ER OROS PAL 9 mg														
SCREENING	243	811.5	139.42	800.0	536	1250								
BASELINE	245	816.4	144.51	800.0	517	1429								
AVERAGE PREDOSE	245	814.5	133.53	800.7	562	1429								
DAY 4:4H PST-DS	234	726.7	134.00	706.0	480	1277	815.7	234	-89.0	8.00	122.36	-79.2	-543	378
DAY 4:10H PST-DS	229	745.5	136.36	732.0	476	1250	819.4	229	-73.8	8.49	128.55	-75.3	-674	280
DAY 4:22H PST-DS	226	767.6	142.49	750.0	458	1304	816.7	226	-49.1	8.13	122.27	-41.0	-387	318
DAY 8:4H PST-DS	221	747.9	123.79	732.0	496	1200	819.0	220	-71.3	8.20	121.61	-64.8	-525	270
DAY 8:10H PST-DS	216	769.9	125.03	750.0	444	1224	824.4	215	-54.6	9.05	132.71	-43.7	-498	299
DAY 8:22H PST-DS	220	790.1	136.84	779.0	465	1304	819.6	219	-29.9	8.72	129.04	-19.7	-520	302
DAY 15:PRE-DS	211	816.3	149.53	800.0	488	1250	820.6	210	-3.8	9.17	132.94	-4.7	-412	308
DAY 15:1-2H PST-DS	211	779.5	144.41	759.0	469	1304	819.8	210	-40.7	9.64	139.75	-45.3	-559	302
DAY 15:4H PST-DS	210	759.0	136.72	741.0	508	1277	818.8	209	-59.8	9.08	131.28	-60.0	-739	271
DAY 29	188	827.2	159.46	811.0	541	1333	829.3	187	-2.9	8.99	122.96	-7.8	-348	399
DAY 36:PRE-DS	157	857.3	165.01	857.0	556	1395	832.0	156	25.5	12.12	151.41	13.7	-292	421
DAY 36:1-2H PST-DS	156	831.4	158.58	816.5	531	1304	833.4	155	-1.4	11.33	141.08	6.0	-370	307
DAY 36:4H PST-DS	151	822.4	140.00	811.0	556	1277	837.1	152	-14.4	10.30	126.96	-23.3	-502	327
DAY 43	160	853.9	150.40	839.0	496	1364	830.7	159	22.6	10.38	130.90	12.5	-491	428
END POINT	243	821.3	152.58	811.0	496	1364	815.3	242	5.5	8.45	131.49	6.7	-491	428
ER OROS PAL 12 mg														
SCREENING	240	793.0	142.82	774.0	504	1200								
BASELINE	242	804.9	150.29	774.0	403	1364								
AVERAGE PREDOSE	242	799.2	133.83	773.8	453	1320								
DAY 4:4H PST-DS	218	700.3	126.70	674.0	469	1395	796.0	218	-95.6	8.51	125.70	-95.7	-481	349
DAY 4:10H PST-DS	211	722.5	132.38	690.0	462	1304	796.7	211	-74.2	8.68	126.09	-70.7	-413	288
DAY 4:22H PST-DS	212	737.5	136.33	714.0	500	1304	793.9	212	-56.4	8.47	123.39	-53.5	-471	339
DAY 8:4H PST-DS	213	721.7	123.64	698.0	500	1277	796.2	213	-74.5	8.36	122.01	-67.3	-492	261
DAY 8:10H PST-DS	207	742.0	136.36	723.0	522	1304	794.2	207	-52.2	8.81	126.80	-51.3	-440	355
DAY 8:22H PST-DS	210	761.2	147.09	732.0	488	1364	796.0	210	-34.8	9.49	137.59	-32.5	-451	370
DAY 15:PRE-DS	198	766.1	145.46	741.0	488	1277	792.2	198	-26.1	8.44	118.72	-29.0	-446	249
DAY 15:1-2H PST-DS	194	739.8	143.68	710.0	429	1500	791.4	194	-51.6	9.83	136.90	-56.2	-451	454
DAY 15:4H PST-DS	194	726.7	149.32	706.0	417	1429	787.6	194	-60.8	11.04	153.78	-43.0	-481	582
DAY 29	174	794.6	161.75	779.0	513	1364	788.0	174	6.5	10.31	135.97	-9.8	-382	432
DAY 36:PRE-DS	150	809.6	159.18	800.0	435	1364	796.3	150	13.3	10.48	128.35	4.3	-325	324
DAY 36:1-2H PST-DS	148	795.8	148.95	779.0	550	1277	796.9	148	-1.0	10.86	132.17	-18.7	-333	364
DAY 36:4H PST-DS	146	777.8	138.12	759.0	526	1200	794.3	146	-16.4	11.06	133.58	-15.7	-347	353
DAY 43	152	816.8	147.83	805.5	536	1277	798.8	152	18.0	10.22	125.98	25.3	-331	394
END POINT	238	790.2	154.41	769.0	513	1277	799.4	238	-9.2	8.82	136.04	-8.3	-407	471
ER OROS PAL 15 mg														
SCREENING	112	804.9	147.71	789.0	513	1277								
BASELINE	113	814.6	136.35	800.0	488	1200								
AVERAGE PREDOSE	113	810.1	131.32	795.0	511	1238								
DAY 4:4H PST-DS	105	701.2	112.35	682.0	492	1132	810.9	105	-109.7	9.76	100.03	-108.7	-359	142
DAY 4:10H PST-DS	101	734.5	133.43	706.0	476	1176	810.3	101	-75.8	11.49	115.46	-74.0	-389	384
DAY 4:22H PST-DS	105	749.4	144.97	723.0	504	1250	809.9	105	-60.5	11.60	118.86	-50.0	-421	243
DAY 8:4H PST-DS	106	743.8	135.97	706.0	517	1154	807.6	106	-63.8	12.24	125.98	-59.8	-373	310
DAY 8:10H PST-DS	103	758.0	126.96	732.0	545	1132	810.4	103	-52.4	12.26	124.46	-61.3	-421	230
DAY 8:22H PST-DS	105	775.7	151.91	750.0	469	1364	810.1	105	-34.5	12.96	132.81	-26.3	-415	260
DAY 15:PRE-DS	101	798.7	151.61	789.0	517	1224	809.3	101	-10.6	13.18	132.41	-16.3	-412	293
DAY 15:1-2H PST-DS	99	765.9	132.52	732.0	550	1200	812.3	99	-46.4	16.06	159.77	-45.0	-479	317
DAY 15:4H PST-DS	101	741.5	120.81	732.0	438	1154	807.7	101	-66.2	13.27	133.36	-59.7	-410	171
DAY 29	93	802.9	139.27	789.0	561	1200	803.3	93	-0.5	14.65	141.32	-6.0	-368	365
DAY 36:PRE-DS	76	831.5	134.32	822.0	571	1154	804.7	76	26.8	18.68	162.82	9.7	-366	385
DAY 36:1-2H PST-DS	80	802.3	140.14	789.0	492	1176	803.9	80	-1.7	16.75	149.80	-0.2	-380	417
DAY 36:4H PST-DS	78	793.3	129.84	789.0	541	1154	805.8	78	-12.6	16.68	147.34	-25.3	-352	324
DAY 43	82	833.1	118.63	827.5	550	1176	805.4	82	27.7	14.79	133.96	37.3	-313	396
END POINT	113	822.2	131.10	822.0	550	1250	810.1	113	12.1	12.42	132.04	25.3	-313	396
Olanzapine 10 mg														
SCREENING	364	799.5	146.42	779.0	504	1333								
BASELINE	364	815.5	149.07	805.5	513	1250								
AVERAGE PREDOSE	364	807.0	132.72	791.0	529	1271								
DAY 4:4H PST-DS	340	781.7	148.73	769.0	469	1304	807.1	340	-25.1	6.68	123.23	-28.5	-560	309
DAY 4:10H PST-DS	330	779.6	153.73	759.0	469	1463	807.2	330	-27.6	7.66	139.10	-25.7	-513	423
DAY 4:22H PST-DS	328	814.4	153.08	800.0	522	1364	808.9	328	5.5	7.08	128.17	2.9	-428	470
DAY 8:4H PST-DS	332	769.3	133.52	750.0	469	1200	806.1	332	-36.8	7.71	140.49	-36.7	-510	343
DAY 8:10H PST-DS	326	774.5	141.16	750.0	500	1304	806.2	326	-31.7	7.70	139.00	-35.7	-519	432
DAY 8:22H PST-DS	327	812.0	145.62	789.0	531	1395	805.8	327	6.2	7.24	130.96	-0.7	-494	497
DAY 15:PRE-DS	321	807.8	139.16	789.0	513	1304	805.4	321	2.4	7.57	135.60	6.7	-512	412
DAY 15:1-2H PST-DS	310	766.6	139.70	750.0	513	1250	805.3	310	-38.7	8.26	145.45	-32.7	-573	453
DAY 15:4H PST-DS	307	757.3	141.87	732.0	500	1154	805.8	307	-48.5	8.21	143.82	-42.3	-581	415
DAY 29	262	774.4	129.83	759.0	492	1277	804.7	262	-30.4	8.54	138.23	-26.0	-492	327
DAY 36:PRE-DS	221	823.2	143.12	822.0	513	1200	808.2	221	15.0	9.31	138.45	27.0	-442	311
DAY 36:1-2H PST-DS	224	810.1	146.83	800.0	508	1395	808.1	224	2.0	9.08	135.88	-3.2	-418	489
DAY 36:4H PST-DS	217	798.2	153.20	779.0	465	1364	808.7	217	-10.5	9.80	144.35	-17.7	-453	399
DAY 43	220	823.5	148.41	811.0	531	1364	807.7	220	15.8	9.17	136.04	26.8	-421	324
END POINT	357	796.7	145.95	779.0	522	1364	807.1	357	-10.4	7.26	137.24	3.7	-421	362

III. Small to Moderate Dose Dependent QTc Interval Prolongation Effects Near Tmax (at 22 hours-post-dose that generally showed a numerically greater prolongation over treatment days that included a 22-hour post-dose assessment time-point which was on Days 4 and Day 8).

A. QT raw Interval Results.

It is not surprising that QT-raw interval results showed a mean decrease (from the average pre-dose value) during Pal treatment that was similar to the previously described, time-dependent and dose-dependent Pal group mean changes in RR interval (which decreased) and heart rate (which increased). These observations on raw QT interval are likely reflecting a secondary drug effect due to the drug-induced effect on increasing heart rate, given that the QT interval can be influenced by changes in heart. Therefore, the results on raw QT interval are difficult to interpret.

B. QTc Interval Results

Since raw QT interval is dependent on changes in heart rate, the sponsor provided additional QT interval results on corrected QT interval values (QTc) using Fridericia, Bazett's, linear sagie and linear derived methods for correcting raw QT interval values for changes in heart rate.

The following describes the methodology used by the sponsor for calculating each type of QTc interval in their studies:

- Linear Derived: QTcLD (sec) = QT+b[1–RR], where b is the estimated slope using a linear regression techniques as described in Section 3.11.2.1 of the CSR for Study – SCH-1009. This method of QTc is described by the sponsor as a linear model that "incorporates all drug free QT/RR interval data" and is also intended to correct for study specific differences in this data.
- Bazett: $QTcB=QT/RR_{0.5}$
- Sagie: QTlc=QT + 0.154 (1-RR), and
- Fridericia: $QTcF=QT/RR_{(1/3)}$

Calculation of Day Averaged ECG Parameters

The following describes methods for calculating day-averaged QTc parameters (copied from the CSR):

> The primary endpoint was the difference with placebo (Day 1) in day-averaged QTcLD values. Day-averaged parameters were calculated for the 7 days with complete ECG profiles: Days 1 to 4 and 8 to 10. Since times between ECG intervals on a day are unequally spaced, the day-average was calculated as a weighed mean: $\left(\sum_{i=1}^{10}\left(\frac{(V_i+V_{i-1})}{2}*(T_i-T_{i-1})\right)\right)\Big/(T_{10}-T_0)$ with V_i the value (e.g. QTcLD) at time T_i. T_0 being the first assessment on a day (scheduled at 8:00), T_1 being the next (scheduled at 8:30), continuing until the last T_{10} (scheduled at 20:00). Parameters were considered missing, if more than 3 values out of 11 constituting the average are missing. If more than 2 assessments between T_1 (+30min) and T_8 (+4h) were missing, the weighted average was set to missing.

The results on QTc using these various methods are described in the following paragraphs. Summary tables of the data are provided after these reviewer comments.

i) QT-Bazett's Interval Results:

- *The QTc using Bazett's correction revealed clear dose- and time-dependent effects for QT prolongation (which was greater with each increasing dose-level).*
- *While QTcB is generally used for cases when heart rate is low, note that QTcB results show some evidence for dose-dependent QT prolongation at time-points near Tmax (22 hours post-dose).*
- *It is noteworthy that time-points in which QTcB prolongation effects appear to be most prominent is at 22 hours post-dose time-points which is near Tmax, as well as earlier time-points on Day 4 of treatment (Days 4 and 8 were the only days that had both of the 4-hour and 22-hour post-dose time-points).*
- *Given that QTcB is influenced by heart rate and is more appropriately used as a method of correction for low heart rates, the results at least at 4 hour-post-dose time-points may not be reflecting a true QT prolongation effect.*
- *Despite the caveat regarding the significant limitations with using QTcB values to examine potential QT prolongation effects, time-dependent and dose-dependent Pal effects were observed using other methods for determining QTc and a study, described later that was a special safety study on this topic, revealed QT prolongation effects that in part, were dependent on Cmax, at least in a dynamic fashion as discussed later in this review.*

The following are key considerations with interpreting QTc interval effects:

- *A static versus dynamic drug-effect is a key consideration with interpreting the result. One important consideration regarding the influence of heart rate on QT interval results is that drug effects on heart rate as well as on QT interval may be a dynamic effect, rather than a static effect, as previously discussed with respect to heart rate changes and as suggested by the results that were previously shown on heart rate.*
- *QT interval changes are strongly influenced by heart rate.*
- *Given potential dynamic changes in heart rate and in turn, the influence of heart rate changes on QT interval, then the selection of an appropriate QTc interval calculation for any given time-point may also need to be based on dynamic changes (e.g. the rate of change over time) rather than static effects (e.g. the absolute value at a given time-point) which may also vary from one time-point to another (e.g. consider physiological changes over time that may in turn influence the rate of the change of a given ECG parameter).*
- *Despite the caveats to using Bazett's correction method, the time-dependent changes in QTcB interval cannot be ignored and may be reflecting a QT prolongation effect.*
- *Yet, QTcB interval results are likely to be an exaggerated representation of a real drug effect since heart rate is generally not abnormally low in Pal treated subjects.*

Summary Tables with the Sponsor's QTcB Interval Results

The QTcB interval results described above, are shown below and are taken from the sponsor's appendix summary table (as above).

Selected time-points in the data shown below were highlighted or underlined by the undersigned reviewer for demonstration purposes as follows:

- *Yellow highlighting (denoting the 22 hour post-dose time-point),*
- *Green underlining (denoting 4 hour post-dose time-points) and*
- *Other highlighted time-points denote additional time-points where QTc appears to have increased.*

It is important to note when comparing the 12 and 15 mg Pal groups that in the first week of treatment the 15 mg group received 12 mg daily.

Since only selected groups are shown a dose-dependent effect is not clear from the tables below. However, QTc results using other methods are shown later that include results from several Pal groups at different dose-levels that show evidence for a dose-dependent effects (e.g. see QTcF results that are shown later).

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

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind 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)														
QTC INTERVAL BAZETT (ms)														
Placebo														
SCREENING	353	408.4	23.13	408.0	339	481								
BASELINE	355	406.2	22.58	406.0	342	468								
AVERAGE PREDOSE	355	408.2	20.53	406.3	339	460								
DAY 4:4H PST-DS	327	407.8	20.99	407.0	353	488	408.5	327	-0.8	0.87	15.79	-1.3	-42	53
DAY 4:10H PST-DS	322	406.2	21.91	406.5	341	471	408.6	322	-2.4	1.00	17.87	-1.7	-61	74
DAY 4:22H PST-DS	323	406.6	23.36	408.0	333	472	408.6	323	-1.9	0.92	16.61	-3.0	-64	48
DAY 8:4H PST-DS	315	406.1	22.16	407.0	335	463	408.0	315	-1.8	1.00	17.67	-1.0	-62	62
DAY 8:10H PST-DS	311	406.2	22.06	405.0	340	468	407.9	311	-1.7	1.05	18.54	-3.3	-49	70
DAY 8:22H PST-DS	307	407.0	23.72	407.0	342	469	407.7	307	-0.7	1.06	18.64	-1.3	-63	75
DAY 15:PRE-DS	278	405.3	23.66	407.0	336	488	407.8	278	-2.5	1.10	18.38	-2.0	-56	55
DAY 15:1-2H PST-DS	280	404.0	23.25	403.0	344	492	407.8	280	-3.7	1.10	18.42	-3.3	-54	68
DAY 15:4H PST-DS	278	405.8	22.26	407.0	338	481	407.8	278	-2.1	1.10	18.37	0.0	-74	55
DAY 29	205	409.4	24.04	408.0	347	468	408.0	205	1.3	1.34	19.16	0.7	-49	65
DAY 36:PRE-DS	136	407.6	26.03	405.0	345	486	408.2	136	-0.6	1.72	20.10	0.1	-45	58
DAY 36:1-2H PST-DS	134	406.3	24.25	408.0	339	471	408.1	134	-1.8	1.73	20.03	-0.8	-63	73
DAY 36:4H PST-DS	136	406.9	24.73	406.0	347	470	408.0	136	-1.1	1.68	19.61	-0.7	-49	72
DAY 43	139	406.3	22.88	407.0	330	473	406.6	139	-0.3	1.38	16.28	-1.3	-34	51
MAXIMUM VALUE	350	426.4	21.63	427.5	352	492	408.2	350	18.2	0.93	17.32	17.2	-37	75
END POINT	350	408.4	23.32	409.0	330	473	408.2	350	0.2	1.02	19.03	-0.7	-54	65

ER OROS PAL 12 mg														
SCREENING	239	411.1	23.05	409.0	358	480								
BASELINE	241	408.9	23.57	407.0	342	474								
AVERAGE PREDOSE	241	411.9	21.73	410.0	360	472								
DAY 4:4H PST-DS	216	420.2	23.19	418.5	359	505	412.0	216	8.1	1.29	19.00	7.0	-41	119
DAY 4:10H PST-DS	210	418.0	22.08	415.5	363	502	412.3	210	5.7	1.20	17.33	5.7	-52	72
DAY 4:22H PST-DS	209	421.1	21.60	421.0	362	482	412.3	209	8.8	1.27	18.30	9.3	-66	53
DAY 8:4H PST-DS	211	418.2	20.68	418.0	361	476	412.0	211	6.2	1.27	18.41	6.0	-56	70
DAY 8:10H PST-DS	207	417.6	21.33	417.0	370	483	412.2	207	5.4	1.31	18.80	6.0	-56	55
DAY 8:22H PST-DS	209	420.4	21.86	419.0	361	490	412.0	209	8.3	1.26	18.15	8.0	-45	60
DAY 15:PRE-DS	198	416.1	21.93	416.0	357	490	412.9	198	3.1	1.23	17.30	4.3	-53	49
DAY 15:1-2H PST-DS	191	412.1	21.66	410.0	362	463	412.5	191	-0.4	1.35	18.70	0.0	-78	48
DAY 15:4H PST-DS	192	415.9	21.93	416.5	311	468	412.9	192	3.0	1.41	19.80	2.5	-104	63
DAY 29	174	413.5	22.32	414.0	337	467	413.7	174	-0.1	1.35	17.81	1.0	-58	35
DAY 36:PRE-DS	149	414.7	20.40	417.0	342	475	412.8	149	1.9	1.47	17.96	3.0	-46	45
DAY 36:1-2H PST-DS	147	411.2	21.57	413.0	353	476	412.9	147	-1.7	1.61	19.53	-1.7	-60	54
DAY 36:4H PST-DS	144	415.3	21.08	415.0	355	481	413.4	144	1.9	1.46	17.55	2.3	-62	44
DAY 43	150	413.2	21.81	414.0	356	477	413.3	150	-0.1	1.42	17.44	-1.7	-40	55
MAXIMUM VALUE	238	436.6	20.61	435.5	376	505	411.6	238	25.0	1.11	17.10	23.3	-42	118
END POINT	238	413.2	21.17	414.0	356	477	411.6	238	1.5	1.19	18.41	1.0	-45	55
ER OROS PAL 15 mg														
SCREENING	112	411.3	21.21	412.0	359	463								
BASELINE	113	407.5	21.39	409.0	357	459								
AVERAGE PREDOSE	113	410.4	19.40	411.5	359	454								
DAY 4:4H PST-DS	101	417.8	18.41	419.0	364	461	409.4	101	8.4	1.64	16.64	8.5	-31	69
DAY 4:10H PST-DS	100	416.2	21.47	417.5	339	480	410.9	100	5.3	1.95	19.50	5.8	-109	44
DAY 4:22H PST-DS	105	416.9	21.07	419.0	362	474	410.6	105	6.3	1.69	17.28	3.7	-27	52
DAY 8:4H PST-DS	105	415.1	20.07	416.0	360	463	410.4	105	4.7	1.67	17.06	4.0	-30	62
DAY 8:10H PST-DS	103	414.5	19.47	415.0	361	453	410.3	103	4.2	1.94	19.65	3.7	-62	48
DAY 8:22H PST-DS	105	417.1	23.93	417.0	351	479	410.4	105	6.7	2.18	22.34	3.3	-53	92
DAY 15:PRE-DS	100	411.8	22.46	411.0	364	466	410.2	100	1.5	1.95	19.46	1.3	-43	74
DAY 15:1-2H PST-DS	99	411.7	20.25	411.0	363	459	410.1	99	1.6	1.97	19.55	0.5	-41	57
DAY 15:4H PST-DS	100	412.6	20.06	413.5	361	454	410.2	100	2.4	1.86	18.57	4.3	-60	57
DAY 29	93	412.8	19.54	415.0	358	453	410.6	93	2.3	2.08	20.05	3.7	-62	48
DAY 36:PRE-DS	74	411.6	19.19	411.0	371	455	410.6	74	1.0	2.42	20.92	-2.4	-77	44
DAY 36:1-2H PST-DS	79	409.2	19.41	409.0	360	460	411.1	79	-1.8	2.30	20.41	1.0	-85	39
DAY 36:4H PST-DS	77	411.1	19.41	412.0	373	453	410.8	77	0.6	2.44	21.43	-0.5	-65	63
DAY 43	81	410.5	19.89	412.0	360	455	409.8	81	0.7	1.89	17.03	1.0	-46	42
MAXIMUM VALUE	113	433.9	18.49	433.0	384	480	410.4	113	23.5	1.63	17.32	21.7	-17	92
END POINT	113	410.4	20.73	413.0	353	459	410.4	113	0.0	1.62	17.25	1.7	-46	42

The table below shows heart rate changes of the 15 mg group to allow for comparisons with the above QTcB table, since QT interval values can be dependent on heart rate.

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)														
ER OROS PAL 15 mg														
AVERAGE PREDOSE	113	76.6	12.17	76.3	49	118								
DAY 4:4H PST-DS	105	87.6	13.26	88.0	53	122	76.5	105	11.1	1.05	10.79	11.7	-15	48
DAY 4:10H PST-DS	101	84.1	13.98	85.0	51	126	76.6	101	7.5	1.19	11.96	7.0	-40	34
DAY 4:22H PST-DS	105	82.7	14.44	83.0	48	119	76.7	105	6.1	1.15	11.83	4.7	-21	38
DAY 8:4H PST-DS	106	83.1	13.73	85.0	52	116	76.8	106	6.3	1.23	12.64	6.0	-26	36
DAY 8:10H PST-DS	103	81.2	12.50	82.0	53	110	76.6	103	4.5	1.20	12.15	5.5	-37	33
DAY 8:22H PST-DS	105	80.1	14.82	80.0	44	128	76.7	105	3.5	1.33	13.62	1.7	-28	42
DAY 15:PRE-DS	101	77.9	14.84	76.0	49	116	76.8	101	1.1	1.29	12.95	1.3	-39	43
DAY 15:1-2H PST-DS	99	80.5	12.60	82.0	50	109	76.4	99	4.0	1.45	14.46	5.3	-43	39
DAY 15:4H PST-DS	101	83.1	13.72	82.0	52	137	76.9	101	6.2	1.32	13.25	6.7	-26	41
DAY 29	93	76.9	12.76	76.0	50	107	77.2	93	-0.3	1.41	13.58	0.5	-40	34
DAY 36:PRE-DS	76	74.0	11.92	73.0	52	105	77.0	76	-3.0	1.76	15.35	-1.8	-51	32
DAY 36:1-2H PST-DS	80	77.1	13.76	76.0	51	122	77.1	80	-0.0	1.73	15.49	-1.3	-42	53
DAY 36:4H PST-DS	78	77.6	12.64	76.0	52	111	77.0	78	0.7	1.69	14.96	1.7	-37	42
DAY 43	82	73.5	10.78	72.5	51	109	77.0	82	-3.5	1.40	12.69	-5.0	-44	26
END POINT	113	74.8	11.80	73.0	48	109	76.6	113	-1.8	1.20	12.74	-2.3	-44	26

ii. QTc-Fridericia (QTcF) Interval Results. The Fridericia calculation for QTc may be a more appropriate method for calculating QT, since this method is used when heart rate is increased, as was observed with Pal treatment.

As observed with QTcB interval, a dose-dependent and time-dependent effect of Pal appears to exist with QTcF as outlined below:

- *It is notable that the 22 hour post-dose time-points generally revealed the largest mean increases, independent of which method of calculation that was employed (as observed for QTcB and other methods shown later).*
- *Only Days 4 and 8 had the 22 hour post-dose time-point.*
- *Given that 22 hours post-dose is reported by the sponsor as Tmax for Pal (based on Phase I results) this time-point may be reflecting a drug effect on prolonging QT, similar to that observed for QTcB interval.*
- *It is of potential concern that the mean increase at this time-point in greater on Day 8 than Day 4, as shown below, since steady state levels would be expected to be achieved by Day 8.*
- *Additional mean increases can be observed on subsequent treatment days in which the assessment time-point for the given treatment day is not specified or is specified as a pre-dose time-point. The pre-dose time-point would potentially be only within a few hours of Tmax of the preceding dose, given the reported Tmax of 22 hours. Yet, subjects could be discharged after Day 14 from the study. Assessments conducted on days that did not include PK analyses methods (involving multiple and frequent blood sampling over a given study day) were likely to vary across subjects and relative to their dosing. Refer to Seciton 7.1.X for discussion on this potential concern.*
- *The magnitude of the effect on QTc interval appears to be dose-dependent as described in the following. The maximum group mean intervals observed (such as at the post-22 hour post-dose time points), increases across Pal groups of increasing dose-levels (e.g. values of the 3 mg Pal group to the 12 and 15 mg Pal groups, shown in summary tables, below). It is critical to note that the 15 mg group received 12 mg daily during week 1 of treatment (15 mg daily was given thereafter).*

The Potential Role of PK on QT prolongation is likely to exist (at least in part, independent of heart rate changes) due to the following observations:

- *The QTc prolongation effects may be dependent on Cmax levels*
- *Cmax levels may increase over time with multiple dosing and in the presence of a potential accumulation of the drug (e.g. consider potential redistribution of the drug that in turn may either increase plasma levels or increase concentration in the myocardium).*
- *Greater effects may be revealed in conditions that may increase Cmax, such as the following examples:*
  - *Consider potential drug accumulation that may occur with multiple dosing.*
  - *Consider the known food effects of Pal on plasma levels of Pal (in which approximately a 50% increase in plasma levels was observed in the fed compared to fasted states in Phase I food effect studies).*
  - *Other factors that may influence QT interval or Pal drug levels must also be considered (e.g. concomitant medications, among others.*

Theoretically fluctuations in drug levels are at a minimum once steady state is achieved, such that if Cmax levels plays a critical role in QT prolongation effects, then QT prolongation effects

would be attenuated after about 4-5 days of Pal treatment. Yet a degree of fluctuating levels does exist after steady state and can be influenced by other factors, as previously outlined above, as well as be between individual differences.

Refer to the last section of this review for further comment and recommendations.

Summary Tables of QTcF Results

The QTc Fridericia interval results described above are shown below and are taken from Appendix 2.7.4.6.2.1 of the SCS. Some of the results are highlighted by the undersigned reviewer for demonstration purposes.

It is important to note when comparing the 12 and 15 mg Pal groups that in the first week of treatment the 15 mg group received 12 mg daily.

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

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind 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 FRIDERICIA (ms)														
ER OROS PAL 15 mg														
SCREENING	112	395.5	18.39	394.0	357	451								
BASELINE	113	393.0	18.31	391.0	349	445								
AVERAGE PREDOSE	113	395.1	17.35	394.0	356	444								
DAY 4:4H PST-DS	103	393.1	14.96	393.0	350	429	394.2	103	-1.1	1.22	12.36	-0.3	-38	39
DAY 4:10H PST-DS	100	394.5	18.57	393.0	337	465	395.6	100	-1.1	1.48	14.79	-2.0	-74	29
DAY 4:22H PST-DS	105	396.2	18.27	396.0	352	441	395.3	105	0.9	1.31	13.40	1.3	-32	43
DAY 8:4H PST-DS	105	394.2	17.29	394.0	357	439	395.0	105	-0.8	1.20	12.27	-0.3	-33	28
DAY 8:10H PST-DS	103	395.0	17.62	394.0	350	439	395.0	103	-0.0	1.49	15.10	2.3	-47	29
DAY 8:22H PST-DS	105	398.7	20.26	397.0	349	463	395.1	105	3.6	1.62	16.59	1.0	-33	63
DAY 15:PRE-DS	100	395.3	17.58	393.5	357	443	394.9	100	0.4	1.40	14.02	0.0	-29	34
DAY 15:1-2H PST-DS	99	393.0	17.65	391.0	353	436	394.9	99	-1.9	1.36	13.53	-2.5	-42	31
DAY 15:4H PST-DS	100	391.7	17.30	391.0	354	433	394.7	100	-3.0	1.42	14.18	-3.2	-41	31
DAY 29	93	397.0	15.54	395.0	362	435	394.7	93	2.3	1.61	15.55	3.3	-44	45
DAY 36:PRE-DS	74	398.2	14.72	399.0	364	432	394.9	74	3.2	1.78	15.28	3.9	-43	33
DAY 36:1-2H PST-DS	79	393.6	15.78	393.0	350	433	395.5	79	-1.9	1.59	14.12	1.7	-46	24
DAY 36:4H PST-DS	77	394.9	14.28	394.0	372	426	395.2	77	-0.3	1.81	15.91	0.3	-44	37
DAY 43	81	397.6	17.69	397.0	361	441	394.3	81	3.3	1.55	13.99	3.7	-32	43
MAXIMUM VALUE	113	410.9	17.07	410.0	373	465	395.1	113	15.8	1.34	14.29	15.8	-13	63
END POINT	113	396.4	17.52	396.0	354	441	395.1	113	1.2	1.34	14.21	1.7	-33	46
ER OROS PAL 12 mg														
SCREENING	239	394.6	19.49	393.0	353	468								
BASELINE	241	393.4	19.03	393.0	343	455								
AVERAGE PREDOSE	241	395.7	18.16	395.0	352	451								
DAY 4:4H PST-DS	216	395.1	18.17	394.0	346	454	395.6	216	-0.6	0.94	13.78	-0.5	-42	84
DAY 4:10H PST-DS	210	395.1	18.01	394.5	359	467	396.0	210	-0.9	0.94	13.60	-1.8	-70	55
DAY 4:22H PST-DS	209	399.4	17.26	399.0	360	451	395.8	209	3.6	1.01	14.67	4.7	-53	42
DAY 8:4H PST-DS	211	395.3	16.80	395.0	350	460	395.6	211	-0.2	0.97	14.08	0.0	-55	51
DAY 8:10H PST-DS	207	396.4	17.21	395.0	351	458	395.6	207	0.9	0.99	14.29	2.0	-61	43
DAY 8:22H PST-DS	209	400.8	17.60	400.0	355	454	395.7	209	5.1	0.95	13.66	5.3	-42	44
DAY 15:PRE-DS	198	397.0	17.71	397.0	347	445	396.1	198	0.8	0.98	13.85	1.0	-50	36
DAY 15:1-2H PST-DS	191	391.0	17.81	389.0	347	439	395.7	191	-4.8	1.00	13.77	-4.0	-72	24
DAY 15:4H PST-DS	192	393.4	17.70	393.5	332	433	395.8	192	-2.5	1.01	14.06	-1.8	-73	24
DAY 29	174	396.7	17.63	396.0	350	454	396.5	174	0.2	0.95	12.57	0.5	-47	31
DAY 36:PRE-DS	149	399.3	15.80	399.0	353	439	396.4	149	2.8	1.18	14.37	4.0	-33	36
DAY 36:1-2H PST-DS	147	394.8	16.35	393.0	358	440	396.4	147	-1.6	1.21	14.70	-2.0	-38	33
DAY 36:4H PST-DS	144	397.3	16.76	396.0	362	446	396.8	144	0.5	1.14	13.66	1.3	-38	35
DAY 43	150	398.6	17.59	399.0	352	449	397.1	150	1.5	1.02	12.50	1.2	-29	47
MAXIMUM VALUE	238	411.6	17.61	410.5	362	467	395.5	238	16.1	0.89	13.76	16.8	-35	84
END POINT	238	396.2	17.16	395.0	352	449	395.5	238	0.7	0.86	13.24	0.3	-35	47

ER OROS PAL 3 mg														
SCREENING	127	393.4	20.29	393.0	349	458								
BASELINE	127	392.9	19.83	393.0	347	449								
AVERAGE PREDOSE	127	394.3	18.58	394.7	351	453								
DAY 4:4H PST-DS	118	389.9	17.85	388.0	354	441	394.7	118	-4.8	1.10	11.98	-2.5	-40	24
DAY 4:10H PST-DS	113	389.4	18.41	389.0	338	449	395.0	113	-5.6	1.18	12.59	-6.3	-37	25
DAY 4:22H PST-DS	118	395.3	20.73	396.0	339	456	395.0	118	0.4	1.18	12.83	0.3	-29	40
DAY 8:4H PST-DS	112	392.3	19.28	391.5	343	449	394.4	112	-2.2	1.26	13.38	-2.3	-43	35
DAY 8:10H PST-DS	106	391.8	18.43	391.0	350	455	394.7	106	-2.9	1.15	11.83	-3.0	-35	27
DAY 8:22H PST-DS	113	396.0	19.26	395.0	347	458	394.5	113	1.5	1.11	11.81	1.0	-35	39
DAY 15:PRE-DS	104	393.6	19.84	393.0	342	441	394.3	104	-0.7	1.21	12.33	-0.2	-31	36
DAY 15:1-2H PST-DS	103	390.9	17.73	388.0	359	458	394.7	103	-3.8	1.25	12.71	-5.3	-35	39
DAY 15:4H PST-DS	104	391.1	18.53	390.0	352	443	394.6	104	-3.5	1.34	13.65	-4.7	-36	36
DAY 29	86	394.4	18.69	395.5	351	441	394.9	86	-0.5	1.44	13.37	-0.8	-31	33
DAY 36:PRE-DS	66	397.6	18.66	397.5	359	446	398.1	66	-0.5	1.39	11.28	-1.2	-27	27
DAY 36:1-2H PST-DS	69	393.5	19.37	391.0	352	457	397.5	69	-4.0	1.41	11.70	-2.0	-30	25
DAY 36:4H PST-DS	67	395.1	18.48	396.0	352	462	396.6	67	-1.5	1.50	12.29	-2.0	-35	25
DAY 43	70	396.4	18.45	397.0	358	440	397.3	70	-0.9	1.72	14.35	-0.2	-41	35
MAXIMUM VALUE	124	406.9	18.78	407.0	359	462	394.4	124	12.5	0.96	10.72	12.3	-14	40
END POINT	124	394.4	19.76	395.0	342	442	394.4	124	0.1	1.30	14.45	0.2	-41	35
Olanzapine 10 mg														
SCREENING	362	393.0	17.26	392.0	352	439								
BASELINE	364	391.2	18.20	392.0	339	438								
AVERAGE PREDOSE	364	393.1	16.31	393.3	348	444								
DAY 4:4H PST-DS	333	390.5	19.24	390.0	339	464	392.9	333	-2.4	0.72	13.18	-3.0	-37	56
DAY 4:10H PST-DS	327	390.6	18.89	391.0	337	442	393.4	327	-2.8	0.73	13.21	-2.3	-52	50
DAY 4:22H PST-DS	321	393.6	18.47	394.0	352	441	392.7	321	0.8	0.67	12.01	0.7	-40	33
DAY 8:4H PST-DS	330	392.0	18.43	393.0	337	454	393.3	330	-1.4	0.69	12.56	-0.7	-37	44
DAY 8:10H PST-DS	324	393.2	19.70	393.5	344	547	393.3	324	-0.1	0.80	14.43	-1.3	-43	121
DAY 8:22H PST-DS	327	395.3	19.71	395.0	331	466	393.2	327	2.0	0.80	14.54	1.3	-52	58
DAY 15:PRE-DS	321	393.9	18.57	395.0	336	456	393.4	321	0.6	0.69	12.28	1.3	-49	43
DAY 15:1-2H PST-DS	308	390.5	18.69	390.0	338	446	393.1	308	-2.6	0.77	13.57	-2.7	-64	30
DAY 15:4H PST-DS	306	391.9	18.46	393.0	335	451	393.2	306	-1.3	0.76	13.34	0.2	-55	38
DAY 29	260	394.9	18.97	396.0	336	443	394.1	260	0.8	0.87	14.05	0.7	-53	40
DAY 36:PRE-DS	219	395.8	18.50	395.0	343	445	393.9	219	1.9	0.90	13.28	1.3	-37	36
DAY 36:1-2H PST-DS	224	395.1	19.02	395.0	350	446	394.1	224	1.0	0.90	13.47	1.0	-45	34
DAY 36:4H PST-DS	215	396.0	18.70	396.0	353	449	394.1	215	1.9	0.93	13.61	2.0	-40	47
DAY 43	219	394.3	19.08	395.0	346	445	394.1	219	0.2	0.93	13.73	0.0	-57	38
MAXIMUM VALUE	357	409.3	20.16	409.0	363	547	393.3	357	16.0	0.71	13.33	14.7	-24	121
END POINT	357	393.4	20.74	392.0	345	543	393.3	357	0.1	0.82	15.42	-0.7	-57	117
Placebo														
SCREENING	353	393.0	19.89	391.0	339	463								
BASELINE	355	392.3	18.44	390.0	347	447								
AVERAGE PREDOSE	355	393.5	17.18	392.3	342	444								
DAY 4:4H PST-DS	327	391.6	17.56	391.0	345	471	394.0	327	-2.3	0.69	12.46	-3.0	-40	48
DAY 4:10H PST-DS	322	391.3	18.52	390.0	341	447	394.0	322	-2.7	0.79	14.16	-2.5	-46	56
DAY 4:22H PST-DS	323	393.9	19.32	394.0	335	450	394.1	323	-0.2	0.76	13.61	0.0	-42	44
DAY 8:4H PST-DS	315	390.6	18.40	389.0	325	450	393.7	315	-3.1	0.75	13.26	-2.7	-41	40
DAY 8:10H PST-DS	311	391.4	18.16	390.0	330	448	393.7	311	-2.3	0.79	13.91	-2.7	-41	45
DAY 8:22H PST-DS	307	394.7	19.54	396.0	337	452	393.5	307	1.2	0.78	13.71	0.7	-47	59
DAY 15:PRE-DS	278	393.8	18.85	394.0	339	472	393.8	278	0.0	0.80	13.28	-0.6	-50	43
DAY 15:1-2H PST-DS	280	389.8	18.39	390.0	335	450	393.8	280	-4.0	0.79	13.21	-3.3	-41	52
DAY 15:4H PST-DS	278	391.1	18.38	391.0	329	457	393.8	278	-2.7	0.78	13.02	-2.2	-42	39
DAY 29	205	394.6	19.55	393.0	345	454	394.3	205	0.3	0.94	13.44	0.3	-46	52
DAY 36:PRE-DS	136	395.8	20.87	394.5	343	457	394.8	136	1.0	1.25	14.60	-2.2	-31	40
DAY 36:1-2H PST-DS	134	392.7	18.59	391.0	339	442	394.8	134	-2.1	1.21	14.04	-4.0	-39	31
DAY 36:4H PST-DS	136	393.3	19.71	393.5	344	446	394.7	136	-1.3	1.20	13.99	-3.0	-37	48
DAY 43	139	395.5	19.89	396.0	332	451	393.7	139	1.8	1.15	13.51	2.3	-32	40
MAXIMUM VALUE	350	407.7	19.25	408.0	334	472	393.5	350	14.2	0.69	12.95	13.7	-29	59
END POINT	350	394.1	19.25	394.0	332	451	393.5	350	0.6	0.78	14.59	0.7	-39	55

Note that the Olanzapine group shows minimal to no effect on QTc intervals.

