PROTOCOL A0081096

PROSPECTIVE RANDOMIZED 12-WEEK CONTROLLED STUDY OF VISUAL FIELD CHANGE IN SUBJECTS WITH PARTIAL SEIZURES RECEIVING PREGABALIN OR PLACEBO

STATISTICAL ANALYSIS PLAN (SAP)

Version:

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List of Abbreviations Used

AE	Adverse Event
ANCOVA	Analysis of Covariance
CI	Confidence Interval
C-SSRS	Columbia Suicide Severity Rating Scale
SBQ-R	Suicide Behaviors Questionnaire
MHRA	Mental Health Risk Assessment
C-CASA	Columbia-Classification Algorithm of Suicide Assessment
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	United States Food and Drug Administration
GABA	Gamma-aminobutyric Acid
IRC	Internal Review Committee
MD	Mean Deviation
MedDRA	The Medical Dictionary for Regulatory Activities
PASS	Post-Authorization Safety Studies
PHQ	Patient Health Questionnaire
PT	Preferred Term
SPERT	Safety Planning, Evaluation and Reporting Team
S-STS	Sheehan Sucidality Tracking Scale
VFT	Visual Field Test
VA	Visual Acuity
ETDRS	Early Treatment Diabetic Retinopathy Study

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

The statistical analysis plan (Version 2, dated July 07th, 2008) has been amended to incorporate the changes in conjunction with the amendment of the study protocol dated December 12th, 2011.

The SAP (Version 3, dated March 23rd, 2012) has been amended to incorporate the changes in conjunction with the study protocol dated December 15th, 2015.

The statistical analysis plan (SAP) has been also amended to redefine the visits for the analyses of the study endpoints (eg, visual field test, visual acuity, and mean deviation). Section A.1.3 has been added to define the algorithm for visual acuity scoring. Changes made to the previous version have been summarized below:

Version	Date	Author(s)	Summary of Changes/Comments
2	July 07, 2008	PPD	
3	March 23, 2012	PPD	**Changes in Section 2 Introduction**: **Old**: This study is being performed as a Phase IV commitment to assess visual fields in subjects taking pregabalin as compared to placebo. **To**: The purpose of this statistical analysis plan is to outline the proposed statistical analysis methods for protocol A0081096. This analysis plan provides additional details concerning the statistical analyses that were originally outlined in the study protocol A0081096 dated December 12th 2012. *Pregabalin (Lyrica®) has been approved in over 110 countries to date for varying neuropathic pain indications and for adjunctive treatment of patients with partial seizures and for generalized anxiety disorder. Lyrica is approved in the United States for management of neuropathic pain associated with diabetic peripheral neuropathy or postherpetic neuralgia, for the adjunctive treatment of adult patients with partial onset seizures, and for management of fibromyalgia. Lyrica is approved in European Union countries for the treatment of peripheral neuropathic pain, adjunctive treatment of partial seizures with or without secondary generalization, and for the treatment of generalized anxiety disorder. Since initial market approval of Lyrica in 2004 through Jan 31, 2011, it is estimated that more than 11,700,000 patient years of exposure will have accumulated worldwide. More detailed*

			information, including efficacy results in adults and the possible risks associated with administration of pregabalin, are summarized in the Core Data Sheet. *Prospectively planned ophthalmologic assessments, including visual acuity testing, formal visual field testing and dilated funduscopic examination, were performed in the pregabalin clinical development program for all of the initial indications.* *Formal visual field testing was conducted in over 2400 patients treated with pregabalin for neuropathic pain, chronic pain syndromes, intractable epilepsy, or generalized anxiety disorder in randomized controlled clinical trials of up to 3 months in duration and in over 3600 patients in open-label trials of up to 4 years in duration. Ophthalmologic assessments were included in the program due to concerns expressed at the time on emerging reports of visual field disturbances with the anticonvulsant vigabatrin, a gamma-aminobutyric acid (GABA)-transaminase inhibitor. The mechanism of the visual field defects with vigabatrin is unknown but was considered as possibly related to its GABA mechanism. As a structural derivative of GABA, regulatory agencies considered similarity of pregabalin to vigabatrin as possible. Subsequently, it became clearer that the mechanism of action of pregabalin was not related to GABA-transaminase inhibition or to a GABA related mechanism. While the mechanism of action of pregabalin is not completely understood, results in animal models indicate that binding to the alpha-2-delta subunit of voltage-gated calcium channels may be involved in the activity of pregabalin.* *In controlled pregabalin studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in the majority of patients during treatment. In patients assessed with prospectively planned ophthalmologic testing, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.*

			This study is a Post-Authorization Safety Studies (PASS). It is being conducted as a commitment agreed upon with the United States Federal Drug Administration (FDA) regulatory agency. **Changes in Section 2.1 Study Design**: **Old**: *This is a Phase IV, multicenter, double-blind, randomized controlled trial to measure visual field sensitivity in subjects with partial epilepsy dosed with pregabalin or placebo. Pregabalin will be dosed at 300 mg/day for 11 weeks after one-week initiation with 150 mg/day, followed by one-week tapering of 150 mg/day*. **To**: *This is a Phase IV, multicenter, double-blind, randomized, placebo-controlled trial to measure visual field sensitivity in subjects with partial epilepsy dosed with pregabalin or placebo. Pregabalin will be dosed at 300 mg/day for 11 weeks after one-week initiation with 150 mg/day, followed by one-week tapering of 150 mg/day. Total treatment period will be 13 weeks*. **Changes in Section 2.2 Study Objectives:** **Old**: The objective of the study is to *monitor visual fields in subjects with partial epilepsy receiving pregabalin or placebo for 12 weeks under highly controlled conditions.* **To**: The objective of the study is *to evaluate visual fields in subjects with partial epilepsy receiving 12 weeks treatment of pregabalin compared to placebo*. **Old**: *The primary endpoint is the proportion of subjects with a decrease in the threshold value from baseline to termination for any five points (in either eye) at the $p<0.05$ level repeated in the same five points on subsequent computerized automated perimetry testing (Humphrey 24-2 SITA standard).* **To**: *The primary endpoint is the proportion of subjects with a decrease in the threshold value from baseline to termination in any five or more points (in either eye) at the $p<0.05$ level repeated in the same five points on subsequent computerized automated perimetry testing (Humphrey 24-2 SITA standard). The primary endpoint*

