NCT02192099

Study ID: GLYX13-C-203

Title: Open Label Extension for Subjects with Inadequate/Partial Response to Antidepressants during the Current Episode of Major Depressive Disorder Previously Treated with Rapastinel (GLYX-13) (Extension of GLYX13-C-202, NCT01684163)

Statistical Analysis Plan Date: 11 Dec 2018

Naurex, Inc., an indirect subsidiary of Allergan, plc
5 Giralda Farms
Madison, NJ, 07940

GLYX13-C-203

Open Label Extension for Subjects with Inadequate/Partial Response to Antidepressants during the Current Episode of Major Depressive Disorder Previously Treated with Rapastinel (GLYX-13) (Extension of GLYX13-C-202, NCT01684163)

STATISTICAL ANALYSIS PLAN

Final: 11 Dec 2018

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1.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
BP	blood pressure
bpm	beats per minute
[redacted]	[redacted]
CPK	creatinine phosphokinase
[redacted]	[redacted]
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram
GGT	gamma glutamyltransferase
[redacted]	[redacted]
hCG	human chorionic gonadotropin
HDDL	high-density lipoprotein
[redacted]	[redacted]
IV	intravenous
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
PCS	potentially clinically significant
[redacted]	[redacted]
[redacted]	[redacted]
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCI	Structured Clinical Interview for Depression

SD	standard deviation
[redacted]	[redacted]
SI	Le Système International d'Unités (International System of Units)
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal

2.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses for efficacy and safety assessments as outlined and/or specified in the final study protocol and the most recent amendment (version 03 dated 23 Nov 2016).

This is a Phase 2, open-label, safety study of rapastinel (GLYX-13). Up to 100 subjects who participated in clinical study GLYX13-C-202 (NCT01684163), in which they completed 12 weeks of treatment of either rapastinel (GLYX-13) or placebo, will enter the extension study and receive additional rapastinel (GLYX-13) treatment. Participation in the study may continue until rapastinel (GLYX-13) is approved for marketing in the United States or until the study is ended by the Sponsor.

Following 1 month at the dose level, subjects who were assigned to placebo during the randomized withdrawal period of GLYX13-C-202 are eligible to participate, and will begin at the dose level to which the subject was assigned during the stabilization period of GLYX13-C-202. The investigator may continue the same dose level and dose interval, or may change the dose level and dose interval. The investigator will complete a treatment plan that outlines the dose level and dose interval at which rapastinel (GLYX-13) will be administered. The investigator, at the investigator's discretion, may change the treatment plan to alter dose level and/or dose interval based on the subject's depression status.

Investigator will begin treatment based on the dose level (5 mg/kg or 10 mg/kg) to which the subject was assigned during participation in GLYX13-C-202; subjects originally assigned to 5 mg/kg will receive 225 mg/3 mL, and subjects originally assigned to 10 mg/kg will receive 450 mg/3 mL. If subject experiences adverse event(s) (AEs) that the investigator believes may be associated with rapastinel (GLYX-13), the investigator may decrease dose level from 450 mg to 225 mg. If at any point the subject cannot tolerate the minimum 225 mg unit dose, the subject should be discontinued from the study. There are 3 dose groups (despite weekly or biweekly dosing schedule):

- Low dose group consisting of all subjects whose dose level is 225 mg or 5 mg/kg;
- High dose group consisting of all subjects whose dose level is 450 mg or 10 mg/kg;
- Mixed dose group consisting of all subjects who changed dose level between low dose (225 mg or 5 mg/kg) and high dose (450 mg or 10 mg/kg).

At the screening visit, the Structured Clinical Interview for Depression (SCID) will be administered to determine whether any exclusionary conditions have arisen since subject's completion of GLYX13-C-202. The Columbia Suicide Severity Rating Scale (C-SSRS) will be administered. A physical examination will be conducted to ascertain if significant changes have occurred since the subject ended participation in GLYX13-C-202. Blood and urine samples will be obtained for laboratory analysis. Antidepressant agents used since the subject ended participation in GLYX13-C-202 will be recorded.

On Week 1 Day 1, subjects will arrive at the investigative site having fasted for at least 10 hours, with water as desired. Each subject's eligibility will be confirmed; then a physical examination will be performed, and blood and urine samples for laboratory analysis will be obtained. Vital signs will be assessed and mass recorded. Electrocardiogram (ECG) will be recorded, [redacted] Each subject will then receive an intravenous (IV) dose of rapastinel (GLYX-13) (225 mg or 450 mg unit dose) in a "slow bolus" injection in an upper extremity vein within approximately 1 to 2 minutes. Subjects will be discharged following determination by the investigator that they are medically able to leave. The aforementioned procedures must be repeated within 24 hours before dosing if screening assessments were performed greater than 7 days before study drug dosing.

Subjects will return to the study site during the first month on the schedule (weekly or biweekly) to which they were assigned in GLYX13-C-202. After the first month, subjects will return to the study site on a schedule defined by the treatment plan set by the investigator. [redacted]. Rapastinel (GLYX-13) will be administered. Subjects will remain in the study unit until determination by the investigator that they are medically able to leave the study unit.

[redacted]. ECG will be recorded and blood and urine samples will be obtained for laboratory analysis. Rapastinel (GLYX-13) will be administered. Subjects will remain in the study unit until determination by the investigator that they are medically able to leave (see Schedule of Evaluations,

[redacted]

3.0 OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective of this study is to examine the safety of long-term repeat exposure to rapastinel (GLYX-13) in subjects who participated in GLYX13-C-202.

The primary endpoint of this study is to examine the number of subjects who experience an AE over the course of the study.

4.0 SUBJECT POPULATIONS

Subject disposition will be summarized using all enrolled subjects, whether or not the study drug was received.

4.1 SAFETY POPULATION

The Safety Population will consist of all subjects who received any injection of study drug. All safety analyses will be based on this population.

4.2 FULL ANALYSIS SET

The Full Analysis Set will consist of all subjects who received any injection of study drug and who have at least 1 postbaseline efficacy assessment. All efficacy analyses will be produced using this population and it will be considered the primary efficacy population.