The dose-equivalency between olanzapine and Pal is not clear such that a direct comparison between these drugs on safety results is difficult to interpret. However, the Olanzapine dose employed was 10 mg daily, which is a recommended dose-level in approved labeling for this drug. The recommended starting dose of Pal in proposed labeling is 6 mg with recommended dose increases of up to 12 mg and the lowest recommended dose is 3 mg.

Note that above mean increases in QTc observed for the 12 mg dose-levels. The 6 mg dose-level which is not shown above, had mean increases in QTcF of 1.0, 1.9 at 22 hours post-dose on Days 4 and 8 and up to a mean increase of 2.9 msec which occurred on Day 36, pre-dose (which

would correspond to approximately 24 hours after previous dose and only 2 hours after the anticipated Tmax which is reported to be 22 hours post-dose).

iii. QTc Linear Derived Results. The sponsor notes that QTc linear derived (QTcLD) mean increases of up to 3.1 in the HD Pal group during treatment (up to 4.4 in the next highest-dose-level; in the 12 mg Pal group) at 22 hours post-dose on Days 4 and 8 (assessment days that included the 22 hour post-dose time-point) which was observed in all Pal groups. It is important to note that the HD (15 mg/day) group received 12 mg daily on Days 1-7 of the short term trials. The 22 hour post-dose time-point coincides with Tmax, according to the sponsor.

Another notable observation is that there is a numerical trend for a greater mean increase in QTc LD on the Day 8 compared to Day 4 (22-hour post-dose) assessments as follows: 0.3 and 1.6 msec in the 3 mg Pal group, 0,8 and 1.6, msec in the 6 mg Pal group, 2.2 and 2.6 msec in the 9 mg Pal group, and 2.7 and 4.4 msec in the 15 mg Pal group, on Days 4 and 8, respectively (at the 22 hour-post-dose assessment). The Day 15, 29, 36 and 43 assessments did not include a 22-hour post-dose assessment and the possibility for between individual variance on the timing of these assessments needs to be considered, among other considerations.

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

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase (continued)

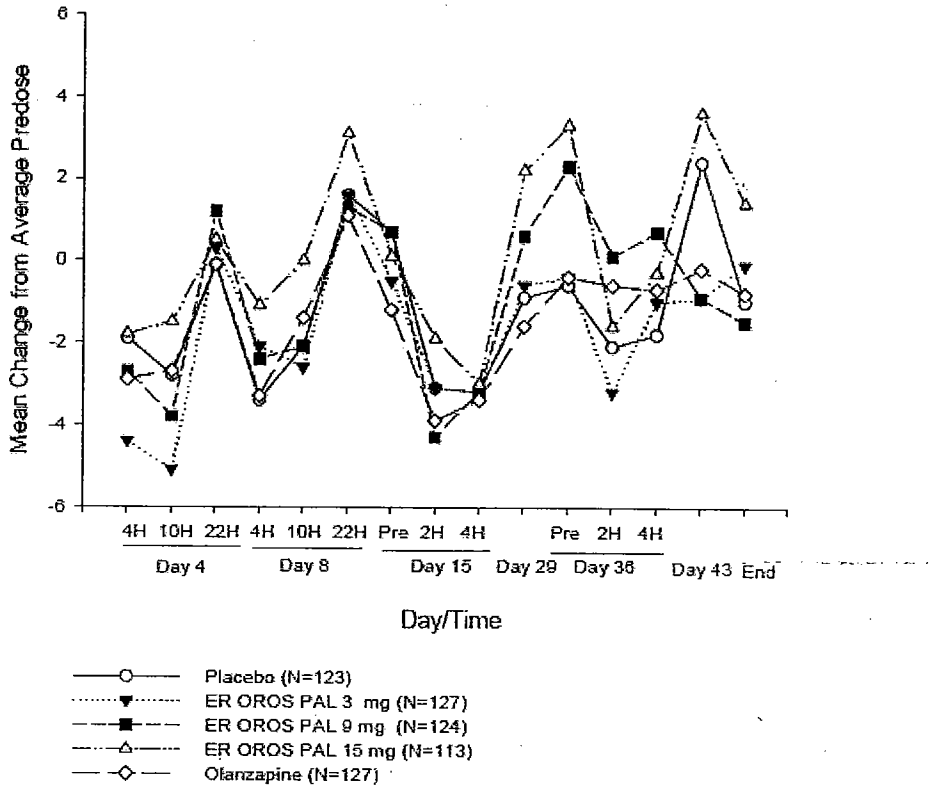
Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	change from average predose N	Mean	SE	SD	Med	Min	Max
QTC LINEAR DERIVED (ms)														
Placebo														
SCREENING	353	392.9	18.75	391.0	342	458								
BASELINE	355	392.1	17.60	390.0	345	444								
AVERAGE PREDOSE	355	393.1	16.28	392.0	342	440								
DAY 4:4H PST-DS	327	391.4	16.49	391.0	351	466	393.5	327	-2.1	0.66	11.99	-2.0	-36	48
DAY 4:10H PST-DS	322	391.1	17.74	390.0	344	444	393.6	322	-2.5	0.76	13.64	-2.8	-41	54
DAY 4:22H PST-DS	323	393.5	18.73	394.0	332	450	393.7	323	-0.1	0.75	13.43	0.0	-74	40
DAY 8:4H PST-DS	315	390.5	17.55	389.0	330	448	393.3	315	-2.8	0.72	12.71	-2.3	-42	38
DAY 8:10H PST-DS	311	391.2	17.40	390.0	336	447	393.3	311	-2.1	0.75	13.26	-2.7	-38	44
DAY 8:22H PST-DS	307	394.3	18.74	395.0	342	451	393.1	307	1.2	0.75	13.15	0.7	-42	56
DAY 15:PRE-DS	278	393.1	18.69	393.0	336	469	393.3	278	-0.2	0.79	13.20	-0.7	-45	43
DAY 15:1-2H PST-DS	280	389.6	17.32	390.0	341	446	393.4	280	-3.8	0.75	12.52	-3.3	-39	51
DAY 15:4H PST-DS	278	390.8	17.70	391.0	333	455	393.4	278	-2.7	0.75	12.48	-2.3	-40	39
DAY 29	205	394.1	18.46	393.0	350	451	393.9	205	0.2	0.90	12.90	0.3	-43	47
DAY 36:PRE-DS	136	394.9	19.92	394.0	345	454	394.3	136	0.5	1.20	14.04	-1.7	-37	36
DAY 36:1-2H PST-DS	134	392.1	17.91	391.0	340	440	394.3	134	-2.2	1.20	13.84	-3.3	-37	29
DAY 36:4H PST-DS	136	392.8	18.81	392.5	347	445	394.2	136	-1.5	1.18	13.71	-1.8	-37	51
DAY 43	139	395.2	19.36	396.0	332	451	393.4	139	1.7	1.14	13.42	1.5	-30	43
MAXIMUM VALUE	350	406.7	18.26	407.0	341	469	393.1	350	13.6	0.66	12.29	13.0	-25	57
END POINT	350	393.5	18.48	393.0	332	451	393.1	350	0.4	0.75	13.94	0.2	-36	57

ER OROS PAL 15 mg														
SCREENING	112	395.2	17.50	393.5	361	449								
BASELINE	113	393.2	17.38	392.0	352	445								
AVERAGE PREDOSE	113	394.9	16.42	394.3	359	443								
DAY 4:4H PST-DS	103	392.2	13.74	392.0	354	424	394.0	103	-1.8	1.12	11.36	-0.7	-36	33
DAY 4:10H PST-DS	100	393.8	17.45	392.0	337	463	395.3	100	-1.5	1.40	14.03	-2.0	-68	30
DAY 4:22H PST-DS	105	395.6	17.01	394.0	355	441	395.0	105	0.5	1.20	12.31	0.7	-31	33
DAY 8:4H PST-DS	105	393.7	16.19	393.0	360	439	394.7	105	-1.1	1.08	11.08	-0.3	-31	23
DAY 8:10H PST-DS	103	394.8	16.58	394.0	354	438	394.8	103	0.0	1.39	14.07	1.0	-43	27
DAY 8:22H PST-DS	105	397.9	19.33	397.0	350	460	394.9	105	3.1	1.49	15.22	1.0	-27	60
DAY 15:PRE-DS	100	394.8	16.60	393.0	359	443	394.7	100	0.1	1.32	13.19	0.4	-29	31
DAY 15:1-2H PST-DS	99	392.8	16.45	391.0	358	434	394.7	99	-1.9	1.29	12.83	-1.7	-39	27
DAY 15:4H PST-DS	100	391.5	16.23	391.0	358	430	394.5	100	-3.0	1.32	13.20	-3.5	-36	29
DAY 29	93	396.7	15.08	394.0	362	433	394.5	93	2.2	1.53	14.71	2.0	-35	37
DAY 36:PRE-DS	74	398.1	13.76	399.0	368	429	394.8	74	3.3	1.66	14.31	2.3	-35	33
DAY 36:1-2H PST-DS	79	393.7	15.12	394.0	354	433	395.3	79	-1.6	1.52	13.48	2.0	-40	22
DAY 36:4H PST-DS	77	394.7	13.42	393.0	374	426	395.0	77	-0.3	1.71	15.00	0.5	-41	32
DAY 43	81	397.8	16.95	397.0	360	439	394.2	81	3.6	1.48	13.33	3.7	-26	42
MAXIMUM VALUE	113	409.6	16.04	409.0	376	463	394.9	113	14.7	1.26	13.43	14.7	-14	60
END POINT	113	396.4	16.93	396.0	358	439	394.9	113	1.4	1.28	13.63	1.3	-32	43

The following figure illustrates the above described time-dependent pattern of QTcLD taken from the CSR of Study 305. This figure was selected since it comes from one of the placebo controlled, competed Phase III short-term Study 305 which employed the highest Pal dose-level (15 mg/day) and therefore, shows a clear treatment group effect that is dose-dependent with most prominent effects observed at 22 hour post-dose (on Days 4, 8 and 15 which included this post-dose time-point) and at approximately 24 hours post-dose on assessment Days 36 and on Day 43.

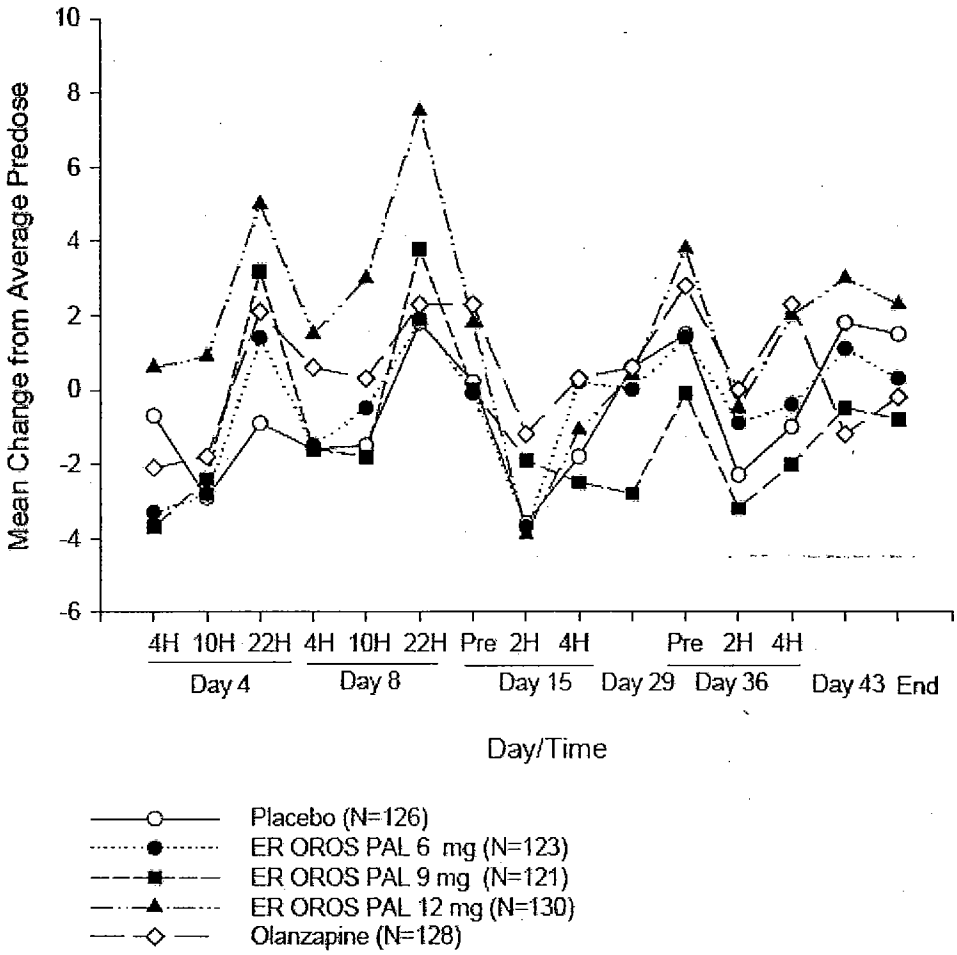
Figure 18: QTcLD Mean Changes From Predose Over Time
(Study R076477-SCH-305: Safety Analysis Set)



Note Fluctuations and Potential Time-dependent Changes in QTc in the Placebo Group
It is noteworthy that the placebo group appears to show fluctuations in mean QTc interval that almost follows a similar time-dependent pattern that was observed for active drug-groups.

The following figure is similar to the above figure, except it is of results from Study 303 which had the next highest dose-level employed in short-term, non-elderly, Phase III trials (as copied from the CSR). Note that the group mean increase in QTcLD group mean increase was greatest in the 12 mg Pal group (7.5 msec maximal group mean increase) compared to placebo (group mean increase of 1.8 msec) that occurred 22 hours post-dose on Day.

Figure 18: QTcLD Mean Changes From Predose Over Time
(Study R076477-SCH-303 Safety Analysis Set)



N is sample size at average predose timepoint
Cross-reference: Attachment 11.1

Note fluctuations in the placebo group that appear to follow to some extent, a similar time-dependent pattern as in the Pal groups.

iv. QTc Interval Values Exceeding 500 msec were Observed but Were Not Generally Consistent with a Drug Effect. The upper end of the treatment group range for QTc interval values (using any method for correction) for any given treatment Pal group exceeded 450 msec on several time-points among various treatment groups. However, this observation did not appear to be drug-related due to the following reasons. The placebo group also showed a maximum value of

450 msec or greater. Furthermore, several treatment groups showed values exceeding 450 msec prior to treatment (at baseline or screening time-points). The results incidence of outliers is discussed in a separate subsection of this review.

IV. Clinically Unremarkable Dose-Dependent Mean Increase in PR Interval

Group mean changes (from the pre-dose average value) on PR interval fluctuated over time in any given treatment group and any observable mean change failed to be of a magnitude to be considered clinically remarkable. However a drug effect on PR appears to exist, as outlined in below that could be reflecting an indirect rather than a direct or primary drug effect on PR:

- *An overall trend for a dose-dependent group mean increase in PR interval appeared to occur and the magnitude of this increase appeared to be greater with each increase in dose-level of Pal and to be more consistently increased over time (more time-points showed a mean increase with each increasing dose-level).*
- *The maximum group mean peak interval in the HD Pal group (15 mg) was 4.3 msec which occurred on Day 8 at 10 hours post-dose with a smaller mean increase observed at this same time-point (10 hours post-dose) on Day 4. These Pal results are compared to mean changes of only 0.5 to -1.9 observed during DB placebo treatment (most time-points had negative values for PR in the placebo group and the maximum placebo group mean increase of 0.5 msec occurred on the same time-point as the peak increase observed in the 15 mg Pal group which was on Day 8 at 10 hours post-dose).*

Summary tables on PR interval Results

The data are shown below (excerpts from Appendix 2.7.4.6.2.1 of the SCS) with highlighting and green underlining of results that were inserted by the undersigned reviewer for demonstration purposes (only the HD Pal and placebo group results are shown). Yellow highlighting denotes the 10 hour-post dose time-points (peak mean increases and secondary peak increases in PR interval in the Pal group).

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

Output DECG01: ECG: Means and Mean Changes from Pre-treatment over Time - Double-Blind Phase (continued)

Analysis Set: Safety

							Base	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max

PR INTERVAL (ms)														
Placebo														
SCREENING	354	152.3	20.95	152.0	88	238								
BASELINE	355	152.6	20.78	152.0	102	250								
AVERAGE PREDOSE	355	152.7	19.79	151.3	97	225								
DAY 4:4H PST-DS	326	153.1	21.78	151.0	110	238	152.7	326	0.4	0.59	10.73	-0.8	-31	65
DAY 4:10H PST-DS	323	152.9	20.64	152.0	104	234	152.5	323	0.3	0.59	10.47	0.3	-42	36
DAY 4:22H PST-DS	324	152.8	21.27	153.0	106	244	152.4	324	0.4	0.61	10.95	1.0	-38	30
DAY 8:4H PST-DS	315	151.8	19.94	150.0	102	227	152.7	315	-0.8	0.62	11.01	0.0	-44	48
DAY 8:10H PST-DS	311	153.4	20.44	152.0	111	209	152.8	311	0.5	0.62	10.95	0.7	-41	31
DAY 8:22H PST-DS	307	151.7	22.07	151.0	100	240	152.7	307	-1.0	0.60	10.49	-1.0	-43	33
DAY 15:PRE-DS	278	152.2	21.83	150.0	106	226	152.9	278	-0.7	0.63	10.58	0.0	-32	34
DAY 15:1-2H PST-DS	281	151.2	20.88	149.0	101	233	153.1	281	-1.9	0.62	10.39	-1.7	-36	29
DAY 15:4H PST-DS	279	151.1	21.17	148.0	104	211	152.9	279	-1.7	0.65	10.79	-1.7	-35	31
DAY 29	206	151.6	21.22	152.0	112	224	153.4	206	-1.9	0.81	11.61	-1.8	-48	30
DAY 36:PRE-DS	136	153.5	17.47	155.5	103	212	153.3	136	0.2	0.82	9.57	0.5	-28	32
DAY 36:1-2H PST-DS	136	151.6	18.71	154.0	104	196	153.4	136	-1.8	0.95	11.06	-1.3	-29	25
DAY 36:4H PST-DS	136	152.2	17.79	151.0	110	205	153.3	136	-1.2	0.91	10.66	0.2	-29	20
DAY 43	139	153.0	20.04	152.0	106	217	154.3	139	-1.3	0.91	10.71	-0.3	-34	36
END POINT	350	150.6	20.74	150.0	102	219	152.7	350	-2.1	0.57	10.67	-2.0	-33	36
ER OROS PAL 15 mg														
SCREENING	112	151.7	21.46	150.0	108	223								
BASELINE	113	152.7	21.69	150.0	109	223								
AVERAGE PREDOSE	113	152.3	21.88	148.3	114	223								
DAY 4:4H PST-DS	105	153.7	21.79	150.0	113	233	152.4	105	1.3	0.99	10.10	1.0	-23	51
DAY 4:10H PST-DS	100	155.4	24.91	150.5	104	250	153.6	100	1.7	1.34	13.43	0.2	-59	75
DAY 4:22H PST-DS	105	153.1	23.36	149.0	110	259	153.1	105	-0.1	1.19	12.19	0.0	-22	83
DAY 8:4H PST-DS	106	153.4	22.20	150.5	110	215	152.7	106	0.8	0.96	9.91	1.0	-32	42
DAY 8:10H PST-DS	103	156.4	24.33	154.0	109	246	152.1	103	4.3	1.16	11.81	3.0	-21	65
DAY 8:22H PST-DS	105	152.8	20.43	150.0	116	218	152.4	105	0.5	1.14	11.68	0.5	-46	36
DAY 15:PRE-DS	101	152.5	21.79	151.0	112	221	151.8	101	0.7	0.95	9.57	1.0	-28	21
DAY 15:1-2H PST-DS	99	152.9	22.21	151.0	110	215	152.3	99	0.6	1.07	10.60	0.5	-37	34
DAY 15:4H PST-DS	100	150.9	21.60	150.0	106	216	151.7	100	-0.7	0.89	8.90	-1.0	-28	20
DAY 29	93	153.5	22.82	153.0	106	212	152.0	93	1.6	1.17	11.33	0.3	-23	40
DAY 36:PRE-DS	75	154.9	24.22	150.0	116	258	153.0	75	2.0	1.24	10.70	2.5	-20	35
DAY 36:1-2H PST-DS	79	154.4	22.51	154.0	114	212	153.7	79	0.7	1.15	10.26	0.0	-24	26
DAY 36:4H PST-DS	78	153.9	25.12	151.5	108	228	153.3	78	0.6	1.24	10.97	-1.0	-25	43
DAY 43	82	154.8	23.08	154.5	110	238	153.2	82	1.6	1.33	12.01	1.3	-34	36
END POINT	113	153.3	22.28	152.0	110	238	152.3	113	1.0	1.08	11.51	0.3	-34	36

V. Overall Conclusion of ECG Results

A clinically significant finding in the above ECG results is a Pal-induced increase in heart rate that is dose and time-dependent. It is possible that greater effects could have been revealed if the study were specifically designed for capturing Tmax and maximal drug effects on heart rate, such as the following consideration. It is critical to consider a potentially dynamic rather than a static drug effect on heart rate (as well as for other clinical parameters) in which the peak heart rate effects occurred at time-points when the placebo group also show increases, while increases in the pal groups were larger.

Despite limitations with the study design of the Phase III trials, it is also notable that various methods for calculation QTc revealed some evidence for dose-dependent effects on prolonging QTc interval near Tmax (which is reported to be at 22 hours post-dose). The largest prolongation effects were observed with QTcB which is not an optimal calculation method for QTc, since Pal generally induced increases in heart rate and heart rate was generally not abnormally low. However, Pal effects on increasing heart rate were not as prominent at the 22 hour post-dose time-points, as observed at other time-points (at the 4 hour post-dose time-points which generally showed the greatest mean increases). Consequently the magnitude of QTcB interval changes may be more accurate at the 22 hour post-dose time-points than at the 4 hour post-dose time-points. The largest group mean increase at the 22 hour post-dose time-point was 8.8 on the first assessment day during treatment (on Day 4) in the 12 mg Pal group (6.2 mean increase was observed in the 15 mg Pal group at 22 hours post-dose on Day 4, which received

12 mg Pal daily during this first week of treatment). This mean increase compares to a mean change of -1.9 in the placebo group at this time-point on this assessment day. It is important to note that a mean increase in heart rate was observed on Day 4, such that QTcB interval values may be an exaggerate representation of a real drug effects in which the actual drug effects may be smaller than values revealed by the Bazett's method for calculation QTc interval.

Using other approaches in calculating QTc that may be more valid methods for determining Pal effects on QT interval (QTcFridericia and lindear derived or linear sagie approaches) a dose-dependent and time-dependent effect of Pall on prolonging QTc interval was also generally revealed. However, the magnitude of this effect was generally moderate to small. A Pal group mean increase of up to 5.1 msec was revealed on Day 8 near Tmax (at the 22 hour time-point) in the 12 mg group for QTc Fridericia interval and a mean increase of up to 3.1 msec was revealed on this same treatment day and time-point in the 15 mg Pal group for QTc linear-derived interval (note that the 15 mg group received 12 mg over the first 7 days of treatment). Figures of QTcLD results in Study -303 showed peak mean increases of up to approximately 7.5 msec on Day 8 (22 hour-post-dose) in the 12 mg Pal group.

A clinically significant concern is that greater QT interval prolongation effects of Pal may occur under conditions that increase Cmax or increase the risk of QT prolongations. The following are key observation that suggest a Cmax dependent effect on Pal induced QT prolongation. QTc interval prolongation effects appeared to be dose-dependent, were generally greatest at a time-point near Tmax (22 hours post-dose) and generally increased over duration of treatment when assessments were conducted near Tmax (Day 8 generally showed greater mean increases than Day 4 near Tmax, which were the only 2 days that had this assessment time-point). As previously discussed it is important to consider the known prominent food effects on plasma Pal levels, the potential for drug accumulation with multiple dosing and other factors that may increase Cmax or factors that may increase risk of QT interval prolongation (e.g. consider concomitant medications).

Pal effects of decreasing RR were generally observed that appear to be secondary to Pal effects on heart rate. The observations on RR do not appear to be clinically remarkable.

Dose-dependent effects of Pal treatment on prolonging PR appear to exist, but the magnitude of the Pal group mean increases in PR were not clinically remarkable.

Results of Elderly Phase III Trial -302

Reviewer Comments. *The descriptive statistical ECG results from Study -302 failed to reveal any new or clinically remarkable findings that were not previously described in this review for the non-elderly, short-term trial dataset (in the previous subsection of this review). Pal group mean increases (from the average pre-dose value) in heart rate were observed during treatment, as shown below (selected sections from Attachment 11.1 of the CSR for this study).*

Study R076477-SCH-302

Output DECG01A: ECG: Means and Mean Changes from Pre-treatment over Time

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)														
Placebo														
SCREENING	37	73.1	13.10	69.0	50	103								
BASELINE	38	72.2	11.57	72.0	50	99								
AVERAGE PREDOSE	38	72.5	11.23	72.2	51	93								
DAY 4:4H PST-DS	35	71.4	11.85	69.0	51	102	72.9	35	-1.5	1.69	10.01	-1.3	-25	17
DAY 4:10H PST-DS	36	69.3	13.16	65.5	47	98	72.5	36	-3.3	2.02	12.14	-0.7	-28	29
DAY 4:22H PST-DS	36	66.3	10.82	63.0	48	100	72.5	36	-6.2	1.52	9.14	-6.5	-27	11
DAY 8:4H PST-DS	35	69.5	11.78	68.0	47	93	72.6	35	-3.0	2.18	12.91	-3.0	-37	27
DAY 8:10H PST-DS	35	68.5	9.56	67.0	54	89	72.6	35	-4.1	2.10	12.40	-2.0	-30	17
DAY 8:22H PST-DS	34	66.2	8.82	67.5	50	87	72.7	34	-6.5	1.81	10.58	-5.2	-29	13
DAY 15	33	68.1	11.41	68.0	49	97	73.1	33	-5.0	1.90	10.89	-3.7	-30	11
DAY 29	31	71.1	12.72	67.0	51	105	72.3	31	-1.2	2.45	13.65	0.3	-28	42
DAY 43	25	68.9	12.62	67.0	49	96	71.3	25	-2.4	2.54	12.68	-1.3	-34	21
END POINT	37	69.5	12.28	68.0	49	96	72.5	37	-3.1	2.14	13.04	-1.3	-34	21
ER OROS PAL														
SCREENING	76	76.5	13.53	78.0	50	103								
BASELINE	76	72.5	14.58	71.5	42	105								
AVERAGE PREDOSE	76	74.7	12.10	75.5	51	100								
DAY 4:4H PST-DS	74	78.1	14.56	78.0	48	128	74.5	74	3.5	1.14	9.79	3.8	-25	33
DAY 4:10H PST-DS	72	78.3	12.92	76.5	50	113	75.0	72	3.3	1.33	11.31	3.2	-27	42
DAY 4:22H PST-DS	72	77.3	14.85	75.5	47	120	74.9	72	2.5	1.20	10.22	1.3	-21	25
DAY 8:4H PST-DS	72	77.9	14.28	77.0	50	123	74.4	72	3.5	1.39	11.83	2.5	-26	36
DAY 8:10H PST-DS	70	78.3	15.04	78.0	49	123	74.2	70	4.1	1.47	12.29	3.2	-29	41
DAY 8:22H PST-DS	72	77.6	18.56	75.0	45	150	74.7	72	2.9	1.64	13.94	0.8	-23	51
DAY 15	72	75.2	15.64	74.0	46	114	74.4	72	0.8	1.42	12.07	1.3	-33	24
DAY 29	68	75.3	16.52	73.5	48	156	74.6	68	0.8	1.62	13.32	0.2	-31	57
DAY 43	64	71.1	10.19	69.0	51	102	74.5	64	-3.4	1.39	10.33	-3.2	-27	16
END POINT	76	72.7	11.91	70.0	51	116	74.7	76	-2.1	1.28	11.18	-1.8	-27	32

The following shows results on RR results (taken from Attachment 11.1 of the CSR)

Study R076477-SCH-302

Output DECG01A: ECG: Means and Mean Changes from Pre-treatment over Time (continued)

Analysis Set: Safety

	N	Mean	SD	Med	Min	Max	Base Mean	N	change from average predose Mean	SE	SD	Med	Min	Max
RR (ms)														
Placebo														
SCREENING	37	846.7	148.36	870.0	583	1200								
BASELINE	38	854.1	146.17	833.5	674	1200								
AVERAGE PREDOSE	38	852.2	135.54	839.0	647	1170								
DAY 4:4H PST-DS	35	861.6	134.14	870.0	588	1176	846.7	35	14.9	20.73	122.65	14.0	-232	281
DAY 4:10H PST-DS	36	895.5	160.59	916.0	612	1277	851.7	36	43.7	24.93	149.55	7.0	-296	331
DAY 4:22H PST-DS	36	927.3	145.14	952.0	600	1250	851.7	36	75.5	19.49	116.93	73.2	-153	331
DAY 8:4H PST-DS	35	887.3	151.74	882.0	645	1277	851.9	35	35.3	27.28	161.42	31.7	-293	462
DAY 8:10H PST-DS	35	892.7	120.54	896.0	674	1111	851.9	35	40.7	25.33	149.86	25.3	-230	392
DAY 8:22H PST-DS	34	922.3	125.67	899.0	690	1200	850.6	34	71.7	23.39	136.41	52.8	-173	436
DAY 15	33	903.9	143.35	882.0	619	1224	846.4	33	57.5	22.80	130.95	35.0	-135	372
DAY 29	31	868.1	144.78	896.0	571	1176	855.4	31	12.7	26.12	145.44	-11.0	-377	300
DAY 43	25	898.5	156.49	896.0	625	1224	869.8	25	28.7	30.22	151.11	24.7	-232	403
END POINT	37	888.7	149.95	882.0	625	1224	851.5	37	37.2	25.65	156.05	12.7	-232	403
ER OROS PAL														
SCREENING	76	810.1	148.77	769.0	583	1200								
BASELINE	76	862.6	180.70	839.0	571	1429								
AVERAGE PREDOSE	76	831.2	141.24	804.2	600	1176								
DAY 4:4H PST-DS	74	795.2	149.12	769.0	469	1250	833.1	74	-37.9	12.13	104.37	-55.3	-324	296
DAY 4:10H PST-DS	72	786.9	129.20	784.0	531	1200	828.8	72	-41.9	13.95	118.38	-43.0	-321	315
DAY 4:22H PST-DS	72	804.5	156.50	794.5	500	1277	829.4	72	-24.9	12.34	104.71	-16.3	-278	195
DAY 8:4H PST-DS	72	795.9	147.14	779.0	488	1200	835.3	72	-39.4	14.95	126.83	-24.5	-349	315
DAY 8:10H PST-DS	70	794.4	152.54	769.0	488	1224	838.5	70	-44.1	15.39	128.76	-42.2	-386	373
DAY 8:22H PST-DS	72	814.1	183.32	800.0	400	1333	832.3	72	-18.2	14.99	127.20	-24.0	-302	303
DAY 15	72	831.9	172.38	811.0	526	1304	835.3	72	-3.4	16.09	136.53	-19.8	-226	462
DAY 29	68	828.3	157.16	816.5	385	1250	834.2	68	-5.9	16.40	135.20	-6.7	-320	373
DAY 43	64	860.9	121.15	870.0	588	1176	835.9	64	25.0	14.44	115.53	32.7	-253	333
END POINT	76	845.7	127.72	857.0	517	1176	831.2	76	14.5	13.24	115.41	12.6	-253	333

The following table shows QT Bazett and QTc-Fridericia Interval results (from Attachment 11.1 of the CSR).