			will be analyzed using a non- inferiority analysis. **A new Section 2.3 Statistical Power and Sample Size Considerations has been included** **Changes in Section 3 Interim Analyses, Final Analyses and Unblinding:** **Old**: Interim Analyses, Final Analyses and Unblinding **To**: Interim Analyses, Data Monitoring Committee, Final Analyses, and Unblinding **Old**: No interim analyses are planned. **To**: No interim analysis has been planned for this study. *This study will use an Internal Review Committee (IRC).* The IRC for this study will be independent of the study team and will not be involved in the conduct of the study otherwise. The Pfizer colleagues comprising the independent IRC and their responsibilities will be defined in an IRC Charter. The IRC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter. Communication between the IRC and the Study Team will be from the IRC Chair to the clinical lead or delegate to the Study Team. The possible IRC recommendations and the method of communicating the IRC recommendations will be stated in the Charter. *Changes in Section 5.1 Full Analysis Set:* **Old**: The Full Analysis Set (referred to in the protocol as the intent-to-treat (ITT) population) *is defined as all subjects randomized to treatment who received at least one dose of study medication.* Since data will not be imputed for patients who do not have a baseline or for patients who do not have post-baseline data for a specific parameter, such patients will not be in the FAS for that parameter. **To**: The Full Analysis Set (referred to in the protocol as the intent-to-treat (ITT) population) *is defined as all subjects randomized to treatment who received at least one dose of study medication.* Since data will not be imputed for patients who do not have a baseline or for

			patients who do not have post-baseline data for a specific parameter, such patients will not be in the FAS for that parameter. Subjects who had a decrease in at least 5 points at termination but did not return for a repeat test will be included in the ITT set and will be assumed to have a confirmed decrease for VFT analysis. **Changes in Section 6.2 Safety Endpoints Second Paragraph:** **Old**: The primary endpoint (proportion of patients with deterioration) is determined as follows: A patient with 5 or more points that are $p<0.05$ at termination (ie, a 1 in the database) that were not significant (a 0 in the database) at baseline is required to have a repeat test. If at the repeat test 5 or more of the same points are $p<0.05$, then that patient is considered to have deterioration. This comparison is done separately for each eye, and a patient is considered to have deterioration if this is true for either eye. **To**: The primary endpoint (proportion of patients with deterioration) is determined as follows: Baseline and all other visits for visual field test (VFT) will be based on the visits defined by the central reader. There are 2 tests performed for the Screening visit, these values will not be used for baseline determination. A point will be considered abnormal at baseline only if it was abnormal ($p<0.05$) at both baseline tests. A patient with 5 or more points that are $p<0.05$ at termination (ie, a value of 1 in the database) that were not significant (a 0 in the database) at baseline is required to have a repeat test. If at the repeat test 5 or more of the same points are $p<0.05$, then that patient is considered to have deterioration. This assessment is done separately for each eye, and a patient is considered to have deterioration if this is true for either eye. **Old**: Mean Deviation (MD) is a global index of visual field depression. The MD ranges from 0 decibels (dB) (no defect) to about -32 dB (end-stage damage). *Change in mean deviation from baseline to termination will be computed for each subject. Baseline mean deviation will be the average of the two mean deviations from the Baseline visit, and termination will be the mean deviation at the Week 12 visit (or the last available after*

			Day 1 for subjects who terminate early). If a repeat test was done at termination, the mean deviation from the repeat test will be used. For each subject, the worst eye (ie, the eye with the greatest decrease in mean deviation) will be used in the analysis. **To**: Mean Deviation (MD) is a global index of visual field depression. The MD ranges from 0 decibels (dB) (no defect) to about -32 dB (end-stage damage). *Change in mean deviation from baseline to termination will be computed for each subject.* Baseline and all other visits for mean deviation will be based on the visits defined by the central reader. *Baseline mean deviation will be the average of the two mean deviations from the Baseline visit, and termination will be the mean deviation at the Week 12 visit (or the last available after Day 1 for subjects who terminate early). If a repeat test was done at termination, the mean deviation from the repeat test will be used. For each subject, the worst eye (ie, the eye with the greatest decrease in mean deviation) will be used in the analysis.* **Old**: Visual Acuity (best corrected) is measured using ETDRS charts. It is expressed in terms of number of letters correctly identified. A patient who identified all letters correctly in the 20/20 line and all previous lines would have a score of 55 letters (as this is the 11th line, and there are 5 letters per line). **To**: *The best corrected visual acuity (with glasses or best possible glasses prescription) will be measured using the ETDRS charts. The letters on chart A are read using the right eye and chart B using the left eye. The subject starts at the top of the chart and begins to read down the chart. The subject reads down the chart until they reach a row where a minimum of three letters on a line cannot be read. The subject is scored by how many letters could be correctly identified*. Details of visual acuity scoring have been defined in Section A.1.3. **Old**: *Other safety parameters, including adverse events, physical examination results, vital signs, body weight, clinical laboratory results, and subject assessment of seizure frequency as compared to before taking study medication, will be summarized by treatment group, but not analyzed inferentially*.

			To: *Other safety parameters, including adverse events, physical examination results, vital signs, body weight, clinical laboratory results, and subject assessment of seizure frequency as compared to before taking study medication, and Sheehan Suicidality Tracking Scale (S-STS) will be summarized by treatment group, but not analyzed inferentially.* **Changes in Section 6.3 Other Endpoints** **Old***:* There are no other endpoints being reported in this study. **To**: Screening ophthalmologic assessment (Dilated Funduscopic) and self-administered Patient Health Questionnaire (PHQ-8) will be summarized by treatment group. **Changes in Section 8.2.3 Other Safety Analyses** **Old***: Other safety parameters, including adverse events, physical examination results, vital signs, body weight, clinical laboratory results, and subject assessment of seizure frequency as compared to before taking study medication, will be summarized by treatment group, but not analyzed inferentially.* **To***: Other safety parameters, including adverse events, physical examination results, vital signs, body weight, clinical laboratory results, and subject assessment of seizure frequency as compared to before taking study medication, and Sheehan Sucidality Tracking Scale (S-STS) will be summarized by treatment group, but not analyzed inferentially*. Ophthalmologic assessment and self-administered Patient Health Questionnaire (PHQ-8) completed at the screening visit will be summarized by treatment group. CCI [redacted] **A new Section 8.2.3.2 Sheehan Suicidality Tracking Scale (S-STS) has been included.** **A new Section 8.2.3.3 Ophthalmologic Assessment (Dilated Funduscopic) and Patient Health Questionnaire (PHQ-8) has been included.**

			A new Section 8.2.4 Concomitant Medication has been included. **Changes in Section 8.2.5 Summary of Safety Analyses:** **Old**: Missing data for VFT analyses LOCF. **To**: Missing data for VFT analyses Not Applicable. **Changes in Appendix A.1.1 Definition and use of visit windows in reporting**: **Old**: Analyses will be conducted using change from baseline to the week 12 visit (or the last visit after Day 1 for patients who discontinue prior to week 12). Week 15 follow up assessments (or the assessments conducted approximately 2 weeks after discontinuation of treatment, for subjects who discontinue early) will be excluded from consideration. Additional considerations for determination of Visual Field Deterioration are given in section A.1.2. **To**: Analyses will be conducted using change from baseline to the week 12 visit (or the last visit after Day 1 for patients who discontinue prior to week 12). Week 15 follow up assessments and for early terminators, the assessments conducted approximately 2 weeks after discontinuation of treatment will be excluded from analysis consideration. For VFT and MD, Baseline and all other visits including the repeat visits will be based on the visits defined by the central reader. Additional considerations for determination of Visual Field Deterioration are given in Section A.1.2. For visual acuity the following week assignments will be used for the planned visits: **Changes in Appendix A.1.2 Additional considerations for determination of Visual Field Deterioration:** An eye map has been included in Appendix A.1.2 and the example table has been updated with the actual test points' names.

