopmental delay be observed to be not within the range of normal development by the evaluating pediatrician, pediatric neurologist, or psychologist, an additional interview may be conducted up to 36 months of age).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The specific endpoints for this study are:

- *Physical/safety measures (occipital-frontal head circumference, length, weight) and vital signs (blood pressure, pulse rate, respiratory rate, temperature).*
- *Neurological measures (mental status, cranial nerves, motor and sensory systems, reflexes).*
- *Psychological measures: Bayley Infant Neurodevelopmental Screener (BINS), Bzoch-League Receptive Expressive Emergent Language Test, third edition (REEL-3).*

The above measures will be used by the investigators to complete a maturation and development assessment CRF.

Descriptive assessments of the neurologists and psychologists may be incorporated into the Clinical Study Report on an individual basis.

3.2. Secondary Endpoint(s)

Endpoints are not distinguished as primary vs. secondary in the protocol. All are listed in the Primary Endpoint(s) section.

3.3. Other Endpoints

There are no other endpoints in this protocol.

3.4. Baseline Variables

Baseline variables are those collected at the initial visit.

3.5. Safety Endpoints

See Section 3.1.

3.5.1. Adverse Events

All observed or volunteered SAEs and non-serious neurological or neuro-developmental AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported. Non-serious, non-neurological AEs will not be collected.

All AEs reported in the study will be summarized; there is no separate determination of 'treament emergent' AEs because no study drug was directly administered to subjects in the study.

4. ANALYSIS SETS

4.1. Full Analysis Set

The primary analysis set for this study will be the Safety Population, defined as all subjects enrolled into the study. Subjects will be classified according to which treatment the mother was classified as receiving for safety analyses in the original tanezumab clinical study.

4.2. Per Protocol Analysis Set

No per protocol analysis set is defined for this study.

4.3. Safety Analysis Set

See Section 4.1.

4.4. Other Analysis Sets

No other analysis sets are defined for this study.

5. GENERAL METHODOLOGY AND CONVENTIONS

The final summaries will be performed at study data set release after last subject last visit.

5.1. Hypotheses and Decision Rules

There are no statistical hypotheses or decision rules in this study.

5.2. General Methods

Results will be presented by the treatment group which the mother was classified as receiving for safety analyses in the original tanezumab clinical study.

Listings will include visit, visit date, calculated study day relative to date of birth and windowed study day. Windowed study days will be determined using windows as defined in Appendix 1.1.

Vital signs data (including body length, head circumference and body weight) will be summarized descriptively by windows defined in 3 month intervals over the first 2 years and then 6 month intervals afterwards. Also these data will be summarized based on windows defined relative to target ages for comparison to normative data. No inferential statistical methods will be utilized. Study day windows are described inAppendix 1.1.

5.3. Methods to Manage Missing Data

Summaries and listings will include only observed data. No imputation methodologies will be employed for missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

This study is designed to evaluate neurological safety related to both pregnancy outcomes as well as hypothetical risk of adverse development outcomes. However, the sample size…will

not be sufficient to generate more than a description of the safety outcomes outlined in the study endpoints. These results will be summarized as counts and associated rates of occurrence of each endpoint (stratified by randomized treatment arm from the original tanezumab clinical study the parent was identified through) as well as narrative descriptions of individual cases.

6.2. Secondary Endpoint(s)

There are no separate secondary endpoints.

6.3. Other Endpoint(s)

There are no separate other endpoints.

6.4. Subset Analyses

There are no planned subset analyses.

6.5. Baseline and Other Summaries and Analyses

Baseline data will be summarized.

6.6. Safety Summaries and Analyses

Standard safety reporting tables will list the safety data (including Adverse Events and Serious Adverse Events) as well as list patient demographics, disposition and summary status. A non-standard table will be produced listing parental characteristics to include the study, center, patient ID, and treatment group of the mother, and SAE report number associated with the pregnancy. Additional non-standard tables will list the outcome post delivery (newborn length, weight and head circumference) as well as investigator responses on the maturation and development assessment form.

In addition, a listing will be produced to evaluate exposure (days) from conception. The exposure is defined as

- ✓ the date from conception to last dose (injection) + 16 week for tanezumab, and
- ✓ the date from conception to the end of treatment for oral treatment group (tramadol).

7. INTERIM ANALYSES

7.1. Introduction

No interim analyses are planned for this study other than those done for the safety monitoring committee (SMC) and potentially for regulatory submission.

7.2. Interim Analyses and Summaries

The detail of interim analysis and summaries follows the SMC SAP.

Interim summaries of these data may be produced for inclusion in a regulatory submission. In this case, a snap-shot of the database will be taken and stored, then the data will be

summarized based on this analysis plan. If a clinical study that a mother participated in has not been unblinded at the time of a regulatory submission, the mother's treatment will be indicated as blinded.

8. APPENDICES

Appendix 1. DATA DERIVATION DETAILS

Appendix 1.1. Definition and Use of Visit Windows in Reporting

Interval Based Study Windows

For the assessments made at study visits interval based study day windows are shown below. When multiple observations occur in a window, the observation closest to the window midpoint will be used, noting that the latter will be used in the case of a tie. If multiple observations occur in the last interval the last observation will be used.

Visit Window label	Window midpoint day	Study days
0-≤3 months	45	0 – 90
>3-≤6 months	135	91-180
>6-≤9 months	225	181-270
>9-≤12 months	315	271-360
>12-≤15 months	405	361-450
>15-≤18 months	495	451-540
>18-≤21 months	585	541-630
>21-≤24 months	675	631-720
>24-≤30 month	810	721-900
>30-≤36 months	990	901-1080
Etc…as needed		

Target Age Study Windows

To account for any early or late scheduled visits (compared to the target patient ages for normative data) we define ‘windows’ to be able to allocate each observation to a single specific study day window relative to date of birth. For the assessments made at study visits these study day windows are shown below. When multiple observations occur in a window, the observation closest to the target age will be used, noting that the latter will be used in the case of a tie.

Target Window label	Target Age	Study Days
0 – 2 months	<60 days	0-74
8 months	225 days	210-240
15 months	435	420-450