Study R076477-SCH-302

Output DECG01A: ECG: Means and Mean Changes from Pre-treatment over Time (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)														
Placebo														
SCREENING	37	427.7	26.52	423.0	371	496								
BASELINE	38	425.7	21.83	423.5	389	479								
AVERAGE PREDOSE	38	426.5	23.33	427.8	389	488								
DAY 4:4H PST-DS	35	422.5	23.75	418.0	381	485	424.8	35	-2.3	3.32	19.64	-3.0	-39	48
DAY 4:10H PST-DS	36	417.2	21.59	417.0	382	461	425.2	36	-8.0	2.99	17.96	-8.5	-36	47
DAY 4:22H PST-DS	36	420.1	19.81	418.0	384	460	425.2	36	-5.1	2.67	16.02	-5.3	-42	24
DAY 8:4H PST-DS	34	416.0	19.89	418.0	372	447	422.9	34	-7.0	2.70	15.75	-5.2	-34	31
DAY 8:10H PST-DS	35	419.2	19.21	419.0	375	459	424.8	35	-5.6	2.69	15.91	-5.5	-36	31
DAY 8:22H PST-DS	34	421.3	18.08	422.0	385	453	425.4	34	-4.1	2.74	15.98	-2.2	-43	32
DAY 15	33	420.1	19.85	420.0	370	469	426.3	33	-6.2	3.92	22.52	-8.0	-64	41
DAY 29	31	423.0	18.44	428.0	369	460	425.5	31	-2.5	3.58	19.92	-2.3	-53	28
DAY 43	25	418.7	17.78	419.0	384	458	423.6	25	-4.9	3.93	19.14	-4.0	-58	27
MAXIMUM VALUE	37	440.2	19.61	439.0	407	485	426.3	37	13.9	2.60	15.84	12.7	-31	48
END POINT	37	422.8	19.90	423.0	384	479	426.3	37	-3.5	3.23	19.67	1.0	-63	27
ER OROS PAL														
SCREENING	74	432.6	26.27	436.0	381	495								
BASELINE	76	425.3	25.98	428.0	337	505								
AVERAGE PREDOSE	76	429.7	24.17	431.0	375	497								
DAY 4:4H PST-DS	70	425.6	24.85	423.0	379	499	428.4	70	-2.9	1.96	16.44	-1.0	-43	27
DAY 4:10H PST-DS	72	429.3	24.29	429.0	373	498	428.7	72	0.6	2.26	19.17	-0.3	-39	57
DAY 4:22H PST-DS	72	433.0	26.62	432.5	378	529	428.8	72	4.2	2.08	17.67	5.2	-45	39
DAY 8:4H PST-DS	71	427.1	21.80	426.0	369	497	427.3	71	-0.2	2.39	20.18	-0.3	-63	43
DAY 8:10H PST-DS	70	428.6	22.38	426.5	385	490	428.0	70	0.6	2.44	20.43	1.3	-56	44
DAY 8:22H PST-DS	71	429.5	24.09	428.0	372	485	427.4	71	2.1	2.68	22.57	5.7	-99	53
DAY 15	72	427.2	24.39	427.0	380	475	428.0	72	-0.8	2.39	20.26	-0.5	-41	59
DAY 29	67	426.2	24.81	430.0	378	496	428.4	67	-2.1	2.15	17.58	-1.5	-35	45
DAY 43	63	425.6	27.22	424.0	366	506	428.3	63	-2.7	2.71	21.53	-1.0	-74	77
MAXIMUM VALUE	76	450.8	23.58	449.0	405	529	429.7	76	21.1	1.85	16.10	20.3	-14	77
END POINT	76	429.1	28.75	427.0	366	506	429.7	76	-0.6	2.54	22.11	-0.3	-74	77
QTC INTERVAL FRIDERICIA (ms)														
Placebo														
SCREENING	37	415.0	25.46	413.0	367	471								
BASELINE	38	413.8	19.18	415.5	374	452								
AVERAGE PREDOSE	38	414.3	21.42	410.0	366	462								
DAY 4:4H PST-DS	35	411.3	24.03	406.0	371	470	412.2	35	-0.9	2.56	15.12	0.0	-31	39
DAY 4:10H PST-DS	36	408.8	23.12	405.5	362	471	413.0	36	-4.2	2.33	14.00	-4.8	-29	48
DAY 4:22H PST-DS	36	414.3	22.60	412.5	374	459	413.0	36	1.4	2.63	15.81	4.0	-33	39
DAY 8:4H PST-DS	34	406.4	18.77	405.5	367	441	411.1	34	-4.7	2.20	12.81	-3.0	-45	15
DAY 8:10H PST-DS	35	410.7	20.67	411.0	360	464	412.6	35	-1.8	2.00	11.86	-4.0	-29	24
DAY 8:22H PST-DS	34	415.2	16.39	414.5	381	455	413.0	34	2.2	2.07	12.07	2.5	-24	32
DAY 15	33	412.2	19.39	416.0	370	446	413.6	33	-1.3	2.88	16.54	-1.0	-36	29
DAY 29	31	412.3	19.80	412.0	370	455	413.5	31	-1.2	2.75	15.29	0.3	-41	33
DAY 43	25	410.3	19.13	407.0	383	448	412.9	25	-2.5	2.58	12.90	-4.0	-34	30
MAXIMUM VALUE	37	428.8	22.15	426.0	390	471	414.1	37	14.7	2.00	12.17	13.0	-8	48
END POINT	37	413.7	21.75	409.0	382	467	414.1	37	-0.3	2.46	14.95	-2.7	-34	33
ER OROS PAL														
SCREENING	74	416.8	23.40	417.5	370	466								
BASELINE	76	413.6	22.14	412.5	337	480								
AVERAGE PREDOSE	76	415.6	22.55	413.5	360	472								
DAY 4:4H PST-DS	70	409.3	22.09	405.0	373	482	414.9	70	-5.6	1.62	13.59	-6.3	-48	24
DAY 4:10H PST-DS	72	411.7	22.98	408.0	369	476	414.4	72	-2.7	2.11	17.89	-1.5	-45	45
DAY 4:22H PST-DS	72	416.3	24.44	414.0	346	506	414.4	72	1.9	1.92	16.28	2.5	-44	37
DAY 8:4H PST-DS	71	410.4	20.57	409.0	348	470	413.8	71	-3.4	2.07	17.47	0.7	-59	40
DAY 8:10H PST-DS	70	411.3	20.55	412.0	359	462	414.4	70	-3.0	2.14	17.87	-0.3	-52	37
DAY 8:22H PST-DS	71	413.5	22.12	415.0	354	462	413.7	71	-0.2	2.39	20.16	2.0	-81	44
DAY 15	72	413.0	21.73	414.5	363	460	414.1	72	-1.1	1.81	15.39	-1.0	-35	43
DAY 29	67	412.0	24.08	412.0	361	491	414.7	67	-2.6	1.90	15.56	-0.7	-49	45
DAY 43	63	414.5	25.32	415.0	360	502	414.3	63	0.2	2.30	18.28	3.0	-51	69
MAXIMUM VALUE	76	431.8	23.85	431.0	378	506	415.6	76	16.2	1.63	14.21	15.5	-16	69
END POINT	76	416.8	26.69	415.5	360	502	415.6	76	1.2	2.17	18.94	2.8	-51	69

Results of QTcLD are shown below given possible QT prolongation effects noted for the short-term trial dataset.

Study R076477-SCH-302

Output DECG01A: ECG: Means and Mean Changes from Pre-treatment over Time (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)													
Placebo													
SCREENING	37	414.2	24.13	412.0	368	464							
BASELINE	38	412.9	17.92	413.0	377	451							
AVERAGE PREDOSE	38	413.4	20.07	409.5	370	455							
DAY 4:4H PST-DS	35	411.0	23.32	405.0	373	469	411.4	35	-0.4	2.56	15.15	1.5	-34	42
DAY 4:10H PST-DS	36	408.6	22.97	405.0	365	472	412.1	36	-3.5	2.40	14.43	-5.3	-32	52
DAY 4:22H PST-DS	36	414.3	21.83	412.0	377	458	412.1	36	2.1	2.61	15.64	3.5	-35	38
DAY 8:4H PST-DS	34	406.1	18.01	405.0	370	440	410.4	34	-4.3	2.14	12.47	-2.2	-43	15
DAY 8:10H PST-DS	35	410.8	20.10	411.0	365	465	411.7	35	-0.9	1.99	11.76	-2.7	-29	24
DAY 8:22H PST-DS	34	414.9	15.83	414.5	384	453	412.1	34	2.8	1.98	11.55	1.8	-20	33
DAY 15	33	411.8	18.47	415.0	370	445	412.7	33	-0.9	2.63	15.08	-0.7	-34	25
DAY 29	31	412.0	19.49	412.0	370	454	412.7	31	-0.7	2.68	14.91	-1.0	-37	37
DAY 43	25	410.0	18.61	405.0	384	447	412.2	25	-2.2	2.44	12.21	-3.7	-28	30
MAXIMUM VALUE	37	428.1	21.68	425.0	392	472	413.2	37	14.9	1.97	11.99	12.7	-8	52
END POINT	37	413.4	21.24	408.0	384	465	413.2	37	0.3	2.37	14.42	-1.3	-28	37
ER OROS PAL														
SCREENING	74	415.3	22.16	416.0	373	465								
BASELINE	76	412.3	21.29	412.0	337	472								
AVERAGE PREDOSE	76	414.3	21.56	411.8	362	465								
DAY 4:4H PST-DS	70	408.1	20.85	405.0	375	478	413.8	70	-5.6	1.55	12.97	-5.5	-47	23
DAY 4:10H PST-DS	72	410.5	21.77	407.0	371	470	413.2	72	-2.7	1.99	16.90	-2.7	-43	42
DAY 4:22H PST-DS	72	414.6	23.24	413.5	351	498	413.1	72	1.4	1.84	15.62	1.3	-43	36
DAY 8:4H PST-DS	71	409.4	19.68	407.0	352	466	412.7	71	-3.3	1.99	16.75	0.3	-57	38
DAY 8:10H PST-DS	70	410.2	19.39	410.0	362	461	413.2	70	-3.0	2.02	16.94	-1.0	-47	35
DAY 8:22H PST-DS	71	411.8	21.59	413.0	358	457	412.6	71	-0.8	2.38	20.09	0.7	-87	43
DAY 15	72	411.6	21.08	413.5	365	460	413.0	72	-1.4	1.75	14.88	-1.7	-35	40
DAY 29	67	411.0	23.24	410.0	363	489	413.5	67	-2.5	1.87	15.33	-0.8	-50	44
DAY 43	63	413.9	24.17	415.0	363	500	413.1	63	0.8	2.17	17.26	3.8	-42	68
MAXIMUM VALUE	76	429.9	22.90	428.0	380	500	414.3	76	15.6	1.57	13.66	14.8	-16	68
END POINT	76	415.8	25.50	415.0	363	500	414.3	76	1.5	2.08	18.15	3.7	-42	68

Results of Ongoing Open-Label Extension Long-Term Trials (-702, -703, -704, -705)

Reviewer Comments. *While noting previously described serious limitations with this longterm dataset the following conclusions can be made from this safety dataset (comments and conclusions are based on group mean numerical comparisons of results provided in Appendix 2.7.4.6.2.2. found in the SCS, results of any statistical analyses could not be found in the SCS).*

Results were generally similar to those observed in the short-term trials and did not reveal any new clinically, remarkable findings that are not already described in this review for the short-term trial dataset.

I. Pal Group Mean Increases in Heart Rate.

The conclusions are generally based on data in which over 50 assessed subjects, which was generally for time-points of up to 24 weeks of OL treatment in the > 3 month subgroups, as previously discussed in this review).

As observed with the short-term trial datasets, group mean increases (from the average pre-dose value) in heart rate were observed during DB or during OL Pal treatment in subjects that previously received DB placebo.

Subjects previously receiving DB Pal showed little to no mean increases in heart rate during OL Pal treatment.

Note that a group mean increase of up to 8.4 bpm was observed at week 1 of OL Pal treatment in the DB-Placebo/OL-Pal ≤ 3month subgroup.

The treatment group that previously received olanzapine (DB) showed group mean increases in heart rate upon being switched to OL Pal treatment in the extension trial that continued for several weeks during OL Pal treatment.

A Caveat. *It is critical to note that a flexible dose design was employed during OL trials, in contrast to the fixed dose design in DB trials. Furthermore, consider potential between subject differences on the actual timing of assessments and on dosing (as previously discussed in Section 7.1.X). See these results below (taken from Appendix 2.7.4.6.2.2). Also as previously noted, some data points have insufficient sample sizes.*

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

Output CSCL01. ECG. Means and Mean Changes from Pre-treatment over Time - Open-Label Phase

Analysis Set: Safety

							Pass	change from average readings					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SD	SD	Med	Min	Max
HEART RATE (beats/min)														
Pla/Pal <=1 months														
BASELINE (DB)	107	71.6	11.72	71.0	47	102								
AVERAGE EXPOSURE	107	74.1	11.39	73.7	51	101								
DAY 4 (DB) .4H PST	106	75.2	11.74	74.0	50	105	74.1	106	1.1	1.08	11.06	1.7	-25	37
DAY 4 (DB) .10H PST	104	74.6	13.82	73.5	52	116	74.2	104	0.4	1.18	12.03	0.7	-30	37
DAY 4 (DB) .22H PST	103	70.9	13.44	70.0	48	100	71.9	102	-1.0	1.07	10.77	-4.0	-27	30
DAY 8 (DB) .4H PST	106	74.7	13.45	73.5	47	111	74.2	104	0.5	1.32	12.66	0.0	-37	50
DAY 8 (DB) .10H PST	106	75.5	12.87	74.0	52	115	74.2	104	1.3	1.22	12.63	1.4	-29	34
DAY 8 (DB) .22H PST	106	71.3	13.12	71.0	45	103	74.2	104	-1.1	1.15	11.87	-1.2	-31	19
DAY 15 (DB)	21	66.2	9.67	67.0	49	83	73.0	21	-6.8	2.31	10.59	-6.0	-30	9
DAY 15 (DB).PRE-DS	95	74.0	14.64	70.0	48	115	74.5	95	-0.5	1.36	13.27	-1.4	-36	30
DAY 15 (DB).1-2H PST	95	77.6	14.42	76.0	50	109	74.5	95	3.1	1.52	14.84	3.7	-34	40
DAY 15 (DB).4H PST	95	76.9	13.84	76.0	52	109	74.5	95	3.4	1.46	13.44	3.5	-25	37
DAY 29 (DB)	95	74.5	13.82	73.0	51	115	74.4	95	0.4	1.39	12.72	1.5	-28	38
DAY 36 (DB).PRE-DS	16	72.7	13.62	70.5	48	101	74.0	16	-1.3	1.98	11.90	-3.2	-26	32
DAY 36 (DB).1-2H PST	18	76.4	11.10	76.5	54	101	73.6	18	3.8	1.81	11.36	3.2	-17	19
DAY 36 (DB).4H PST	16	75.2	13.33	74.0	52	101	73.5	16	1.7	2.06	12.33	1.5	-26	33
DAY 43 (DB)	83	70.5	12.41	68.0	49	103	73.5	82	-1.0	1.66	11.95	-1.1	-34	36
END POINT (DB)	107	76.4	14.37	73.0	49	130	74.1	107	1.3	1.32	13.78	1.0	-34	38
BASE (OPEN)	107	74.9	14.36	73.0	49	130	74.1	107	0.8	1.39	13.38	0.0	-34	38
DAY 4 (OPEN)	97	82.1	16.73	81.0	45	132	74.2	97	7.9	1.68	16.62	8.1	-26	64
WEEK 1 (OPEN)	95	82.6	15.80	81.0	56	112	74.1	95	8.4	1.57	15.36	8.0	-27	38
WEEK 2 (OPEN)	90	80.4	15.11	80.0	54	114	74.7	90	5.7	1.58	15.11	6.2	-30	38
WEEK 4 (OPEN)	74	76.7	14.84	75.5	42	111	74.2	74	2.2	1.44	12.42	-1.0	-22	36
WEEK 8 (OPEN)	36	77.1	15.21	76.0	49	115	76.2	36	0.8	2.11	13.07	0.0	-31	36
WEEK 16 (OPEN)	1	66.0		66.0	66	66	85.7	1	-19.7			-19.7	-20	-20
END POINT (OPEN)	106	76.6	14.63	76.0	42	115	74.1	106	1.4	1.34	12.77	1.2	-31	38
Pla/Pal >1 months														
BASELINE (DB)	124	71.4	12.52	71.5	48	114								
AVERAGE EXPOSURE	124	74.7	11.39	75.2	49	109								
DAY 4 (DB) .4H PST	125	76.3	14.32	76.0	49	132	75.0	125	1.5	1.02	11.43	1.7	-30	40
DAY 4 (DB) .10H PST	125	74.3	13.91	75.0	45	127	74.5	125	0.5	1.04	11.62	-0.1	-26	38
DAY 4 (DB) .22H PST	125	72.7	13.65	71.0	47	115	74.7	125	-1.0	0.92	10.41	-2.1	-26	36
DAY 8 (DB) .4H PST	127	75.2	13.06	74.0	47	106	74.7	127	0.5	1.18	12.36	0.0	-26	48
DAY 8 (DB) .10H PST	126	73.1	13.63	73.0	45	113	74.4	126	-1.4	1.16	13.03	-1.0	-32	42
DAY 8 (DB) .22H PST	126	72.3	14.00	71.0	42	108	74.7	126	-2.5	1.18	13.21	-3.0	-31	43
DAY 15 (DB)	5	71.0	15.02	70.0	54	97	71.4	5	1.6	2.70	6.11	4.0	-13	11
DAY 15 (DB).PRE-DS	116	72.2	15.04	69.0	37	114	74.8	116	-2.6	1.16	12.42	-2.5	-22	55
DAY 15 (DB).1-2H PST	117	74.5	14.06	73.0	48	109	74.8	117	-0.4	1.13	12.68	-0.1	-30	41
DAY 15 (DB).4H PST	118	74.8	15.76	73.0	48	139	75.0	118	-0.2	1.22	13.27	-0.5	-30	40
DAY 29 (DB)	106	74.7	14.37	73.0	50	112	73.9	106	0.7	1.40	14.36	0.0	-25	63
DAY 36 (DB).PRE-DS	79	73.1	15.69	74.0	47	106	74.7	79	-1.6	1.64	13.71	-3.7	-31	43
DAY 36 (DB).1-2H PST	78	74.9	15.65	74.5	48	139	74.9	79	-0.0	1.69	14.02	-1.2	-33	44
DAY 36 (DB).4H PST	78	74.1	13.87	76.0	45	111	74.9	79	-0.8	1.62	14.36	-3.2	-37	41
DAY 43 (DB)	88	71.7	14.36	70.0	47	101	74.5	88	-1.8	1.36	11.79	-1.8	-32	35
END POINT (DB)	124	73.0	14.86	71.5	47	113	74.7	124	-1.8	1.32	13.76	-3.1	-34	63
BASE (OPEN)	124	72.8	14.63	71.5	47	113	74.7	124	-1.9	1.31	13.64	-3.1	-34	63
DAY 8 (OPEN)	123	82.8	15.32	83.0	52	135	74.6	123	8.2	1.32	12.45	8.1	-24	49
WEEK 1 (OPEN)	121	80.4	14.04	80.0	46	109	74.6	121	5.8	1.35	12.69	7.0	-22	42
WEEK 2 (OPEN)	121	77.2	13.33	79.0	47	108	74.4	122	3.5	1.06	11.66	4.3	-28	41
WEEK 4 (OPEN)	126	76.5	14.39	76.5	47	109	74.8	126	0.9	1.23	13.84	-0.5	-28	42
WEEK 8 (OPEN)	126	76.5	13.92	73.0	45	113	74.9	126	0.5	1.22	13.80	-0.5	-24	43
WEEK 16 (OPEN)	119	75.5	13.45	74.0	48	115	74.6	119	0.9	1.22	13.29	1.0	-31	42
WEEK 24 (OPEN)	78	76.6	14.39	73.5	48	109	73.8	78	1.8	1.62	14.41	1.7	-25	42
WEEK 40 (OPEN)	16	74.7	16.93	71.0	51	102	76.2	16	-0.7	3.39	13.13	0.1	-21	33
WEEK 52 (OPEN)	2	80.0	1.41	80.0	79	81	62.2	2	17.8	0.50	0.71	17.8	17	18
END POINT (OPEN)	124	76.4	14.31	74.0	49	109	74.7	124	0.7	1.30	13.63	0.0	-31	42
Pal/Pal <=1 months														
BASELINE (DB)	176	77.2	15.04	77.0	46	148								
AVERAGE EXPOSURE	176	78.1	13.56	77.7	49	134								
DAY 4 (DB) .4H PST	175	85.2	14.79	85.0	52	132	78.2	175	6.9	0.91	12.06	7.7	-19	48
DAY 4 (DB) .10H PST	171	84.2	14.86	84.0	50	130	77.7	171	7.2	0.82	10.92	7.0	-32	54
DAY 4 (DB) .22H PST	171	82.8	15.33	81.0	48	130	78.2	171	4.6	1.06	13.01	3.7	-32	48
DAY 8 (DB) .4H PST	175	81.8	13.31	80.0	50	130	78.0	175	3.8	0.89	11.76	5.1	-29	38
DAY 8 (DB) .10H PST	172	81.6	13.13	81.5	49	133	77.7	172	3.9	0.92	12.14	3.7	-33	41
DAY 8 (DB) .22H PST	177	81.8	15.67	81.0	44	128	77.9	177	3.9	1.06	13.93	3.7	-26	42
DAY 15 (DB)	24	73.8	14.97	73.5	51	114	76.2	24	-2.5	2.30	11.12	-1.7	-32	18

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DAY 15 (DB),PBR-DS	183	59.4	15.67	78.0	48	135	59.4	183	1.0	1.02	13.84	0.8	-58	45
DAY 15 (DB),1-2H PBT	160	82.2	14.04	83.0	56	119	78.6	160	3.9	1.16	14.11	3.7	-52	36
DAY 15 (DB),4H PBT	148	81.8	14.16	84.0	60	118	76.7	142	5.1	1.12	13.66	5.1	-40	37
DAY 22 (DB)	161	77.9	13.13	77.0	51	117	78.2	162	-0.4	1.08	13.43	-0.4	-51	36
DAY 36 (DB),PBR-DS	105	77.2	14.92	76.0	44	138	78.5	105	-1.1	1.32	13.48	-0.1	-38	38
DAY 36 (DB),1-2H PBT	107	78.1	13.87	79.0	50	112	78.2	107	-0.2	1.35	14.01	-0.1	-46	53
DAY 36 (DB),4H PBT	104	79.2	13.43	77.5	56	111	78.0	104	1.1	1.44	14.68	1.2	-52	42
DAY 43 (DB)	127	71.1	11.66	74.0	50	111	77.7	127	-1.6	1.04	11.77	-1.0	-52	36
END POINT (DB)	178	76.8	13.78	76.0	48	131	78.1	178	-1.1	0.93	13.45	-1.7	-52	33
WASH (OPEN)	178	76.8	13.78	76.0	48	131	78.1	178	-1.1	0.92	13.36	-1.6	-52	38
DAY 4 (OPEN)	167	78.5	12.95	78.0	47	119	77.5	167	1.0	1.02	12.74	0.1	-32	37
WEEK 1 (OPEN)	163	77.9	13.64	78.0	52	133	77.8	163	0.9	0.92	11.69	0.7	-52	36
WEEK 2 (OPEN)	136	79.2	12.91	79.0	51	139	78.3	136	1.9	1.19	13.89	1.1	-48	42
WEEK 4 (OPEN)	73	79.4	13.58	78.0	51	114	79.8	72	-0.4	1.37	11.64	-0.2	-42	37
WEEK 8 (OPEN)	13	71.4	10.86	78.0	58	93	77.8	12	-6.9	2.36	10.56	-6.2	-24	12
WEEK 16 (OPEN)	2	91.0	6.08	86.0	76	87	84.1	3	-1.1	6.07	10.63	-6.1	-6	11
WEEK 24 (OPEN)	1	89.0	4.34	89.0	86	92	88.7	2	10.1	9.34	13.20	10.1	1	20
END POINT (OPEN)	172	79.0	14.33	77.0	51	139	77.8	172	1.1	1.01	13.32	1.1	-48	44
Pali/Pali >3 months														
BASELINE (DB)	504	74.6	13.47	76.0	42	133								
AVERAGE PERIOD	504	76.6	13.16	76.2	42	128								
DAY 4 (DB),4H PBT	454	81.8	14.16	84.0	42	134	76.7	454	5.2	0.62	11.81	5.1	-32	54
DAY 4 (DB),10H PBT	482	81.6	13.86	81.0	46	119	76.7	482	5.0	0.67	12.64	5.0	-40	55
DAY 4 (DB),22H PBT	488	78.6	14.06	79.0	44	130	76.8	484	3.7	0.65	13.08	3.7	-22	58
DAY 8 (DB),4H PBT	501	81.7	13.61	83.0	47	131	76.7	501	6.0	0.62	11.60	5.1	-26	46
DAY 8 (DB),10H PBT	496	79.7	13.30	80.0	46	117	76.6	496	4.1	0.64	11.96	4.0	-27	40
DAY 8 (DB),22H PBT	499	77.2	13.84	76.0	44	139	76.7	498	1.6	0.66	12.24	0.7	-38	60
DAY 15 (DB)	24	76.0	15.64	73.5	46	113	70.8	24	4.1	1.83	10.66	5.8	-27	12
DAY 15 (DB),PBR-DS	460	76.4	14.40	76.0	38	133	76.0	460	0.4	0.63	12.71	0.0	-39	53
DAY 15 (DB),1-2H PBT	469	79.6	14.58	79.0	48	140	76.9	469	3.6	0.66	14.22	3.7	-44	61
DAY 15 (DB),4H PBT	468	81.2	14.98	80.0	42	144	76.9	469	5.3	0.66	14.15	4.1	-28	66
DAY 22 (DB)	472	76.6	13.54	76.0	44	120	76.7	472	-0.1	0.66	12.34	0.0	-40	46
DAY 36 (DB),PBR-DS	293	71.8	14.81	73.0	43	163	76.2	292	-3.1	0.67	13.31	-3.7	-51	75
DAY 36 (DB),1-2H PBT	293	76.4	13.82	78.0	44	139	76.0	291	-0.7	0.65	12.86	-0.7	-42	51
DAY 36 (DB),4H PBT	289	76.0	13.22	76.0	39	135	76.0	289	-0.1	0.63	12.60	0.0	-37	47
DAY 43 (DB)	414	73.8	13.35	73.0	44	113	76.9	413	-3.0	0.69	12.13	-3.7	-34	37
END POINT (DB)	506	74.3	13.48	73.0	44	117	76.6	504	-1.3	0.66	12.30	-3.0	-24	43
WASH (OPEN)	506	74.6	13.33	73.0	44	114	76.6	504	-1.6	0.65	12.17	-3.1	-24	37
DAY 4 (OPEN)	476	76.5	13.43	74.0	44	119	76.8	475	-0.2	0.69	12.56	-0.7	-41	42
WEEK 1 (OPEN)	487	76.2	12.84	74.0	42	110	76.6	486	-0.3	0.66	12.40	-0.7	-45	51
WEEK 2 (OPEN)	483	76.1	13.11	74.0	44	116	76.7	481	-0.6	0.67	12.53	-1.0	-38	51
WEEK 4 (OPEN)	453	74.7	13.70	74.0	42	119	76.7	453	-1.0	0.67	12.69	-1.0	-40	42
WEEK 8 (OPEN)	471	74.9	14.16	74.0	42	130	76.6	471	-0.9	0.68	12.86	-0.7	-42	42
WEEK 16 (OPEN)	276	76.6	13.17	74.0	44	115	76.2	274	-0.7	0.71	12.79	-0.7	-46	51
WEEK 24 (OPEN)	248	74.5	13.54	74.0	41	114	76.2	248	-1.8	0.87	13.69	-1.7	-38	35
WEEK 40 (OPEN)	60	77.4	14.92	76.5	52	113	74.6	60	1.7	1.92	13.66	1.8	-26	41
WEEK 52 (OPEN)	6	69.5	14.67	63.0	51	95	68.7	6	0.1	2.67	6.75	-0.1	-9	6
END POINT (OPEN)	504	74.4	14.02	73.0	41	119	76.6	503	-1.2	0.67	14.12	-1.7	-42	51
Olan/Pali <3 months														
BASELINE (DB)	108	76.1	14.04	73.5	51	111								
AVERAGE PERIOD	106	77.5	13.63	76.5	47	114								
DAY 4 (DB),4H PBT	106	79.4	17.44	76.0	48	118	77.2	106	3.1	1.15	11.92	1.0	-22	44
DAY 4 (DB),10H PBT	104	80.0	15.00	79.0	41	118	77.2	104	3.6	1.19	12.04	1.7	-27	44
DAY 4 (DB),22H PBT	100	76.0	15.67	76.0	44	115	76.6	100	-0.5	1.11	11.00	-0.7	-28	33
DAY 8 (DB),4H PBT	104	81.4	15.76	83.0	50	138	77.2	104	4.2	1.37	12.97	5.0	-29	42
DAY 8 (DB),10H PBT	103	80.2	15.68	80.0	46	119	77.2	103	3.1	1.18	12.08	3.0	-27	33
DAY 8 (DB),22H PBT	100	76.6	14.64	76.5	48	113	77.2	100	-0.6	1.10	12.02	-0.1	-32	41
DAY 15 (DB),PBR-DS	106	76.5	14.43	76.0	46	116	77.4	106	-1.0	1.13	12.17	-1.7	-30	33
DAY 15 (DB),1-2H PBT	101	81.0	15.19	81.0	48	117	77.2	101	3.8	1.30	12.84	4.1	-32	39
DAY 15 (DB),4H PBT	99	82.4	16.14	83.0	52	120	77.2	98	5.2	1.35	12.63	4.0	-21	40
DAY 22 (DB)	89	79.7	13.36	79.0	52	111	77.0	89	2.6	1.17	11.01	2.0	-26	38
DAY 36 (DB),PBR-DS	73	74.6	14.38	71.0	58	134	76.2	73	-1.7	1.10	10.31	-4.0	-31	39
DAY 36 (DB),1-2H PBT	76	76.8	14.89	76.0	47	138	76.6	76	0.1	1.19	11.39	0.2	-34	31
DAY 36 (DB),4H PBT	74	79.5	18.05	79.0	44	139	76.2	74	3.1	1.54	13.31	3.1	-21	45
DAY 43 (DB)	71	76.4	15.44	74.0	44	113	77.1	71	-0.7	1.46	12.17	-1.1	-22	42
END POINT (DB)	106	77.0	15.37	76.5	44	115	77.6	106	-0.6	1.34	12.72	-1.7	-32	42
WASH (OPEN)	106	76.6	14.75	76.0	44	113	77.6	106	-0.9	1.30	12.32	-1.0	-29	42
DAY 4 (OPEN)	89	86.9	16.40	88.0	58	132	77.9	89	8.9	1.55	14.63	9.1	-27	44
WEEK 1 (OPEN)	90	81.6	15.00	81.0	52	127	76.8	90	5.8	1.30	12.36	6.1	-22	46
WEEK 2 (OPEN)	78	81.9	13.67	80.0	54	142	77.1	78	4.7	1.48	13.11	3.8	-26	47
WEEK 4 (OPEN)	66	76.8	14.09	76.0	51	134	77.8	66	-3.0	1.84	13.66	-4.0	-30	32
WEEK 8 (OPEN)	21	79.9	13.59	81.0	60	102	77.9	22	3.1	2.82	13.16	3.4	-34	29
WEEK 16 (OPEN)	1	64.0		64.0	64	64	86.0	1	-21.0			-21.0	-21	-21
END POINT (OPEN)	102	78.3	15.86	76.0	50	136	77.6	102	0.7	1.32	13.63	-0.7	-27	42
Olan/Pali >3 months														
BASELINE (DB)	142	76.2	13.39	76.0	48	114								
AVERAGE PERIOD	142	77.6	11.43	78.0	49	111								
DAY 4 (DB),4H PBT	139	79.2	14.82	77.0	46	134	77.6	139	1.8	1.09	12.83	1.0	-32	40
DAY 4 (DB),10H PBT	136	80.1	14.11	78.0	47	116	77.4	136	1.7	1.15	13.39	1.7	-20	51
DAY 4 (DB),22H PBT	138	76.9	13.49	76.0	47	111	77.4	138	-1.5	1.02	12.03	-1.1	-22	34
DAY 8 (DB),4H PBT	139	79.2	12.76	78.0	52	111	77.6	139	1.7	1.14	13.48	1.7	-28	32
DAY 8 (DB),10H PBT	138	79.2	12.81	80.0	50	114	77.5	138	1.9	1.15	13.64	1.7	-42	61
DAY 8 (DB),22H PBT	141	76.6	12.30	76.0	42	103	77.6	141	-0.9	1.01	11.95	-1.0	-28	35
DAY 15 (DB),PBR-DS	140	76.4	12.84	76.0	51	103	77.6	140	-1.1	0.99	11.78	-1.0	-25	34
DAY 15 (DB),1-2H PBT	139	80.4	14.37	80.0	52	116	77.5	139	3.9	1.34	14.57	3.0	-25	49
DAY 15 (DB),4H PBT	139	80.8	14.63	81.0	54	114	77.5	139	3.3	1.32	15.18	3.7	-24	44
DAY 22 (DB)	126	79.8	12.74	79.0	55	122	77.2	126	3.6	1.18	14.48	3.6	-34	60
DAY 36 (DB),PBR-DS	121	76.0	12.45	74.0	50	115	77.2	121	-3.2	1.12	13.56	-3.1	-35	32
DAY 36 (DB),1-2H PBT	120	76.1	12.64	76.0	48	105	77.1	120	-1.0	1.10	13.13	-0.7	-29	37
DAY 36 (DB),4H PBT	120	76.6	13.89	76.5	54	113	77.1	120	-0.5	1.29	13.47	-0.1	-29	37
DAY 43 (DB)	121	74.4	11.67	74.5	52	109	77.0	122	-3.6	1.10	12.30	-3.0	-26	29
END POINT (DB)	142	76.8	11.60	76.0	52	109	77.5	142	-1.7	1.02	12.35	-1.7	-26	31
WASH (OPEN)	142	76.6	11.42	76.0	52	109	77.5	142	-1.9	1.00	11.94	-1.7	-25	29
DAY 4 (OPEN)	116	84.9	13.36	86.0	56	115	77.2	116	7.6	1.33	14.14	8.0	-24	45
WEEK 1 (OPEN)	116	82.6	13.67	81.0	56	117	77.4	116	5.1	1.19	13.82	4.1	-37	53
WEEK 2 (OPEN)	113	79.4	13.23	76.5	55	109	77.2	113	1.7	1.34	13.96	1.7	-22	35
WEEK 4 (OPEN)	100	78.4	13.86	77.0	48	114	77.2	100	1.2	1.38	13.93	0.0	-26	38
WEEK 8 (OPEN)	100	78.4	14.82	77.5	48	126	77.5	100	0.9	1.36	14.86	-0.5	-32	62
WEEK 16 (OPEN)	124	77.8	15.19	74.0	47	137	77.5	124	0.2	1.30	14.61	0.3	-20	53
WEEK 24 (OPEN)	94	74.9	14.53	74.0	45	115	77.0	94	-3.3	1.71	15.69	-3.2	-34	41
WEEK 40 (OPEN)	16	72.2	17.55	68.5	51	106	77.1	16	-4.9	2.86	11.44	-4.2	-32	12
END POINT (OPEN)	142	77.1	15.00	76.0	45	119	77.6	142	-0.4	1.31	14.50	-0.7	-34	41

Note the DB-olanzapine/OL-Pal subgroups showed group mean increases in heart rate after switching from DB olanzapine to OL-Pal. It is not clear if this observation is reflecting an interruption of treatment between the DB and OL trials, or a differential drug or dose-level effect on heart rate between these two drugs (e.g. Pal may induce greater effects on heart rate than olanzapine or the dose-level of Pal may results in greater exposure to active drug than exposure to olanzapine at the doses employed). However, the dose-equivalency between olanzapine is Pal is not clear. Therefore, results of active drug comparisons are difficult to interpret.

Similar observations are described in this review under Section 7.1.8 on vital sign results.