			Appendix A.1.3 Calculation of Visual Acuity Score has been included. CCI [redacted] **Appendix A.1.5 Sheehan-Suicidality Tracking Scale (S-STS) has been included.**
4	Feb 16 ,2016	PPD	As of protocol amendment, dated December 15, 2015 the following changes has been incorporated: 1. The Sheehan Suicidality Tracking Scale has been replaced by the Columbia Suicide Severity Rating Scale (C-SSRS), For subjects who randomized prior to Amendment 4, S-STS will be mapped to Columbia-Classification Algorithm of Suicide Assessment (C-CASA) and for subjects who randomized after amendment 4, C-SSRS will be mapped to Columbia-Classification Algorithm of Suicide Assessment (C-CASA). 2. SBQ-R has been added at screening. 3. Core Data Sheet (CDS) has been replaced by Investigator's Brochure (IB). 4. The schedule of activities and introduction text have been updated accordingly. 5. To be consistent with new version of the protocol, some wording has changed in the introduction section of this SAP and other section. 6. Additional SAP amendment not related to protocol 4th amendment: • Mental Health Risk Assessment (MHRA); • Added the SAS code for primary endpoint.
5	Sep 30, 2020	PPD	1. Per protocol amendment (amendment 5) and adjusted the sample size and power of the study using the observed mean deviation (MD) common standard deviation (SD = 1.3) from a 15 March 2019 dataset prepared for the annual IRC review. Common SD changed from 5.6 dB from literature[1] at the time of design of the study to observed common SD 1.3 dB

2. INTRODUCTION

The purpose of this statistical analysis plan is to outline the proposed statistical analysis methods for protocol A0081096. This analysis plan provides additional details concerning the statistical analyses that were originally outlined in the study protocol A0081096 dated December 12th 2012, and the subsequent amendment of the protocol dated December 15, 2015.

Pregabalin (Lyrica®) has been approved in over130 countries to date for varying neuropathic pain indications and for adjunctive treatment of patients with partial seizures and for generalized anxiety disorder. Lyrica is approved in the United States for management of neuropathic pain associated with diabetic peripheral neuropathy or postherpetic neuralgia, for the adjunctive treatment of adult patients with partial onset seizures, and for management of fibromyalgia. Lyrica is approved in European Union countries for the treatment of peripheral neuropathic pain, adjunctive treatment of partial seizures with or without secondary generalization, and for the treatment of generalized anxiety disorder.[2] Since initial market approval of Lyrica in 2004 through 2014, it is estimated that more than 28.5 million patient years of exposure will have accumulated worldwide. More detailed information, including efficacy results in adults and the possible risks associated with administration of pregabalin, can be found in the current Investigator Brochure (IB).

Prospectively planned ophthalmologic assessments, including visual acuity testing, formal visual field testing and dilated funduscopic examination, were performed in the pregabalin clinical development program for all of the initial indications.

Formal visual field testing was conducted in over 2400 patients treated with pregabalin for neuropathic pain, chronic pain syndromes, intractable epilepsy, or generalized anxiety disorder in randomized controlled clinical trials of up to 3 months in duration and in over 3600 patients in open-label trials of up to 4 years in duration. Ophthalmologic assessments were included in the program due to concerns expressed at the time on emerging reports of visual field disturbances with the anticonvulsant vigabatrin, a gamma-aminobutyric acid (GABA)-transaminase inhibitor. The mechanism of the visual field defects with vigabatrin is unknown but was considered as possibly related to its GABA mechanism. As a structural derivative of GABA, regulatory agencies considered similarity of pregabalin to vigabatrin as possible. Subsequently, it became clearer that the mechanism of action of pregabalin was not related to GABA-transaminase inhibition or to a GABA related mechanism. While the mechanism of action of pregabalin is not completely understood, results in animal models indicate that binding to the alpha-2-delta subunit of voltage-gated calcium channels may be involved in the activity of pregabalin.

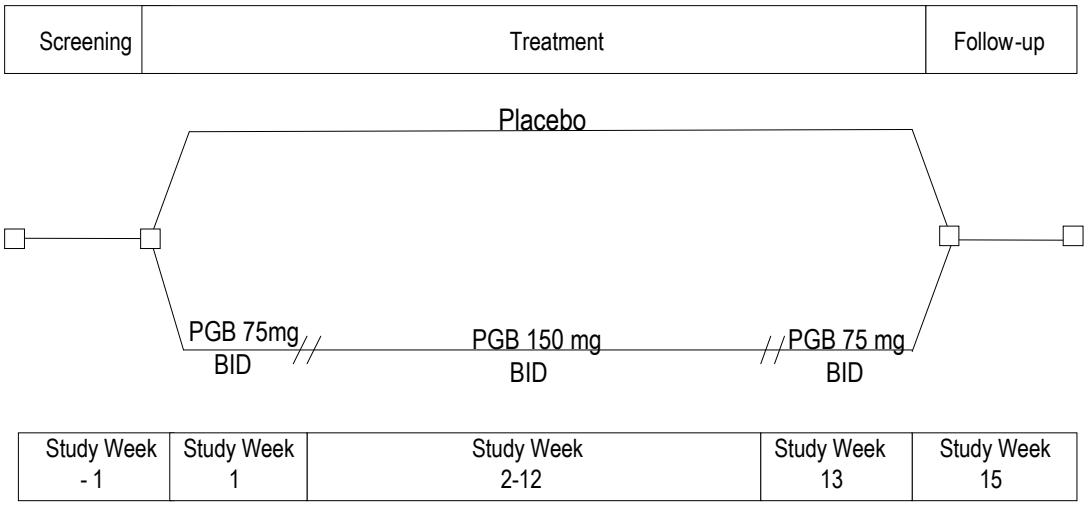
In controlled pregabalin studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in the majority of patients during treatment. In patients assessed with prospectively planned ophthalmologic testing, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of

pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.

This study is a Post-Authorization Safety Studies (PASS). It is being conducted as a commitment agreed upon with the United States Federal Drug Administration (FDA) regulatory agency.

2.1. Study Design

This is a Phase IV, multicenter, double-blind, randomized, placebo-controlled trial to measure visual field sensitivity in subjects with partial epilepsy dosed with pregabalin or placebo. Pregabalin will be dosed at 300 mg/day for 11 weeks after one-week initiation with 150 mg/day, followed by one-week tapering of 150 mg/day. Total treatment period will be 13 weeks.



