CLINICAL PROTOCOL

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

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Compound Name:	Tanezumab
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APPENDICES

PROTOCOL SUMMARY

This is a multicenter, prospective, cohort study with enhanced physical and neurodevelopmental surveillance to characterize the neurological 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 (A4091056, A4091057, A4091058, A4091059, A4091061, A4091063) at any investigational site. The post-natal monitoring will include assessments at birth (0-2 months), approximately 8 months and approximately 15 months of age and up to a maximum of 36 months of age as needed.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visit and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

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 Assessments	BINS[a]			X	X
	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).

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Tanezumab (PF-04383119, formerly RN624) is under development for the relief of signs and symptoms of osteoarthritis (OA), and management of moderate to severe chronic pain in conditions such as chronic low back pain (CLBP), and cancer pain due to bone metastasis.

1.2. Background and Rationale

1.2.1. Description of Investigational Product

Tanezumab is a humanized immunoglobulin G Type 2 (IgG2) monoclonal antibody, derived from a murine precursor by grafting the murine complementarity determining regions onto a human antibody framework, followed by extensive site-directed mutagenesis using proprietary technology to improve binding affinity and specificity. A mutation was performed in the Fc portion of the antibody to decrease its ability to activate complement or to support antibody dependent cell-mediated cytotoxicity.

Tanezumab is highly potent in sequestering Nerve Growth Factor (NGF) and preventing interaction with its receptors. Tanezumab and/or its murine precursor have been shown to be an effective analgesic in nonclinical animal models of pathological pain including arthritis, cancer pain, and post-surgical pain models.

The administration of a monoclonal antibody against human NGF, such as tanezumab, offers the potential to provide a novel, effective treatment of pain without the adverse effects or limited efficacy of currently available therapies.

1.2.2. Role of Nerve Growth Factor

During mammalian development, NGF is required for the survival and growth of several populations of neurons. However, NGF is not required for neuronal survival in adulthood. The role of NGF in the adult mammal appears to principally be as a modulator of nociceptive neuronal activity. Thus, NGF plays an important role in modulation of the pain response.[1,2]

Anti-NGF antibodies were widely used to study the function of NGF from 1970 to about 1990, before the other members of the neurotrophic factor (NTF) family were discovered. Polyclonal antisera generated against NGF purified from mouse submaxillary gland were generally used in these studies.

Studies investigating the potential role of NGF in pre- and post-natal development of rodents by using direct injections of polyclonal antisera, the generation of female rodents autoimmune to their own NGF, and genetic knockouts of the NGF gene, have suggested that NGF is important for the proper embryonic development of sympathetic neurons, a subset of peripheral primary afferent neurons and perhaps for a small population of cholinergic neurons of the basal forebrain in rodents.[3,4] The conclusions from these studies need to be interpreted with caution due to the limitations of the methods used and the knowledge base available at the time they were performed. First, the antisera bind to many different sites on NGF and are immunologically active, thereby potentially mediating toxic effects not due to

NGF deprivation per se. Second, since the vast majority of these studies took place before it was known that NGF is one of a closely related family of proteins, it is likely that many of the sera used in these studies cross react to those other members and hence some of the effects seen may be due to deprivation of molecules other than NGF. Tanezumab is specific for NGF, but is not expected to completely block all NGF.[5,6]

Evidence available in the literature describes differences in transfer across the placenta into the embryo for IgG subclasses with transfer being greater for IgG1 and lower for IgG2. Unlike most therapeutic antibodies, tanezumab belongs to the IgG2 subclass rather than the more frequently employed IgG1 subclass. Organogenesis in humans is complete by gestation Day 56, and since IgG2 placental transfer is minimal during this period and the recommended human dosing interval for tanezumab is every 8 weeks (about every 56 days) the likelihood of significant embryonic exposure to a therapeutic antibody during this period is low.[7]

An analysis of the predicted tanezumab exposure in female partners via semen from male subjects was conducted and confirmed that tanezumab exposure via semen does not result in biologically relevant exposure to the fetus. The margin between partner exposure and the Minimum Anticipated Biological Effect Level (MABEL) is greater than 300-fold using very conservative estimates.[8] The lack of genotoxic risk and lack of tanezumab-related effects on reproductive endpoints in non-human primates further supports no need for contraceptive requirements for men in any clinical studies of tanezumab or a need to monitor children of male subjects in tanezumab studies.

1.2.3. Safety of Tanezumab During Pregnancy and Study Rationale

As of February 2015, a total of 32 clinical studies involving over 11,000 subjects have been conducted (refer to Tanezumab Investigator Brochure, Feb 2015). Tanezumab is currently being studied as a treatment for osteoarthritis chronic lower back and cancer pain in an ongoing Phase 3 development program in approximately 6900 additional subjects to evaluate the efficacy and safety of tanezumab administered subcutaneously (SC). Additional subject populations may be considered in the future as part of the overall development plan for tanezumab.

Based on the mechanism of action of tanezumab, there could be a potential neurological developmental risk to a fetus, but the actual risk is unknown. The non-clinical assessment of tanezumab effects on primate pre-and postnatal development included: (1) an enhanced prenatal and postnatal development study (ePPND) and (2) a primate modified embryofetal development study to evaluate tanezumab effects on pre-and post-natal development when given in the first trimester. See the Investigator's Brochure for summaries of these early development studies.

Results from the ePPND study assessing the effects of tanezumab on prenatal and postnatal development when administered weekly by Intravenous (IV) injection to maternal cynomologous monkeys has shown an increase in total pregnancy loss (sum of embryo-fetal losses and stillbirths) in all treatment groups in comparison to concurrent controls. Gross morphological evaluations of the stillborn animals in this study did not reveal any

observations to suggest a cause of death. The significance of these findings to humans is uncertain at this time.

Strategies have been incorporated into the tanezumab development program to mitigate the risk of pregnancy for women of childbearing potential (WOCBP) and are available in the individual study protocols. Adherence to these requirements will be expected across all ongoing and planned clinical studies with tanezumab.

