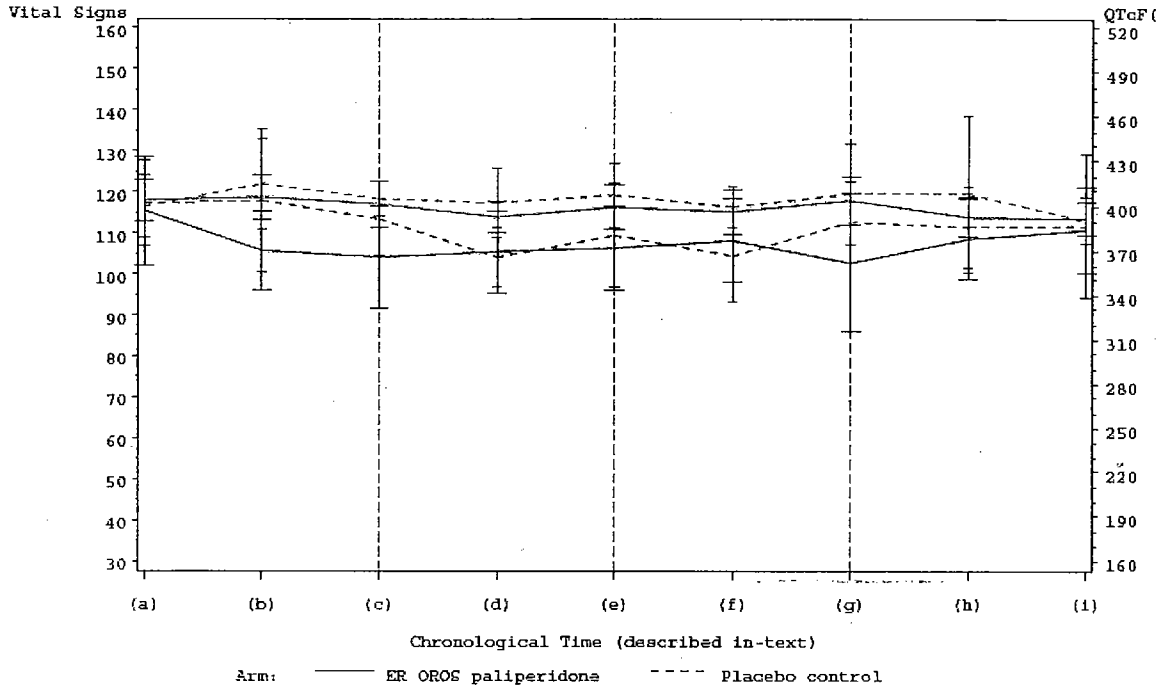
R076477—P01—1005: Mean+ —SD plots on Raw Data for Vital Signs Parameters and QT

Vital Signs Parameter=SBP(mmHg) when Standing+2m Race=WHITE

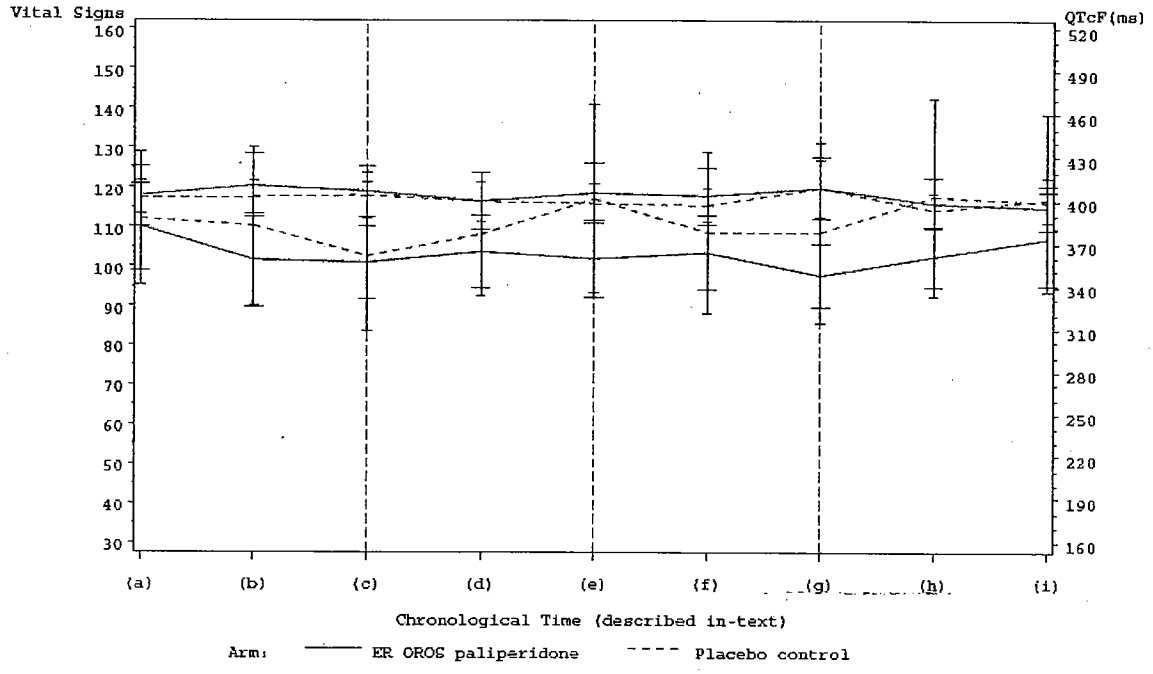


Vertical Lines indicate Tmax, Black used for Vital Signs, Green for QTcF

Appears This Way
On Original

R076477-P01-1005: Mean+-SD plots on Raw Data for Vital Signs Parameters and QTcF

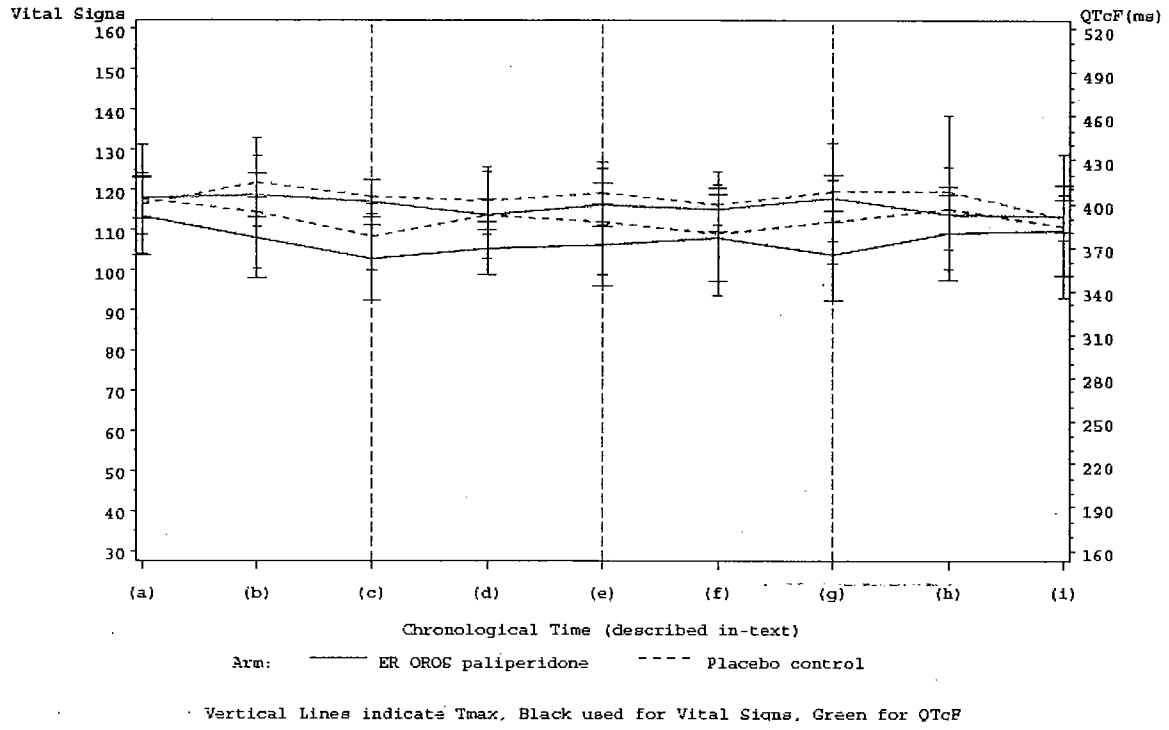
Vital Signs Parameter=SBP(mmHg) when Supine Race=ASIAN



Vertical Lines indicate Tmax, Black used for Vital Signs, Green for QTcF

Appears This Way
On Original

R076477-P01-1005: Mean+-SD plots on Raw Data for Vital Signs Parameters and QTcF



Note the table below shows comparable PK properties when comparing "Asian" to "white" subjects, yet the "asian" group had more AEs of postural dizziness than the "white" group following Pal treatment (29% compared to 13% in these groups, respectively).

Appears This Way
On Original

Table 1: Comparison of paliperidone plasma pharmacokinetic parameters of both ethnic groups

	Caucasian	Japanese	Japanese/ Caucasian ratio[1] (%)	90% CI (%)
3 mg SD data				
n	24	23	47	47
t_{max} (h)	25.02 ± 2.90	22.86 ± 4.27	-	-
C_{max} (ng/mL)	5.59 ± 2.84	6.60 ± 2.19	129.46	101.50 - 165.13
AUC_{0-24h} (ng.h/mL)	59.4 ± 27.4	79.9 ± 24.3	-	-
AUC_{∞} (ng.h/mL)	218 ± 114[2]	241 ± 84.2	118.70[5]	93.85 - 150.12[5]
$t_{1/2}$ (h)	20.8 ± 4.82[3]	19.6 ± 3.45[4]	-	-
CL/F (mL/min)	306 ± 194[2]	237 ± 97.2	-	-
3 mg MD data				
n	23	23	46	46
$C_{trough\ Day\ 11}$ (ng/mL)	11.0 ± 7.05	10.2 ± 4.12	-	-
$t_{max,ss}$ (h)	13.14 ± 8.92	14.26 ± 9.38	-	-
$C_{max,ss}$ (ng/mL)	12.5 ± 7.05	11.8 ± 3.95	102.56	82.63 - 127.30
$C_{avg,ss}$ (ng/mL)	10.1 ± 5.82	9.60 ± 3.26	-	-
$AUC_{0-24,ss}$ (ng.h/mL)	243 ± 140	230 ± 78.2	101.97	82.46 - 126.11
FI (%)	45.8 ± 18.4	42.5 ± 12.6	-	-
$t_{1/2}$ (h)	27.6 ± 4.20	25.4 ± 3.51	-	-
CL/F (mL/min)	265 ± 128	242 ± 80.8	-	-
6 mg SD data				
n	24	23	47	47
t_{max} (h)	23.80 ± 1.94	22.89 ± 3.76	-	-
C_{max} (ng/mL)	12.7 ± 6.19	13.8 ± 8.22	105.37	82.92 - 133.89
AUC_{0-24h} (ng.h/mL)	142 ± 57.8	173 ± 87.6	-	-
AUC_{∞} (ng.h/mL)	513 ± 256	565 ± 368[2]	109.80[5]	86.92 - 138.69[5]
$t_{1/2}$ (h)	23.6 ± 3.74	22.9 ± 6.48	-	-
CL/F (mL/min)	246 ± 132	216 ± 78.6[2]	-	-

[1] The presented ratio is calculated as the geometric mean. Ratio and CI are constructed on log-scale and backtransformed. [2] n=22. [3] n=23. [4] n=24. [5] n=46.

C. Vital sign and Safety Related Results from a Food Effect Phase I Studies P01-1008 and P01-1012 with Vital Sign Assessments Conducted hourly Post-dose

The following was also provided in Section 7.1.8.3.1 of this review but is copied below for the convenience of the reader and since it relates to the topic of cardiovascular effects near Tmax, discussed in previous sections.

Caveat on Phase III results on BP and Timing of Assessments Relative to Dose, PK and other Potential Time-dependent Confounding Variable and Relative to Fed Versus Fasted Conditions.

The sponsor was asked to provide data for vital sign results near Tmax ideally from a schizophrenia trial but the Phase III trials and the QT prolongation study, Trial –SCH-1009 did not include assessments at multiple time-points in order to enhance capturing Tmax or other time-dependent confounding variables. Study -1009 only included baseline and end-of-study vital sign assessments (this study is described under Section 7.1.12). The sponsor provided results of Study SCH-1009 in response to this inquiry which is described in the previous

subsection of this section (Section 7.1.13 B) but had a limited number of subjects and used 3 and 6 mg dose-levels. Also vital signs were only conducted at pre-dose, 24 and 48 hour post-dose time-points on selected treatment days.

It is first notable that both food effect studies did not include ECG assessments during study drug exposure (end-of-study and screening assessments were conducted).

P01-1008 SD 15 mg Pal (and Phase III formulations) Food Effect study (in bed for up to 36 hours post-dose).

The undersigned found results of Study P01-1008 in the N000 submission that had vital sign assessments hourly over 36 hours with some additional time-points thereafter at 48, 72 and 96 hours post-dose. This study used the 15 mg Phase III formulation in fasted state, 15 mg in fasted state and 15 mg fed state which should the following results on supine BP:

- *Increase BP (from predose values) occurred in all groups starting near 29 or 30 hours post-dose in under each fasted treatment condition and near 25 hours post-dose in the fed condition that appeared to peak at 36 hours (but possibly later since the next assessment did not occur until 48 hours post-dose) in each of the fasted conditions and in the fed condition.*
- *The maximum mean increase in BP (systolic) observed at 36 hours was highest in the fed- condition (13.5 mmHg), next highest in the fasted condition (9.9 mmHg) and lowest in the Phase III fasted condition (7.3 mmHg).*
- *Peak BP increases may be in part be reflecting the time-point upon which subjects were not longer required to be in bed (following their 36 hour PK sampling). Yet, differences were observed between treatment conditions with the fed state being associated with the greatest increase in BP. Maximum mean increase in sBP may be even greater than the above values since the above values were found in the last hourly vital sign assessment (at 36 hours-post-dose) while the next hourly assessment did not occur until 48hours post-dose with little to no change in BP observed at this time-point.*
- *Given the above findings it is critical to note that subjects were to remain in bed through the 36 hour time-point (for blood sampling) and subjects received lunch at 4 hours PK sampling). Dosing was given in the morning.*
- *Group mean decreases occurred in all 3 treatment conditions at most time-points during the first 24 hours or longer after dosing with the greatest decreases occurring in the Phase III fasted condition..*

Only selected sections of this CSR was reviewed (SAEs, ADOs, Attachment 5.1 on vital sign results and other selected sections).

The following table shows the results discussed above (taken from Attachment 5.1 in the CSR of this Phase I study).

STUDY JJPRD R076477-P01-1008

Output DVS.01: Vital Signs - Descriptive Statistics (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change N	change Mean	change SE	change SD	change Med	change Min	change Max
Supine SBP(mmHg)														
SCREENING														
Screening	90	123.0	9.58	123.5	103	140								
PH3 FASTED														
Predose	66	117.4	9.28	116.0	100	141								
1H	66	113.6	10.23	114.0	89	143	117.4	66	-3.8	1.09	8.85	-3.5	-33	39
2H	66	113.9	9.44	113.5	92	142	117.4	66	-3.5	0.99	8.06	-4.0	-21	16
3H	66	114.9	9.26	114.0	96	138	117.1	65	-2.6	1.07	8.60	-1.0	-22	12
4H	66	114.0	8.79	113.5	99	136	117.4	66	-3.3	1.04	8.43	-4.0	-30	15
5H	66	116.8	9.15	116.0	99	142	117.4	66	-0.5	1.06	8.63	-1.0	-21	19
6H	66	114.1	9.83	113.0	94	140	117.4	66	-3.3	1.16	9.41	-2.0	-27	21
7H	66	110.1	9.76	110.0	90	154	117.4	66	-7.2	1.25	10.16	-7.5	-29	27
8H	66	108.7	8.52	108.0	91	140	117.4	66	-8.6	1.14	9.30	-9.5	-29	20
9H	66	108.6	8.70	107.0	93	139	117.3	65	-8.9	1.12	9.05	-9.0	-33	12
10H	66	110.6	10.05	108.5	94	154	117.4	66	-6.7	1.26	10.22	-7.0	-25	27
11H	66	113.3	9.55	112.0	97	130	117.4	66	-4.1	0.99	8.01	-4.0	-24	13
12H	66	113.6	8.99	114.0	94	136	117.4	66	-3.8	1.22	9.89	-3.0	-27	19
13H	66	110.4	7.89	109.0	97	132	117.1	65	-6.9	1.02	8.22	-6.0	-28	12
14H	66	111.5	11.21	109.0	92	140	117.4	66	-5.9	1.15	9.31	-5.5	-30	22
15H	66	109.0	7.85	110.0	90	129	117.4	66	-8.4	1.17	9.48	-8.0	-29	15
16H	66	108.7	7.70	108.0	93	127	117.4	66	-8.7	1.08	8.80	-7.5	-29	12
17H	66	107.5	7.95	107.0	88	128	117.4	66	-9.9	1.13	9.19	-8.0	-29	11
18H	66	108.1	8.63	107.0	84	129	117.4	66	-9.3	1.18	9.56	-9.0	-35	11
19H	66	109.1	10.46	107.0	87	138	117.4	66	-8.3	1.19	9.68	-8.0	-29	15
20H	66	109.7	8.83	111.0	92	131	117.4	66	-7.6	1.16	9.46	-9.0	-24	19
21H	66	108.9	8.56	109.0	87	129	117.4	66	-8.5	1.15	9.30	-8.0	-31	17
22H	66	110.0	9.10	109.0	92	127	117.4	66	-7.3	1.26	10.21	-7.0	-35	16
23H	66	109.9	9.46	110.0	77	127	117.4	66	-7.5	1.33	10.79	-7.0	-44	16
24H	66	113.5	8.97	112.0	97	138	117.4	66	-3.8	1.12	9.13	-4.0	-21	15
25H	66	116.9	8.68	117.0	96	137	117.4	66	-0.6	1.08	8.76	-0.5	-19	18
26H	66	118.3	10.23	118.5	97	143	117.4	66	1.0	1.29	10.36	2.0	-22	23
27H	66	116.9	10.37	116.0	94	150	117.4	66	-0.6	1.23	10.02	1.0	-23	29
28H	66	115.2	8.72	114.5	94	135	117.4	66	-2.1	1.13	9.21	-3.5	-22	21
29H	66	117.9	11.49	117.5	100	176	117.4	66	0.5	1.39	11.29	-1.0	-21	43
30H	66	117.7	11.04	117.5	99	154	117.4	66	0.3	1.28	10.41	-1.5	-26	22
31H	66	118.7	11.00	118.0	99	156	117.4	66	1.3	1.44	11.67	1.5	-27	24
32H	66	118.0	9.57	116.0	102	140	117.4	66	0.7	1.09	8.84	1.0	-29	20
33H	66	118.1	9.38	118.0	101	143	117.4	66	0.8	1.16	9.41	1.0	-27	25
34H	66	121.4	9.43	121.5	104	152	117.4	66	4.1	1.14	9.25	3.5	-23	31
35H	66	121.7	10.15	121.0	105	160	117.4	66	4.3	1.20	9.72	4.0	-20	39
36H	66	124.7	10.78	124.0	103	157	117.4	66	7.3	1.20	9.72	7.0	-15	36
48H	66	116.5	9.44	116.0	98	141	117.4	66	-0.8	1.12	9.09	-1.5	-22	25
72H	66	118.7	9.85	117.5	99	148	117.4	66	1.3	1.02	8.25	1.0	-22	18
96H	66	120.3	9.69	118.0	98	141	117.4	66	2.9	1.12	9.11	3.0	-15	26
FASTED														
Predose	63	116.2	7.80	114.0	104	134								
1H	63	112.8	8.91	112.0	93	143	116.2	63	-3.4	1.19	9.33	-5.0	-29	23
2H	63	114.5	10.01	114.0	95	143	116.2	63	-1.8	1.44	11.41	-3.0	-22	33
3H	63	114.4	9.80	115.0	93	133	116.2	63	-1.9	1.19	9.44	-3.0	-20	22
4H	63	114.7	9.51	115.0	94	140	116.2	63	-1.5	1.04	8.25	-1.0	-18	24
5H	63	115.7	7.56	116.0	97	134	116.3	62	-0.6	1.20	9.48	0.5	-28	23
6H	63	114.0	8.02	113.0	93	133	116.4	62	-2.7	1.22	9.64	-3.0	-32	18
7H	63	108.9	8.73	108.0	89	134	116.2	63	-7.4	1.18	9.33	-7.0	-32	12
8H	63	108.0	10.33	106.0	85	141	116.2	63	-8.3	1.30	10.33	-8.0	-30	19
9H	63	108.5	9.88	107.0	79	134	116.2	63	-7.8	1.34	10.60	-7.0	-34	27
10H	63	110.6	9.38	110.0	85	137	116.1	62	-5.8	1.13	8.89	-5.5	-27	15
11H	63	113.5	10.91	112.0	90	146	116.2	63	-2.7	1.31	10.39	-4.0	-26	27
12H	63	112.9	9.91	112.0	93	135	116.3	63	-3.4	1.29	10.23	-2.0	-25	23
13H	63	111.6	9.87	112.0	90	140	116.2	63	-4.7	1.38	10.94	-7.0	-24	35
14H	63	110.3	9.26	111.0	87	127	116.3	62	-5.9	1.14	8.97	-5.5	-24	17
15H	63	109.7	10.75	110.0	84	129	116.2	63	-6.5	1.28	10.17	-7.0	-27	18
16H	63	109.0	9.38	109.0	90	130	116.2	63	-7.3	1.15	9.09	-7.0	-22	16
17H	63	108.4	10.21	109.0	90	134	116.2	63	-7.9	1.12	8.89	-8.0	-27	11

18H	63	110.2	10.11	110.0	88	134	116.2	63	-6.0	1.21	9.62	-6.0	-26	15
19H	63	110.2	9.35	110.0	94	141	116.2	63	-6.0	1.18	9.38	-6.0	-29	23
20H	63	109.2	8.15	110.0	93	131	116.2	63	-7.0	1.09	8.64	-8.0	-27	14
21H	63	110.4	9.92	110.0	89	134	116.2	63	-5.9	1.23	9.78	-6.0	-33	15
22H	63	111.7	11.55	110.0	93	164	116.2	63	-4.5	1.69	13.32	-6.0	-30	57
23H	63	110.6	7.87	109.0	96	129	116.2	63	-5.7	1.21	9.60	-5.0	-30	22
24H	63	113.7	10.75	114.0	90	157	116.2	63	-2.6	1.47	11.64	-4.0	-38	28
25H	63	117.0	8.71	117.0	94	138	116.2	63	0.8	1.30	10.28	1.0	-31	30
26H	63	117.5	11.23	117.0	94	147	116.2	63	1.2	1.54	12.19	2.0	-31	29
27H	63	115.4	9.96	115.0	97	145	116.2	63	-0.9	1.16	9.19	0.0	-18	19
28H	63	115.1	9.66	114.0	94	144	116.2	63	-1.2	1.13	8.97	0.0	-20	20
29H	63	115.7	9.71	115.0	95	135	116.2	63	-0.5	1.13	8.93	-1.0	-18	21
30H	62	118.8	11.71	117.0	94	165	116.1	62	2.7	1.30	10.26	1.5	-15	36
31H	63	118.3	9.23	118.0	101	142	116.2	63	2.1	1.08	8.55	3.0	-19	18
32H	63	117.7	10.22	117.0	96	140	116.2	63	1.5	1.15	9.09	2.0	-23	24
33H	63	120.1	9.33	120.0	99	142	116.2	63	3.9	1.09	8.66	4.0	-16	26
34H	63	122.5	10.59	121.0	101	153	116.2	63	6.2	1.20	9.52	7.0	-18	29
35H	63	122.9	10.93	123.0	96	150	116.2	63	6.7	1.31	10.38	6.0	-22	39
36H	63	126.1	11.71	126.0	102	155	116.2	63	9.9	1.40	11.08	9.0	-16	45
48H	63	117.3	7.73	117.0	99	134	116.2	63	1.1	1.00	7.93	0.0	-20	22
72H	63	118.6	11.31	118.0	102	157	116.2	63	2.4	1.35	10.74	2.0	-16	33
96H	63	117.8	10.21	114.0	101	145	116.2	63	1.5	1.11	8.81	1.0	-18	25
[redacted] FED														
Predose	72	115.5	7.93	114.0	101	138								
1H	72	116.2	10.11	116.5	95	156	115.5	72	0.7	0.94	8.00	1.0	-15	30
2H	72	114.7	11.04	115.0	91	150	115.5	72	-0.8	1.20	10.21	0.0	-22	33
3H	72	112.8	8.60	112.0	94	133	115.5	72	-2.8	0.83	7.01	-2.0	-20	10
4H	72	116.1	10.15	115.5	94	152	115.5	72	0.5	0.91	7.71	1.0	-14	24
5H	72	118.4	9.45	118.0	100	142	115.5	72	2.9	1.08	9.17	1.5	-19	31
6H	72	116.5	10.39	116.0	99	144	115.5	72	0.9	1.09	9.27	0.0	-24	25
7H	72	111.8	8.55	112.0	86	135	115.5	72	-3.7	1.06	8.99	-4.0	-27	22
8H	72	110.4	8.03	109.0	95	132	115.5	72	-5.1	1.10	9.34	-4.5	-28	20
9H	72	110.5	9.00	110.5	90	137	115.5	72	-5.1	1.07	9.10	-5.0	-36	18
[redacted] FED														
10H	72	111.2	9.79	111.5	86	134	115.5	71	-4.4	1.28	10.75	-6.0	-44	22
11H	72	115.0	8.76	115.0	97	145	115.5	72	-0.5	1.04	8.84	-1.0	-24	33
12H	72	114.7	11.10	115.0	95	154	115.5	72	-0.8	1.38	11.67	-1.0	-31	40
13H	72	112.9	9.69	113.0	92	135	115.6	71	-2.5	1.13	9.49	-3.0	-29	31
14H	72	112.1	10.10	110.0	92	133	115.5	72	-3.5	1.19	10.11	-4.5	-28	20
15H	72	111.2	8.44	111.0	91	130	115.5	72	-4.4	1.10	9.36	-3.5	-25	16
16H	72	111.0	10.10	110.0	90	136	115.5	72	-4.5	1.36	11.55	-3.0	-34	27
17H	72	108.1	9.34	108.0	89	131	115.5	72	-7.4	1.18	9.99	-7.0	-30	19
18H	72	110.8	10.48	109.0	88	138	115.5	72	-4.7	1.16	9.88	-4.0	-26	18
19H	72	109.7	9.56	109.0	90	129	115.5	72	-5.8	1.15	9.79	-5.5	-28	17
20H	72	110.3	9.02	110.0	90	132	115.5	72	-5.3	1.11	9.44	-5.0	-23	19
21H	72	110.9	9.74	111.0	94	145	115.5	72	-4.6	1.15	9.79	-6.0	-20	31
22H	72	111.6	10.48	111.5	86	139	115.5	72	-3.9	1.34	11.40	-5.5	-28	25
23H	72	112.2	8.97	112.0	90	138	115.5	72	-3.4	1.22	10.37	-2.0	-25	22
24H	72	115.3	9.20	115.0	94	143	115.5	72	-0.2	1.09	9.21	0.0	-20	25
25H	72	118.6	11.10	117.0	95	150	115.5	72	3.1	1.29	10.99	2.5	-22	32
26H	72	118.3	10.90	115.5	99	150	115.5	72	2.8	1.39	11.77	1.0	-25	36
27H	72	116.1	9.37	115.0	96	147	115.5	72	0.5	1.28	10.84	-0.5	-24	27
28H	72	116.5	9.34	116.0	94	154	115.5	72	1.0	1.29	10.99	2.0	-20	42
29H	72	120.4	10.32	119.5	88	154	115.5	72	4.8	1.37	11.63	4.0	-23	42
30H	71	120.4	11.30	119.0	92	162	115.4	71	5.0	1.33	11.19	4.0	-27	50
31H	71	120.8	10.84	120.0	97	163	115.6	71	5.2	1.41	11.90	3.0	-22	51
32H	72	121.5	10.49	121.5	97	154	115.5	72	6.0	1.33	11.28	5.0	-17	42
33H	72	123.9	10.93	123.0	107	162	115.5	72	8.4	1.24	10.49	7.0	-20	42
34H	71	124.7	11.75	122.0	103	164	115.6	71	9.1	1.53	12.92	8.0	-18	52
35H	72	126.2	9.94	125.0	105	150	115.5	72	10.7	1.21	10.26	9.5	-15	38
36H	70	128.8	11.74	127.0	106	166	115.3	70	13.5	1.46	12.22	11.5	-12	48
48H	71	119.2	9.81	118.0	99	148	115.6	71	3.6	1.24	10.45	3.0	-23	31
72H	71	118.2	9.37	117.0	97	143	115.6	71	2.6	1.25	10.52	3.0	-19	32
96H	71	119.2	10.44	118.0	99	151	115.6	71	3.6	1.21	10.19	2.0	-18	33

Supine HR showed mean increases that appeared to coincide with the above mean BP increases as shown in the following (taken from Attachment 5.1 of the CSR):

STUDY JJPRD R076477-P01-1008

Output DVS.01: Vital Signs - Descriptive Statistics

Analysis Set: Safety

							Base	change					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
Supine pulse(/min)														

PH3 FASTED														
Predose	66	58.3	8.46	58.5	44	90								
1H	66	56.8	6.96	56.0	42	77	58.3	66	-1.5	0.93	7.52	-0.5	-33	11
2H	66	57.5	7.92	57.0	43	77	58.3	66	-0.8	1.09	8.74	0.0	-35	23
3H	65	56.2	7.59	56.0	43	78	58.6	64	-2.5	1.10	8.79	-2.0	-40	20
4H	66	58.1	8.23	58.0	42	87	58.3	66	-0.2	0.90	7.30	0.5	-18	24
5H	66	67.1	8.06	66.0	54	93	58.3	66	8.8	1.15	9.30	9.0	-11	37
6H	66	67.9	9.74	67.0	50	104	58.3	66	9.6	1.32	10.69	10.0	-20	35
7H	66	62.7	9.69	61.5	44	97	58.3	66	4.4	1.20	9.73	5.0	-20	28
8H	66	60.1	8.99	60.0	43	98	58.3	66	1.8	1.18	9.55	2.0	-30	29
9H	66	60.8	9.35	60.0	43	85	58.0	65	2.5	1.22	9.83	2.0	-27	37
10H	66	59.3	7.76	59.0	46	77	58.3	66	1.0	0.92	7.45	1.5	-19	17
11H	66	65.5	8.48	64.0	49	87	58.3	66	7.2	1.13	9.15	9.0	-23	36
12H	66	63.7	8.94	63.5	44	94	58.3	66	5.4	1.11	8.99	4.0	-22	25
13H	66	59.2	7.56	59.5	45	84	58.4	65	0.9	1.00	8.04	1.0	-25	28
14H	66	58.9	8.41	58.0	40	90	58.3	66	0.6	1.23	9.95	-1.0	-21	32
15H	66	57.3	8.90	57.0	40	96	58.3	66	-1.0	1.15	9.32	-0.5	-24	33
16H	66	55.6	9.14	54.0	40	89	58.3	66	-2.7	1.14	9.27	-2.5	-30	20
17H	66	55.8	8.95	55.5	38	84	58.3	66	-2.5	1.02	8.32	-3.0	-19	18
18H	66	56.8	10.17	55.5	40	86	58.3	66	-1.5	1.12	9.10	-2.0	-25	27
19H	66	56.2	9.14	55.5	40	86	58.3	66	-2.1	1.05	8.50	-2.5	-20	29
20H	66	57.3	11.08	56.5	39	100	58.3	66	-0.9	1.36	11.04	-1.5	-26	31
21H	66	56.8	9.25	57.0	40	99	58.3	66	-1.5	1.09	8.84	-1.0	-26	30
22H	66	56.9	10.15	56.0	37	97	58.3	66	-1.4	1.09	8.84	-1.5	-19	28
23H	66	59.7	9.66	58.0	41	97	58.3	66	1.4	1.24	10.04	0.0	-29	32
24H	66	66.0	13.67	64.5	43	123	58.3	66	7.7	1.62	13.15	7.0	-28	54
25H	66	68.7	11.19	67.0	49	111	58.3	66	10.4	1.21	9.81	10.0	-11	42
26H	66	73.5	11.76	70.0	54	117	58.3	66	15.2	1.27	10.31	15.0	-8	48
27H	66	70.0	11.66	69.0	50	117	58.3	66	11.7	1.30	10.54	10.0	-7	48
28H	66	69.8	12.54	68.0	49	113	58.3	66	11.5	1.68	13.68	9.0	-16	56
29H	66	75.3	13.29	73.5	55	130	58.3	66	17.0	1.71	13.87	15.0	-8	61
30H	66	74.8	12.41	74.0	53	122	58.3	66	16.5	1.49	12.12	15.0	-5	53
31H	66	73.2	11.44	74.0	50	119	58.3	66	14.9	1.42	11.50	15.0	-15	50
32H	66	69.0	13.09	68.0	50	127	58.3	66	10.7	1.57	12.77	8.0	-18	58
33H	66	67.2	11.65	65.0	51	115	58.3	66	8.9	1.35	10.94	8.0	-15	46
34H	66	65.7	11.38	65.0	45	111	58.3	66	7.4	1.42	11.50	7.5	-20	42
35H	66	72.7	12.11	72.0	54	113	58.3	66	14.4	1.42	11.51	13.0	-15	48
36H	66	75.7	11.51	75.0	56	116	58.3	66	17.4	1.38	11.21	16.0	-9	48
48H	66	66.2	10.05	66.0	45	99	58.3	66	7.9	1.23	9.96	7.5	-20	30
72H	66	64.2	9.22	63.0	46	96	58.3	66	5.9	1.08	8.80	7.0	-17	31
96H	66	64.7	9.51	64.5	42	87	58.3	66	6.4	1.24	10.07	7.5	-25	33
[redacted] FASTED														
Predose	63	58.6	11.50	57.0	42	110								
1H	63	55.9	8.60	54.0	40	80	58.6	63	-2.7	1.07	8.49	-1.0	-41	21
2H	63	58.0	10.14	57.0	43	85	58.6	63	-0.6	1.22	9.67	0.0	-28	36
3H	63	57.5	9.11	56.0	40	79	58.6	63	-1.1	1.11	8.80	0.0	-38	16
4H	63	59.7	8.79	59.0	41	80	58.6	63	1.0	1.21	9.62	3.0	-41	19
5H	63	66.4	10.33	64.0	51	105	58.6	62	7.8	1.16	9.12	9.0	-25	28
6H	63	68.5	9.93	68.0	50	95	58.7	62	9.5	1.22	9.62	11.0	-28	27
7H	63	62.5	9.37	61.0	44	100	58.6	63	3.9	1.18	9.33	5.0	-36	21
8H	63	59.2	9.14	60.0	41	102	58.6	63	0.6	1.32	10.48	2.0	-49	18
9H	63	59.2	8.99	60.0	42	90	58.6	63	0.6	1.13	9.00	1.0	-42	21
10H	63	60.3	9.07	59.0	46	88	58.6	62	1.7	1.08	8.48	3.0	-36	18
11H	63	66.6	10.55	64.0	51	100	58.6	63	8.0	1.10	8.76	9.0	-13	29
12H	63	64.9	10.74	62.0	50	103	58.6	63	6.3	1.09	8.66	7.0	-25	28
13H	63	61.2	10.08	60.0	43	90	58.6	63	2.6	1.05	8.32	4.0	-26	30
14H	63	58.3	10.26	57.0	43	95	58.7	62	-0.2	1.04	8.18	0.0	-23	27
15H	63	57.0	10.66	56.0	42	105	58.6	63	-1.6	1.30	10.32	-1.0	-22	52
16H	63	56.1	9.92	56.0	41	78	58.6	63	-2.5	1.12	8.88	-2.0	-32	18
17H	63	55.0	7.90	54.0	39	75	58.6	63	-3.6	1.06	8.41	-3.0	-37	12
18H	63	56.0	9.16	54.0	40	81	58.6	63	-2.6	1.12	8.86	-3.0	-31	22
19H	63	56.3	9.10	55.0	41	88	58.6	63	-2.3	0.93	7.42	-2.0	-33	22
20H	63	57.1	8.62	56.0	37	79	58.6	63	-1.5	1.16	9.20	-1.0	-40	23
21H	63	58.0	8.95	57.0	44	79	58.6	63	-0.6	1.03	8.18	0.0	-34	17
22H	63	59.3	10.77	58.0	40	101	58.6	63	0.7	1.06	8.44	0.0	-15	21