5.0 SUBJECT DISPOSITION

The number of subjects included in the Safety Population and Full Analysis Set will be summarized overall and by study center.

The number and percentage of subjects completing and prematurely discontinuing during the study will be presented overall. Reasons for premature discontinuation as recorded on the termination page of the electronic case report form will be summarized (number and percentage) overall for the Safety Population.

5.1 PROTOCOL DEVIATIONS

The number and percentage of subjects with significant protocol deviations will be summarized overall for the Safety Population. Protocol deviations will be defined, including significance classification, in the Protocol Deviation Requirement Specification.

6.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age, sex, ethnicity, race, weight) and other baseline characteristics will be summarized overall for the Safety Population.

Medical and surgical history, and psychiatric history will be summarized overall for the Safety Population. *Prior medication* will be defined as any medication started before the date of first dose of study drug. *Concomitant medication* will be defined as any medication taken on or after the date of first dose of study drug.

The use of prior medication will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class and overall for the Safety Population. Concomitant medications will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class and overall for the Safety Population. Multiple medication use of the same therapeutic class by a subjects will only be counted once. Prior and concomitant psychotropic medication, as well as any medications for the treatment of depression will be summarized for Safety Population.

The *WHO Drug Dictionary Enhanced*, will be used to classify prior and concomitant medications by therapeutic class and drug name.

7.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

7.1 EXTENT OF EXPOSURE

Exposure to rapastinel for the Safety Population will be summarized descriptively overall for treatment duration, calculated as the number of days from the date of first study drug taken to the date of last dose taken, inclusively. Subject-years, calculated as the sum of the treatment durations of all subjects divided by 365.25, will also be presented overall similarly using descriptive statistics.

Quarterly dose and overall quarterly dose of study drug will also be summarized overall using descriptive statistics. Quarterly dose for a subject is defined as the total doses taken during 1 quarter interval. Overall quarterly dose for a subject is defined as the total doses divided by total number of quarters over the treatment period.

7.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for a specified period is defined as the total number of doses actually taken by a subject during that period divided by the number of doses that were expected to be taken during the same period multiplied by 100. The total number of doses actually taken during a specific time period is calculated as the sum of doses taken during that study period as obtained from the study medication exposure record. The number of doses expected to be taken for a specific study period will be the number of visits that a subject was prescribed rapastinel IV in that study period. Descriptive statistics for treatment compliance during each quarter and during the study period till the end of participation will be presented overall for the Safety Population.

7.3 WEIGHT ADJUSTED DOSE OF RAPASTINEL

Per initial protocol, each subject received 5 mg/kg or 10 mg/kg in study GLYX13-C-203. In Amendment 3 of protocol, subjects originally assigned to 5 mg/kg in GLYX13-C-202 will receive 225 mg unit dose and subjects originally assigned to 10mg/kg in GLYX13-C-202 will receive 450 mg unit dose.

The dose of rapastinel for each subject will be divided by corresponding subject's weight assessed at the first visit at which each subject received either 225 mg unit dose or 450 mg unit dose and summarized descriptively by 225 mg or 450 mg treatment group for Safety Population. If subject had missing weight at that visit, the last non-missing weight assessment prior to that visit will be used in analysis.

8.0 EFFICACY ANALYSES

[redacted]

9.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population.

The safety parameters will include AEs, clinical laboratory, vital signs, and ECG parameters. For each safety parameter, the last non-missing safety assessment before the first dose of study drug in study GLYX13-C-203 will be used as the baseline for all analyses of that safety parameter.

9.1 ADVERSE EVENTS

AEs will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA).

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it was not present before the first dose of study drug or was present before the date of the first dose of study drug and increased in severity during the study period till the end of participation. If more than 1 AE was reported before the first dose of study drug and coded to the same preferred term, then the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the study. An AE that occurs more than 30 days after the date of the last dose of study drug will not be considered as a TEAE. An AE that becomes serious on or after the first dose of study drug will also be considered as TEAE.

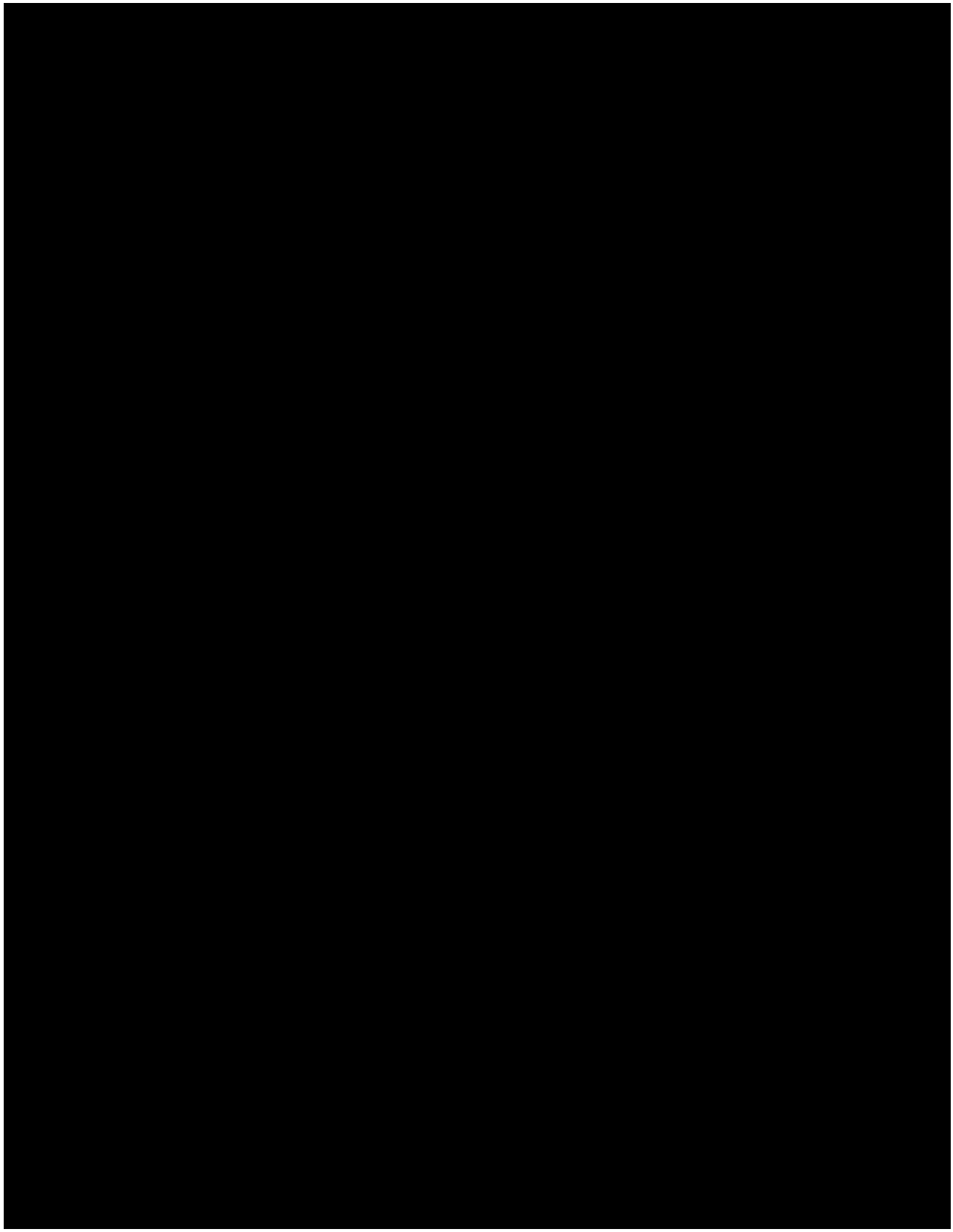
The number and percentage of subjects reporting TEAEs will be tabulated by SOC and preferred term and further categorized by severity and causal relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship. The distribution of TEAEs by severity and relationship to study drug will be summarized. An AE that occurs more than 30 days after the date of the last dose of study drug will not be summarized.