As of February 2015, twelve cases of pregnancy have been reported across the entire tanezumab program (which consists of a total of >11,000 subjects). Two cases were reported in studies for interstitial cystitis [redacted] The outcome of the pregnancy reported in Study [redacted] was a healthy full-term [redacted] who was found to have no abnormalities on clinical examination including neurological and cognitive skills examination (in the Month 2, Month 8 and Month 14 post-natal). The outcome of the pregnancy in Study [redacted] was a full-term baby [redacted] who had normal neurological and cognitive development up to 15 months. Six pregnancies were reported in chronic low back pain studies [redacted] Three of these cases [redacted] involved a female partner of a male patient enrolled in the study (paternal exposure). The outcomes of all of the paternal exposure pregnancies in Study [redacted] and Study [redacted] (all paternal exposure) were live births of healthy infants. Two pregnancies in Study [redacted] were cases of maternal exposure and resulted in live births of healthy infants. The outcome of the remaining pregnancy in Study [redacted] also a case of maternal exposure, was elective abortion. There were four pregnancies reported in osteoarthritis studies [redacted] The outcome of the pregnancy in Study [redacted] and [redacted] a case of maternal exposure in both studies, was live birth of a healthy infant. The outcome of the remaining 2 pregnancies, all cases of maternal exposure, were spontaneous miscarriage in Study [redacted] and elective abortion in Study [redacted]. In summary, only one Serious Adverse Event (SAE) (nystagmus) was reported in these infants and despite the small sample size and lack of comparator group in the [redacted] Exposure in Utero (EIU) follow up study, the data did not provide evidence of a deleterious effect of in utero exposure to tanezumab either via maternal or paternal exposure on the resulting infants.[9]

To assess the safety of infants potentially exposed in-utero to investigational drug due to maternal participation in any ongoing or planned clinical study with tanezumab, this study will evaluate the postpartum neurologic and cognitive development of infants up to the age of 15 months based on neurological examinations and standardized evaluations of cognitive development. The sponsor will attempt to enroll all eligible infants. However, because pregnant women are excluded from tanezumab clinical studies and pregnancies during clinical studies are discouraged, the sponsor does not anticipate a substantial number of potential subjects. Therefore, this study is not intended to generate any formal statistical inferences, but rather to follow-up and characterize the outcomes of all pregnancies to women subjects of childbearing potential (WOCBP) within the clinical program.

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigator's Brochure (IB). The Single Reference Safety Document for any comparator agent in a parent study is its approved product label.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. 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. Endpoints

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).

3. 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.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Reporting and tracking of exposure in-utero should be performed as outlined in the tanezumab study the parent was participating in and is not within the scope of this protocol. Monitoring of pregnancy outcomes is within the scope of the tanezumab clinical study in which the parent was participating.

Once a pregnancy or maternal exposure has been identified from one of these studies, the female clinical study participant and mother of the infant (the subject), will be invited to enroll her infant in this postnatal monitoring protocol by the investigator. For the child to participate in this study, the mother of the subject must review, agree and sign an informed consent document explaining the details of the postnatal follow-up.

4.1. Inclusion Criteria

Subject eligibility is to be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Subject is an infant born to a mother who was exposed to study drug on a tanezumab clinical study (tanezumab, placebo or comparator).

2. The infant's mother (who was the tanezumab clinical study participant) must review, agree and sign an informed consent document explaining the details of the perinatal and post-natal follow-up. Where local regulations mandate, the male parent would also review and sign the informed consent.

3. Parent(s) or legal guardian must be willing and able to comply with scheduled visits and study procedures.

4.2. Exclusion Criteria

There are no exclusion criteria for participating in this study.

4.3. Randomization Criteria

Not applicable.

4.4. Lifestyle Guidelines

Not applicable.

5. STUDY TREATMENTS

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).

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

Attempts will be made to enroll all cases of EIU irrespective of prior therapy.

5.2. Breaking the Blind

Not applicable.

5.3. Investigational Product Supplies

Not applicable.

5.3.1. Dosage Form(s) and Packaging

Not applicable.

5.3.2. Preparation and Dispensing

Not Applicable.

5.3.3. Administration

Not applicable.

5.4. Compliance

Not applicable.

5.5. Investigational Product Storage and Investigational Product Accountability

Not applicable.

5.6. Concomitant Medications

Not applicable.

5.7. Rescue/Escape/Salvage Therapy

Not applicable.

6. STUDY PROCEDURES

6.1. Screening

There is no screening period for participation in this study. Informed consent must be obtained before any study procedures are conducted.

6.2. Study Period

The enrolled infants will participate from birth to at least the age of 15 months. The planned visits are outlined below. Neonatal/pediatric evaluations should be performed by a designated physician, such as a pediatric neurologist and a clinical psychologist (neurodevelopmental scales) who will be identified by the investigator or Pfizer.

6.2.1. (Visit 1) Newborn (0-2 Months of Age: Birth or at Any Time within 2 Months of Age)

6.2.1.1. History and Physical Examination

Demographic data from the parents (obstetrics history, history of previous children) and estimated date of conception and gestational age at birth should be collected and recorded in a consultation report as provided by the obstetrician or gynecologist to the investigator as well as added to the CRF. Dosing dates with study drug are considered part of the initial protocol where the exposed mother participated but last maternal dosing date should be added to the current CRF.

Consultation reports and overall clinical impression of immediate pre-parturition maternal status provided by an obstetrician/gynecologist or practitioner are to be reported to the investigator. This information is to be maintained as a source document, a de-identified copy of which will be forwarded to the Sponsor within 35 days of receipt/completion.

Consultation reports and overall clinical impression from attending birth physician assessment of delivery difficulty: number/characterizations of any complications as minor or major reported to the investigator. This information is to be maintained as a source document, a de-identified copy of which will be forwarded to the Sponsor within 35 days of receipt/completion. Physical examination to include measurements of occipital-frontal head circumference, length, weight and post-birth age (weeks), and systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature. The examiner will provide a report to the investigator.

6.2.1.2. Neurological Examination (Pediatrician or Pediatric Neurologist)

The neurologic examination will evaluate all cranial nerves except I (smell), IX (taste) and XI (shoulder shrug). Motor examination will include evaluation of muscle tone, bulk and movement. Sensory examination will include test of temperature and superficial pain (homologous dermatomes using cold tuning fork, neurological examination pin) and deep

pain by pressure on Achilles tendon. Reflex evaluation will include biceps, brachioradialis, patellar, and Achilles tendons. Evaluation for persistence of developmental reflexes including Moro reflex, palmar and planter grasp, and tonic neck response will be evaluated. Autonomic nervous system evaluation will include examining pupillary reaction, heart rate changes in response to activity, and inquiring about abnormal sweating.

The pediatrician's or pediatric neurologist's consultation report which describes the outcome of each assessment and overall clinical impression of the pediatric neurological examination will be provided to the investigator.