23H	63	59.2	9.59	59.0	41	84	59.6	63	0.6	1.02	8.06	2.0	-26	15
24H	63	66.1	12.28	64.0	45	100	59.6	63	7.5	1.55	12.33	7.0	-20	30
25H	63	70.3	11.73	69.0	49	108	59.6	63	11.7	1.30	10.29	12.0	-12	30
26H	63	73.5	11.61	71.0	50	107	59.6	63	14.9	1.46	11.56	15.0	-17	46
27H	63	70.4	13.42	68.0	47	124	59.6	63	11.8	1.34	10.64	11.0	-15	44
28H	63	68.2	11.20	66.0	50	108	59.6	63	9.6	1.12	8.89	10.0	-10	32
29H	63	73.2	12.01	71.0	56	119	59.6	63	14.6	1.31	10.40	13.0	-13	42
30H	62	74.5	10.73	74.0	54	109	59.5	62	16.0	1.34	10.51	17.0	-15	39
31H	63	71.8	11.10	71.0	51	104	59.6	63	13.2	1.26	10.02	13.0	-19	37
32H	63	68.0	10.68	67.0	44	106	59.6	63	9.3	1.07	8.48	9.0	-16	29
33H	63	66.4	10.40	66.0	48	96	59.6	63	7.8	1.17	9.31	7.0	-23	27
34H	63	65.1	10.12	63.0	48	97	59.6	63	6.5	1.08	8.54	7.0	-20	28
35H	63	72.7	11.08	72.0	54	116	59.6	63	14.1	1.07	8.49	14.0	-9	37
36H	63	77.0	10.63	78.0	54	104	59.6	63	18.4	1.31	10.41	19.0	-12	46
48H	63	66.6	9.40	67.0	45	92	59.6	63	8.0	1.32	10.44	10.0	-27	32
72H	63	64.7	9.25	64.0	44	94	59.6	63	6.1	1.17	9.32	6.0	-24	26
96H	63	63.8	9.64	64.0	42	86	59.6	63	5.2	1.49	11.81	7.0	-48	29
[redacted] FED														
Predose	72	58.8	9.70	58.0	40	98								
1H	72	66.3	9.63	66.0	50	95	58.8	72	7.5	0.86	7.26	7.0	-12	24
2H	72	65.6	10.45	65.0	44	100	58.8	72	6.7	0.91	7.74	6.0	-9	29
3H	72	62.1	8.65	61.0	45	88	58.8	72	3.3	0.87	7.35	3.0	-17	24
4H	72	63.0	9.26	62.0	42	93	58.8	72	4.1	0.86	7.27	4.0	-15	25
5H	72	66.9	9.67	66.0	48	100	58.8	72	8.0	0.87	7.36	8.0	-10	25
6H	72	66.9	10.61	64.5	45	99	58.8	72	8.0	1.04	8.83	7.0	-10	32
7H	72	62.9	9.95	62.0	42	91	58.8	72	4.1	0.90	7.63	4.0	-13	28
8H	72	62.2	9.63	62.0	43	92	58.8	72	3.3	1.19	10.02	3.5	-22	37
9H	72	61.0	9.53	60.0	46	92	58.8	72	2.1	1.04	8.79	1.0	-18	28
10H	72	62.1	10.29	62.0	42	100	58.8	71	3.2	1.00	8.43	3.0	-20	24
11H	72	66.3	10.23	65.5	43	99	58.8	72	7.5	0.94	8.00	7.0	-11	31
12H	72	66.8	10.45	67.0	45	99	58.8	72	8.0	1.01	8.57	7.0	-15	31
13H	72	62.4	10.81	60.5	41	105	58.8	71	3.6	1.19	10.04	2.0	-19	37
14H	72	60.3	8.93	59.0	46	94	58.8	72	1.4	0.99	8.31	2.0	-24	26
15H	72	58.7	10.36	57.0	43	90	58.8	72	-0.1	1.07	9.11	-1.0	-27	25
16H	72	59.3	10.67	58.5	41	109	58.8	72	0.5	1.25	10.59	0.5	-33	33
17H	72	57.1	9.31	57.0	40	87	58.8	72	-1.8	1.08	9.18	-2.0	-31	22
18H	72	57.4	8.34	57.0	42	88	58.8	72	-1.4	1.05	8.92	-1.0	-29	22
19H	72	58.7	10.15	58.0	42	96	58.8	72	-0.1	1.11	9.39	0.5	-39	27
20H	72	58.9	9.17	57.0	44	91	58.8	72	0.0	1.27	10.80	0.0	-38	29
21H	72	59.3	8.87	59.0	42	85	58.8	72	0.4	1.14	9.65	0.5	-33	29
22H	72	61.6	10.19	60.5	43	84	58.8	72	2.7	1.39	11.81	2.0	-32	37
23H	72	63.8	11.45	62.0	44	121	58.8	72	5.0	1.41	11.99	5.0	-32	45
24H	72	68.8	10.99	67.0	45	117	58.8	72	10.0	1.29	10.94	10.5	-13	41
25H	72	75.6	13.78	73.5	54	140	58.8	72	16.7	1.57	13.30	15.5	-14	91
26H	72	77.2	12.29	75.0	54	118	58.8	72	18.4	1.46	12.36	18.0	-12	46
27H	72	75.0	12.98	74.0	53	119	58.8	72	16.2	1.52	12.91	16.0	-5	50
28H	72	74.2	13.09	73.0	53	122	58.8	72	15.4	1.44	12.23	15.0	-8	46
29H	72	78.4	13.64	76.0	56	129	58.8	72	19.6	1.50	12.71	16.5	-1	61
30H	71	78.4	14.66	76.0	54	132	58.8	71	19.6	1.51	12.69	18.0	-3	64
31H	71	76.0	12.62	74.0	54	118	58.7	71	17.3	1.38	11.64	16.0	-6	51
32H	72	73.8	16.34	70.5	52	153	58.8	72	15.0	1.76	14.91	13.0	-7	95
33H	72	73.3	16.65	70.0	45	136	58.8	72	14.4	1.76	14.94	11.0	-11	70
34H	71	70.9	12.21	70.0	51	105	58.7	71	12.2	1.37	11.53	10.0	-7	48
35H	72	78.4	13.42	77.0	57	134	58.8	72	19.6	1.42	12.02	19.0	-1	66
36H	70	80.5	14.50	79.0	53	152	58.3	70	22.3	1.65	13.77	20.0	-3	84
48H	71	70.2	10.97	71.0	48	108	58.9	71	11.3	1.14	9.61	11.0	-12	40
72H	71	67.2	10.64	67.0	44	107	58.8	71	8.3	1.06	8.90	7.0	-14	29
96H	71	65.9	9.56	64.0	48	93	58.8	71	7.1	1.08	9.41	7.0	-15	23

It appears that the above study did not include orthostatic vital sign measures during treatment but reported AEs of orthostatic hypotension that were greatest in the 15 mg fed state compared to fasted [redacted] and fasted Phase III formulation conditions (7%, 5% and 2%) respectively. The most ADOs occurred in the

No SAEs or deaths occurred.

ADOs of dystonia were observed in a few subjects in the 15 mg Phase III fasted and 15 mg [redacted] fed conditions. One ADO due to tachycardia and dyspnea occurred in the fed [redacted] condition but not in the fasted conditions.

The most ADOs occurred in the 15 mg fed state as shown below (found in the CSR).

Table 10: Adverse Events Leading to Discontinuation of Treatment
(Study R076477-P01-1008: All Subjects Analysis Set)

Subj. nr. Age (Yrs) Race	Period Treatment Group	Body System Preferred Term Reported Term	Onset Time Duration	Outcome Action Taken Con.rx Taken	Severity Relationship Serious
Treatment A: 15 mg ER OROS paliperidone Phase 3 formulation in fasted state					
100802	Period 2	Centr & periph nervous system disorders	1d 10:25	Resolved	Moderate
33	PH3	Dystonia	2:00	Permanent stop	Possible
White	FASTED	Acute dystonia		Yes	No
		Psychiatric disorders	1d 9:55	Resolved	Moderate
		Anxiety	4:30	Permanent stop	Possible
		Anxiety		No	No
100808	Period 1	Psychiatric disorders	2d 16:20	Resolved	Mild
32	PH3	Depression	0:30	Permanent stop	Probable
White	FASTED	Depression		No	No
		Psychiatric disorders	3d 16:20	Unknown	Moderate
		Depression		Permanent stop	Probable
		Depression		No	No
		Psychiatric disorders	2d 14:20	Resolved	Moderate
		Paranoid reaction	2:00	Permanent stop	Probable
		Paranoia		No	No
100819	Period 1	Centr & periph nervous system disorders	1d 4:49	Resolved	Moderate
26	PH3	Dystonia	0:36	Permanent stop	Probable
White	FASTED	Acute dystonia		Yes	No
100864	Period 1	Centr & periph nervous system disorders	1d 11:09	Resolved	Moderate
24	PH3	Dystonia	2:01	Permanent stop	Probable
White	FASTED	Acute dystonia		Yes	No
100875	Period 1	Psychiatric disorders	4d 7:45	Resolved	Moderate
21	PH3	Agitation	5d 20:00	Permanent stop	Possible
White	FASTED	Agitation		No	No
		Psychiatric disorders	4d 10:15	Resolved	Moderate
		Depression	5d 11:30	Permanent stop	Possible
		Depressed		No	No
		Psychiatric disorders	4d	Resolved	Moderate
		Somnolence	8d	Permanent stop	Possible
		Somnolance		No	No
Treatment B: 15 mg ER OROS paliperidone [redacted] formulation in fasted state					
100828	Period 1	Centr & periph nervous system disorders	6:30	Resolved	Moderate
23	[redacted]	Hyperkinesia	1d 5:45	Permanent stop	Probable
White	FASTED	Akathisia		Yes	No
100862	Period 3	Centr & periph nervous system disorders	13:45	Resolved	Moderate
29	[redacted]	Ptosis	10:05	Permanent stop	Probable
Black	FASTED	Ptosis		Yes	No
100851	Period 2	Respiratory system disorders	4d 23:40	Resolved	Moderate
29	[redacted]	Coughing	8d 13:00	Permanent stop	Doubtful
White	FASTED	Productive cough		Yes	No
		Respiratory system disorders	4d 23:40	Resolved	Moderate
		Pharyngitis	11d 3:45	Permanent stop	Doubtful
		Sore throat		Yes	No
		Skin and appendages disorders	4d 23:40	Resolved	Mild
		Sweating increased	8d 0:00	Permanent stop	Doubtful
		Night sweats		Yes	No

Treatment C: 15 mg ER OROS paliperidone [redacted] formulation after consumption of a high-fat breakfast					
100811	Period 1	Centr & periph nervous system disorders	1d 5:55	Resolved	Moderate
19	[redacted] FED	Dystonia	8:02	Permanent stop	Probable
White		Acute dystonia		Yes	No
100813	Period 1	Heart rate and rhythm disorders	1d 3:00	Resolved	Moderate
29	[redacted] FED	Tachycardia	1d 6:03	Permanent stop	Probable
Asian		Sinus tachycardia		Yes	No
		Respiratory system disorders	1d 6:55	Resolved	Moderate
		Dyspnoea	17:01	Permanent stop	Possible
		Dyspnoea		Yes	No
100816	Period 1	Centr & periph nervous system disorders	0:18	Persisting	Moderate
23	[redacted] FED	Headache	5d 1:42	Permanent stop	Possible
White		Headache		Yes	No
100824	Period 1	Centr & periph nervous system disorders	1d 1:55	Resolved	Moderate
27	[redacted] FED	Dizziness	8:55	Permanent stop	Possible
Asian		Dizziness		Yes	No
100859	Period 1	Respiratory system disorders	6d	Resolved	Moderate
24	[redacted] FED	Upper resp tract infection	4d	Permanent stop	Not related
White		Respiratory tract infection		Yes	No
100861	Period 1	Centr & periph nervous system disorders	1d 4:27	Resolved	Moderate
20	[redacted] FED	Dystonia	1:18	Permanent stop	Probable
White		Acute dystonia		Yes	No
100872	Period 1	Centr & periph nervous system disorders	1d 10:05	Resolved	Moderate
35	[redacted] FED	Dystonia	3:50	Permanent stop	Probable
Black		Acute dystonia		Yes	No
		Centr & periph nervous system disorders	1d 12:05	Resolved	Moderate
		Hyperkinesia	3:00	Permanent stop	Probable
		Akathisia		Yes	No
		Psychiatric disorders	2d 12:00	Resolved	Moderate
		Anxiety	18:05	Permanent stop	Possible
		Anxiety		No	No

Table 10: Adverse Events Leading to Discontinuation of Treatment (continued)
(Study R076477-P01-1008: All Subjects Analysis Set)

Note: One additional subject (100856) discontinued at the start of Period 2 due to adverse events he experienced in Period 1 with Treatment C. The adverse events he experienced in Period 1 were not of significant severity to warrant withdrawal of the subject by the investigator, but the subject was concerned and anxious that the adverse events could potentially be more severe in the following period and decided to discontinue from the study before proceeding to Period 2. The different adverse events the subject experienced during Period 1 are described in a narrative.

Cross-reference: Appendix 3.6.4

The above subject 100856 had postural hypotension, dystonia and other events that ultimately lead to an ADO in period 2.

AEs of tachycardia or palpitations were reported in 5 total subjects and were reported twice in some subjects such that: 4 of these AEs occurred in the fed contions, 2 of these AEs occurred in the fasted [redacted] condition and 2 AEs were reported in the fasted Phase III condition.

SD 12 mg Pal Food Effect, Postural Study (in bed versus ambulatory) P01-1012
Note that respiratory (nasal congestion), musculoskeletal (e.g. muscle spasm), vomiting and dizziness occurred in a larger incidence of subjects in the fed versus fasted conditions (coped from the CSR in the 120-Day SUR).

Table 9: Incidence of Common Treatment-Emergent Adverse Events by Body System and Preferred Term
(Study PALIOROS-P01-1012: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Fed Ambulant (Treatment A) (N=62) n (%)	Fasted Ambulant (Treatment B) (N=64) n (%)	Fasted Bed (Treatment C) (N=64) n (%)	Total (N=74) n (%)
Total no. subjects with adverse events	15 (24)	16 (25)	12 (19)	36 (49)
Nervous system disorders	10 (16)	9 (14)	9 (14)	24 (32)
Dizziness	7 (11)	5 (8)	3 (5)	12 (16)
Headache	2 (3)	4 (6)	5 (8)	9 (12)
Somnolence	2 (3)	1 (2)	1 (2)	4 (5)
Disturbance in attention	2 (3)	1 (2)	0	3 (4)
Gastrointestinal disorders	5 (8)	4 (6)	5 (8)	14 (19)
Nausea	2 (3)	2 (3)	1 (2)	5 (7)
Vomiting	3 (5)	0	1 (2)	4 (5)
General disorders and administration site conditions	4 (6)	1 (2)	2 (3)	7 (9)
Asthenia	0	0	2 (3)	2 (3)
Psychiatric disorders	1 (2)	4 (6)	2 (3)	7 (9)
Anxiety	0	2 (3)	0	2 (3)
Respiratory, thoracic and mediastinal disorders	4 (6)	1 (2)	3 (5)	7 (9)
Nasal congestion	3 (5)	0	2 (3)	4 (5)
Musculoskeletal and connective tissue disorders	3 (5)	1 (2)	2 (3)	6 (8)
Muscle spasms	2 (3)	0	0	2 (3)
Infections and infestations	0	2 (3)	0	2 (3)
Upper respiratory tract infection	0	2 (3)	0	2 (3)

NOTE: Incidence is based on the number of subjects, not the number of events
Only adverse events with an incidence of st least 2.5% in at least 1 treatment group are included.

There were no deaths or SAEs and only 3 ADOs of dystonic-related reactions in 2 subjects (1 in the fed and the other in the fasted state) and a respiratory system ADO (nasal congestion) in the fasted treatment condition.

The following additional safety findings are noted:

- "One subject (000027) experienced adverse events that included palpitations, heart rate increased, and blood pressure increased after receiving 12 mg ER OROS paliperidone in Treatment A (Attachment 3.1) (see Section 4.4.2.2). According to the vitals signs measurements, this subject experienced pulse rates above the normal range during the study

(maximum of 146 bpm 30 hours after study medication administration)." Treatment A is the fed condition.

The below table shows mean increases in heart rate that were greatest in the fed condition (from the CSR).

STUDY PALIOROS-P01-1012

Output DVS.01: Vital Signs: Descriptive Statistics on Raw Data and Change from Baseline

Analysis Set: Safety

							Base	change					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
Supine pulse(/min)														
SCREENING														
-	74	67.4	10.11	67.0	51	89								
FED AMBULANT														
Predose	62	60.2	6.75	59.0	51	79	60.2							
9H	62	65.0	9.25	62.5	52	89	60.2	62	4.7	1.12	8.85	3.0	-17	28
24h	58	64.7	10.01	62.0	51	98	60.2	58	4.4	1.19	9.10	3.5	-12	36
30H	58	79.1	13.49	78.0	58	146	60.2	58	18.8	1.80	13.69	18.0	-10	84
48h	58	70.9	11.80	68.0	52	121	60.2	58	10.6	1.42	10.79	10.0	-13	59
72h	57	72.6	12.11	71.0	52	110	60.3	57	12.4	1.57	11.87	14.0	-17	49
96h	58	68.0	11.27	65.0	52	107	60.2	58	7.8	1.40	10.65	6.0	-11	45
FASTED AMBULANT														
Predose	64	60.0	6.12	59.0	51	80	60.0							
9H	64	62.5	8.73	60.5	51	89	60.0	64	2.4	0.92	7.38	2.0	-19	18
24h	59	63.2	9.36	62.0	50	89	59.4	59	3.8	1.11	8.52	2.0	-20	30
30H	59	76.0	11.08	78.0	52	98	59.4	59	16.7	1.34	10.30	19.0	-6	39
48h	59	68.1	10.23	68.0	52	98	59.4	59	8.7	1.21	9.32	8.0	-5	37
72h	58	71.0	10.45	70.0	52	96	59.3	58	11.7	1.43	10.88	9.5	-15	43
96h	58	66.9	10.66	64.5	50	99	59.4	58	7.5	1.26	9.61	6.0	-16	37
FASTED BED														
Predose	64	60.7	7.65	59.0	51	79	60.7							
9H	64	64.5	9.76	62.5	50	86	60.7	64	3.8	1.17	9.39	3.0	-26	26
24h	62	63.7	9.32	61.0	51	85	60.6	62	3.1	1.27	9.99	2.0	-26	27
30H	62	77.5	10.50	79.0	53	112	60.6	62	16.9	1.66	13.06	17.0	-12	56
48h	61	69.4	10.21	69.0	50	89	60.6	61	8.8	1.41	11.04	8.0	-21	39
72h	60	69.6	9.00	69.0	48	94	60.7	60	8.9	1.25	9.65	9.0	-21	33
96h	60	68.2	9.49	68.0	51	96	60.7	60	7.5	1.34	10.41	7.5	-23	36

Supine SBP results are shown below.

Appears This Way
On Original

Output DVS.01: Vital Signs: Descriptive Statistics on Raw Data and Change from Baseline (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	Change N	Change Mean	Change SE	Change SD	Change Med	Change Min	Change Max
Supine SBP(mmHg)														
SCREENING														
-	74	118.1	9.72	118.5	100	136								
FED AMBULANT														
Predose	62	116.7	10.51	117.0	97	139	116.7							
9H	62	114.2	9.89	112.5	98	138	116.7	62	-2.5	1.29	10.15	-1.0	-29	28
24h	58	114.0	11.10	112.5	95	140	116.6	58	-2.7	1.55	11.82	-3.0	-33	29
30H	58	120.2	9.83	121.5	100	140	116.6	58	3.5	1.43	10.89	4.5	-23	26
48h	58	121.2	10.12	121.5	100	140	116.6	58	4.6	1.20	9.18	6.0	-15	29
72h	57	120.4	9.80	121.0	98	138	116.9	57	3.6	1.25	9.42	3.0	-23	27
96h	58	119.9	11.58	120.5	97	140	116.6	58	3.3	1.45	11.05	1.0	-18	42
FASTED AMBULANT														
Predose	64	115.4	11.05	113.5	92	138	115.4							
9H	64	109.9	9.95	107.5	96	136	115.4	64	-5.5	1.21	9.71	-6.0	-31	17
24h	59	113.6	11.56	112.0	91	139	115.6	59	-2.0	1.51	11.58	-2.0	-25	24
30H	59	119.5	10.97	118.0	99	139	115.6	59	3.8	1.43	11.01	3.0	-22	37
48h	59	119.4	9.63	118.0	98	139	115.6	59	3.8	1.14	8.78	4.0	-18	22
72h	58	118.8	9.83	119.0	94	139	115.9	58	2.9	1.36	10.37	2.5	-16	27
96h	58	118.0	9.24	119.5	98	139	115.7	58	2.3	1.25	9.52	3.0	-23	27
FASTED BED														
Predose	64	116.7	10.92	116.0	99	139	116.7							
9H	64	112.9	10.25	110.0	96	139	116.7	64	-3.8	1.30	10.42	-3.0	-38	21
24h	62	113.8	10.29	113.0	98	139	116.6	62	-2.8	1.32	10.37	-1.5	-30	23
30H	62	119.2	10.82	117.0	100	159	116.6	62	2.6	1.75	13.75	3.5	-38	60
48h	61	120.1	9.35	120.0	100	139	116.4	61	3.7	1.31	10.26	4.0	-20	30
72h	60	121.1	11.28	121.0	90	140	116.7	60	4.4	1.38	10.66	6.0	-26	25
96h	60	119.0	9.95	118.0	100	140	116.7	60	2.3	1.03	7.98	2.5	-17	16

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The submission does not include special safety trials. This drug class is not known to show withdrawal or abuse potential effects in Phase III trials (refer to labeling of approved drugs).

7.1.14 Human Reproduction and Pregnancy Data

The submission does not include special safety trials. The sponsor indicates that there were not pregnancies during any of the clinical trial.

7.1.15 Assessment of Effect on Growth

The submission does not include special safety studies.

7.1.16 Overdose Experience

The following is italicized since it contains some reviewer comments and conclusions by the undersigned reviewer (unless otherwise specified).

Section 7.1.18 on a review of the literature revealed overdose cases involving Ris that generally did not reveal any new findings that differ from that already described in this review. Note one

overdose subject had QT prolongation. See section 7.1.12 of a special QT interval study conducted with IR Pal.

Note some SAEs and/or ADOs of "overdose" or related events in Pal trials, as indicated in previous sections of this review. A description of any new remarkable findings that differ from that already described in other sections of this review. The SCS has a section focusing on overdose experience (section 6.5 in 2.7.4 of the submission). Overdoses occurring in the Phase III trials were reviewed by the sponsor and 3 subjects are described as having "excessive" overdoses of 24 g, 270 mg and an estimated overdose of 135 to 405 mg in each of these 3 subjects, respectively (numbers 300095, 300359 and 50215, respectively). Subject 50215 who had the highest estimated dose, was admitted to the hospital on the day of ingestion (exact times were not found in the sponsor's summary) with "prominent dysarthria" and a blood pressure of 100/60 mmHg. The subject was a 35 year old male. Subject 300359 (270 mg overdose) became unsteady and fell. CPK was 342 on admission and his urine drug screen was positive for tetrahydrocannabinol. The 24 mg overdose was associated with nausea, sedation and headache. All 3 subjects recovered from their AEs associated with overdose.

Additional subjects were found by the sponsor to have "overdoses" (in excess of assigned dose level) ranging from 6 mg to as high as 60 mg. The observations of these subjects, as described in section 6.5 of the SCS did not yield any new and remarkable clinical information.

7.1.17 Postmarketing Experience

Paliperidone is not marketed in any country (as previously described in this review). Therefore, there is no postmarketing information on the drug. However, risperidone is marketed and is metabolized to the active compound of Pal (9-OH risperidone) as previously described. The submission contains some postmarketing information on risperidone. Postmarketing information of US marketed drugs is provided in periodic safety reports and other submission under the Risperdol® NDA. Postmarketing information on risperidone is also described in current approved Risperdol® labeling.

The Clinical Overview Module 2.5 of the submission summarizes the postmarketing information on risperidone based on the sponsor's results of their pharmacovigilance database (through 4/30/05, in which risperidone was first licensed as an antipsychotic agent in 1992 in the UK). The sponsor indicates that the frequency of case reports of "pituitary tumor, enlargement or related abnormalities for risperidone" is rare (<0.01%) and that their data do not provide evidence for an increased risk for breast cancer in males and females treated with the drug. Worldwide exposure of risperidone is also reported to be over 22 million person-years.

Reviewer Comment. *In the opinion of the undersigned reviewer, postmarketing data poses major limitations in finding a potential safety signal, such that failure to show a safety signal is not adequately assuring that a potential safety signal does not exist.*

Refer to Section 9 of this review for recommendations relevant to a potential carcinogenicity of Pal.

7.1.18 Review of the Literature

Methods of the Sponsor's Literature Search. The sponsor conducted a search of the literature using several standard databases (e.g. Medline, Embase and others) using search terms of 9-hydroxyrisperidone, 9-OH-resperidone, 9-hydroxy-risperidone, paliperidone, and CAS Registry Number 144598-75.4.

237 publications were retrieved from the search. 88 of these articles were selected for review of the full text on the basis of these selected articles containing reference to "safety, tolerability, toxicity, adverse event(s), overdose, pregnancy, lactation, or QT prolongation" found in the title or in the abstract of the given article. However, if the term "toxic" appeared in a given title or abstract, and was used in the context of plasma levels in absence of clinical toxicity or safety information (e.g. articles focusing on methods for monitoring plasma levels), then article was not reviewed by the sponsor.

The results of the sponsor's search are outlined below, as part of the reviewer's comments.

Reviewer Comments on the Results of the Sponsor's Review of the Literature. *The sponsor's review of the literature generally did not review any new or remarkable clinical information. The following are some key findings described in the review:*

- *Potential risperidone-drug interactions are suggested.*
- *Additional articles on pharmacokinetic properties of risperidone*
- *A few articles on QT prolongation in which the following findings are noted by the undersigned reviewer:*
  - *One article (Admamantidis, MM, et al., 2000) is reported to show that Ris is similar to a class III anti-arrhythmic drug with respect to potential arrhtymogenic properties depending on "predisposing factors" based on drug effects on the action potentials recorded from rabbit purkinje fibers (1 uM Ris and 3 uM 9-OH-Ris resulted in a +99±14% and +118±28% change in "class III effects," respectively, in which a "drastic" lengthening in the duration of the action potential and an early-after-depolarization were observed).*
  - *Preclinical evidence for greater binding of 9-OH Ris in myocardium compared to plasma (Titier et cal., 2002).*
- *Extrapyramidal side effects (EPS): EPS rated on the SAAS was found to be correlated to plasma levels of 9-OH Ris and Ris, respectively (Spearman's ρ=0.76, $p<0.01$ between active antipsychotic fraction and SAS score (Yoshimura, et cal, 2001).*
- *Prolactin serum levels were weakly correlated with serums levels of 9-OH Ris (Spearman's ρ=0.28, p value could not be found in the review) and were not correlated with Ris (Bruggeman, et al., 2003).*
- *A few overdose cases involving Ris are reported in the literature but generally did not reveal any new, clinically remarkable findings. However, it is notable that one case of a 21 year old schizophrenia female patient who ingested 50 tablets of 2 mg Ris had sinus tachycardia of 149 bpm and QTc of 414 mscec (type of correction could not be found in the review) at 4 hours post drug intake. 9-OH Ris serum levels were 100 ng/ml and at 48 hours post-ingestion serum levels decreased to 59 ng/ml. Generally, QT or QTc*

intervals of less than 450 msec are not considered clinically remarkable. However, a QT prolongation effect of Ris must be considered which may have greater clinical relevance in patients at risk. Although, note that this patient was female, of which females are generally considered show a longer QT interval than males and may be at greater risk for QT prolongation or adverse effects of QT prolongation.

It is not clear if above key findings are reproduceable. However, the above findings are generally not unexpected given the existing knowledge of drugs in this drug class. Regarding potential drug-drug interactions in the literature, OCPB input on Pal-drug interactions is pending.

7.2 Adequacy of Patient Exposure and Safety Assessments

See previous subsections regarding limitations with the safety data provided. Refer to the final section of this review for comments and recommendations.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Description of Studies, Safety Datasets and other Aspects of Exposure and Safety Assessments. To avoid redundancy, refer to Section 4 for a description of studies and overall enumeration of subjects and refer to Subsection 7.2.1.3 provides the enumeration of subjects by duration of a given treatment. Section 7.1 describes each safety dataset (pooled and unpooled datasets) and the safety assessments conducted.

Patient Exposure. This subsection provides more detailed information in the enumeration of subjects that was not provided elsewhere in this review and within accordance with the Clinical Review MAPP. Enumeration of subjects by treatment group or condition of a given safety dataset is provided as well as enumeration of subjects by additional subcategories (e.g. subcategorized by disposition, number of completers).

Tables in this section were copied from the submission.

Pooled Pivotal Phase III Trials (-303, -304, and -305). The table below is of the 3 pivotal Phase III trials that were pooled for safety analyses.

Enumeration of Safety Populations and Completers in Completed Phase III trials.

Table 3: Number of Subjects Randomly Assigned to Each Treatment Group
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: All Randomized Subjects)

		ER OROS PAL						Olanzapine
	Placebo (N=360) n (%)	3 mg (N=127) n (%)	6 mg (N=235) n (%)	9 mg (N=247) n (%)	12 mg (N=242) n (%)	15 mg (N=115) n (%)	Total (N=966) n (%)	10 mg (N=366) n (%)
All randomized subjects	360 (100)	127 (100)	235 (100)	247 (100)	242 (100)	115 (100)	966 (100)	366 (100)
Subjects evaluable for safety[a]	355 (99)	127 (100)	235 (100)	246 (>99)	242 (100)	113 (98)	963 (>99)	364 (99)

[a] Subjects who received at least 1 dose of study medication.

The following enumerates subjects in various treatment by disposition categories.