The incidence of common (in $\geq$ 2% of subjects) TEAEs during the study period till the end of participation will be summarized by preferred term and will be sorted by decreasing frequency.

An SAE that occurred between the date of the first dose of study drug and 30 days after the date of the last dose of study drug, inclusive, will be considered a treatment-emergent SAE (TESAE). The number and percentage of subjects who have TESAEs will be summarized by preferred term. In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term.

The incidence of TEAEs leading to premature discontinuation of study drug during the study period till the end of participation will be summarized by preferred term, and will be sorted by decreasing frequency.

Listings will be presented for all subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any). All subjects with SAEs, including SAEs reported during the screening period and subjects discontinuing because of AEs occurring before the start of study drug, will be included in these listings.



[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]

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[redacted]

10.0 HEALTH OUTCOMES ANALYSES

No health outcomes analyses are planned for this study.

11.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

12.0 DETERMINATION OF SAMPLE SIZE

This study is open to subjects who participated in clinical study GLYX13-C-202 at specified investigative sites. Up to 100 subjects are eligible.

13.0 COMPUTER METHODS

[redacted]

14.0 DATA HANDLING CONVENTIONS

14.1 SUMMARY STATISTICS

The following statistical summaries will be presented for each type of data:

- Continuous variables will be summarized by descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum, and maximum values).

- Categorical variables will be summarized by frequency distributions (counts and percentages).

14.2 VISIT TIME WINDOWS

Table 14.2–1 below presents the weekly visits assigned for efficacy and safety analyses corresponding to the range of treatment days (window) in the study during which an actual visit may have occurred.

Table 14.2–1. Weekly Visit Time Windows

Derived Visit	***Scheduled Visit Day***[a]	***Window***
Baseline		**the last non-missing assessment before the first dose of study drug**
Visit 1 (Day 1)	Day 1	Dosing Day Day = 1
Visit 2 (Week 1)	Day 7	Days [2, 10]
Visit 3 (Week 2)	Day 14	Days [11, 17]
Visit 4 (Week 3)	Day 21	Days [18, 24]
Visit 5 (Week 4)	Day 28	Days [25, 31]
Visit 6 (Week 5)	Day 35	Days [32, 38]
Visit 7 (Week 6)	Day 42	Days [39, 45]
Visit 8 (Week 7)	Day 49	Days [46, 52]
Visit 9 (Week 8)	Day 56	Days [53, 59]
Visit 10 (Week 9)	Day 63	Days [60, 66]
Visit 11 (Week 10)	Day 70	Days [67, 73]
Visit 12 (Week 11)	Day 77	Days [74, 80]
Visit 13 (Week 12)	Day 84	Days [81, 87]
Visit 14 (Week 13)	Day 91	Days [88, 94]
Visit 15 (Week 14)	Day 98	Days [95, 101]
Visit 16 (Week 15)	Day 105	Days [102, 108]
Visit 17 (Week 16)	Day 112	Days [109, 115]
Visit 18 (Week 17)	Day 119	Days [116, 122]