Schedule of Activities

Protocol Activity		Screening	Baseline	Wk 0 Randomization	Wk 1	Wk 6	Wk 12 (Or ET)	Week 15 (Follow-Up)
Visit Number[n]		1	2	3[m]	4	5	6	7
Informed Consent		X						
Inclusion/Exclusion Criteria		X	X	X				
History/Diagnosis/Demographics		X						
Physical Examination[p]		X					X	
Concomitant Medication		X	X	X	X	X	X	X
Body Weight		X	X		X	X	X	X
Vital Signs (Sitting BP/HR)		X	X		X	X	X	
ECG (Singlet)		X						
EEG		X[a]						
CT or MRI		X[b]						
Clinical Laboratory	1) Hematology[c]	X					X	
	2) Chemistry[d]	X					X	
	3) Urinalysis[e]	X					X	
Urine Pregnancy Test[f]		X					X	
Urine Drug Screen		X						
Ophthalmic Examination	1) External Eye Exam	X					X	X[g]
	2) ETDRS Acuity	X	X			X	X	X[g]
	3) Intraocular Pressure	X						
	4) Dilated Funduscopic	X						
	5) VFT (24-2 SITA)	X[h,l]	X[h,l]			X[h]	X[h]	X[g,h]
Patient assessment of seizure frequency							X	
Investigational product Dispensing				X[i,j]	X[k]	X[k]	X[j]	
Sheehan-Suicidality Tracking Scale (S-STS)[o,r]		X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)[o,r]		X	X	X	X	X	X	X
Suicidal Behaviors Questionnaire – Revised (SBQ-R)[r]		X						
Patient Health Questionnaire–8 (PHQ-8)		X						
Assessment of need to complete a risk assessment[r]		X	X	X	X	X	X	X
Adverse Events Report		X----------						----------X

a. Subjects who have not had a test within 2 years. See inclusion criteria 1.

b. Subjects who have not had a test within 3 years. See inclusion criteria 4.

c. Hemoglobin, hematocrit, RBC count, WBC count, platelet count.

d. Electrolytes (Na, K, Ca, Cl, bicarbonate), creatinine, BUN, glucose, AST, ALT, alkaline phosphatase, bilirubin, CK, uric acid, albumin, total protein.

e. Specific gravity, PH, Glucose (qualitative), Protein (qualitative), Blood (qualitative), Ketones, Nitrite and Microscopy if urine dipstick is positive for blood or protein.

f. Childbearing potential female subjects only.

g. Subjects who have had visual findings on Week 12 and subsequently confirmed.

h. A repeat may be necessary upon the confirmation from central reader.

i. Recommend subject to take first dose in the evening.

j. Titration/tapering dose.

k. Treatment dose.

l. Conduct 2 tests.

m. Usually occur between the 3rd – 7th day after Baseline (Visit 2) when the verification of VFT is available.

n. Screening procedures can be completed within 21 days prior to Baseline; Study Visits 4 – 7 have a ±3 days window.

o. The "Lifetime" assessment is completed at Screening and the "Since Last Visit" assessment is completed at **all** other visits.

p. Including neurological exam at screening.

q. A risk assessment must be performed and documented if the subject meets the criteria detailed in Protocol.

r. Subjects screened/randomized under Amendment 3 will continue the S-STS for assessment of suicidal ideation and behaviour. Subjects screened/randomized under Amendment 4 will have suicidal ideation and behaviour assessed by the C-SSRS and the SBQ-R.

2.2. Study Objectives

The objective of the study is *to evaluate visual fields in subjects with partial epilepsy receiving 12 weeks treatment of pregabalin compared to placebo.*

2.3. Statistical Power and Sample Size Considerations

The study will be powered to show non-inferiority of pregabalin with respect to placebo on the mean deviation score from the Humphrey threshold test, a secondary endpoint. Non-inferiority from placebo will be declared with respect to mean deviation if the lower bound of the 95% 2-sided confidence interval of the difference in mean deviation scores between pregabalin and placebo is greater than -2.0 decibels (dB). Assuming the mean deviation scores to be equal and assuming estimated common standard deviation of 1.3 dB, then the proposed sample size of 187 subjects will provide greater than 85% power to show non-inferiority of pregabalin to placebo.

The estimated common standard deviation of 1.3 dB, from the 15 March 2019 dataset prepared for the annual Internal Review Committee (IRC) blinded review (refer to Section 9.6), was used to re-estimate the sample size for the secondary endpoints. Previously, at the time of study design, a common standard deviation of 5.6 dB had been used for the sample size determination based on literature.[2] Table 1 below used common standard deviation (1.3) and the number of enrolled subjects (n=187) to estimate the study power.

Table 1. Study 1096 Sample Size and Power for the Secondary Endpoint

Total Number of enrolled subject	*Common Standard Deviation*	*Non-inferiority Margin*	*Power*
187	*1.3*	*-2.0*	*>99.9%*

For the primary endpoint, the proposed sample size will provide >99.9% power to show non-inferiority of pregabalin to placebo with respect to the proportion of subjects with a repeated decrease in the same 5 visual field points, with non-inferiority declared if the upper bound of the 95% confidence interval for the difference between pregabalin and placebo does not exceed 10% and assuming a proportion of subjects meeting primary endpoint definition of 1% for both groups. Table 2 below provided the estimated power for the primary endpoint.

Table 2. Study 1096 Sample Size and Power for the Primary Endpoint

Total Number of enrolled subjects	*Proportion of Subjects Meeting Primary Endpoint Definition*	*Non-inferiority Margin*	*Power*
187	*1%*	*10%*	*>99.9%*

3. INTERIM ANALYSES, DATA MONITORING COMMITTEE, FINAL ANALYSES AND UNBLINDING

No interim analysis has been planned for this study.

This study will use an Internal Review Committee (IRC).

The IRC for this study will be independent of the study team and will not be involved in the conduct of the study otherwise. The Pfizer colleagues comprising the independent IRC and their responsibilities will be defined in an IRC Charter. The IRC will be responsible for ongoing monitoring of the safety of subjects in the study according to the Charter. Communication between the IRC and the Study Team will be from the IRC Chair to the clinical lead or delegate to the Study Team. The possible IRC recommendations and the method of communicating the IRC recommendations will be stated in the Charter.

The final analyses will be performed after requirements for final release of the randomization codes have been met, and the official database is released.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The null hypothesis is that the proportion of patients with deterioration in the pregabalin group is greater than or equal to 10% higher than in the placebo group. The alternative hypothesis is that the difference in proportions (pregabalin minus placebo) is less than 10%. That is:

H0: πPGB - πPBO $\geq$10%

Ha: PGB - πPBO <10%

In these hypothesis statements π is the parameter for the proportion of patients with deterioration in the respective treatment group.

4.2. Statistical Decision Rules

The difference in proportions between pregabalin and placebo will be compared using a 2-sided 95% confidence interval (CI). Non-inferiority will be demonstrated if the upper CI bound is less than 0.10 (10%).