Table 4: Study Completion/ Withdrawal Information
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
	Placebo (N=355) n (%)	3 mg (N=127) n (%)	6 mg (N=235) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)	15 mg (N=113) n (%)	Total (N=963) n (%)	10 mg (N=364) n (%)
Completed	142 (40)	70 (55)	131 (56)	164 (67)	155 (64)	82 (73)	602 (63)	228 (63)
Withdrawn	213 (60)	57 (45)	104 (44)	82 (33)	87 (36)	31 (27)	361 (37)	136 (37)
Subject choice (subject withdrew consent)	36 (10)	17 (13)	28 (12)	28 (11)	29 (12)	6 (5)	108 (11)	33 (9)
Lost to follow-up	6 (2)	1 (1)	9 (4)	2 (1)	10 (4)	2 (2)	24 (2)	11 (3)
Adverse event	18 (5)	3 (2)	16 (7)	10 (4)	14 (6)	4 (4)	47 (5)	21 (6)
Death	0	0	0	0	0	0	0	1 (<1)
Study medication non-compliance	3 (1)	1 (1)	0	0	3 (1)	2 (<2)	6 (1)	4 (1)
Lack of efficacy	144 (41)	31 (24)	46 (20)	42 (17)	29 (12)	14 (12)	162 (17)	59 (16)
Other	6 (2)	4 (3)	5 (2)	0	2 (1)	3 (3)	14 (1)	7 (2)

1 Elderly (unpooled) Phase III Trial, -302. The following enumerates subjects in various treatment by disposition categories.

Table 5: Study Completion/ Withdrawal Information
(Study R076477-SCH-302 Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)	Total (N=114) n (%)
Completed	26 (68)	64 (84)	90 (79)
Withdrawn	12 (32)	12 (16)	24 (21)
Lack of efficacy	6 (16)	3 (4)	9 (8)
Adverse event	3 (8)	5 (7)	8 (7)
Subject choice (subject withdrew consent)	1 (3)	2 (3)	3 (3)
Death	1 (3)	0	1 (1)
Study medication non-compliance	0	1 (1)	1 (1)
Other[a]	1 (3)	1 (1)	2 (2)

[a] These included discontinuation on Day 36 due to personal circumstances for the subject in the paliperidone group and discontinuation on Day 32 due to lack of study medication at the site for the subject in the placebo group.
Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec4.1

The following discussion is the enumeration of subjects receiving 6 mg or higher daily doses of Paliperidone in Phase III trials. The dose-level of at least 6 mg was chosen for this discussion since this is the recommended dose for treatment in proposed labeling. Although, note that proposed labeling also suggests a 3 mg daily dose level, as well as higher than 6 mg dose-levels as being effective.

The following outlines the number of ITT Safety subjects and completers in completed Phase III trials of subjects receiving at least 6 mg daily of Paliperidone, as specified:

- *In the 3 pivotal Phase III trials (Studies -303, -304, and -305):*
  - *806 subjects received at least one dose of 6-15 mg of Paliperidone (the Intent-to-treat Safety Population) and an additional 127 subjects were in the ITT safety population of the 3 mg Paliperidone groups*
  - *532 subjects in the 6 to 15 mg Paliperidone group completed the study and 70 subjects in the 3 mg groups completed the study.*

In the elderly phase III 3-12 mg flexible daily dose trial (-302):

- *76 elderly patients received at least one 3-12 mg daily dose of Paliperidone.*
- *64 subjects were completers.*

Ongoing Phase III "Prevention of Recurrence" Trial -301. This ongoing trial has a DB phase and assignment to study drug remains blinded. As of the 5/31/05 cut-off date 462 subjects enrolled in this study. Since this study remains blinded and is ongoing, only information on SAEs and deaths are provided (e.g. enumeration of subjects by treatment, duration of treatment, and other exposure information cannot be found or are not provided, and the sponsor clearly states that safety results on AEs and clinical parameters are not included in the submission).

Enumeration of Subjects in Longer Term Open-label Extension Trials.

Long term exposure was only examined in the above tabulated open-label (OL) extension trials (-702, -703, -704, -705).

Table 6: Study Completion/ Withdrawal Information Through 31 May 2005
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705 Safety Analysis Set)

	---- Pla/Pali ----		---- Pali/Pali ----		---- Olan/Pali ----		- Total Paliperidone -	
	Pali Duration, n (%)		Pali Duration, n (%)		Pali Duration, n (%)		Pali Duration, n (%)	
	≤3 months (N=107)	>3 months (N=128)	≤3 months (N=178)	>3 months (N=505)	≤3 months (N=106)	>3 months (N=143)	≤3 months (N=391)	>3 months (N=776)
Completed	0	5 (4)	0	9 (2)	0	0	0	14 (2)
Ongoing *	46 (43)	97 (76)	83 (47)	364 (72)	31 (29)	107 (75)	160 (41)	568 (73)
Withdrawn	61 (57)	26 (20)	95 (53)	132 (26)	75 (71)	36 (25)	231 (59)	194 (25)
Subject choice(subject withdrew consent)	23 (21)	11 (9)	34 (19)	62 (12)	27 (25)	14 (10)	84 (21)	87 (11)
Lost to follow-up	7 (7)	7 (5)	15 (8)	15 (3)	9 (8)	1 (1)	31 (8)	23 (3)
Adverse event	7 (7)	3 (2)	15 (8)	19 (4)	19 (18)	4 (3)	41 (10)	26 (3)
Death	0	0	0	0	0	1 (1)	0	1 (<1)
Other	24 (22)	5 (4)	31 (17)	36 (7)	20 (19)	16 (11)	75 (19)	57 (7)

* As of 31 May 2005.

So far (as of the May 31, 2005 cut-off date), only 14 subjects have completed the OL extension trials.

The Safety Update Report (SUR) provides additional safety information from the OL extension trial dataset from the following subjects that are enumerated in the table below on the basis of exposure (as copied from the SUR). Note that the number of subjects receiving Pal treatment for at least 6 months and for at least 12 months, respectively, meets ICH guidelines.

Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 1 November 2005
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

	-- Pla/Pali -- (N=236)	-- Pali/Pali -- (N=685)	-- Olan/Pali -- (N=249)	---- Total ---- (N=1170)
Total duration of study medication (day)				
N	236	685	249	1170
Category, n (%)				
Week 1-4	35 (15)	4 (1)	44 (18)	83 (7)
Week 5-8	17 (7)	41 (6)	18 (7)	76 (6)
Week 9-12	17 (7)	58 (8)	16 (6)	91 (8)
Week 13-16	5 (2)	48 (7)	13 (5)	66 (6)
Week 17-20	5 (2)	36 (5)	6 (2)	47 (4)
Week 21-24	20 (8)	22 (3)	11 (4)	53 (5)
Week 25-28	30 (13)	14 (2)	23 (9)	67 (6)
Week 29-32	13 (6)	99 (14)	13 (5)	125 (11)
Week 33-36	7 (3)	45 (7)	9 (4)	61 (5)
Week 37-40	4 (2)	31 (5)	7 (3)	42 (4)
Week 41-44	19 (8)	23 (3)	24 (10)	66 (6)
Week 45-48	9 (4)	27 (4)	15 (6)	51 (4)
Week 49-52	36 (15)	44 (6)	34 (14)	114 (10)
> week 52	19 (8)	193 (28)	16 (6)	228 (19)
Mean (SD)	195.4 (126.82)	247.0 (126.33)	188.8 (131.15)	224.2 (130.23)
Median	183.0	237.0	189.0	218.0
Range	(1;391)	(26;453)	(2;379)	(1;453)

tmb18_t1.rtf generated by tmb18.sas

Enumeration of Subjects in Phase I/II Trials.

The 17 Pooled Phase I/II trials of healthy subjects (includes some cross-over studies and some placebo controlled trials) enumerates subjects in this safety dateset.

- Paliperidone, OROS®: 275 subjects
- Immediate release (IR) or other formulations of paliperidone: 219 subjects
- Placebo: 62 subjects

- Risperidone: 52 subjects

The 3 schizophrenia Phase I trials were pooled for integrated safety analyses with subjects receiving at least one dose of study drug enumerated as follows:

- Paliperidone, OROS®: 111 subjects
- IR formulations of paliperidone: 34 subjects
- Risperidone: 55 subjects

Other Phase I/IIa studies are shown in a separate set of tables below that were not pooled for integrated safety analyses since these studies differed drastically in study design such as in the patient population examined (e.g. renal impaired patients) or in were a study focusing on a specific and unique objective (e.g. a study focusing on cardiovascular effects). These 7 studies consisted of a total of 298 subjects received IR or OROS paliperidone of which 93 of these subjects had schizophrenia or schizoaffective disorder.

Section 7.2.1.3 below provides exposure to study drug in various studies.

7.2.1.1 Study type and design/patient enumeration

See section 4 of overall study design of each study and enumeration of subjects.

7.2.1.2 Demographics

Demographic information was previously described in Section 6.1.4 for the completed Phase III trials. Phase I studies were generally conducted on healthy adults, unless otherwise specified in summary tables in Section 4 of this review.

7.2.1.3 Extent of exposure (dose/duration)

Although this subsection only focuses on treatment by dose-level and by duration, in accordance with the MAPP. Other aspects of the extent of exposure were previously provided.

Pooled Completed Pivotal Phase III Trials The following table summarizes exposure by duration of treatment in the pooled, pivotal Phase III trials (of primarily non-elderly adults) which used a parallel-group, fixed-dose design (copied from the submission).

Table 8: Extent of Exposure
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS PAL						Olanzapine
	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	Total (N=963)	10 mg (N=364)
Total duration, days								
N	355	127	235	246	242	113	963	364
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ 7	33 (9)	10 (8)	23 (10)	19 (8)	26 (11)	6 (5)	84 (9)	26 (7)
8 - 14	34 (10)	8 (6)	22 (9)	13 (5)	12 (5)	2 (2)	57 (6)	14 (4)
15 - 21	71 (20)	19 (15)	22 (9)	18 (7)	16 (7)	10 (9)	85 (9)	41 (11)
22 - 28	45 (13)	10 (8)	21 (9)	16 (7)	18 (7)	5 (4)	70 (7)	31 (9)
29 - 35	22 (6)	6 (5)	11 (5)	13 (5)	8 (3)	4 (4)	42 (4)	19 (5)
≥ 36	150 (42)	74 (58)	136 (58)	167 (68)	162 (67)	86 (76)	625 (65)	233 (64)
Mean (SD)	28.4 (13.66)	32.1 (13.44)	31.3 (14.17)	34.5 (12.87)	33.3 (13.95)	36.3 (11.50)	33.3 (13.47)	33.7 (12.73)
Median	28.0	41.0	41.0	42.0	42.0	42.0	42.0	42.0
Range	(1;50)	(1;48)	(1;48)	(1;49)	(1;51)	(1;47)	(1;51)	(1;52)

Note: The duration of exposure includes days on which subjects did not actually take study medication.

Completed Elderly Phase III Trial (Study -302). The following table summarizes exposure (in duration) and the overall mean and median dose-level in subjects in the elderly flexible dose (3-12 mg/day) Phase III trial (copied from the submission):

Table 9: Extent of Exposure
(Study R076477-SCH-302 Safety Analysis Set)

	Placebo (N=38)	ER OROS PAL (N=76)
Total duration, days		
N	38	76
Category, n (%)		
≤ 7	3 (8)	4 (5)
8 - 14	3 (8)	1 (1)
15 - 21	1 (3)	1 (1)
22 - 28	3 (8)	1 (1)
29 - 35	2 (5)	3 (4)
≥ 36	27 (71)	66 (87)
Mean (SD)	34.9 (12.85)	38.8 (9.37)
Median	42.0	42.0
Range	(3;45)	(4;45)

Note: The duration of exposure includes days on which subjects did not actually take study medication.
Cross-reference: SCH-302/Sec4.6

Ongoing Phase III Prevention Relapse Trial -301
This study has a DB phase and is ongoing with data blinded such that information by treatment group and duration is not provided at this time.

Ongoing Open Label Studies. These studies are ongoing 6 month (in the elderly study, -702) or 52 week OL Pal trials (primarily non-elderly Phase III trials, -703, -704 and -705).

These trials are the sponsor's main source for providing longterm safety, yet trials remain ongoing. See subsection 7.2.3 for a discussion relevant for adequacy of overall exposure and for longterm exposure, while the data supporting conclusions under subsection 7.2.3 are provided below, as required by the Clinical Review MAPP.

The sponsor provides safety data of ITT safety population using a May 31, 2005 cut-off except for deaths and serious adverse events in which an August 31, 2005 cut-off date was employed (in the N000 submission). Updated information was reviewed in a 120-Day SUR which covers exposure (section 7.2.9).

The following table shows exposure duration, mean and median dose for OL trials of which trial employed a flexible dose design of 3 to 12 mg daily of OL Paliperidone using starting daily dose of 6 mg (table is copied from the N000 submission). See section 7.2.9 for updated information.

Table 10: Extent of Exposure to Open-Label ER OROS Paliperidone Through 31 May 2005 (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705 Safety Analysis Set)

	Pla/Pali (N=235) n (%)	Pali/Pali (N=683) n (%)	Olan/Pali (N=249) n (%)
Total duration, days			
N	235	683	249
Category, n (%)			
Week 1-4	40 (17)	123 (18)	54 (22)
Week 5-8	40 (17)	87 (13)	30 (12)
Week 9-12	27 (11)	71 (10)	22 (9)
Week 13-16	8 (3)	45 (7)	19 (8)
Week 17-20	13 (6)	39 (6)	23 (9)
Week 21-24	26 (11)	68 (10)	20 (8)
Week 25-28	21 (9)	66 (10)	24 (10)
Week 29-32	14 (6)	51 (7)	18 (7)
Week 33-36	16 (7)	39 (6)	8 (3)
Week 37-40	13 (6)	47 (7)	13 (5)
Week 41-44	13 (6)	26 (4)	13 (5)
Week 45-48	1 (<1)	8 (1)	2 (1)
Week 49-52	1 (<1)	9 (1)	2 (1)
> Week 52	2 (1)	4 (1)	1 (<1)
Mean (SD)	127.8 (94.30)	131.8 (94.29)	121.8 (93.25)
Median	124.0	133.0	112.0
Range	(1;366)	(1;371)	(2;376)

Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 31 May 2005 (Studies R076477-SCH-702, -703, -704, and -705: Safety Analysis Set)

	Pla/Pali (N=235)	Pali/Pali (N=683)	Olan/Pali (N=249)	Total (N=1167)
Total duration of ER OROS paliperidone (day)				
N	235	683	249	1167
Category, n (%)				
Week 1-4	40 (17)	4 (1)	54 (22)	98 (8)
Week 5-8	40 (17)	53 (8)	30 (12)	123 (11)
Week 9-12	27 (11)	121 (18)	22 (9)	170 (15)
Week 13-16	8 (3)	82 (12)	19 (8)	109 (9)
Week 17-20	13 (6)	49 (7)	23 (9)	85 (7)
Week 21-24	26 (11)	30 (4)	20 (8)	76 (7)
Week 25-28	21 (9)	58 (8)	24 (10)	103 (9)
Week 29-32	14 (6)	72 (11)	18 (7)	104 (9)
Week 33-36	16 (7)	59 (9)	8 (3)	83 (7)
Week 37-40	13 (6)	49 (7)	13 (5)	75 (6)
Week 41-44	13 (6)	36 (5)	13 (5)	62 (5)
Week 45-48	1 (<1)	37 (5)	2 (1)	40 (3)
Week 49-52	1 (<1)	16 (2)	2 (1)	19 (2)
> week 52	2 (1)	17 (2)	1 (<1)	20 (2)
Mean (SD)	127.8 (94.30)	171.5 (95.45)	121.8 (93.25)	152.1 (97.46)
Median	124.0	171.0	112.0	140.0
Range	(1;366)	(26;414)	(2;376)	(1;414)

The following table provides mean, median and range of dose-levels of OL trials, combined (as copied from the submission).

Table 11: Paliperidone Exposure - (Mean, Mode, Minimum, and Maximum)
(Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705: Safety Analysis Set)

	Pla/Pali (N=235)	Pali/Pali (N=683)	Olan/Pali (N=249)	Total (N=1167)
Mean dose (days on drug only)				
N	235	681	247	1163
Mean (SD)	9.9 (2.27)	9.8 (2.43)	9.7 (2.13)	9.8 (2.34)
Median	9.3	9.0	9.0	9.0
Range	(3;15)	(3;27)	(3;15)	(3;27)
Mode dose (days on drug only)				
N	233	679	247	1159
Mean (SD)	10.0 (2.59)	9.9 (2.78)	9.7 (2.49)	9.9 (2.68)
Median	9.0	9.0	9.0	9.0
Range	(3;15)	(3;27)	(3;15)	(3;27)
Minimum dose (days on drug only)				
N	235	681	247	1163
Mean (SD)	8.2 (1.99)	8.2 (2.10)	8.2 (1.90)	8.2 (2.04)
Median	9.0	9.0	9.0	9.0
Range	(3;15)	(3;27)	(3;15)	(3;27)
Maximum dose (days on drug only)				
N	235	681	247	1163
Mean (SD)	11.0 (2.76)	11.1 (3.27)	11.2 (3.18)	11.1 (3.15)
Median	12.0	9.0	9.0	12.0
Range	(3;27)	(6;36)	(6;30)	(3;36)

Only exposure during the open label phase is included.

Longterm Exposure When Combining Exposure of DB Lead-in Trials with Exposure of OL Extension Trials.

The following table enumerates total Paliperidone subjects in the safety data set by duration of Paliperidone exposure when combining the 6-week exposure during the DB phase lead-in Studies -302, -303, -304 and -305 with exposure during the OL extension studies (the 26-week Study -702 and the 52-week Studies -703, -704, -705). Also mean and median dose-levels are provided in the table that follows (as provided by the sponsor).

Table 13: Total Duration of Paliperidone Exposure - Double-Blind + Open-Label – Through 31 May 2005
(Studies R076477-SCH-302, -303, -304, -305, -702, -703, -704, and -705: Safety Analysis Set)

	Total Paliperidone (N=1523)
Total duration of study medication (day)	
N	1523
Category, n (%)	
Week 1-4	322 (21)
Week 5-8	255 (17)
Week 9-12	170 (11)
Week 13-16	109 (7)
Week 17-20	85 (6)
Week 21-24	76 (5)
Week 25-28	103 (7)
Week 29-32	104 (7)
Week 33-36	83 (5)
Week 37-40	75 (5)
Week 41-44	62 (4)
Week 45-48	40 (3)
Week 49-52	19 (1)
> Week 52	20 (1)
Mean (SD)	121.7 (101.79)
Median	89.0
Range	(1;414)

Table 14: Mean, Mode, Minimum, and Maximum ER OROS Paliperidone Doses - Double-Blind + Open-Label
(Studies R076477-SCH-302, -303, -304, -305, -702, -703, SCH-704, and SCH-705: Safety Analysis Set)

	Total Paliperidone (N=1523)
Mean dose (days on drug only)	
N	1521
Mean (SD)	9.4 (2.63)
Median	9.0
Range	(3;17)
Mode dose (days on drug only)	
N	1509
Mean (SD)	9.4 (3.13)
Median	9.0
Range	(3;27)
Minimum dose (days on drug only)	
N	1521
Mean (SD)	7.7 (2.55)
Median	9.0
Range	(0;15)
Maximum dose (days on drug only)	
N	1521
Mean (SD)	11.0 (3.80)
Median	12.0
Range	(3;60)

See a discussion and reviewer comments on longterm exposure relevant to ICH guidelines in section 7.2.3, in accordance with the Clinical Review MAPP.

Phase I/II Trials.
A total of 152 subjects in the above healthy subject Phase I/II trials received at least one dose of 3 to 6 mg of Paliperidone and 200 subjects received at least one dose of a higher dose level of 9 to 15 mg. Most subjects completed these trials (generally over 90% of subjects in any given group among the trials).

Refer to section 4 of the number of subjects in each set of pooled Phase I and individual Phase I/II trials.

Refer to Section 7.2.9 for updated longterm exposure and safety information that met ICH guidelines for longterm exposure.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

In accordance with the Clinical Review MAPP this subsection describes secondary datasources.

The 120-Day SUR provided the bulk of longterm exposure data, although up to approximately 6 months of longterm exposure results were provided in the N000, as previous discussed.

See Section 4 for a listing of additional submissions and the review strategy.

Refer to section 7.2.3 regarding a more detailed discussed on longterm exposure relevant to ICH guidelines (in accordance with the MAPP).

A review of the literature is provided in this review. Pal has not been marketed in any country such that postmarketing data does not exist. The sponsor provided some postmarketing information on Risperdol,® as described in section 7.1.17 of this review. Current approved labeling of Risperdol® provides postmarketing information and other safety information on this related drug.

To avoid redundancy and to enhance continuity and flow in this review results of other sections describing safety results from the above secondary data sources are not described in this section.

The last section of this review provides recommendations relevant to safety.

7.2.2.1 Other studies

Other studies are addressed in other sections of this review (refer to Section 7.1 and Section 4 of this review and section 7.1.12).

7.2.2.2 Postmarketing experience

Paliperidone is not approved for the market in any country, as previously described, in subsection 7.1.17 which also discusses postmarketing information on the approved related drug, risperidone (Risperdol®).

7.2.2.3 Literature

Refer to Section 7.1.18 which includes a description of methodology and findings found in the submission, as previous described.

7.2.3 Adequacy of Overall Clinical Experience

In accordance with the Clinical Review MAPP, this section discusses adequacy in meeting ICH guidelines on the extent and duration of exposure for assessing safety.

Reviewer Comment.
The information provided in the 120-Day SUR met ICH guidelines for 6 and 12 month exposure and ICH guidelines were met for short-term exposure within an adequate dose-range (as provided in the N000 submission).

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This topic is regarding preclinical information. Refer to Section 3 of this review for any relevant and significant preclinical findings identified and conveyed to the undersigned reviewer by the Pharmacology Toxicology Reviewer who is conducting the preclinical review.

7.2.5 Adequacy of Routine Clinical Testing

Concerns with the clinical data were previously discussed in appropriate sections in this review. Refer to the last section of this review for any additional comments or recommendations that may apply to this topic.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Refer to Section 3 of this review which describes any relevant and significant issues conveyed by the OCPB reviewer conducting the review of studies on this topic that were submitted in this NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

See the final section of this review.

7.2.8 Assessment of Quality and Completeness of Data

Several questions remain at the time of this writing regarding quality and completeness of the safety results. Before discussing questions relevant to this topic, it is important to note that clinical research databases and the ability to capture all adverse events can be a challenge in any given clinical trial (e.g. consider the AE coding system that may be employed, consider the potential diversity across investigators in how a clinical situation may be assessed and diagnosed that may be subject to the clinical practices of their region, their training and other factors). While keeping this in mind, questions remain regarding the quality and completeness in capturing all subjects with a specific type of adverse event in the AE database, such as suicidality (refer to Section 4.1.4.6) and possibly others that occurred during the treatment phase of clinical trials (e.g. such as events believed to be part of an overall pre-existing condition and/or adverse events captured using a broader AE term that could have been reported using a term such as "excacerbation of schizophrenia"). Note the following:

- *The sponsor made an effort to identify subjects with suicidality that were reported using another SAE term that they did not capture in their results on suicidality (they reported these uncaptured subjects in the original N00 submission). This is described in section 7.4.1.6 of this review. The sponsor accomplished this by reviewing safety alert forms. So the following questions remain:*
  - *Could there could be additional uncaptured subjects that were not considered as requiring a safety alert form (so were not reviewed for suicidality)? It would seem that any subject with suicidality would have a Safety Alert form submitted (even it another term were used such as "exacerbation of schizophrenia") since suicidality is potentially life-threatening but it is not clear to the undersigned reviewer if this was the case for all such subjects (e.g. if the investigator considered it to be part of an overall condition).*
  - *Are other subjects that were not captured for a given specific type of AE because they were events considered as part of an overall condition or reported using a broader AE term?*

While it is helpful to use broader AE terms such as "exacerbation of schizophrenia" that could be considered clinically representative of the overall clinical picture at the time of the event(s) (such as a subject who becomes suicidal and increasingly psychotic who is believed to have these events as part of their disorder), it is also important to include more specific AE terms that do not infer causality (e.g. psychosis, suicidal ideations). Without recording these additional terms (as AE terms in the CRF) it would appear that these more specific events would not be captured in the sponsor's AE database. Also if a given set of events were not considered to be of the nature to warrant submitting a safety alert report then it is not clear how multiple events would be recorded in the case that

one term is believed to capture all events (e.g. "dizziness" in a patient that was also having a decrease in blood pressure). Section 7.1.4.6 of this review for more details on capturing and enumerating events of suicidality. Teleconference minutes with the sponsor's clarification on their search methods for revealing uncaptured cases of suicidality are provided later in this subsection (to be entered in DFS as a separate document).

- *In addition to the above, there is also the question of capturing subjects who withdrew from the study early for reasons that may be unclear (e.g. subjects who withdrew consent or were noncompliant that in turn, led to early withdrawal). Early withdraw such as a subject that is noncompliant or a subject who withdraws consent (or possibly who has exacerbation of their psychotic symptoms) could in some cases be associated with clinically remarkable adverse events or an SAE at or near the time that the given subject was noncompliant leading to their early withdrawal. The sponsor was inquired about this concern and was given examples of subjects (see Attachment 1 of this review for a listing of these subjects to which a response is anticipated but appear to be pending at this time). The following is one example of these subjects:*
  - Subject 503018 in Study -305 in the original NDA submission was withdrawn due to noncompliance" after 4 days of stopping the study drug (drug stopped on Day 20 and withdrew "due to noncompliance" on Day 24) who had abnormal LFTs on Day 15 and "onward" (elevations of up to approximately 5 times the ULN, first observed on Day 15). Values normalized on Day 29 (9 days post-treatment cessation). This subject was found in the narrative section of subjects but was not checked off in the narrative summary table (preceding the narratives) as having either an SAE or as "premature discontinued." This subject cannot be found in line listings of SAEs or ADOs. The narrative indicates that the elevations in LFTs were not reported as AEs. Please clarify and provide the rationale for how events of elevated LFTs were actually reported in subjects and clarify why the drug was stopped and why the subject was noncompliant.
  - Subject 100057 also had AEs that he could not tolerate on the same day of having study medication stopped "permanently on Day 22 as the subject withdrew consent." This subject is recorded on the narrative summary table as only having an SAE and is not checked off as being an adverse dropout (the "premature discontinued" column on page 1773). The following are excerpts from the narrative page 1815:

The subject was discharged from the hospital portion of the study on Day 20. At the scheduled Day 22 visit, he reported side-effects that he "could not tolerate" (restlessness and inability to sleep) (source: CIOMS). Study medication was permanently stopped on Day 22 as the subject withdrew consent. Vital signs were within normal limits but slightly higher than at earlier readings (138/91 mmHg standing; 141/72 mmHg supine); temperature was 36.4 degrees. Laboratory analyses on Day 22 (end of study) revealed a creatine kinase (CK) of 2201 U/L (reference range: 18-198 U/L); all other laboratory values were reported within the normal range. At baseline (Day -2), the baseline creatine kinase value was 186 U/L. The serious adverse events "elevated CK" and "neuroleptic malignant syndrome (acute EPS side effects)" were reported on Day 24 and Day 25, respectively; the elevated CK was considered life threatening.

- *Another reason for concern in identifying and enumerating subjects with a specific type of adverse event is that subjects with clinically remarkable adverse events could not be found described in key and relevant in-text sections of the integrated safety summary section of the NDA which was found in the SCS (a few remarkable subjects were described in some key sections of the SCS but often subject numbers were not provided with reference to a narrative location). The following subject is an example (the sponsor was inquired about this subject and others as listed in Attachemtn 1 of this*

review (to which responses are either pending or were received and are under review). This subject was found briefly described in an in-text safety section of one of the study reports (CSRs) of the Phase III trials (on page 122 of the CSR of Study -304). It is also not clear to the undersigned reviewer if "exacerbation of schizophrenia" in this subject which was reported as an AE leading to early withdraw (reported as an adverse dropout) occurred secondarily to the clinically remarkable cardiovascular events (e.g. a given subject may not report symptoms or may not appear to be in physical distress due to an acute psychotic state that may have been exacerbated secondarily to undetected physical distress):

- *Subject 300541 had "syncope," bradycardia and "pauses" described but the terms syncope and pause or sinus pause could not be found in line listings of ADOs or SAEs (although the SAE listing has this subject listed with terms of bradycardia, dizziness, heart rate irregular and hypotension as preferred terms and as verbatim terms except the heart rate irregular had the verbatim term of delay in pulse). The SAE listing also shows that no action was taken with treatment ("none" listed under the "Action Taken with Treatment" column). According to the narrative and the ADO line-listing of this subject, the study drug was stopped due to "exacerbation of schizophrenia" (the ADO line listing indicates that the study was drug stopped on Day 5). The above cardiac related SAEs were reported on Day 5 (hypotension and dizziness) and Day 6 (heart rate irregular and bradycardia). This subject also met outlier criteria for orthostatic hypotension but a description of this subject in in-text sections of the SCS focusing on orthostatic hypotension, potential pro-arrhythmic related events, on SAEs or ADOs, or on subjects who were clinically remarkable outliers on vital signs or ECG assessments could not be found in the SCS (a word search for this subject in the SCS pdf file was conducted by the undersigned using the subject's number and results are shown below).*
- *The following are the results of a search in the SCS for this subject (by the undersigned reviewer) by using the "find" tool in the PDF file of the SCS (using the subject number):*
  - *The subject number was found by the PDF "find" tool in the line listings for ADOs and SAEs, as above which was on pages 1809 and 1861 of the SCS (in appendices).*
  - *The subject number was also found in the narratives on page 2555 (a 2 page narrative) in an appendix of the SCS.*
  - *The subject number was also found in a listing of subjects meeting outlier criteria on page 308 of a 475 page table in an appendix of the SCS on page 4350 (which is page 308 of the 475 page table). In this table a standing and supine HRs of 38 and 40 bpm, respectively which were listed on Day 6 of the study compared to standing and supine heart rates of 80-92 and 90-76 bpm, respectively on previous assessments (includes: 2 baseline assessments and assessments on Days 2, 3, and 4.*
  - *The above subject is described from a clinical perspective in Section 7.1.3.3. C of this review but it is noteworthy that 3 subjects with sinus pauses and syncope are described in olanzapine labeling.*

Section 9 of this review discusses this issue further and a listing of outstanding questions in which responses are yet to be received at the time of this righting are provided in the Attachment 1of this review. Section 4.1 provides a list of responses received so far but that have not been fully reviewed due to their late arrival during the review cycle.

On a final note, limitations found with some of the safety results of some of the clinical parameters were previously described in this review preceding the presentation of the results in each corresponding section (e.g. refer to Section 7.1.7.3.1 on laboratory parameters regarding limitations with urinalysis results, and of results on parameters that were found for only about half the subjects in a given treatment group). However, other data was provided that generally appeared to offset these limitations.

The following summarizes meeting notes to be entered into DFS (Team Leader, Dr. Ni Khin concurred on the minutes below) in which the sponsor provided further clarification on their methods in finding uncpatured subjects in the results on suicidality (after the undersigned reviewer reviewed their N005 response to our question related to this topic):

> In our Tcon today at 1:30 pm with Dr. Michelle Kramer and Heddie, Dr. Kramer explained to us (Drs. Ni Khin, Team Leader and Dr. Karen Brugge, reviewer) that all CIOMS forms (so any and all SAEs) of the Phase III trials were reviewed for any comments of suicidality, aggression or agitation that may have been written on the CIOMS forms by the investigator. If such comments were found in a given CIOMS but were not coded in the CRFs as suicidality-related AEs or SAEs, then the investigator was asked why (by the sponsor). If the investigator did not think it should be coded as a separate AE or SAE, then comments were transferred over to the comment section of the CRFs but were not coded as AEs or SAEs and were therefore not captured in their AE, ADO or SAE database. Therefore, if for example a given patient had suicidality related events (e.g. complained of suicidal thoughts) but the investigator thought it was part of there overall clinical condition or that it was adequately captured by another SAE term (e.g. exacerbation of schizophrenia) then suicidality was not coded and captured in the database as an SAE or AE of suicidality.

The following are examples of subjects identified in a response submission (N005 dated 6/15/06) from the sponsor about suicidality cases in which suicidality was not reported as an AE or SAE term:

- 300381 ER OROS PAL 6 mg (see example below of suicidality comments that the sponsor found upon review of CIOMS forms)
- 300301 ER OROS PAL 12 mg
- And Others

In the original N000 submission on page 1898 in the SCS the following comments on suicidality were found by the sponsor in the CIOMS forms for each of these subjects (as copied from the submission):

```
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 1 NEW RECORD OUTSIDE
FIELD: 13. OTHER - ABNORMAL - NICOTINE WITHDRAWAL
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 2 PT. REFUSED VITAL SIGNS
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 3 PT. REFUSED TO
PARTICIPATE AND COMPLY WITH POST-STUDY VISIT.
```

R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 4 PER SAE REPORT, SUBJECT PRESENTED TO ER ON [redacted] WITH SUICIDAL IDEATION. PER CLINICAL ASSESSMENT THIS IS A SUICIDAL IDEATION. PER [redacted], THE INVESTIGATOR DOES NOT WANT TO ADD SUICIDAL IDEATION
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 5 INVESTIGATOR EXPLAINS: SUBJECT [redacted] HAD TWO HOPITALISATIONS ONE BEGINNING [redacted] .BOTH ARE CONSIDERED EXACERBATION OF SCHIZOPHRENIA.
R076477-SCH-304-0028-300381 ER OROS PAL 6 mg YES YES 6 SUICIDAL IDEATION IS CONSIDERED A PART OF THE CLINICAL SYMPTOMS AND NOT A DIAGNOSIS SEPARATELY.BOTH HOSPITALISATIONS ARE SERIOUS

R076477-SCH-304-0041-300301 ER OROS PAL 12 mg YES YES 1 PER SAE REPORT, SUBJECT WANTED TO COMMIT SUICIDE AND HAS POSSIBLE SUICIDAL IDEATION PER CLINICAL ASSESSMENT. PER [redacted] THE INVESTIGATOR DOES NOT WANT TO ADD SUICIDAL IDEATION TO CRF.
R076477-SCH-304-0041-300301 ER OROS PAL 12 mg YES YES 2 INVESTIGATOR EXPLAINS: THE PATIENT DID REPORT SUICIDAL IDEATION WITHOUT A PLAN TO A POLICE OFFICER PRIOR TO HOSPITALISATION ADMISSION [redacted] AFTER HE HAD BEEN ASSAULTED.