II. Clinically Unremarkable Pal-Group Mean Increase in PR Interval *As observed in the short-term trial dataset, the group mean PR interval numerically increased (from the pre-dose average value) during Pal treatment in subjects switched from DB Olanzapine to OL Pal treatment and subjects switched from DB-placebo to OL Pal. However, the group mean increases were clinically unremarkable in the magnitude of this apparent drug-effect and mean increases generally did not appear to increase over time for at least up to week 24 of OL treatment (where samples sizes were over 50 subjects).*

III. Pal Group Mean Decreases in RR Interval
As observed in the short-term trial dataset, RR interval results show group mean decreases in RR interval as shown below (selected sections are taken from appendix 2.7.4.6.2.2 of the SCS). The numerical mean decreases generally, did not appear to increase in magnitude over time during OL treatment for at least up to week 24 of OL treatment (where samples sizes were over 50 subjects).

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

Output EGCGD1, ECG, Means and Mean Changes from Pre-treatment over Time - Open-Label Phase

Analysis Set: Safety

							Base	change from average predose					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SD	SD	Med	Min	Max
RRAVT RATE (beats/min)													

XR (mg)														
Pla/Pall <=1 months														
BASELINE (DB)	107	827.1	139.81	621.0	688 1277									
AVERAGE PREDOSE	107	821.8	130.58	611.7	632 1162									
DAY 4 (DB),4H PST	106	817.7	128.92	611.0	671 1200	824.4	105	-16.7	12.39	134.5%	-15.1	-424	261	
DAY 4 (DB),10H PST	104	828.1	142.66	616.5	617 1168	821.1	104	-5.0	13.30	134.63	-11.0	-358	331	
DAY 4 (DB),22H PST	101	831.7	141.03	627.0	688 1268	836.4	102	35.1	15.72	139.43	44.7	-315	398	
DAY 8 (DB),4H PST	106	828.5	142.17	627.5	696 1273	832.5	106	-4.0	13.36	137.44	-1.8	-308	462	
DAY 8 (DB),10H PST	106	816.9	136.54	611.0	625 1132	832.8	106	-16.0	12.32	134.31	-21.7	-382	314	
DAY 8 (DB),22H PST	106	842.2	146.40	646.0	683 1233	832.8	106	29.5	15.06	139.67	21.2	-288	498	
DAY 15 (DB)	21	824.2	136.67	656.0	682 1214	852.2	21	71.0	17.65	134.34	47.1	-335	368	
DAY 15 (DB),PRE-DS	86	840.4	154.44	667.0	622 1214	827.3	86	13.4	16.80	138.68	13.0	-337	418	
DAY 15 (DB),1-2H PST	86	799.5	148.63	709.0	660 1200	828.1	86	-28.6	16.02	147.73	-34.0	-480	268	
DAY 15 (DB),4H PST	86	801.2	143.04	709.0	660 1295	827.3	86	-26.8	16.12	148.69	-29.1	-430	332	
DAY 29 (DB)	86	827.8	146.65	611.0	622 1176	830.0	86	-3.3	14.86	134.38	-16.0	-342	337	
DAY 36 (DB),PRE-DS	36	851.7	158.37	861.0	694 1262	859.2	36	24.4	22.89	137.35	18.0	-247	355	
DAY 36 (DB),1-2H PST	36	801.4	138.68	794.5	694 1111	823.4	36	-23.1	20.04	133.66	-25.9	-338	269	
DAY 36 (DB),4H PST	36	819.7	138.47	811.0	694 1132	824.7	36	-16.0	12.41	134.46	-17.7	-336	349	
DAY 43 (DB)	52	836.8	146.32	683.0	682 1214	852.1	52	13.7	19.68	141.36	17.0	-274	402	
END POINT (DB)	107	821.6	143.27	621.0	688 1214	821.6	107	-10.1	14.46	149.68	-13.0	-346	403	
BASE (OPEN)	107	829.6	145.77	621.0	688 1214	821.6	107	-8.2	14.16	147.46	-9.7	-343	469	
DAY 4 (OPEN)	97	760.5	167.01	741.0	465 1213	824.7	97	-78.2	16.72	164.83	-66.1	-462	408	
WEEK 1 (OPEN)	96	747.8	136.98	741.0	526 1071	824.0	96	-86.3	13.46	131.16	-86.1	-406	284	
WEEK 2 (OPEN)	90	767.0	129.78	760.0	526 1111	824.7	90	-67.7	13.42	137.17	-71.7	-320	286	
WEEK 4 (OPEN)	74	817.6	178.27	758.5	541 1413	821.4	74	-13.8	17.32	149.68	7.0	-346	492	
WEEK 8 (OPEN)	36	808.3	161.11	789.0	522 1214	821.7	36	6.6	22.21	137.39	-3.0	-326	349	
WEEK 16 (OPEN)	1	989.0		989.0	989 989	702.7	1	286.3			286.3	286	286	
END POINT (OPEN)	106	813.2	152.91	900.0	522 1412	824.4	106	-21.2	14.32	146.36	-23.5	-346	498	
Pla/Pall >1 months														
BASELINE (DB)	128	840.3	142.96	827.5	526 1214									
AVERAGE PREDOSE	128	828.2	134.72	801.8	602 1212									
DAY 4 (DB),4H PST	125	807.7	153.15	789.0	465 1214	826.8	126	-18.0	11.33	134.69	-21.7	-462	317	
DAY 4 (DB),10H PST	125	828.9	157.82	900.0	472 1213	831.5	125	-3.6	12.32	135.47	-3.7	-474	460	
DAY 4 (DB),22H PST	125	854.1	160.04	945.0	532 1272	829.7	125	24.4	10.91	131.92	24.6	-284	506	
DAY 8 (DB),4H PST	127	822.6	146.77	911.0	566 1272	829.2	127	-6.7	12.42	139.92	-1.3	-431	404	
DAY 8 (DB),10H PST	126	850.2	162.13	921.0	531 1213	831.1	126	19.1	12.42	140.71	8.1	-336	431	
DAY 8 (DB),22H PST	125	849.9	164.54	946.0	566 1295	828.7	125	21.2	12.05	141.65	28.7	-339	386	
DAY 15 (DB)	9	851.4	162.34	867.0	618 1071	858.6	9	-7.1	34.84	104.65	-62.7	-105	300	
DAY 15 (DB),PRE-DS	116	846.0	173.14	870.0	526 1422	828.2	116	27.7	14.36	154.69	14.2	-269	749	
DAY 15 (DB),1-2H PST	117	826.2	163.87	911.0	550 1500	827.9	117	7.4	14.86	160.68	-3.7	-487	627	
DAY 15 (DB),4H PST	118	826.2	170.94	923.0	465 1500	826.4	118	9.9	14.38	154.03	-3.7	-394	617	
DAY 29 (DB)	106	823.2	158.43	922.0	526 1200	827.6	106	-4.4	15.76	161.44	-8.0	-692	292	
DAY 36 (DB),PRE-DS	79	859.8	190.33	911.0	631 1277	830.4	79	29.4	18.54	164.76	33.7	-500	432	
DAY 36 (DB),1-2H PST	78	836.6	176.83	911.0	584 1260	827.2	78	8.7	19.39	170.40	5.5	-579	446	
DAY 36 (DB),4H PST	78	840.2	168.70	789.0	641 1232	827.2	78	12.1	20.25	178.75	11.8	-567	434	
DAY 43 (DB)	58	871.2	172.43	917.5	534 1277	821.0	58	38.8	14.58	140.67	40.1	-320	350	
END POINT (DB)	128	836.7	176.44	915.0	526 1277	828.2	128	28.4	12.58	142.37	31.6	-692	367	
BASE (OPEN)	128	857.8	174.09	919.0	526 1272	828.2	128	29.6	12.92	147.60	31.6	-692	367	
DAY 4 (OPEN)	123	750.2	141.02	733.0	480 1132	830.8	123	-80.5	11.30	134.34	-78.0	-526	265	
WEEK 1 (OPEN)	121	770.6	142.53	760.0	550 1204	830.2	121	-59.7	12.39	136.30	-66.0	-428	339	
WEEK 2 (OPEN)	121	794.9	148.46	769.0	554 1273	831.7	122	-37.0	12.31	135.54	-46.9	-443	404	
WEEK 4 (OPEN)	126	822.2	163.64	794.5	554 1277	826.5	126	-4.3	13.52	154.35	-0.8	-472	460	
WEEK 8 (OPEN)	126	822.1	162.55	921.0	604 1203	826.2	126	-4.1	12.38	149.58	-1.0	-412	482	
WEEK 16 (OPEN)	115	819.4	149.61	911.0	532 1234	830.1	113	-10.7	12.01	141.54	-9.7	-440	466	
WEEK 24 (OPEN)	78	821.0	161.72	916.5	550 1234	829.4	78	-18.4	18.71	165.16	-19.7	-670	367	
WEEK 40 (OPEN)	15	841.9	184.12	933.0	554 1176	826.0	15	16.9	37.14	144.01	-19.0	-197	551	
WEEK 52 (OPEN)	1	750.0	12.73	750.0	741 759	975.0	2	-225.0	8.67	12.26	-225.0	-234	-216	
END POINT (OPEN)	128	821.4	162.54	911.0	550 1234	828.2	128	-6.9	12.12	142.78	-1.8	-670	336	
Pall/Pall <=1 months														
BASELINE (DB)	178	806.6	160.62	779.0	402 1204									
AVERAGE PREDOSE	178	796.6	136.67	790.0	452 1238									
DAY 4 (DB),4H PST	175	716.9	126.06	706.0	448 1132	795.2	175	-78.4	9.39	104.35	-73.1	-359	164	
DAY 4 (DB),10H PST	171	728.0	127.99	714.0	442 1260	789.6	171	-71.8	7.65	99.67	-71.0	-357	354	
DAY 4 (DB),22H PST	171	750.0	143.82	713.0	580 1260	794.0	171	-44.0	6.79	112.74	-39.8	-342	338	
DAY 8 (DB),4H PST	175	724.9	125.05	706.0	462 1300	796.4	175	-61.9	9.62	132.73	-63.0	-372	261	
DAY 8 (DB),10H PST	173	727.1	122.82	718.5	488 1234	800.5	173	-63.4	9.31	129.43	-69.5	-454	265	
DAY 8 (DB),22H PST	177	761.8	156.35	741.0	468 1264	797.3	177	-36.0	9.86	131.45	-10.1	-422	383	
DAY 15 (DB)	24	844.6	170.60	916.5	526 1176	817.1	24	27.6	17.09	132.72	11.1	-226	361	
DAY 15 (DB),PRE-DS	162	794.0	160.40	769.0	488 1234	792.5	162	-8.5	9.63	137.61	-13.7	-412	366	
DAY 15 (DB),1-2H PST	160	750.6	132.34	721.0	584 1091	792.2	160	-41.7	10.72	132.11	-46.7	-380	279	
DAY 15 (DB),4H PST	149	727.5	131.99	714.0	508 1200	789.2	149	-51.8	10.46	137.68	-46.7	-446	259	
DAY 29 (DB)	162	791.2	135.17	779.0	613 1176	791.2	162	-0.0	20.32	137.32	1.1	-306	333	
DAY 36 (DB),PRE-DS	106	804.1	149.07	789.0	436 1264	790.6	106	13.6	13.34	137.09	-0.7	-269	362	
DAY 36 (DB),1-2H PST	107	789.2	130.01	769.0	492 1260	792.2	107	-2.1	12.48	132.04	-1.2	-380	296	
DAY 36 (DB),4H PST	104	776.2	133.17	774.0	541 1071	795.2	104	-20.0	12.32	134.85	-24.0	-352	279	
DAY 43 (DB)	127	817.2	122.75	811.8	496 1200	790.6	127	18.7	10.62	119.60	21.0	-295	356	
END POINT (DB)	178	802.7	131.40	800.0	496 1260	796.6	178	6.2	9.38	125.36	11.1	-311	396	
BASE (OPEN)	178	802.4	131.58	800.0	496 1260	796.6	178	6.0	9.35	123.47	11.1	-295	396	
DAY 4 (OPEN)	167	785.4	132.83	769.0	504 1273	801.1	167	-15.7	10.37	132.44	-9.0	-377	282	
WEEK 1 (OPEN)	163	791.2	135.33	769.0	451 1184	798.1	163	-8.9	9.02	116.20	-11.7	-259	339	
WEEK 2 (OPEN)	116	776.4	122.08	769.0	492 1176	792.2	116	-16.5	11.46	132.61	-11.0	-439	280	
WEEK 4 (OPEN)	73	777.0	131.53	769.0	526 1176	795.4	73	1.6	12.18	111.18	-1.0	-352	380	
WEEK 8 (OPEN)	11	864.7	114.48	867.5	645 1014	802.2	12	53.4	27.04	119.22	46.2	-217	247	
WEEK 16 (OPEN)	3	726.7	58.92	696.0	690 782	724.7	3	1.0	52.37	92.44	51.0	-106	99	
WEEK 24 (OPEN)	1	696.0	26.16	696.0	696 696	698.2	2	-78.7	71.32	100.89	-78.7	-150	-7	
END POINT (OPEN)	173	791.1	134.60	779.0	492 1176	795.6	173	-14.9	10.04	132.17	-19.0	-439	280	
Pall/Pall >1 months														
BASELINE (DB)	504	822.3	160.16	900.0	402 1439									
AVERAGE PREDOSE	504	821.2	132.13	796.8	511 1439									
DAY 4 (DB),4H PST	454	727.0	134.77	714.0	484 1295	820.7	454	-93.7	5.44	130.84	-91.8	-542	178	
DAY 4 (DB),10H PST	483	758.5	135.32	741.0	508 1264	820.2	483	-61.8	5.55	130.67	-61.7	-474	384	
DAY 4 (DB),22H PST	484	779.5	146.72	759.0	560 1264	819.4	484	-39.9	5.80	137.65	-30.7	-431	434	
DAY 8 (DB),4H PST	501	796.2	131.86	781.0	496 1273	828.7	501	-64.5	5.42	131.35	-60.7	-425	310	
DAY 8 (DB),10H PST	496	774.1	132.04	760.0	512 1264	821.9	496	-47.5	5.67	126.35	-43.0	-428	342	
DAY 8 (DB),22H PST	492	802.7	147.74	789.0	465 1264	820.4	492	-18.1	5.91	131.92	-16.4	-328	383	
DAY 15 (DB)	34	832.9	178.58	827.5	531 1204	832.2	34	-29.4	18.97	136.44	-31.5	-386	276	
DAY 15 (DB),PRE-DS	468	811.0	152.17	800.0	488 1439	817.8	468	-8.5	6.17	136.48	-8.3	-464	608	
DAY 15 (DB),1-2H PST	469	791.6	152.01	769.0	429 1500	818.1	469	-26.6	7.04	160.75	-28.2	-669	464	
DAY 15 (DB),4H PST	468	761.1	143.64	760.0	417 1413	816.9	468	-51.7	6.80	145.66	-46.7	-739	582	
DAY 29 (DB)	473	821.9	156.39	900.0	580 1264	820.9	472	0.6	6.17	133.54	-8.4	-442	432	
DAY 36 (DB),PRE-DS	393	841.9	162.37	813.0	558 1295	815.5	392	28.4	7.32	141.39	21.8	-366	431	
DAY 36 (DB),1-2H PST	391	822.7	151.81	811.0	432 1264	817.0	391	8.9	6.94	133.33	3.7	-292	434	
DAY 36 (DB),4H PST	389	814.7	146.62	800.0	444 1519	816.9	389	-2.2	6.92	136.67	-7.8	-347	604	
DAY 43 (DB)	434	839.6	160.69	913.0	521 1264	819.2	433	20.1	6.37	132.62	24.0	-421	439	

END POINT (DB)	505	831.6	158.40	923.0	517	1264	821.2	504	11.4	6.04	136.67	17.8	-491	418
BASE (OPEN)	504	827.6	158.09	911.0	526	1264	821.2	505	16.0	6.54	134.05	21.0	-491	418
DAY 4 (OPEN)	476	819.9	148.37	911.0	504	1264	819.9	476	0.0	6.67	142.24	1.1	-474	467
WEEK 1 (OPEN)	467	819.4	139.31	911.0	500	1256	821.9	486	-2.4	6.35	135.47	4.2	-515	482
WEEK 2 (OPEN)	483	824.1	145.63	911.0	517	1264	820.6	481	3.4	6.12	134.33	3.7	-446	418
WEEK 4 (OPEN)	493	820.5	152.03	911.0	485	1256	820.6	493	9.9	6.31	137.97	6.0	-455	459
WEEK 8 (OPEN)	473	820.2	152.62	911.0	462	1256	819.2	471	10.7	6.69	143.04	3.7	-413	535
WEEK 16 (UPEN)	376	820.2	148.09	911.0	532	1264	813.8	374	6.1	7.52	154.44	1.1	-579	619
WEEK 24 (UPEN)	348	822.2	155.42	911.0	526	1462	812.6	348	15.8	8.87	155.46	14.0	-506	539
WEEK 40 (UPEN)	50	801.4	164.75	784.0	504	1112	829.1	50	-25.6	30.06	141.80	-19.7	-147	348
WEEK 52 (UPEN)	6	837.6	148.07	963.0	632	984	838.4	6	-0.8	36.48	81.67	1.7	-100	135
END POINT (OPEN)	504	826.2	160.59	923.0	504	1462	821.2	503	13.9	7.04	167.85	16.0	-578	538
Olan/Pal1 <=1 months														
BASELINE (DB)	106	814.9	148.59	916.5	541	1176								
AVERAGE EXPOSUR	106	804.0	145.12	796.0	538	1071								
DAY 4 (DB),4H PST	105	790.9	166.48	789.0	469	1260	806.0	105	-15.1	11.12	114.00	-26.0	-321	237
DAY 4 (DB),10H PST	104	796.3	156.17	769.0	462	1463	806.9	104	-10.6	14.49	147.72	-21.6	-512	432
DAY 4 (DB),22H PST	100	822.9	176.63	800.0	532	1364	811.1	100	10.8	13.11	131.12	3.9	-403	470
DAY 8 (DB),4H PST	104	746.2	163.11	731.0	469	1260	807.0	104	-61.8	17.72	139.90	-44.2	-465	343
DAY 8 (DB),10H PST	103	777.0	161.67	760.0	504	1364	807.1	105	-30.2	12.12	125.34	-34.0	-434	389
DAY 8 (DB),22H PST	100	811.5	166.34	784.5	531	1260	807.5	100	4.1	13.12	131.25	-3.7	-484	335
DAY 15 (DB),PRE-DS	105	812.4	164.52	789.0	517	1364	801.9	105	8.6	15.91	162.64	23.1	-612	352
DAY 15 (DB),1-2H PST	101	767.8	149.31	741.0	512	1260	807.2	101	-29.3	14.34	144.12	-18.7	-532	362
DAY 15 (DB),4H PST	99	758.2	167.43	731.0	500	1164	807.7	99	-49.4	12.62	134.55	-49.1	-591	292
DAY 29 (DB)	89	774.8	173.39	769.0	541	1164	807.7	89	-32.9	12.62	119.11	-28.5	-472	343
DAY 36 (DB),PRE-DS	73	821.9	161.31	946.0	526	1260	816.8	73	16.1	13.62	116.35	16.0	-350	292
DAY 36 (DB),1-2H PST	76	812.2	166.79	789.5	508	1256	813.6	76	-1.5	15.36	133.92	-6.5	-418	412
DAY 36 (DB),4H PST	74	795.1	166.17	769.5	465	1264	816.5	74	-21.1	16.56	145.79	-12.2	-358	348
DAY 43 (DB)	71	817.8	163.85	811.0	531	1264	808.6	71	8.4	15.80	132.14	24.2	-388	334
END POINT (DB)	106	810.2	162.83	784.5	532	1264	804.0	106	6.3	17.34	134.36	15.2	-398	362
BASE (OPEN)	106	812.8	159.17	800.0	531	1264	804.0	106	8.9	12.93	133.58	15.8	-398	336
DAY 4 (OPEN)	89	718.7	161.11	681.0	482	1260	800.8	89	-83.1	16.33	144.34	-84.1	-511	394
WEEK 1 (OPEN)	90	741.0	137.01	731.0	472	1112	810.8	90	-69.8	12.39	116.09	-63.2	-395	328
WEEK 2 (OPEN)	78	752.2	117.04	750.0	482	1111	806.9	78	-54.6	14.00	122.63	-40.8	-416	261
WEEK 4 (OPEN)	66	817.3	143.62	800.0	526	1176	802.2	66	15.0	10.06	148.80	40.0	-426	337
WEEK 8 (OPEN)	21	776.5	149.15	716.5	588	1200	797.7	22	-23.2	18.12	131.90	-26.1	-281	241
WEEK 16 (UPEN)	1	928.0		928.0	928	928	796.7	1	221.1			221.3	231	231
END POINT (OPEN)	103	796.7	154.55	789.0	517	1200	804.0	103	-7.3	17.61	138.68	-1.7	-395	277
Olan/Pal1 >1 months														
BASELINE (DB)	143	811.8	147.60	789.0	536	1259								
AVERAGE EXPOSUR	143	798.6	121.83	778.7	544	1242								
DAY 4 (DB),4H PST	139	781.8	160.30	779.0	526	1304	729.1	139	-15.1	11.07	130.53	-24.0	-381	109
DAY 4 (DB),10H PST	136	771.5	134.43	769.0	522	1277	800.1	136	-28.6	11.27	131.43	-21.2	-463	165
DAY 4 (DB),22H PST	138	816.2	148.60	800.0	541	1277	800.0	138	16.2	10.71	125.79	16.8	-360	335
DAY 8 (DB),4H PST	139	737.7	130.34	769.0	541	1164	798.5	139	-20.9	11.62	136.81	-26.3	-364	104
DAY 8 (DB),10H PST	138	776.6	129.60	760.0	526	1200	799.1	139	-21.5	11.70	137.43	-24.7	-444	432
DAY 8 (DB),22H PST	141	804.2	138.81	769.0	532	1256	798.1	141	6.1	10.50	132.43	-3.1	-356	497
DAY 15 (DB),PRE-DS	140	806.4	139.85	789.0	550	1176	798.9	140	6.6	20.79	137.68	7.0	-350	412
DAY 15 (DB),1-2H PST	139	769.7	139.90	760.0	517	1132	798.6	139	-28.7	12.60	148.66	-24.0	-443	463
DAY 15 (DB),4H PST	139	767.1	141.97	741.0	526	1111	798.6	139	-31.4	12.52	152.34	-27.0	-415	415
DAY 29 (DB)	128	771.0	132.91	769.0	492	1052	801.6	128	-30.6	12.68	143.52	-31.5	-495	130
DAY 36 (DB),PRE-DS	122	822.2	137.45	811.0	522	1200	800.9	121	21.4	12.18	146.03	33.1	-197	331
DAY 36 (DB),1-2H PST	120	810.0	134.80	800.0	571	1260	801.7	120	8.3	12.67	137.63	1.0	-259	400
DAY 36 (DB),4H PST	120	806.2	134.11	784.0	531	1111	801.7	120	3.6	12.56	141.85	-1.1	-325	199
DAY 43 (DB)	123	826.6	128.04	806.5	550	1164	802.6	123	23.7	11.68	137.91	29.5	-295	307
END POINT (DB)	143	810.1	125.54	789.0	550	1164	798.6	143	11.6	10.72	138.36	23.0	-356	307
BASE (OPEN)	143	813.0	134.84	789.0	550	1164	798.6	143	13.6	10.41	134.46	23.1	-295	307
DAY 4 (UPEN)	136	724.9	117.39	706.0	532	1051	800.2	136	-75.5	11.98	139.19	-83.0	-492	278
WEEK 1 (OPEN)	136	746.9	122.17	741.0	515	1071	800.2	136	-54.4	11.02	139.39	-43.7	-442	283
WEEK 2 (OPEN)	133	736.8	130.60	764.0	554	1051	800.4	132	-63.6	11.76	135.31	-21.6	-463	192
WEEK 4 (OPEN)	140	789.5	142.44	779.0	526	1234	800.2	140	-10.9	12.10	144.36	-9.0	-369	162
WEEK 8 (OPEN)	140	792.8	161.35	774.0	441	1260	798.3	140	-5.4	12.91	162.73	-1.7	-462	482
WEEK 16 (UPEN)	124	800.8	164.92	811.0	472	1277	798.9	124	1.8	12.65	160.93	-16.2	-810	167
WEEK 24 (UPEN)	94	822.4	166.30	811.0	522	1232	806.7	94	15.7	14.82	172.59	33.1	-355	483
WEEK 40 (UPEN)	16	876.4	202.64	876.5	671	1176	807.9	16	68.4	35.12	140.49	33.6	-304	442
END POINT (OPEN)	143	808.1	161.19	800.0	504	1232	798.6	143	9.6	12.79	163.06	8.7	-336	483

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IV. QTc Interval Results

A. Pal Group Mean QTcBazett's Interval Results *See selected results below showing group mean increases in QTc Bazetts Interval during OL Pal treatment for the subgroups that previously received DB placebo or DB olanzapine in the lead-in studies. It is difficult to interpret the magnitude of QTcB prolongation in the subgroups showing this effect given the previously discussed limitations using the QTcB method.*

Negligible to absent QTB prolongation occurred during OL Pal treatment in the subgroup that previously received DB Pal treatment.

Failure to show remarkable group mean increases during OL Pal in the subgroup that previously received DB Pal may be due to the timing of the assessments which was not held constant relative to dosing and varied across subjects given the nature of this outpatient OL longterm study (as previously discussed under Section 7.1.X. of this review). These OL studies

were not designed to capture ECG drug effects at Tmax (given the outpatient nature of the study and assessment time-point variation across individuals and relative to dosing at least for outpatient study days). Furthermore, a flexible dose regimen was employed and finally a placebo control group was not included.

Results below are taken form appendix 2.7.4.6.2.2 of the SCS.

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

Output ECGV01. 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	SD	Med	Min	Max
QTC INTERVAL BAZETT (ms)													
Pla/Pali <=3 months													
BASELINE (DB)	107	411.5	23.79	413.0	342	462							
AVERAGE PREDOSE	107	412.2	22.06	413.7	360	474							
DAY 4 (DB),4H PST	106	412.0	21.86	410.0	378	474	412.7	106	-0.7	1.64	16.86	-1.0	-28	53
DAY 4 (DB),10H PST	104	415.0	21.91	411.0	366	471	413.1	104	-1.1	1.75	18.17	-1.7	-48	74
DAY 4 (DB),22H PST	103	412.1	23.03	411.0	352	472	413.1	102	-1.0	1.68	16.12	-1.7	-32	47
DAY 8 (DB),4H PST	106	410.3	22.12	411.5	335	456	412.6	106	-2.1	1.65	17.11	-1.8	-45	62
DAY 8 (DB),10H PST	106	412.4	23.30	414.0	341	468	412.5	106	-0.0	1.82	18.73	-1.2	-44	69
DAY 8 (DB),22H PST	106	413.0	23.30	413.0	358	469	412.5	106	0.5	1.82	18.73	0.7	-44	75
DAY 15 (DB)	21	421.7	19.19	421.0	370	451	427.9	21	-6.2	4.60	21.08	-7.7	-64	33
DAY 15 (DB),PRE-DS	84	408.6	25.30	407.5	351	488	409.1	84	-0.6	2.30	19.32	1.8	-60	63
DAY 15 (DB),1-2H PST	85	406.9	23.70	406.0	357	492	409.4	85	-1.8	2.12	19.61	-1.1	-46	62
DAY 15 (DB),4H PST	85	408.7	22.33	409.0	357	483	408.7	85	0.1	1.96	18.04	-0.1	-37	65
DAY 29 (DB)	85	416.0	23.33	416.0	362	468	413.9	85	1.1	2.05	18.94	3.1	-52	69
DAY 36 (DB),PRE-DS	16	406.1	27.30	401.0	349	462	406.6	16	-1.5	3.44	30.66	-3.2	-46	49
DAY 36 (DB),1-2H PST	16	407.7	24.24	409.5	344	460	406.8	16	1.9	3.14	30.00	1.9	-40	35
DAY 36 (DB),4H PST	16	407.8	22.83	408.5	364	458	406.0	16	1.9	2.92	28.38	-1.3	-32	64
DAY 43 (DB)	83	408.6	22.99	407.0	361	468	409.8	83	-1.1	2.07	18.81	-3.1	-58	34
MAXIMUM VALUE (DB)	107	432.8	21.39	434.0	382	492	412.2	107	20.5	1.61	16.70	18.3	-10	75
END POINT (DB)	107	413.9	23.71	416.0	341	468	412.2	107	1.6	1.76	18.19	3.0	-58	67
BASE (OPEN)	107	413.6	22.86	416.0	341	460	412.2	107	1.5	1.72	17.82	1.6	-58	67
DAY 4 (OPEN)	96	422.2	23.76	427.0	366	477	412.6	96	9.4	2.01	19.67	10.7	-46	66
WEEK 1 (OPEN)	96	421.2	25.45	423.0	368	490	411.8	96	9.5	1.94	18.87	11.3	-47	53
WEEK 2 (OPEN)	89	420.2	23.12	423.0	352	478	413.7	89	6.6	1.82	17.25	6.7	-38	68
WEEK 4 (OPEN)	73	414.2	24.74	416.0	328	466	414.4	73	-0.2	2.60	21.34	3.3	-57	42
WEEK 8 (OPEN)	16	418.9	24.09	417.0	367	455	416.2	16	2.6	4.34	34.82	3.3	-62	70
WEEK 16 (OPEN)	1	402.0		402.0	402	402	418.7	1	-16.7			-16.7	-17	-17
MAXIMUM VALUE (OPEN)	106	422.4	23.49	421.5	352	459	412.2	106	20.2	1.62	16.61	18.8	-39	70
END POINT (OPEN)	106	414.2	25.67	416.0	328	459	412.2	106	3.6	2.09	30.50	3.8	-57	70
Pla/Pali >3 months														
BASELINE (DB)	128	406.3	23.17	408.0	342	459								
AVERAGE PREDOSE	128	407.0	20.19	406.7	339	455								
DAY 4 (DB),4H PST	125	407.0	21.45	407.0	353	455	407.2	125	-0.2	1.42	15.97	-1.0	-42	44
DAY 4 (DB),10H PST	125	406.1	22.12	406.0	341	451	406.9	125	-1.8	1.68	17.70	-1.7	-59	49
DAY 4 (DB),22H PST	125	406.2	22.69	406.0	346	460	407.2	125	-1.0	1.46	16.34	-1.7	-45	49
DAY 8 (DB),4H PST	127	404.4	21.62	406.0	335	447	407.0	127	-2.6	1.49	16.79	-1.0	-59	42
DAY 8 (DB),10H PST	126	403.9	22.91	403.0	340	455	406.9	126	-3.1	1.64	18.42	-4.2	-46	70
DAY 8 (DB),22H PST	126	406.9	24.16	407.0	349	459	407.0	126	-1.0	1.64	18.34	-1.1	-62	58
DAY 15 (DB)	2	418.9	22.86	418.9	384	459	416.2	2	3.6	6.62	18.87	-3.1	-19	41
DAY 15 (DB),PRE-DS	116	404.2	23.19	407.5	336	455	406.1	116	-1.9	1.88	16.15	-0.5	-56	36
DAY 15 (DB),1-2H PST	117	401.9	25.14	400.0	344	459	406.5	117	-4.6	1.67	18.10	-3.7	-54	40
DAY 15 (DB),4H PST	116	401.6	23.15	405.0	339	453	405.4	116	-3.8	1.69	18.20	0.4	-62	44
DAY 29 (DB)	106	408.1	23.69	406.0	361	461	407.6	106	0.4	1.89	19.35	-1.0	-37	65
DAY 36 (DB),PRE-DS	79	408.3	25.88	406.0	345	486	407.4	79	0.9	2.35	20.92	3.3	-42	58
DAY 36 (DB),1-2H PST	76	405.1	25.14	407.0	339	471	407.5	76	-3.1	2.37	20.62	-1.0	-62	72
DAY 36 (DB),4H PST	78	404.6	24.72	405.5	347	470	407.4	78	-1.9	2.34	19.82	-0.7	-48	72
DAY 43 (DB)	88	406.4	23.04	408.5	330	473	407.3	88	-0.7	1.76	16.38	-1.5	-34	61
MAXIMUM VALUE (DB)	128	428.1	21.34	429.0	382	486	407.0	128	21.1	1.47	16.66	20.1	-25	73
END POINT (DB)	128	406.9	23.65	407.5	330	473	407.0	128	-0.1	1.73	19.59	-0.8	-48	65
BASE (OPEN)	128	406.9	23.35	408.0	330	473	407.0	128	-0.1	1.74	19.70	-1.0	-48	65
DAY 4 (OPEN)	123	411.6	21.91	411.0	352	464	407.1	123	6.6	1.46	16.23	7.3	-29	64
WEEK 1 (OPEN)	121	411.2	22.35	411.0	345	462	407.0	121	6.2	1.66	18.36	9.0	-61	54
WEEK 2 (OPEN)	120	409.7	20.42	410.5	351	460	406.9	120	3.8	1.40	15.32	3.3	-58	41
WEEK 4 (OPEN)	125	407.8	19.67	407.0	355	451	406.9	125	1.0	1.70	19.05	0.7	-58	77
WEEK 8 (OPEN)	124	408.0	21.65	404.0	341	472	406.6	124	1.4	1.62	18.09	1.2	-41	51
WEEK 16 (OPEN)	119	407.2	23.62	409.0	348	474	407.1	119	0.7	1.72	18.80	1.3	-52	48
WEEK 24 (OPEN)	78	408.9	21.15	410.0	360	461	401.8	78	6.8	2.15	18.73	8.7	-54	48
WEEK 40 (OPEN)	15	411.7	23.10	420.0	378	444	406.5	15	6.1	4.52	18.10	6.1	-32	38
WEEK 52 (OPEN)	3	421.5	10.61	411.5	424	439	392.8	2	28.7	14.09	13.80	14.7	25	53
MAXIMUM VALUE (OPEN)	128	428.7	17.97	429.0	384	474	407.0	128	21.7	1.32	14.94	21.0	-15	77
END POINT (OPEN)	128	409.5	22.74	411.0	356	474	407.0	128	2.5	1.82	20.66	3.8	-54	53
Pali/Pali <=3 months														
BASELINE (DB)	174	410.7	21.80	413.0	359	466								
AVERAGE PREDOSE	174	414.1	21.50	416.0	369	471								
DAY 4 (DB),4H PST	174	415.2	20.90	420.0	364	472	414.2	174	5.0	1.37	16.73	5.0	-42	69
DAY 4 (DB),10H PST	171	419.6	21.92	420.0	369	502	413.5	171	5.8	1.38	16.71	5.7	-51	72
DAY 4 (DB),22H PST	171	419.9	23.61	421.0	362	482	414.7	171	5.2	1.42	18.53	4.7	-66	62
DAY 8 (DB),4H PST	174	418.0	19.12	418.0	368	471	414.2	174	3.7	1.35	16.43	3.6	-46	62
DAY 8 (DB),10H PST	171	417.5	22.38	418.0	345	482	414.2	172	3.3	1.60	18.73	3.6	-72	60
DAY 8 (DB),22H PST	174	419.1	23.32	417.0	362	490	413.9	174	5.3	1.62	20.12	6.0	-29	65

