DB750001 Cardiac Safety Data Review Meeting Summary – Cohort 1-3
Meeting Date: 13July2016

Attendees:

Name	Role	X = present
Jessica Cornette	iCardiac Project Manager	X
Borje Darpo, M.D., Ph.D.	iCardiac Chief Scientific Officer	X
Nijad Kifayeh, M.I.P.H.	Sunovion Clinical Trial Manager	X
Ken Koblan, Ph.D.	Sunovion Global Project Medical Lead	X
Robert Lew, Ph.D.	Sunovion Director of Pharmacology	X
Robert Silva, Ph.D.	Sunovion Project Medical Lead	X
Estela Skende, M.S.	Sunovion Translational Medicine and Bioanalytical Sciences	X
Katrina Thompson	Sunovion Clinical Trial Manager	X

Purpose of meeting: Review of Cardiac Safety Data – Cohort 1-3 to determine any the clinical significance and any potential impact on the conduct of the trial

General findings:
The number and frequency of findings identified from the holter analysis across the three completed cohorts (0.1, 0.25 and 0.5 mg) were discussed. The frequency of total cardiac events was higher with increasing dose from 0.1 to 0.5 mg. The frequency of Frequent Ventricular Ectopic (FVE) beats across cohorts was also highlighted as a potential concern. The following table was discussed in detail and focused on the potential of these cases to represent a potential drug related signal or were indicative of normal variation generally observed in 24-hour holter data observed in a healthy normal population.

Dose	Subject Id	Time of Dose	Abnormalities Observed	Time relative to dosing	iCardiac Comments in Summary for each cohort
0.1	001001014	9:00	Second Degree AV Block - Type I; Two episodes of 2nd deg AVB with pauses up to 1.7 sec during daytime The subject has a tendency to bradycardia during night which also is considered as a physiologic finding.	5-6 hr post dose (15:34 and 15:36)	Based on this preliminary assessment performed on blinded data from Cohort 1-3, DSP-1200 at the studied dose does not seem to have a meaningful effect on ECG parameters that would be concerning in terms of dose escalation. The observed episodes of AV block are not clinically concerning in the absence of an effect on the mean PR interval.
	001001011	9:40	One 3-beat run of SVT	Unk	
	001001010	10:13	Frequent Supraventricular Premature Beats (APBs) (100/24hr) There are total of 167 supraventricular premature beats not in clusters – they could represent a variant of normal.	Variable	
0.25	001001038	9:20	FVE - Frequent Ventricular Ectopic Beats (VEs) (> 200/24hrs); OTH - Other - ventricular couplets; More than 1000 VES/24h were observed, mostly unifocal, and with several couplets. There are total of 1346 ventricular ectopic beats not in clusters, rarely observed in young healthy individuals	baseline and after dose	
	001001031	11:20	FVE - Frequent Ventricular Ectopic Beats (VEs) (> 200/24hrs); All VES were observed in the afternoon, between 4:00 PM and 5:00 PM. There were 360 VES in a cluster.	3 -5 hr after dose	