6.2.2. (Visit 2) 8 Months of Age (Anytime during the 8th Month)

6.2.2.1. Physical Examination

Refer to History and Physical Examination as described previously.

6.2.2.2. Neurological Examination (Pediatrician or Pediatric Neurologist)

Refer to Neurological Examination as described previously.

6.2.2.3. Developmental Assessment (Clinical Psychologist)

Developmental assessment (cognitive, social, language, gross and fine motor skills, neurological intactness) is recommended to be performed by a clinical psychologist utilizing the BINS and REEL-3. If a clinical psychologist is unavailable or cannot be readily located, the pediatrician or pediatric neurologist can perform the developmental assessments. The neonatal/pediatric evaluations should be performed in a blinded fashion (the evaluator is not informed to the treatment the infant's mother received).

Manuals for the collection of the BINS and REEL-3 will be provided to the parent protocol site and then forwarded to the relevant expert for data collection at the evaluation.

Consultation reports which describe outcome of each assessment and overall clinical impression from developmental assessment will be provided in a report to the investigator and entered in the CRF. This information is to be maintained as a source document, a de-identified copy of which will be forwarded to the Sponsor within 35 days of receipt/completion. The outcome of the clinical assessment by the psychologist will be reviewed by the investigator and overall clinical impression will be documented in the case report form.

6.2.3. (Visit 3) 15 Months of Age (Anytime during the 15th Month)

Assessments performed at Visit 2 will be repeated at Visit 3 to allow for evaluation of further development of cognitive function and the motor, sensory and autonomic functions.

The need for further neurologic or neurodevelopmental evaluations will be determined at the 15 month visit by the pediatric neurologist, developmental psychologist, or pediatrician and conveyed to the investigator. If there are no outstanding significant adverse events (AEs) present at the 15 month visit, participation in this current protocol will be considered

completed and additional follow up will not be required. See Section 6.3 below for additional details if outstanding significant neurological or neuro-developmental AEs remain.

Submission of consultation reports and overall clinical impression to be submitted as previously described.

6.3. End of Treatment/Follow-up Visit

The need for further physical, neurologic or developmental evaluations will be determined at the 15 month visit by the pediatrician, pediatric neurologist or psychologist and scheduled to occur approximately within a 6 month period as clinically indicated. If there are no outstanding significant neurological or neurodevelopmental adverse events are present at the approximate 6 month follow up visit, participation in this current protocol will be considered completed and additional follow up will not be required. Submission of consultation reports and overall clinical impression to be submitted as previously described.

6.4. Post-study Subject Interview (If Applicable)

The need for additional post-study follow up visits as will be clinically determined subsequent to the Visit 3 (15 month visit) plus approximate 6 month visit as outlined above. Thus, this post-study subject interview period is for continued evaluations approximately every 6 months until the neurological or neurodevelopmental event(s) are considered resolved, or determined to be clinically stable and the case can be closed, up to a maximum of 36 months. Submission of consultation reports and overall clinical impression to be submitted as previously described.

6.5. Subject Withdrawal

Subjects (parents of the infants) may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject (infant) outcome, if possible. The investigator should inquire about the reason for withdrawal, request the parent/subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

If the subject (parents of the infant) withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that

he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

The physical and neurological examinations must be performed by a pediatrician or pediatric neurologist with experience in rating neurodevelopment skills in neonates.

Raters for the BINS and REEL-3 scales should have experience in rating neurobehavioral development in pediatrics; a clinical psychology degree is recommended. If a clinical psychologist is unavailable or cannot be readily located, the pediatrician or pediatric neurologist can perform the developmental assessments.

If the subject is seen by another healthcare professional during the follow-up, the investigator should also obtain a report and the information is to be maintained as a source document.

7.1. History and Physical Examination (Performed by a Pediatrician or Pediatric Neurologist)

7.1.1. Physical Examination

Each infant will undergo a physical examination at the three visits. Details of the physical examination can be found in the Study Period section.

7.2. Neurological Examination

The neurologic examination will be performed by the pediatric neurologist and should assess the mental status, cranial nerves, motor and sensory systems and reflexes of the infant. Details of the neurological examination can be found in the Study Period section.

7.3. Developmental Assessment (Performed by Pediatrician, Pediatric Neurologist or Clinical Psychologist)

Development assessments (cognitive, social, language, gross, and fine motor skills, neurological intactness) will be performed by a clinical psychologist at Visits 2 and 3 utilizing the BINS and REEL-3. If a clinical psychologist is not available to perform these assessments, then the pediatrician or pediatric neurologist can perform them.

7.3.1. Bayley Infant Neurodevelopmental Screener (BINS)

BINS is a validated instrument designed specifically for a high-risk infant population. It consists of 11-13 items for different age levels that assess cognitive, social, language, gross, and fine motor skills. The BINS also includes items that measure neurological intactness, such as ratings of active and passive tone in the upper and lower extremities, and scoring of quality of movement of the upper and lower extremities. The BINS form is attached in Appendix 2.

7.3.2. Bzoch-League Receptive-Expressive Emergent Language Test (3rd Edition) (REEL-3)

The Receptive-Expressive Emergent Language Test, 3rd edition, is designed to identify infants and toddlers who have language impairments or who have other disabilities that affect language development.[10] The REEL-3 has two core subtests, Receptive Language and Expressive Language, and a supplementary subtest, Inventory of Vocabulary Words. Results are obtained from a caregiver interview.

The REEL-3 is based on a contemporary linguistic model. It includes current studies relating to normative base, reliability, and validity. The normative sample includes 1112 infants and toddlers from around the United States. The demographic characteristics of the sample were matched to those of the United States according to the 2000 census. The normative sample was stratified on the basis of age, gender, race, ethnic group membership, and United States geographic location only. Standard scores, percentile ranks, and age equivalents are provided. The average reliability coefficients for all the test scores are high (exceeding .90). Test/retest studies show that the REEL-3 is stable over time.

The REEL-3 test is attached in Appendix 3.

7.4. Banking Samples

No sample are planned to be collected or banked for exploratory research.

7.5. Suicidality Assessment

Due to the age of the subjects relevant to the current protocol, no suicidality assessments will be obtained.

8. ADVERSE EVENT REPORTING

8.1. 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 as described in the following sections. Non-serious, non-neurological AEs will not be collected (See Appendix 4 for additional guidance).