Table 14.2–1. Weekly Visit Time Windows

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Visit 19 (Week 18)	Day 126	Days [123, 129]
Visit 20 (Week 19)	Day 133	Days [130, 136]
Visit 21 (Week 20)	Day 140	Days [137, 143]
Visit 22 (Week 21)	Day 147	Days [144, 150]
Visit 23 (Week 22)	Day 154	Days [151, 157]
Visit 24 (Week 23)	Day 161	Days [158, 164]
Visit 25 (Week 24)	Day 168	Days [165, 171]
Visit 26 (Week 25)	Day 175	Days [172, 178]
Visit 27 (Week 26)	Day 182	Days [179, 185]
Visit 28 (Week 27)	Day 189	Days [186, 192]
Visit 29 (Week 28)	Day 196	Days [193, 199]
Visit 30 (Week 29)	Day 203	Days [200, 206]
Visit 31 (Week 30)	Day 210	Days [207, 213]
Visit 32 (Week 31)	Day 217	Days [214, 220]
Visit 33 (Week 32)	Day 224	Days [221, 227]
Visit 34 (Week 33)	Day 231	Days [228, 234]
Visit 35 (Week 34)	Day 238	Days [235, 241]
Visit 36 (Week 35)	Day 245	Days [242, 248]
Visit 37 (Week 36)	Day 252	Days [249, 255]
Visit 38 (Week 37)	Day 259	Days [256, 262]
Visit 39 (Week 38)	Day 266	Days [263, 269]
Visit 40 (Week 39)	Day 273	Days [270, 276]
Visit 41 (Week 40)	Day 280	Days [277, 283]
Visit 42 (Week 41)	Day 287	Days [284, 290]
Visit 43 (Week 42)	Day 294	Days [291, 297]
Visit 44 (Week 43)	Day 301	Days [298, 304]
Visit 45 (Week 44)	Day 308	Days [305, 311]
Visit 46 (Week 45)	Day 315	Days [312, 318]
Visit 47 (Week 46)	Day 322	Days [319, 325]
Visit 48 (Week 47)	Day 329	Days [326, 332]
Visit 49 (Week 48)	Day 336	Days [333, 339]
Visit 50 (Week 49)	Day 343	Days [340, 346]
Visit 51 (Week 50)	Day 350	Days [347, 353]
Visit 52 (Week 51)	Day 357	Days [354, 360]
Visit 53 (Week 52)	Day 364	Days [361, 367]
Visit 54 (Week 53)	Day 371	Days [368, 374]
Visit 55 (Week 54)	Day 378	Days [375, 381]
Visit 56 (Week 55)	Day 385	Days [382, 388]
Visit 57 (Week 56)	Day 392	Days [389, 395]
Visit 58 (Week 57)	Day 399	Days [396, 402]

Table 14.2–1. Weekly Visit Time Windows

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Visit 59 (Week 58)	Day 406	Days [403, 409]
Visit 60 (Week 59)	Day 413	Days [410, 416]
Visit 61 (Week 60)	Day 420	Days [417, 423]
Visit 62 (Week 61)	Day 427	Days [424, 430]
Visit 63 (Week 62)	Day 434	Days [431, 437]
Visit 64 (Week 63)	Day 441	Days [438, 444]
Visit 65 (Week 64)	Day 448	Days [445, 451]
Visit 66 (Week 65)	Day 455	Days [452, 458]
Visit 67 (Week 66)	Day 462	Days [459, 465]
Visit 68 (Week 67)	Day 469	Days [466, 472]
Visit 69 (Week 68)	Day 476	Days [473, 479]
Visit 70 (Week 69)	Day 483	Days [480, 486]
Visit 71 (Week 70)	Day 490	Days [487, 493]
Visit 72 (Week 71)	Day 497	Days [494, 500]
Visit 73 (Week 72)	Day 504	Days [501, 507]
Visit 74 (Week 73)	Day 511	Days [508, 514]
Visit 75 (Week 74)	Day 518	Days [515, 521]
Visit 76 (Week 75)	Day 525	Days [522, 528]
Visit 77 (Week 76)	Day 532	Days [529, 535]
Visit 78 (Week 77)	Day 539	Days [536, 542]
Visit 79 (Week 78)	Day 546	Days [543, 549]
Visit 80 (Week 79)	Day 553	Days [550, 556]
Visit 81 (Week 80)	Day 560	Days [557, 563]
Visit 82 (Week 81)	Day 567	Days [564, 570]
Visit 83 (Week 82)	Day 574	Days [571, 577]
Visit 84 (Week 83)	Day 581	Days [578, 584]
Visit 85 (Week 84)	Day 588	Days [585, 591]
Visit 86 (Week 85)	Day 595	Days [592, 598]
Visit 87 (Week 86)	Day 602	Days [599, 605]
Visit 88 (Week 87)	Day 609	Days [606, 612]
Visit 89 (Week 88)	Day 616	Days [613, 619]
Visit 90 (Week 89)	Day 623	Days [620, 626]
Visit 91 (Week 90)	Day 630	Days [627, 633]
Visit 92 (Week 91)	Day 637	Days [634, 640]
Visit 93 (Week 92)	Day 644	Days [641, 647]
Visit 94 (Week 93)	Day 651	Days [648, 654]
Visit 95 (Week 94)	Day 658	Days [655, 661]
Visit 96 (Week 95)	Day 665	Days [662, 668]
Visit 97 (Week 96)	Day 672	Days [669, 675]
Visit 98 (Week 97)	Day 679	Days [676, 682]

Table 14.2–1. Weekly Visit Time Windows

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Visit 99 (Week 98)	Day 686	Days [683, 689]
Visit 100 (Week 99)	Day 693	Days [690, 696]
Visit 101 (Week 100)	Day 700	Days [697, 703]
Visit 102 (Week 101)	Day 707	Days [704, 710]
Visit 103 (Week 102)	Day 714	Days [711, 717]
Visit 104 (Week 103)	Day 721	Days [718, 724]
Visit 105 (Week 104)	Day 728	Days [725, 731]
Visit 106 (Week 105)	Day 735	Days [732, 738]
Visit 107 (Week 106)	Day 742	Days [739, 745]
Visit 108 (Week 107)	Day 749	Days [746, 752]
Visit 109 (Week 108)	Day 756	Days [753, 759]
Visit 110 (Week 109)	Day 763	Days [760, 766]
Visit 111 (Week 110)	Day 770	Days [767, 773]
Visit 112 (Week 111)	Day 777	Days [774, 780]
Visit 113 (Week 112)	Day 784	Days [781, 787]
Visit 114 (Week 113)	Day 791	Days [788, 794]
Visit 115 (Week 114)	Day 798	Days [795, 801]
Visit 116 (Week 115)	Day 805	Days [802, 808]
Visit 117 (Week 116)	Day 812	Days [809, 815]
Visit 118 (Week 117)	Day 819	Days [816, 822]
Visit 119 (Week 118)	Day 826	Days [823, 829]
Visit 120 (Week 119)	Day 833	Days [830, 836]
Visit 121 (Week 120)	Day 840	Days [837, 843]
Visit 122 (Week 121)	Day 847	Days [844, 850]
Visit 123 (Week 122)	Day 854	Days [851, 857]
Visit 124 (Week 123)	Day 861	Days [858, 864]
Visit 125 (Week 124)	Day 868	Days [865, 871]
Visit 126 (Week 125)	Day 875	Days [872, 878]
Visit 127 (Week 126)	Day 882	Days [879, 885]
Visit 128 (Week 127)	Day 889	Days [886, 892]
Visit 129 (Week 128)	Day 896	Days [893, 899]
Visit 130 (Week 129)	Day 903	Days [900, 906]
Visit 131 (Week 130)	Day 910	Days [907, 913]
Visit 132 (Week 131)	Day 917	Days [914, 920]
Visit 133 (Week 132)	Day 924	Days [921, 927]
Visit 134 (Week 133)	Day 931	Days [928, 934]
Visit 135 (Week 134)	Day 938	Days [935, 941]
Visit 136 (Week 135)	Day 945	Days [942, 948]
Visit 137 (Week 136)	Day 952	Days [949, 955]
Visit 138 (Week 137)	Day 959	Days [956, 962]