	001001033	11:40	HR3 - Average Hourly Daytime Heart Rate < 50 bpm (daytime defined as 7 am-10 pm); OTH - Other - Occasional VPB's. Daytime bradycardia. Average, hourly daytime heart rate < 50 bpm during one hour (between 09:00 AM and 10:00 AM)	Pre-4 hr post dose	
	001001028	12:00	OTH - Other - Rare VPBs	Variable	
	001001025	12:20	OTH - Other - Occasional VPB's	Variable	
	001001035	11:00	OTH - Other - One ventricular couplet	Variable	
Dose	**Subject Id**	**Time of Dose**	**Abnormalities Observed**	**Time relative to dosing**	**iCardiac Comments in Summary for each cohort**
0.5	001001042	09:30	SVT - Supraventricular Tachycardia (lasting > 10 beats); OTH - Other - Rare APB's (total of 29 over 24 hours) and Limited 1st deg AVB; one event of short (11 beats) and slow (similar rate to sinus rhythm, max 118bpm) supraventricular tachycardia.	4.5 hr after dose and several times after until 19.5 hr post dose	Based on this preliminary assessment performed on blinded data from Cohort 1-3, DSP-1200 at the studied dose does not seem to have a meaningful effect on ECG parameters that would be concerning in terms of dose escalation. The observed episodes of AV block are not clinically concerning in the absence of an effect on the mean PR interval.
	001001049	09:50	SD1 - Second Degree AV Block - Type I (4 episodes of AVB during night- and daytime; daytime between 8:50-09:02AM- max. 2.6 sec); SD2 - Second Degree AV Block Type II (one episode of advanced second degree AVB type 2: 1 with 2 consecutive pauses 2.5 seconds - corresponding to heart rate 24 bpm (during nighttime 01:31AM); This second degree AV block type II observed during night could be a variant of normal.	before dosing and after	
	001001063	10:10	OTH - Other - Brief periods of nonparoxysmal accelerated junctional rhythm at night.	?	
	001001052	10:50	FSV - Frequent Supraventricular Premature Beats (APBs) (100/24hr); there are 131 APBs. There are 125 APBs clustered between 3:30-3:50 PM. There were 129 total APBs seen, 125 of which were seen during this window.	4 - 7 hr post dose	
	001001054	11:10	OTH - Other - Very rare VPCs and APCs	?	
	001001046	09:50	• **001001046 T WAVE CATEGORICAL FINDING @8Hr Postdose BIPHASIC;** • Day 7 ECG showed inverted T waves in inferior leads and V3-V6; asymptomatic with normal vitals; Inverted T wave in V3 resolved and T wave in V4 was biphasic; subject kept overnight for observation and discharged in the morning when ECG was normal	8 hr post dose; Day 7 post dose	

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Discussion:
It was noted that the findings highlighted in the consolidated analysis are likely the result of routine variations observed during 24 hour holter monitoring. Data derived from holter monitoring was noted not to be a component of the high precision ECG analysis. 24 hour holter monitoring is not routinely performed in early phase healthy volunteer studies and it is Dr. Darpo's opinion that these findings represent normal variation in this population.

The following specific findings were noted:

- Frequent Supraventricular Premature Beats. There is no clinical concern with these findings
- Ventricular Ectopic Beats: There are no PR or QS interval changes accompanying these holter findings which would indicate a drug effect. Therefore in the absence of any electrophysiological effect there is no evidence that these changes are drug related and there is no clinical concern
- 2nd Degree AV block: This is rarely seen in a healthy population. 2nd degree AV block, Type I does not pose a clinical concern. 2nd degree AV block, Type II is a more significant finding and was seen in one subject (001001049). In the absence of any effect on the PR interval, it is unlikely that this finding is drug related.
- T-wave inversion: This finding was seen in one patient (001001046) at 8 hrs and 7 days post dose. While there is measurable drug at 8 hours, the subject had a normal ECG at discharge and a follow up stress test has been requested for this subject. There is no immediate concern with continuation of the study with this single finding as the clinical relevance is unknown.

Conclusion:
There is no clinical concern at this time with the consolidated cardiac safety findings analyzed for the first 3 cohorts. In the opinion of Dr. Darpo there is no issue with continuing the dose escalation strategy for this study and no additional assessments are recommended. This summary and the data in the attachment will be reviewed and confirmed by an additional cardiac safety expert, Dr. Wojciech Zareba Chief Medical Officer at iCardiac and Professor of Medicine at the University of Rochester Medical Center. Escalation to Cohort 4 will be contingent upon Sunovion review of this summary and the outcome of the routine Safety Review Team Meeting.

Post-meeting note: All relevant findings have now also been reviewed by Dr Zareba, University of Rochester, who agrees with the assessment; It seems unlikely that these events represent drug-induced arrhythmias.

Summary prepared by: Katrina Thompson, Director, Clinical Trial Management

Signatures below indicate agreement with the recommendation and conclusions described above.