5. ANALYSIS SETS

5.1. Full Analysis Set

The Full Analysis Set (referred to in the protocol as the intent-to-treat (ITT) population) *is defined as all subjects randomized to treatment who received at least one dose of study medication*.

Since data will not be imputed for patients who do not have a baseline or for patients who do not have post-baseline data for a specific parameter, such patients will not appear in the FAS analyses for that parameter. Subjects who had a decrease in at least 5 points at termination but did not return for a repeat test will be included in the FAS set and will be assumed to have a confirmed decrease for VFT analysis. Termination is the VFT performed at Week 12 or the last available post-treatment VFT for subjects who did not complete the study (per Protocol Section 9.4.1).

5.2. 'PER PROTOCOL' Analysis Set

The primary analysis will be performed on the Per Protocol population.

The Per Protocol population is a subset of the ITT population, and excludes subjects who had a decrease in at least 5 points at termination but did not return for a repeat test. The Per Protocol population may also exclude subjects with major protocol violations; the list of subjects excluded will be determined prior to breaking the blind. The expectation is that the PP subset will be close in the number of subjects to the to the number of subjects randomized.

5.3. Safety Analysis Set

In this study, all parameters to be analyzed are safety parameters. The primary analysis of the primary parameter will be performed using the Per Protocol population, with a supplementary analysis that uses the ITT population. All other safety data will be summarized using the ITT population.

5.4. OTHER ANALYSIS SETS

Not applicable.

5.5. Treatment Misallocations

Subjects who were:

- Randomized but not treated are not in the ITT population and will thus be excluded from all safety summaries.
- Randomized but took incorrect treatment will be reported under the treatment actually received for all safety summaries.

5.6. Protocol Deviations

The list of protocol deviations will be compiled prior to database closure. Subjects who *had a decrease in at least 5 points at termination* (the Week 12 VFT or last available post-treatment VFT) *but did not return for a repeat test* will be excluded from the Per Protocol population, as will patients with certain protocol deviations (to be determined based on clinical judgment prior to breaking the blind.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

Not applicable, as this is a safety study without efficacy endpoints.

6.2. Safety Endpoints

Primary Endpoint:

The primary endpoint is the proportion of subjects with a decrease in the threshold value from baseline to termination in any five or more points (in either eye) at the p<0.05 level repeated in the same five points on subsequent computerized automated perimetry testing (Humphrey 24-2 SITA standard).

The primary endpoint is derived from the Humphrey 24-2 SITA Standard visual field analyzer. For each eye there are 52 test points. For each test point, the Humphrey analyzer determines the threshold value for sensitivity to light by the subject. In addition, for each of the 52 points, the test provides probabilities ($p<0.05$, $p<0.02$, etc) that a patient with normal vision of the same age would have the same result, ie, that the measured value at that point was at or below the respective percentile of the age-specific empiric distribution at that position of the field for normal subjects. For each of the 52 test points for each eye, the data received from the Central Reader will contain a 1 if $p<0.05$ or a 0 otherwise. (see Appendix A.1.2).

The primary endpoint (proportion of patients with deterioration) is determined as follows: Baseline and all other visits for visual field test (VFT) will be based on the visits defined by the central reader. There are 2 tests performed for the Screening visit, these values will not be used for baseline determination. A point will be considered abnormal at baseline only if it was abnormal ($p<0.05$) at both baseline tests. A patient with 5 or more points that are $p<0.05$ at termination (ie, a value of 1 in the database) that were not significant (a 0 in the database) at baseline is required to have a repeat test. If at the repeat test 5 or more of the same points are $p<0.05$, then that patient is considered to have deterioration. This assessment is done separately for each eye, and a patient is considered to have deterioration if this is true for either eye.

Secondary Endpoints:

Mean Deviation (MD) is a global index of visual field depression. The MD ranges from 0 decibels (dB) (no defect) to about -32 dB (end-stage damage). *Change in mean deviation from baseline to termination will be computed for each subject.* Baseline and all other visits for mean deviation will be based on the visits defined by the central reader and study treatment dates. *Baseline mean deviation will be the average of the two mean deviations from the Baseline visit, and termination will be the mean deviation at the Week 12 visit (or the last post-treatment values available after Day 1 for subjects who terminate early). If a repeat test was done at termination, the mean deviation from the repeat test will be used. For each subject, the worst eye (ie, the eye with the greatest decrease in mean deviation) will be used in the analysis.*

The best corrected visual acuity (with glasses or best possible glasses prescription) will be measured using the Early Treatment Diabetic Retinopathy Study(ETDRS) charts. The letters on chart A are read using the right eye and chart B using the left eye. The subject starts at the top of the chart and begins to read down the chart. The subject reads down the chart until they reach a row where a minimum of three letters on a line cannot be read. The subject is scored by how many letters could be correctly identified. Details of visual acuity scoring have been defined in Appendix A.1.3. *Change in visual acuity from baseline to termination will be computed for each subject. Baseline will be defined as the last visual acuity assessment prior to receiving study medication, and termination will be the visual acuity assessment at the Week 12 visit (or the last post-treatment assessment available after Day 1 for subjects who terminate early). If acuity was assessed at a repeat visit at termination, the acuity from the repeat test will be used. For each subject, the worst eye (ie, the eye with the greatest decrease in visual acuity) will be used in the analysis.*

Other Safety Endpoints:

Other safety parameters, including adverse events, physical examination results, vital signs, body weight, clinical laboratory results, and subject assessment of seizure frequency as compared to before taking study medication. Sheehan Suicidality Tracking Scale (S-STS),and Columbia Suicide Severity Scale (C-SSRS) will be summarized by treatment group, but not analyzed inferentially. For subjects who randomized prior to Amendment 4, -STS will be mapped to Columbia-Classification Algorithm of Suicide Assessment (C-CASA) and for subjects who randomized after amendment 4, C-SSRS will be mapped to Columbia-Classification Algorithm of Suicide Assessment (C-CASA) before being analysed.

Any adverse events (AE) occurring following start of treatment should be counted as treatment emergent. Events that occur in a non-treatment period after treatment was initiated (for example, washout or follow-up) will be counted as treatment emergent and attributed to treatment.

6.3. Other Endpoints

Screening ophthalmologic assessment (Dilated Funduscopic), SBQ-R and self-administered Patient Health Questionnaire (PHQ-8) will be summarized for both treatments combined and by treatment group. For subjects who require Mental Health Risk Assessment (MHRA), it may be assessed at screening, baseline and post treatment, eg, for those subjects who require evaluation.

6.4. Covariates

The covariate for Mean Deviation is the baseline MD, which is the average *of the two mean deviations from the Baseline visit.*

The covariate for Visual Acuity is the baseline visual acuity, *defined as the last visual acuity assessment prior to receiving study medication.*

7. HANDLING OF MISSING VALUES

For each endpoint, if the Week 12 test is missing then the last available post-treatment test after Day 1 will be used, eg, a last observation carried forward (LOCF) approach will be taken. *Data will not be imputed for subjects who do not have any VFTs* or visual acuity tests *after baseline* or for subjects who do not have a baseline; rather such subjects will not contribute to the analysis of that endpoint.