Table 14.2–1. Weekly Visit Time Windows

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Visit 139 (Week 138)	Day 966	Days [963, 969]
Visit 140 (Week 139)	Day 973	Days [970, 976]
Visit 141 (Week 140)	Day 980	Days [977, 983]
Visit 142 (Week 141)	Day 987	Days [984, 990]
Visit 143 (Week 142)	Day 994	Days [991, 997]
Visit 144 (Week 143)	Day 1001	Days [998, 1004]
Visit 145 (Week 144)	Day 1008	Days [1005, 1011]
Visit 146 (Week 145)	Day 1015	Days [1012, 1018]
Visit 147 (Week 146)	Day 1022	Days [1019, 1025]
Visit 148 (Week 147)	Day 1029	Days [1026, 1032]
Visit 149 (Week 148)	Day 1036	Days [1033, 1039]
Visit 150 (Week 149)	Day 1043	Days [1040, 1046]
Visit 151 (Week 150)	Day 1050	Days [1047, 1053]
Visit 152 (Week 151)	Day 1057	Days [1054, 1060]
Visit 153 (Week 152)	Day 1064	Days [1061, 1067]
Visit 154 (Week 153)	Day 1071	Days [1068, 1074]
Visit 155 (Week 154)	Day 1078	Days [1075, 1081]
Visit 156 (Week 155)	Day 1085	Days [1082, 1088]
Visit 157 (Week 156)	Day 1092	Days [1089, 1095]
Visit 158 (Week 157)	Day 1099	Days [1096, 1102]
Visit 159 (Week 158)	Day 1106	Days [1103, 1109]
Visit 160 (Week 159)	Day 1113	Days [1110, 1116]
Visit 161 (Week 160)	Day 1120	Days [1117, 1123]
Visit 162 (Week 161)	Day 1127	Days [1124, 1130]
Visit 163 (Week 162)	Day 1134	Days [1131, 1137]
Visit 164 (Week 163)	Day 1141	Days [1138, 1144]
Visit 165 (Week 164)	Day 1148	Days [1145, 1151]
Visit 166 (Week 165)	Day 1155	Days [1152, 1158]
Visit 167 (Week 166)	Day 1162	Days [1159, 1165]
Visit 168 (Week 167)	Day 1169	Days [1166, 1172]
Visit 169 (Week 168)	Day 1176	Days [1173, 1179]
Visit 170 (Week 169)	Day 1183	Days [1180, 1186]
Visit 171 (Week 170)	Day 1190	Days [1187, 1193]
Visit 172 (Week 171)	Day 1197	Days [1194, 1200]
Visit 173 (Week 172)	Day 1204	Days [1201, 1207]
Visit 174 (Week 173)	Day 1211	Days [1208, 1214]
Visit 175 (Week 174)	Day 1218	Days [1215, 1221]
Visit 176 (Week 175)	Day 1225	Days [1222, 1228]
Visit 177 (Week 176)	Day 1232	Days [1229, 1235]
Visit 178 (Week 177)	Day 1239	Days [1236, 1242]

Table 14.2–1. Weekly Visit Time Windows

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Visit 179 (Week 178)	Day 1246	Days [1243, 1249]
Visit 180 (Week 179)	Day 1253	Days [1250, 1256]
Visit 181 (Week 180)	Day 1260	Days [1257, 1263]
Visit 182 (Week 181)	Day 1267	Days [1264, 1270]
Visit 183 (Week 182)	Day 1274	Days [1271, 1277]
Visit 184 (Week 183)	Day 1281	Days [1278, 1284]
Visit 185 (Week 184)	Day 1288	Days [1285, 1291]
Visit 186 (Week 185)	Day 1295	Days [1292, 1298]
Visit 187 (Week 186)	Day 1302	Days [1299, 1305]
Visit 188 (Week 187)	Day 1309	Days [1306, 1312]
Visit 189 (Week 188)	Day 1316	Days [1313, 1319]
Visit 190 (Week 189)	Day 1323	Days [1320, 1326]
Visit 191 (Week 190)	Day 1330	Days [1327, 1333]
Visit 192 (Week 191)	Day 1337	Days [1334, 1340]
Visit 193 (Week 192)	Day 1344	Days [1341, 1347]
Visit 194 (Week 193)	Day 1351	Days [1348, 1354]
Visit 195 (Week 194)	Day 1358	Days [1355, 1361]
Visit 196 (Week 195)	Day 1365	Days [1362, 1368]
Visit 197 (Week 196)	Day 1372	Days [1369, 1375]
Visit 198 (Week 197)	Day 1379	Days [1376, 1382]
Visit 199 (Week 198)	Day 1386	Days [1383, 1389]
Visit 200 (Week 199)	Day 1393	Days [1390, 1396]
Visit 201 (Week 200)	Day 1400	Days [1397, 1403]
Visit 202 (Week 201)	Day 1407	Days [1404, 1410]
Visit 203 (Week 202)	Day 1414	Days [1411, 1417]
Visit 204 (Week 203)	Day 1421	Days [1418, 1424]
Visit 205 (Week 204)	Day 1428	Days [1425, 1431]
Visit 206 (Week 205)	Day 1435	Days [1432, 1438]
Visit 207 (Week 206)	Day 1442	Days [1439, 1445]
Visit 208 (Week 207)	Day 1449	Days [1446, 1452]
Visit 209 (Week 208)	Day 1456	Days [1453, 1459]
Visit 210 (Week 209)	Day 1463	Days [1460, 1466]
Visit 211 (Week 210)	Day 1470	Days [1467, 1473]
Visit 212 (Week 211)	Day 1477	Days [1474, 1480]
Visit 213 (Week 212)	Day 1484	Days [1481, 1487]
Visit 214 (Week 213)	Day 1491	Days [1488, 1494]
Visit 215 (Week 214)	Day 1498	Days [1495, 1501]
Visit 216 (Week 215)	Day 1505	Days [1502, 1508]
Visit 217 (Week 216)	Day 1512	Days [1509, 1515]
Visit 218 (Week 217)	Day 1519	Days [1516, 1522]