Approved by: Borje Darpo, M.D., Ph.D., Chief Scientific Officer, iCardiac Date: July 21 2016

Approved by: Wojciech Zareba, M.D., Ph.D., Chief Medical Officer, iCardiac Date: July 21, 2016

Attachment A:

Consolidated Cardiac findings from Cohorts 1-3

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DB750001 Discussion on Cardiac Findings cohorts 1-3

Discussion Points

Study uses High Precision QT evaluation

- Could cardiac abnormalities be random events and are normal for healthy population?
- Could there be a trend related to investigational drug and dose dependent?
  - Projections on D_2 occupancy show that cardiac abnormalities unlikely related to expected pharmacology

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DB750001 Summary of Cardiac Abnormal Events

Dose	Subject Id	Time of Dose	Abnormalities Observed	Relative to Dosing?	iCardiac Comments in Summary for each cohort
0.1	001001014		Second Degree AV Block - Type I; Two episodes of 2nd deg AVB with pauses up to 1.7 sec during daytime	?	Based on this preliminary assessment performed on blinded data from Cohort 1-3, DSP-1200 at the studied dose does not seem to have a meaningful effect on ECG parameters that would be concerning in terms of dose escalation. The observed episodes of AV block are not clinically concerning in the absence of an effect on the mean PR interval.
	001001011		One 3-beat run of SVT	?	
	001001010		Frequent Supraventricular Premature Beats (APBs) (100/24hr)	?	
0.25	**001001038**	9:20	FVE - Frequent Ventricular Ectopic Beats (VEs) (> 200/24hrs); OTH - Other - ventricular couplets; More than 1000 VES/24h were observed, mostly unifocal, and with several couplets	baseline and after dose	
	001001031	11:20	FVE - Frequent Ventricular Ectopic Beats (VEs) (> 200/24hrs); All VES were observed in the afternoon, between 4:00 PM and 5:00 PM	3 -5 hr after dose	
	001001033		HR3 - Average Hourly Daytime Heart Rate < 50 bpm (daytime defined as 7 am-10 pm); OTH - Other - Occasional VPB's. Daytime bradycardia. Average, hourly daytime heart rate < 50 bpm during one hour (between 09:00 AM and 10.00 AM)		
	001001028		OTH - Other - Rare VPBs		
	001001025		OTH - Other - Occasional VPB's		
	001001035		OTH - Other - One ventricular couplet		
0.5	001001042	09:30	SVT - Supraventricular Tachycardia (lasting > 10 beats); OTH - Other - Rare APB's and Limited 1st deg AVB; one event of short (11 beats) and slow (similar rate to sinus rhythm, max 118bpm) supraventricular tachycardia.	4.5 hr after dose and several times after till 19.5 hr post dose	
	001001049	09:50	SD1 - Second Degree AV Block - Type I (4 episodes of AVB during night- and daytime; daytime between 8:50-09:02AM- max. 2.6 sec); SD2 - Second Degree AV Block Type II (one episode of advanced second degree AVB type 2: 1 with 2 consecutive pauses 2 5 seconds - corresponding to heart rate 24 bpm (during nighttime 01:31AM); From a clinical point of view, this is something between AVB type 2 and 3rd degree AVB.	before dosing and after	
	001001063	10:10	OTH - Other - Brief periods of nonparoxysmal accelerated junctional rhythm at night.	?	
	001001052	10:50	FSV - Frequent Supraventricular Premature Beats (APBs) (100/24hr); There are 125 APBs clustered between 3:30-3:50 PM. There were 129 total APBs seen, 125 of which were seen during this window.	4 - 7 hr post dose	
	001001054	11:10	OTH - Other - Very rare VPCs and APCs	?	
	001001046	09:50	• **001001046 T WAVE CATEGORICAL FINDING @8Hr Postdose BIPHASIC;** • Day 7 ECG showed inverted T waves in inferior leads and V3-V6; asymptomatic with normal vitals; Inverted T wave in V3 resolved and T wave in V4 was biphasic; subject kept overnight for observation and discharged in the morning when ECG was normal	8 hr post dose; Day 7 post dose	