7.2.9 Additional Submissions, Including Safety Update

7.2.9.1 120-Day Safety Update Report

The 4 month Safety Update Report was submitted. Italicized text is used for sections that contain reviewer comments.

The bulk of safety data in the SUR comes from the OL extension trial safety dataset which includes ongoing trials (Studies -702 through -705 combined). This dataset now meets ICH guidelines for exposure of at least 12 months, whereas this dataset only met ICH guidelines for 6 month exposure in the original submission. Therefore, the focus of the review of the SUR is on results from this longterm safety dataset. The table below was provided by the sponsor and shows the results on Pal exposure in this dataset.

Table 12: Total Duration of Paliperidone Exposure – Double-Blind + Open-Label – Through 1 November 2005
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

	— Pla/Pali — (N=336)	— Pali/Pali — (N=685)	— Olza/Pali — (N=249)	— Total — (N=1170)
Total duration of study medication (day)				
N	236	685	249	1170
Category, n (%)				
Week 1-4	35 (15)	4 (1)	44 (18)	83 (7)
Week 5-8	17 (7)	41 (6)	18 (7)	76 (6)
Week 9-12	17 (7)	58 (8)	16 (6)	91 (8)
Week 13-16	5 (2)	48 (7)	13 (5)	66 (6)
Week 17-20	5 (2)	36 (5)	6 (2)	47 (4)
Week 21-24	20 (8)	23 (3)	11 (4)	53 (5)
Week 25-28	30 (13)	14 (2)	23 (9)	67 (6)
Week 29-32	13 (6)	99 (14)	13 (5)	125 (11)
Week 33-36	7 (3)	45 (7)	9 (4)	61 (5)
Week 37-40	4 (2)	31 (5)	7 (3)	42 (4)
Week 41-44	19 (8)	23 (3)	24 (10)	66 (6)
Week 45-48	9 (4)	27 (4)	15 (6)	51 (4)
Week 49-52	36 (15)	44 (6)	34 (14)	114 (10)
> week 52	19 (8)	193 (28)	16 (6)	228 (19)
Mean (SD)	195.4 (126.82)	247.0 (126.33)	188.8 (131.15)	224.2 (130.23)
Median	183.0	237.0	189.0	218.0
Range	(1;391)	(26;453)	(2;379)	(1;453)

tnb813_tl.rtf generated by tesh13.sas

The remainder of the safety data in the SUR is from unpooled studies that include the following:

- *Sudy -301: the "preventions of recurrence" trial that was ongoing at the time of the N000 submission but is now completed,*
- *Study -701: the OL extension study of which Study -301 was the lead-in study.*

The focus of the review of the SUR was on safety data from the pooled longterm OL extension trial dataset (-702 through -705, combined) for the portions of safety data that are described in this review.

Only SAEs and ADOs from the unpooled studies were reviewed, since these 2 trials (studies -301 and -701) provide limited longterm safety data, in contrast to the information provided by the OL extension-trial longterm-safety dataset.

The following paragraphs discuss the rationale for the above-described review strategy.

The longterm OL extension trial dataset (-702 through -705, combined) is an integrated safety dataset that has a substantially larger sample size of subjects receiving at least 6 months and at least 12 months of Pal treatment, respectively than the unpooled Studies -301 and -701. In the integrated OL trial dataset a total of 1170 subjects received OL treatment of which 228 subjects received over 52 weeks of Pal treatment (this enumeration includes Pal treatment in subjects assigned to DB Pal in the lead-in short-term Phase III trials). The remainder of safety data in the SUR came from unpooled trials (-301 and -701) with smaller sample sizes of subjects exposed to shorter duration of treatment. Only approximately 241 subjects received only 14 weeks of treatment in Study -301and only a few subjects received over 16 weeks of OL Pal

treatment in the OL extension trial to Study -301 (e.g. 9 subjects so far have received 17-20 weeks of treatment and only 6 subjects have received 49-52 weeks of treatment, based on Table 8 on page 57 of the SUR). Therefore, the combined dataset of Studies -702 through -705 is the focus of this review and for the purpose of examining safety results with longterm treatment.

Short-term DB placebo controlled Phase III data was also limited in the SUR, since only one study, Study -301 had a placebo controlled, DB phase. The N000 provided sufficient safety information on short-term safety that came from an integrated short-term Phase III dataset of pivotal trials (Studies -303, -304 and -305, combined). The sample size of randomized DB Pal subjects in Study -301 is only approximately 100 subjects of which only approximately 20 subjects exceeded 12 weeks of DB treatment. This sample size is contrasted to the substantially larger sample size of subjects in the pivotal Phase III trials (Studies -303, -304 and -305, combined) that are already provided in the original NDA and previously described in this review. Therefore, only SAEs and ADOs in from the unpooled studies -701 and -301 that were provided in the SUR were reviewed.

Reviewer Comments/Caveats on the Above Results
The integrated longterm (OL extension trial) dataset was presented in the N000 submission with treatment groups subdivided by duration of OL Pal treatment (≤3 months versus > 3 months for each treatment group categorized by previous DB drug assignment in the lead-in study). In the SUR, this updated dataset is presented with the treatment subgroups categorized by duration of exposure as follows: ≤ 6months versus > 6 months categories. As previously noted more subjects were exposed to over 6 months of treatment in this updated dataset. The rationale for subdividing groups in this manner is not clear to the undersigned, since it would be more informative to have presented data over time for all subjects combined (but subdivided only by previous DB treatment assignment and not by duration of exposure). Perhaps one reason for the sponsor subdividing subjects by duration of exposure is that the longer exposed subgroup is more likely to represent subjects who tolerate the drug better than at least some of the subjects who had less time of exposure in these ongoing OL trials.

One potential concern about the disposition of the subjects is discussed in the following. Table 4 in the SUR shows that 30% or more of subjects in any given treatment subgroup with 6 months or less exposure (in the OL extension trial dataset) withdrew early for "other" reason (not due to other reasons: withdrew consent, lost to follow-up, due to an AE, or death). It is recommended that the sponsor be inquired about why these subjects withdrew early since it represents a large proportion of subjects. Despite this large dropout of subjects, the sample size of subjects remaining in the study is sufficient and meets ICH guidelines, as previously discussed.

Deaths
The following table is a comprehensive listing of all deaths of all Phase I-III trials as of the November 1, 2005 cut-off day. There are no deaths that occurred after the cut-off date through

Phase 3 Open-Label Studies					
Treatment Group: Pla/Pali, ≤6 months					
100431 (R076477-SCH-703)	50 Male	Bronchopneumonia Bronchopneumonia	45[3]	None	Not related
Treatment Group: Pali/Pali, >6 months					
100416 (R076477-SCH-703)	42 Female	Completed suicide Fall from 3rd floor	238	None	Not related
Treatment Group: Olan/Pali, >6 months					
200416 (R076477-SCH-703)	31 Female	Completed suicide suicide with medication[4]	238	None	Not related

Note: Gray shading indicates a death that occurred after the cut-off date for NDA 31-999 (31 May 2005) and before the cut-off date for this Update (1 November 2005).

[1] Study day is in reference to the start of double-blind medication, except for Subject 100744 (start of run-in phase).

[2] Relationship based on assessment of investigator.

[3] Subject was withdrawn from the study due to a serious adverse event (electrocardiogram QT corrected interval prolonged) and died of non-treatment-emergent bronchopneumonia 4 days after receiving the last dose of study medication.

[4] Subject ingested venlafaxine and lorazepam.

SAEs.

SAEs and ADOs in Study -301.

Reviewer Comment and Summary: *No new, unexpected ADOs and SAEs were reported that are not already found in the N000 submission, with some possible exceptions. These possible exceptions were incorporated in previous sections of this review that focused on individual subjects with remarkable events, SAEs or ADOs in a previous section (Section 7.1.3.3) of this review.*

ADOs of Potential Hemodynamic or Cardiac Drug Effects. These subjects were incorporated in Section 7.1.3.3 of this review. An additional new ADO (new by nature of the event) was found that was not previously reported that appears to be an isolated event, associated with risk factors in a patient with positive past history for this event. Therefore, it does not appear t be drug-related. The following provides more information on this subject:

> *Venous thrombosis was reported as an SAE in subject 100738 but this subject had a prior event of this nature 1 month prior to this study (phlebitis) and had risk factors (49 year old, obese, woman with chronic hepatitis by history).*

The following table was provided in the SUR.

Table 31: Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term - Run-In and Stabilization Phases (Study R076477-SCH-301: All Treated Analysis Set)

Body System or Organ Class Dictionary-derived Term	ER OROS PAL (RI/ST) (N=530) n (%)
Total no. subjects with serious AE	30 (6)
Psychiatric disorders	25 (5)
Schizophrenia	10 (2)
Psychotic disorder	8 (2)
Agitation	4 (1)
Aggression	2 (<1)
Suicidal ideation	2 (<1)
Depression	1 (<1)
Hallucination	1 (<1)
Intentional self-injury	1 (<1)
Paranoia	1 (<1)
Suicide attempt	1 (<1)
Injury, poisoning and procedural complications	2 (<1)
Injury	1 (<1)
Intentional overdose	1 (<1)
Blood and lymphatic system disorders	1 (<1)
Thrombocytopenia	1 (<1)
Gastrointestinal disorders	1 (<1)
Swollen tongue	1 (<1)
Hepatobiliary disorders	1 (<1)
Cholelithiasis	1 (<1)
Nervous system disorders	1 (<1)
Akathisia	1 (<1)
Dyskinesia	1 (<1)
Tremor	1 (<1)
Social circumstances	1 (<1)
Social problem	1 (<1)

tsfae105_tsfae05.rtf generated by tsfae05.sas.

6 subjects, each with the following respective SAEs were also ADOs (study drug was permanently discontinued): intentional overdose and suicide attempt (1 subject), suicidal ideation, swollen tongue, thrombocytopenia, agitation, and cholelithiasis.

SAEs of schizophrenia and aggression in 1 subject lead to a dose adjustment and dyskinesia and akathisia in another subject lead to a temporary cessation of treatment.

Table 32: Treatment-Emergent Serious Adverse Events by Preferred Term - Double-Blind Phase
(Study R076477-SCH-301: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)	Total (N=206) n (%)
Total no. subjects with serious AE	16 (16)	8 (8)	24 (12)
Psychiatric disorders	15 (15)	6 (6)	21 (10)
Schizophrenia	10 (10)	5 (5)	15 (7)
Psychotic disorder	4 (4)	0	4 (2)
Agitation	0	1 (1)	1 (<1)
Completed suicide*	1 (1)	0	1 (<1)
Suicidal ideation	1 (1)	0	1 (<1)
Injury, poisoning and procedural complications	1 (1)	1 (1)	2 (1)
Gun shot wound*	1 (1)	0	1 (<1)
Treatment noncompliance	0	1 (1)	1 (<1)
Vascular disorders	0	2 (2)	2 (1)
Hypertension	0	1 (1)	1 (<1)
Venous thrombosis	0	1 (1)	1 (<1)
Cardiac disorders	0	1 (1)	1 (<1)
Tachycardia	0	1 (1)	1 (<1)
Musculoskeletal and connective tissue disorders	0	1 (1)	1 (<1)
Musculoskeletal chest pain	0	1 (1)	1 (<1)

* This event resulted in death of subject (see Section 2.1.2).
tsfae106_tsfae05.rtf generated by tsfae05.sas.

Best Possible Copy

Table 33: Serious Adverse Events Through 1 November 2005
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=13) n (%)	Pla/Pali >6 months (N=67) n (%)	Pali/Pali <=6 months (N=2) n (%)	Pali/Pali >6 months (N=70) n (%)	Pali(NO DB)/Pali <=6 months (N=59) n (%)	Pali(NO DB)/Pali >6 months (N=24) n (%)
Total no. subjects with serious adverse events	2 (15)	3 (4)	0	1 (1)	0	0
Psychiatric disorders	1 (8)	2 (3)	0	1 (1)	0	0
Schizophrenia	0	1 (1)	0	1 (1)	0	0
Paranoia	0	1 (1)	0	0	0	0
Suicide attempt	1 (8)	0	0	0	0	0
Injury, poisoning and procedural complications	0	1 (1)	0	0	0	0
Tibia fracture	0	1 (1)	0	0	0	0
Nervous system disorders	1 (8)	0	0	0	0	0
Syncope	1 (8)	0	0	0	0	0

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 33: Serious Adverse Events Through 1 November 2005 (Continued)
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Total Pali <=6 months (N=74) n (%)	Total Pali >6 months (N=161) n (%)
Total no. subjects with serious adverse events	2 (3)	4 (2)
Psychiatric disorders	1 (1)	3 (2)
Schizophrenia	0	2 (1)
Paranoia	0	1 (1)
Suicide attempt	1 (1)	0
Injury, poisoning and procedural complications	0	1 (1)
Tibia fracture	0	1 (1)
Nervous system disorders	1 (1)	0
Syncope	1 (1)	0

See footnotes on the first page of the table.
tzfae08_t1.rtf generated by tzfae08.sas.

Table 34: Serious Adverse Events Through 1 November 2005
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Total no. subjects with serious adverse events	17 (17)	12 (9)	40 (19)	56 (12)	33 (31)	14 (10)	90 (22)	82 (11)
Psychiatric disorders	12 (12)	9 (7)	35 (17)	43 (9)	30 (28)	11 (8)	77 (19)	63 (8)
Psychotic disorder	7 (7)	2 (1)	14 (7)	20 (4)	12 (11)	4 (3)	33 (8)	26 (3)
Schizophrenia	2 (2)	3 (2)	15 (7)	15 (3)	13 (12)	3 (2)	30 (7)	21 (3)
Depression	0	2 (1)	1 (<1)	4 (1)	2 (2)	1 (1)	3 (1)	7 (1)
Agitation	2 (2)	1 (1)	3 (1)	2 (<1)	5 (5)	1 (1)	10 (2)	4 (1)
Hallucination, auditory	0	0	0	4 (1)	0	0	0	4 (1)
Suicidal ideation	2 (2)	1 (1)	3 (1)	3 (1)	0	0	5 (1)	4 (1)
Acute psychosis	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Anxiety	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Completed suicide	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Depressed mood	0	0	0	2 (<1)	0	0	0	2 (<1)
Aggression	2 (2)	1 (1)	0	0	4 (4)	0	6 (1)	1 (<1)
Alcoholism	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Confusional state	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Delusion	0	0	2 (1)	1 (<1)	0	0	2 (<1)	1 (<1)
Paranoia	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia, paranoid type	0	0	0	1 (<1)	0	0	0	1 (<1)
Self-injurious ideation	0	0	0	1 (<1)	1 (1)	0	1 (<1)	1 (<1)
Sleep disorder	0	1 (1)	0	0	0	0	0	1 (<1)
Suicide attempt	1 (1)	1 (1)	2 (1)	0	1 (1)	0	4 (1)	1 (<1)
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Insomnia	0	0	1 (<1)	0	2 (2)	0	3 (1)	0

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 34: Serious Adverse Events Through 1 November 2005 (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Infections and infestations								
Nasopharyngitis	0	0	0	2 (<1)	0	0	0	2 (<1)
Bronchitis acute	0	0	0	1 (<1)	0	0	0	1 (<1)
Cellulitis	0	0	0	1 (<1)	0	0	0	1 (<1)
Measles	0	0	0	1 (<1)	0	0	0	1 (<1)
Perianal abscess	0	0	0	1 (<1)	0	0	0	1 (<1)
Pulmonary tuberculosis	0	0	0	0	0	1 (1)	0	1 (<1)
Sinusitis	0	0	0	1 (<1)	0	0	0	1 (<1)
Urinary tract infection	0	0	0	1 (<1)	0	0	0	1 (<1)
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	0	0	0	0	1 (1)	0	1 (<1)	0
Nervous system disorders	1 (1)	2 (1)	4 (2)	5 (1)	1 (1)	0	6 (1)	7 (1)
Akathisia	0	0	0	2 (<1)	1 (1)	0	1 (<1)	2 (<1)
Dizziness	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Dystonia	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Ischaemic stroke	0	1 (1)	0	0	0	0	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Transient ischaemic attack	1 (1)	0	0	0	0	0	1 (<1)	0

See footnotes on the first page of the table.

Table 34: Serious Adverse Events Through 1 November 2005 (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
General disorders and administration site conditions	0	0	1 (<1)	4 (1)	1 (1)	0	2 (<1)	4 (1)
Pyrexia	0	0	0	2 (<1)	0	0	0	2 (<1)
Cyst	0	0	0	1 (<1)	0	0	0	1 (<1)
Irritability	0	0	0	1 (<1)	0	0	0	1 (<1)
Chills	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
Injury, poisoning and procedural complications								
Fall	0	0	0	1 (<1)	0	0	0	1 (<1)
Road traffic accident	0	1 (1)	0	0	0	0	0	1 (<1)
Traumatic haematoma	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Alcohol poisoning	1 (1)	0	0	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Overdose	0	0	0	0	1 (1)	0	1 (<1)	0
Investigations	1 (1)	0	0	2 (<1)	0	0	1 (<1)	2 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Metabolism and nutrition disorders	0	0	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Diabetes mellitus	0	0	0	1 (<1)	0	0	0	1 (<1)
Hyponatraemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Hypokalaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (<1)	0	1 (1)	0	2 (<1)
Benign neoplasm of skin	0	0	0	0	0	1 (1)	0	1 (<1)
Colon neoplasm	0	0	0	1 (<1)	0	0	0	1 (<1)

See footnotes on the first page of the table.

Table 34: Serious Adverse Events Through 1 November 2005 (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (<1)	1 (<1)	0	1 (1)	1 (<1)	2 (<1)
Asthma	0	0	0	0	0	1 (1)	0	1 (<1)
Dyspnoea	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Pneumonia aspiration	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood and lymphatic system disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Anaemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Gastrointestinal disorders	1 (1)	1 (1)	0	0	0	0	1 (<1)	1 (<1)
Crohn's disease	0	1 (1)	0	0	0	0	0	1 (<1)
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Hepatobiliary disorders	0	0	0	1 (<1)	0	0	0	1 (<1)
Cholelithiasis	0	0	0	1 (<1)	0	0	0	1 (<1)
Cardiac disorders	1 (1)	0	2 (1)	0	2 (2)	0	5 (1)	0
Bundle branch block	1 (1)	0	0	0	0	0	1 (<1)	0
Myocardial infarction	0	0	1 (<1)	0	0	0	1 (<1)	0
Sinus tachycardia	0	0	0	0	1 (1)	0	1 (<1)	0
Tachycardia	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Social circumstances	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0

See footnotes on the first page of the table

120

The following additional SAEs were found on page 121 of SUR (copied from the submission):

"Serious Adverse Events From 2 November 2005 through 31 December 2005
Reports of serious adverse events were received by the sponsor for 9 subjects in the ongoing open-label Phase 3 trials from 2 November 2005 through 31 December 2005. No subjects died. There was 1 suicide attempt (by overdose with acebutolol hydrochloride) and 1 overdose (a subject who took an extra 15 mg dose of ER OROS paliperidone for 8 days due to disturbed sleep; this subject was subsequently hospitalized for suicidal ideation and schizophrenia). The other non-fatal serious adverse events involved hospitalizations for exacerbations of schizophrenia (n=3), psychotic disorder (n=2), and anxiety, agitation, varicocele, suicidal ideation, and delusion (n=1 each). Clinical safety reports (CIOMS forms) for these subjects are provided in Appendix 3.6."

ADOs in Studies -301, -701 and ADOs of the Pooled, OL-trial Dataset

Table 35: Treatment-Emergent Adverse Events Leading to Study Discontinuation by MedDRA Preferred Term - Run-In and Stabilization Phases (Study R076477-SCH-301: All Treated Analysis Set)

Body System or Organ Class Dictionary-derived Term	ER OROS PAL (RI/ST) (N=530) n (%)
Total no. subjects who discontinued due to AE	27 (5)
Psychiatric disorders	10 (2)
Aggression	2 (<1)
Agitation	2 (<1)
Insomnia	2 (<1)
Anxiety	1 (<1)
Depression	1 (<1)
Hallucination, auditory	1 (<1)
Schizophrenia	1 (<1)
Suicidal ideation	1 (<1)
Suicide attempt	1 (<1)
Investigations	6 (1)
Blood pressure increased	1 (<1)
Electrocardiogram QRS complex prolonged	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (<1)
Electrocardiogram QT prolonged	1 (<1)
Electrocardiogram T wave abnormal	1 (<1)
Electrocardiogram T wave inversion	1 (<1)
Nervous system disorders	5 (1)
Akathisia	2 (<1)
Headache	2 (<1)
Tremor	1 (<1)
Skin and subcutaneous tissue disorders	2 (<1)
Dermatitis allergic	1 (<1)
Pruritus	1 (<1)
Rash	1 (<1)
Rash erythematous	1 (<1)
Blood and lymphatic system disorders	1 (<1)
Thrombocytopenia	1 (<1)
Eye disorders	1 (<1)
Vision blurred	1 (<1)
Gastrointestinal disorders	1 (<1)
Swollen tongue	1 (<1)
Hepatobiliary disorders	1 (<1)
Cholelithiasis	1 (<1)
Injury, poisoning and procedural complications	1 (<1)
Intentional overdose	1 (<1)
Musculoskeletal and connective tissue disorders	1 (<1)
Muscle spasms	1 (<1)
Reproductive system and breast disorders	1 (<1)
Amenorrhoea	1 (<1)
Galactorrhoea	1 (<1)

tsfae108_tsfae07.rtf generated by tsfae07.sas.

Table 36: Treatment-Emergent Adverse Events Leading to Study Discontinuation by MedDRA Preferred Term - Double-Blind Phase (Study R076477-SCH-301: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Placebo (N=102) n (%)	ER OROS PAL (N=104) n (%)	Total (N=206) n (%)
Total no. subjects who discontinued due to AE	1 (1)	3 (3)	4 (2)
Vascular disorders	0	2 (2)	2 (1)
Hypertension	0	1 (1)	1 (<1)
Venous thrombosis	0	1 (1)	1 (<1)
Cardiac disorders	0	1 (1)	1 (<1)
Tachycardia	0	1 (1)	1 (<1)
Eye disorders	0	1 (1)	1 (<1)
Visual disturbance	0	1 (1)	1 (<1)
Gastrointestinal disorders	1 (1)	0	1 (<1)
Nausea	1 (1)	0	1 (<1)
Musculoskeletal and connective tissue disorders	0	1 (1)	1 (<1)
Musculoskeletal chest pain	0	1 (1)	1 (<1)
Nervous system disorders	0	1 (1)	1 (<1)
Sedation	0	1 (1)	1 (<1)

tsfae107_tsfae07.rtf generated by tsfae07.sas.

Table 37: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=13) n (%)	Pla/Pali >6 months (N=67) n (%)	Pali/Pali <=6 months (N=2) n (%)	Pali/Pali >6 months (N=70) n (%)	Pali(NO DB)/Pali <=6 months (N=59) n (%)	Pali(NO DB)/Pali >6 months (N=24) n (%)
Total no. subjects with adverse events	3 (23)	2 (3)	0	1 (1)	3 (5)	0
Psychiatric disorders	1 (8)	1 (1)	0	1 (1)	1 (2)	0
Anxiety	0	1 (1)	0	0	0	0
Depression	0	1 (1)	0	0	1 (2)	0
Suicidal ideation	0	0	0	1 (1)	0	0
Suicide attempt	1 (8)	0	0	0	0	0
Investigations	0	1 (1)	0	0	0	0
Electrocardiogram QT prolonged	0	1 (1)	0	0	0	0
Gastrointestinal disorders	0	0	0	0	1 (2)	0
Vomiting	0	0	0	0	1 (2)	0
Nervous system disorders	2 (15)	0	0	0	1 (2)	0
Dizziness	0	0	0	0	1 (2)	0
Dyskinesia	1 (8)	0	0	0	0	0
Syncope	1 (8)	0	0	0	0	0
Tremor	1 (8)	0	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	1 (2)	0
Amenorrhoea	0	0	0	0	1 (2)	0

Note: Percentages calculated with the number of subjects in each group as denominator.

Table 37: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Open-Label Study R076477-SCH-701: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Total Pali <=6 months (N=74) n (%)	Total Pali >6 months (N=161) n (%)
Total no. subjects with adverse events	6 (8)	3 (2)
Psychiatric disorders	2 (3)	2 (1)
Anxiety	0	1 (1)
Depression	1 (1)	1 (1)
Suicidal ideation	0	1 (1)
Suicide attempt	1 (1)	0
Investigations	0	1 (1)
Electrocardiogram QT prolonged	0	1 (1)
Gastrointestinal disorders	1 (1)	0
Vomiting	1 (1)	0
Nervous system disorders	3 (4)	0
Dizziness	1 (1)	0
Dyskinesia	1 (1)	0
Syncope	1 (1)	0
Tremor	1 (1)	0
Reproductive system and breast disorders	1 (1)	0
Amenorrhoea	1 (1)	0

See footnotes on the first page of the table.
tzfae10_t1.rtf generated by tzfae10.sas.

125

Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Total no. subjects with adverse events	10 (10)	5 (4)	30 (14)	14 (3)	18 (17)	8 (6)	58 (14)	27 (4)
Psychiatric disorders	4 (4)	4 (3)	19 (9)	9 (2)	10 (9)	5 (4)	33 (8)	18 (2)
Depression	1 (1)	1 (1)	2 (1)	3 (1)	1 (1)	1 (1)	4 (1)	5 (1)
Psychotic disorder	2 (2)	0	3 (1)	3 (1)	3 (3)	2 (1)	8 (2)	5 (1)
Anxiety	0	1 (1)	0	0	1 (1)	1 (1)	1 (<1)	2 (<1)
Insomnia	0	0	3 (1)	1 (<1)	1 (1)	1 (1)	4 (1)	2 (<1)
Acute psychosis	0	0	0	0	0	1 (1)	0	1 (<1)
Depressed mood	0	0	0	0	0	1 (1)	0	1 (<1)
Depressive symptom	0	1 (1)	0	0	0	0	0	1 (<1)
Paranoia	0	1 (1)	1 (<1)	0	0	0	1 (<1)	1 (<1)
Polydipsia psychogenic	0	0	0	1 (<1)	0	0	0	1 (<1)
Schizophrenia	0	0	2 (1)	1 (<1)	3 (3)	0	5 (1)	1 (<1)
Suicidal ideation	1 (1)	0	1 (<1)	1 (<1)	2 (2)	0	4 (1)	1 (<1)
Aggression	0	0	0	0	1 (1)	0	1 (<1)	0
Agitation	0	0	1 (<1)	0	2 (2)	0	3 (1)	0
Alcoholism	0	0	0	0	1 (1)	0	1 (<1)	0
Confusional state	0	0	3 (1)	0	0	0	3 (1)	0
Delusion	0	0	2 (1)	0	1 (1)	0	3 (1)	0
Hallucination	0	0	1 (<1)	0	0	0	1 (<1)	0
Hallucination, auditory	0	0	1 (<1)	0	0	0	1 (<1)	0
Homicidal ideation	0	0	1 (<1)	0	0	0	1 (<1)	0
Hostility	0	0	1 (<1)	0	0	0	1 (<1)	0
Suicide attempt	0	0	1 (<1)	0	0	0	1 (<1)	0

Note: Percentages calculated with the number of subjects in each group as denominator.

127

Appears This Way
On Original

Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Nervous system disorders (continued)								
Akathisia	0	0	2 (1)	0	0	2 (1)	2 (<1)	2 (<1)
Convulsion	0	0	0	1 (<1)	0	0	0	1 (<1)
Dyskinesia	0	1 (1)	0	0	0	0	0	1 (<1)
Extrapyramidal disorder	0	0	1 (<1)	0	0	1 (1)	1 (<1)	1 (<1)
Hypertonia	0	0	0	0	0	1 (1)	0	1 (<1)
Mental impairment	0	0	0	0	0	1 (1)	0	1 (<1)
Coordination abnormal	0	0	1 (<1)	0	0	0	1 (<1)	0
Dizziness	0	0	0	0	2 (2)	0	2 (<1)	0
Dysarthria	0	0	1 (<1)	0	0	0	1 (<1)	0
Dystonia	0	0	1 (<1)	0	0	0	1 (<1)	0
Grand mal convulsion	0	0	1 (<1)	0	0	0	1 (<1)	0
Lethargy	0	0	1 (<1)	0	0	0	1 (<1)	0
Sedation	0	0	1 (<1)	0	0	0	1 (<1)	0
Tremor	1 (1)	0	0	0	0	0	1 (<1)	0
Investigations	1 (1)	1 (1)	1 (<1)	3 (1)	2 (2)	0	4 (1)	4 (1)
Weight increased	0	1 (1)	0	1 (<1)	0	0	0	2 (<1)
Alanine aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Aspartate aminotransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood creatine phosphokinase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Blood prolactin increased	0	1 (1)	0	0	0	0	0	1 (<1)
Electrocardiogram QT corrected interval prolonged	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
Gamma-glutamyltransferase increased	0	0	0	1 (<1)	0	0	0	1 (<1)
Electrocardiogram T wave abnormal	0	0	0	0	1 (1)	0	1 (<1)	0
Hepatic enzyme increased	0	0	0	0	1 (1)	0	1 (<1)	0
Weight decreased	0	0	1 (<1)	0	0	0	1 (<1)	0

See footnotes on the first page of the table.

Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Reproductive system and breast disorders	0	0	2 (1)	1 (<1)	0	1 (1)	2 (<1)	2 (<1)
Erectile dysfunction	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Galactorrhoea	0	0	0	0	0	1 (1)	0	1 (<1)
Retrograde ejaculation	0	0	1 (<1)	0	0	0	1 (<1)	0
Injury, poisoning and procedural complications	1 (1)	0	2 (1)	1 (<1)	0	0	3 (1)	1 (<1)
Traumatic haematoma	0	0	0	1 (<1)	0	0	0	1 (<1)
Accidental overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Intentional overdose	0	0	1 (<1)	0	0	0	1 (<1)	0
Self mutilation	1 (1)	0	0	0	0	0	1 (<1)	0
Metabolism and nutrition disorders	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Hyponatraemia	0	0	0	1 (<1)	0	0	0	1 (<1)
Anorexia	0	0	1 (<1)	0	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Pneumonia aspiration	0	0	0	1 (<1)	0	0	0	1 (<1)
Dyspnoea	0	0	1 (<1)	0	0	0	1 (<1)	0
Cardiac disorders	1 (1)	0	3 (1)	0	2 (2)	0	6 (1)	0
Myocardial infarction	0	0	1 (<1)	0	0	0	1 (<1)	0
Myocardial ischaemia	0	0	1 (<1)	0	0	0	1 (<1)	0
Palpitations	0	0	0	0	1 (1)	0	1 (<1)	0
Sinus tachycardia	1 (1)	0	0	0	1 (1)	0	2 (<1)	0
Tachycardia	0	0	1 (<1)	0	0	0	1 (<1)	0
Eye disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Vision blurred	0	0	0	0	1 (1)	0	1 (<1)	0

See footnotes on the first page of the table.

Appears This Way
On Original

Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Gastrointestinal disorders	1 (1)	0	1 (<1)	0	3 (3)	0	5 (1)	0
Constipation	0	0	0	0	1 (1)	0	1 (<1)	0
Dysphagia	0	0	1 (<1)	0	0	0	1 (<1)	0
Nausea	0	0	0	0	1 (1)	0	1 (<1)	0
Peptic ulcer	1 (1)	0	0	0	0	0	1 (<1)	0
Vomiting	0	0	0	0	2 (2)	0	2 (<1)	0
General disorders and administration site conditions	0	0	1 (<1)	0	1 (1)	0	2 (<1)	0
Fatigue	0	0	1 (<1)	0	0	0	1 (<1)	0
Oedema	0	0	0	0	1 (1)	0	1 (<1)	0
Infections and infestations	1 (1)	0	1 (<1)	0	0	0	2 (<1)	0
Hepatitis A	0	0	1 (<1)	0	0	0	1 (<1)	0
Pneumonia	1 (1)	0	0	0	0	0	1 (<1)	0
Musculoskeletal and connective tissue disorders	1 (1)	0	1 (<1)	0	2 (2)	0	4 (1)	0
Arthralgia	0	0	0	0	1 (1)	0	1 (<1)	0
Joint stiffness	1 (1)	0	0	0	0	0	1 (<1)	0
Muscle rigidity	0	0	1 (<1)	0	0	0	1 (<1)	0
Muscle twitching	0	0	0	0	1 (1)	0	1 (<1)	0
Skin and subcutaneous tissue disorders	0	0	1 (<1)	0	0	0	1 (<1)	0
Acne	0	0	1 (<1)	0	0	0	1 (<1)	0
Social circumstances	0	0	2 (1)	0	2 (2)	0	4 (1)	0
Alcohol use	0	0	1 (<1)	0	0	0	1 (<1)	0
Drug abuser	0	0	1 (<1)	0	2 (2)	0	3 (1)	0

See footnotes on the first page of the table.