Pali/Pali <=1 months													
DAY 15 (DB)	24	428.4	21.97	427.0	392	466	429.7	24	-1.3	2.92	18.34	-1.2	-35	59
DAY 15 (DB),PRE-DS	162	411.7	22.06	413.0	356	458	411.7	162	0.1	1.42	17.45	-0.2	-44	74
DAY 15 (DB),1-2H PST	160	412.4	19.80	411.5	362	463	411.5	160	0.9	1.44	17.63	1.2	-65	63
DAY 15 (DB),4H PST	146	414.1	19.17	414.0	366	462	412.9	142	1.1	1.34	16.32	1.3	-42	57
DAY 29 (DB)	160	416.1	20.56	416.5	357	467	416.1	160	1.0	1.46	17.54	1.0	-41	48
DAY 29 (DB),PRE-DS	103	416.2	22.02	416.0	352	475	413.4	103	1.8	1.86	18.86	3.7	-46	41
DAY 29 (DB),1-2H PST	106	412.2	20.61	410.0	352	476	413.8	106	-1.7	1.57	16.18	-1.6	-46	36
DAY 29 (DB),4H PST	104	416.2	20.69	414.0	371	481	413.5	104	1.8	1.76	17.56	-0.2	-35	63
DAY 43 (DB)	126	416.2	21.71	416.0	364	471	416.4	125	-0.2	1.36	15.13	-0.7	-26	42
MAXIMUM VALUE (DB)	178	427.9	20.33	427.0	382	502	414.1	178	22.7	1.10	14.71	21.6	-14	74
END POINT (DB)	178	414.1	21.84	414.0	352	471	414.1	178	-0.1	1.38	17.02	-0.7	-42	59
BASE (OPEN)	178	414.2	21.96	414.5	352	471	414.1	178	0.1	1.16	15.85	-0.6	-42	59
DAY 4 (OPEN)	164	416.2	24.30	416.0	366	498	414.5	164	0.7	1.50	19.68	0.6	-42	47
WEEK 1 (OPEN)	161	414.0	20.42	416.0	354	466	413.8	161	0.2	1.18	16.40	-1.0	-42	40
WEEK 2 (OPEN)	136	414.8	22.62	416.5	362	468	414.8	136	0.1	1.75	20.43	0.2	-42	64
WEEK 4 (OPEN)	73	414.5	21.56	416.0	362	467	416.2	72	-0.9	1.56	16.58	-1.5	-26	17
WEEK 8 (OPEN)	13	401.2	28.68	400.5	379	442	410.5	12	-9.1	6.60	23.80	-4.6	-28	14
WEEK 16 (OPEN)	3	417.0	14.79	399.0	395	457	414.4	3	1.6	13.52	24.62	-5.0	-24	40
WEEK 24 (OPEN)	3	417.0	1.41	417.0	416	418	413.3	3	3.7	10.34	14.62	3.7	-7	14
MAXIMUM VALUE (OPEN)	173	426.9	21.61	424.0	362	490	413.9	173	13.0	1.30	15.75	11.0	-22	64
END POINT (OPEN)	173	416.1	21.02	416.0	352	471	413.9	173	2.2	1.42	18.68	1.3	-42	64
Pali/Pali >1 months														
BASELINE (DB)	504	409.2	23.18	410.0	337	477								
AVERAGE REDUCE	504	412.6	20.65	411.8	358	475								
DAY 4 (DB),4H PST	450	417.1	20.00	416.0	358	474	412.5	450	4.6	0.75	16.53	4.1	-41	52
DAY 4 (DB),10H PST	481	416.0	20.32	414.0	332	469	412.6	481	3.5	0.82	17.82	3.3	-103	44
DAY 4 (DB),22H PST	479	419.0	21.11	419.0	342	467	412.6	479	6.4	0.82	17.85	6.3	-49	64
DAY 8 (DB),4H PST	499	416.4	20.58	416.0	336	476	412.6	498	3.8	0.81	18.01	4.2	-42	52
DAY 8 (DB),10H PST	496	416.1	20.35	416.0	342	478	412.5	494	3.6	0.81	18.11	3.7	-42	55
DAY 8 (DB),22H PST	496	417.5	22.54	417.0	346	482	412.5	495	5.1	0.85	18.92	5.0	-49	71
DAY 15 (DB)	34	424.6	25.61	420.0	380	471	423.7	34	0.1	2.42	13.97	1.8	-37	47
DAY 15 (DB),PRE-DS	468	412.9	22.02	413.0	340	483	411.7	467	1.1	0.84	17.92	1.1	-49	47
DAY 15 (DB),1-2H PST	467	410.7	21.08	411.0	357	474	411.9	466	-1.1	0.89	19.07	-3.0	-78	55
DAY 15 (DB),4H PST	467	411.6	20.93	414.0	312	483	411.6	464	1.8	0.91	19.43	1.5	-104	48
DAY 29 (DB)	473	412.7	21.89	413.0	337	496	412.8	472	-0.2	0.86	18.69	1.6	-62	74
DAY 29 (DB),PRE-DS	393	411.1	21.66	413.0	342	512	411.8	391	-0.8	0.94	18.66	-0.1	-77	63
DAY 29 (DB),1-2H PST	391	409.2	22.32	408.0	340	481	411.7	390	-1.6	1.02	20.15	-1.6	-95	72
DAY 29 (DB),4H PST	386	410.6	20.61	411.0	351	474	411.2	384	-0.7	0.97	19.07	0.3	-90	45
DAY 43 (DB)	429	411.5	21.52	411.0	351	506	412.5	429	-1.0	0.92	19.34	-0.1	-71	77
MAXIMUM VALUE (DB)	506	426.5	18.67	417.0	386	522	412.5	504	23.5	0.65	14.69	23.7	-17	77
END POINT (DB)	506	412.2	22.35	413.0	351	506	412.5	504	-0.4	0.86	19.39	0.0	-71	77
BASE (OPEN)	506	412.1	22.38	413.0	351	506	412.5	504	-0.5	0.86	19.37	0.0	-71	77
DAY 4 (OPEN)	476	412.4	21.86	413.0	331	498	412.5	474	-0.1	0.84	18.98	0.5	-64	62
WEEK 1 (OPEN)	486	411.5	21.94	410.0	339	488	412.5	485	-0.9	0.83	18.97	-0.1	-69	65
WEEK 2 (OPEN)	483	412.1	20.52	411.0	349	472	412.7	481	-0.6	0.84	19.45	-1.7	-66	65
WEEK 4 (OPEN)	453	410.7	21.83	411.0	321	478	412.8	452	-3.1	0.85	19.88	-0.6	-77	67
WEEK 8 (OPEN)	471	410.0	21.41	410.0	349	467	412.5	470	-1.6	0.88	19.06	-1.3	-69	59
WEEK 16 (OPEN)	374	411.0	20.63	414.0	359	478	412.7	372	0.1	1.05	20.23	0.3	-72	70
WEEK 24 (OPEN)	247	412.6	22.37	414.0	354	488	412.6	247	0.1	1.32	20.73	-0.6	-67	69
WEEK 40 (OPEN)	50	411.7	19.09	413.0	376	442	409.4	50	2.3	2.47	17.43	3.0	-29	49
WEEK 52 (OPEN)	6	422.4	6.62	425.0	411	430	408.4	6	14.0	4.54	20.00	13.7	-11	42
MAXIMUM VALUE (OPEN)	504	428.9	21.04	429.0	378	525	412.6	503	16.3	0.80	17.92	16.0	-36	170
END POINT (OPEN)	504	412.2	21.72	411.5	350	479	412.6	503	-0.1	0.91	19.73	0.0	-69	70
Olan/Pali <=1 months														
BASELINE (DB)	106	407.2	21.27	407.0	344	464								
AVERAGE REDUCE	106	411.0	18.47	409.2	367	462								
DAY 4 (DB),4H PST	104	409.1	22.34	411.5	352	465	410.2	104	-1.0	1.66	35.94	-1.5	-37	35
DAY 4 (DB),10H PST	103	410.0	21.52	410.0	348	462	410.3	102	-0.2	1.62	16.64	-0.1	-48	49
DAY 4 (DB),22H PST	98	408.9	23.42	407.0	349	465	409.8	98	-0.5	1.62	16.19	-3.1	-59	32
DAY 8 (DB),4H PST	103	412.3	22.70	411.0	342	462	410.6	103	1.5	1.80	18.16	1.1	-34	57
DAY 8 (DB),10H PST	103	412.0	21.62	414.0	354	466	410.6	102	1.4	1.63	17.07	1.2	-40	53
DAY 8 (DB),22H PST	100	414.0	23.50	411.0	354	480	410.4	100	3.6	1.82	18.17	1.4	-42	52
DAY 15 (DB),PRE-DS	101	410.2	22.33	409.0	362	476	411.1	100	-0.9	1.74	17.82	-0.1	-42	52
DAY 15 (DB),1-2H PST	99	411.1	22.38	410.0	357	465	410.2	99	1.0	1.87	19.65	1.7	-33	54
DAY 15 (DB),4H PST	99	412.8	21.04	413.0	356	469	410.4	99	1.4	1.86	18.62	2.1	-33	53
DAY 29 (DB)	89	414.4	20.71	416.0	357	464	410.7	88	3.7	1.79	16.83	3.7	-39	51
DAY 29 (DB),PRE-DS	73	410.2	21.61	413.0	356	467	408.6	72	1.4	1.86	15.92	1.7	-36	42
DAY 29 (DB),1-2H PST	76	409.6	20.51	409.5	356	457	409.7	76	0.1	2.04	17.76	1.6	-41	50
DAY 29 (DB),4H PST	74	412.7	22.08	416.0	361	473	409.2	74	1.6	2.34	19.13	5.1	-45	52
DAY 43 (DB)	71	411.6	21.35	413.0	365	468	410.2	71	1.4	1.82	15.46	1.3	-21	37
MAXIMUM VALUE (DB)	106	421.6	21.17	416.0	379	480	411.0	106	21.5	1.44	14.86	21.3	-13	61
END POINT (DB)	106	411.2	21.79	408.5	357	464	411.0	106	0.1	1.86	16.06	-0.1	-32	41
BASE (OPEN)	106	409.3	21.86	408.5	357	464	411.0	106	-1.2	1.61	16.62	-0.1	-42	41
DAY 4 (OPEN)	98	416.6	21.06	417.0	356	462	409.6	98	6.7	2.12	19.91	7.0	-51	61
WEEK 1 (OPEN)	90	417.2	20.63	416.5	361	462	411.7	90	5.6	1.95	18.46	7.2	-48	48
WEEK 2 (OPEN)	77	411.2	13.92	416.0	372	464	410.2	77	1.9	1.62	13.83	1.1	-27	16
WEEK 4 (OPEN)	66	406.7	20.73	406.0	359	462	410.6	66	-3.8	2.35	16.65	-5.0	-42	43
WEEK 8 (OPEN)	23	410.9	19.48	417.5	365	440	411.2	22	-0.3	2.60	16.88	0.5	-25	30
WEEK 16 (OPEN)	1	379.0		379.0	379	379	416.2	1	-37.1			-17.1	-37	-37
MAXIMUM VALUE (OPEN)	103	424.6	20.33	426.0	355	469	410.3	103	14.1	1.68	17.10	14.0	-48	61
END POINT (OPEN)	103	410.1	22.67	408.0	355	468	410.3	103	-0.2	1.70	17.32	0.0	-48	48

Olan/Pali >1 months														
BASELINE (DB)	143	406.4	23.61	406.0	332	473								
AVERAGE PERIOD	143	409.9	20.54	408.0	345	474								
DAY 4 (DB),4H PST	136	406.9	22.62	406.5	343	476	408.5	136	-1.6	1.64	17.97	-1.2	-52	51
DAY 4 (DB),10H PST	136	409.2	21.86	408.5	358	468	409.2	136	0.0	1.69	19.65	0.2	-62	60
DAY 4 (DB),22H PST	136	409.0	23.00	410.0	356	462	408.5	136	0.5	1.44	16.75	0.0	-45	49
DAY 8 (DB),4H PST	128	408.6	19.82	409.0	362	461	408.9	128	-0.2	1.55	18.15	-1.0	-52	47
DAY 8 (DB),10H PST	127	410.6	21.74	411.0	352	465	408.2	127	1.7	1.66	19.33	0.7	-49	55
DAY 8 (DB),22H PST	141	410.0	23.69	406.0	358	472	408.2	141	1.1	1.76	20.83	1.0	-42	64
DAY 15 (DB),PRE-DS	140	409.6	22.07	410.0	354	465	409.0	140	0.7	1.42	16.96	0.0	-44	51
DAY 15 (DB),1-2H PST	139	408.2	23.16	410.0	348	459	409.0	139	-0.8	1.76	20.73	-1.1	-49	68
DAY 15 (DB),4H PST	138	410.8	22.36	411.5	350	466	408.9	138	1.8	1.65	19.38	1.0	-42	67
DAY 29 (DB)	126	412.8	24.03	417.0	332	473	409.2	126	3.6	1.92	21.54	1.8	-51	66
DAY 36 (DB),PRE-DS	119	408.3	23.93	411.0	350	462	409.8	119	-0.7	1.90	20.75	-0.7	-60	49
DAY 36 (DB),1-2H PST	120	409.9	25.02	409.5	354	475	409.2	120	0.6	1.86	20.33	1.2	-55	55
DAY 36 (DB),4H PST	118	411.4	23.78	411.0	361	468	409.1	118	3.3	1.85	20.16	1.5	-55	56
DAY 42 (DB)	123	406.1	23.33	406.5	348	470	409.0	122	-3.0	1.72	17.95	-4.2	-62	29
MAXIMUM VALUE (DB)	143	422.2	18.77	421.0	378	478	409.0	143	23.3	1.35	16.11	23.7	-26	68
END POINT (DB)	143	407.0	22.86	409.0	342	478	409.0	143	-3.0	1.61	19.04	-3.0	-62	38
BASE (OPEN)	143	407.0	23.52	409.0	342	478	409.0	143	-3.1	1.61	18.84	-3.0	-62	38
DAY 4 (OPEN)	134	416.6	21.32	416.0	352	476	409.2	134	6.3	1.62	18.75	7.0	-62	52
WEEK 1 (OPEN)	134	416.0	21.34	416.5	364	468	407.9	134	7.1	1.46	16.80	6.7	-33	48
WEEK 2 (OPEN)	132	410.2	22.58	411.5	348	461	408.7	132	1.6	1.64	18.83	1.5	-61	55
WEEK 4 (OPEN)	139	409.0	21.86	406.0	362	466	408.8	139	0.1	1.62	19.36	1.1	-58	49
WEEK 8 (OPEN)	128	409.4	22.78	411.0	348	478	409.2	128	0.3	1.59	18.64	1.5	-55	42
WEEK 16 (OPEN)	128	408.8	22.82	406.0	364	476	409.2	126	-0.3	1.86	20.66	-0.1	-29	73
WEEK 24 (OPEN)	84	406.2	25.11	406.5	346	466	406.1	84	0.2	2.16	19.83	0.7	-57	39
WEEK 40 (OPEN)	16	396.9	31.16	396.5	337	443	398.3	16	-1.4	7.96	31.83	3.1	-41	32
MAXIMUM VALUE (OPEN)	143	428.7	18.82	426.0	371	478	409.0	143	19.7	1.35	16.14	20.1	-26	73
END POINT (OPEN)	143	409.7	23.72	414.0	337	476	409.0	143	0.7	1.69	20.22	1.7	-29	73

B. QTc Fridericia Results The following are selected sections of the sponsor's summary table (as above) on QTc Fridericia results for selected treatment groups. OL Pal treatment failed to show remarkable group mean changes in QTc Fridericia following DB Pal treatment (for assessment weeks that had at least 50 subjects which included up to a 24 week assessment time-point in some subgroups). However, these OL trials have several major study design limitations that may lead to failure to reveal a clear drug effect on QTc interval (e.g. considerations on potential subject variance on timing of assessments and dosing, among other limitations as previously noted).

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

Output D05CD3: ECG: Means and Mean Changes from Pre-treatment over Time - Open-Label Phase (continued)

Analysis Set: Safety

						Data	-------- Change from average predose --------					
	N	Mean	SD	Med	Min	Max	Mean	N	Mean	SE	SD	Med	Min	Max

Pali/Pali <=3 months														
BASELINE (SE)	176	395.1	20.02	356.0	342	465								
AVERAGE PERIOD	176	397.6	19.99	357.2	354	465								
DAY 4 (SE),4H PST	174	395.9	20.12	356.0	350	460	397.6	174	-1.8	1.01	12.39	-1.1	-49	39
DAY 4 (SE),10H PST	171	397.1	20.03	357.0	357	467	397.6	171	-0.6	1.12	14.63	-0.7	-70	66
DAY 4 (SE),22H PST	171	399.1	20.37	358.0	357	461	397.8	171	1.2	1.15	14.98	1.7	-62	62
DAY 8 (SE),4H PST	174	396.2	19.11	354.5	340	454	397.8	174	-1.4	1.06	14.04	-1.1	-56	44
DAY 8 (SE),10H PST	173	396.0	19.66	354.0	332	459	398.0	172	-2.1	1.12	16.13	-1.1	-71	46
DAY 8 (SE),22H PST	176	399.4	19.84	357.0	344	463	397.6	176	1.8	1.12	16.35	1.7	-61	63
DAY 15 (SE)	34	415.1	19.32	411.5	381	456	414.1	34	1.0	2.16	15.60	0.4	-32	43
DAY 15 (SE),PRE-DS	162	394.1	19.03	353.5	354	439	394.9	162	-0.8	1.14	14.08	-0.7	-45	29
DAY 15 (SE),1-2H PST	160	392.2	17.88	359.0	352	439	394.7	160	-3.5	1.15	14.09	-3.8	-72	43
DAY 15 (SE),4H PST	148	392.7	17.92	353.0	357	442	395.1	148	-3.4	1.08	13.17	-1.1	-69	31
DAY 29 (SE)	160	399.5	19.73	358.5	351	464	398.4	160	1.1	1.13	13.89	0.0	-31	33
DAY 36 (SE),PRE-DS	103	399.7	19.32	359.0	356	465	396.8	103	3.4	1.39	14.11	3.7	-26	40
DAY 36 (SE),1-2H PST	106	396.5	18.33	363.0	358	462	397.2	106	-1.8	1.12	11.68	-1.6	-38	30
DAY 36 (SE),4H PST	104	397.2	19.36	356.5	356	463	397.1	104	0.2	1.12	11.62	-0.6	-25	37
DAY 43 (SE)	126	401.9	20.30	359.0	358	464	400.1	126	1.6	1.14	12.72	1.1	-28	36
MAXIMUM VALUE (SE)	176	413.7	19.97	411.0	376	467	397.6	176	16.1	0.91	12.08	15.7	-12	63
END POINT (SE)	176	398.4	19.91	357.0	359	464	397.6	176	0.8	1.08	13.33	0.3	-30	43
BASE (OPEN)	176	398.5	19.96	357.0	358	464	397.6	176	0.9	0.99	13.16	0.6	-32	43
DAY 4 (OPEN)	164	398.2	21.43	358.5	337	472	399.5	164	-0.1	1.30	14.91	-0.6	-39	32
WEEK 1 (OPEN)	161	397.3	19.43	354.0	354	467	397.4	161	-0.1	1.04	13.16	1.1	-34	34
WEEK 2 (OPEN)	136	396.8	20.40	356.0	357	468	398.8	136	-1.1	1.16	15.82	-0.7	-68	37
WEEK 4 (OPEN)	73	396.4	16.77	356.5	356	434	397.1	73	-0.8	1.64	13.80	-0.6	-32	33
WEEK 8 (OPEN)	11	398.2	19.82	367.0	367	432	394.6	11	4.1	4.34	14.62	4.6	-32	19
WEEK 16 (OPEN)	3	395.0	10.41	380.0	385	408	395.6	3	1.4	14.62	25.14	0.1	-32	19
WEEK 24 (OPEN)	1	394.0	4.34	394.0	391	397	398.2	1	-4.2	16.68	12.33	-4.2	-21	12
MAXIMUM VALUE (OPEN)	173	406.2	19.30	407.0	362	472	397.6	173	8.7	0.94	12.30	8.0	-20	36
END POINT (OPEN)	173	398.4	19.41	356.0	356	468	397.6	173	0.9	1.07	14.04	1.0	-69	37
Pali/Pali >3 months														
BASELINE (SE)	504	395.5	19.42	356.0	337	470								
AVERAGE PERIOD	504	398.2	18.38	357.1	355	465								
DAY 4 (SE),4H PST	490	396.6	17.47	354.0	357	462	398.1	490	-1.5	0.86	12.48	-1.7	-61	33
DAY 4 (SE),10H PST	481	396.6	18.15	354.0	337	463	398.1	481	-1.5	0.82	13.80	-1.7	-74	44
DAY 4 (SE),22H PST	479	401.0	18.39	401.0	346	466	398.1	479	1.9	0.88	13.30	3.7	-37	40
DAY 8 (SE),4H PST	499	396.6	18.09	356.0	342	460	398.1	498	-1.5	0.82	14.08	-0.7	-58	51
DAY 8 (SE),10H PST	496	397.0	18.08	356.0	357	462	397.9	494	-0.9	0.82	13.68	0.0	-52	42
DAY 8 (SE),22H PST	496	401.5	18.31	400.0	346	461	398.0	496	3.6	0.83	14.08	4.0	-44	43
DAY 15 (SE)	14	409.9	24.04	411.5	367	460	411.2	14	-1.3	2.64	15.41	-1.0	-25	30
DAY 15 (SE),PRE-DS	464	397.8	18.65	357.0	350	470	397.9	467	0.7	0.82	13.34	1.0	-60	37
DAY 15 (SE),1-2H PST	457	393.1	17.75	351.0	350	459	397.1	456	-4.0	0.81	12.98	-4.0	-62	28
DAY 15 (SE),4H PST	457	394.2	17.31	355.0	332	443	396.9	456	-3.6	0.86	14.15	-3.7	-72	40
DAY 29 (SE)	473	398.2	18.67	358.0	350	491	398.4	472	-0.1	0.84	13.54	0.7	-49	45
DAY 36 (SE),PRE-DS	293	398.4	17.62	358.0	357	446	396.9	291	1.5	0.75	14.84	1.7	-42	42
DAY 36 (SE),1-2H PST	291	395.1	17.77	354.0	345	457	396.9	290	-1.8	0.76	14.52	-1.3	-46	50
DAY 36 (SE),4H PST	285	395.9	16.57	356.0	352	462	396.4	284	-0.7	0.72	14.11	-0.7	-57	35
DAY 43 (SE)	429	398.2	19.40	357.0	344	502	398.8	428	0.8	0.71	14.72	1.0	-51	60
MAXIMUM VALUE (SE)	504	414.6	17.98	414.0	372	502	398.2	504	16.5	0.82	11.66	16.0	-19	63
END POINT (SE)	504	395.0	19.69	356.0	344	502	398.2	504	0.8	0.85	14.69	1.2	-51	60
BASE (OPEN)	504	395.2	19.80	356.0	344	502	398.2	504	1.0	0.85	14.64	1.1	-51	60
DAY 4 (OPEN)	478	398.0	18.52	357.0	342	482	398.0	474	0.1	0.82	13.48	-0.7	-44	39
WEEK 1 (OPEN)	486	397.2	18.89	356.0	348	468	398.1	486	-0.8	0.85	14.38	0.0	-52	48
WEEK 2 (OPEN)	483	398.1	18.64	357.0	345	486	398.2	480	-0.2	0.87	14.80	-0.7	-62	55
WEEK 4 (OPEN)	493	397.2	19.06	357.0	316	465	398.3	492	-1.2	0.89	15.06	-0.1	-79	41
WEEK 8 (OPEN)	471	396.2	17.82	356.0	354	459	398.8	470	-1.8	0.88	14.84	-1.0	-62	41
WEEK 16 (OPEN)	374	398.5	18.32	359.0	352	460	397.7	372	0.7	0.76	14.65	0.7	-50	41
WEEK 24 (OPEN)	347	398.8	18.60	358.0	348	464	397.8	347	1.5	0.94	14.86	1.0	-44	38
WEEK 40 (OPEN)	50	395.8	15.54	396.0	365	447	395.8	50	-0.0	1.70	12.01	-0.7	-24	30
WEEK 52 (OPEN)	5	414.2	18.88	419.0	387	423	408.2	5	13.5	6.92	15.48	13.7	-2	34
MAXIMUM VALUE (OPEN)	504	411.1	19.60	410.0	364	479	398.1	503	13.0	0.83	13.59	13.0	-22	117
END POINT (OPEN)	504	398.4	19.49	356.0	346	462	398.1	503	0.6	0.86	14.91	0.7	-62	61
Olan/Pali <=3 months														
BASELINE (SE)	106	391.0	17.65	393.5	342	429								
AVERAGE PERIOD	106	391.1	15.10	396.8	351	436								
DAY 4 (SE),4H PST	104	391.9	17.33	393.0	349	427	395.1	104	-3.1	1.09	11.01	-3.8	-29	31
DAY 4 (SE),10H PST	101	392.2	18.32	393.0	341	442	395.0	100	-3.7	1.19	12.02	-3.1	-35	33
DAY 4 (SE),22H PST	96	394.4	19.07	396.0	362	439	394.7	98	-0.2	1.31	12.98	-0.5	-37	39
DAY 8 (SE),4H PST	103	391.8	18.09	396.0	355	446	395.1	102	-3.1	1.16	12.77	-3.7	-35	44
DAY 8 (SE),10H PST	103	391.8	17.41	395.0	344	427	394.2	102	-3.2	1.10	12.08	-3.0	-26	35
DAY 8 (SE),22H PST	100	398.7	18.08	398.0	342	467	394.6	100	3.9	1.48	14.77	3.3	-28	58
DAY 15 (SE),PRE-DS	106	396.1	17.65	396.0	358	466	395.1	106	-0.0	1.18	12.69	0.7	-38	43
DAY 15 (SE),1-2H PST	99	392.2	19.08	393.0	346	446	394.5	98	-3.2	1.34	13.22	-3.8	-37	39
DAY 15 (SE),4H PST	99	393.9	18.34	396.0	356	461	394.8	98	-1.9	1.36	12.43	-1.7	-38	33
DAY 29 (SE)	89	396.2	17.58	396.0	349	429	395.1	88	1.1	1.37	12.54	0.0	-22	34
DAY 36 (SE),PRE-DS	73	396.7	17.82	396.0	342	441	394.8	73	3.7	1.55	13.36	1.0	-26	34
DAY 36 (SE),1-2H PST	76	394.6	17.63	394.0	352	446	394.6	76	-0.1	1.55	13.54	-0.1	-28	33
DAY 36 (SE),4H PST	74	395.4	18.14	396.0	359	448	394.4	74	1.1	1.64	14.13	1.0	-34	47
DAY 43 (SE)	71	396.7	17.12	397.0	360	429	394.6	71	1.1	1.56	13.13	0.0	-23	36
MAXIMUM VALUE (SE)	106	411.5	18.33	410.5	372	467	395.1	106	16.4	1.32	12.59	15.0	-10	59
END POINT (SE)	106	395.7	18.45	394.5	346	448	395.1	106	0.7	1.37	13.06	-0.1	-31	36
BASE (OPEN)	106	394.8	18.48	393.0	346	449	395.1	106	-0.1	1.32	13.63	-1.0	-32	36
DAY 4 (OPEN)	98	391.9	17.22	391.5	355	432	393.5	98	-1.6	1.55	14.50	-0.5	-55	28
WEEK 1 (OPEN)	90	396.0	17.67	396.0	352	440	396.2	90	-0.2	1.38	13.34	0.2	-44	39
WEEK 2 (OPEN)	77	391.4	15.73	394.0	359	439	394.7	77	-1.1	1.12	9.82	-1.1	-20	32
WEEK 4 (OPEN)	66	392.1	17.09	390.0	352	436	394.2	66	-2.2	1.65	12.31	-3.1	-22	39
WEEK 8 (OPEN)	21	392.6	13.97	393.0	364	416	395.8	22	-2.2	2.01	9.45	-3.1	-17	15
WEEK 16 (OPEN)	1	376.0		376.0	376	376	393.2	1	-18.1			-18.1	-18	-18
MAXIMUM VALUE (OPEN)	103	401.7	17.41	403.0	359	441	394.4	103	6.9	1.34	12.64	7.7	-44	32
END POINT (OPEN)	103	391.6	17.52	391.0	356	441	394.4	103	-0.7	1.39	12.85	-0.7	-44	39

Glan/Pall >1 mm/hr

BASELINE (EG)	143	391.6	19.63	354.0	122	432								
AVERAGE PERIOD1	143	391.0	16.58	353.0	148	444								
DAY 4 (EG) .4H PST	116	389.8	19.61	355.0	344	448	392.6	116	-3.7	1.38	13.72	-3.8	-36	16
DAY 4 (EG) .10H PST	116	391.2	19.49	351.0	354	441	391.4	116	-2.2	1.39	13.89	-1.2	-34	16
DAY 4 (EG) .22H PST	116	394.2	19.13	354.0	352	440	392.5	116	1.7	0.98	11.34	1.0	-40	12
DAY 8 (EG) .4H PST	118	391.1	16.76	351.0	348	432	392.9	118	-1.8	1.01	11.07	-0.7	-37	17
DAY 8 (EG) .10H PST	117	392.8	17.97	351.0	344	438	392.9	117	-0.6	1.12	12.14	-0.6	-45	13
DAY 8 (EG) .22H PST	141	394.6	19.45	354.0	347	442	392.9	141	1.7	1.36	14.94	0.1	-52	46
DAY 15 (EG) .PRE-DS	140	394.4	19.31	356.0	342	449	393.0	140	1.4	1.60	12.32	1.1	-22	12
DAY 15 (EG) .1-2H PST	119	389.8	18.58	356.0	339	438	391.0	119	-3.1	1.11	12.06	-3.0	-37	30
DAY 15 (EG) .4H PST	118	391.8	19.38	353.0	345	447	392.9	118	-1.1	1.02	11.11	0.6	-33	28
DAY 29 (EG)	126	394.2	20.12	357.0	336	443	393.0	126	0.9	1.36	15.14	1.2	-52	40
DAY 36 (EG) .PRE-DS	119	394.4	19.37	353.0	351	445	393.2	119	1.2	1.37	13.83	1.8	-37	16
DAY 36 (EG) .1-2H PST	120	394.8	20.18	354.0	350	440	391.6	120	1.2	1.38	14.84	1.6	-45	24
DAY 36 (EG) .4H PST	118	396.0	19.79	356.0	352	443	393.0	118	3.0	1.34	13.64	3.0	-40	28
DAY 43 (EG)	123	392.7	20.06	351.0	346	445	391.4	122	-0.7	1.32	14.61	-0.1	-67	28
MAXIMUM VALUE (EG)	143	410.0	19.39	404.0	368	449	391.0	143	17.0	0.97	11.66	16.7	-24	46
END POINT (EG)	143	392.2	19.77	353.0	346	445	391.0	143	-0.7	1.32	14.67	-0.1	-67	28
BASE (OPEN)	143	392.4	19.81	353.0	346	445	391.0	143	-0.6	1.32	14.72	-0.1	-67	28
DAY 4 (OPEN)	134	391.0	12.68	361.0	342	446	391.2	134	-0.1	1.11	12.86	1.0	-38	26
WEEK 1 (OPEN)	134	394.4	18.28	354.0	346	441	392.1	134	3.3	1.04	12.31	3.4	-42	28
WEEK 2 (OPEN)	131	392.6	17.83	353.0	348	432	392.9	132	-0.6	1.18	13.56	-0.2	-38	25
WEEK 4 (OPEN)	129	392.1	17.68	353.0	355	441	393.0	128	-0.8	1.18	15.10	-1.3	-51	28
WEEK 8 (OPEN)	118	392.6	17.92	353.0	352	461	392.9	118	-0.1	1.20	14.10	0.2	-46	34
WEEK 16 (OPEN)	124	392.7	19.63	351.0	355	463	393.2	124	-0.5	1.35	15.02	-0.8	-61	50
WEEK 24 (OPEN)	84	392.6	19.64	353.0	348	439	390.8	84	1.7	1.52	13.91	1.7	-35	38
WEEK 40 (OPEN)	16	396.2	20.73	388.0	347	438	393.1	16	3.1	2.72	10.87	3.8	-20	22
MAXIMUM VALUE (OPEN)	143	406.8	16.48	406.0	366	462	393.0	143	13.8	1.02	12.33	13.7	-30	50
END POINT (OPEN)	143	394.0	19.76	353.0	347	462	393.0	143	1.0	1.38	15.30	1.7	-61	50

QTc linear derived and linear sagie interval results were generally clinically unremarkable during OL Pal treatment for assessment weeks that had at least up to 50 subjects who were assessed which included assessments for up to 24 weeks of OL treatment in subgroups.

Results of Ongoing Trials -301 and -701

Results from these ongoing trials are not provided in the original submission since they are ongoing with blinded data.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Refer to Table series 10.2 in the appendix of this review for criteria used for outlier ECG values.

Results of Short-Term Phase III Trials (-303, -34, -305).

Reviewer Comment. *The following comments are based on numerical comparisons between treatment groups of results provided in summary tables found in the SCS or in the SCS appendices (results of statistical group comparisons could not be found in these summary tables).*

A Greater Incidence in High Heart Rate Outliers in Pal Groups compared to the Placebo Group.

The sponsor's results below (as provided in the SCS) show numerically greater incidence of outliers for high heart rate in Pal groups compared to the placebo group.

Greater Incidence in High PR Interval Outliers in Some Pal Groups compared to the Placebo Group

High PR interval outlier results show inconsistently greater incidence among Pal groups compared to the placebo group (based on numerical comparisons). Since this observation appears to be inconsistent among Pal groups and does not appear to increase with increasing dose-level, then these results, alone do not provide sufficient evidence for a drug effect on PR

prolongation. However, a small mean increase in PR interval (compared to pre-dose values) was observed in Phase III trials, as previously described under the preceding section of this review.

Clinically Unremarkable QRS and QTraw Interval Results. *Results on QRS and QTraw interval outliers is unremarkable.*

Table 85: Number of Subjects With Treatment-Emergent Abnormal ECG Values During the Double-Blind Period (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
Heart rate	350	124	232	243	238	113	950	357
Abnormally high	79 (23)	39 (31)	77 (33)	92 (38)	99 (42)	33 (29)	340 (36)	111 (31)
Abnormally low	29 (8)	6 (5)	4 (2)	10 (4)	13 (5)	2 (2)	35 (4)	22 (6)
PR interval	350	124	232	243	238	113	950	357
Abnormally high	6 (2)	7 (6)	4 (2)	5 (2)	6 (3)	6 (5)	28 (3)	7 (2)
Abnormally low	0	0	0	0	0	0	0	0
QRS interval	350	124	232	243	238	113	950	357
Abnormally high	2 (1)	0	0	1 (<1)	0	1 (1)	2 (<1)	3 (1)
Abnormally low	0	0	0	0	0	0	0	0
QT interval	350	124	232	243	238	113	950	357
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.

QTc Interval Results Show a Greater Incidence of High Outliers in Some Pal group Compared to Placebo.

The table below shows results on outliers on QTc intervals (as provided in the SCS). These results show a numerically greater incidence in outliers on the maximum increase in QTc interval from the average pre-dose values to DB treatment values (for the <30 msec, and 30-60 msec categories) in the HD Pal group (15 mg) compared to the placebo and olanzapine groups. However, the numerical group differences between the HD Pal group and placebo or olanzapine groups were small.

The over 60 msec category also showed a slightly higher incidence in at least the 12 mg Pal group for increased QTc for all methods for calculating QTc. However, in most cases only 1 subject met the over 60 msec criterion level. The exception was with QTc Bazett's (QTcB) which is a method for QT interval correction that is intended for correcting for low heart rate values. Since heart rate generally increased with Pal treatment QTcB interval results may be misleading, at least regarding the magnitude of a potential QT prolongation effect.

Table 90: Distribution of Maximum Changes From Average Predose Value in Corrected QT Values (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Placebo (N=355) n (%)	ER OROS PAL 3 mg (N=127) n (%)	ER OROS PAL 6 mg (N=235) n (%)	ER OROS PAL 9 mg (N=246) n (%)	ER OROS PAL 12 mg (N=242) n (%)	ER OROS PAL 15 mg (N=113) n (%)	Total Paliperidone (N=963) n (%)	Olanzapine 10 mg (N=364) n (%)
QTcLD	350	124	232	242	238	113	949	357
<30 (ms)	318 (91)	118 (95)	214 (92)	223 (92)	219 (92)	100 (88)	874 (92)	315 (88)
30-60 (ms)	32 (9)	6 (5)	18 (8)	19 (8)	18 (8)	13 (12)	74 (8)	41 (11)
>60 (ms)	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
QTcF	350	124	232	242	238	113	949	357
<30 (ms)	308 (88)	118 (95)	208 (90)	221 (91)	212 (89)	96 (85)	855 (90)	308 (86)
30-60 (ms)	42 (12)	6 (5)	24 (10)	21 (9)	25 (11)	16 (14)	92 (10)	48 (13)
>60 (ms)	0	0	0	0	1 (<1)	1 (1)	2 (<1)	1 (<1)
QTlc	350	124	232	242	238	113	949	357
<30 (ms)	317 (91)	117 (94)	213 (92)	225 (93)	218 (92)	99 (88)	872 (92)	318 (89)
30-60 (ms)	33 (9)	7 (6)	19 (8)	17 (7)	19 (8)	14 (12)	76 (8)	38 (11)
>60 (ms)	0	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
QTcB	350	124	232	242	238	113	949	357
<30 (ms)	276 (79)	96 (77)	156 (67)	170 (70)	150 (63)	76 (67)	648 (68)	253 (71)
30-60 (ms)	68 (19)	25 (20)	74 (32)	71 (29)	82 (34)	34 (30)	286 (30)	97 (27)
>60 (ms)	6 (2)	3 (2)	2 (1)	1 (<1)	6 (3)	3 (3)	15 (2)	7 (2)

Note: Percentages calculated with the number of subjects per parameter as denominator.