Subjects who *had a decrease in at least 5 points at termination but did not return for a return test* will be excluded from the Per Protocol set. In the analysis of the ITT population, such patients will be assumed to have a confirmed decrease.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical METHODS

The primary analysis will compare the difference in proportions for the primary endpoint (based on a 2x2 contingency table combined across centers) using a 2-sided 95% confidence interval. Because it is expected that the proportions will be small for each treatment group, unconditional exact methods (StatXact or Proc-StatXact)[2] will be used to compute the confidence interval. Or the following code may be used.

```
 /***

***  Hypothetic Example of calculated Exact approximation 95% CI

***  where there are 4 cases of deterioration and all 4 belong to PGB

***/

%macro pairs(x1px2=,nper=);

%do x1=0 %to &x1px2;

  data a;

  x2=&x1px2 -&x1;

  r=0; d=1; w=&nper-&x1; output;

  r=1; d=1; w=&x1; output;

  r=0; d=2; w=&nper - x2; output;

  r=1; d=2; w=x2; output;

  run;

proc freq data=a;
```

```
  tables d*r / norow nocol nopct exact riskdiff(cl=newcombe);
  exact riskdiff(method=score);
  weight w;
  output out=diffs riskdiff;
run;
data diffs2; set diffs;
keep x1 n1 x2 n2 _rdif2_ xl_rdif2 xu_rdif2;
x1=&x1; n1=&nper; x2=(&x1px2 - &x1); n2=&nper;
run;
proc append base=pairvary data=diffs2; run;
%end;
%mend pairs;
**********************************;
%pairs(x1px2=4,nper=142); * where there are 4 cases of deterioration
                           and all 4 belong to PGB
run;
```

Continuous measures (MD, visual acuity) will be analyzed using an ANCOVA main effects model, with treatment and study center in the model and the respective baseline score as a covariate. Output from the ANCOVA models will include adjusted (least squares) means and standard errors for each treatment group, p-values for the pregabalin versus placebo comparison, and 95% confidence intervals on the difference in LS means between pregabalin and placebo.

The only time point analyzed is Week 12 (or last observation, for patients who terminate early). Ophthalmologic data collected at Week 6 and follow-up will be summarized descriptively but not analyzed inferentially, unless it is used as the termination time point in the primary analysis

Centers with fewer than 4 patients will be combined with other centers prior to breaking the blind. Centers with 4 or more patients may be combined with other centers as needed, or may be left as separate centers. The pooling will be done geographically if possible. These pooled centers will be used in place of center in the analyses that include center in the model.

8.2. Statistical Analyses

8.2.1. Primary Analysis

The primary endpoint will be analyzed using a non- inferiority analysis. The difference in proportions between pregabalin and placebo in the per protocol population will be compared using a 2-sided 95% confidence interval (CI). Non-inferiority will be demonstrated if the upper CI bound is less than 0.10 (10%).

The primary analysis is based on the Per Protocol set and the primary endpoint proportion of patients with visual field deterioration. A 2-sided 95% confidence interval on the difference in proportions between pregabalin and placebo will be constructed using unconditional exact methods. To support interpretation of the primary analysis, an analysis as described above but based on the ITT population rather than the Per Protocol set, will be performed. In this analysis, patients with a decrease in ≥5 points at termination but no repeat visit will be treated as if they did have a repeat visit that confirmed the decrease.

8.2.2. Secondary Analyses

Mean Deviation

Change in mean deviation from baseline to termination will be computed for each subject. Baseline mean deviation will be the average of the two mean deviations from the Baseline visit, and termination will be the mean deviation at the Week 12 visit (or the last available after Day 1 for subjects who terminate early). If a repeat test was done at termination, the mean deviation from the repeat test will be used. For each subject, the worst eye (ie, the eye with the greatest decrease in mean deviation) will be used in the analysis. Change in mean deviation will be analyzed for the ITT population using analysis of covariance (ANCOVA), with treatment and center in the model and the baseline mean deviation as the covariate. Least squares means will be obtained from the model and a 2-sided 95% confidence interval will be constructed on the difference in least squares means between pregabalin and placebo.

Non-inferiority with respect to mean deviation will be demonstrated if the lower bound of the CI is greater than –2.0 dB.

Visual Acuity

Visual acuity (best-corrected, measured using ETDRS charts) is expressed in terms of number of letters correctly identified. Change in visual acuity from baseline to termination will be computed for each subject. Baseline will be defined as the last visual acuity assessment prior to receiving study medication, and termination will be the visual acuity assessment at the Week 12 visit (or the last available after Day 1 for subjects who terminate early). If acuity was assessed at a repeat visit at termination, the acuity from the repeat test will be used. For each subject, the worst eye (ie, the eye with the greatest decrease in visual acuity) will be used in the analysis. Change in visual acuity will be analyzed for the ITT population using ANCOVA, with treatment and center in the model and the baseline acuity as the covariate.

8.2.3. Other Safety Analyses

Other safety parameters, including adverse events, physical examination results, vital signs, body weight, clinical laboratory results, subject assessment of seizure frequency as compared to before taking study medication, and S-STS/C-SSRS will be summarized by treatment group, but not analyzed inferentially. Screening ophthalmologic assessment (Dilated Funduscopic), SBQ-R and self-administered Patient Health Questionnaire (PHQ-8) will be summarized for both treatments combined and by treatment group. Mental Health Risk Assessment (MHRA) will be summarized at screening, baseline and post treatment.

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8.2.3.2. Suicidal Ideation and Behavior Assessment (S-STS/C-SSRS)

Both S-STS and C-SSRS will be mapped to Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes described in Appendix A.1.5 and will be summarized descriptively by visit using count (percentage) for each C-CASA category. Percentages in a given visit will be based on the number of subjects assessed in that visit in the respective treatment groups.

The S-STS and C-SSRS data will also be presented in data listing.

8.2.3.3. Ophthalmologic Assessment (Dilated Funduscopic), PHQ-8, SBQ-R, MHRA

The external eye exam and funduscopic examination (normal/abnormal/not done) conducted at screening will be summarized descriptively using count (percentage) by treatment group.

The 8-question PHQ will be summarized for each question by its response categories using count and percentages. Percentages will be based on the number of subjects who answered the question in the respective treatment groups.

Ophthalmologic assessment and PHQ-8 data will also be presented in data listing.

Summary, using count and percentages, and listing of screening Suicide Behavior Questionnaire (SBQ-R) will be provided by treatment group.

Mental Health Risk Assessment (MHRA) will be summarized at screening, baseline and post treatment and presented in a data listing

8.2.4. Prior and Concomitant Medications

Prior and concomitant medications will be summarized for each treatment group. All medications will also be presented in data listing.