Table 38: Treatment-Emergent Adverse Events Leading to Study Discontinuation (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Vascular disorders	0	0	0	0	1 (1)	0	1 (<1)	0
Hypertension	0	0	0	0	1 (1)	0	1 (<1)	0

See footnotes on the first page of the table.
tsfae10_t1.rtf generated by tsfae10.sas.

Common Adverse Events of the Integrated OL Safety Dataset

The sponsor provide several tables that were generally 20 or more pages each on common AEs (in the appendix of the SUR). In place of in-text summary tables the sponsor described the following with respect to common AEs, as copied out of this section of the SUR:

> "The most common adverse event among subjects treated with ER OROS paliperidone and placebo was insomnia, while the most common event among subjects treated with olanzapine was somnolence. Of the adverse events reported by 5% or more of the subjects in any treatment group, the following preferred terms had differences in incidence of ≥3% between the ER OROS paliperidone and other groups:
> • Headache, akathisia, somnolence, extrapyramidal disorder, dizziness, hypertonia, insomnia, psychotic disorder, depression, tachycardia, and sinus tachycardia were more

common among subjects who received ER OROS paliperidone than among those who received placebo;
• Headache, akathisia, extrapyramidal disorder, tremor, hypertonia, insomnia, anxiety, psychotic disorder, schizophrenia, depression, nausea, vomiting, tachycardia, and nasopharyngitis were more common among subjects who received ER OROS paliperidone than among those who received olanzapine;
• Somnolence and sedation were more common among subjects who received olanzapine than among those who received placebo or ER OROS paliperidone.
• The percentages of subjects reporting any adverse event and, in most cases, the percentages of subjects reporting the common adverse events were higher for subjects who received ER OROS paliperidone for >6 months than for subjects who received treatment for ≤6 months.
These results are similar to those presented in the SCS of NDA 21-999 using a cut-off date of 31 May 2005."

Laboratory Parameter Results

Laboratory trial data results of Completed Study -301:

SAEs and/or ADOs due to Laborateory-related AEs:

One subject had thrombocytopenia as an SAE and an ADO that occurred due to laboratory related AEs (as described in Section 3.2.1 of the SUR). Subject 100847 (40 year old male) was found in the line listing as the SAE and ADO due to thrombocytopenia which occurred during the stabilization OL treatment phase of this study (on Day 71 of the study and Day 15 of this study phase). No other ADOs or SAEs occurred due to laboratory related AEs in Study 301.

Statistical Descriptive Results. *Results were generally did not reveal any new remarkable findings that are not already described in this review, although the following additional observations are noted.*

Comment and Caveat. *Some of the cell sizes for a given data-point (on a given parameter in a given treatment group at a given time-point) were small such that mean values may deviate or be skewed from values at other time-points within the same treatment group (note that treatment groups are subdivided into ≤ 6months and > 6 month subgroups with respect to duration of exposure, as previously described). Consequently, cell sizes of approximately 100 subjects for a given time-point in a given treatment group are considered more valid and were the focus of this review.*

Another major limitation with all safety data from OL trials is the absence of placebo group. Yet, even in the absence of a placebo group one can examine the data to determine if the data yielded remarkable and/or unexpected signal that was not revealed in the placebo controlled short-term trials.

This updated dataset allows for examination of safety parameters over time through 1 year of exposure in contrast to the data provided in the N000 submission at which point the sample size of subject exposed to 1 year of treatment was small.

Please note the following semantics employed in sections below. The > 6 month and ≤ 6 month subgroups are also referred to as "exposure" subgroups in this review.

Laboratory trial data results of OL extension trial dataset (-702 through -705, combined):
SAEs and ADOs due to Laboratory-related AEs were the following:
The SUR describes the following SAEs due to laboratory parameter abnormalities (in 1 subject each) were: anemia, CPK increased, hyponatremia and hypokalemia

Note that one SAE was cholelithiasis was found by the undersigned reviewer, as described in Section 7.1.3.3 (under a subsection on LFTs).

Statistical Descriptive Results. *While noting the above caveats the results generally failed to reveal any new remarkable findings that differ from that already described in this review although the following additional observations are noted:*

- *Mean decreases in HgB values are typically -3.0 g/l or sometimes greater were observed during the OL longterm treatment.*

  It is also noteworthy that the olanzapine OL groups showed similar decreases in mean HgB values.

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DLAB03: Laboratory Values: Means and Mean Changes Over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base		Change from baseline					
	N	Mean	SD	Med	Min	Max	Mean (SD)	N	Mean	SE	SD	Med	Min	Max
HEMOGLOBIN (g/l)														
Pla/Pali <=6 months														
SCREENING (DB)	97	144.62	16.051	143.00	112.0	190.0								
BASELINE (DB)	98	145.72	15.811	147.00	112.0	194.0								
DAY 15 (DB)	96	146.96	15.642	147.00	108.0	191.0	145.68 (15.956)	96	1.29	0.917	8.009	1.00	-16.0	20.0
DAY 43 (DB)	59	143.37	15.974	143.00	107.0	171.0	143.47 (15.756)	59	-0.10	1.073	8.246	0.00	-24.0	18.0
END POINT (DB)	98	144.55	15.238	143.00	107.0	179.0	145.72 (15.811)	98	-1.17	0.905	8.956	0.00	-26.0	22.0
BASE (OPEN)	98	144.55	15.238	143.00	107.0	179.0	145.72 (15.811)	98	-1.17	0.905	8.956	0.00	-26.0	22.0
WEEK 12 (OPEN)	15	130.67	9.529	130.00	115.0	149.0	133.53 (12.506)	15	-2.87	2.214	8.576	-6.00	-17.0	15.0
WEEK 24 (OPEN)	56	140.41	13.863	138.00	114.0	178.0	143.09 (14.073)	56	-2.68	1.239	9.274	-3.00	-26.0	19.0
END POINT (OPEN)	62	139.44	13.759	138.00	114.0	178.0	142.50 (14.053)	62	-3.06	1.236	9.734	-3.00	-32.0	19.0
Pla/Pali >6 months														
SCREENING (DB)	134	143.22	14.415	144.50	92.0	175.0								
BASELINE (DB)	137	144.66	15.307	146.00	81.0	179.0								
DAY 15 (DB)	132	144.15	15.507	143.50	95.0	187.0	144.53 (15.422)	132	-0.38	0.618	7.105	-1.00	-21.0	16.0
DAY 43 (DB)	92	144.58	16.347	145.50	94.0	199.0	144.54 (16.370)	92	0.03	0.985	9.443	0.50	-27.0	37.0
END POINT (DB)	136	144.36	14.936	145.00	94.0	199.0	144.59 (15.343)	136	-0.23	0.749	8.740	0.50	-27.0	37.0
BASE (OPEN)	137	144.55	15.023	145.00	94.0	199.0	144.66 (15.307)	137	-0.10	0.756	8.853	0.00	-27.0	37.0
WEEK 12 (OPEN)	8	126.75	12.714	128.00	111.0	144.0	133.13 (14.096)	8	-6.38	1.413	3.998	-6.50	-11.0	-1.0
WEEK 24 (OPEN)	127	141.33	15.858	141.00	89.0	178.0	144.88 (15.434)	127	-3.55	0.925	10.420	-3.00	-44.0	25.0
WEEK 52 (OPEN)	42	138.38	15.633	138.00	102.0	169.0	139.95 (16.050)	42	-1.57	1.507	9.763	-2.50	-25.0	21.0
END POINT (OPEN)	129	140.96	15.798	140.00	98.0	178.0	144.66 (15.509)	129	-3.70	0.925	10.508	-3.00	-44.0	23.0
Pali/Pali <=6 months														
SCREENING (DB)	201	144.18	15.589	145.00	94.0	183.0								
BASELINE (DB)	205	145.75	15.771	147.00	89.0	187.0								
Pali/Pali <=6 months														
DAY 15 (DB)	200	142.46	15.555	143.00	98.0	184.0	145.67 (15.888)	199	-3.38	0.570	8.044	-3.00	-24.0	35.0
DAY 43 (DB)	150	142.14	15.147	144.50	99.0	172.0	145.66 (15.736)	149	-3.57	0.707	8.628	-4.00	-27.0	33.0
END POINT (DB)	206	142.24	15.639	145.00	99.0	174.0	145.66 (15.759)	204	-3.61	0.579	8.263	-4.00	-27.0	33.0
BASE (OPEN)	207	142.38	15.708	145.00	99.0	174.0	145.75 (15.771)	205	-3.56	0.575	8.240	-4.00	-27.0	33.0
WEEK 12 (OPEN)	10	127.00	12.138	123.00	114.0	152.0	128.90 (12.444)	10	-1.80	3.431	10.850	0.00	-30.0	8.0
WEEK 24 (OPEN)	114	143.51	16.691	145.50	84.0	181.0	146.88 (16.735)	114	-3.37	0.943	10.073	-3.00	-32.0	46.0
END POINT (OPEN)	124	142.19	16.920	144.00	84.0	181.0	145.42 (17.118)	124	-3.23	0.908	10.107	-3.00	-32.0	46.0
Pali/Pali >6 months														
SCREENING (DB)	458	142.14	15.360	142.00	80.0	192.0								
BASELINE (DB)	469	143.10	15.906	144.00	82.0	184.0								
DAY 15 (DB)	456	139.80	15.202	140.50	83.0	176.0	143.11 (15.789)	454	-3.33	0.386	8.219	-3.00	-28.0	38.0
DAY 43 (DB)	408	139.68	15.748	140.00	85.0	181.0	143.04 (15.855)	406	-3.38	0.441	8.882	-3.00	-34.0	25.0
END POINT (DB)	469	139.93	15.656	140.00	85.0	181.0	143.12 (15.934)	467	-3.21	0.409	8.840	-3.00	-34.0	25.0
BASE (OPEN)	471	139.97	15.730	140.00	85.0	181.0	143.10 (15.906)	469	-3.15	0.408	8.836	-3.00	-34.0	25.0
WEEK 12 (OPEN)	43	131.49	13.213	131.00	90.0	163.0	133.26 (13.146)	43	-1.77	1.496	9.810	-1.00	-28.0	17.0
WEEK 24 (OPEN)	423	140.89	14.290	142.00	75.0	174.0	142.73 (15.885)	420	-1.83	0.528	10.829	-2.00	-56.0	30.0
WEEK 52 (OPEN)	121	142.54	13.912	143.00	109.0	174.0	143.97 (15.079)	120	-1.23	1.008	11.044	-1.00	-31.0	41.0
END POINT (OPEN)	432	141.22	13.773	142.00	97.0	174.0	142.99 (15.847)	429	-1.63	0.499	10.334	-2.00	-36.0	41.0

- *Platelet count shows decreases that were numerically greater with 6 months or greater treatment compared to less than 6 months of Pal treatment as described in the following and as shown below (copied sections of Appendix 5.3.1).*

Mean decreases during Pal treatment appeared greater with increasing exposure over time based on numerical comparisons of the larger treatment subgroups such as the in the following subgroups (shown below with results from additional subgroups): DB Pal/OL Pal > 6 month group and total Pal > 6 month group in which mean decreases were approached over -20 1 giga/l or greater by 6 months of OL treatment and generally continued to be over -20 giga/l through OL treatment endpoint (including the 12 month time-point) as compared to mean changes that were generally less than -10 on previously time-points.

Note that mean decreases were smaller during Olanzapine DB treatment than during Pal treatment.

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DLAB02: Laboratory Values: Means and Mean Changes Over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base	Change from baseline					
	N	Mean	SD	Med	Min	Max	Mean (SD)	N	Mean	SE	SD	Med	Min	Max
PLATELETS (giga/l)														
Pla/Pali >6 months														
SCREENING (DB)	131	254.35	61.443	250.00	127.0	415.0								
BASELINE (DB)	137	262.17	70.364	256.00	62.0	434.0								
DAY 15 (DB)	130	275.10	67.372	266.00	105.0	456.0	261.72 (70.053)	130	13.38	4.307	49.110	11.50	-127.0	210.0
DAY 43 (DB)	91	273.41	76.752	272.00	96.0	507.0	265.70 (73.146)	91	7.70	5.239	49.980	3.00	-109.0	194.0
END POINT (DB)	135	274.76	77.037	259.00	91.0	507.0	262.71 (70.625)	135	12.04	4.611	53.579	8.00	-109.0	194.0
BASE (OPEN)	137	274.75	77.684	266.00	91.0	507.0	262.17 (70.364)	137	12.61	4.587	53.693	8.00	-109.0	194.0
WEEK 12 (OPEN)	8	264.63	53.573	275.50	122.0	374.0	230.25 (110.891)	8	34.38	25.507	72.145	40.00	-95.0	140.0
WEEK 24 (OPEN)	126	250.17	66.596	245.50	93.0	505.0	262.50 (71.406)	126	-12.33	5.065	56.861	-11.50	-147.0	194.0
WEEK 52 (OPEN)	42	266.33	64.505	268.00	138.0	428.0	270.57 (66.799)	42	-4.24	9.418	61.036	-3.00	-135.0	194.0
END POINT (OPEN)	129	251.84	66.523	254.00	93.0	432.0	263.72 (71.769)	129	-11.88	5.143	58.410	-10.00	-147.0	194.0
Pali/Pali <=6 months														
SCREENING (DB)	198	279.05	74.521	281.00	128.0	564.0								
BASELINE (DB)	205	288.07	79.430	283.00	131.0	543.0								
DAY 15 (DB)	199	275.09	78.876	273.00	109.0	535.0	289.43 (79.195)	198	-14.51	4.287	60.321	-8.00	-268.0	175.0
DAY 43 (DB)	148	281.15	77.454	275.00	129.0	538.0	289.43 (79.887)	148	-7.82	4.489	54.606	-3.50	-208.0	177.0
END POINT (DB)	206	281.57	81.715	275.00	109.0	638.0	288.47 (79.416)	204	-6.69	3.942	56.302	-3.50	-237.0	177.0
BASE (OPEN)	207	281.21	81.690	275.00	109.0	638.0	288.97 (79.430)	205	-6.65	3.923	56.169	-3.00	-237.0	177.0
WEEK 12 (OPEN)	10	226.20	60.716	191.50	163.0	348.0	227.90 (72.839)	10	-0.80	12.620	39.908	16.50	-79.0	48.0
WEEK 24 (OPEN)	113	284.13	76.480	282.00	136.0	526.0	294.09 (81.441)	113	-9.96	5.280	56.122	-7.00	-245.0	172.0
END POINT (OPEN)	123	279.22	76.625	277.00	136.0	526.0	288.63 (82.579)	123	-9.41	4.944	54.831	-6.00	-245.0	172.0
Pali/Pali >6 months														
SCREENING (DB)	456	277.52	79.810	266.00	91.0	691.0								
BASELINE (DB)	469	283.30	82.382	272.00	108.0	657.0								
DAY 15 (DB)	450	275.76	77.854	267.00	118.0	648.0	283.23 (82.430)	449	-7.41	2.462	52.179	-7.00	-260.0	276.0
DAY 43 (DB)	403	270.80	79.124	262.00	103.0	657.0	283.16 (82.231)	401	-12.21	2.725	54.562	-9.00	-245.0	229.0
END POINT (DB)	468	272.38	79.726	262.50	103.0	657.0	284.01 (82.058)	466	-11.49	2.482	53.570	-8.00	-245.0	229.0
BASE (OPEN)	471	271.61	80.275	262.00	103.0	657.0	283.30 (82.382)	469	-11.54	2.469	53.460	-7.00	-245.0	229.0
WEEK 12 (OPEN)	43	252.35	96.708	222.00	114.0	528.0	263.70 (90.482)	43	-11.35	10.517	68.963	-6.00	-217.0	175.0
WEEK 24 (OPEN)	419	259.79	73.683	259.00	61.0	530.0	284.53 (84.274)	416	-24.73	3.970	62.607	-21.50	-342.0	197.0
WEEK 52 (OPEN)	121	267.07	73.288	257.00	111.0	513.0	283.85 (78.297)	120	-18.74	5.200	56.958	-12.50	-257.0	112.0
END POINT (OPEN)	429	260.81	74.054	251.00	80.0	530.0	284.43 (83.764)	426	-23.85	2.989	61.685	-20.50	-342.0	197.0
Olan/Pali <=6 months														
SCREENING (DB)	104	264.37	73.841	254.00	106.0	535.0								
BASELINE (DB)	105	273.27	74.845	269.00	139.0	518.0								
DAY 15 (DB)	105	262.91	78.775	250.00	64.0	568.0	273.34 (75.081)	103	-10.09	5.711	57.961	-10.00	-169.0	177.0
DAY 43 (DB)	70	264.09	65.869	258.00	152.0	437.0	269.54 (75.296)	68	-4.66	5.694	46.953	-1.50	-125.0	122.0
END POINT (DB)	105	269.14	73.140	255.00	104.0	537.0	273.34 (75.081)	103	-3.57	5.226	53.036	-3.00	-158.0	177.0
BASE (OPEN)	107	268.60	72.366	255.00	104.0	537.0	273.27 (74.845)	105	-4.07	5.034	51.586	-2.00	-158.0	177.0
WEEK 24 (OPEN)	62	268.98	71.110	259.00	127.0	473.0	285.13 (74.919)	60	-14.82	6.338	49.096	-15.50	-143.0	128.0
END POINT (OPEN)	62	268.98	71.110	259.00	127.0	473.0	285.13 (74.919)	60	-14.82	6.338	49.096	-15.50	-143.0	128.0
Olan/Pali >6 months														
SCREENING (DB)	136	277.24	76.404	264.50	126.0	553.0								
BASELINE (DB)	139	281.72	72.668	277.00	141.0	545.0								
DAY 15 (DB)	133	282.70	72.957	269.00	105.0	539.0	284.00 (72.672)	133	-1.30	4.532	52.271	-6.00	-131.0	170.0
DAY 43 (DB)	130	285.87	79.328	266.00	134.0	512.0	286.87 (72.495)	119	-0.08	4.609	50.279	-3.00	-118.0	153.0
END POINT (DB)	137	284.17	77.200	265.00	134.0	512.0	283.47 (72.404)	136	1.49	4.255	49.617	-2.00	-118.0	153.0
BASE (OPEN)	140	282.41	77.362	262.50	134.0	512.0	281.72 (72.668)	139	1.45	4.163	49.076	-1.00	-118.0	153.0
WEEK 24 (OPEN)	127	260.47	75.137	255.00	90.0	522.0	285.70 (73.368)	125	-24.47	5.108	57.114	-25.00	-213.0	174.0
WEEK 52 (OPEN)	38	259.39	62.008	249.00	123.0	377.0	276.63 (86.076)	38	-17.24	11.251	69.358	-5.00	-212.0	71.0
END POINT (OPEN)	131	263.49	74.185	255.00	100.0	522.0	283.46 (73.631)	129	-19.19	5.293	60.115	-19.00	-212.0	174.0

Total Pali <=6 months														
SCREENING (DB)	399	272.23	72.844	267.00	89.0	564.0								
BASELINE (DB)	408	270.61	77.108	267.00	77.0	543.0								
DAY 15 (DB)	406	269.56	77.234	259.50	64.0	568.0	278.84 (77.078)	397	-9.25	2.863	57.036	-7.00	-268.0	177.0
DAY 43 (DB)	278	275.74	76.047	272.00	127.0	638.0	278.69 (78.830)	275	-2.44	3.025	50.172	-1.00	-208.0	177.0
END POINT (DB)	409	275.89	78.863	271.00	104.0	638.0	278.93 (77.185)	405	-2.68	2.653	53.382	-2.00	-237.0	177.0
BASE (OPEN)	412	275.54	78.647	271.00	104.0	638.0	278.61 (77.108)	408	-2.80	2.622	52.954	-2.00	-237.0	177.0
WEEK 12 (OPEN)	15	237.60	73.067	215.00	150.0	453.0	243.08 (65.851)	25	-5.48	8.174	40.871	-3.00	-89.0	63.0
WEEK 24 (OPEN)	231	272.17	73.332	268.00	127.0	526.0	284.22 (78.638)	229	-11.58	3.481	52.671	-8.00	-245.0	172.0
END POINT (OPEN)	247	269.86	74.232	266.00	127.0	526.0	281.67 (78.851)	245	-11.48	3.337	52.237	-8.00	-245.0	172.0
Total Pali >6 months														
SCREENING (DB)	723	273.27	76.581	263.00	91.0	691.0								
BASELINE (DB)	745	279.12	78.859	269.00	62.0	657.0								
DAY 15 (DB)	713	276.94	75.095	267.00	105.0	648.0	279.45 (78.884)	712	-2.47	1.955	52.173	-3.00	-200.0	276.0
DAY 43 (DB)	614	274.13	78.889	264.00	96.0	657.0	281.28 (79.276)	611	-6.88	2.167	53.564	-5.00	-245.0	229.0
END POINT (DB)	740	275.00	78.812	264.00	91.0	657.0	280.01 (78.684)	737	-4.79	1.975	53.619	-4.00	-245.0	229.0
BASE (OPEN)	748	274.22	79.270	263.00	91.0	657.0	279.12 (78.859)	745	-4.67	1.960	53.599	-3.00	-245.0	229.0
WEEK 12 (OPEN)	51	254.27	95.405	223.00	114.0	528.0	258.45 (93.539)	51	-4.18	9.907	70.751	-5.00	-217.0	175.0
WEEK 24 (OPEN)	672	258.11	72.685	259.50	61.0	539.0	280.58 (80.381)	667	-22.34	2.349	60.663	-20.00	-342.0	197.0
WEEK 52 (OPEN)	201	265.46	69.251	269.00	111.0	513.0	279.69 (77.412)	200	-15.41	4.264	60.296	-9.00	-257.0	194.0
END POINT (OPEN)	689	259.64	72.731	253.00	80.0	530.0	280.34 (80.073)	684	-20.71	2.328	60.874	-19.00	-342.0	197.0

- *Given the above results on outliers on low platelet count it is noted that clinically unremarkable mean decreases in reticulocyte count were observed during OL Pal treatment that appeared to be numerically larger in the over 6 month exposed total Pal subgroup compared to the 6 month and under exposed subgroup. Results below also include those from the DB Placebo/OL Pal subgroups as well to allow for treatment group and placebo versus Pal treatment comparisons.*

Studies R076477-SCH-302, R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305

Output CLA302, Laboratory Values, Means and Mean Changes Over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean (SD)	N	change from baseline Mean	SE	SD	Med	Min	Max
RETICULOCYTES (%)														
Total Pali <=6 months														
BASELINE (DB)	407	1.36	0.542	1.30	0.1	14.1								
DAY 15 (DB)	394	1.39	0.767	1.30	0.1	9.2	1.62 (0.954)	381	0.01	0.047	0.923	0.00	-14.0	3.0
DAY 43 (DB)	276	1.31	1.495	1.30	0.2	24.2	1.63 (0.719)	254	0.13	0.095	1.509	0.00	-4.6	23.6
END POINT (DB)	406	2.01	3.172	1.60	0.1	41.7	1.63 (0.844)	403	0.13	0.095	1.914	0.00	-4.6	27.6
BASE (OPEN)	410	2.01	3.162	1.60	0.1	41.7	1.62 (0.842)	407	0.13	0.094	1.905	0.00	-4.6	27.6
WEEK 12 (OPEN)	25	1.53	0.962	1.30	0.2	4.1	1.64 (0.761)	25	0.09	0.353	0.764	0.00	-1.1	1.1
WEEK 24 (OPEN)	137	1.50	0.622	1.50	0.5	4.0	1.64 (0.704)	136	-0.04	0.055	0.643	-0.05	-3.3	1.8
END POINT (OPEN)	144	1.40	0.672	1.30	0.2	4.1	1.64 (0.731)	143	-0.06	0.059	0.619	0.00	-3.3	1.1
Total Pali >6 months														
SCREENING (DB)	691	1.72	1.332	1.50	0.1	22.0								
BASELINE (DB)	724	1.80	0.971	1.60	0.1	8.3								
DAY 15 (DB)	693	1.80	1.092	1.60	0.1	13.2	1.80 (0.787)	691	0.00	0.040	1.062	0.00	-9.6	16.6
DAY 43 (DB)	591	1.76	1.247	1.50	0.1	24.2	1.80 (1.309)	568	-0.04	0.054	1.301	0.00	-9.6	24.6
END POINT (DB)	722	1.78	1.197	1.60	0.1	24.2	1.80 (0.876)	717	-0.02	0.046	1.193	0.00	-9.6	24.6
BASE (OPEN)	735	1.78	1.196	1.60	0.1	24.2	1.80 (0.871)	734	-0.02	0.044	1.154	0.00	-9.6	24.6
WEEK 12 (OPEN)	40	1.43	1.191	1.15	0.1	6.2	1.50 (1.079)	40	-0.06	0.344	1.732	0.00	-9.3	4.0
WEEK 24 (OPEN)	543	1.70	0.939	1.50	0.1	7.5	1.79 (0.997)	527	-0.10	0.059	0.974	-0.10	-9.3	7.1
WEEK 52 (OPEN)	136	1.67	0.776	1.50	0.1	6.0	1.84 (1.064)	129	-0.15	0.076	1.048	-0.20	-8.9	3.3
END POINT (OPEN)	691	1.71	0.932	1.50	0.1	9.5	1.80 (0.956)	666	-0.11	0.050	0.972	-0.10	-8.9	7.1
Pla/Pali <=6 months														
SCREENING (DB)	95	1.65	0.662	1.50	0.1	3.5								
BASELINE (DB)	97	1.65	0.674	1.50	0.2	4.3								
DAY 15 (DB)	95	1.71	0.736	1.70	0.1	3.7	1.66 (0.681)	94	0.05	0.049	0.475	0.00	-0.9	1.6
DAY 43 (DB)	69	2.38	1.696	1.70	0.5	24.2	1.63 (0.706)	68	0.42	0.415	3.454	0.10	-1.6	23.8
END POINT (DB)	98	1.89	1.376	1.60	0.1	24.2	1.65 (0.674)	97	0.24	0.152	2.464	0.00	-1.6	23.8
BASE (OPEN)	98	1.89	1.376	1.60	0.1	24.2	1.65 (0.674)	97	0.24	0.152	2.464	0.00	-1.6	23.8
WEEK 12 (OPEN)	15	1.41	0.724	1.30	0.2	2.6	1.43 (0.726)	15	-0.03	0.142	0.551	0.10	-1.1	0.9
WEEK 24 (OPEN)	64	1.69	0.670	1.50	0.5	4.0	1.73 (0.715)	64	-0.07	0.094	0.752	-0.10	-1.9	1.8
END POINT (OPEN)	83	1.71	0.731	1.70	0.2	4.0	1.68 (0.714)	83	0.02	0.088	0.800	0.00	-1.9	1.8
Pla/Pali >6 months														
SCREENING (DB)	125	1.66	0.508	1.60	0.1	4.0								
BASELINE (DB)	133	1.67	0.508	1.70	0.1	2.8								
DAY 15 (DB)	126	1.73	0.561	1.70	0.1	4.5	1.68 (0.815)	126	0.04	0.044	0.491	0.10	-1.9	1.4
DAY 43 (DB)	96	1.64	0.829	1.60	0.1	8.3	1.61 (0.911)	96	-0.07	0.085	0.834	-0.10	-1.6	1.3
END POINT (DB)	131	1.66	0.828	1.70	0.1	4.5	1.66 (0.805)	131	-0.00	0.044	0.502	0.00	-1.6	2.3
BASE (OPEN)	133	1.67	0.808	1.70	0.1	4.5	1.67 (0.804)	133	-0.00	0.043	0.496	0.00	-1.6	1.3
WEEK 12 (OPEN)	2	0.80	0.565	0.80	0.2	1.4	0.95 (1.060)	2	-0.05	0.004	0.057	0.00	-0.6	0.4
WEEK 24 (OPEN)	124	1.67	1.203	1.50	0.1	9.5	1.66 (0.877)	120	0.07	0.108	1.052	0.00	-2.4	7.1
WEEK 52 (OPEN)	40	1.57	0.700	1.50	0.1	3.9	1.70 (0.932)	36	-0.11	0.122	0.615	-0.20	-1.6	1.3
END POINT (OPEN)	126	1.68	1.218	1.50	0.1	9.5	1.62 (0.855)	123	0.07	0.101	1.119	-0.05	-2.4	7.1

- *Creatine kinase was inconsistently elevated (group mean increases) but also show mean decreases in some subgroups. Standard deviations were large (up to at least approximately ±883 U/l for given subgroup on a given time-point). Therefore, results are difficult to interpret.*

- *Mean increases in prolactin were observed during OL Pal treatment but these elevations generally did not increase in magnitude over time of treatment as shown in the following table (copied sections of Appendix 5.3.1).*

Output ELAB02: Laboratory Values: Means and Mean Changes Over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean (SD)	N	change from baseline Mean	SE	SD	Med	Min	Max
PROLACTIN (ng/ml)														
Pali/Pali >6 months														
SCREENING (DB)	470	41.55	48.388	25.25	2.3	385.0								
BASELINE (DB)	475	24.71	18.759	12.67	0.9	446.4								
DAY 15 (DB)	472	88.61	66.413	68.59	4.5	473.8	24.75 (38.905)	471	63.99	3.108	67.445	46.90	-260.0	436.9
DAY 36 (DB)	401	81.27	65.140	60.95	3.5	549.9	23.26 (38.167)	400	58.15	3.173	63.451	41.41	-176.5	512.1
DAY 43 (DB)	405	82.24	68.935	62.79	3.7	750.4	21.95 (32.518)	405	60.41	3.433	69.082	45.17	-248.0	713.6
END POINT (DB)	476	81.21	67.503	61.05	3.7	750.4	24.71 (38.759)	475	56.61	3.185	69.422	42.37	-248.0	713.6
BASE (OPEN)	476	80.92	67.419	60.89	3.7	750.4	24.71 (38.759)	475	56.31	3.181	69.325	42.19	-248.0	713.6
WEEK 12 (OPEN)	43	84.96	76.098	71.07	5.2	378.3	34.29 (41.072)	43	50.67	10.504	68.877	32.99	-29.2	345.4
WEEK 24 (OPEN)	432	74.86	63.312	56.83	3.9	576.0	24.39 (39.753)	432	50.48	3.116	64.771	36.25	-322.3	539.1
WEEK 52 (OPEN)	128	69.79	50.563	57.71	2.8	225.4	21.52 (24.265)	128	48.27	4.672	52.858	40.61	-133.7	213.5
END POINT (OPEN)	440	72.53	62.764	53.58	2.8	576.0	24.55 (39.564)	440	47.98	3.094	64.891	33.41	-322.3	539.1
Total Pali >6 months														
SCREENING (DB)	742	42.61	51.254	25.19	1.4	385.0								
BASELINE (DB)	753	24.77	37.605	12.68	0.9	446.4								
DAY 15 (DB)	739	64.01	64.690	41.94	1.2	473.8	24.75 (37.793)	738	39.39	2.463	66.920	22.93	-260.0	436.9
DAY 36 (DB)	614	60.11	62.948	40.56	2.5	549.9	23.94 (38.146)	613	36.23	2.567	63.568	21.20	-227.2	512.1
DAY 43 (DB)	608	60.93	65.693	40.76	2.4	750.4	22.54 (32.742)	607	38.44	2.717	66.943	21.41	-248.0	713.6
END POINT (DB)	753	57.84	63.422	37.01	2.1	750.4	24.72 (37.611)	752	33.16	2.421	66.396	17.68	-248.0	713.6
BASE (OPEN)	754	57.66	63.256	37.01	2.1	750.4	24.77 (37.605)	753	32.93	2.414	66.238	17.46	-248.0	713.6
WEEK 12 (OPEN)	51	81.43	73.811	56.59	5.2	378.3	31.78 (38.235)	51	49.65	9.351	66.778	31.17	-29.2	345.4
WEEK 24 (OPEN)	698	75.98	64.083	57.06	3.5	576.0	24.66 (38.413)	698	51.23	2.446	64.622	36.22	-322.3	539.1
WEEK 52 (OPEN)	208	71.57	64.845	54.06	1.8	593.8	23.06 (29.221)	208	48.51	4.499	63.443	38.91	-133.7	515.7
END POINT (OPEN)	709	71.76	63.266	52.44	1.8	593.8	24.72 (38.244)	709	47.05	2.425	64.559	33.38	-322.3	539.1

The Incidence of Outliers on Laboratory Parameters in the OL Extension Trial Safety dataset.
A Caveat: *comparisons between exposure subgroups (>6 month versus ≤ 6 month subgroups) could be misleading since the incidence is determined using a LOCF approach (that is, treatment groups are subdivided by duration of exposure rather than showing the groups combined with the incidence over time).*

Results are generally similar to those previously described, although the following are potentially notable or relevant findings (all other parameters not described or shown below generally had an incidence of 0-1% in the Total Pal ≤ 6month and > 6 month subgroups):

- *Lipid Profile Alterations: As previously described drug induced alterations in lipid profile appear to exist, as suggested by results taken from Table 69 of the SUR that are shown below.*
- *Outliers on High CPK levels: As previously described there were outliers on high CPK but not on low CPK levels.*
- *Outliers in Low Reticulocyte Count that appears to be greater after over 6 months exposure compared to 6 months and less exposure. Numerically greater incidence of outliers on low compared to high reticulocyte count that was generally more robust in the over 6 month exposed subgroups compared to the 6 month and under, exposed subgroup.*

  While the incidence of low reticulocyte count, appears to reflect a Pal effect (in light of similar findings in placebo controlled trials, as previously described in this review), a comparison between the exposure subgroups (over 6 months versus 6 months and under subgroups) may not reflect a true time-dependent phenomenon

with respect to duration of exposure. Although, these results together with other results described in this review are suggestive of such a greater effect over time of exposure. For example, the previously described results of mean platelet count over time within a given treatment group showed a slight (albeit clinically unremarkable) time-dependent decrease which supports the observations on the incidence of low platelet count when comparing the two exposure subgroups.