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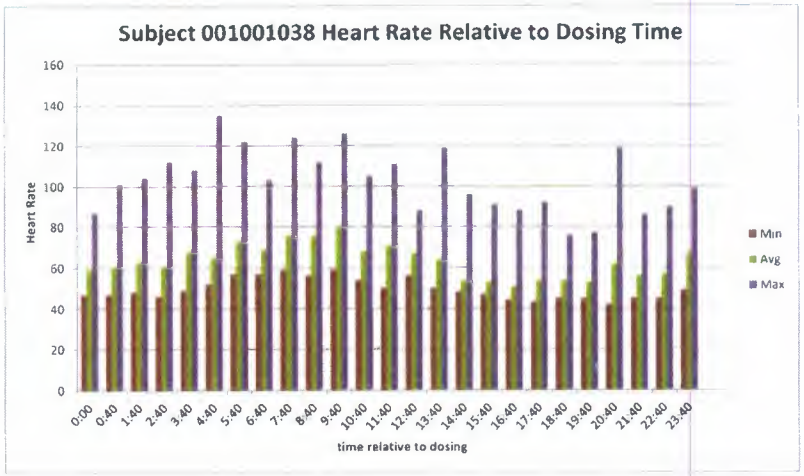
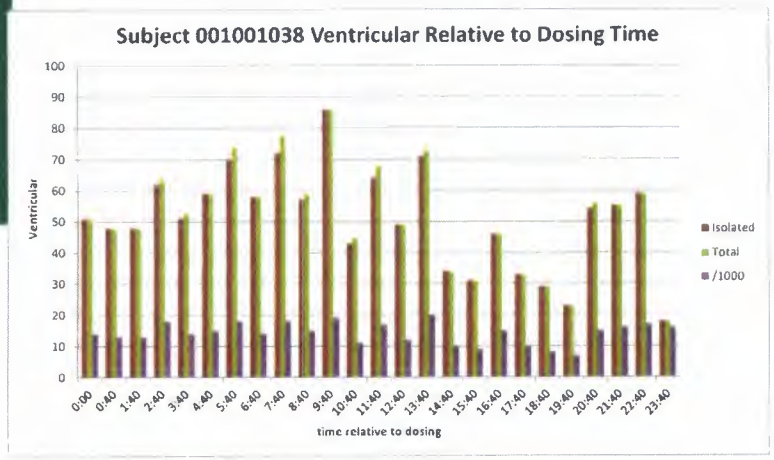
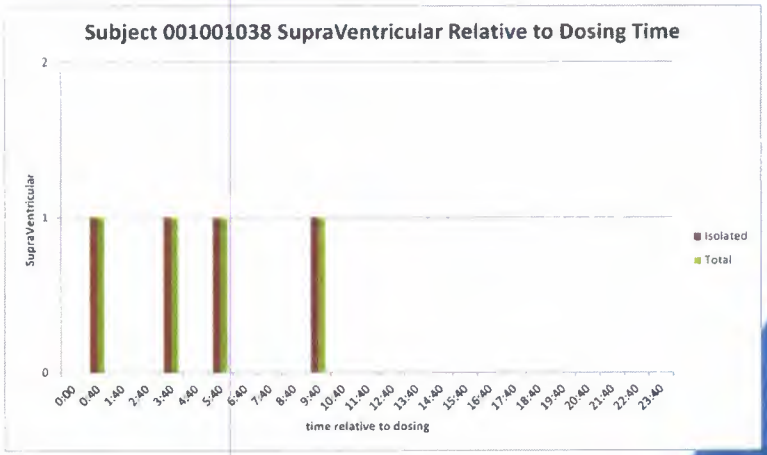
Subject 001001038 (0.25 mg)