Table 14.2–1. Weekly Visit Time Windows

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Visit 219 (Week 218)	Day 1526	Days [1523, 1529]
Visit 220 (Week 219)	Day 1533	Days [1530, 1536]
Visit 221 (Week 220)	Day 1540	Days [1537, 1543]
Visit 222 (Week 221)	Day 1547	Days [1544, 1550]
Visit 223 (Week 222)	Day 1554	Days [1551, 1557]
Visit 224 (Week 223)	Day 1561	Days [1558, 1564]
Visit 225 (Week 224)	Day 1568	Days [1565, 1571]
Visit 226 (Week 225)	Day 1575	Days [1572, 1578]
Visit 227 (Week 226)	Day 1582	Days [1579, 1585]
Visit 228 (Week 227)	Day 1589	Days [1586, 1592]
Visit 229 (Week 228)	Day 1596	Days [1593, 1599]
Visit 230 (Week 229)	Day 1603	Days [1600, 1606]
Visit 231 (Week 230)	Day 1610	Days [1607, 1613]
Visit 232 (Week 231)	Day 1617	Days [1614, 1620]
Visit 233 (Week 232)	Day 1624	Days [1621, 1627]
Visit 234 (Week 233)	Day 1631	Days [1628, 1634]
Visit 235 (Week 234)	Day 1638	Days [1635, 1641]
Visit 236 (Week 235)	Day 1645	Days [1642, 1648]
Visit 237 (Week 236)	Day 1652	Days [1649, 1655]
Visit 238 (Week 237)	Day 1659	Days [1656, 1662]
Visit 239 (Week 238)	Day 1666	Days [1663, 1669]
Visit 240 (Week 239)	Day 1673	Days [1670, 1676]
Visit 241 (Week 240)	Day 1680	Days [1677, 1683]
Visit 242 (Week 241)	Day 1687	Days [1684, 1690]
Visit 243 (Week 242)	Day 1694	Days [1691, 1697]
Visit 244 (Week 243)	Day 1701	Days [1698, 1704]
Visit 245 (Week 244)	Day 1708	Days [1705, 1711]
Visit 246 (Week 245)	Day 1715	Days [1712, 1718]
Visit 247 (Week 246)	Day 1722	Days [1719, 1725]
Visit 248 (Week 247)	Day 1729	Days [1726, 1732]
Visit 249 (Week 248)	Day 1736	Days [1733, 1739]
Visit 250 (Week 249)	Day 1743	Days [1740, 1746]
Visit 251 (Week 250)	Day 1750	Days [1747, 1753]
Visit 252 (Week 251)	Day 1757	Days [1754, 1760]
Visit 253 (Week 252)	Day 1764	Days [1761, 1767]
Visit 254 (Week 253)	Day 1771	Days [1768, 1774]
Visit 255 (Week 254)	Day 1778	Days [1775, 1781]
Visit 256 (Week 255)	Day 1785	Days [1782, 1788]
Visit 257 (Week 256)	Day 1792	Days [1789, 1795]
Visit 258 (Week 257)	Day 1799	Days [1796, 1802]

Table 14.2–1. Weekly Visit Time Windows

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Visit 259 (Week 258)	Day 1806	Days [1803, 1809]
Visit 260 (Week 259)	Day 1813	Days [1810, 1816]
Visit 261 (Week 260)	Day 1820	Days [1817, 1823]
End of study	Final or termination visit during the study period	

a Relative to the date of the first dose of the study drug. For example, Day 1 = the date of the first dose of study drug.

Table 14.2–2 below presents the end-of-quarter visits assigned for efficacy and safety analyses corresponding to the range of treatment days (window) in the study during which an actual visit may have occurred.