The results below show a numerically greater incidence of outliers on maximum changes in QTc values in the Pal compared to placebo groups but group differences are small except for QTcB interval results.

QTcB interval results showed a remarkable incidence of outliers in Pal groups compared to the placebo group that appeared to be dose-dependent (incidence of 17% and 23% in the 15 mg and 12 mg Pal groups, an incidence of 15% or less in lower dose Pal groups and an incidence of 11% in the placebo group for outliers of 450 msec or greater on QTcB). QTcB results are difficult to interpret from at least the perspective of a magnitude of an effect on QT prolongation since QTcB is most appropriately used for low heart rates, rather than for elevations in heart rate which was observed with Pal treatment at least at some time-points that appeared to attenuate or become absent over time, as previously explained.

The incidence of QTcF prolongation of 450 to less than 480 msec was 2.9% greatest in the 12 mg Pal group compared to 1.7% in the placebo group. See the table below for additional results.

Table 88: Maximum Increases of Corrected QT Intervals From Average Predose Value (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Treatment Group and Evaluation at Average Predose															
	Placebo (N=355)				ER OROS PAL 3 mg (N=127)				ER OROS PAL 6 mg (N=235)				ER OROS PAL 9 mg (N=246)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD																
Maximum value																
Normal	345	0	0	345	121	1	0	122	226	0	0	226	238	0	0	238
>=450 - <480	5	0	0	5	1	1	0	2	5	1	0	6	3	1	0	4
>=480	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	350	0	0	350	122	2	0	124	231	1	0	232	241	1	0	242
QTcF																
Maximum value																
Normal	344	0	0	344	121	1	0	122	225	0	0	225	236	0	0	236
>=450 - <480	6	0	0	6	1	1	0	2	6	1	0	7	5	1	0	6
>=480	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	350	0	0	350	122	2	0	124	231	1	0	232	241	1	0	242
QTlc																
Maximum value																
Normal	344	0	0	344	121	1	0	122	226	0	0	226	235	0	0	235
>=450 - <480	6	0	0	6	1	1	0	2	5	1	0	6	6	1	0	7
>=480	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	350	0	0	350	122	2	0	124	231	1	0	232	241	1	0	242
QTcB																
Maximum value																
Normal	304	6	0	310	105	0	0	105	193	0	0	193	208	0	0	208
>=450 - <480	33	2	0	35	15	3	0	18	31	3	0	34	25	6	0	31
>=480	4	1	0	5	1	0	0	1	2	3	0	5	3	0	0	3
Total	341	9	0	350	121	3	0	124	226	6	0	232	236	6	0	242

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

(continued)

Table 88: Maximum Increases of Corrected QT Intervals From Average Predose Value (continued) (Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

	Treatment Group and Evaluation at Average Predose															
	ER OROS PAL 12 mg (N=242)				ER OROS PAL 15 mg (N=113)				Total Paliperidone (N=963)				Olanzapine 10 mg (N=364)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD																
Maximum value																
Normal	234	0	0	234	111	0	0	111	930	1	0	931	353	0	0	353
>=450 - <480	4	0	0	4	2	0	0	2	15	3	0	18	3	0	0	3
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	238	0	0	238	113	0	0	113	945	4	0	949	357	0	0	357
QTcF																
Maximum value																
Normal	230	1	0	231	111	0	0	111	923	2	0	925	353	0	0	353
>=450 - <480	7	0	0	7	2	0	0	2	21	3	0	24	3	0	0	3
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	237	1	0	238	113	0	0	113	944	5	0	949	357	0	0	357
QTlc																
Maximum value																
Normal	234	0	0	234	111	0	0	111	927	1	0	928	353	0	0	353
>=450 - <480	4	0	0	4	2	0	0	2	18	3	0	21	3	0	0	3
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	238	0	0	238	113	0	0	113	945	4	0	949	357	0	0	357
QTcB																
Maximum value																
Normal	183	0	0	183	94	0	0	94	783	0	0	783	294	1	0	295
>=450 - <480	43	7	0	50	16	2	0	18	130	21	0	151	55	4	0	59
>=480	3	2	0	5	1	0	0	1	10	5	0	15	2	1	0	3
Total	229	9	0	238	111	2	0	113	923	26	0	949	351	6	0	357

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

See Section 7.1.3.3.G for descriptions of subjects with QT prolongation that may be considered remarkable cases or were reported as ADOs. A description of individual subjects could not be found in in-text sections of the SCS but were found in QT related sections in CSRs, by the undersigned reviewer.

Results of the Elderly Short-Term Phase III Trial (-302).

Results are shown below. The incidence of outliers on high heart rate was remarkably greater in the Pal group compared to the placebo group, while results on other parameters were clinically unremarkable.

Table 86: Number of Subjects with Treatment-Emergent Abnormal ECG Values During the Double-Blind Period (Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)
Heart rate	37	76
Abnormally high	2 (5)	19 (25)
Abnormally low	5 (14)	6 (8)
PR interval	36	76
Abnormally high	2 (6)	4 (5)
Abnormally low	0	0
QRS interval	37	76
Abnormally high	0	1 (1)
Abnormally low	0	0
QT interval	37	76
Abnormally high	0	0
Abnormally low	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.
Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec6.5.3

The results below (as provided in the SCS) show a greater incidence of outliers for prolonged QTcB interval in both categories (the 450 to less than 480 msec category and the 480 msec or longer category). As previously noted, the results on QTcB are difficult to interpret regarding the magnitude of a Pal treatment effect on QT prolongation since QTB is more appropriate when heart rate is low rather than elevated.

Table 89: Maximum Increases of Corrected QT Intervals From Average Predose Value (Study R076477-SCH-302)

	Treatment Group and Evaluation at Average Predose							
	Placebo (N=38)				ER OROS PAL (N=76)			
	Norm	≥450	≥480	Total	Norm	≥450	≥480	Total
QTcLD								
Maximum value								
Normal	30	0	0	30	63	1	0	64
≥450 - <480	4	3	0	7	5	4	0	9
≥480	0	0	0	0	2	1	0	3
Total	34	3	0	37	70	6	0	76
QTcF								
Maximum value								
Normal	30	0	0	30	62	1	0	63
≥450 - <480	4	3	0	7	6	4	0	10
≥480	0	0	0	0	2	1	0	3
Total	34	3	0	37	70	6	0	76
QTlc								
Maximum value								
Normal	30	0	0	30	64	1	0	65
≥450 - <480	4	3	0	7	4	4	0	8
≥480	0	0	0	0	2	1	0	3
Total	34	3	0	37	70	6	0	76
QTcB								
Maximum value								
Normal	27	0	0	27	39	1	0	40
≥450 - <480	4	4	1	9	19	10	0	29
≥480	0	1	0	1	2	4	1	7
Total	31	5	1	37	60	15	1	76

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

QTcB interval results showed a remarkable incidence of outliers in Pal and placebo groups as shown in the table below (copied from the SCS) with a greater incidence in the Pal group. Overall the Pal group showed slightly greater incidence of outliers in the 30 msec and over categories compared to the placebo group for QTc interval using any given method for calculation QTc, except for QTcB which showed larger group differences, as shown below. The magnitude of QTcB changes are difficult to interpret since QTcB is more appropriate in the presence of low rather than elevated heart rate, as previously discussed.

These observations that appear to show a drug effect on QTc prolongation were revealed despite serious limitations of this elderly Phase III trial which had small sample sizes, particularly in the placebo group and used a flexible dose design (3-12 mg/day) rather than examining a fixed

dose-response curve, along with other limitations that can impact on the ability to capture a real drug effect on QT interval (e.g. assessments were not timed specifically to capture a given subject near Tmax of Pal exposure).

Table 91: Distribution of Maximum Changes From Average Predose Value in Corrected QT Values (Study R076477-SCH-302: Safety Analysis Set)

	Placebo (N=38) n (%)	ER OROS PAL (N=76) n (%)
QTcLD	37	76
<30 (ms)	33 (89)	65 (86)
30-60 (ms)	4 (11)	10 (13)
>60 (ms)	0	1 (1)
QTcF	37	76
<30 (ms)	33 (89)	64 (84)
30-60 (ms)	4 (11)	11 (14)
>60 (ms)	0	1 (1)
QTlc	37	76
<30 (ms)	33 (89)	66 (87)
30-60 (ms)	4 (11)	9 (12)
>60 (ms)	0	1 (1)
QTcB	37	76
<30 (ms)	30 (81)	54 (71)
30-60 (ms)	7 (19)	21 (28)
>60 (ms)	0	1 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.
Note: All of the increases of >60 msec in corrected QT intervals were observed in 1 subject, Subject 200723.
Cross-reference: Mod5.3.5.1\R076477-SCH-302\Sec6.5.3.2

See Section 7.1.3.3. G for a description of ADOs of QT prolongation in the elderly Phase III trial.

Results of Ongoing Open-Label Extension Trials (-702 through -705).

Reviewer Comment. *The results below (as provided in the SCS) show a higher incidence of outliers for each of the following:*

- *High heart rate than for low heart rate and for*
- *High PR interval than for low PR interval.*

In the absence of a control group the results are difficult to interpret but they are consistent with previously described results of placebo controlled short term trials that showed evidence for a drug-induced increase in heart rate and small potential effects on PR prolongation, but the later observation was inconsistent across Pal groups. .

Table 87: 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 ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) n (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
Heart rate	106	128	173	504	103	143	382	775
Abnormally high	32 (30)	34 (27)	21 (12)	90 (18)	28 (27)	40 (28)	81 (21)	164 (21)
Abnormally low	3 (3)	9 (7)	2 (1)	30 (6)	2 (2)	5 (3)	7 (2)	44 (6)
PR interval	105	128	172	504	103	143	380	775
Abnormally high	1 (1)	3 (2)	2 (1)	10 (2)	0	3 (2)	3 (1)	16 (2)
Abnormally low	0	0	0	0	0	0	0	0
QRS interval	106	128	173	504	103	143	382	775
Abnormally high	1 (1)	2 (2)	1 (1)	2 (<1)	1 (1)	0	3 (1)	4 (1)
Abnormally low	0	0	0	0	0	0	0	0
QT interval	106	128	173	504	103	143	382	775
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.

The tables below show up to 2.8% of Pal subjects (in the DB Pal/OL Pal > 3 month subgroup) who were outliers in QTc F,QTcLD, QTcL intervals of 450 msec or greater during OL treatment (OL treatment was 3-12 mg/day flexible dose in all subjects in these OL trials). Note that this large group of subjects (N=503 of which over 50 subjects are reported to have been in at least 24 weeks of the OL treatment phase) were in the over 3 month group including receiving DB Pal treatment in lead-in studies. The incidence for outliers in the < 3month subgroup of this DB Pal/OL Pal group was 2.3% or less for QTcF, QTcLD and QTcL interval prolongation. These results compare to an incidence of outliers of at least 450 msec on QTcF, QTcLD, QTcL intervals in the non-elderly short-term trial dataset, as follows (from studies -303, -304 and -305, combined and as previously shown):

- *3% or less among Pal groups (3, 6, 9, 12, and 15 mg/day groups)*
- *1.7% or less in the placebo group*

As with the short term trial dataset the QTcB interval showed the most remarkable Pal group incidence of outliers (of 450 msec or greater) as follows:

- *An incidence of approximately 12% in the over 3 month Pal-DB/Pal-OL subgroup*

The above results are compared to the following incidence of outliers on QTcB interval of at least 450 msec in the non-elderly short term trial dataset, as follows:

- *17% in the 15 mg Pal group,*
- *23% in the 12 mg Pal group,*
- *15% or less in lower dose Pal groups (3, 6 and 9 mg groups) and*
- *11% in the placebo group.*

It is difficult to interpret results of OL, non-placebo controlled trials and compare results across different studies. However, the incidence observed in OL treated subjects did not exceed the incidence observed in the DB trials. Yet, the DB trials were better designed for capturing subjects near Tmax and included more frequent ECG assessments.

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

	Treatment Group and Evaluation at Average Predose															
	Pla/Pali <=3 months (N=107)				Pla/Pali >3 months (N=128)				Pali/Pali <=3 months				Pali/Pali >3 months (N=505)			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD																
Maximum value																
Normal	103	1	0	104	126	0	0	126	170	0	0	170	490	1	0	491
>=450 - <480	2	0	0	2	2	0	0	2	1	2	0	3	6	5	0	11
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	105	1	0	106	128	0	0	128	171	2	0	173	497	6	0	503
QTcF																
Maximum value																
Normal	102	1	0	103	126	0	0	126	169	0	0	169	488	1	0	489
>=450 - <480	3	0	0	3	2	0	0	2	2	2	0	4	8	4	0	12
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2
Total	105	1	0	106	128	0	0	128	171	2	0	173	497	6	0	503
QTlc																
Maximum value																
Normal	103	1	0	104	126	0	0	126	169	0	0	169	490	1	0	491
>=450 - <480	2	0	0	2	2	0	0	2	2	2	0	4	6	5	0	11
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	105	1	0	106	128	0	0	128	171	2	0	173	497	6	0	503
QTcB																
Maximum value																
Normal	86	0	0	86	110	3	0	113	150	2	0	152	438	6	0	444
>=450 - <480	15	3	0	18	14	1	0	15	15	5	0	20	44	13	0	57
>=480	1	1	0	2	0	0	0	0	1	0	0	1	0	2	0	2
Total	102	4	0	106	124	4	0	128	165	8	0	173	482	21	0	503

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

(continued)

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

	Treatment Group and Evaluation at Average Predose															
	- Olan/Pali <=3 months (N=106) -				- Olan/Pali >3 months (N=143) -				- Total Pali <=3 months (N=391) -				- Total Pali >3 months (N=776) -			
	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total	Norm	>=450	>=480	Total
QTcLD																
Maximum value																
Normal	103	0	0	103	143	0	0	143	376	1	0	377	759	1	0	760
>=450 - <480	0	0	0	0	0	0	0	0	3	2	0	5	8	5	0	13
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	103	0	0	103	143	0	0	143	379	3	0	382	768	6	0	774
QTcF																
Maximum value																
Normal	103	0	0	103	142	0	0	142	374	1	0	375	756	1	0	757
>=450 - <480	0	0	0	0	1	0	0	1	5	2	0	7	11	4	0	15
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2
Total	103	0	0	103	143	0	0	143	379	3	0	382	768	6	0	774
QTlc																
Maximum value																
Normal	103	0	0	103	142	0	0	142	375	1	0	376	758	1	0	759
>=450 - <480	0	0	0	0	1	0	0	1	4	2	0	6	9	5	0	14
>=480	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total	103	0	0	103	143	0	0	143	379	3	0	382	768	6	0	774
QTcB																
Maximum value																
Normal	94	0	0	94	126	1	0	127	330	2	0	332	674	10	0	684
>=450 - <480	8	1	0	9	14	2	0	16	38	9	0	47	72	16	0	88
>=480	0	0	0	0	0	0	0	0	1	2	0	3	0	2	0	2
Total	102	1	0	103	140	3	0	143	369	13	0	382	746	28	0	774

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

It is critical to note the higher incidence of outliers in the over 3 month subgroups compared to the ≤ 3 month subgroups for subjects who continued on active drug in contrast to subjects that previously received DB placebo (in which the ≤ 3 month and > 3 month subgroups were generally similar on the incidence of outliers).

See results from 120-Day SUR showing a similar numerical trend for greater incidence with increasing exposure.

Appears This Way
On Original

Table 93: 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 ≤3 months (N=107) n (%)	Pla/Pali >3 months (N=128) n (%)	Pali/Pali ≤3 months (N=178) n (%)	Pali/Pali >3 months (N=505) N (%)	Olan/Pali ≤3 months (N=106) n (%)	Olan/Pali >3 months (N=143) n (%)	Total Pali ≤3 months (N=391) n (%)	Total Pali >3 months (N=776) n (%)
QTcLD	106	128	173	503	103	143	382	774
<30 (ms)	97 (92)	115 (90)	166 (96)	462 (92)	102 (99)	130 (91)	365 (96)	707 (91)
30-60 (ms)	9 (8)	13 (10)	7 (4)	40 (8)	1 (1)	13 (9)	17 (4)	66 (9)
>60 (ms)	0	0	0	1 (<1)	0	0	0	1 (<1)
QTcF	106	128	173	503	103	143	382	774
<30 (ms)	94 (89)	114 (89)	166 (96)	460 (91)	102 (99)	127 (89)	362 (95)	701 (91)
30-60 (ms)	12 (11)	14 (11)	7 (4)	42 (8)	1 (1)	16 (11)	20 (5)	72 (9)
>60 (ms)	0	0	0	1 (<1)	0	0	0	1 (<1)
QTlc	106	128	173	503	103	143	382	774
<30 (ms)	97 (92)	116 (91)	168 (97)	463 (92)	102 (99)	129 (90)	367 (96)	708 (91)
30-60 (ms)	9 (8)	12 (9)	5 (3)	39 (8)	1 (1)	14 (10)	15 (4)	65 (8)
>60 (ms)	0	0	0	1 (<1)	0	0	0	1 (<1)
QTcB	106	128	173	503	103	143	382	774
<30 (ms)	78 (74)	99 (77)	150 (87)	401 (80)	86 (83)	106 (74)	314 (82)	606 (78)
30-60 (ms)	26 (25)	26 (20)	22 (13)	97 (19)	16 (16)	36 (25)	64 (17)	159 (21)
>60 (ms)	2 (2)	3 (2)	1 (1)	5 (1)	1 (1)	1 (1)	4 (1)	9 (1)

Note: Percentages calculated with the number of subjects per parameter as denominator.

Results of Ongoing Trials -301 and -701
Results from these ongoing trials are not provided in the original submission since they are ongoing with blinded data.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Refer to Sections 7.1.1-3 regarding ADOs, SAEs and deaths in the study. Also refer to Sections 7.1.3.3 and 7.1.4.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

The sponsor did not conduct any clinical studies relevant to carcinogenicity and studies were not designed to explore potential carcinogenicity effects. According to the sponsor their postmarketing data fails to show a signal for tumors (as described on page 236 of SCS).

7.1.12 Special Safety Studies

The following lettered subheadings were selected (rather than numbered subheadings) to simplify the layout of this subsection for the reader (rather than increasing the number of digits from 7.1.12 to 7.1.12.1, etc).

A. A Special Safety Study on QT Prolongation Effects of Paliperidone, Study R076477-SCH-1009 (-SCH-1009).

Summary of the Objective and Study Design of Study –SCH-1009.
The following describes the protocol which was reviewed as a special protocol assessment (6/25/04 N050 MS submission) and as an amended protocol (N089 12/14/04 submission) under IND 65850.

This DB, active-moxifloxacin controlled, multicenter (17 US sites) study examined the effects of IR Paliperidone to placebo treatment (in a cross-over design) on QT interval in patients with schizophrenia or schizoaffective disorder (18-50 years old, generally healthy with ECG parameter values within a normal cut- off value). The study was conducted in an inpatient setting.

Treatment. All subjects will first receive placebo on Day 1 and subjects commenced active treatment on Day 2 as follows (placebo dummy dosing was employed and all treatment capsules were identical in appearance):

- IR Pal group: 4 mg po on Day 2, 6 mg on Day 3, and 8 mg QD on Days 4-8.
- Moxifloxacin group: placebo treatment with dummy dosing on Days 1-7, then a single dose (SD) of 400 mg po moxifloxacin on Day 8

All treatment capsules were identical in appearance and placebo dummy dosing was employed to maintain the DB study design.

Key Eligibility Criteria
The following are selected, key inclusion criteria (copied from the CSR) that included meeting specified values on ECG parameters and on body weight:

- Men or women between the ages of 18 and 50 years, inclusive;
- Diagnosis of schizophrenia or schizoaffective disorder as defined by DSM-IV criteria, with no exacerbation of psychosis for at least 3 months before screening;
- Normal 12-lead ECG, with:
  - Normal sinus rhythm (heart rate between 50 and 100 beats per minute [bpm]);
  - QTcB interval ≤430 ms for men, and ≤450 ms for women;
  - QRS interval <110 ms;
  - PR interval <200 ms;
- Weight ≥50 kg (≥110 lb), with a body mass index (BMI) ≥18 and ≤35 kg/m^2;

The following are selected, key exclusion criteria that included meeting outlier criteria relevant to cardiac related parameters or having pre-existing conditions or risk factors (copied from the CSR) :

- Clinically significant abnormality on ECG at screening or on Day -1 of the study;
- Heart rhythm disturbance known or suggested by history, or demonstrated on ECG at screening;
- Blood pressure outside the normal range (supine systolic blood pressure <90 or >140 mmHg and/or diastolic blood pressure <50 or >90 mmHg);
- Unusual T-wave morphology in a majority of the ECG leads (e.g. bifid T waves, low T waves) or prominent U waves at screening;
- History of additional risk factors for TdP, such as heart failure, hypokalemia, family history of known long QT syndrome (LQTS), or sudden unexplained death at a young age (≤ 40 years) in a first degree relative such as a biological parent, sibling, or offspring;
- More than 10 cigarettes smoked per day;

Limited use of ibuprofen, benztropine, lorazepam and zolpidem treatment were permitted, as needed for appropriate symptoms (as specifed in the CSR) within restrictions outlined in Section 3.8 of the CSR (also benztropine or lorazepam could not be given during 6 hours prio to ECG recordings).

ECG and PK Assessments ECG assessments and blood samples for Paliperidone plasma levels were conducted at multiple time-points from Day 1 of placebo treatment, Day 2, Day 3-8 during active treatment, as well as on post-treatment ECG assessments on Days 9 and 10 after the 8-day blinded treatment phase. Assessments were also included on time-points near the anticipated Tmax after each daily dose on Days 1-4 and Day 8 (including a pre-dose assessment on these days) and at similar time-points on the 2 post-treatment days, Days 9 and 10 (corresponding to the same time-points used on treatment Days 1-4 and 8). Pre-dose assessments will be conducted on all treatment days (a -24 hour assessment on Day -1 will be conducted) and at the same corresponding time on each post-treatment day. Sections 9.3 and 9.3.1 of the protocol (under the IND) described ECG assessment methods and ECG reading methods. These sections also describe methods addressing potential confounding variables such as activity prior to readings, diurnal effects, effects of meals and others.

Tables 10.4 and 10.5 in the Appendix of this review provide the study schedule and the schedule for ECG assessments and PK blood sampling, respectively (as provided in the CSR).

Other Safety Assessments. Vital signs (no orthostatic measures) will be conducted at baseline and at the end of the study (not during treatment). Laboratory assessments and recording adverse events are included as safety assessments and screening tests will be performed as specified and as listed in the Time and Events Schedule in Table 10.3 series in the appendix of this review.

Concomitant Medications. Benztropine, lorazepam, zolpidem, ibuprofen or acetaminophen are allowed concomitant drugs on a PRN basis (as specified in Section 8). However, benztropine and lorazepam are not permitted on the days of ECG assessments. The following information was provided on concomitant medication use during the study. The table below was a part of the sponsor table in which the incidence of the more commonly used medications are shown (an incidence of at least 5%).

Attachment 1.4.2: Concomitant Therapies Administered Between Days 1 and 8 (Ph Analysis Set)

STUDY R076477-SCH-1009

Output DSUB.07: Summary of Concomitant Therapies within 8 Days of Start of Study Medic

Analysis Set: PD
Prior/concomitant Medication: Concom

Medication Generic Term	PALIPERIDONE (N=42) n (%)	MOXIFLOXACIN (N=57) n (%)	Total (N=99) n (%)
Lorazepam	26 (62)	31 (54)	57 (58)
Zolpidem tartrate	20 (48)	19 (33)	39 (39)
Ibuprofen	9 (21)	10 (18)	19 (19)
Paracetamol	3 (7)	9 (16)	12 (12)
Benzatropine mesilate	6 (14)	1 (2)	7 (7)
Zolpidem	1 (2)	6 (11)	7 (7)
Famotidine	1 (2)	4 (7)	5 (5)
Multivitamins	1 (2)	3 (5)	4 (4)
Sertraline hydrochloride	2 (5)	2 (4)	4 (4)
Amlodipine besilate	1 (2)	2 (4)	3 (3)
Hydrocortisone	0	3 (5)	3 (3)
Mylanta	2 (5)	1 (2)	3 (3)
Cepacol lozenge	0	2 (4)	2 (2)
Docusate sodium	1 (2)	1 (2)	2 (2)
Fluoxetine hydrochloride	1 (2)	1 (2)	2 (2)
Lansoprazole	0	2 (4)	2 (2)
Lisinopril	2 (5)	0	2 (2)

Concomitant Cardiovascular Conditions
Upon request the sponsor provided information on pre-existing cardiovascular conditions.

Reviewer Comment. *The most common cardiovascular condition was hypertension with a few subjects showing heart rate abnormalities (e.g. intermittent bradycardia or rapid pulse, each in 1 subject) or ECG abnormalities (e.g. first degree AV block in 1 subject, T wave abnormality in another subject).*

STUDY R076477-SCH-1009

Output: Medical History: Cardiovascular Abnormalities Reported at Screening

Analysis Set: Safety

Treatment Arm	Subject Number	Sex	Age	Reported Term for Condition
MOXIFLOXACIN	109021	MALE	46	SINUS BRADYCARDIA - INTERMITTENT
	109071	MALE	51	HYPERTENSION
	109086	MALE	46	PALPITATIONS BEGINNING IN 2000, ENDING IN 2001 DUE TO INCREASE IN DOSAGE OF SEROQUEL. HIGH AND LOW HEART BEAT.
	109098	MALE	23	HYPERTENSION MAR 2001 - MAY 2001
	109112	MALE	47	LATE ENTRY: HAS BEEN TREATED WITH NORVASC & HYPERTENSION HAS REMAINED STABLE 1SMAROS
	109121	MALE	31	POOR HEART SURGERY DUE TO STAB WARD 1997
	109126	MALE	27	TERMINALLY NEGATIVE IN V1
	109133	MALE	46	HYPERCHLORESTEROLEMIA
	109150	MALE	27	T WAVE ABNORMALITIES
	109157	MALE	42	HISTORY OF LABIL HYPERTENSION
	109163	FEMALE	46	DILATED CARDIOMYOPATHY - 1997
	109197	MALE	40	H/O HYPERTENSION CONTROLLED WITH DIET; LEFT VENTRICULAR HYPERTROPHY
	109218	FEMALE	41	PREGNANCY INDUCED HIGH BLOOD PRESSURE IN 1991. CONTROLLED WITH MEDICATION.
	109220	MALE	28	HYPERTENSION
	109237	FEMALE	48	CONTINUOUS HEART MURMUR SINCE 1970 CONT HIGH BLOOD PRESSURE SINCE 2000, TREATED WITH BENICAR
PALIPERIDONE	109024	MALE	47	HYPERTENSION; STABLE ON MEDICATION
	109029	FEMALE	32	HX OF CHEST DISCOMFORT, CHEST TENDERNESS
	109047	MALE	46	HTN - START 2000, STOP 2003
	109064	FEMALE	48	RAPID PULSE - RESOLVED
	109072	MALE	43	HYPERTENSION
	109099	MALE	42	PROLONGED PR INTERVAL FIRST DEGREE A-V BLOCK
	109103	MALE	39	HYPERTENSION ONSET 2002
	109135	MALE	37	HYPERTENSION WITH HIGH CHOLESTASIS
	109159	FEMALE	31	HEART MURMUR AS A CHILD
	109166	MALE	42	HIGH BLOOD PRESSURE
	109203	MALE	46	HISTORY OF HYPERTENSION SINCE 2002 STABLE AND CONTROLLED
	109223	MALE	50	HYPERTENSION

Pharmacogenomics Blood samples were collected (upon informed consent) for genetic analysis, since some genotypes may be associated with QT prolongation effects.

Calculations of QTc Interval and Dav-averaged QTcLD Parameters

The following outlines equations used for calculation QTc intervals:

- Linear Derived: QTcLD (sec) = QT+b[1–RR], where b is the estimated slope using a linear regression techniques as described in Section 3.11.2.1 of the CSR. Also refer to Section 7.1.9.3.1. This method of QTc is described by the sponsor as a linear model that "incorporates all drug free QT/RR interval data" and is also intended to correct for study specific differences in this data.
- Bazett: $QTcB=QT/RR_{0.5}$
- Sagie: QTlc=QT + 0.154 (1-RR), and
- Fridericia: $QTcF=QT/RR_{(1/3)}$

Calculation of Day Averaged ECG Parameters

The following describes methods for calculating day-averaged QTc parameters (copied from the CSR):

> The primary endpoint was the difference with placebo (Day 1) in day-averaged QTcLD values. Day-averaged parameters were calculated for the 7 days with complete ECG profiles: Days 1 to 4 and 8 to 10. Since times between ECG intervals on a day are unequally spaced, the day-average was calculated as a weighed mean: $\left(\sum_{i=2}^{10}\left(\frac{(V_i+V_{i-1})}{2}*(T_i-T_{i-1})\right)\right)\Big/(T_{10}-T_0)$ with V_i the value (e.g. QTcLD) at time T_i. T_0 being the first assessment on a day (scheduled at 8:00), T_1 being the next (scheduled at 8:30), continuing until the last T_{10} (scheduled at 20:00). Parameters were considered missing, if more than 3 values out of 11 constituting the average are missing. If more than 2 assessments between T_1 (+30min) and T_8 (+4h) were missing, the weighted average was set to missing.

Study Results

The summary tables and figures shown below were provided in the SCS or in the CSR of the submission.

Reviewer Comments on results shown below. *Note that maximal least square mean increases in QTcLD interval from baseline to a given post-dose time-point is at 1.5 hours post-dose on each Pal treatment day which is near the anticipated Tmax for this IR formulation. Note that greater prolongation occurs with higher dose-levels (when comparing results of the 8 mg dose-level to each of the 2 lower daily dose-levels of 4 mg and 6 mg, respectively) and over successive treatment days which includes successive treatment days in which the daily dose-level was fixed (between Days 4 and 8 during which Pal subject received a daily dose of 8 mg). However, the 6 mg dose-level (given on Day 3) shows a similar increase in QTc intervals to that observed with the lower daily dose-level of 3 mg given on Day 2. It is difficult to determine if the similar prolongation effects of Pal at these two lower dose-levels is reflecting a potential influence of time of exposure (e.g. where there may be some physiological adaptation to the QT prolongation effects with repeated or prolonged exposure) or if these findings truly reflect that the 3 mg and 6 mg dose-levels have a similar effect on QT interval. Finally, it is important to note that the QT prolongation effects are reversible upon dechallenge.*

Another critical consideration with interpreting the results is that a greater QT prolongation effect may have been observed at daily dose-levels above the 3 mg dose-level if Pal subject had not been titrated to the higher dose-levels. That is, a study using a fixed dose, parallel group design to examine different Pal dose-levels may have yielded greater prolongation effects at dose-levels above the 3 mg dose-level. Consider the possibility for a degree of physiological adaptation to a drug effect on QT prolongation that may occur over time with multiple dosing. The sponsor suggests that such an adaptation may be occurring based on results described later in this review Consequently, the daily dose-levels above 3 mg, (e.g. the 6 mg and 8 mg dose-levels employed in the study) may actually show greater QT prolongation effects in Pal-drug naïve subjects or in subjects that do not undergo adequate titration to the higher dose-levels.

While considering that QT prolongation effects at daily dose-levels above 3 mg may be greater than that observed in Study -1009, note that the least square mean values for QTcLD exceeded 10 msec at 1.5 hour post-dose on Day 8 in Pal subjects. The upper limit of the 90% confidence interval (CI) exceeded 10 msec at this same 1.5 hour post-dose time-point on Day 2 (the first day of Pal treatment which was at the 4 mg daily dose-level in which QTcLD was 11.9 msec), and again on Days 4 and 8 (12.3 and 13.6 msec, respectively). The upper limit of the 90% CI for QTcLD interval on Day 3 (at the 6 mg daily dose-level) reached 9.4 msec at the 1.5 hour post-dose time-point. None of the Pal subjects had prolonged QTc values (exceeding 450 msec for males or 470 msec for females) except for QTcB which was prolonged in 7 out of 72 Pal subjects (approximately 10%). However, 3-4% of subjects showed borderline prolongation of QTc interval during Pal treatment (values of 430-450 msec for men and 450-470 msec for women), except for QTcB which showed borderline prolongation in 31 out of 72 Pal subjects (43%).

26 to 28% of Pal subjects showed a 30-60 msec increase from baseline to their maximal on-treatment values in QTc interval for any of the correction methods, except for QTcB interval which showed a 30-60 msec increase in 82% of Pal subjects. None of the Pal subjects showed a QTc increase of greater than 60 msec, except for QTcB in which only 1 Pal subject showed an of over 60 msec increase. As previously described QTcB values are not considered accurate in determining the degree of QT prolongation since heart rate is increased by Pal.

Given the above comments, it is also notable the large between subject variance on plasma levels, the large effect of food on plasma levels based on food effect Phase I results, among other factors that can lead to higher plasma levels. PK results are shown below with further reviewer comments.

Table 108: Day-Averaged QTcLD: Least Square Mean Differences From Day 1 (Study R076477-SCH-1009: Per-Protocol Analysis Set)

Treatment Arm	Visit	Treatment Group	LSMean (SE)	LSMean Difference (SE)	90% CI on LSMean Difference[a,b]
IR Paliperidone (N=44)	Day 1	Placebo	387.6 (2.22)		
	Day 2	4 mg IR q.d.	390.6 (2.23)	3.0 (1.10)	(1.18; 4.79)
	Day 3	6 mg IR q.d.	388.1 (2.22)	0.6 (1.09)	(-1.23; 2.36)
	Day 4	8 mg IR q.d.	390.5 (2.23)	2.9 (1.10)	(1.13; 4.75)
	Day 8	8 mg IR q.d.	393.0 (2.22)	5.5 (1.09)	(3.66; 7.25)
	Day 9	Posttreatment	390.5 (2.22)	3.0 (1.09)	(1.18; 4.77)
	Day 10	Posttreatment	389.8 (2.22)	2.2 (1.09)	(0.45; 4.05)
Moxifloxacin (N=58)	Day 1	Placebo	391.8 (1.87)		
	Day 2	Placebo	391.8 (1.87)	-0.0 (0.84)	(-1.40; 1.36)
	Day 3	Placebo	390.6 (1.87)	-1.2 (0.84)	(-2.59; 0.17)
	Day 4	Placebo	391.1 (1.87)	-0.7 (0.84)	(-2.09; 0.67)
	Day 8	400 mg q.d.	396.1 (1.87)	4.3 (0.84)	(2.88; 5.64)
	Day 9	Posttreatment	393.1 (1.87)	1.3 (0.84)	(-0.10; 2.65)
	Day 10	Posttreatment	390.8 (1.87)	-1.0 (0.84)	(-2.38; 0.38)

[a] The 2-sided 90% confidence intervals around the mean difference in day-averaged QTcLD during and after paliperidone treatment compared with day-averaged QTcLD on during placebo treatment (Day 1) was constructed using the estimated least-squares means and variances from the mixed models with treatment as a fixed effect and subject as a random effect.

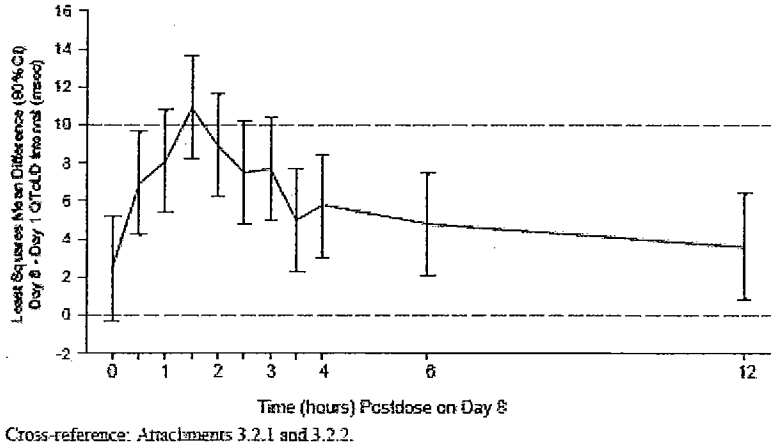
[b] The mean effect of IR paliperidone 8 mg at steady-state (Day 8) on QTc interval was considered "negative" if the 2-sided 90% confidence interval excluded 10 msec. Assay sensitivity was confirmed, i.e., moxifloxacin 400 mg had a positive effect on QTc interval if the 2-sided 90% confidence interval excluded 0 msec.