Table 69: Treatment-Emergent Markedly Abnormal Laboratory Results (Continued)
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=309) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
LDL (mmol/L)	61	135	125	439	62	135	248	709
Abnormally high	3 (5)	7 (5)	7 (6)	23 (5)	5 (8)	8 (6)	15 (6)	38 (5)
Abnormally low	12 (20)	20 (15)	15 (12)	53 (12)	13 (21)	20 (15)	40 (16)	93 (13)
HDL (mmol/L)	64	135	129	442	63	136	256	713
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	1 (2)	14 (10)	12 (9)	40 (9)	6 (10)	10 (7)	19 (7)	64 (9)
Cholesterol (mmol/L)	65	135	131	446	64	136	260	717
Abnormally high	2 (3)	2 (1)	2 (3)	3 (1)	1 (2)	2 (1)	5 (2)	7 (1)
Abnormally low	0	0	0	0	0	0	0	0
Triglycerides (mmol/L)	64	135	131	446	64	136	259	717
Abnormally high	1 (2)	1 (1)	1 (1)	4 (1)	0	1 (1)	3 (1)	6 (1)
Abnormally low	0	0	0	0	0	0	0	0
Creatine kinase (U/L)	65	134	129	446	62	135	256	715
Abnormally high	1 (2)	2 (1)	2 (2)	1 (<1)	2 (3)	4 (3)	5 (2)	7 (1)
Abnormally low	0	0	0	0	0	0	0	0
Platelets (giga/L)	62	129	123	429	62	131	247	689
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	0	1 (1)	0	4 (1)	0	1 (1)	0	6 (1)
Reticulocytes (%)	61	126	123	424	60	131	244	681
Abnormally high	1 (2)	4 (3)	0	9 (2)	0	5 (4)	1 (<1)	18 (3)
Abnormally low	2 (3)	13 (10)	3 (2)	25 (6)	0	4 (3)	5 (2)	42 (6)

Vital Sign Results of Open Label Extension Trials Safety dataset (-702 throuth -05, combined)
SAEs and ADOs due to Vital Sign Parameters

The sponsor notes that the following SAEs and/or ADOs due to tachycardia or sinus tachycardia were reported and occurred in the ≥ 6 month exposure subgroups:

- *Subject 200601 (SAE and ADO)*
- *Subject 201366 (ADO)*
- *Subject 500603 (SAE and ADO)*
- *Subject 200303 (SAE)*

In-text descriptions of these subjects could not be found in the SUR. Several of these subjects were previously described in the sub-sections on SAEs 7.1.2 focusing on tachycardia in the absence of concurrent orthostatic and/or ischemia-related events.

In a separate section of the SUR focusing on orthostatic hypotension (section 2.1.6.5.2) the sponsor notes that there were no SAEs or ADOs due to orthostatic hypotension.

An in-text listing or discussion of other type of vital sign outliers, ADOs or SAEs could not be found in the SUR (e.g. due to non-postural hypotension, low heart rate or other subjects with remarkable vital signs or vital-sign related events, other than those of tachycardia and orthostatic hypotension, as above). Refer to previous summary tables for ADOs and SAEs and Section 7.1.3.3 of this review for descriptions of individual subjects found from other sources.

Descriptive Statistical Results: *These results failed to yield any new remarkable findings that are not already described in this review (see section 7.1.8 for more details on assessment time-points and on the results).*

Incidence of Outliers
Results on the incidence of outliers are generally similar to that previously described in this review and in the original NDA submission.

A Caveat: *Comparisons between exposure groups on the incidence of outliers may be misleading since the greater the number of assessments and the greater duration of monitoring subjects leads to a greater chance of detecting outliers. However, if a greater incidence is observed in the > 6 month exposure subgroup compared to the ≤ 6 month subgroup for outliers in one direction (e.g. high values) but not in the other direction (e.g. low values) on a given parameter, this finding may suggest a real time-dependent effect. However, statistical descriptive results failed to show mean increases in heart rate during OL treatment in the group of subjects that previously received DB pal treatment.*

Potentially new and notable findings (not previously described in this review) revealed from the results in the updated safety summary are the following:

- *A numerically greater incidence of decreased supine systolic BP and in decreased diastolic BP compared to the incidence of increased values on these parameters as shown in the table below (coped from Table 74 of the SUR).*
- *Small numerical trends for a greater incidence of the following cardiovascular effects of Pal in each of the > 6 month exposed subgroups compared to each of their corresponding ≤ 6 month subgroups:*
  - *Increased standing heart rate,*
  - *Decreased standing and*
  - *Decreased supine systolic BP.*

These findings may be reflective of having a greater chance of meeting outlier criteria associated with longer term monitoring of subjects. However, these trends for generally observed for almost all subgroups and the direction of vital sign changes are generally

consistent with Pal effects observed in the short-term trials. Although, short-term trials of primarily non-elderly subjects did not reveal a consistent or dose-dependent Pal effects on the incidence in decreased supine systolic BP. However, the single elderly Phase III trial that was conducted (-302) revealed a numerical trend for a greater incidence of decreased supine systolic BP in the Pal compared to placebo group (while noting this was a small study).

Table 74: Number of Subjects With Abnormal Vital Sign Values During the Open-Label Period
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 Months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Standing pulse classification	99	137	209	476	108	141	416	754
Decrease >=15 and value <=50	0	1 (1)	1 (<1)	3 (<1)	1 (1)	1 (1)	2 (<1)	4 (1)
Increase >=15 and value >=100	38 (38)	45 (33)	45 (22)	114 (24)	30 (28)	38 (27)	103 (25)	197 (26)
Supine pulse classification	99	137	209	476	108	141	416	754
Decrease >=15 and value <=50	0	6 (4)	0	16 (3)	1 (1)	4 (3)	1 (<1)	26 (3)
Increase >=15 and value >=100	14 (14)	20 (15)	24 (11)	47 (10)	18 (17)	16 (11)	56 (13)	83 (11)
Standing SBP classification	99	137	209	476	108	141	416	754
Decrease >=20 and value <=90	3 (3)	10 (7)	16 (8)	33 (7)	4 (4)	12 (9)	23 (6)	55 (7)
Increase >=20 and value >=180	0	0	1 (<1)	4 (1)	0	1 (1)	1 (<1)	5 (1)
Supine SBP classification	99	137	209	476	108	141	416	754
Decrease >=20 and value <=90	3 (3)	5 (4)	9 (4)	22 (5)	3 (3)	6 (4)	14 (3)	33 (4)
Increase >=20 and value >=180	1 (1)	0	3 (1)	2 (<1)	1 (1)	0	5 (1)	3 (<1)
Standing DBP classification	99	137	209	476	108	141	416	754
Decrease >=15 and value <=50	5 (5)	2 (1)	4 (2)	5 (1)	1 (1)	3 (2)	10 (2)	10 (1)
Increase >=15 and value >=105	3 (3)	8 (6)	5 (2)	11 (2)	3 (3)	5 (4)	11 (3)	24 (3)
Supine DBP classification	99	137	209	476	108	141	416	754
Decrease >=15 and value <=50	1 (1)	3 (2)	4 (2)	14 (3)	3 (3)	2 (1)	8 (2)	19 (3)
Increase >=15 and value >=105	1 (1)	4 (3)	5 (2)	5 (1)	0	0	6 (1)	9 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.
tsfvs06_t1.rtf generated by tsfvs06.sas.

In a separate section of the SUR focusing on orthostatic hypotension (section 2.1.6.5.2) the incidence of outliers on orthostatic hypotension is somewhat numerically larger in the table below than was previously reported and as previously described in this review, as shown below (copied from the SUR).

Table 56: Number of Subjects With Treatment-Emergent Orthostatic Hypotension at Anytime During the Open-Label Period
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Total no. subjects with orthostatic hypotension	4 (4)	9 (7)	7 (3)	30 (6)	4 (4)	7 (5)	15 (4)	46 (6)
Pulse(std-sup)>15 and DBP(std-sup)<-10	3 (3)	6 (4)	3 (1)	21 (4)	1 (1)	6 (4)	7 (2)	33 (4)
Pulse(std-sup)>15 and SBP(std-sup)<-20	1 (1)	4 (3)	6 (3)	14 (3)	3 (3)	4 (3)	10 (2)	22 (3)

Note: Percentages calculated with the number of subjects in each group as denominator.
tsfvs04_t1.rtf generated by tsfvs04.sas.

The above results also suggest a greater incidence of outliers on this parameter after over 6 months exposure compared to exposure at 6 months or under. However, in the absence of a placebo control group and given that the incidence was determined using an LOCF approach (rather than over time), the results are not considered conclusive evidence for a greater effect on the incidence of outliers on orthostatic hypotension with prolonged treatment. Despite this caveat, it is notable that in the previously shown table that the incidence of outliers on low standing SBP showed a similar pattern for greater incidence in the over 6 month exposed subgroup compared to the ≤ 6 month subgroup which was not observed in the direction of outliers for a high standing SBP. This observation is highly suggestive of a real Pal effect over time rather than an effect of greater time of monitoring independent of Pal treatment.

The results on the incidence of tachycardia-related AEs suggest a similar pattern for a numerically greater incidence in the over 6 month subgroups compared to the 6 month and under subgroups, as described in a separate section of the SUR that focuses on selected AEs including tachycardia. Results are shown below (copied from the SUR).

Table 41: Treatment-Emergent Tachycardia-Related Adverse Events By MedDRA Preferred Term - Open-Label Phase
(Studies R076477-SCH-702, 703, 704, and 705: Safety Analysis Set)

Tachycardia-Related Group Dictionary-derived Term	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)
Total no. subjects with Tachycardia-Related AE	10 (10)	18 (13)	12 (6)	48 (10)	7 (6)	19 (13)
Tachycardia	10 (10)	18 (13)	12 (6)	48 (10)	7 (6)	19 (13)
Heart rate increased	1 (1)	0	0	3 (<1)	0	1 (1)
Sinus tachycardia	8 (8)	11 (8)	2 (1)	22 (5)	5 (5)	7 (5)
Tachycardia	1 (1)	9 (7)	10 (5)	35 (7)	3 (3)	11 (8)

Note: Percentages calculated with the number of subjects in each group as denominator.
tsfae33_t1.rtf generated by tsfae33.sas

Refer to the last section of this review for additional comments and recommendations.

ECG Results of Open Label Extension Trials Safety dataset (-702 throuth -05, combined)
SAEs and ADOs due to Abnormal ECG Parameters

See previous summary tables for the incidence of SAEs and ADOs due to ECG parameters.

In a separate section of the SUR focusing on orthostatic hypotension (section 2.1.6.5.2) the sponsor notes that there were no SAEs or ADOs due to orthostatic hypotension.

Descriptive Statistical Results: *The results (mean and median change from baseline) failed to yield any new remarkable findings that are not already described in this review (see section 7.1.8 for more details on assessment time-points and on the results), except for some of the following observations that were observed in subjects exposed over 6 months (noting that now the sample sizes are remarkably larger for these longer term exposures than samples sizes in the previous original NDA submission)*

A Potentially Greater Group Mean QT Prolongation Effect was Observed with Over 6 months of Treatment Compared to Mean Changes Observed with Less than 6 Months of Treatment.

QTraw interval results showed the most remarkable group mean increases at 6 month and at 1 year (52 week) time-points and showed at least trends for group mean increases at all time-points beyond the 8 week OL time-point.

The greatest group mean increase occurred at 52 weeks which was 7.2 (median increase was 11.0 msec), although the group variance was large (SD±25.2 msec) as may be expected since timing of assessments relative to dosing on a given day was not held constant.

QTraw interval results showed more remarkable prolongation effects than the QTc results. Since, ECG assessments during the OL study phase showed little to no change in HR (as shown later in this section of this review), it is appropriate to consider QTraw interval results over the QTc results. QTc interval results at these later time-points are likely to be a less accurate reflection of true drug effects on QT interval, since correction methods were employed correct for the case when alterations in HR are observed.

Also, note that RR interval (shown later in this section) unexpectedly showed group mean increases at these later time-points rather than showing the mean decreases that were observed at earlier time-points in the DB phase. These RR results are consistent with early drug effects on increasing HR, and the absence of this effect at later time-points (refer to the section below for possible explanations for the observed increases in RR interval). Also see the last section of this review for further comment and recommendations.

One concern is that OL results on QT interval (or QTc interval) are likely to be an underestimation of true QT interval effects since the timing of ECG assessments were not tightly controlled to capture peak plasma levels or were not obtained over multiple time-points on a given day to capture peak levels for a given individual. Also consider food effects and other factors impacting PK, as well as dynamic changes in the cardiovàscular system that may influence results.

While theoretically, subjects are in steady state from a PK perspective during OL longterm treatment, Pal levels nevertheless, fluctuate over time and vary widely across individuals. Moreover, levels can further be altered by factors that influence PK. For example, consider the large food effect of Pal on PK.

The following tables were copied out of appendices to the SUR for the over 6 month DB Pal/OL Pal group (this is the group with longest continuous Pal treatment of all subgroups shown in summary tables by the sponsor).

Output DBXG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
QT INTERVAL (ms)														
BASELINE (DB)	475	371.5	30.11	368.0	294	470								
AVERAGE PREDOSE	475	371.9	28.16	369.0	302	477								
DAY 4 (DB) :4H PST	463	357.5	29.03	354.0	285	460	371.9	463	-14.5	0.99	21.26	-14.3	-103	70
DAY 4 (DB) :10H PST	456	361.6	29.35	360.0	284	465	372.3	456	-10.7	1.08	23.06	-9.5	-128	68
DAY 4 (DB) :22H PST	456	367.8	30.63	364.0	290	480	371.9	456	-4.1	1.06	22.63	-2.8	-99	67
DAY 8 (DB) :4H PST	469	361.2	28.47	358.0	301	464	372.0	468	-10.8	1.04	22.54	-9.8	-87	63
DAY 8 (DB) :10H PST	467	364.0	28.78	361.0	300	476	371.9	466	-7.9	1.08	23.30	-7.0	-99	68
DAY 8 (DB) :22H PST	468	371.7	29.92	370.0	299	483	371.7	467	0.1	1.11	24.06	1.3	-105	69
DAY 15 (DB)	44	385.0	35.68	386.5	306	447	386.7	44	-1.7	3.68	24.40	-1.7	-44	58
DAY 15 (DB) :PRE-DS	419	370.7	29.61	369.0	287	462	370.5	418	0.1	1.17	23.89	0.9	-92	73
DAY 15 (DB) :1-2H PST	421	361.9	29.00	359.0	284	471	370.5	420	-8.6	1.21	24.75	-7.8	-95	59
DAY 15 (DB) :4H PST	422	360.2	28.31	359.5	287	454	370.1	421	-9.8	1.21	24.78	-9.3	-115	53
DAY 29 (DB)	450	371.9	30.21	370.0	298	475	371.8	449	0.1	1.07	22.66	-0.7	-74	58
DAY 36 (DB) :PRE-DS	369	375.6	30.93	376.0	304	457	370.2	368	5.3	1.30	25.03	3.7	-69	81
DAY 36 (DB) :1-2H PST	370	369.7	28.12	367.0	296	444	370.3	369	-0.6	1.21	23.29	-1.0	-66	62
DAY 36 (DB) :4H PST	363	369.8	27.79	369.0	303	457	370.6	362	-0.9	1.20	22.80	-0.7	-68	62
DAY 43 (DB)	414	376.2	29.33	374.5	307	493	372.0	413	4.1	1.14	23.10	5.0	-74	70
END POINT (DB)	476	374.8	29.33	372.0	307	493	371.9	475	2.8	1.08	23.49	4.0	-75	70
BASE (OPEN)	476	375.3	29.42	373.0	307	493	371.9	475	3.3	1.09	23.69	4.3	-75	70
DAY 4 (OPEN)	455	371.3	28.78	370.0	292	475	371.7	454	-0.4	1.13	24.04	-1.0	-77	63
WEEK 1 (OPEN)	462	372.1	28.11	371.0	305	456	372.2	461	-0.2	1.13	24.29	0.0	-98	66
WEEK 2 (OPEN)	462	371.9	29.20	372.0	294	458	371.9	461	-0.0	1.17	25.14	1.3	-69	65
WEEK 4 (OPEN)	468	372.3	29.55	370.0	282	469	372.0	468	0.3	1.19	25.48	1.4	-109	69
WEEK 8 (OPEN)	469	371.8	29.24	371.0	293	460	371.7	468	0.1	1.17	25.22	0.3	-83	79
WEEK 16 (OPEN)	470	374.0	30.66	372.0	301	479	372.1	469	1.8	1.21	26.15	1.3	-92	113
WEEK 24 (OPEN)	440	377.4	30.04	375.0	295	498	371.9	439	5.4	1.27	26.54	5.0	-83	98
WEEK 40 (OPEN)	269	372.6	29.91	369.0	296	474	369.7	268	2.9	1.61	26.32	2.2	-60	85
WEEK 52 (OPEN)	119	376.9	30.11	374.0	301	472	369.7	119	7.2	2.31	25.20	11.0	-56	80
END POINT (OPEN)	476	377.2	29.69	376.0	301	498	371.9	475	5.3	1.20	26.23	4.7	-58	85

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DBXG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
RR (ms)														
QTC INTERVAL FRIDERICIA (ms)														
Pal1/Pal1 >6 months														
BASELINE (DB)	475	396.6	19.69	398.0	337	470								
AVERAGE PREDOSE	475	398.9	18.14	398.7	355	465								
DAY 4 (DB) :4H PST	463	396.7	17.83	395.0	353	462	398.8	463	-2.1	0.57	12.34	-1.7	-42	39
DAY 4 (DB) :10H PST	456	396.9	18.23	397.0	337	453	399.0	456	-2.1	0.62	13.29	-1.3	-74	44
DAY 4 (DB) :22H PST	456	401.4	19.33	402.0	346	456	398.8	456	2.5	0.62	13.23	3.2	-37	40
DAY 8 (DB) :4H PST	469	397.3	18.05	397.0	342	460	399.0	468	-1.6	0.64	13.93	-1.2	-59	51
DAY 8 (DB) :10H PST	467	397.6	18.74	397.0	333	462	398.8	466	-1.2	0.67	14.52	-0.3	-71	46
DAY 8 (DB) :22H PST	468	402.1	19.11	401.0	346	463	398.8	467	3.3	0.65	14.04	4.0	-44	63
DAY 15 (DB)	44	410.3	22.04	411.5	363	460	411.6	44	-1.3	2.18	14.46	-0.5	-35	30
DAY 15 (DB) :PRE-DS	419	397.9	18.44	397.0	350	470	397.6	418	0.2	0.65	13.30	1.2	-50	37
DAY 15 (DB) :1-2H PST	421	393.8	17.31	393.0	350	456	397.7	420	-3.9	0.62	12.81	-4.0	-63	32
DAY 15 (DB) :4H PST	422	394.6	17.35	395.0	332	443	397.4	421	-2.8	0.70	14.42	-2.7	-73	40
DAY 29 (DB)	450	399.0	18.71	399.0	350	469	399.0	449	-0.0	0.65	13.79	0.7	-49	34
DAY 36 (DB) :PRE-DS	369	399.3	17.17	399.0	356	465	397.7	368	1.5	0.72	13.72	1.3	-43	41
DAY 36 (DB) :1-2H PST	370	395.6	17.60	395.0	345	457	397.6	369	-2.0	0.76	14.69	-1.7	-46	50
DAY 36 (DB) :4H PST	363	397.0	17.20	396.0	352	462	397.5	362	-0.5	0.74	14.06	-0.5	-44	37
DAY 43 (DB)	414	399.8	19.30	399.0	344	502	398.9	413	0.8	0.70	14.25	0.7	-51	69
MAXIMUM VALUE (DB)	476	415.1	17.89	414.0	373	502	398.9	475	16.1	0.53	11.64	16.0	-19	69
END POINT (DB)	476	399.4	19.21	399.0	344	502	398.9	475	0.5	0.65	14.12	0.3	-51	69
BASE (OPEN)	476	399.7	19.29	399.0	344	502	398.9	475	0.8	0.65	14.15	1.0	-51	69
DAY 4 (OPEN)	455	398.7	19.24	398.0	343	482	398.7	454	-0.1	0.64	13.74	-0.5	-44	38
WEEK 1 (OPEN)	462	398.2	18.99	396.0	348	468	399.1	461	-0.9	0.65	13.99	0.3	-52	43
WEEK 2 (OPEN)	462	399.0	18.63	398.0	345	454	398.9	461	0.1	0.67	14.39	-0.3	-62	51
WEEK 4 (OPEN)	468	397.7	18.86	398.0	316	465	399.0	468	-1.3	0.69	14.95	-0.7	-79	41
WEEK 8 (OPEN)	469	397.6	17.90	397.0	354	459	398.8	468	-1.2	0.68	14.77	-0.5	-63	38
WEEK 16 (OPEN)	470	398.2	18.59	400.0	352	460	399.0	469	0.2	0.66	14.35	0.7	-50	40
WEEK 24 (OPEN)	440	400.9	18.78	400.0	348	487	399.0	439	2.0	0.72	15.04	1.7	-44	42
WEEK 40 (OPEN)	269	399.0	17.77	399.0	346	452	396.8	268	2.1	0.86	14.13	2.0	-50	40
WEEK 52 (OPEN)	118	399.9	18.18	399.0	342	456	397.1	119	2.8	1.32	14.42	2.3	-35	38
MAXIMUM VALUE (OPEN)	476	414.2	19.56	413.5	364	578	398.9	475	15.3	0.62	13.48	14.7	-21	137
END POINT (OPEN)	476	401.2	19.03	401.0	342	487	398.9	475	2.3	0.67	14.68	2.3	-50	40
QTC LINEAR SAGIE (ms)														

Pali/Pali >6 months														
BASELINE (DB)	475	397.6	18.82	398.0	337	469								
AVERAGE PREDOSE	475	399.9	17.13	399.7	360	464								
DAY 4 (DB) :4H PST	463	397.8	16.46	397.0	358	462	399.7	463	-1.9	0.54	11.65	-1.7	-40	35
DAY 4 (DB) :10H PST	456	398.2	16.84	397.5	338	452	399.9	456	-1.7	0.59	12.58	-1.0	-70	45
DAY 4 (DB) :22H PST	456	402.3	16.98	402.0	353	456	399.7	456	2.5	0.59	12.58	2.7	-35	48
DAY 8 (DB) :4H PST	469	398.6	16.80	398.0	337	459	399.9	468	-1.2	0.61	13.23	-1.0	-56	49
DAY 8 (DB) :10H PST	467	399.0	17.44	398.2	340	461	399.7	466	-0.7	0.64	13.76	-0.4	-66	47
DAY 8 (DB) :22H PST	468	402.9	17.84	402.0	347	461	399.7	467	3.2	0.62	13.44	3.3	-44	59
DAY 15 (DB)	44	410.4	21.10	410.0	368	461	411.9	44	-1.5	2.13	14.12	-0.3	-34	29
DAY 15 (DB) :PRE-DS	419	399.0	17.50	398.0	345	468	398.6	418	0.4	0.63	12.88	1.3	-46	36
DAY 15 (DB) :1-2H PST	421	395.2	16.18	395.0	357	455	398.6	420	-3.4	0.61	12.52	-3.5	-69	38
DAY 15 (DB) :4H PST	422	396.0	16.21	397.0	369	442	398.4	421	-2.4	0.69	14.16	-2.5	-97	38
DAY 29 (DB)	450	399.8	17.87	399.0	339	468	400.0	449	-0.1	0.63	13.36	0.7	-50	42
DAY 36 (DB) :PRE-DS	369	399.9	16.61	400.0	351	464	398.7	368	1.2	0.69	13.24	1.0	-38	40
DAY 36 (DB) :1-2H PST	370	396.7	16.84	396.0	345	456	398.6	369	-1.9	0.74	14.21	-1.3	-46	49
DAY 36 (DB) :4H PST	363	398.2	16.30	398.0	354	462	398.5	362	-0.3	0.72	13.62	0.3	-47	35
DAY 43 (DB)	414	400.7	18.46	400.0	348	500	399.8	413	0.9	0.67	13.69	1.0	-48	68
MAXIMUM VALUE (DB)	476	415.3	16.91	414.0	376	500	399.8	475	15.5	0.51	11.21	15.3	-19	68
END POINT (DB)	476	400.5	18.31	400.0	348	500	399.8	475	0.6	0.62	13.48	1.0	-48	68
BASE (OPEN)	476	400.7	18.39	400.0	348	500	399.8	475	0.9	0.62	13.52	1.3	-48	68
DAY 4 (OPEN)	455	399.7	18.34	399.0	330	479	399.6	454	0.1	0.63	13.37	0.0	-50	44
WEEK 1 (OPEN)	462	399.4	18.05	398.0	341	464	400.0	461	-0.6	0.63	13.49	0.3	-53	39
WEEK 2 (OPEN)	462	400.2	17.56	399.0	347	451	399.8	461	0.3	0.64	13.73	0.3	-62	51
WEEK 4 (OPEN)	468	398.8	18.04	399.0	319	464	399.9	468	-1.1	0.67	14.48	0.0	-76	40
WEEK 8 (OPEN)	469	398.5	17.08	398.0	352	458	399.7	468	-1.2	0.66	14.22	-0.8	-60	38
WEEK 16 (OPEN)	470	400.3	17.63	401.0	354	459	399.9	469	0.3	0.63	13.75	0.5	-48	39
WEEK 24 (OPEN)	440	401.4	18.46	401.0	337	487	399.8	439	1.6	0.71	14.80	1.7	-43	57
WEEK 40 (OPEN)	269	399.9	16.80	400.0	351	450	397.8	268	2.1	0.83	13.64	2.5	-50	37
WEEK 52 (OPEN)	119	401.1	17.40	400.0	350	456	398.2	119	2.9	1.29	14.08	3.0	-38	38
MAXIMUM VALUE (OPEN)	476	414.6	18.28	414.0	369	553	399.8	475	14.8	0.58	12.59	14.3	-20	112
END POINT (OPEN)	476	401.8	18.48	401.0	337	487	399.8	475	2.0	0.66	14.29	2.3	-48	38
QTC LINEAR DERIVED (ms)														
Pali/Pali >6 months														
BASELINE (DB)	475	395.1	18.84	397.0	337	468								
AVERAGE PREDOSE	475	398.2	17.28	398.6	358	464								
DAY 4 (DB) :4H PST	463	395.5	16.73	395.0	355	461	398.2	463	-2.6	0.54	11.60	-2.3	-41	33
DAY 4 (DB) :10H PST	456	396.2	17.13	395.0	337	451	398.3	456	-2.2	0.59	12.58	-1.7	-68	43
DAY 4 (DB) :22H PST	456	400.3	17.28	400.0	351	457	398.2	456	2.1	0.59	12.58	2.3	-37	38
DAY 8 (DB) :4H PST	469	396.5	17.02	396.0	338	459	398.3	468	-1.8	0.61	13.21	-1.5	-57	48
DAY 8 (DB) :10H PST	467	397.1	17.67	396.0	339	461	398.1	466	-1.0	0.64	13.71	-0.3	-65	45
DAY 8 (DB) :22H PST	468	401.2	18.02	400.0	347	460	398.1	467	3.1	0.62	13.49	3.7	-47	60
DAY 15 (DB)	44	409.3	21.31	408.5	365	460	410.8	44	-1.5	2.14	14.17	-1.3	-35	28
DAY 15 (DB) :PRE-DS	419	397.4	17.64	397.0	346	467	397.0	418	0.4	0.63	12.87	1.0	-48	38
DAY 15 (DB) :1-2H PST	421	393.3	16.35	392.0	355	455	397.0	420	-3.7	0.60	12.39	-3.3	-66	34
DAY 15 (DB) :4H PST	422	393.9	16.34	394.5	313	442	396.8	421	-2.8	0.68	14.00	-3.0	-91	37
DAY 29 (DB)	450	398.3	17.99	397.0	341	467	398.3	449	-0.1	0.63	13.26	0.7	-50	41
DAY 36 (DB) :PRE-DS	369	398.5	16.79	398.0	352	464	397.1	368	1.4	0.69	13.28	1.0	-40	41
DAY 36 (DB) :1-2H PST	370	395.2	16.86	394.5	345	455	396.9	369	-1.8	0.73	14.10	-1.0	-44	47
DAY 36 (DB) :4H PST	363	395.5	16.40	396.0	356	462	396.8	362	-0.3	0.71	13.49	0.3	-43	36
DAY 43 (DB)	414	399.4	18.57	398.6	347	500	398.2	413	1.1	0.67	13.66	1.3	-48	68
MAXIMUM VALUE (DB)	476	413.6	17.29	413.0	373	500	398.2	475	15.1	0.52	11.26	15.3	-20	68
END POINT (DB)	476	399.0	18.44	398.0	347	500	398.2	475	0.7	0.62	13.48	1.0	-48	68
BASE (OPEN)	476	399.3	18.52	398.5	347	500	398.2	475	1.0	0.62	13.53	1.3	-48	68
DAY 4 (OPEN)	455	398.2	18.43	398.0	331	478	398.0	454	0.1	0.63	13.32	0.0	-47	42
WEEK 1 (OPEN)	462	397.9	18.14	396.0	345	462	398.4	461	-0.6	0.63	13.47	0.0	-50	39
WEEK 2 (OPEN)	462	398.6	17.75	398.0	346	449	398.2	461	0.3	0.64	13.76	0.3	-61	50
WEEK 4 (OPEN)	468	397.3	18.16	397.0	318	463	398.3	468	-1.0	0.67	14.50	-0.2	-78	41
WEEK 8 (OPEN)	469	397.0	17.14	396.0	354	457	398.1	468	-1.1	0.66	14.21	-0.7	-61	37
WEEK 16 (OPEN)	470	398.7	17.83	399.0	354	458	398.3	469	0.4	0.63	13.68	0.7	-49	39
WEEK 24 (OPEN)	440	400.0	18.39	399.0	340	487	398.2	439	1.8	0.70	14.70	2.0	-42	53
WEEK 40 (OPEN)	269	398.3	16.97	397.0	350	451	396.1	268	2.2	0.84	13.75	2.3	-48	38
WEEK 52 (OPEN)	119	399.6	17.68	398.0	347	455	396.4	119	3.2	1.30	14.19	4.0	-35	40
MAXIMUM VALUE (OPEN)	476	413.1	18.51	412.0	367	549	398.2	475	14.9	0.58	12.60	14.3	-19	110
END POINT (OPEN)	476	400.4	18.50	399.0	340	487	398.2	475	2.1	0.66	14.34	2.0	-49	40

Output DECG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base	-------- Change from average predose --------						
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
QTC INTERVAL BAZETT (ms)														

Pal1/Pal1 >6 months														
BASELINE (DB)	475	410.2	23.12	411.0	337	477								
AVERAGE PREDOSE	475	413.5	20.50	414.0	359	475								
DAY 4(DB):4H PST	463	418.2	20.03	417.0	359	474	413.4	463	4.8	0.78	16.69	4.7	-41	69
DAY 4(DB):10H PST	456	416.1	20.01	416.0	339	468	413.5	456	2.6	0.80	17.11	2.2	-109	44
DAY 4(DB):22H PST	456	419.6	20.63	420.0	362	467	413.4	456	6.2	0.82	17.42	6.0	-48	64
DAY 8(DB):4H PST	469	417.0	20.29	417.0	336	476	413.6	468	3.4	0.81	17.51	3.0	-63	62
DAY 8(DB):10H PST	467	415.9	20.78	416.0	345	480	413.4	466	2.5	0.86	18.62	3.6	-72	60
DAY 8(DB):22H PST	468	418.5	22.14	418.0	346	479	413.5	467	5.1	0.85	18.31	5.3	-69	65
DAY 15(DB)	44	424.2	23.66	425.0	380	471	425.0	44	-0.8	2.70	17.92	-0.5	-35	47
DAY 15(DB):PRE-DS	419	412.7	21.74	413.0	344	483	412.1	418	0.3	0.86	17.66	1.2	-53	74
DAY 15(DB):1-2H PST	421	411.1	20.27	411.0	357	474	412.4	420	-1.3	0.89	18.28	-2.0	-78	57
DAY 15(DB):4H PST	422	413.3	20.46	414.0	313	483	412.2	421	1.1	0.95	19.57	1.3	-104	64
DAY 29(DB)	450	413.6	22.12	413.5	337	478	413.8	449	-0.1	0.88	18.55	1.0	-62	74
DAY 36(DB):PRE-DS	369	412.2	20.85	413.0	350	522	412.6	368	-0.5	0.94	18.04	-0.2	-77	63
DAY 36(DB):1-2H PST	370	409.6	21.61	408.0	344	481	412.4	369	-2.8	1.03	19.76	-2.0	-85	73
DAY 36(DB):4H PST	363	411.6	20.52	412.0	351	474	412.0	362	-0.4	0.99	18.83	0.3	-65	63
DAY 43(DB)	414	412.4	21.99	412.0	351	506	413.4	413	-1.0	0.90	18.26	-0.7	-62	77
MAXIMUM VALUE (DB)	476	437.0	18.51	436.0	386	522	413.5	475	23.4	0.67	14.57	22.5	-17	77
END POINT (DB)	476	412.7	21.89	413.0	351	506	413.5	475	-0.9	0.83	18.18	-0.3	-62	77
BASE (OPEN)	476	412.8	21.91	413.0	351	506	413.5	475	-0.7	0.83	18.19	-0.3	-62	77
DAY 4(OPEN)	455	413.5	22.48	414.0	331	498	413.4	454	0.1	0.87	18.59	0.3	-63	63
WEEK 1(OPEN)	462	412.2	21.72	411.0	339	488	413.6	461	-1.4	0.84	17.94	-1.0	-69	55
WEEK 2(OPEN)	462	413.7	21.05	414.0	349	473	413.5	461	0.2	0.85	18.22	0.0	-66	64
WEEK 4(OPEN)	468	411.5	21.77	412.0	321	478	413.7	468	-2.2	0.86	18.54	-1.0	-77	45
WEEK 8(OPEN)	469	411.7	21.91	410.0	349	471	413.4	468	-1.7	0.89	19.22	-1.3	-69	68
WEEK 16(OPEN)	470	413.0	20.99	414.0	350	474	413.5	469	-0.5	0.89	19.31	0.3	-73	67
WEEK 24(OPEN)	440	413.9	23.00	415.0	337	488	413.6	439	0.3	0.96	20.07	0.7	-67	68
WEEK 40(OPEN)	369	413.3	20.77	414.0	355	477	411.4	268	1.9	1.09	17.87	2.0	-59	58
WEEK 52(OPEN)	119	412.4	19.33	412.0	359	466	411.9	119	0.5	1.68	18.37	1.0	-66	48
MAXIMUM VALUE (OPEN)	476	432.2	21.14	433.0	378	625	413.5	475	18.7	0.79	17.11	18.0	-27	170
END POINT (OPEN)	476	414.3	22.68	415.0	337	482	413.5	475	0.7	0.88	19.17	2.0	-67	58

The following are QT and QTc interval results for the placebo/Pal group (heart rate in this group increased as expected upon switching subjects from DB placebo to OL Pal).