Table 14.2–2. End-of-Quarter Visit Time Windows

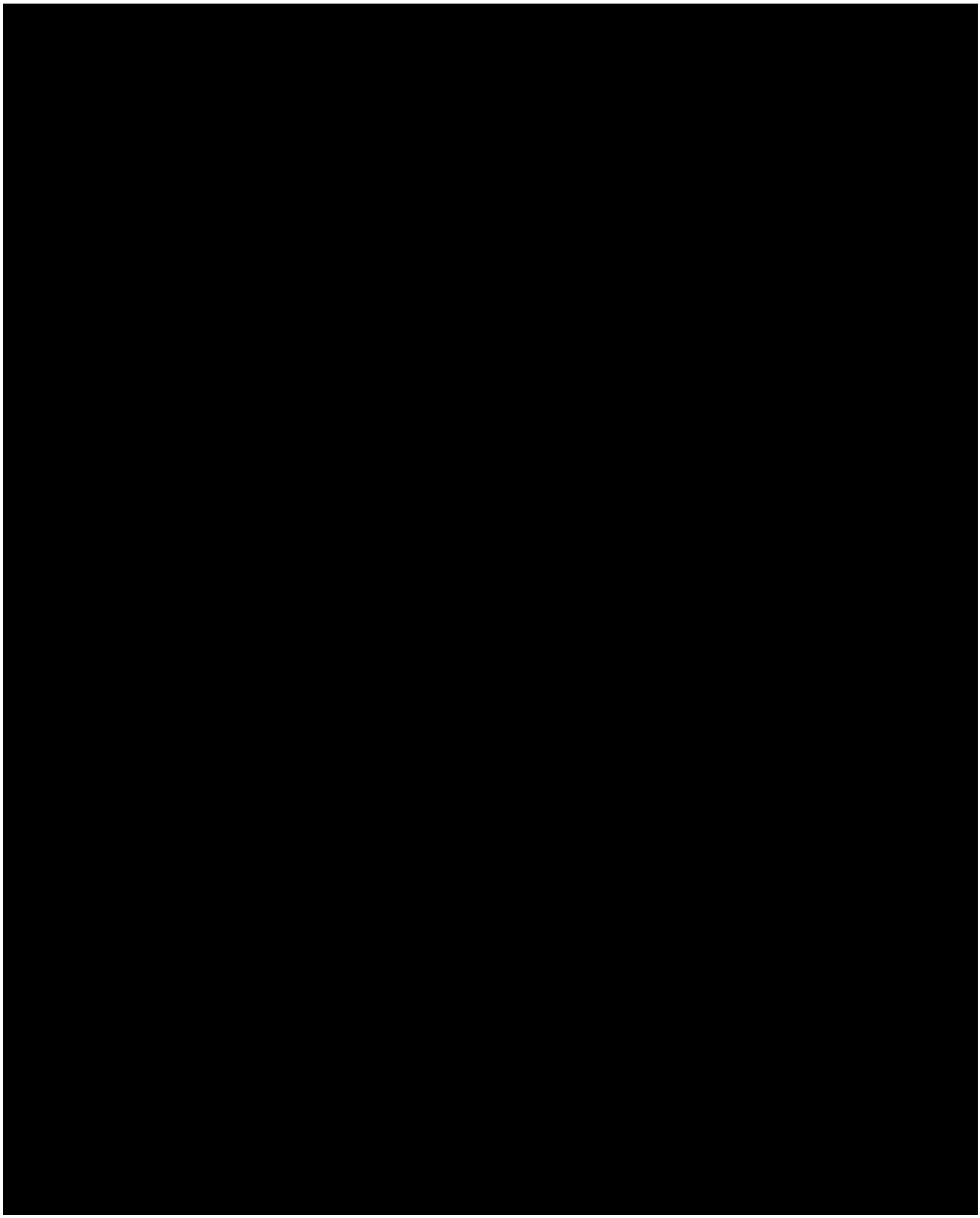
Derived Visit	***Scheduled Visit Day[a]***	***Window***
Baseline		**the last non-missing assessment before the first dose of study drug**
Visit 1 (Day 1)	Day 1	Dosing Day Day = 1
Visit 2 (Year 1 End of Quarter 1)	Day 91	Days [2, 136]
Visit 3 (Year 1 End of Quarter 2)	Day 182	Days [137, 227]
Visit 4 (Year 1 End of Quarter 3)	Day 273	Days [228, 318]
Visit 5 (Year 1 End of Quarter 4)	Day 364	Days [319, 409]
Visit 6 (Year 2 End of Quarter 1)	Day 455	Days [410, 500]
Visit 7 (Year 2 End of Quarter 2)	Day 546	Days [501, 591]
Visit 8 (Year 2 End of Quarter 3)	Day 637	Days [592, 682]
Visit 9 (Year 2 End of Quarter 4)	Day 728	Days [683, 773]
Visit 10 (Year 3 End of Quarter 1)	Day 819	Days [774, 864]
Visit 11 (Year 3 End of Quarter 2)	Day 910	Days [865, 955]
Visit 12 (Year 3 End of Quarter 3)	Day 1001	Days [956, 1046]
Visit 13 (Year 3 End of Quarter 4)	Day 1092	Days [1047, 1137]
Visit 14 (Year 4 End of Quarter 1)	Day 1183	Days [1138, 1228]
Visit 15 (Year 4 End of Quarter 2)	Day 1274	Days [1229, 1319]
Visit 16 (Year 4 End of Quarter 3)	Day 1365	Days [1320, 1410]
Visit 17 (Year 4 End of Quarter 4)	Day 1456	Days [1411, 1501]
Visit 18 (Year 5 End of Quarter 1)	Day 1547	Days [1502, 1592]
Visit 19 (Year 5 End of Quarter 2)	Day 1638	Days [1593, 1683]
Visit 20 (Year 5 End of Quarter 3)	Day 1729	Days [1684, 1774]
Visit 21 (Year 5 End of Quarter 4)	Day 1820	Days [1775, 1865]
End of study	Final or termination visit during the study period	

a Relative to the date of the first dose of the study drug. For example, Day 1 = the date of the first dose of study drug.

Visit Day is calculated as (visit date - date of the first dose of the study drug + 1). If a subject has 2 or more values for a given endpoint within the same window, the value with collection date closest to the scheduled day will be used for analysis; if there are 2 values whose collection dates are equidistant from the scheduled day, the value corresponding to the later date will be used for analysis.

14.3 DERIVED EFFICACY VARIABLES

Unless specified otherwise, the total score at a particular visit will be calculated using (sum of non-missing items) × (total number of items) / (number of non-missing items) only if the number of missing items is less than or equal to the specified number for each variable; if the number of missing items is greater than the specified number for each variable, the total score will be set to missing.



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[redacted]

14.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a subject has repeated assessments before the start of the first treatment, the results from the final non-missing assessment made prior to the start of the study treatment will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

14.5 MISSING DATE OF STUDY DRUG

When the date of the last dose of the study drug during the study treatment phase is missing for a subject in the Safety Population all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last available dosing record date will be used as the last dose date.

14.6 MISSING SEVERITY TO STUDY DRUG IN ADVERSE EVENTS

If the severity is missing for an AE started on or after the date of the first dose of the study drug, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summary, while the actual values should be presented in data listings.

14.7 MISSING RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the relationship to the study drug is missing for an AE started on or after the date of the first dose of the study drug, a causality of "Related" will be assigned. The imputed values for relationship to the study drug will be used for incidence summary, while the actual values should be presented in data listings.

14.8 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date is incomplete (ie, partial missing).

Missing day and month

- If the year is the same as the year of the date of the first dose of study drug, then the day and month of the date of the first dose of study drug will be assigned to the missing fields.

- If the year is before the year of the date of the first dose of study drug, then December 31 will be assigned to the missing fields.