For these SAEs and non-serious neurological or neuro-developmental AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to Pfizer or its designated representative. For all SAEs and non-serious neurological or neuro-developmental AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject (or subject's parent(s)/legal guardian) provides informed consent, through the subject's last visit. Informed consent is obtained prior to the subject's participation in the study, ie, prior to undergoing any study related procedure.

SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

For non-serious neurological or neuro-developmental AEs, the reporting period to Pfizer or its designated representative begins from the time that the subject (or subject's parent(s)/legal guardian) provides informed consent, through the subject's last visit. All AEs are to be reported using the CRF.

AEs (serious and non-serious neurological or neuro-developmental) should be recorded on the CRF through the subject's last visit.

8.3. Definition of an Adverse Event

In this study, an AE is any untoward medical occurrence in an infant exposed to study drug via maternal exposure in the parent study; the event need not necessarily have a causal relationship with the treatment or usage.

A standard list of examples of AEs is shown below (not all of these examples are applicable to this protocol):

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency;

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

This section is not applicable as no study medication is administered during this study.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be a relevant AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

This section is not applicable as no study medication is administered during this study.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate,

and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines that a SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

This section is not applicable as the protocol subject in question is an infant.

8.11. Occupational Exposure

This section is not applicable as no study medication is administered during this study.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

Each study subject's parent(s)/legal guardian will be questioned about AEs. The investigator is to record all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s).

8.14. Reporting Requirements

Each neurologic and neuro-developmental AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. NonSerious Adverse Event Reporting Requirements

All neurological or neuro-developmental AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

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.

9.1. Sample Size Determination

This study is designed to enroll all subjects who are eligible. No formal statistical comparisons are anticipated and, therefore, no sample size estimates have been calculated.

9.2. Efficacy Analysis

This study is not designed to evaluate efficacy.

9.3. Analysis of Other Endpoints

No other endpoints other than those outlined in the Safety Analysis will be evaluated.

9.4. Safety Analysis

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, as described previously, 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.

9.5. Interim Analysis

No interim analysis will be conducted within the format of the current protocol.

9.6. Data Monitoring Committee

An independent external Safety Monitoring Committee (SMC) has been instituted for the tanezumab clinical program and will provide oversight for this study. The committee will be composed of at least one rheumatologist, pediatric neurologist with NGF expertise, statistician and epidemiologist. The SMC will review unblinded safety data including (but not limited to) adverse events and serious adverse events on a regular basis throughout the trial. The SMC will have written operating procedures and a charter, including a specific description of the scope of their responsibilities.

Pfizer Standard Operating Procedures regarding periodic safety reviews by the study team and the Tanezumab Risk Management Committee will be followed. This committee will be composed of members inside and outside the immediate study team who will review blinded safety data from individual studies as well as data pooled across the studies on an ongoing basis. A safety review plan will be in place governing the frequency and extent of the safety review.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate

regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term Case report Form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document is to be available at the investigative site as well as at Pfizer that clearly identifies those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or in any other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject or his/her legally acceptable representative/or parent(s) or legal guardian (as the protocol subject is an infant), is fully informed about the nature and objectives of the study and possible risks associated with participation.

If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, legal guardian, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Subject recruitment efforts are not required for this study because subjects will be children born to mothers in a separate tanezumab study.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

The End of Trial in all participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, investigational product safety problems, or at the discretion of Pfizer. This protocol will remain open until as long as the interventional tanezumab studies are active (plus 112 days of the last dose of the last study) to extend to the follow up period of the infant up to 36 months of age. In addition, Pfizer retains the right to discontinue development of tanezumab at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrial.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in

adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts Europe (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publication by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “Publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BINS	Bayley Infant Neurodevelopmental Screener
CDS	core data sheet
CLBP	chronic lower back pain
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DAI	dosage and administration instructions
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EIU	exposure in utero
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRQL	health-related quality of life
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IOBU-SDMC	Internal Oncology Business Unit-Safety Data Monitoring Committee
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device

Abbreviation	Term
IVR	interactive voice response
IWR	interactive web response
LFT	liver function test
LPD	local product document
LSLV	last subject last visit
MABEL	minimum anticipated biological effect level
N/A	not applicable
NGF	nerve growth factor
NTF	note to file
OA	osteoarthritis
OBU	Oncology Business Unit
PCD	primary completion date
PFS	pre-filled syringe
PT	prothrombin time
REEL	Bzoch-League Receptive Expressive Emergent Language Test
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCL	Supply Chain Lead
SIB	suicidal ideation and behavior
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
ULN	upper limit of normal
US	United States
USPI	United States package insert
WOCBP	women of child bearing potential