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DEAG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	change from average predose Mean	SE	SD	Med	Min	Max
QT INTERVAL (ms)														
Pla/Pal1 <=6 months														
BASELINE (DB)	99	372.1	30.07	372.0	320	444								
AVERAGE PREDOSE	99	372.5	29.12	370.0	317	443								
DAY 4(DB):4H PST	96	367.6	33.40	365.0	296	462	372.2	96	-4.6	2.31	22.68	-5.2	-56	44
DAY 4(DB):10H PST	95	373.1	32.62	371.0	304	492	373.5	95	-0.3	2.23	21.71	-3.0	-53	59
DAY 4(DB):22H PST	92	379.3	32.32	373.5	303	489	374.4	92	4.9	2.29	21.93	2.0	-39	61
DAY 8(DB):4H PST	98	369.2	34.52	367.0	285	463	372.5	98	-3.3	2.45	24.26	-3.0	-92	79
DAY 8(DB):10H PST	98	369.5	32.35	369.0	289	439	372.4	98	-2.9	2.17	21.45	-3.3	-60	48
DAY 8(DB):22H PST	97	376.3	32.82	376.0	297	473	372.3	97	4.0	2.10	20.71	2.0	-32	59
DAY 15(DB)	21	400.7	34.06	401.0	327	456	390.7	21	10.0	4.02	18.42	9.3	-31	55
DAY 15(DB):PRE-DS	74	369.8	31.26	371.5	312	457	368.2	74	1.6	1.40	20.62	0.0	-52	47
DAY 15(DB):1-2H PST	76	359.2	28.55	359.5	296	443	368.5	76	-9.3	2.64	23.01	-9.3	-71	41
DAY 15(DB):4H PST	76	360.3	29.73	359.5	297	438	367.7	76	-7.4	2.59	22.62	-7.3	-62	67
DAY 29(DB)	73	375.1	35.15	374.0	305	457	374.7	73	0.4	2.64	22.52	-1.7	-48	78
DAY 36(DB):PRE-DS	32	369.3	33.05	365.0	321	443	371.3	32	-2.0	3.88	21.93	-1.1	-43	39
DAY 36(DB):1-2H PST	32	361.5	28.24	356.0	313	433	369.4	32	-8.0	3.70	20.92	-8.8	-53	34
DAY 36(DB):4H PST	30	364.9	25.52	365.5	320	410	369.9	30	-5.0	3.71	20.32	-6.8	-44	43
DAY 43(DB)	50	380.6	37.04	374.5	310	474	378.1	50	2.5	3.39	23.97	-1.2	-47	60
END POINT (DB)	99	373.3	35.89	371.0	305	474	372.5	99	0.9	2.78	27.62	-0.5	-63	78
BASE (OPEN)	99	374.7	35.68	369.0	305	474	372.5	99	2.2	2.74	27.30	-0.3	-61	78
DAY 4(OPEN)	87	364.6	34.07	366.0	292	467	372.5	87	-7.9	2.64	24.62	-7.0	-64	53
WEEK 1(OPEN)	86	361.6	29.46	358.5	306	438	372.0	86	-10.4	2.63	24.36	-15.0	-59	50
WEEK 2(OPEN)	80	365.2	30.11	363.0	298	460	371.8	80	-6.6	2.68	23.95	-9.0	-75	71
WEEK 4(OPEN)	73	369.9	35.37	367.0	302	483	372.8	73	-3.0	2.96	24.81	-1.7	-62	61
WEEK 8(OPEN)	55	371.8	31.62	365.0	304	463	371.5	55	0.3	3.52	26.08	2.0	-47	62
WEEK 16(OPEN)	26	380.6	31.94	379.5	332	465	377.5	26	3.1	4.95	25.26	6.2	-65	45
WEEK 24(OPEN)	11	383.1	35.70	387.0	310	435	386.2	11	-3.1	10.44	34.64	4.0	-47	48
END POINT (OPEN)	99	373.5	36.35	368.0	294	483	372.5	99	1.0	2.73	27.18	2.7	-70	61

Pla/Pal1 >6 months														
BASELINE (DB)	137	371.9	26.33	372.0	310	451								
AVERAGE PREDOSE	137	370.4	25.27	367.0	316	442								
DAY 4 (DB) :4H PST	135	366.8	28.05	368.0	286	433	370.6	135	-3.8	1.92	22.35	-3.7	-89	50
DAY 4 (DB) :10H PST	135	367.3	29.50	369.0	284	434	370.7	135	-3.4	2.25	26.19	-1.7	-96	64
DAY 4 (DB) :22H PST	136	376.4	30.53	378.5	304	456	370.5	136	6.0	2.20	25.67	6.3	-79	71
DAY 8 (DB) :4H PST	136	366.9	26.19	368.5	306	425	370.6	136	-3.7	2.20	25.68	-3.0	-93	67
DAY 8 (DB) :10H PST	135	371.4	27.95	369.0	293	439	370.9	135	0.4	2.34	27.15	-1.3	-96	75
DAY 8 (DB) :22H PST	135	378.1	29.34	379.0	294	458	370.5	135	7.6	2.28	26.47	10.7	-98	65
DAY 15 (DB)	9	391.8	23.56	401.0	351	425	388.5	9	3.3	9.95	29.86	2.7	-28	74
DAY 15 (DB) :PRE-DS	127	374.7	28.00	376.0	305	441	368.9	127	5.8	2.30	25.89	7.0	-109	80
DAY 15 (DB) :1-2H PST	127	365.9	27.66	367.0	291	432	369.0	127	-3.1	2.38	26.84	-1.0	-87	85
DAY 15 (DB) :4H PST	128	368.3	28.91	370.5	294	450	369.1	128	-0.8	2.28	25.77	1.8	-86	77
DAY 29 (DB)	118	371.0	29.62	370.0	294	452	372.1	118	-1.1	2.55	27.68	1.8	-115	69
DAY 36 (DB) :PRE-DS	84	375.5	32.30	372.0	297	458	368.6	84	6.9	2.98	27.30	8.5	-84	74
DAY 36 (DB) :1-2H PST	83	367.9	27.26	372.0	302	438	369.4	83	-1.5	2.79	25.44	0.5	-83	59
DAY 36 (DB) :4H PST	85	368.9	29.12	370.0	312	455	368.9	85	0.1	3.11	28.67	3.0	-64	110
DAY 43 (DB)	91	377.0	32.62	379.0	310	459	370.7	91	6.2	2.64	25.20	9.0	-58	86
END POINT (DB)	137	373.7	30.54	375.0	306	459	370.4	137	3.4	2.31	26.99	8.3	-115	86
BASE (OPEN)	137	374.0	30.54	376.0	306	459	370.4	137	3.6	2.31	27.03	8.3	-115	86
DAY 4 (OPEN)	131	357.4	31.12	356.0	283	424	370.6	131	-13.2	2.29	26.23	-11.7	-100	65
WEEK 1 (OPEN)	130	361.1	26.38	357.5	303	443	370.6	130	-9.5	2.10	23.91	-8.3	-82	58
WEEK 2 (OPEN)	130	364.1	26.94	364.0	306	454	370.8	130	-6.8	2.17	24.78	-6.7	-96	54
WEEK 4 (OPEN)	132	368.8	29.02	368.0	305	461	370.1	132	-1.3	2.29	26.36	-1.3	-62	71
WEEK 8 (OPEN)	133	369.9	28.43	368.0	287	466	370.3	133	-0.4	2.01	23.23	-2.3	-67	53
WEEK 16 (OPEN)	132	369.2	26.90	369.5	294	432	370.5	132	-1.3	2.18	25.00	-2.0	-73	54
WEEK 24 (OPEN)	129	373.3	28.57	373.0	309	484	370.1	129	3.2	2.46	27.89	2.7	-92	72
WEEK 40 (OPEN)	80	372.1	30.64	368.5	318	443	368.7	80	3.5	2.94	26.27	2.3	-84	59
WEEK 52 (OPEN)	40	374.7	28.31	370.5	313	421	369.8	40	4.8	4.72	29.86	10.0	-66	64
END POINT (OPEN)	137	375.2	30.22	375.0	313	484	370.4	137	4.9	2.47	28.92	5.3	-84	72

The placebo/Pal results for QTc interval are only shown for the over 6 month exposure subgroup since sample sizes were larger than in the ≤ 6 month exposure subgroup.

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DECG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	change from average predose Mean	SE	SD	Med	Min	Max
QTC INTERVAL BAZETT (ms)														
Pla/Pal1 >6 months														
BASELINE (DB)	137	406.9	23.60	408.0	342	468								
AVERAGE PREDOSE	137	408.0	20.52	407.0	339	455								
DAY 4 (DB) :4H PST	135	407.3	21.60	408.0	353	485	408.5	135	-1.2	1.35	15.67	-2.7	-42	53
DAY 4 (DB) :10H PST	135	406.8	21.31	409.0	341	451	407.9	135	-1.1	1.56	18.14	-1.0	-59	74
DAY 4 (DB) :22H PST	136	406.6	22.96	406.5	346	460	408.1	136	-1.5	1.31	15.31	-3.0	-45	47
DAY 8 (DB) :4H PST	136	405.8	22.65	407.0	335	456	408.0	136	-2.3	1.43	16.72	-2.3	-59	62
DAY 8 (DB) :10H PST	135	405.1	23.26	403.0	340	455	408.0	135	-2.8	1.49	17.24	-3.5	-48	59
DAY 8 (DB) :22H PST	135	407.4	24.29	407.0	348	459	408.0	135	-0.6	1.60	18.63	-0.5	-63	75
DAY 15 (DB)	9	424.8	21.11	420.0	404	469	428.1	9	-3.4	5.83	17.49	-7.7	-19	41
DAY 15 (DB) :PRE-DS	127	404.6	22.80	407.0	336	455	406.3	127	-1.7	1.53	17.24	-1.0	-56	51
DAY 15 (DB) :1-2H PST	127	402.6	23.49	401.0	344	468	406.7	127	-4.1	1.67	18.80	-2.7	-54	68
DAY 15 (DB) :4H PST	128	404.4	22.65	407.0	338	462	406.6	128	-2.2	1.69	19.10	0.0	-63	55
DAY 29 (DB)	118	408.7	23.66	407.5	361	461	408.3	118	0.3	1.77	19.26	0.2	-49	65
DAY 36 (DB) :PRE-DS	84	405.9	26.87	403.5	345	486	406.7	84	-0.8	2.28	20.88	-0.6	-45	58
DAY 36 (DB) :1-2H PST	83	405.8	24.03	407.0	339	471	406.8	83	-1.0	2.26	20.63	1.0	-63	73
DAY 36 (DB) :4H PST	85	404.0	24.20	404.0	347	470	406.7	85	-2.7	2.10	19.36	-1.0	-49	72
DAY 43 (DB)	91	406.1	22.53	408.0	330	473	407.5	91	-1.4	1.62	15.45	-2.3	-34	51
MAXIMUM VALUE (DB)	137	428.1	31.08	429.0	363	486	408.0	137	20.1	1.38	16.11	19.0	-25	75
END POINT (DB)	137	408.1	23.52	408.0	330	473	408.0	137	0.1	1.64	19.14	-0.7	-49	65
BASE (OPEN)	137	408.0	23.26	408.0	330	473	408.0	137	0.0	1.64	19.23	-1.0	-49	65
DAY 4 (OPEN)	131	416.3	22.15	417.0	352	464	408.0	131	8.3	1.51	17.28	8.7	-39	66
WEEK 1 (OPEN)	130	415.4	23.15	416.5	345	469	407.8	130	7.5	1.64	18.73	10.0	-51	54
WEEK 2 (OPEN)	130	411.5	20.27	415.0	351	450	407.8	130	3.7	1.45	16.54	4.7	-59	64
WEEK 4 (OPEN)	132	408.8	20.93	409.0	328	451	408.2	132	0.6	1.61	18.53	1.5	-52	77
WEEK 8 (OPEN)	133	410.0	21.54	412.0	341	472	407.8	133	2.2	1.50	17.33	1.3	-41	51
WEEK 16 (OPEN)	132	410.1	22.63	412.5	348	474	408.1	132	2.0	1.65	18.98	1.8	-52	66
WEEK 24 (OPEN)	129	411.6	22.22	412.0	347	463	408.5	129	2.4	1.72	19.53	3.7	-54	48
WEEK 40 (OPEN)	80	412.9	23.10	412.5	370	463	406.8	80	6.1	2.36	21.14	6.0	-51	52
WEEK 52 (OPEN)	40	415.9	18.31	420.0	385	449	407.1	40	8.7	2.64	16.68	6.5	-24	53
MAXIMUM VALUE (OPEN)	137	431.2	17.76	432.0	386	474	408.0	137	23.2	1.27	14.85	22.3	-13	77
END POINT (OPEN)	137	410.8	21.54	411.0	347	463	408.0	137	2.8	1.76	19.94	2.0	-47	66

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DBSG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
QTC INTERVAL FRIDERICIA (ms)														
Pla/Pali >6 months														
BASELINE (DB)	137	394.8	19.23	393.0	347	452								
AVERAGE PREDOSE	137	394.9	17.33	394.0	347	444								
DAY 4 (DB) :4H PST	135	393.1	17.92	393.0	359	467	395.3	135	-2.1	1.08	12.58	-2.7	-40	48
DAY 4 (DB) :10H PST	135	393.0	18.43	393.0	350	441	394.9	135	-2.0	1.29	15.05	-1.3	-46	56
DAY 4 (DB) :22H PST	136	396.0	19.79	395.0	353	459	395.0	136	1.1	1.22	14.22	1.5	-37	44
DAY 8 (DB) :4H PST	136	392.1	18.24	391.5	338	433	395.0	136	-2.8	1.15	13.36	-3.0	-41	40
DAY 8 (DB) :10H PST	135	393.3	18.87	392.0	346	443	395.1	135	-1.7	1.18	13.73	-3.3	-41	45
DAY 8 (DB) :22H PST	135	397.1	19.69	399.0	337	438	394.9	135	2.2	1.22	14.22	2.5	-47	59
DAY 15 (DB)	9	413.3	14.80	416.0	386	435	414.3	9	-1.0	5.51	16.54	-4.7	-20	29
DAY 15 (DB) :PRE-DS	127	394.0	17.28	395.0	339	439	393.2	127	0.8	1.13	12.69	0.5	-36	43
DAY 15 (DB) :1-2H PST	127	389.7	18.70	390.0	335	432	393.5	127	-3.8	1.24	14.00	-3.3	-37	52
DAY 15 (DB) :4H PST	128	391.6	17.48	392.0	329	438	393.5	128	-1.9	1.15	13.07	-1.7	-42	39
DAY 29 (DB)	118	395.5	19.57	394.0	350	452	395.7	118	-0.2	1.28	13.87	-0.3	-46	52
DAY 36 (DB) :PRE-DS	84	395.2	20.80	392.5	343	457	393.4	84	1.8	1.64	15.03	-2.6	-31	40
DAY 36 (DB) :1-2H PST	83	392.4	17.81	391.0	339	442	393.7	83	-1.3	1.55	14.09	-1.5	-36	31
DAY 36 (DB) :4H PST	85	391.7	19.18	392.0	344	446	393.5	85	-1.8	1.50	13.86	-3.0	-35	48
DAY 43 (DB)	91	395.8	19.22	396.0	332	445	394.7	91	1.1	1.30	12.40	1.3	-27	40
MAXIMUM VALUE (DB)	137	411.4	18.01	412.0	362	467	394.9	137	16.5	1.08	12.68	15.3	-14	59
END POINT (DB)	137	396.0	18.60	396.0	332	445	394.9	137	1.1	1.19	13.97	0.7	-27	52
BASE (OPEN)	137	396.0	18.58	396.0	332	445	394.9	137	1.1	1.21	14.14	0.7	-27	52
DAY 4 (OPEN)	131	395.4	19.48	395.0	343	442	395.0	131	0.5	1.23	14.04	-0.3	-30	36
WEEK 1 (OPEN)	130	396.3	18.23	395.5	342	446	394.9	130	1.4	1.21	13.77	2.0	-32	36
WEEK 2 (OPEN)	130	394.8	16.76	395.0	353	427	394.9	130	-0.1	1.16	13.20	-0.2	-33	51
WEEK 4 (OPEN)	132	394.7	16.71	395.0	348	437	394.9	132	-0.2	1.13	13.01	-0.5	-31	38
WEEK 8 (OPEN)	133	395.9	18.27	395.0	351	455	394.7	133	1.2	1.07	12.37	-0.3	-31	43
WEEK 16 (OPEN)	132	395.7	18.72	394.5	353	458	395.0	132	0.7	1.24	14.28	2.0	-35	55
WEEK 24 (OPEN)	129	397.6	17.31	398.0	353	466	395.1	129	2.5	1.24	14.04	3.0	-39	33
WEEK 40 (OPEN)	80	398.3	17.40	396.5	363	443	393.5	80	4.8	1.74	15.52	6.7	-42	32
WEEK 52 (OPEN)	40	401.4	16.30	399.0	368	437	394.2	40	7.2	2.45	15.50	5.7	-25	36
MAXIMUM VALUE (OPEN)	137	411.3	16.28	410.0	360	466	394.9	137	16.4	0.97	11.34	17.0	-9	55
END POINT (OPEN)	137	398.2	17.61	395.0	360	466	394.9	137	3.3	1.34	15.67	3.0	-42	55

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DBSG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
QTC LINEAR SAGIE (ms)														
Pla/Pali >6 months														
BASELINE (DB)	137	395.8	18.85	395.0	344	452								
AVERAGE PREDOSE	137	396.0	16.74	395.3	340	444								
DAY 4 (DB) :4H PST	135	394.4	17.37	395.0	357	463	396.4	135	-2.0	1.05	12.16	-2.0	-36	48
DAY 4 (DB) :10H PST	135	394.4	18.05	394.0	342	441	396.0	135	-1.6	1.26	14.62	-0.3	-42	57
DAY 4 (DB) :22H PST	136	396.9	19.46	397.0	348	459	396.6	136	0.8	1.17	13.61	0.3	-39	41
DAY 8 (DB) :4H PST	136	393.5	18.01	393.0	335	434	396.1	136	-2.5	1.11	13.00	-3.0	-44	41
DAY 8 (DB) :10H PST	135	394.4	18.77	393.0	342	443	396.1	135	-1.7	1.16	13.49	-3.5	-36	46
DAY 8 (DB) :22H PST	135	397.6	19.37	400.0	345	437	396.0	135	1.6	1.19	13.88	1.3	-45	58
DAY 15 (DB)	9	413.4	12.96	414.0	390	431	415.0	9	-1.5	4.86	14.59	-4.3	-19	25
DAY 15 (DB) :PRE-DS	127	394.4	18.13	397.0	331	438	394.3	127	0.1	1.16	13.05	-0.3	-42	45
DAY 15 (DB) :1-2H PST	127	391.1	17.93	392.0	343	432	394.6	127	-3.6	1.17	13.24	-3.3	-35	53
DAY 15 (DB) :4H PST	128	392.5	17.21	393.5	334	437	394.6	128	-2.1	1.12	12.66	-1.7	-41	41
DAY 29 (DB)	118	396.5	18.74	396.0	356	452	396.7	118	-0.2	1.23	13.40	-1.6	-42	48
DAY 36 (DB) :PRE-DS	84	395.2	20.17	393.5	345	451	394.5	84	0.7	1.64	15.07	-2.3	-39	36
DAY 36 (DB) :1-2H PST	83	393.3	17.29	392.0	346	441	394.7	83	-1.4	1.58	14.41	-2.0	-36	27
DAY 36 (DB) :4H PST	85	392.5	18.63	392.0	348	444	394.6	85	-2.1	1.54	14.21	-2.0	-39	46
DAY 43 (DB)	91	396.5	18.84	398.0	332	442	395.7	91	0.8	1.32	12.58	0.3	-26	45
MAXIMUM VALUE (DB)	137	411.8	17.06	412.0	363	463	396.0	137	15.8	1.02	11.96	14.7	-12	58
END POINT (DB)	137	396.6	18.15	397.0	332	442	396.0	137	0.7	1.16	13.62	0.0	-27	48
BASE (OPEN)	137	396.7	18.12	397.0	332	442	396.0	137	0.7	1.17	13.70	0.0	-27	48
DAY 4 (OPEN)	131	396.5	18.22	395.0	348	441	396.0	131	0.5	1.18	13.48	0.0	-30	34
WEEK 1 (OPEN)	130	397.2	17.08	397.5	343	443	395.9	130	1.3	1.17	13.29	2.3	-32	38
WEEK 2 (OPEN)	130	396.1	16.05	397.0	354	427	396.0	130	0.1	1.12	12.82	-0.2	-39	52
WEEK 4 (OPEN)	132	395.6	16.42	397.0	325	434	396.0	132	-0.4	1.14	13.14	0.0	-52	37
WEEK 8 (OPEN)	133	397.1	17.61	396.0	343	455	395.8	133	1.3	1.09	12.52	0.5	-30	48
WEEK 16 (OPEN)	132	396.9	17.94	396.0	348	456	396.1	132	0.8	1.21	13.88	1.0	-33	56
WEEK 24 (OPEN)	129	398.3	16.97	398.0	350	467	396.2	129	2.1	1.23	13.94	3.0	-37	40
WEEK 40 (OPEN)	80	398.7	16.65	397.5	369	442	394.9	80	3.9	1.77	15.85	5.0	-45	31
WEEK 52 (OPEN)	40	402.4	15.43	401.0	373	438	395.7	40	6.7	2.41	15.27	3.8	-28	38
MAXIMUM VALUE (OPEN)	137	411.8	15.48	410.0	366	467	396.0	137	15.8	0.97	11.33	16.0	-10	56
END POINT (OPEN)	137	398.8	17.29	396.0	350	467	396.0	137	2.9	1.34	15.64	3.0	-41	56

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DB0601: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	Change from average predose Mean	SE	SD	Med	Min	Max
QTC LINEAR DERIVED (ms)														
Pla/Pal >6 months														
BASELINE (DB)	137	394.4	18.67	393.0	345	451								
AVERAGE PREDOSE	137	394.5	16.71	394.0	342	443								
DAY 4 (DB) :4H PST	135	392.8	17.33	393.0	358	462	394.9	135	-2.0	1.05	12.17	-2.9	-36	48
DAY 4 (DB) :10H PST	135	392.8	18.07	392.0	344	440	394.6	135	-1.7	1.26	14.60	-1.3	-41	54
DAY 4 (DB) :22H PST	136	395.7	19.39	395.5	349	458	394.6	136	1.1	1.18	13.79	0.3	-37	40
DAY 8 (DB) :4H PST	136	391.9	17.88	391.5	335	433	394.6	136	-2.7	1.12	13.07	-3.9	-42	38
DAY 8 (DB) :10H PST	135	393.1	18.64	392.0	343	442	394.7	135	-1.6	1.17	13.54	-3.0	-37	44
DAY 8 (DB) :22H PST	135	396.4	19.25	399.0	342	435	394.5	135	1.9	1.19	13.80	2.0	-42	56
DAY 15 (DB)	9	412.4	12.87	414.0	388	430	414.0	9	-1.5	4.85	14.55	-4.7	-19	23
DAY 15 (DB) :PRE-DS	127	393.3	17.83	395.0	336	439	392.9	127	0.5	1.15	12.92	0.0	-41	43
DAY 15 (DB) :1-2H PST	127	389.6	17.82	391.0	341	431	393.1	127	-3.5	1.17	13.20	-3.0	-33	51
DAY 15 (DB) :4H PST	128	391.1	17.09	392.5	333	435	393.1	128	-2.1	1.10	12.42	-1.8	-40	39
DAY 29 (DB)	118	395.0	18.73	394.5	354	452	395.3	118	-0.3	1.23	13.38	-0.7	-43	47
DAY 36 (DB) :PRE-DS	84	394.0	19.95	392.0	345	448	393.0	84	1.0	1.62	14.84	-1.7	-37	36
DAY 36 (DB) :1-2H PST	83	392.0	16.98	390.0	340	440	393.3	83	-1.3	1.55	14.08	-2.3	-34	29
DAY 36 (DB) :4H PST	85	391.2	18.42	391.0	347	445	393.1	85	-1.9	1.53	14.11	-1.3	-37	51
DAY 43 (DB)	91	395.3	18.82	397.0	332	439	394.2	91	1.0	1.32	12.63	1.3	-24	43
MAXIMUM VALUE (DB)	137	410.4	17.28	410.0	362	462	394.5	137	15.9	1.03	12.07	15.0	-11	56
END POINT (DB)	137	395.3	18.00	396.0	332	439	394.5	137	0.8	1.16	13.53	0.0	-24	47
BASE (OPEN)	137	395.3	17.99	396.0	332	439	394.5	137	0.8	1.16	13.62	0.0	-24	47
DAY 4 (OPEN)	131	394.3	18.44	392.0	347	440	394.6	131	-0.2	1.19	13.64	-0.7	-29	34
WEEK 1 (OPEN)	130	395.3	17.05	395.0	343	441	394.5	130	0.8	1.16	13.20	1.0	-32	35
WEEK 2 (OPEN)	130	394.3	16.14	394.5	355	426	394.5	130	-0.2	1.12	12.82	-0.7	-36	50
WEEK 4 (OPEN)	132	394.2	16.48	395.0	328	436	394.5	132	-0.3	1.13	12.98	-0.3	-48	37
WEEK 8 (OPEN)	133	395.5	17.71	394.0	344	455	394.4	133	1.2	1.07	12.33	0.0	-29	46
WEEK 16 (OPEN)	132	395.3	17.89	394.5	349	455	394.6	132	0.7	1.20	13.76	1.0	-33	54
WEEK 24 (OPEN)	129	396.9	16.92	397.0	352	468	394.7	129	2.2	1.21	13.75	3.0	-35	36
WEEK 40 (OPEN)	80	397.1	16.57	395.0	366	440	393.3	80	3.8	1.75	15.63	5.0	-43	31
WEEK 52 (OPEN)	40	400.8	15.71	398.5	370	437	394.1	40	6.6	2.46	15.57	4.3	-31	36
MAXIMUM VALUE (OPEN)	137	410.1	15.70	409.0	364	468	394.5	137	15.6	0.96	11.25	16.0	-8	54
END POINT (OPEN)	137	397.5	17.30	395.0	352	468	394.5	137	3.0	1.32	15.50	3.0	-43	54

RR Interval Results

RR interval results below show mean increases at later time-points that were numerically greater at 52 weeks (mean increase of 27.6 msec). These mean increases were not associated with corresponding changes in HR (as shown in the ECG HR results below). Yet heart rate is provide in units of bpm, while RR interval is provided in msec. It is difficult to interpret these results from a clinical perspective but the results may be reflecting Pal effects on QT and PR (combined) as described in the following. The RR prolongation was associated with at least trends for QT prolongation, but note that weeks 4, 8 and 16 show mean RR prolongation of approximately 8 or 9 msec while mean QT prolongation was negligible to small (0.3 to up to 2 msec). Note that a small mean PR prolongation was also observed at these time-points that may be contributing in part, to the results on RR interval. Only results of the DB Pal/OL pal over 6 month subgroup are shown below (the group that represents the longest continuous Pal exposure).

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DEC002: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
RR (ms)														
BASELINE (DB)	475	831.0	155.55	800.0	462	1429								
AVERAGE PREDOSE	475	819.2	136.89	796.7	484	1429								
DAY 4 (DB) :4H PST	467	737.9	133.62	714.0	484	1395	819.3	467	-81.4	5.58	120.48	-81.7	-543	378
DAY 4 (DB) :10H PST	458	761.8	134.04	750.0	508	1304	820.4	458	-58.5	5.91	126.42	-57.8	-674	384
DAY 4 (DB) :22H PST	460	776.1	144.20	759.0	504	1304	818.9	460	-42.7	5.81	124.57	-33.5	-471	353
DAY 8 (DB) :4H PST	472	757.0	129.15	741.0	462	1277	818.5	471	-61.7	5.57	120.95	-56.0	-525	270
DAY 8 (DB) :10H PST	468	772.8	131.14	750.0	488	1304	820.1	467	-47.2	5.90	127.49	-45.7	-498	342
DAY 8 (DB) :22H PST	471	798.1	144.62	789.0	465	1364	818.9	470	-21.0	6.16	133.45	-16.6	-520	381
DAY 15 (DB)	44	835.1	163.14	827.5	531	1176	836.7	44	-1.6	19.02	126.14	-16.2	-186	276
DAY 15 (DB) :PRE-DS	421	815.7	147.44	800.0	496	1277	817.6	420	-1.7	6.58	134.77	-4.0	-454	422
DAY 15 (DB) :1-2H PST	423	784.0	146.28	759.0	496	1500	817.3	422	-33.5	7.21	148.18	-36.5	-559	454
DAY 15 (DB) :4H PST	424	767.8	140.59	750.0	417	1429	816.5	423	-48.7	7.08	145.65	-46.3	-739	582
DAY 29 (DB)	450	819.1	155.92	794.5	500	1364	817.3	449	1.5	6.20	131.41	-6.0	-442	432
DAY 36 (DB) :PRE-DS	370	842.4	163.37	833.0	368	1395	815.7	369	26.8	7.27	139.73	18.3	-366	421
DAY 36 (DB) :1-2H PST	371	824.9	149.85	822.0	432	1277	816.7	370	8.4	7.03	135.22	6.3	-380	417
DAY 36 (DB) :4H PST	367	814.4	141.68	800.0	444	1277	818.0	366	-3.5	6.83	130.68	-6.6	-347	404
DAY 43 (DB)	420	838.6	143.26	833.0	531	1364	818.9	419	19.4	6.27	128.27	28.7	-491	428
END POINT (DB)	476	832.6	142.10	827.5	526	1364	819.2	475	13.2	6.00	130.70	23.3	-491	428
BASE (OPEN)	475	834.3	141.88	833.0	526	1364	819.3	474	14.8	6.04	131.48	24.3	-491	428
DAY 4 (OPEN)	456	815.4	144.11	800.0	504	1364	818.3	455	-3.1	6.57	140.12	-0.3	-478	487
WEEK 1 (OPEN)	463	822.2	134.73	811.0	500	1395	819.7	462	2.3	6.26	134.58	7.8	-618	483
WEEK 2 (OPEN)	462	816.7	140.63	800.0	517	1364	818.9	461	-2.4	6.31	135.49	0.3	-446	428
WEEK 4 (OPEN)	469	827.6	148.53	811.0	465	1395	818.5	469	9.0	6.32	136.93	6.0	-435	499
WEEK 8 (OPEN)	470	827.0	154.62	811.0	462	1395	818.4	469	8.2	6.43	139.30	6.0	-448	526
WEEK 16 (OPEN)	470	829.5	152.35	811.0	522	1395	820.2	469	9.1	6.99	151.44	-0.3	-445	628
WEEK 24 (OPEN)	442	844.8	164.57	833.0	465	1500	819.2	441	25.3	7.42	155.72	19.3	-506	731
WEEK 40 (OPEN)	269	822.8	150.82	811.0	504	1277	818.0	268	5.1	8.71	142.60	11.7	-477	456
WEEK 52 (OPEN)	119	843.0	141.37	811.0	583	1176	815.4	119	27.6	12.73	138.86	22.0	-378	390
END POINT (OPEN)	476	840.1	155.08	822.0	517	1500	819.2	475	21.1	6.77	147.51	17.3	-477	598

PR Interval Results

Clinically unremarkable group mean and median increases in PR interval is observed (as shown below).