8.2.5. Summary of Safety Analyses

Endpoint	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data	Interpretation
Proportion of patients with a deterioration in visual field threshold	Per Protocol	Confidence interval on difference	Treatment	Not Applicable	Primary Analysis. Subjects with a decrease in ≥5 points at termination are required to have a repeat assessment to be part of the analysis.
Proportion of patients with a deterioration in visual field threshold	ITT	Confidence interval on difference	Treatment	Not Applicable	Check for robustness of primary analysis. In this analysis, patients with a decrease in ≥5 points at termination but no repeat assessment will be treated as if they did have a repeat visit that confirmed the decrease.
Mean Deviation (MD)	ITT	ANCOVA	Treatment, Center/ Baseline MD	LOCF	Secondary Analysis
Visual Acuity	ITT	ANCOVA	Treatment, Center/ Baseline Acuity	LOCF	Secondary Analysis

9. REFERENCES

1. Musch DC, Gillespie BW, Motyka BM, Nizoil LM, Mills RP, Lichter PR. Converting to SITA-Standard from Full-Threshold Visual Field Testing in the Follow-Up Phase of a Clinical Trial. *Invest Ophthalmol Vis Sci* 2005; 46:2755-2759.

2. StatXact: Statistical Software for Exact Nonparametric Inference. CYTEL Software Corporation. Cambridge, MA.

10. APPENDICES

Appendix 1. DATA DERIVATION DETAILS

10.1. A.1.1 Definition and Use of Visit Windows in Reporting

Analyses will be conducted using change from baseline to the week 12 visit (or the last visit after Day 1 for patients who discontinue prior to week 12). Week 15 follow up assessments and for early terminators, the assessments conducted approximately 2 weeks after discontinuation of treatment will be excluded from analysis consideration.

For VFT and MD, Baseline and all other visits including the repeat visits will be based on the visits defined by the central reader in conjunction with the dates when treatment was administered. Additional considerations for determination of Visual Field Deterioration are given in Appendix A.1.2.

For visual acuity the following week assignments will be used for the planned visits:

Time (Windowed Week)	Range (Days*)	Target Day
Baseline	[-99 to 1]	1
Week 6	[2 to 62]	42
Week 12	[63 to 95]	84
Week 15 Follow-up	≥96	105
LOCF** Week 12	[2 to 95]	84

*For purposes of windowing, a derived Day will be defined as (Visit Date-First Dose Date) + 1, where Visit Date is a follow-up visit that is greater than the baseline visit. Brackets indicate bound value is included in the window. In the case of two competing visits that are equally distant to the target day, the first visit will be selected as the assigned Week.
**LOCF imputation will be used only if the subject has missing data for Day 84 (Week 12), otherwise the Day 84 and Last Visit will be the same. If LOCF imputation is employed, then the first derived Day in the window closest to the target day will be chosen as the LOCF Week 12 assignment.

If visual acuity was assessed at a repeat visit or if there are multiple assessments at Week 12 window, then the latest of the assessments which is within the Week 12 window will be considered as the visual acuity at termination.

10.2. A.1.2 Additional Considerations for Determination of Visual Field Deterioration

Visual Field Deterioration:

There are 52 test points for each eye. Below is an eye map for visual field test.

1	A	B	C	D	E	F	G	H	I	J
2				2D	2E	2F	2G			
3			3C	3D	3E	3F	3G	3H		
4		4B	4C	4D	4E	4F	4G	4H	4I	
5	5A	5B	5C	5D	5E	5F	5G	5H	5I	5J
6	6A	6B	6C	6D	6E	6F	6G	6H	6I	6J
7		7B	7C	7D	7E	7F	7G	7H	7I	
8			8C	8D	8E	8F	8G	8H		
9				9D	9E	9F	9G			

There are 56 points in the above eye map. While testing the left eye, the points 5A, 6A, 5C, and 6C are left blank, of these 5C & 6C represent the blind spots, and 5A & 6A represent the points near the left ear. Similarly while testing the right eye, the points 5H, 6H, 5J, and 6J are left blank, of these 5H & 6H represent the blind spots, and 5J & 6J represent the points near the right ear.

Let Ti (where i=1, 2, 3,…, 52) represent the 52 test points for each eye. Each of these test points (for each eye and for each visual field test performed) contains a 1 (if abnormal at $p<0.05$) or a 0 otherwise.

Baseline is determined from the 2 tests performed at the baseline visit. For each eye, the baseline value of a test point is 1 only if that point was 1 at both baseline tests. That is, for a specific test point in a specific eye:

Value at 1st Baseline Test	Value at 2nd Baseline Test	Value to be Used as Baseline in the Analysis
0	1	0
1	0	0
0	0	0
1	1	1

Termination visual field deterioration is determined as follows:

If 5 or more test points that were 0 at baseline are 1 at termination for:

a. either eye, then the patient will come in for a repeat visit. If the repeat visit indicates a 1 for at least 5 of the *same* test points in the *same* eye, then the patient is considered to have visual field deterioration.

b. both eyes, then the patient will come in for a repeat visit. If the repeat visit has *at least one* eye with a 1 for at least 5 of the *same* test points, then the patient is considered to have visual field deterioration.

Programmatically, this would be done as follows: If the following condition: [Ti=0 at baseline, Ti=1 at termination and Ti=1 at the repeat test] (where i=1,…, 52 and T represents the test points) is true for ≥5 test points (T1, T2,…T52) for either eye, then that patient is considered to have visual field deterioration.

The following table gives some examples for 5 patients. (Assume that the left eye for Patients 1 and 2 and the right eye for Patients 3 and 5 are not shown because of no test points=1 at either baseline or termination.):

Patient/eye	Test points=1 at baseline	Test points=1 at termination	Test points=1 at repeat visit	Met criteria for deterioration
1/R	2D, 2E 2F	2D, 2E, 2F, 2G, 3C	Not applicable	No, Repeat test not required since <5 new points = 1 at termination.
2/R	2D	3D, 3E, 3F, 3G, 3H, 4B, 4C	2D, 4E, 4F, 4G, 4H, 4I	No. None of the same test points were =1 at both termination and repeat test.
3/L	3C, 3D, 3E	2D, 2E, 2F, 4D, 4E, 4F	2E, 2F, 4D, 4E, 4F	Yes. 2E, 2F, 4D, 4E, 4F are =1 at termination and repeat visit and were not =1 at baseline.
4/R	2D, 2E, 2F, 2G, 3C, 3D	2D, 3E, 3F, 3G, 3H, 4B, 4C	3E, 3F, 3G, 3H, 4C	Yes. 3E, 3F, 3G, 3H, 4C are =1 at termination and repeat visit and were not =1 at baseline.
4/L	2D, 2E, 2F, 2G, 3C, 3D	2D, 3E, 3F, 4F, 4G, 4H	4F, 4G, 4H, 4I, 5B, 5D	No. <5 points = 1 at both termination and repeat tests.
5/L	3C, 3D, 3E	3G, 3H, 4B, 4C, 4D	Not done	Yes for ITT sensitivity analysis as the patient had 5 points=1 at termination that were 0 at baseline; patient excluded from primary analysis (Per Protocol set.) as the patient lacks a repeat test.