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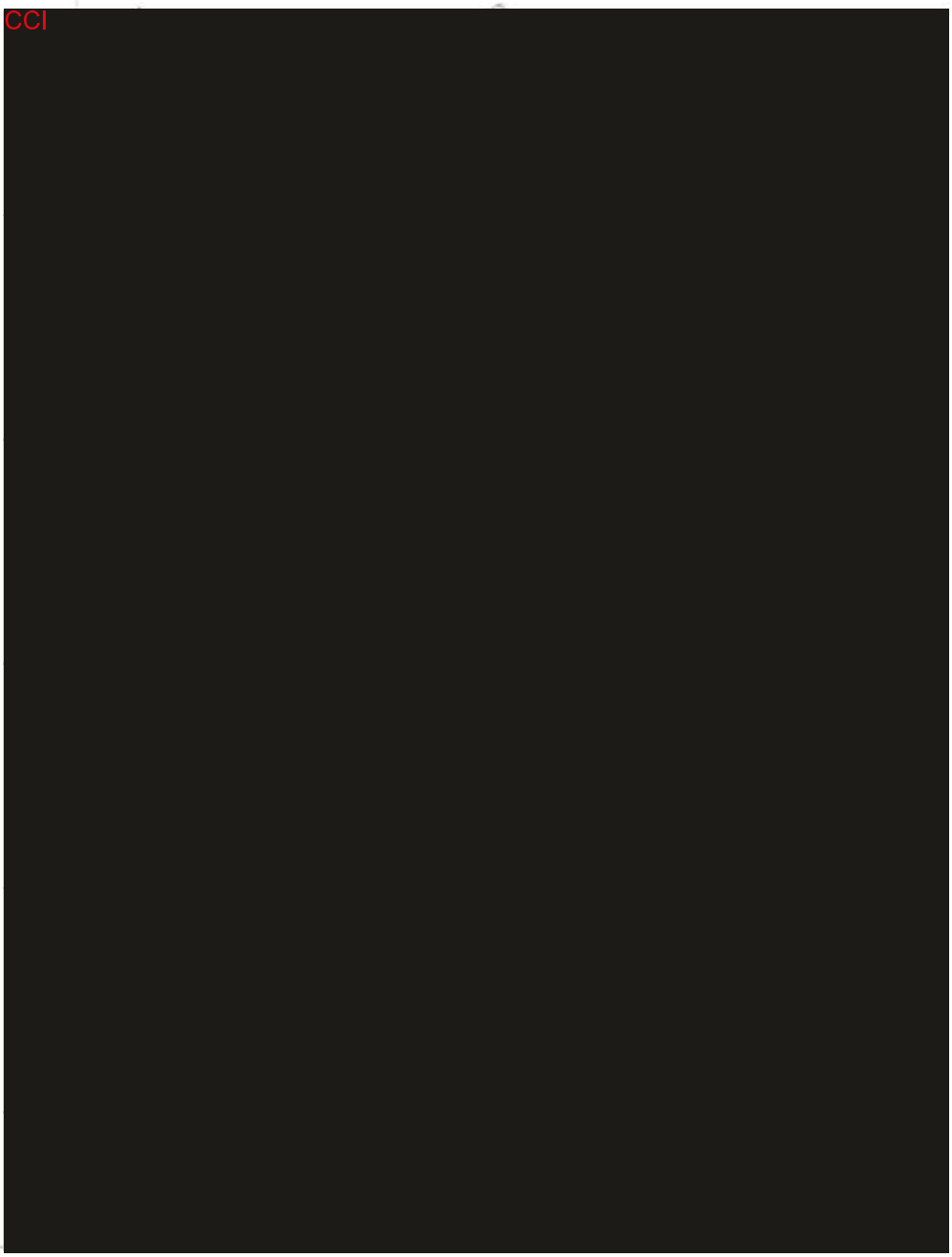