Cross-reference: Mod5.3.5.4\R076477- SCH-1009\Sec7.2.1.1.

Table 109: QTcLD: Least Square Mean Differences From Day 1 on Days 2, 3, 4, 8, 9, and 10 at Each Time Point (Study R076477-SCH-1009: Paliperidone-Treated Subjects [N=44] in the Per Protocol Analysis Set)

Time Postdose	LS Mean Difference	SE	90% CI LL	90% CI UL	LS Mean Difference	SE	90% CI LL	90% CI UL	LS Mean Difference	SE	90% CI LL	90% CI UL
	Day 2 (PAL 4 mg)				Day 3 (PAL 6 mg)				Day 4 (PAL 8 mg)			
Predose	0.70	1.66	-2.00	3.45	0.40	1.66	-2.36	3.11	1.00	1.66	-1.77	3.68
0.5 h	4.70	1.66	2.02	7.46	2.80	1.65	0.07	5.49	5.50	1.65	2.75	8.17
1.0 h	4.90	1.64	2.22	7.60	4.30	1.64	1.58	6.96	5.60	1.64	2.90	8.28
1.5 h	9.30	1.65	6.56	11.98	6.70	1.64	4.04	9.42	9.60	1.64	6.92	12.31
2.0 h	5.50	1.65	2.76	8.18	4.60	1.64	1.94	7.33	7.30	1.64	4.56	9.94
2.5 h	3.40	1.64	0.67	6.06	4.00	1.64	1.35	6.74	4.70	1.65	1.98	7.40
3.0 h	4.00	1.64	1.33	6.71	2.80	1.64	0.10	5.49	7.20	1.66	4.52	9.97
3.5 h	3.40	1.64	0.74	6.12	-0.10	1.64	-2.83	2.56	3.70	1.65	0.95	6.37
4.0 h	2.90	1.64	0.22	5.60	2.00	1.64	-0.65	4.74	3.20	1.65	0.52	5.93
6.0 h	2.00	1.64	-0.74	4.65	-1.30	1.64	-3.94	1.44	1.30	1.64	-1.37	4.01
12.0 h	1.80	1.65	-0.86	4.55	-1.10	1.66	-3.82	1.63	1.30	1.65	-1.45	3.96
	Day 8 (PAL 8 mg)				Day 9 (Posttreatment)				Day 10 (Posttreatment)			
Predose	2.50	1.66	-0.27	5.18	2.00	1.66	-0.74	4.74	0.90	1.66	-1.87	3.61
0.5 h	6.90	1.65	4.21	9.62	4.90	1.65	2.18	7.60	7.20	1.65	4.48	9.89
1.0 h	8.10	1.64	5.40	10.78	4.10	1.64	1.44	6.83	2.20	1.64	-0.51	4.87
1.5 h	10.90	1.64	8.24	13.62	5.00	1.64	2.26	7.65	2.70	1.64	0.04	5.42
2.0 h	8.90	1.64	6.22	11.60	5.30	1.65	2.63	8.04	1.70	1.64	-1.03	4.35
2.5 h	7.50	1.65	4.83	10.24	1.70	1.65	-1.02	4.39	0.40	1.64	-2.26	3.12
3.0 h	7.70	1.64	4.99	10.37	3.40	1.64	0.69	6.08	1.70	1.64	-1.03	4.35
3.5 h	5.00	1.64	2.29	7.67	4.00	1.64	1.31	6.69	1.50	1.64	-1.21	4.17
4.0 h	5.80	1.64	3.06	8.44	1.20	1.65	-1.53	3.89	1.90	1.64	-0.83	4.56
6.0 h	4.80	1.64	2.08	7.46	1.30	1.65	-1.40	4.01	0.90	1.64	-1.78	3.60
12.0 h	3.60	1.65	0.93	6.35	3.80	1.66	1.10	6.54	3.90	1.66	1.20	6.64

The following figure was found in the CSR. The least square mean difference of QTcLD from Day 1 (placebo treatment day) to each assessment time-point on Day 8 (the seventh day of Pal treatment) is shown (using a mixed model with fixed effects for study days, assessment time-points, that was fit to individual QTcLD values for each treatment group).



Cross-reference: Attachments 3.2.1 and 3.2.2.

The following tables summarize the incidence of QTc interval outliers (copied from the CSR).

Table 15: Number of Subjects With a Maximum Change in QTc Interval of 30 to 60 ms or ≥60 ms
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)			Placebo/Moxifloxacin (N=69)		
	Total	QTc Interval ↑ (ms)		Total	QTc Interval ↑ (ms)	
Parameter	n (%)	30-60	>60	n (%)	30-60	>60
QTcLD	19 (26)	19	0	12 (17)	12	0
QTcF	19 (26)	19	0	11 (16)	11	1
QTlc	20 (28)	20	0	13 (19)	13	0
QTcB	59 (82)	59	1	26 (38)	26	0

Number of subjects with a maximum increase in QTc of 30-60 ms or >60 ms at any time during the study relative to time-matched QTc intervals on Day 1 (placebo).

Cross-reference: Attachment 3.4.

Table 16: Number of Subjects With a Maximum QTc Interval That Was Borderline or Prolonged
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)			Placebo/Moxifloxacin (N=69)		
	Total	QTc Interval		Total	QTc Interval	
Parameter	n (%)	Borderline	Prolonged	n (%)	Borderline	Prolonged
QTcLD	2 (3)	2	0	5 (7)	5	0
QTcF	3 (4)	3	0	6 (9)	6	0
QTlc	2 (3)	2	0	5 (7)	5	0
QTcB	31 (43)	31	7	24 (35)	24	1

Note: QTcLD is a derived parameter.
Criteria for Borderline QTc: 430-450 ms for men, 450-470 ms for women
Criteria for Prolonged QTc: >450 ms for men, >470 ms for women

Cross-reference: Attachment 3.5

Table 17: Number of Subjects With Absolute QTc Prolongation ≥450 ms, ≥480 ms, or >500 ms
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)					Placebo/Moxifloxacin (N=69)				
		Maximum QTc Interval (ms)					Maximum QTc Interval (ms)			
	n	Normal	≥450	≥480	>500	n	Normal	≥450	≥480	>500
QTcLD	72	72	0	0	0	69	69	0	0	0
QTcF	72	72	0	0	0	69	69	0	0	0
QTlc	72	72	0	0	0	69	69	0	0	0
QTcB	72	63	8	1	0	69	63	6	0	0

Cross-reference: Attachment 3.6.

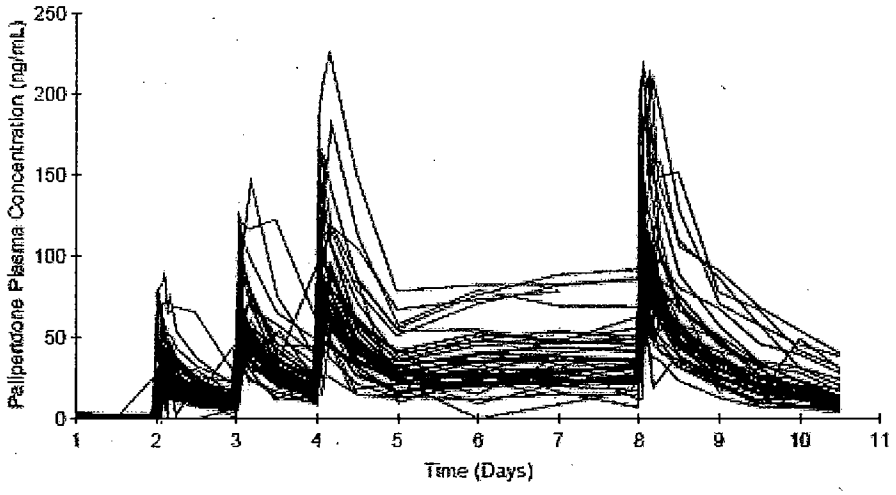
PK Results

The SCS indicates that steady state mean Cmax plasma levels of IR Pal during daily treatment with 8 mg IR Pal was 113 ng/L (using Day 8 data). According to the sponsor, this mean Cmax level is 2-fold higher than mean Cmax level with daily treatment of the highest dosage of Pal (ER OROS Pal formulation) used in the Phase III trials (mean Cmax=57.4 ng/mL with 15 mg OROS Pal/ daily).

Reviewer Comments. *Note that in the scatterplot below, of plasma levels of individual subjects over time, that more subjects exceeded 100 ng/ml on Day 8 (the fifth day on the 8 mg daily dose-level) compared to Day 4 (the first day of the 8 mg daily dose-level). Mean Cmax levels on these days could not be found in the in-text sections of the CSR but according to that described in the CSR steady state levels were reached by Day 6 (the third day at the 8 mg daily dose-level). However, according to that described in the CSR, steady state levels were reached by Day 6 (the third day at the 8 mg daily dose-level). Consequently one should not anticipate higher Cmax levels with longterm treatment beyond levels observed in Day 8. Yet, accumulation of the drug among other factors can also affect plasma levels, such as the known food effect on levels with Pal treatment. With respect to potential drug accumulation the T ½ is long (mean T ½ is 23.2 hours with a range of 10.6 to 51.1 hours, according to that described in the CSR. Furthermore, the relationship between dose-level and mean Cmax and mean AUC-24hr is not linear but instead a 3.2 and 3.5 times greater, respectively, at the 8 mg daily dose-level (on Day 8) compared to exposure at the 4 mg dose-level on day 2. This issue will be discussed later in this review, with respect to [redacted] OROS Pal and anticipated plasma levels relative to anticipated effects on QT prolongation based on results of Study -1009.*

The following table shows plasma levels of each individual subject over time, as provided in the CSR.

Figure 3: Overlay Plasma Concentration-Time Profiles of Paliperidone on Days 1 through 10
(Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



Cross-reference: Attachment 2.3.

The following table provides PK results (as provided in the CSR).

Table 11: Pharmacokinetic Parameters Calculated From the Paliperidone Concentration-Time Profiles on Days 2 through 8 (Study R076477-SCH-1009; Pharmacokinetic Analysis Set)

	Day 2				Day 3	Day 4	Day 5	Day 6	Day 7
	$C_{pre,D2}$ (ng/mL)	$C_{max,D2}$ (ng/mL)	$t_{max,D2}$ (h)	$AUC_{24,D2}$ (ng.h/mL)	$C_{pre,D3}$ (ng/mL)	$C_{pre,D4}$ (ng/mL)	$C_{pre,D5}$ (ng/mL)	$C_{pre,D6}$ (ng/mL)	$C_{pre,D7}$ (ng/mL)
N	63	63	63	58	58	52	49	49	49
Mean	BQL	35.2	2.07	437	10.4	20.7	30.2	35.0	36.9
SD	-	14.9	0.90	198	4.77	10.1	14.1	18.2	18.3
CV%	-	42.3	43.4	45.4	45.9	48.7	46.8	52.1	49.6
Median	BQL	32.7	2.05	420	9.86	18.7	27.1	29.9	33.1
Minimum	BQL	16.0	0.55	109	BQL	8.82	9.90	BQL	8.55
Maximum	26.2	89.3	4.08	1398	26.9	61.8	78.7	82.3	88.6

	Day 8								
	$C_{pre,D8}$ (ng/mL)	$C_{max,D8}$ (ng/mL)	$t_{max,D8}$ (h)	$C_{min,D8}$ (ng/mL)	AUC_τ (ng.h/mL)	$C_{avg,ss}$ (ng/mL)	FI (%)	λ_z (1/h)	$t_{\frac{1}{2},\lambda}$ (h)
N	46	42	42	43	42	42	42	40	40
Mean	37.1	113	2.15	34.6	1531	63.8	128	0.0321	23.2
SD	18.7	43.3	1.12	18.4	647	26.9	30.9	0.00908	6.6
CV%	50.4	38.4	52.1	53.3	42.2	42.2	24.3	28.3	28.4
Median	33.4	102	2.08	30.7	1353	56.4	124	0.0299	23.2
Minimum	6.95	59.8	0.52	6.95	649	27.1	84.2	0.0136	10.6
Maximum	92.0	218	6.08	90.9	3454	144	209	0.0653	51.1

Cross-reference: Attachment 2.6.

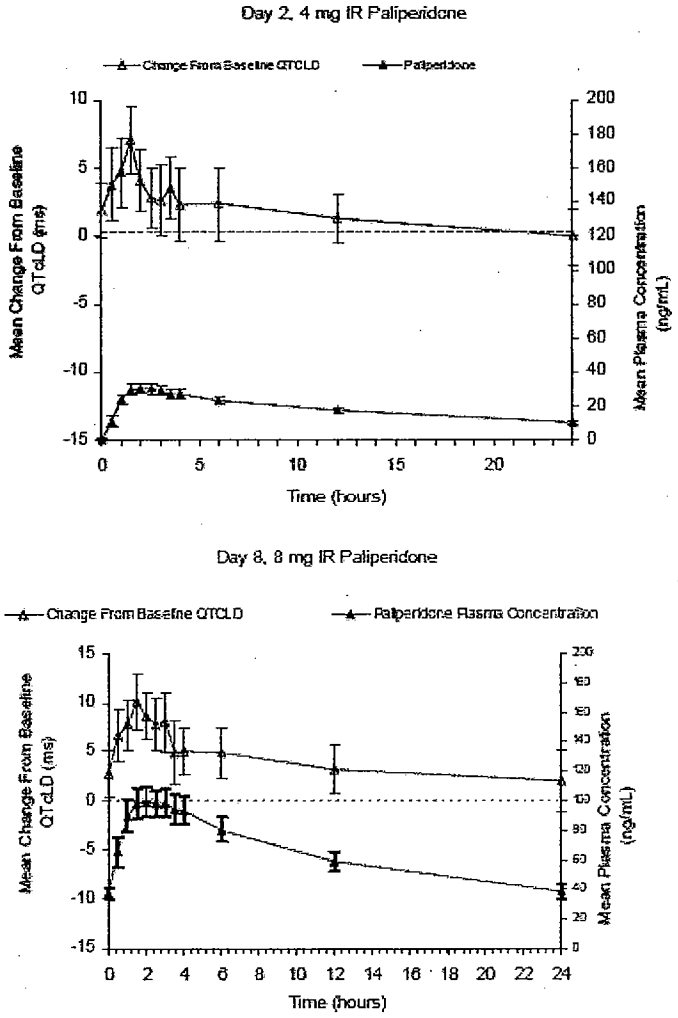
The Relationship between PK and QT Interval Effects of IR Pal

The sponsor indicates that an "apparent" positive relationship was observed between "peak plasma concentration" of IR Pal the mean increase from baseline on QTcLD interval (based on the results on the mean change in QTcLD from Day 1/placebo treatment, to Day 2/4 mg IR Pal treatment and Day 8/8 mg IR Pal and the time-matched mean plasma levels of Pal).

Yet, upon further examination of the PK-PD data (see figures below) the PK-PD relationship is more complex such that a given plasma level of Pal is not always associated with the same degree of QT prolongation effects. According to that described in the CSR, daytime variation in QTcLD influences the interpretation of the results in which the mean increase in QTcLD reaches a peak increase from pre-dose (or peak absolute values) at 4 hours post-dose on Day 1 (placebo treatment day) that was observed in the Pal group. According to the sponsor if mean values in QTcLD following Pal treatment are corrected for the day time variability in the placebo group, then Cmax more closely coincides with maximal mean QTcLD prolongation (see Figure 5 below).

The following figures illustrate mean changes in QTcLD in relation to mean plasma levels of Pal with mean values adjusted for "day-time variance" observed on the placebo treatment day, Day 1 (copied from the CSR).

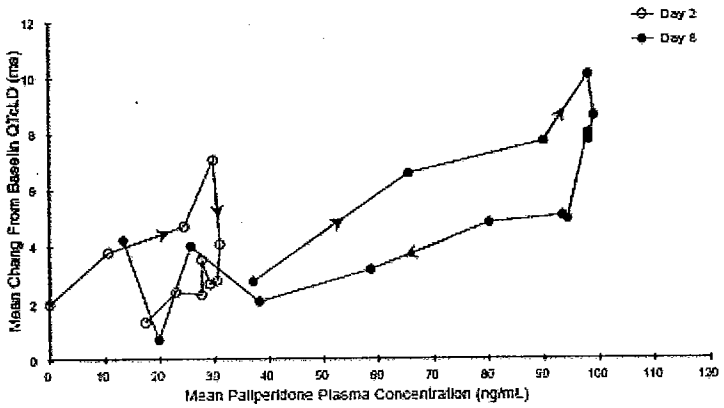
Figure 5: Mean (90% CI) Paliperidone Plasma Concentrations Versus Time-Matched Change From Baseline QTcLD Profiles as a Function of Time
(Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



The sponsor notes that while mean plasma levels remain elevated between 2 and 4 hours post-dose, that mean increases from baseline on QTcLD interval decline over time between the 2 and 4 hour time-points (as shown in the above figure with mean QTcLD values corrected for day time variability observed on the placebo treatment day, Day 1). According to that described in the CSR, these results suggest a potential physiological adaptation to QT prolongation effects with exposure of Pal over time. The figure below illustrates more clearly how initial increases in Pal plasma levels are associated with mean increases in QTcLD interval, yet these mean increases in QTcLD interval decrease in magnitude over subsequent time-points when Pal plasma levels remain constant near Cmax levels (see in the figure below that the mean QTcLD change from baseline decreases while peak mean Pal plasma levels remain elevated at close to

approximately 30 ng/ml on Day 2 or while peak levels remain elevated at close to approximately 95-100 ng/ml on day 8).

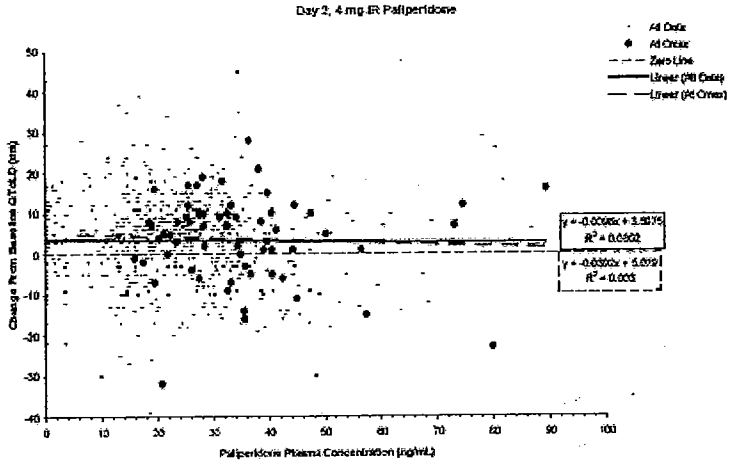
Figure 6: Mean Change From Baseline QTcLD Versus Mean Paliperidone Plasma Concentration (Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



Cross-reference: Attachment 4.5.

The figure below, copied from the CSR, further illustrates the complexity of the PK-PD relationship in which other confounding variables influencing PK and QT interval results must be considered in order to elucidate the role of PK on QT interval prolongation effects.

Figure 7: Scatter Plots of Change From Baseline QTcLD Versus Plasma Concentration of Paliperidone (Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



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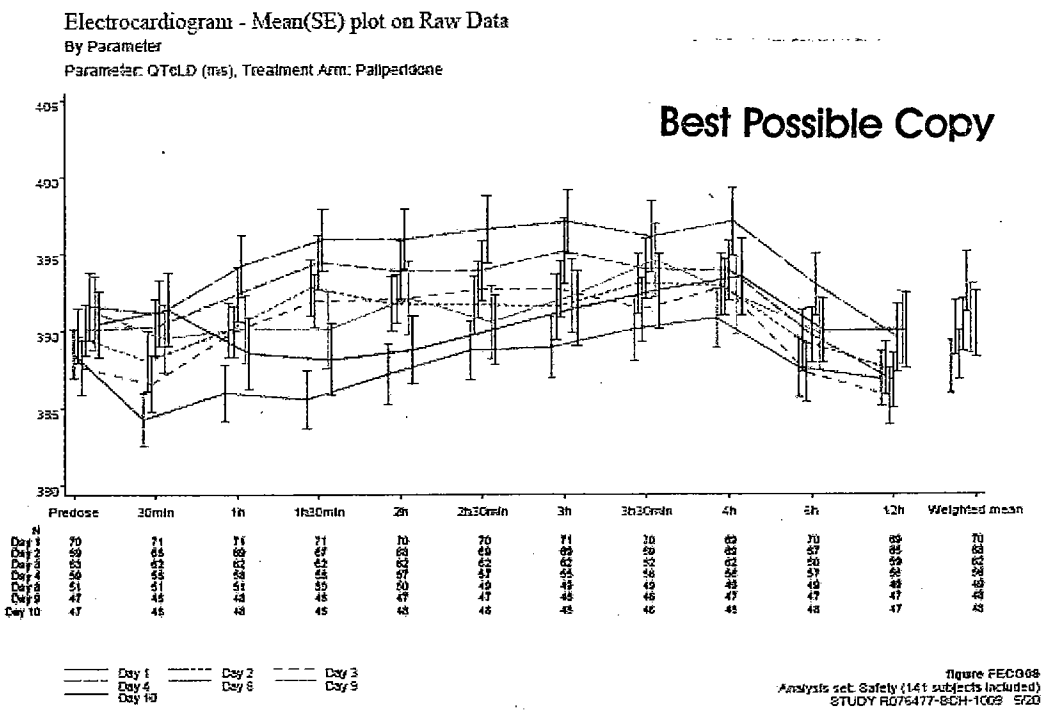
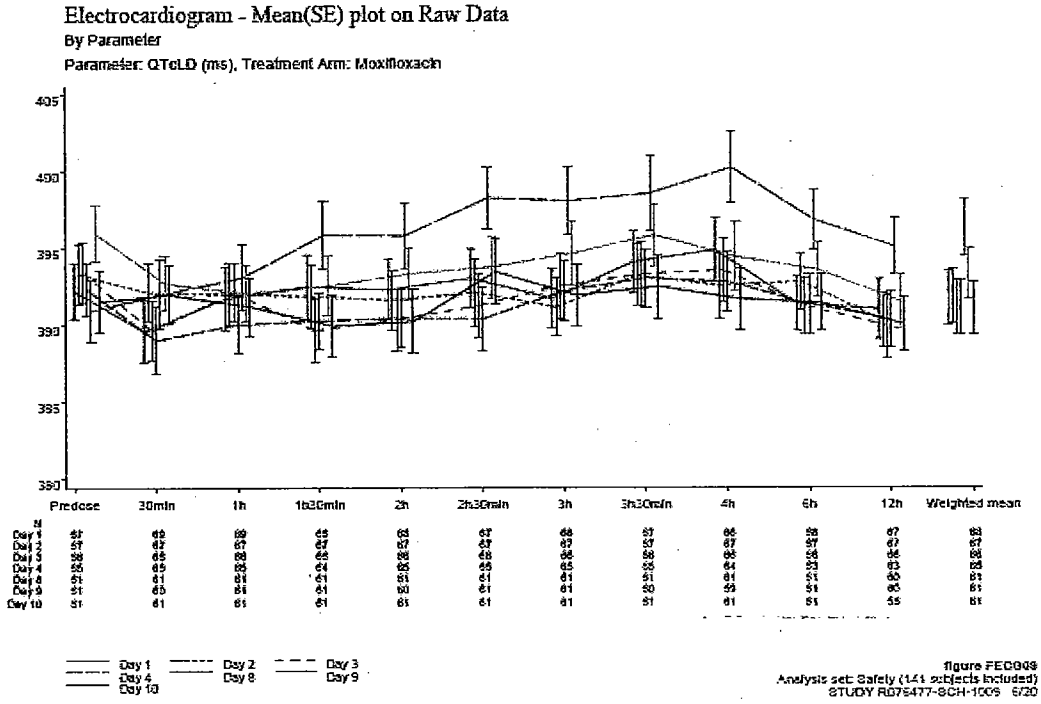
Cross-reference: Attachment 4.13.

Reveiwer Comments. *It is not clear to the undersigned reviewer how the sponsor corrected QTcLD interval data following Pal treatment to control for the day time variance in QTcLD QT inverval that was observed with placebo treatment of which the sponsor notes that peak increases were observed at 4 hours after placebo treatment. This approach may not be adequate, since it does not take into account potential variance across days and QT interval showed increases not only at the 4 hour post-dose time-point but also at other time-points. Statistical methods employed are also based on several assumptions. Figures below show raw mean QTcLD intervals over time on each treatment day of both groups (Pal group received placebo on Day 1, Pal on Days 2-8, then no treatment on Days 9 and 10, while the Moxifloxacin group received placebo on Days -7, then moxifloxacin on Day 8, followed by no treatment on Days 9 and 10). Note that the groups showed a similar magnitude of maximal QTcLD interval increases at Day 8 of treatment (when examining increases relative to pre-dose values or compared to placebo and post-treatment day values at time-points where differences were greatest for the given treatment group).*

Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



The figures below are for QTcF raw mean results over time by each treatment day

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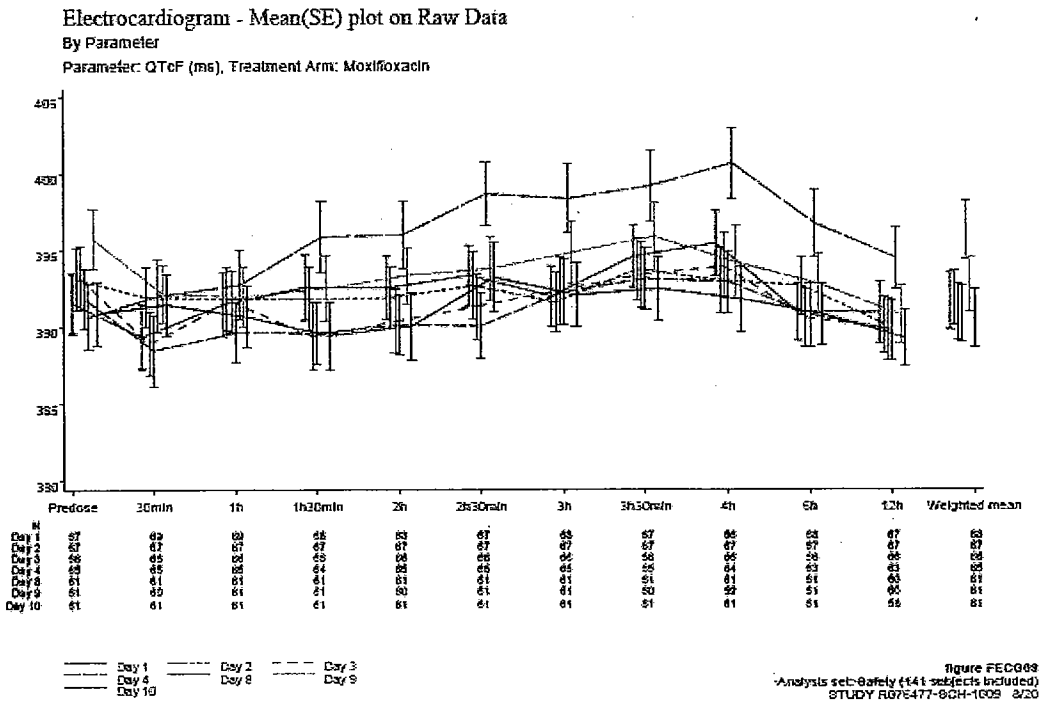

Note in the figures below that HR showed a remarkable increase following increases in QTcF and QTcLD.

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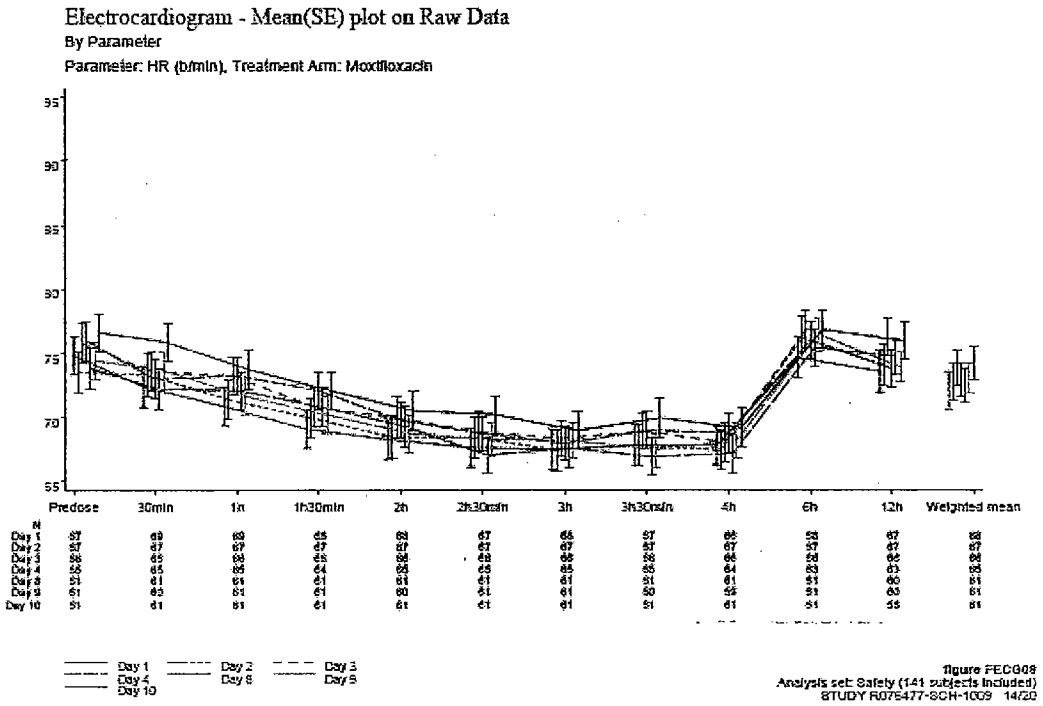
Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



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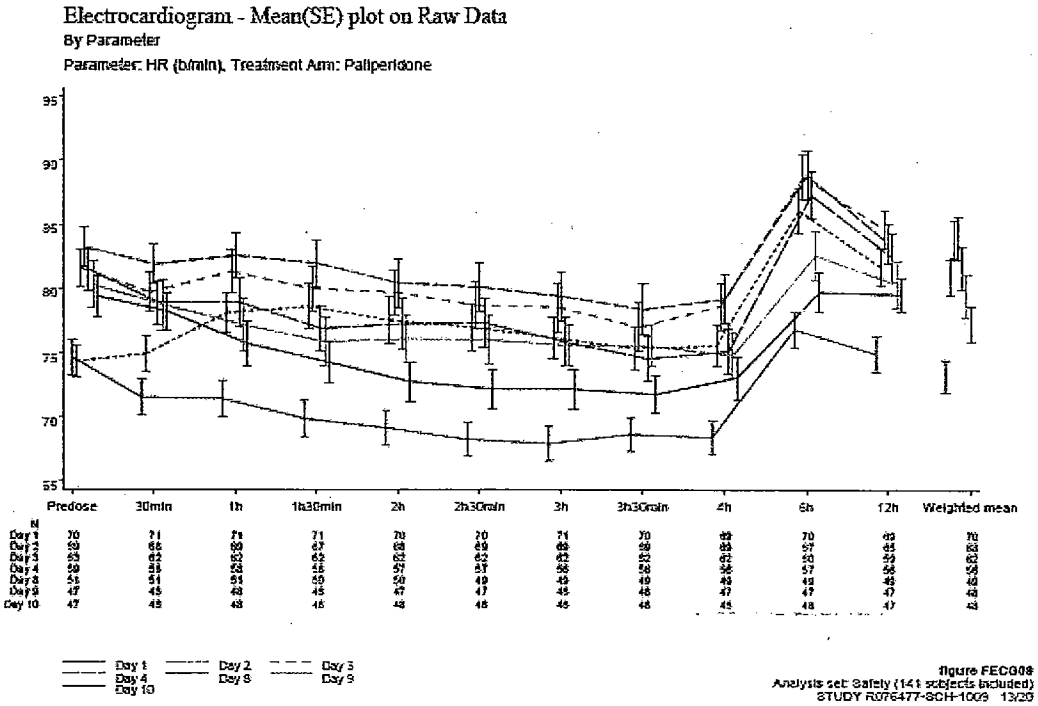
Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



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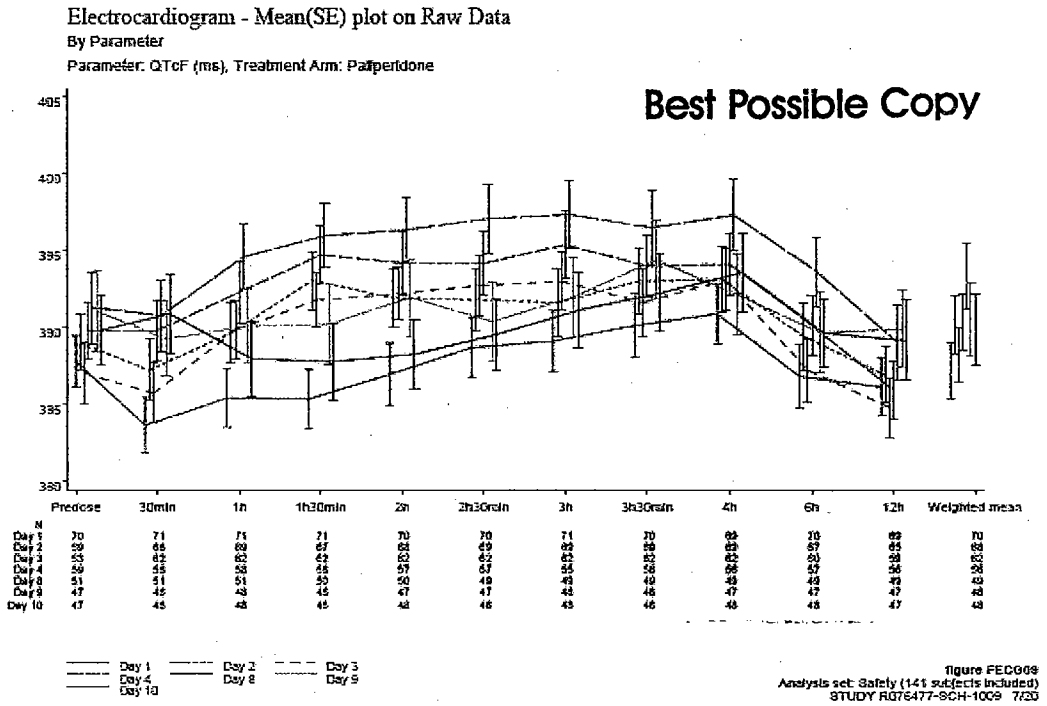
Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



See the figures below showing somewhat sustained elevations in mean QTcLD values between the time-point near Cmax for Pal plasma levels (which occurred at approximately 1.5-2 hours post-dose, as shown in the figures) to approximately 4 hours post-dose of each Pal treatment day, in which plasma levels continued to be elevated near Cmax levels. These results would suggest a close relationship between elevations in plasma elevations with increased QTcLD interval, at least during the first several hours (up to at least 4 hours) following daily dosing. It is not clear if such a relationship would continue to be observed with longterm treatment after steady state levels are achieved, since the study was not designed with this objective. Also one must consider other confounding variables that can lead to elevations in plasma levels or may increase Cmax levels over longterm treatment. Food effects are know to exist such that elevations can occur postprandial compared to the fasted state. The large between individual variance in plasma levels (based on Cmax and AUC values) also suggests the presence of other confounding variables that could lead to increased plasma levels that in turn may be associated with prolongation of QT interval. Consider the potential for accumulation of Pal with longterm treatment, particularly in organ tissues such as the myocardium.

The above factors that can result in higher Pal plasma levels and in turn, may result in greater QT prolongation effects become more critical when attempting to extrapolate results of Study - 1009 using an IR formulation to the ER, OROS formulation that the sponsor seeks to monitor. The CSR of this study indicates that the Day 8 Cmax levels of 8 mg daily IR Pal treatment in the study was 113± 43 (±SD) ng/ml, while Cmax of a 15 mg daily dose of ER OROS Pal used in

clinical trials was 57±30 ng/ml. Yet this comparison does not take into account an approximately 50% increase in plasma levels in the fed state compared to the fasted state, the potential for accumulation of the drug (also consider organ system concentrations and redistribution), potential gender differences and the large between individual variance on plasma levels. Furthermore, one must not only consider risk factors or variables adversely influencing PK, but also risk factors, pre-existing conditions and other variables that can adverse influence QT interval and Pal induced QT interval prolongation. For example, consider greater values observed in women versus men, the influence of pre-existing cardiac conditions, concomitant medications and other factors. A discussion on these issues and data relevant to these issues could not be found in the CSR of Study 1009 (e.g. gender specific results on PK or QT interval could not be found nor a discussion of how gender may confound the results).