In these examples, Patients 3 and 4 are considered to have visual field deterioration and Patients 1 and 2 are not. Note that for Patient 4 only one of the eyes met the criteria on the repeat visit, but that was sufficient.

Confirmation (or lack of confirmation) of deterioration will be done programmatically, as specified above.

10.3. A.1.3 Calculation of Visual Acuity Score

The ETDRS chart will be used to measure the best corrected visual acuity (with glasses or best possible glasses prescription). For the purpose of calculating the visual acuity scores, data will be read starting from the first row and by accumulating the number of letters correctly read until the first instance of row where the number of letters read is <3. This assumes that the contiguous rows between row 1 and the first instance of row with a score of <3 have scores ≥3. If row 1 is non-missing but has a score <3, then data will be read only up to row 1 and the visual acuity score will equal the score of row 1. If row 1 is missing or ND then visual acuity will also be missing. In all other cases data will be read until the row where the score is <3 or ND. Below are some examples of some arbitrary cases for calculating the VA scores:

Dummy SubjID	ETDRS Chart Row	Number of letters Read Correctly (Row Score)	VA Score
101	1	5	Row 1 Score+ Row 2 Score+ Row 3 Score+ Row 4 Score+ Row 5 Score+ Row 6 Score+ Row 7 Score= 5+5+3+5+3+3+2 = 26
	2	5	
	3	3	
	4	5	
	5	3	
	6	3	
	7	2	
	8		
	9		
	10		
	11		
	12		
	13		
	14		
102	1	5	Row 1 Score+ Row 2 Score+ Row 3 Score =5+5+3 = 13
	2	5	
	3	3	
	4	ND	
	5	3	
	6	3	
	7	2	
	8		
	9		
	10		
	11		
	12		
	13		
	14		
103	1	5	Row 1 Score+ Row 2 Score+ Row 3 Score=5+5+3 = 13
	2	5	

Dummy SubjID	ETDRS Chart Row	Number of letters Read Correctly (Row Score)	VA Score
	3	3	
	4	0	
	5	3	
	6	3	
	7	2	
	8		
	9		
	10		
	11		
	12		
	13		
	14		

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10.5. A.1.5 Sheehan-Suicidality Tracking Scale (S-STS)

The eight-item S-STS as shown below will be converted to Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes as described in Table 1.

STS001

SHEEHAN - SUICIDALITY TRACKING SCALE (LIFETIME ASSESSMENT): (Page 2 of 2)

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INSTRUCTIONS: CHOOSE ONLY ONE ANSWER FOR EACH QUESTION.

PLEASE ENSURE THAT ALL DIMENSIONS OF THE QUESTION ARE TAKEN INTO ACCOUNT IN CHOOSING THE APPROPRIATE RESPONSE (FOR EXAMPLE, TIME FRAME, FREQUENCY AND SEVERITY).
THE RESPONSE "NOT AT ALL" TO ANY QUESTION MEANS "NONE" AND MEANS THE THOUGHT OR BEHAVIOR "DID NOT OCCUR AT ALL".

1. Did you ever suffer an accident? (this includes taking too much of your medication accidentally). ☐ (0) No ☐ (1) Yes

IF NO, SKIP TO QUESTION 2.
IF YES, GO TO QUESTION 1a:

	Not at all (0)	A little (1)	Moderately (2)	Very (3)	Extremely (4)
1a. to what extent did you plan or intend to hurt yourself in that accident (either passively or actively)?	☐	☐	☐	☐	☐

IF THE ANSWER TO QUESTION 1a IS 0 (=Not at all), SKIP TO QUESTION 2.
IF IT IS SCORED ≥ 1, GO TO QUESTION 1b:

1b. Did you intend to die as a result of this accident? ☐ (0) No ☐ (1) Yes

How seriously did you ever:	Not at all (0)	A little (1)	Moderately (2)	Very (3)	Extremely (4)
2. think that you would be better off dead or wish you were dead?	☐	☐	☐	☐	☐
3. want to harm yourself or to hurt or to injure yourself?	☐	☐	☐	☐	☐
4. think about suicide?	☐	☐	☐	☐	☐
5. plan for a suicide?	☐	☐	☐	☐	☐
6. take active steps to prepare for a suicide attempt in which you expected or intended to die?	☐	☐	☐	☐	☐

7. Did you ever injure yourself on purpose? ☐ (0) No ☐ (1) Yes

IF NO, SKIP TO QUESTION 8.
IF YES, GO TO QUESTION 7a:

How seriously did you:	Not at all (0)	A little (1)	Moderately (2)	Very (3)	Extremely (4)
7a. deliberately injure yourself without intending to kill yourself?	☐	☐	☐	☐	☐
8. attempt suicide?	☐	☐	☐	☐	☐

Table 1. Universal S-STS Mapping to C-CASA

C-CASA Category	C-CASA Category Number	Eight-item S-STS
Completed Suicide	1	Obtain from SAE
Suicide Attempt	2	'Yes' to Item 1b OR ≥1 to Item 1a and 1b is missing OR ≥1 to Item 8
Preparatory action toward	3	≥1 to Item 6

C-CASA Category	C-CASA Category Number	Eight-item S-STS
imminent suicidal behavior (including interrupted attempt or aborted attempt)		
Suicidal Ideation	4	≥1 to Item 2 OR ≥1 to Item 3 OR ≥1 to Item 4 OR ≥1 to Item 5
Self-injurious behavior with unknown intent	5	n/a
Not enough information, fatal	6	n/a
Self-injurious behavior without suicidal intent	7	EITHER ≥1 to Item 7a OR ≥1 to Item 1a AND "No' to Item 1b
Other (accidental, psychiatric, other)	8	n/a
Not enough information, non fatal	9	n/a

* Note: C-CASA codes 5, 6, 8, and 9 are not applicable to prospectively collected data.

10.6. A.1.6- Columbia – Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an interview based rating scale that systematically assesses suicidal ideation and suicidal behavior. Table 2 describes the mapping of C-SSRS to C-CASA categories.

Table 2. C-SSRS Mapped to C-CASA - Suicidality Events and Codes

C-CASA Event Code	C-CASA Event	C-SSRS Response
1	Completed suicide	As captured in the safety database
2	Suicide attempt	"Yes" on "Actual Attempt"
3	Preparatory acts towards imminent suicidal behavior	"Yes" on any of the following: • "Aborted attempt", or • "Interrupted attempt", or • "Preparatory Acts or Behavior"
4	Suicidal ideation	"Yes" on any of the following: • "Wish to be dead", or • "Non-Specific Active Suicidal Thoughts", or • "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act", or • "Active Suicidal Ideation with Some Intent to Act, without Specific Plan", or • "Active Suicidal Ideation with Specific Plan and Intent"
7	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?"