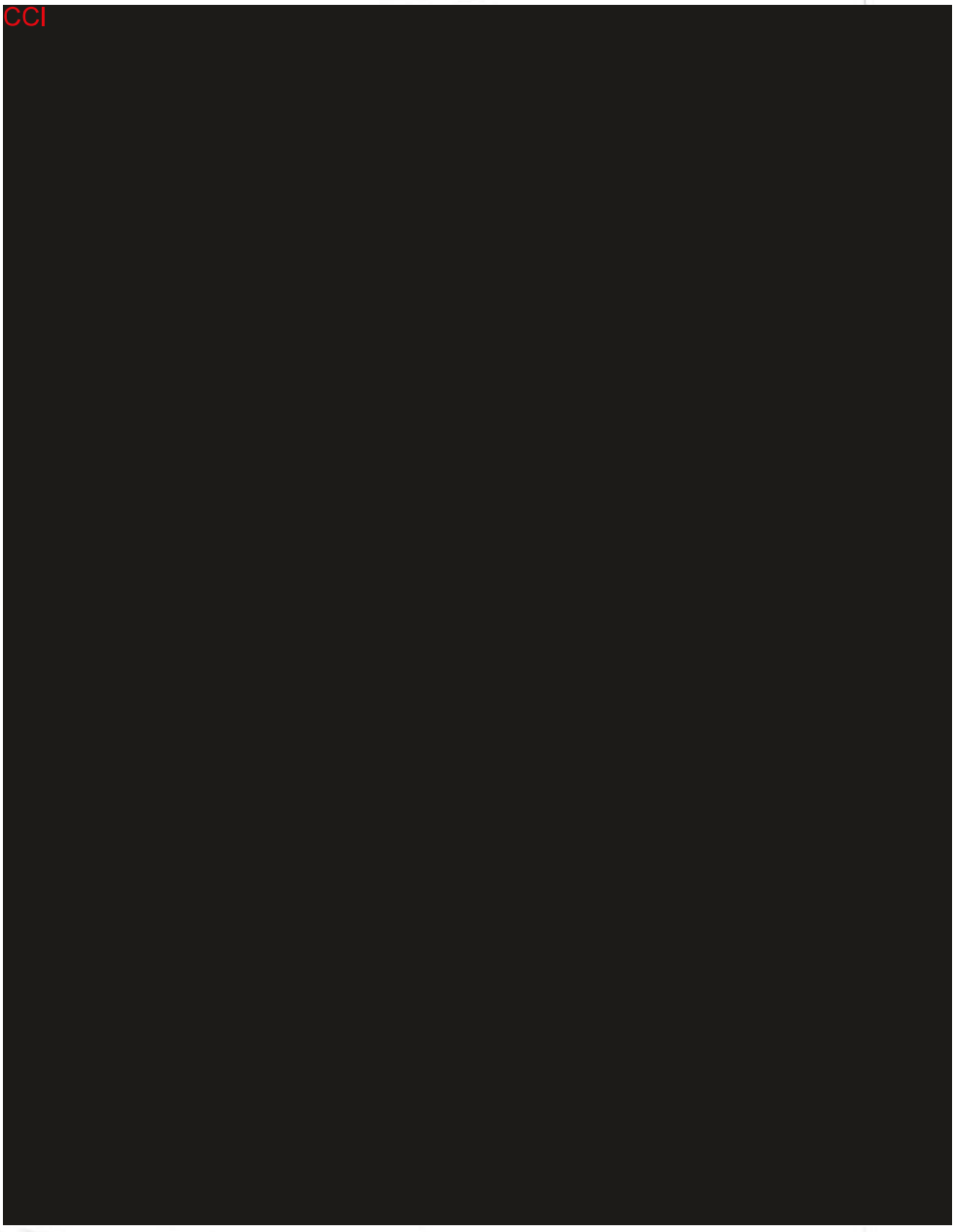
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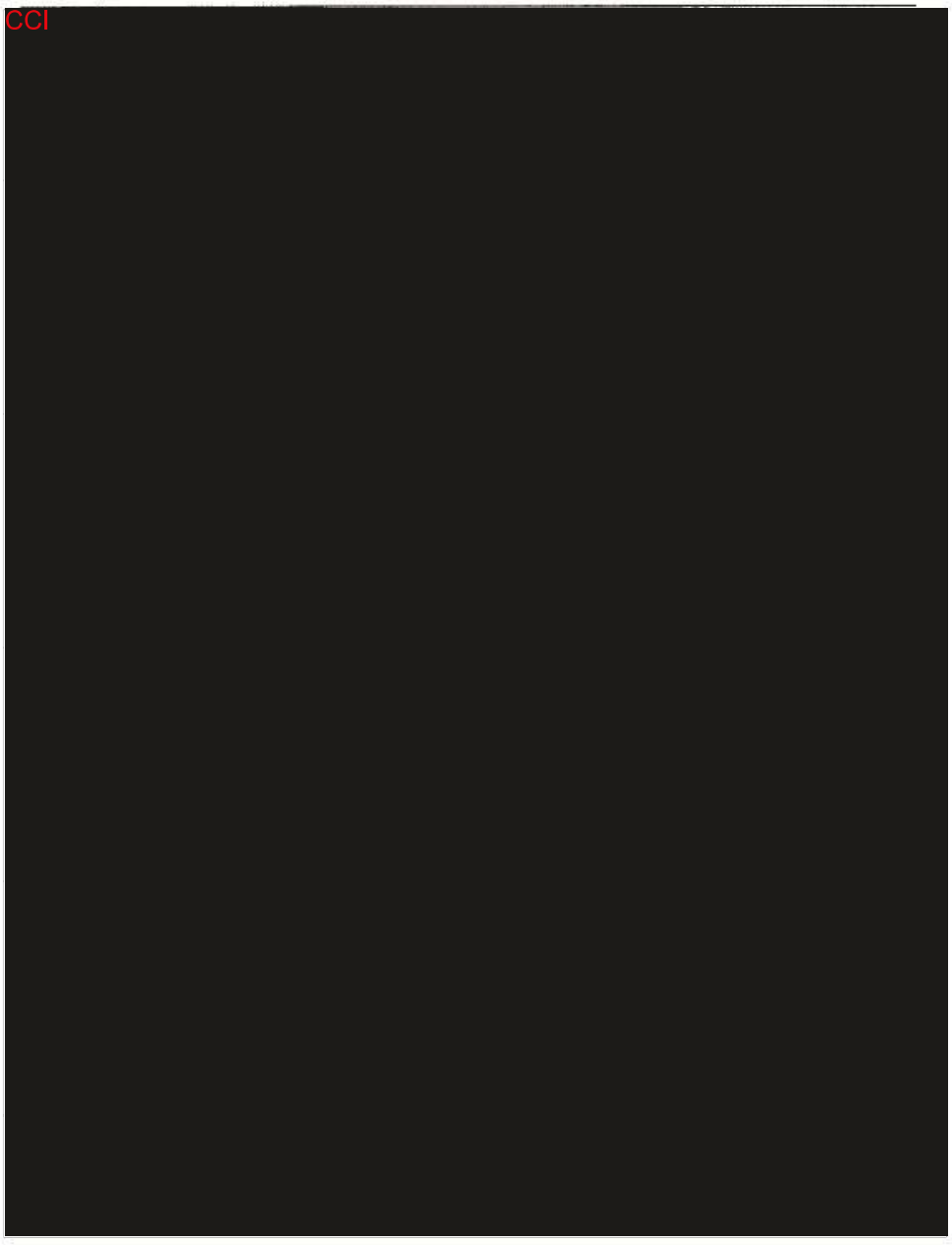
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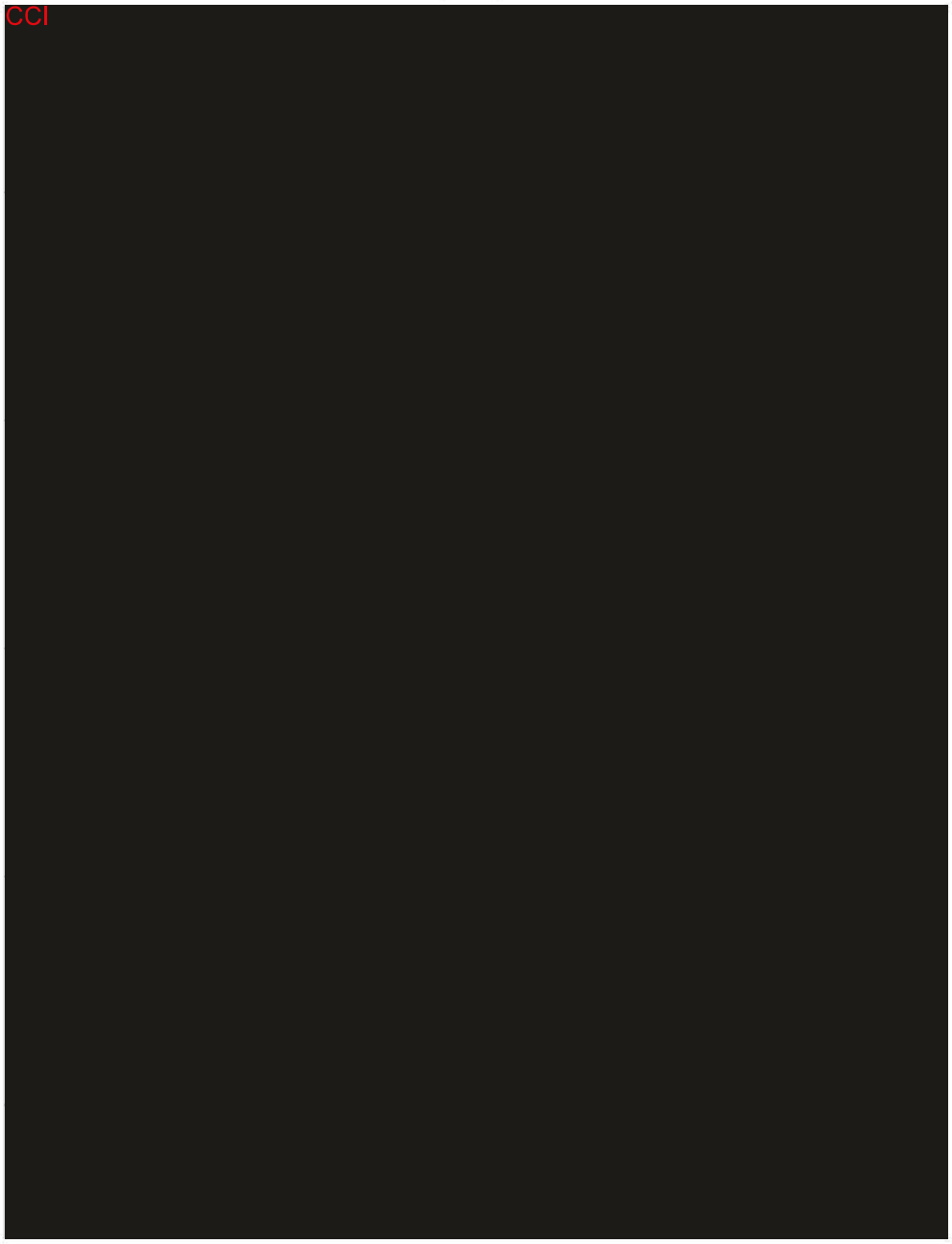
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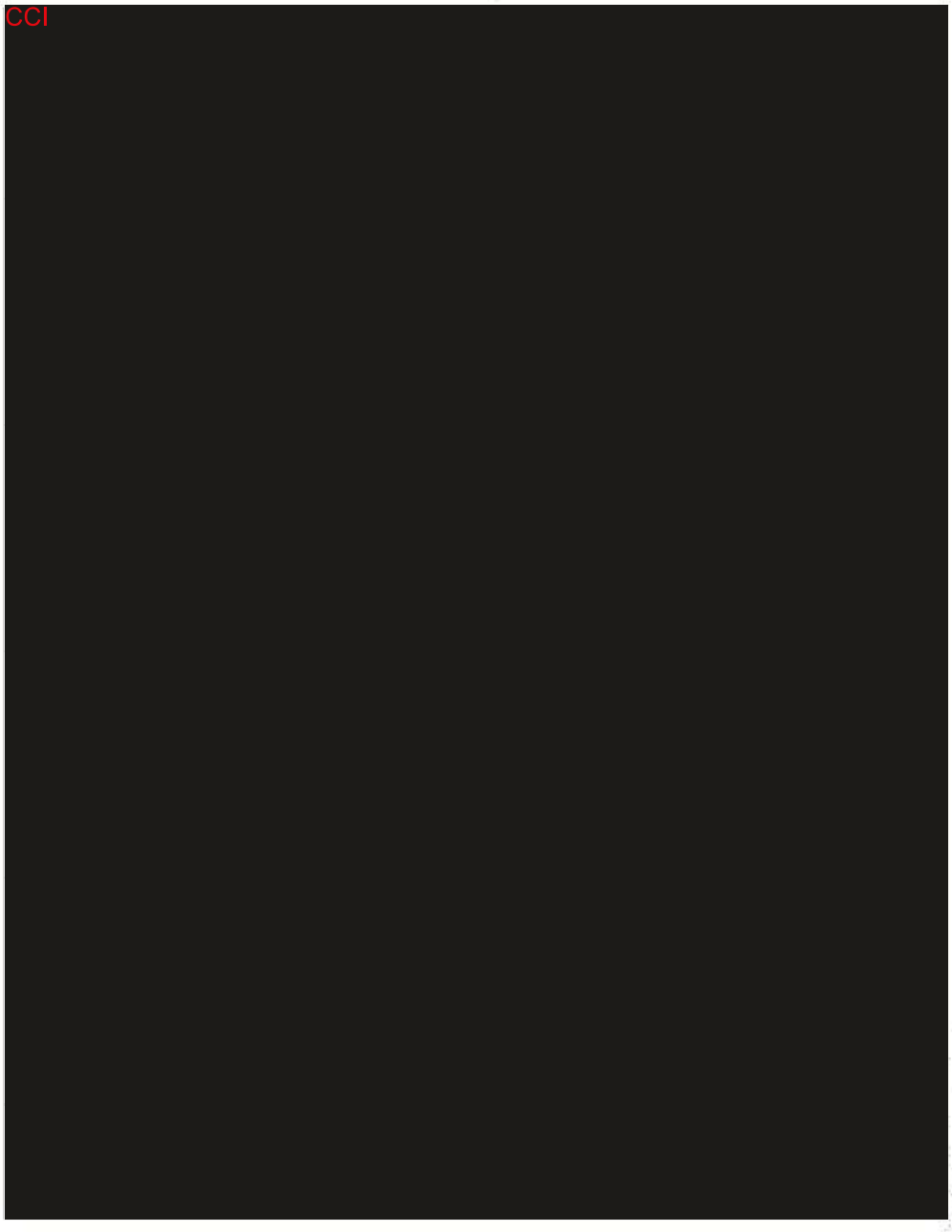
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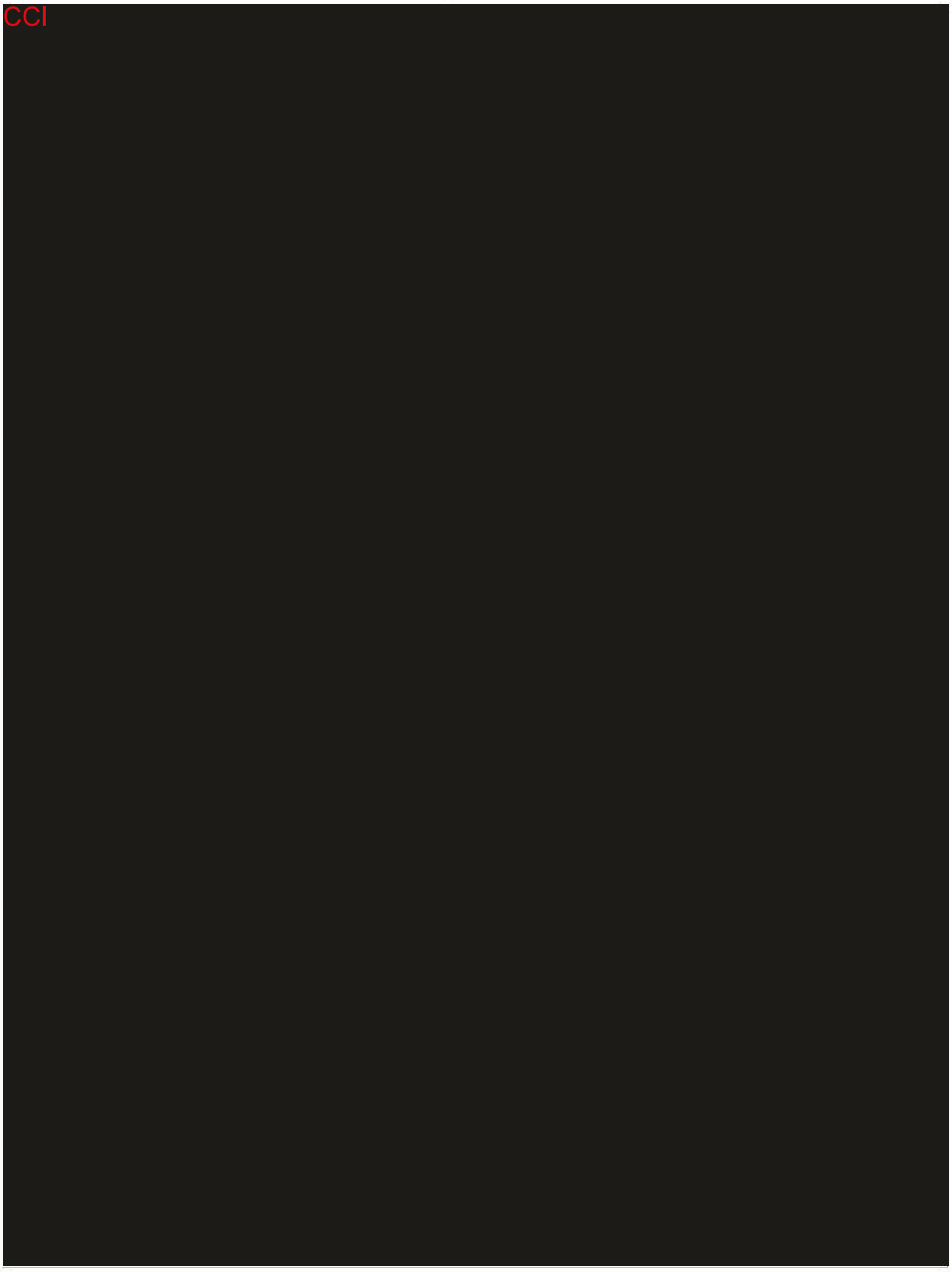
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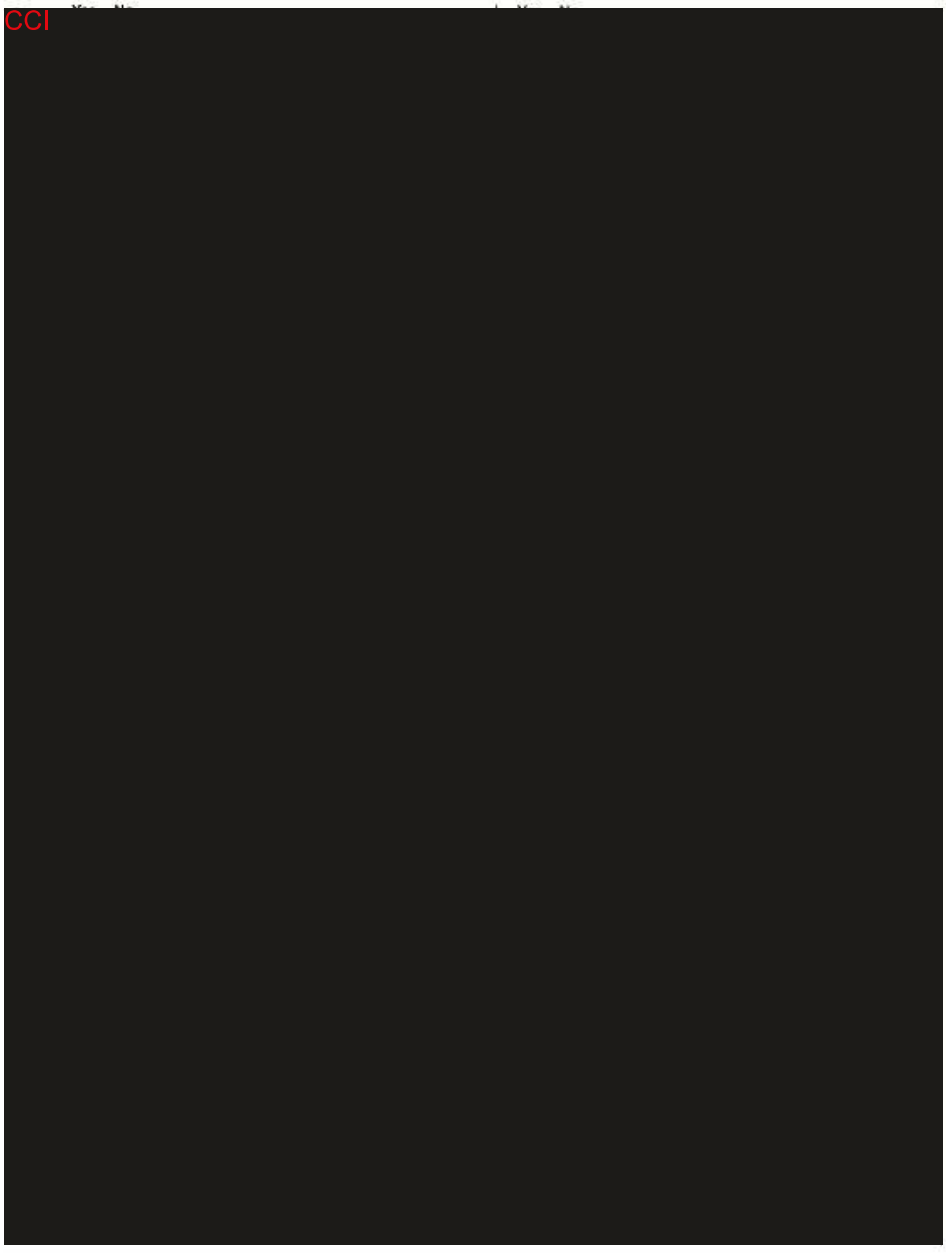
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Appendix 4. Guidance on Reporting Nonserious Adverse Events for A4091065

This list provides general guidance on Sponsor expectations for non-serious adverse event reporting, which will focus on neurologic events that might be due to NGF inhibition. Adverse events of interest include the following:

- Congenital neurological abnormalities (eg, congenital nystagmus).
- Sympathetic nerve abnormalities (eg, bradycardia, syncope, decreased sweating).
- Sensory nerve abnormalities (eg, decreased sensation leading to abnormal number of falls, decreased pain sensation).
- Non-neurological adverse events that could be due to underlying neurologic dysfunction (eg, staring spells that may be indicative of infantile seizure, oculomotor tracking abnormalities).

If the investigator is unsure if an event is neurological in nature, it is recommended that the event is reported.

Investigators are also encouraged to report any non-serious AE that may be considered related to the infant's exposure to tanezumab.