The sponsor was asked to provide more information addressing the potential role of pre-existing concomitant cardiovascular disorders and medications. The sponsor replied in a N005 submission explaining that few subjects were receiving medications that they identified as potentially QT prolonging co-medications: sertraline hydrochloride, fluoxetine hydrochloride, haloperidol, risperidone. Only 1-2% of subjects used one of these medications and 6% of subject used any one of these medications. Also refer to a previous section showing the incidence of common (at least 5%) concomitant medications, noting that lorazepam, zolpidem and related drugs were most commonly used, as well as the anticholingergic agent benztropine mesilate. In the opinion of the undersigned, it is difficult to extrapolate a potential drug-drug interaction effect on QT or other cardiovascular or ECG effects from the data of Study -1009.

The sponsor also provided upon request information on concomitant conditions. Treatment groups showed small group differences on the incidence of pre-existing cardiac conditions (17% of paliperidone subjects compared to 22% of the moxifloxacin subjects). Upon request the sponsor provided a listing of these cardiovascular conditions (a copy of this list was previously provided in this subsection of this review). In the opinion of the undersigned, it is difficult to extrapolate a potential drug-cardiovascular interaction effect from results of Study -1009. As previously summarized, the most common cardiovascular condition was hypertension with a few subjects showing heart rate abnormalities (e.g. intermittent bradycardia or rapid pulse, each in 1 subject) or ECG abnormalities (e.g. first degree AV block in 1 subject, T wave abnormality in another subject). See the final section of this review for further comment and recommendations on the need to better characterize potential drug-drug and drug-disorder interactions effects.

Finally, another consideration with respect to interpreting results on the PK-PD relationship is that QT interval may be more strongly influenced by the rate of increase in plasma concentrations rather than on the absolute levels. A discussion or analyses of data with respect to the rate of increase in plasma levels against QT interval changes over time, cannot be found in the CSR. Although a comment is found in the CSR (page 70) in which it is suggested that smaller effects on QT interval may be "observed when plasma concentrations increase less rapidly, because there is more time for physiological adaptation."

Results of Other ECG Parameters

The following summarizes the incidence of outliers on ECG parameters.

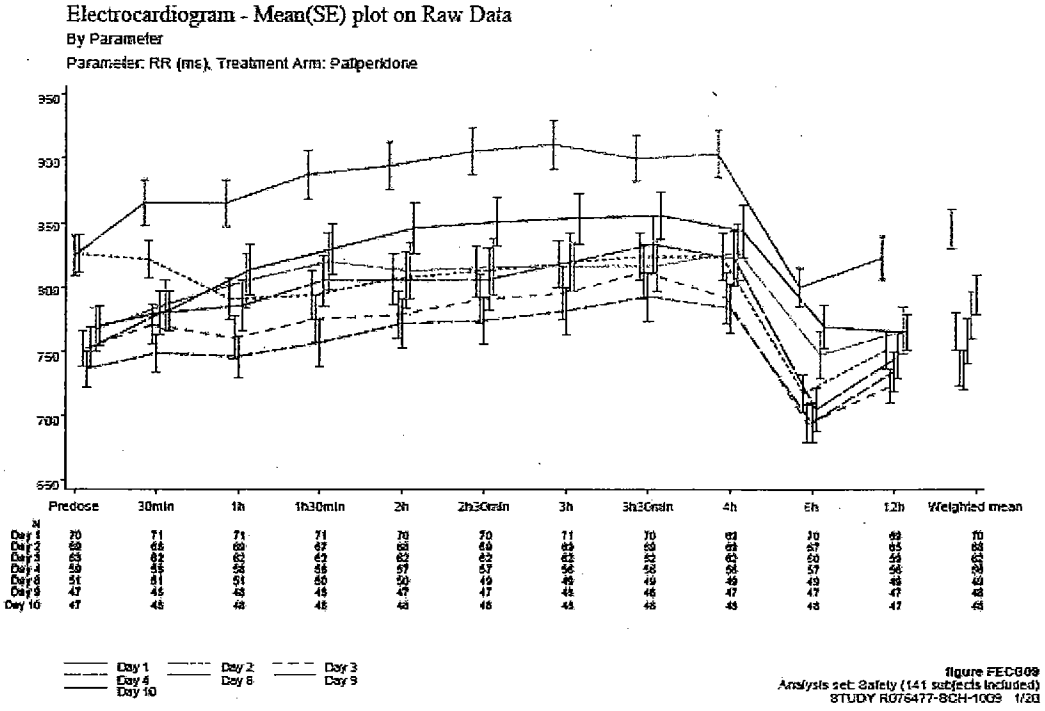
Table 18:Number of Subjects With Potentially Clinically Important Treatment-Emergent ECG Values (Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)		Placebo/Moxifloxacin (N=69)	
	n	(%)	n	(%)
Heart Rate				
> 100 bpm	26	(36)	6	(9)
< 55 bpm	18	(25)	24	(35)
QRS Interval				
> 120 ms	0		1	(1)
PR Interval				
> 200 ms	7	(10)	9	(13)
< 120 ms	4	(6)	6	(9)

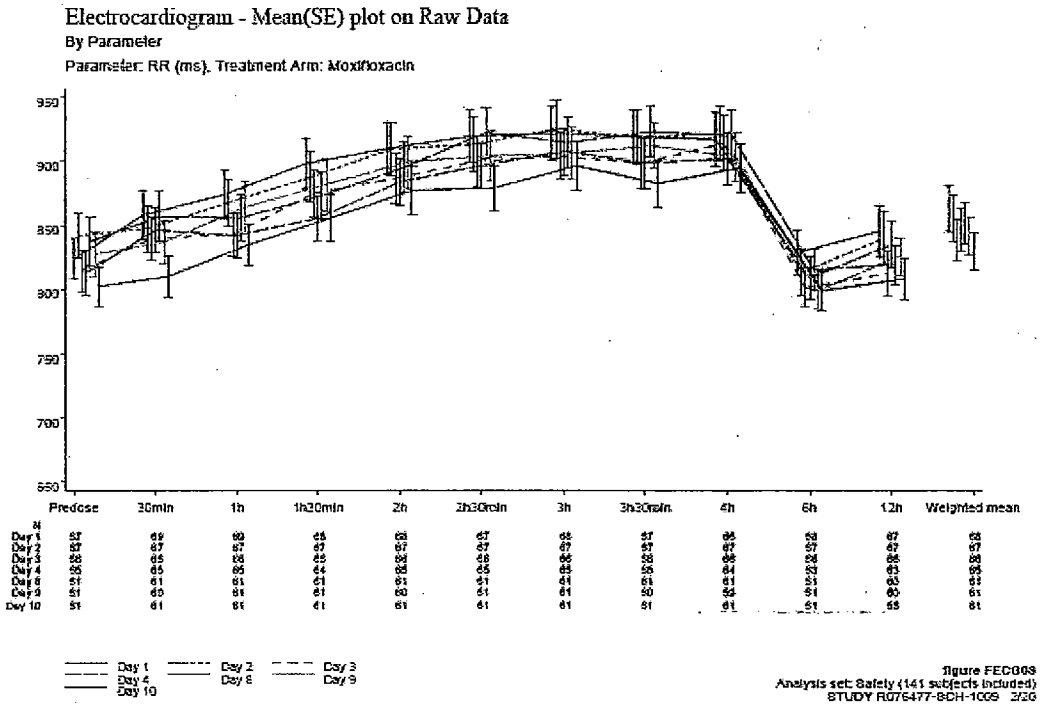
Cross-reference: Attachment 5.1

A graphical representation of study results on raw mean RR for each study day over time is shown below (with a color coded legend for each study day).

Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



A similar graphical representation for HR was previously provided in this review.

Reviewer Comments on Effects of Pal versus Moxiflaxicon Effects on PR Interval. *PR interval values generally showed decreases during treatment days compared to non-treatment days in Paliperidone, while moxifloxacin treated subjects showed not clear PR interval drug effect, as shown in the following tables. It does not appear that the differences between the treatment groups on PR interval effects cannot be accounted for by differential drug effects on HR changes over time or by study day, since the treatment groups appeared to show similar mean increases in HR at similar treatment time-points (see figures of HR, shown previously in this review).*

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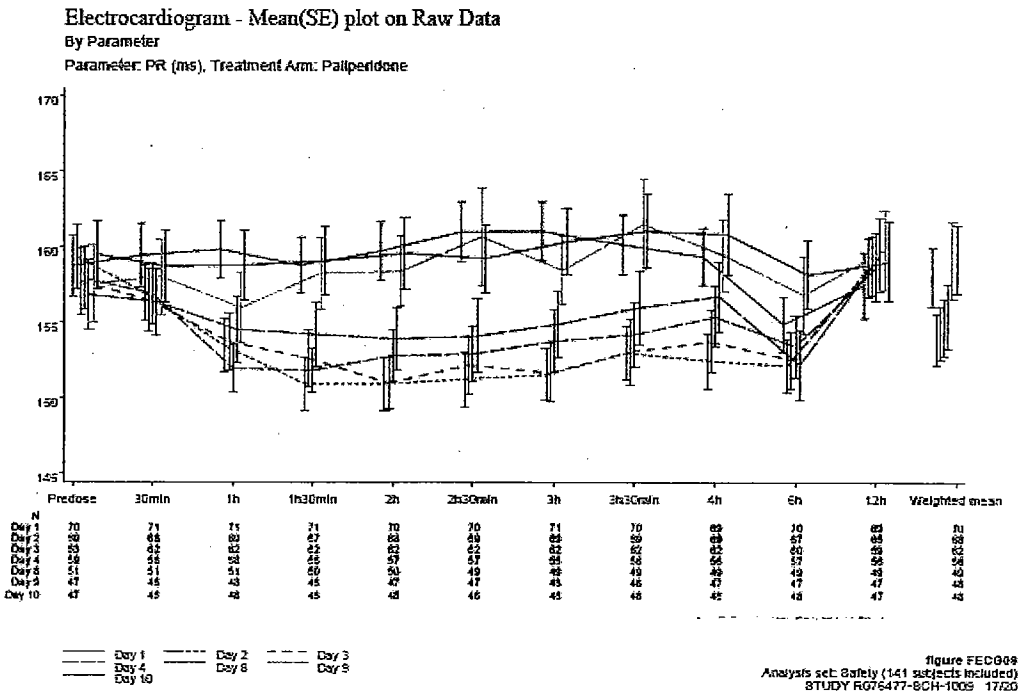
Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time



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Attachment 5.2.2: Plot of Mean Change in ECG Parameters (RR, HR, QT, QTc, PR, QRS, QRS-axis) From Day 1 on Matching Time Points Over Time

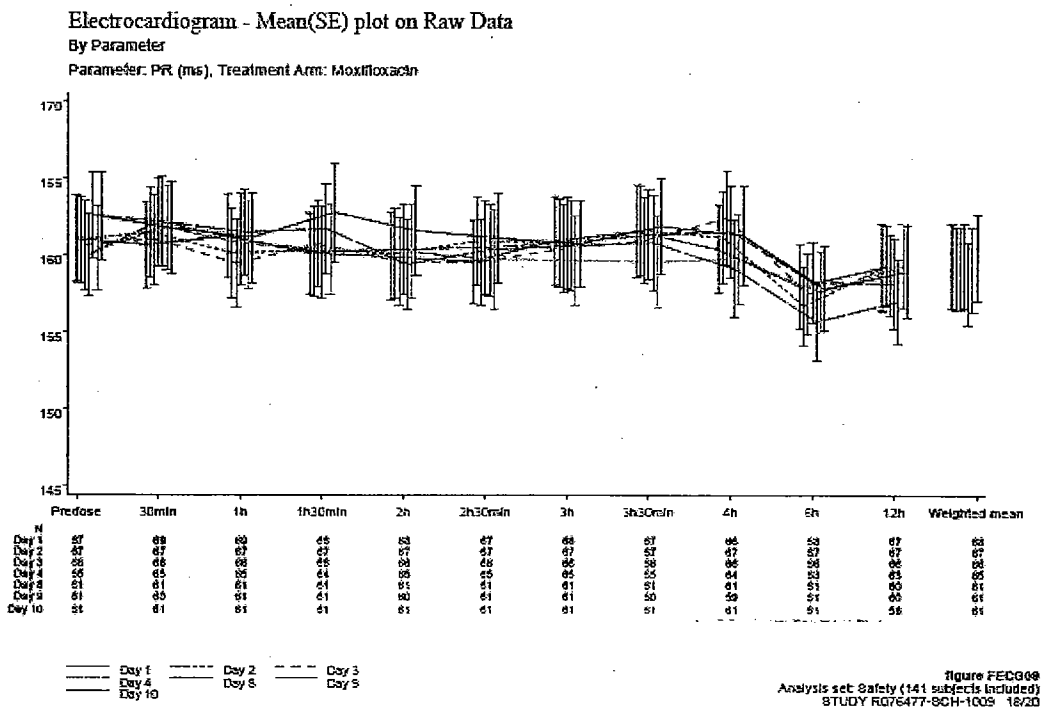
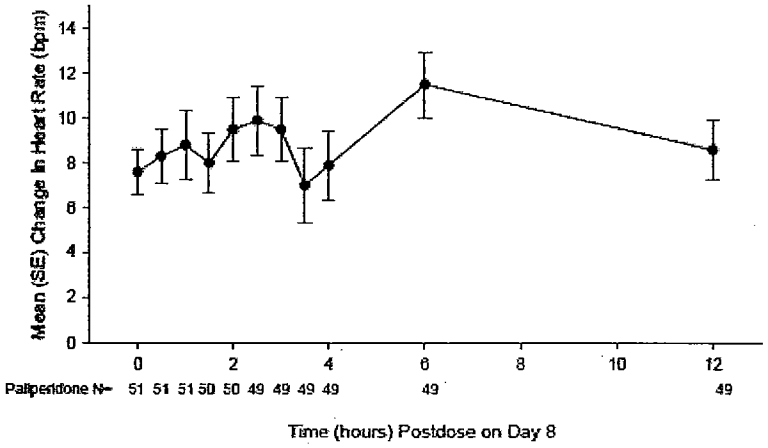


Table 20: Number of Subjects With Treatment-Emergent Changes in T- and U-Wave Morphology
(Study R076477-SCH-1009: Safety Analysis Set)

	IR Paliperidone (N=72)		Placebo/ Moxifloxacin (N=69)	
	n	(%)	n	(%)
T Wave				
Low T Waves	14	(19)	10	(14)
Diphasic (Pos-Neg) T Waves	7	(10)	7	(10)
Flat T Waves	7	(10)	6	(9)
Diphasic (Neg-Pos) T Waves	5	(7)	6	(9)
Slightly Negative T Waves	5	(7)	9	(13)
Deeply Negative T Waves	1	(1)	2	(3)
Notched T Waves	1	(1)	1	(1)
Tall T Waves	0		3	(4)
U Wave				
Yes	2	(3)	1	(1)

Cross-Reference: Attachment 7.

Figure 8: Plot of Mean Change* in Heart Rate on Day 8 Matched Time Points
(Study R076477-SCH-1009: Safety Analysis Set)

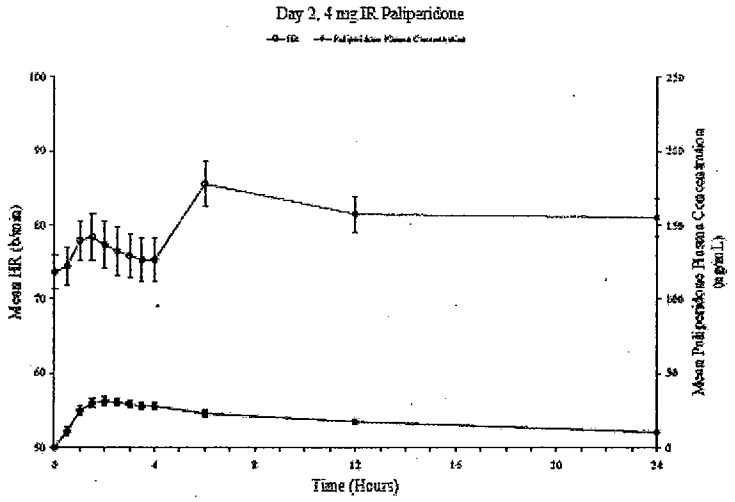


* Mean change from Day 1 (placebo) to Day 8 corresponding timepoints.

Cross-reference: Attachments 5.2.1 and 5.2.2.

The following figure illustrates mean Pal plasma levels with mean heart rate values over time.

Figure 9: Mean (90% CI) Paliperidone Plasma Concentrations and HR Profiles in Function of Time
(Study R076477-SCH-1009; Pharmacokinetic Analysis Set)



Cross-reference: Attachment 6.3.

Reviewer Comment. *The sponsor notes that the initial peak increase in heart rate occurred near the anticipated Tmax and was most prominent after the first dose of Pal (a 4mg dose-level) compared to subsequent days of Pal treatment despite that daily dose-levels were increased on treatment Days 3 (given 6 mg) and 4 (given 8 mg). Heart rate increased again at the 6 hour post-dose assessment time-point which was also observed on the placebo treatment day (Day 1).*

The results suggest that perhaps initial exposure to Pal results in the greatest drug-induced change in heart rate, yet when examining results of day-averaged heart rate the mean change in heart (from Day 1 averaged heart rate values) showed evidence for greater effects with increasing dose-level over subsequent treatment days (mean changes of 7.8, 11.2 and 12.1 bpm on Day 2 at 4 mg, Day 3 at 6 mg and Day 4 at 8 mg, respectively). However, continued treatment at the 8 mg daily dose-level showed evidence for a decreasing Pal induced effect on increased heart rate over subsequent treatment days (Days 4 through 8) at this fixed daily dose-level (when comparing Days 4 and 8 on the day-averaged mean change from the day-averaged value on Day 1 the mean change was 12.1 and 7.3 bpm, respectively). However, it is important to note the large between subject variance on mean changes in heart rate such that this possible PK-PD relationship may not apply to all subjects. It is likely that other factors that influence heart rate affect Pal induced changes in heart rate (e.g. consider underlying diurnal changes in heart rate, among others).

Also note that the incidence of subjects with high PR values (10%) is numerical larger than the incidence of subjects with low PR values (6%) among the Pal subjects.

Vital Sign Results

The study did not include vital sign assessments during treatment, but only at baseline/screening and at the end of the study or upon early withdrawal. Therefore, results on vital sign parameters were unrevealing.

Serious Adverse Events

The following are SAEs observed following Pal treatment in the study:

- "Severe" dystonia was reported as an SAE on day 3 at approximately 4 hours post-dose of 6 mg IR Pal in subject 109043 which led to this subject withdrawing early from the study.

- Subject 109047 had "extrapyramidal disorder" and "dyspnea" ("severe dyspnea" with "neck spasms" and "swollen tongue") reported as SAEs that also led to early study withdrawal. These events occurred on Day 6 following the 6 mg Pal dose.

Adverse Dropouts

In addition to the above SAEs that were also ADOs, the following ADOs occurred after Pal treatment:

- Subject 109004 (limiting adverse event: hyperkinesia)
- Subject 109040 (limiting adverse events: dystonia, hypertonia),
- Subject 109093 (limiting adverse event: bradykinesia),
- Subject 109169 (limiting adverse event: tetany): this subject also had dizziness, tachycardia and other AEs along with "teteny and mild eye abnormality" on Day 2 after the 4 mg dose.

The following ADO involved abnormal ECG (non-specific T wave abnormalities) as described in the following (copied from the CSR):

Subject 109076 (limiting adverse events: tachycardia, abnormal ECG), a 42-year-old man with residual schizophrenia was receiving haloperidol for psychosis, clonazepam for anxiety, and benzatropine for prophylaxis of extrapyramidal symptoms before entering the study. His medical history included headaches, insomnia, anxiety, paranoia, and auditory hallucinations. Haloperidol was discontinued on Day -7 of the screening period. The subject was randomly assigned to the IR paliperidone treatment group. No adverse events were reported after administration of placebo on Day 1. On Day 2, after administration of 4 mg IR paliperidone, the subject's heart rate increased from a predose rate of 77 bpm to a maximum of 127 bpm at 6 hours postdose. The subject's heart rate was 99 bpm 12 hours postdose on Day 2. An adverse event of tachycardia was reported on Day 2. The investigator considered the tachycardia to be of moderate intensity and of probable relationship to study drug. No adverse events were reported on Day 3 after administration of 6 mg IR paliperidone, although low or negative T waves, (non-specific T wave abnormality) was noted on ECG. On Day 4, after administration of 8 mg IR paliperidone, it was reported as an adverse event of moderately severe ECG abnormality. ECG abnormality was considered by the investigator to be of probable relationship to study drug. The subject was discontinued from the study due to tachycardia and ECG abnormality; both events resolved within 2 days after discontinuation of study drug.

The Incidence of Potential Pro-Arrhythmic-related AEs

The following table shows the incidence of potential pro-arrhythmic AEs reported in the study using AE terms (including seizure, syncope, ventricular fibrillation and flutter, TdP, and adverse events consistent with sudden death), as recommended in the ICH E14 Guideline ("The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs").

Table 22: Incidence of Cardiovascular and Potentially Related Adverse Events (Study R076477-SCH-1009: Safety Analysis Set)

	Paliperidone Treatment Group[a]		Moxifloxacin Treatment Group[b]	
	Placebo	IR PAL	Placebo	Moxifloxacin
WHOART Body System	(Day 1)	(Days 2-10)	(Days 1-7)	(Day 8-10)
WHOART Preferred Term	(N=72)	(N=69)	(N=69)	(N=62)
Investigator Verbatim Terms	n (%)	n (%)	n (%)	n (%)
Body as a whole - general disorders				
Syncope	0	0	0	1 (1.6)
syncopal episode				

[a] The paliperidone treatment group received placebo on Day 1 and paliperidone on Days 2 through 8.

[b] The moxifloxacin treatment group received placebo on Days 1 through 7 and moxifloxacin on Day 8.

Cross-reference: Attachment 8.1.1.

Reviewer Comments.
See reviewer comments above, on results of PK and QT interval and the PK-PD relationship. Other study results generally failed to show any clinically remarkable new safety findings. Yet the study did not examine drug effects on vital signs that included assessments near Tmax or other on-treatment time-points.

One potentially notable observation was that one Pal subject (a 42 year old healthy patient) had non-specific T wave changes on Days 3 and 4 of treatment (corresponds to 6 mg and 8 mg treatment days, respectively) along with increased heart rate first observed on Day 2 (corresponds to the first day of Pal treatment in which a 4 mg dose was given). These events led to early study withdraw after the 8 mg treatment on Day 4. No other factors or explanations that would account for these adverse events could be found in the in-text description in the CSR on this subject (109076).

See final section of this review for further comments and recommendations.

B. A Phase I Study with Vital Sign and ECG Results at 24 and 48 Hours after 3mg or 6 mg of OROS Pal

Since Study SCH-1009 did not include vital sign results near Tmax the sponsor was asked to clarify if any Phase I study was conducted that included vital sign measures near Tmax. The sponsor replied in a 6/7/2006 response that a Phase I PK study, Study –P01-1005 included measures of Tmax. This study parallel group, placebo-controlled, double-blind Phase I study was conducted on generally healthy, 20-45 year old Japanese (N=24 of which 14 subjects were male and 10 were female) and Caucasian (N=24; of which 14 were male and 10 were female) subjects. The Japanese subjects had not lived outside of Japan for more than 5 years (and were born in Japan) and were normotensive prior to study entry (were within a specified normal BP range). All subjects had to have a BMI of 18-25 kg/m.^{2} The Caucasian subjects were sex, age (±10% of age by gender) and weight (±30% of weight by gender) matched to the Japanese subjects in the United Kingdom study.

Subjects received a SD of 3 mg of Pal (Day 1) followed by MDs of 3 mg Pal (daily) or placebo on Days 5-11, then on Day 19 subjects received a SD of 6 mg of Pal (all doses given in fasted conditions). Vital sign measures were conducted at screening, pre-dose (on Day 1), then at 24 hours and 48 hours post-dose after the first dose of 3 mg or placebo (study Days 2 and 3, respectively), then at these same post-dose time-points after the last MD of daily 3 mg Pal or placebo (at 24 and 48 hours post-dose on study Days 12 and 13). 24 and 48 hour post-dose assessments were conducted again after the 6 mg SD or placebo treatment (on study Days 20 and 21) and a final end-of study assessment (at 24 and 48 hours post-dose, corresponding to study Days

The sponsor concludes in their 6/7/06 response submission that at Tmax "no changes were observed for either systolic or diastolic blood pressure whereas slight increases in pulse were noted."

Reviewer Comments on Results.
The following results were observed by the undersigned reviewer on the basis of numerical comparisons using results shown in graphs provided in the 6/7/06 response from the sponsor.

When examining the sponsor's graphs provided in their response to our inquiry between treatment group and within group mean values (within each ethnic group) effects can be observed over time that appear to reflect a drug-effect given the timing of the observations relative to dosing and given the PK properties of ER OROS Pal. The results depicted graphically (later in this review) generally showed within-Pal-group mean changes from baseline/predose values (or trends for changes) on various vital sign parameters (specified below) on at least the following assessment time-points: 24 hours after the first dose of 3 mg (corresponds to "c" time-point on the x-axis of the sponsor's figures) and 24 hours after the 6 mg SD treatment (corresponds to the "g" time-point on the x-axis of the sponsor's figures) which is near the anticipated Tmax (compared to the group mean baseline values and values at other assessment time-points). The following summarizes these observations:

- *Treatment group effects were generally observed (between placebo and Pal groups within each ethnic group). Orthostatic changes in HR and BP were generally observed in Pal groups near Tmax (and in some cases at additional post-dose time-points), while the placebo group generally showed little to no change or changes at these time-points.*
- *The "Asian" group appeared to show greater orthostatic changes or group differences in heart rate and blood pressure, than observed in the "White" group. As described later postural dizziness was more commonly reported in the "Asian" Pal group than in the "White" Pal group.*
- *The Asians generally showed greater Pal effects on mean supine systolic BP with treatment group differences of up to approximately 16 mmHg, but results are complicated by fluctuations in this parameter in the placebo group and it is not clear if they are reproduceable. Furthermore, the "white" group results are more difficult to interpret since Pal subjects had a group mean value than placebo subjects prior to treatment on this parameter.*

Supine heart rate generally showed little to no change or minimal treatment group differences (between Pal and placebo groups within each ethnic group).

It is notable that after MD treatment group mean differences on heart rate shows a similar peak effect near Tmax after the first dose of 3 mg to that observed after the last dose of the MD treatment regimen of 3 mg/day (based on numerical comparisons). This observation suggests little to no physiological adjustment or compensation to Pal-induced increases in orthostatic heart rate, similar to that observed for standing systolic BP results described above.

Final Comments on Results Showing Pal Effects

There are several problems with this Phase I study with respect to revealing a potential drug effect on vital signs. Greater Pal effects were observed in the Japanese group compared to the Caucasian group for at least orthostatic vital sign Pal effects that are also consistent with a greater incidence of AEs of postural dizziness, described later in the Japanese Pal group compared to the Caucasian pal group (29% and 13%, respectively). Yet PK properties generally showed similar results in these ethnic groups, as shown later.

The results on supine BP and orthostatic measures could at least in part be reflecting a blood sampling effect, but this potential confounding variable would not explain the time-dependent and treatment group (Pal versus placebo group) effects that appear to exist (based on numerical comparisons) that are previously described in this review. Moreover, the potential confound of blood sampling cannot explain ethnic group differences on orthostatic measures.

Comments on QTcF interval Results

This Phase I study did not show any remarkable changes in QTcF, based on results in graphs provided in the 6/7/06 response submission (also see selected graphs below).

Selected Graphs Provided in the 6/7/06 Response Submission

The figures shown below were provided by the sponsor in which the legend of the graphical displays are as follows in which subjects received a treatment sequence of 3 mg SD, 3 mg MD (Days 1-11, as below), then 6 mg SD on Day 20 (the below legend is copied from their response):

(a) Screening,
(b) Day 1, immediately before first 3mg dose;
(c) Day 2, 24h after first 3mg dose;
(d) Day 3, 48h after first 3mg dose;
(e) Day 12, 24h after last multiple 3mg dose,
(f) Day 13, 48h after last multiple 3mg dose,
(g) Day 20, 24h after first 6mg dose,
(h) Day 21, 48h after first 6mg dose,
(i) End of study

The following outlines treatment found in the CSR of the original NDA submission:

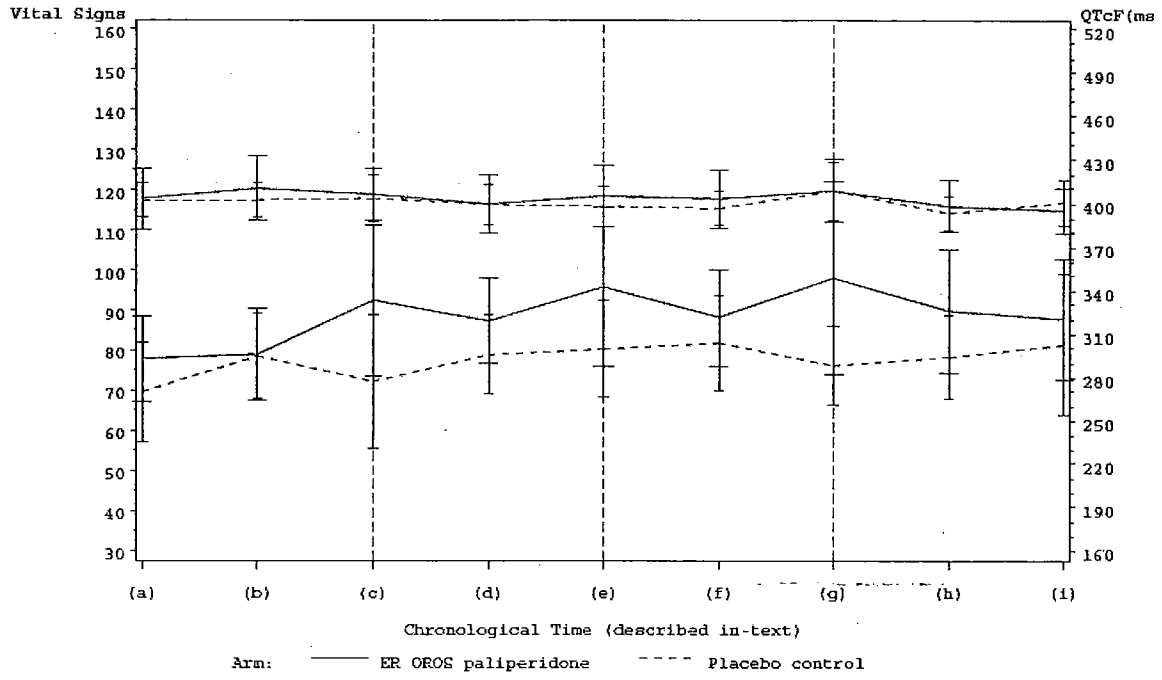
Table 1: Study Treatments

Day 1	Days 2-4	Days 5-11	Days 12-18	Day 19
SD of 3 mg ER OROS paliperidone or placebo	Washout	3 mg ER OROS paliperidone or placebo once daily for 7 days	Washout	SD of 6 mg ER OROS paliperidone or placebo

Cross-reference: Appendix 1.1

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

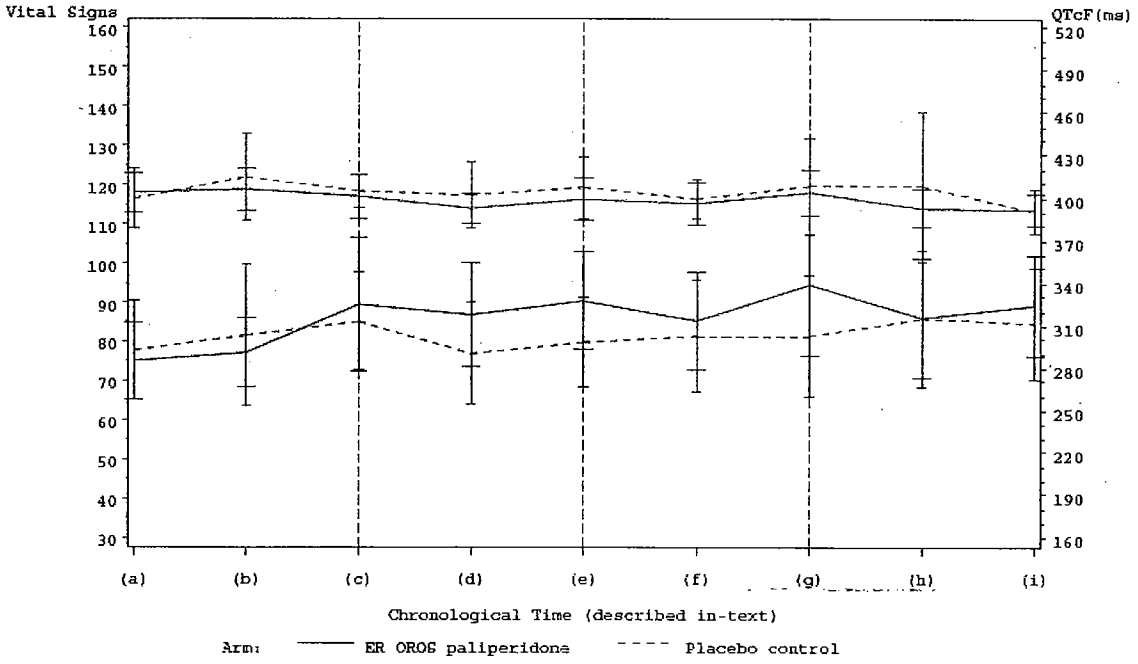
Vital Signs Parameter=Pulse(bpm) when Standing+2m Race=ASIAN



Appears This Way
On Original

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

Vital Signs Parameter=Pulse(bpm) when Standing+3m Race=WHITE

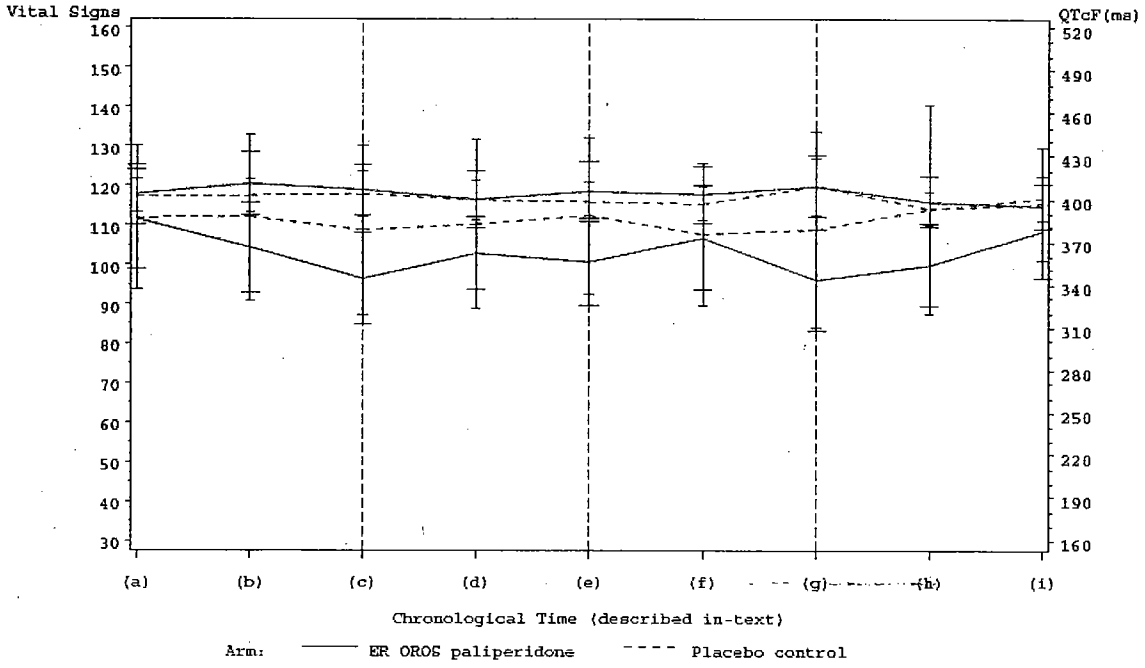


Vertical Lines indicate Tmax, Black used for Vital Signs, Green for QTcF

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 Standing+2m Race=ASIAN



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

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