- If the year is after the year of the date of the first dose of study drug, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year are the same as the month and year of the date of the first dose of study drug, then the day of the first dose of study drug will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of study drug or if both years are the same but the month is before the month of the date of the first dose of study drug, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the first dose of study drug or if both years are the same but the month is after the month of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day.

- If the stop date is after the date of the first dose of study drug, the date of the first dose of study drug will be assigned to the missing start date

- If the stop date is before the date of the first dose of study drug, the stop date will be assigned to the missing start date

14.9 MISSING DATE INFORMATION FOR CONCOMITANT MEDICATIONS

For concomitant medications, incomplete (ie, partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

Incomplete Start Date
The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of study drug, then the day and month of the date of the first dose will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the date of the first dose of study drug, then December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of study drug, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study drug, then the day of the first dose will be assigned to the missing day.

- If either the year is before the year of the date of the first dose of study drug or if both years are the same but the month is before the month of the date of the first dose of study drug, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the first dose of study drug or if both years are the same but the month is after the month of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day.

Incomplete Stop Date
For the purpose of deriving a concomitant medication flag, the following rules will be applied to impute the missing numerical fields. If the date of the last dose of study drug is missing, impute it as described in Section 14.5. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the date of the last dose of study drug, then the day and month of the date of the last dose will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the date of the last dose of study drug, then December 31 will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the date of the last dose of study drug, then January 1 will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of study drug, then the day of the last dose will be assigned to the missing day.

- If either the year is before the year of the date of the last dose of study drug or if both years are the same but the month is before the month of the date of the last dose of study drug, then the last day of the month will be assigned to the missing day.

- If either the year is after the year of the date of the last dose of study drug or if both years are the same but the month is after the month of the date of the last dose of study drug, then the first day of the month will be assigned to the missing day.

15.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no changes to the analyses specified in the final protocol Amendment 3 (version dated 23 Nov 2016).

16.0 REFERENCES

Endicott J, Nee J, Harrison W, Blumenthal R. Quality of Life Enjoyment and Satisfaction Questionnaire: A New Measure. Psychopharmacology Bull. 1993; 29(2):321-6.

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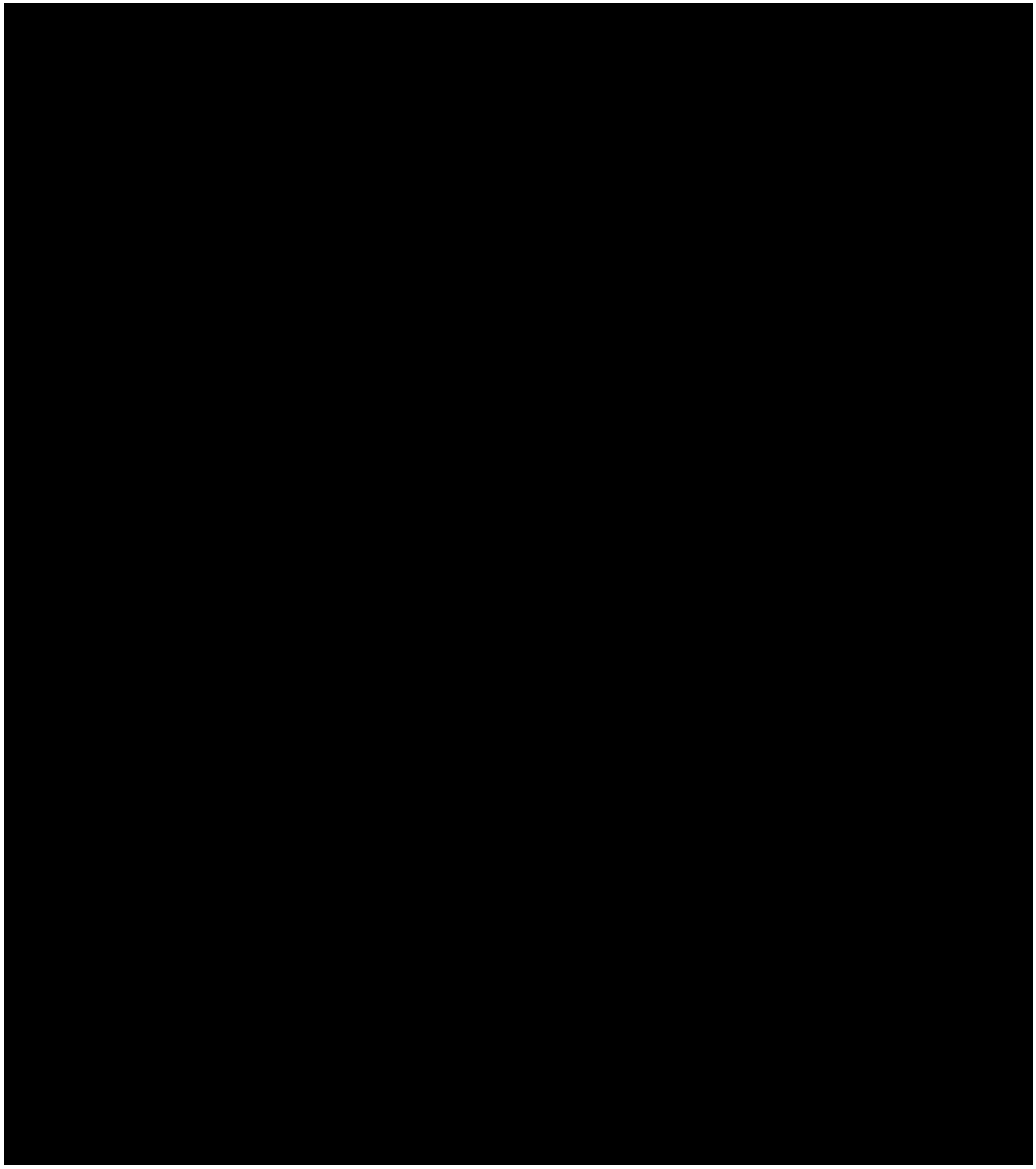

18.0 HISTORY OF CHANGES

Date	Section	Description
12/11/2018	NA	Initial version approval.