Output DEC002: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
PR INTERVAL (ms)														
Pali/Pali >6 months														
BASELINE (DB)	475	151.6	19.92	150.0	95	227								
AVERAGE PREDOSE	475	151.8	19.87	150.3	92	236								
DAY 4 (DB) :4H PST	465	151.8	20.79	151.0	100	240	151.9	465	-0.0	0.47	10.10	0.0	-38	39
DAY 4 (DB) :10H PST	457	154.3	22.03	152.0	104	257	151.9	457	2.4	0.52	11.08	2.0	-26	75
DAY 4 (DB) :22H PST	460	150.8	20.87	150.0	102	232	151.8	460	-1.0	0.48	10.25	-1.3	-44	36
DAY 8 (DB) :4H PST	471	153.4	20.72	151.0	94	228	151.8	470	1.1	0.49	10.61	1.0	-32	46
DAY 8 (DB) :10H PST	468	154.4	20.69	153.0	92	220	151.8	467	2.6	0.52	11.14	2.7	-39	38
DAY 8 (DB) :22H PST	471	152.0	20.83	150.0	84	230	151.7	470	0.3	0.52	11.17	0.2	-41	41
DAY 15 (DB)	44	158.7	21.84	153.5	128	215	162.9	44	-4.2	2.06	13.69	-2.7	-49	16
DAY 15 (DB) :PRE-DS	421	151.5	19.93	150.0	94	221	150.5	420	0.9	0.53	10.94	0.7	-46	49
DAY 15 (DB) :1-2H PST	422	150.6	20.73	148.0	90	272	150.6	421	-0.1	0.56	11.45	-0.3	-43	84
DAY 15 (DB) :4H PST	423	150.6	19.98	150.0	94	216	150.7	422	-0.2	0.52	10.62	-0.3	-45	45
DAY 29 (DB)	450	152.0	20.60	150.0	89	228	151.7	449	0.3	0.52	10.94	0.3	-34	48
DAY 36 (DB) :PRE-DS	370	150.6	20.68	148.0	96	215	150.2	369	0.4	0.61	11.70	0.0	-45	60
DAY 36 (DB) :1-2H PST	371	150.1	20.14	148.0	91	216	150.2	370	-0.1	0.58	11.20	0.6	-48	42
DAY 36 (DB) :4H PST	365	149.9	20.65	148.0	102	228	150.3	364	-0.5	0.62	11.90	0.0	-46	63
DAY 43 (DB)	417	153.3	20.71	152.0	108	237	151.7	416	1.6	0.53	10.82	1.7	-50	29
END POINT (DB)	476	153.3	20.88	152.0	108	237	151.8	475	1.5	0.51	11.07	1.3	-50	39
BASE (OPEN)	475	153.1	20.88	152.0	108	237	151.8	475	1.3	0.51	11.10	1.3	-50	39
DAY 4 (OPEN)	456	152.3	20.67	151.0	94	260	151.7	455	0.6	0.57	12.11	0.0	-50	42
WEEK 1 (OPEN)	462	152.6	21.25	150.0	89	257	151.6	461	1.0	0.56	12.00	0.3	-51	58
WEEK 2 (OPEN)	462	152.5	20.55	151.0	107	226	151.6	461	0.9	0.56	12.06	1.0	-39	73
WEEK 4 (OPEN)	469	152.7	21.68	151.0	97	257	151.6	469	1.1	0.58	12.60	1.0	-63	80
WEEK 8 (OPEN)	470	153.3	20.64	150.0	105	225	151.7	469	1.6	0.53	11.44	2.0	-58	39
WEEK 16 (OPEN)	470	153.6	21.42	152.0	105	238	151.6	469	2.0	0.57	12.36	1.3	-31	85
WEEK 24 (OPEN)	440	152.4	22.02	150.0	91	233	151.3	439	1.0	0.62	13.01	1.7	-43	83
WEEK 40 (OPEN)	269	152.2	20.90	150.0	102	210	149.8	268	2.3	0.76	12.37	1.7	-46	56
WEEK 52 (OPEN)	119	150.9	19.08	149.0	104	197	150.7	119	0.2	1.21	13.24	-1.7	-34	47
END POINT (OPEN)	476	152.8	21.40	151.0	102	233	151.8	475	1.0	0.57	12.43	1.0	-46	47

Heart Rate Results

Results of only the DB-Pal/OL-Pal (Pali/Pali) subgroups with over 6 months exposure are shown below (as provided by the sponsor), since this group represents the subgroup with the longest exposure (since they had DB Pal as well as OL Pal). Heart rate shows little to not change during OL Pal treatment in this subgroup.

As previously discussed, failure to show a positive finding in the OL safety dataset could be associated with aspects of the study design, such as the flexible dose, non-placebo controlled design, and also consider potential between subject variance on the timing of assessments and dosing in these outpatients. The OL trials were not designed to capture time-dependent and PK-dependent effects of Pal. Refer to a previous discussion about assessment time-windows, such as in Section 7.1 X of this review.

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DBXC02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

							Base	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max
HEART RATE (beats/min)														
Pali/Pali <=6 months														
BASELINE (DB)	209	75.7	15.25	77.0	46	149								
AVERAGE PREDOSE	209	77.3	13.56	77.0	49	134								
DAY 4 (DB):4H PST	204	86.1	14.89	86.0	51	128	77.6	204	8.6	0.84	11.96	8.7	-21	54
DAY 4 (DB):10H PST	198	85.5	15.06	85.5	50	130	77.4	198	8.1	0.86	12.17	7.7	-27	54
DAY 4 (DB):22H PST	197	81.7	15.29	82.0	44	120	77.8	197	3.8	0.90	12.65	3.7	-32	48
DAY 8 (DB):4H PST	207	83.7	13.97	85.0	52	121	77.2	207	6.5	0.82	11.79	6.0	-29	46
DAY 8 (DB):10H PST	202	82.9	14.01	83.0	51	117	77.1	202	5.8	0.84	11.96	4.7	-33	40
DAY 8 (DB):22H PST	207	80.3	15.86	81.0	44	128	77.2	207	3.1	0.90	12.94	2.3	-35	48
DAY 15 (DB)	14	74.2	16.28	77.0	46	114	71.3	14	2.9	2.60	9.74	2.3	-14	15
DAY 15 (DB):PRE-DS	193	79.6	16.27	78.0	38	123	77.8	193	1.8	0.89	12.30	1.0	-35	41
DAY 15 (DB):1-2H PST	188	82.9	15.72	83.0	44	140	77.7	188	5.3	1.03	14.92	4.3	-52	61
DAY 15 (DB):4H PST	187	85.0	15.86	85.0	49	137	78.0	187	7.0	1.06	14.52	5.3	-40	54
DAY 29 (DB)	177	77.0	13.65	75.0	48	117	77.1	177	-0.1	1.04	13.77	0.0	-51	36
DAY 36 (DB):PRE-DS	130	76.2	14.31	75.0	44	138	78.1	130	-1.9	1.17	13.31	-1.3	-39	28
DAY 36 (DB):1-2H PST	130	78.5	13.14	78.5	44	115	77.9	130	0.6	1.22	13.91	0.3	-46	32
DAY 36 (DB):4H PST	128	78.9	13.03	78.0	39	108	77.9	128	1.0	1.29	14.58	1.7	-52	41
DAY 43 (DB)	144	75.2	13.35	74.0	47	121	77.5	144	-2.3	1.08	12.96	-1.6	-52	37
END POINT (DB)	203	76.7	14.31	76.0	47	121	77.3	209	-0.7	0.93	13.43	-0.7	-52	43
BASE (OPEN)	209	76.2	14.03	76.0	47	121	77.3	209	-1.1	0.88	12.71	-0.8	-52	37
DAY 4 (OPEN)	178	77.5	14.14	75.0	47	119	77.2	178	0.3	0.98	13.05	-1.0	-37	37
WEEK 1 (OPEN)	187	78.5	14.17	79.0	45	133	77.2	187	1.2	0.84	11.44	2.0	-38	26
WEEK 2 (OPEN)	167	76.8	13.96	76.0	50	139	77.3	167	-0.6	0.99	12.77	0.3	-43	29
WEEK 4 (OPEN)	152	76.6	14.61	75.5	44	124	76.6	152	0.0	0.99	12.20	0.2	-43	39
WEEK 8 (OPEN)	103	75.0	14.72	73.0	43	110	75.7	103	-0.7	1.36	13.79	0.0	-36	34
WEEK 16 (OPEN)	32	76.4	13.36	75.0	51	106	77.1	32	-0.7	2.79	15.79	-3.2	-28	45
END POINT (OPEN)	203	78.6	15.40	78.0	50	139	77.3	203	1.3	0.96	13.71	1.0	-43	45

Studies R076477-SCH-702, R076477-SCH-703, R076477-SCH-704, and R076477-SCH-705

Output DEXG02: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	change from average predose Mean	SE	SD	Med	Min	Max
HEART RATE (beats/min)														
Pali/Pali >6 months														
BASELINE (DB)	475	74.6	13.31	75.0	42	130								
AVERAGE PREDOSE	475	75.8	12.13	76.3	42	125								
DAY 4 (DB) :4H PST	467	83.8	14.06	84.0	43	124	75.8	467	8.0	0.65	11.80	8.0	-32	48
DAY 4 (DB) :10H PST	458	81.1	13.60	80.0	46	118	75.7	458	5.4	0.57	12.16	5.7	-40	55
DAY 4 (DB) :22H PST	460	79.8	14.07	79.0	46	119	75.8	460	4.0	0.57	12.19	2.7	-29	50
DAY 8 (DB) :4H PST	472	81.5	13.36	81.0	47	130	75.8	471	5.7	0.53	11.57	5.3	-26	37
DAY 8 (DB) :10H PST	469	79.8	12.93	80.0	46	123	75.7	467	4.1	0.56	12.10	4.0	-37	41
DAY 8 (DB) :22H PST	471	77.6	13.72	76.0	44	129	75.8	470	1.8	0.59	12.74	0.8	-28	60
DAY 15 (DB)	44	74.6	15.01	72.5	51	113	73.7	44	0.9	1.78	11.82	1.3	-27	22
DAY 15 (DB) :PRE-DS	421	76.0	13.91	75.0	47	121	76.0	420	0.0	0.62	12.77	-0.3	-39	52
DAY 15 (DB) :1-2H PST	423	79.1	14.11	79.0	40	121	76.0	422	3.1	0.67	13.86	3.0	-44	44
DAY 15 (DB) :4H PST	424	80.7	14.20	80.0	42	144	76.1	423	4.6	0.67	13.79	4.0	-38	66
DAY 29 (DB)	450	75.8	13.84	75.5	44	120	75.9	449	-0.1	0.57	12.09	0.0	-40	46
DAY 36 (DB) :PRE-DS	370	74.0	15.06	72.0	43	163	76.1	369	-2.1	0.70	13.41	-2.0	-51	75
DAY 36 (DB) :1-2H PST	371	75.2	13.77	73.0	47	139	76.0	370	-0.9	0.67	12.88	-1.2	-42	53
DAY 36 (DB) :4H PST	367	75.9	13.18	75.0	47	135	75.9	366	0.0	0.65	12.39	0.0	-37	47
DAY 43 (DB)	420	73.7	12.74	72.0	44	113	75.7	419	-2.0	0.57	11.75	-2.7	-34	34
END POINT (DB)	475	74.2	12.82	72.5	44	114	75.8	475	-1.6	0.55	12.02	-2.3	-37	37
BASE (OPEN)	475	74.0	12.82	72.0	44	114	75.8	475	-1.7	0.56	12.11	-2.7	-37	37
DAY 4 (OPEN)	456	75.8	13.08	75.0	44	119	75.8	455	0.0	0.60	12.85	0.0	-41	42
WEEK 1 (OPEN)	463	75.0	12.50	74.0	43	120	75.7	462	-0.7	0.58	12.49	-1.3	-52	51
WEEK 2 (OPEN)	462	75.6	13.06	75.0	44	116	75.8	461	-0.1	0.60	12.89	-0.7	-49	51
WEEK 4 (OPEN)	469	74.8	13.23	74.0	43	129	75.8	469	-1.0	0.59	12.78	-1.0	-40	42
WEEK 8 (OPEN)	470	75.1	14.14	74.0	43	130	75.8	469	-0.7	0.61	13.17	-0.7	-43	50
WEEK 16 (OPEN)	470	74.7	13.27	74.0	43	115	75.7	469	-1.0	0.63	13.54	-0.3	-46	51
WEEK 24 (OPEN)	442	73.6	13.94	72.0	40	129	75.9	441	-2.2	0.66	13.83	-2.0	-53	45
WEEK 40 (OPEN)	269	75.4	13.82	74.0	47	119	75.9	268	-0.5	0.81	13.33	-1.3	-38	41
WEEK 52 (OPEN)	119	73.2	12.27	74.0	51	103	76.0	119	-2.9	1.14	12.40	-2.7	-34	28
END POINT (OPEN)	476	73.8	13.46	73.0	40	116	75.8	475	-2.0	0.62	13.44	-2.9	-53	34

QRS Axis showed a mean decrease of up to -4.2 degrees (±13.8) in the Pali/Pali > 6 month subgroup observed at week 52 and showed at least trends for a group mean decrease on most assessment time-points (this subgroup was selected for the focus of this review due to larger sample sizes of subjects with over 6 months exposure, as previously described).

Incidence of Outliers

Reviewer Comment: *Tables and figures of results are shown after providing the following overall comments.*

The results on overall incidence of outliers on ECG parameters failed to show any new findings that are not already described in this review (see the first table below for results). However, QT interval outlier results are based on absolute values of 500 msec or greater.

The following new finding is revealed by the longer term dataset in the SUR, when the data is examined more closely (using less stringent outlier criteria, when showing scatterplots of individual values or when examining the incidence of outliers on the change of QT interval from a pre-dose averaged value):

- *The subgroups with longer exposure (the ≥6 months) and in particular the treatment groups with continuous antipsychotic exposure (the Pal/Pal and Olanzapine/Pal subgroups) appear to exhibit the following. These groups have subjects with greater QTc values or greater changes in values from the pre-dose averaged value than subgroups with less exposure (the < 6 month subgroups). Small trends for this pattern can be seen with scatterplots of maximal QTc interval values. A small overall upward rather than a downward shift of the scatterplot (towards higher QTc values rather than*

lower QTc values) appears to exist in the ≥ 6month group compared to each corresponding < 6month exposed subgroup. Refer to the scatterplot below of "maximum QTcLD" (Table 14)

A pattern for an overall upward shift of subjects on QTc values (rather than no shift or a downward shift) appears to be more predominant when examining the results of the incidence of subjects showing a change from lower to higher QTc interval values. Refer to Table 15 below of the scatterplot of the "change of QTcLD." These results show a trend for more subjects with higher values or greater shifts are seen in the subgroups with longer Pal exposure (comparing <6 month to ≥ 6 month subgroups). This trend appears to be greatest among the subgroup exposed the longest to continuous Pal treatment which is the ≥6 month DB Pal/OL Pal subgroup and among the ≥ 6month Total Pal group (the total Pal group includes all subjects receiving OL Pal, independent of DB study drug assignment, such that a subgroup of these subjects were the ≥ 6 month DB Pal/OL pal group). These results are shown below.

A caveat to the above observations is that results may not reflect a time-dependent effect since the longer a given subject is observed the greater the likelihood a given subject will eventually show a shift or high QTc interval value. However, when examining descriptive statistical results a greater effects were observed at time-points of 6 moths and over during the OL phase. Furthermore, an examination of the individual scatterplots of QTc values appear to show an overall upward shift of QT interval in the over (such that, not only does there appear to be more subjects with higher QTc values in the ≥ 6 month subgroups, but there also appears to be fewer subjects with lower QTc values in these subgroups compared to the corresponding < 6 month subgroups). Consequently the results on the incidence may be reflecting a true Pal effect for greater QT prolongation effects over time. It may be helpful to examine the incidence of outliers at each assessment time-point (using an OC approach) and to examine the incidence of outliers with decreased or low QTc values. This additional information may be helpful in revealing results that could suggest that the above observations of the ≥ 6 month versus < 6 month subgroups may be reflection a greater incidence of outliers as a function of time and frequency of ECG monitoring versus a true drug effect. In the absence of placebo group the interpretation of results are limited, but are suspicious of a drug effect that was observed in the shorter-term placebo controlled trials that continues with longer term treatment. See the final section of this review for comments and recommendations.

Another caveat to consider regarding the sponsor's results, is that shift tables and scatterplot results were only provided for either QTcLD and/or for QTc using other additional methods. QTcF and QTcB methods (and possibly QTlc, sagie method) may be least accurate since HR did not appeared to show minimal to no change when ECG assessments were conducted (as previously described). Perhaps QTcLD is a better measure, but this measure incorporates drug-free QT/RR data.

QTraw interval results may be more accurate (due to minimal to no HR changes on the ECG assessments). However, similar tables and figures for QTraw results could not be found with these other in-text tables of the QTcLD results in the SUR that are shown below.

Finally the scatterplot tables only show results with respect to maximal QTc values, whereas a scatterplot of median values may be more appropriate depending on the frequency distribution of QT values. Furthermore, showing individual scatterplots for each treatment group but with the exposure subgroups, combined, yet showing results over time (at assessment each time-point) may a more accurate way of showing the results.

Table 84: Number of Subjects With Treatment-Emergent Abnormal ECG Values During the Open-Label Period
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

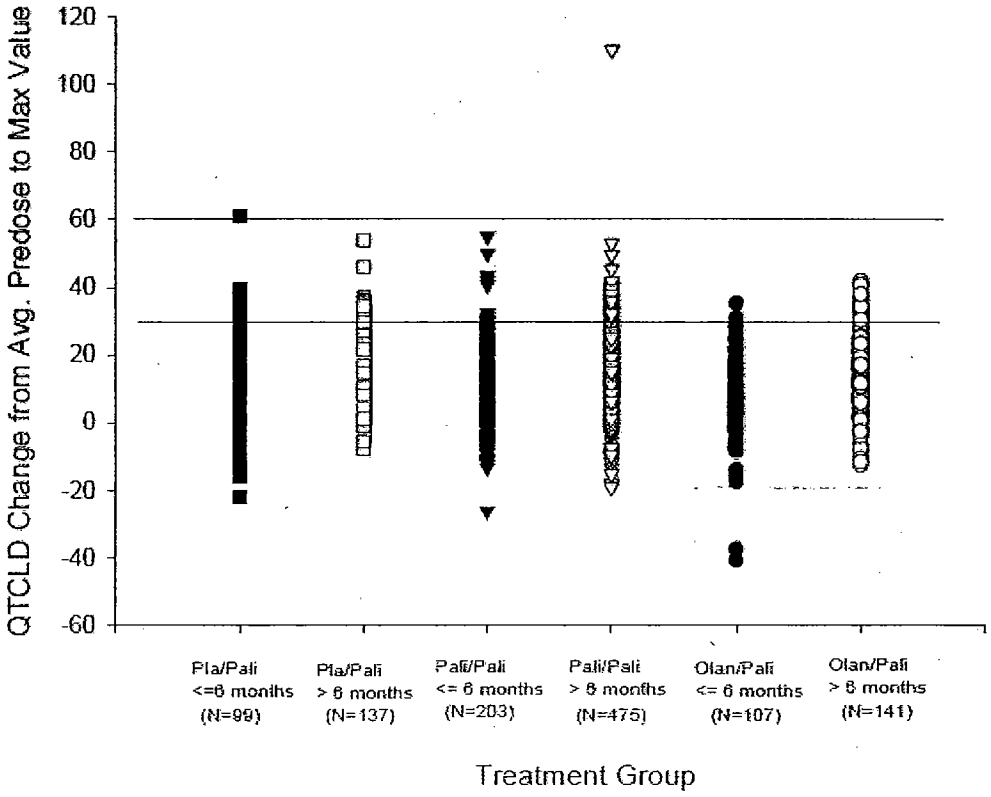
	Pla/Pali ≤6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali ≤6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali ≤6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali ≤6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
Heart rate	99	137	203	476	107	141	409	754
Abnormally high	30 (30)	38 (28)	32 (16)	95 (20)	32 (30)	36 (26)	94 (23)	169 (22)
Abnormally low	2 (2)	14 (10)	7 (3)	35 (7)	4 (4)	7 (5)	13 (3)	56 (7)
PR interval	98	137	202	476	107	141	407	754
Abnormally high	0	4 (3)	1 (<1)	12 (3)	1 (1)	2 (1)	2 (<1)	18 (2)
Abnormally low	0	0	0	0	0	0	0	0
QRS interval	99	137	203	476	107	141	409	754
Abnormally high	2 (2)	1 (1)	1 (<1)	2 (<1)	1 (1)	0	4 (1)	3 (<1)
Abnormally low	0	0	0	0	0	0	0	0
QT interval	99	137	203	476	107	141	409	754
Abnormally high	0	0	0	0	0	0	0	0
Abnormally low	0	0	0	0	0	0	0	0

Note: Percentages calculated with the number of subjects per parameter as denominator.
Note: Heart rate: abnormally low: <=50 bpm, abnormally high: >=100 bpm.
PR interval: abnormally high: >=210 msec.
QRS interval: abnormally low: <=50 msec, abnormally high: >=120 msec.
QT interval: abnormally low: <=200 msec, abnormally high: >=500 msec.
tsfecg06_tsfecg.rtf generated by tsfecg.sas.

The sponsor's focus was on showing results of QTcLD, as in the following scatterplots rather than showing the below scatterplots for QT raw intervals or for QTc interval using other correction methods (these scatterplots were copied from the submission). Reviewer comments of these results were provided

abov

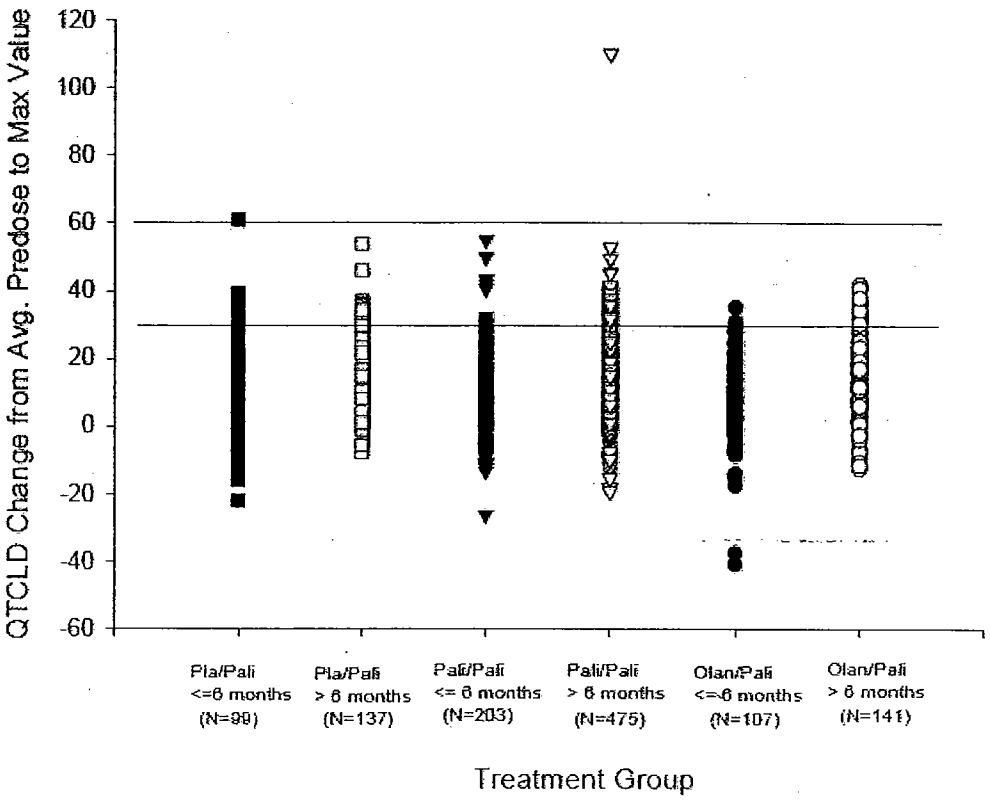
Figure 15: Change in QTcLD From Average Predose Value to Maximum Value During Open-Label Treatment (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)



Note: The subject with a change of more than 100 ms, who also had a maximum value greater than 500 ms, was Subject 201418; a narrative for this subject is presented at the end of this section, following Table 92.

Appears This Way On Original

Figure 15: Change in QTcLD From Average Predose Value to Maximum Value During Open-Label Treatment (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)



Note: The subject with a change of more than 100 ms, who also had a maximum value greater than 500 ms, was Subject 201418; a narrative for this subject is presented at the end of this section, following Table 92.

The following are results of the number or incidence of subjects that met categorical shift criteria (as specified in the tables) for QTc interval using different correction methods. Similar tables for raw QT interval were not found among these in-text summary tables.

The results of DB Pal/OL Pal subgroups were copied below from the sponsor's in-text summary tables since this group of subjects received the longest continuous Pal exposure. Results of Total Pal groups are also shown (includes all subgroup regardless of their DB treatment assignment).

Table 91: Classification of Maximum Corrected QT Intervals During Open-Label Treatment Versus Average Predose Value (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

Treatment Group and Evaluation at Average Predose								
	— Pali/Pali <=6 months — (N=209)				— Pali/Pali >6 months — (N=476)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD								
Maximum value								
Normal	198	0	0	198	462	1	0	463
>=450 - <480	3	2	0	5	6	4	0	10
>=480	0	0	0	0	1	1	0	2
Total	201	2	0	203	469	6	0	475
QTcF								
Maximum value								
Normal	198	0	0	198	458	1	0	459
>=450 - <480	3	2	0	5	10	3	0	13
>=480	0	0	0	0	1	2	0	3
Total	201	2	0	203	469	6	0	475

	— Pali/Pali <=6 months — (N=209)				— Pali/Pali >6 months — (N=476)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTlc								
Maximum value								
Normal	198	0	0	198	460	1	0	461
>=450 - <480	3	2	0	5	8	4	0	12
>=480	0	0	0	0	1	1	0	2
Total	201	2	0	203	469	6	0	475
QTcB								
Maximum value								
Normal	184	1	0	185	396	4	0	400
>=450 - <480	12	5	0	17	57	15	0	72
>=480	0	1	0	1	0	3	0	3
Total	196	7	0	203	453	22	0	475

Note: Normal(Norm)(<450 ms); >=450 ms - <480 ms(>=450); >=480 ms(>=480)

Table 91: Classification of Maximum Corrected QT Intervals During Open-Label Treatment Versus Average Predose Value (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	--- Total Pali <=6 months --- (N=416)				— Total Pali >6 months — (N=754)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD								
Maximum value								
Normal	401	0	0	401	737	1	0	738
>=450 - <480	5	2	0	7	9	4	0	13
>=480	0	1	0	1	1	1	0	2
Total	406	3	0	409	747	6	0	753
QTcF								
Maximum value								
Normal	400	0	0	400	733	1	0	734
>=450 - <480	6	2	0	8	13	3	0	16
>=480	0	1	0	1	1	2	0	3
Total	406	3	0	409	747	6	0	753

	--- Total Pali <=6 months --- (N=416)				— Total Pali >6 months — (N=754)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTlc								
Maximum value								
Normal	401	0	0	401	734	1	0	735
>=450 - <480	5	2	0	7	12	4	0	16
>=480	0	1	0	1	1	1	0	2
Total	406	3	0	409	747	6	0	753
QTcB								
Maximum value								
Normal	365	1	0	366	633	6	0	639
>=450 - <480	31	8	0	39	90	20	0	110
>=480	1	3	0	4	0	4	0	4
Total	397	12	0	409	723	30	0	753

While the above tables generally do not reveal exposure subgroup differences and QTcB and QTcF results are likely to be least informative (since heart rate showed little to no change during OL treatment note the following results from the table below (as found in the submission).

Note that the incidence of outliers for greater shift categories 30 msec and over 60 msec categories, is greater in the > 6 month than the ≤ 6 month exposure subgroups. While this may be reflecting an effect of greater monitoring time-points in the latter subgroup over the former

subgroup rather than an effect of duration of Pal exposure, results on mean QTraw increases suggests QT prolongation occurring after 6 months of treatment compared time-points prior to 6 months of treatment.

Table 92: Distribution of Maximum Changes From Average Predose Value in Corrected QT Values (Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 months (N=99) n (%)	Pla/Pali >6 months (N=137) n (%)	Pali/Pali <=6 months (N=209) n (%)	Pali/Pali >6 months (N=476) n (%)	Olan/Pali <=6 months (N=108) n (%)	Olan/Pali >6 months (N=141) n (%)	Total Pali <=6 months (N=416) n (%)	Total Pali >6 months (N=754) n (%)
QTcLD	99	137	203	475	107	141	409	753
<30 (ms)	90 (91)	121 (88)	192 (95)	422 (89)	104 (97)	128 (91)	386 (94)	671 (89)
30-60 (ms)	8 (8)	16 (12)	11 (5)	52 (11)	3 (3)	13 (9)	22 (5)	81 (11)
>60 (ms)	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
QTcF	99	137	203	475	107	141	409	753
<30 (ms)	88 (89)	118 (86)	193 (95)	418 (88)	102 (95)	128 (91)	383 (94)	664 (88)
30-60 (ms)	10 (10)	19 (14)	10 (5)	56 (12)	5 (5)	13 (9)	25 (6)	88 (12)
>60 (ms)	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
QTlc	99	137	203	475	107	141	409	753
<30 (ms)	90 (91)	120 (88)	194 (96)	423 (89)	103 (96)	129 (91)	387 (95)	672 (89)
30-60 (ms)	8 (8)	17 (12)	9 (4)	51 (11)	4 (4)	12 (9)	21 (5)	80 (11)
>60 (ms)	1 (1)	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
QTcB	99	137	203	475	107	141	409	753
<30 (ms)	76 (77)	100 (73)	167 (82)	369 (78)	83 (78)	107 (76)	326 (80)	576 (76)
30-60 (ms)	20 (20)	34 (25)	35 (17)	100 (21)	23 (21)	33 (23)	78 (19)	167 (22)
>60 (ms)	3 (3)	3 (2)	1 (<1)	6 (1)	1 (1)	1 (1)	5 (1)	10 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.
tsfecg04_tsfecg.rtf generated by tsfecg.sas.

Body Weight Results

The following table summarizes body weight results of the OL trial safety dataset (as found in the SUR).

Table 77: Body Weight and BMI: Change From Baseline to End Point
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Pla/Pali <=6 months (N=99)	Pla/Pali >6 months (N=137)	Pali/Pali <=6 months (N=209)	Pali/Pali >6 months (N=476)	Olan/Pali <=6 months (N=108)	Olan/Pali >6 months (N=141)	Total Pali <=6 months (N=416)	Total Pali >6 months (N=754)
Weight (kg)								
N	73	64	158	240	80	54	311	358
Mean baseline (SD)	75.0 (20.13)	75.8 (18.96)	77.0 (23.46)	74.5 (19.56)	81.9 (22.51)	72.0 (14.57)	77.8 (22.55)	74.4 (18.77)
Mean change (SD)	0.3 (4.34)	0.9 (6.57)	1.5 (4.77)	1.7 (6.31)	1.4 (5.59)	3.3 (5.12)	1.2 (4.91)	1.8 (6.21)
Weight percent change (%)								
N	73	64	158	240	80	54	311	358
Mean baseline (SD)	75.0 (20.13)	75.8 (18.96)	77.0 (23.46)	74.5 (19.56)	81.9 (22.51)	72.0 (14.57)	77.8 (22.55)	74.4 (18.77)
Mean change (SD)	0.7 (5.82)	1.8 (8.67)	1.9 (6.17)	2.6 (7.93)	2.2 (7.10)	4.7 (7.20)	1.7 (6.35)	2.8 (7.99)
Body mass index (kg/m2)								
N	73	64	158	240	80	53	311	357
Mean baseline (SD)	26.5 (6.31)	26.7 (5.82)	26.4 (6.88)	26.7 (6.64)	27.5 (6.76)	24.7 (4.92)	26.7 (6.72)	26.4 (6.30)
Mean change (SD)	0.1 (1.55)	0.3 (2.32)	0.5 (1.63)	0.6 (2.25)	0.5 (1.80)	1.1 (1.72)	0.4 (1.66)	0.6 (2.20)

Baseline is double-blind baseline.
tsfvs08_t1.rtf generated by tsfvs08.sas.

Table 78: Body Weight and BMI: Change From Baseline to End Point by Region for Total ER OROS Paliperidone Group
(Pooled Open-Label Studies R076477-SCH-702, 703, 704, 705: Safety Analysis Set)

	Region: Eastern Europe		Region: North America	
	Total Pali <=6 months (N=141)	Total Pali >6 months (N=420)	Total Pali <=6 months (N=166)	Total Pali >6 months (N=140)
Weight (kg)				
N	106	223	118	63
Mean baseline (SD)	72.9 (17.87)	71.3 (13.22)	90.7 (23.27)	94.1 (24.35)
Mean change (SD)	-0.1 (3.74)	1.4 (4.58)	2.2 (6.11)	2.4 (10.89)
Weight percent change (%)				
N	106	223	118	63
Mean baseline (SD)	72.9 (17.87)	71.3 (13.22)	90.7 (23.27)	94.1 (24.35)
Mean change (SD)	0.2 (5.08)	2.2 (6.54)	2.5 (6.98)	3.2 (11.36)
Body mass index (kg/m2)				
N	106	223	118	63
Mean baseline (SD)	25.4 (5.13)	25.4 (4.48)	29.9 (7.45)	32.2 (8.81)
Mean change (SD)	0.0 (1.30)	0.5 (1.64)	0.7 (1.99)	0.8 (3.74)

Appears This Way
On Original