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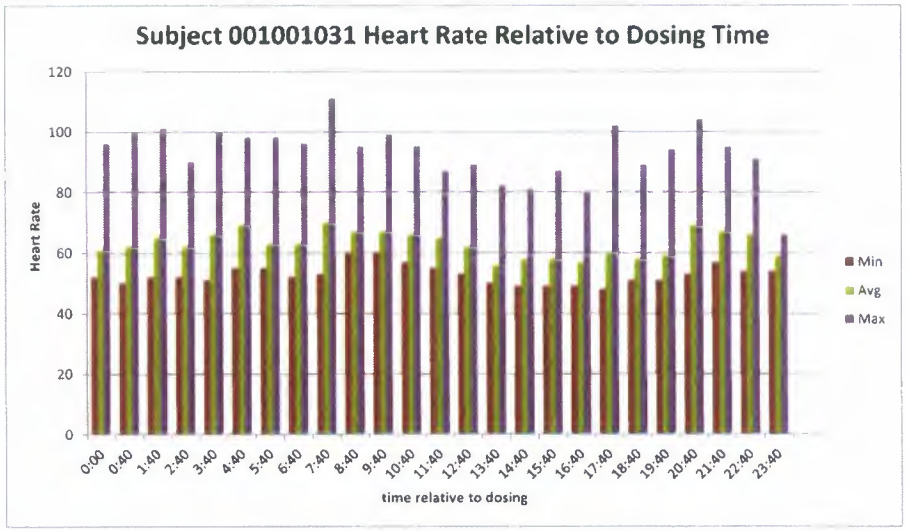
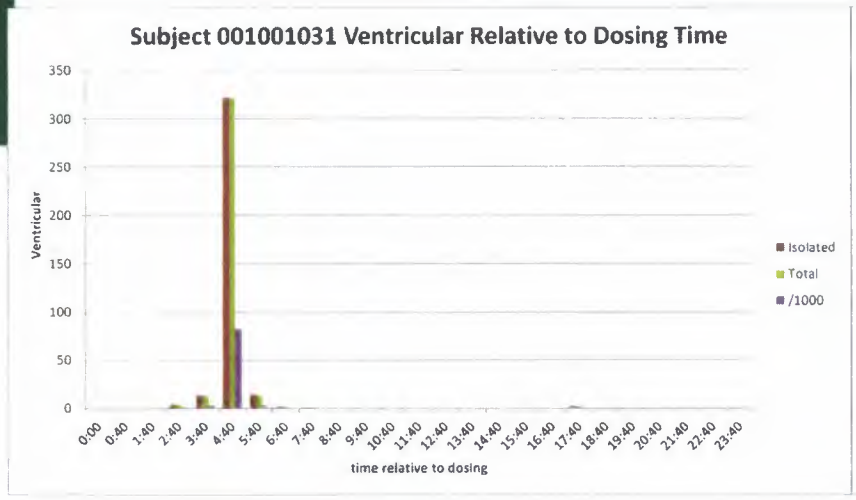
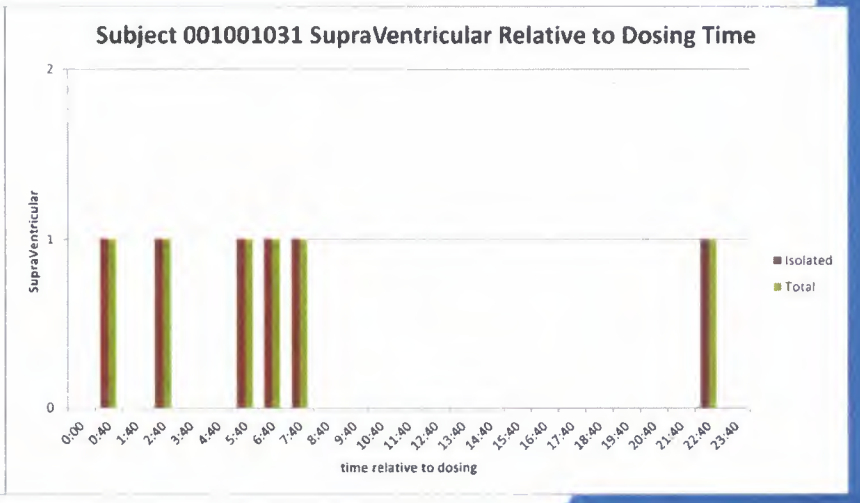
Subject 001001031 (0.25 mg)







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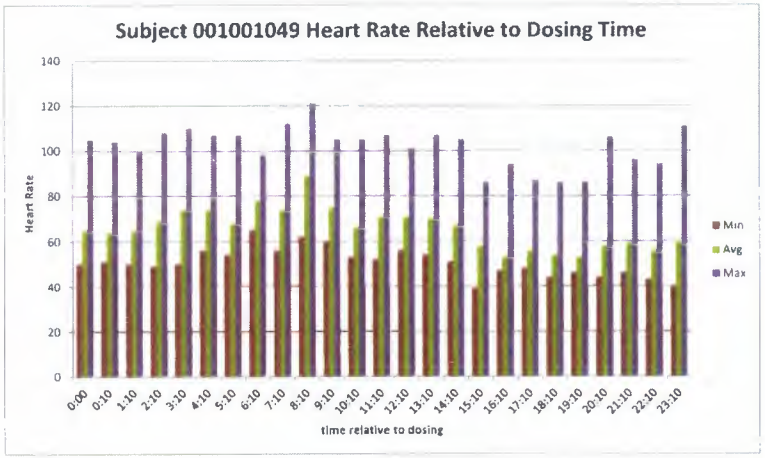
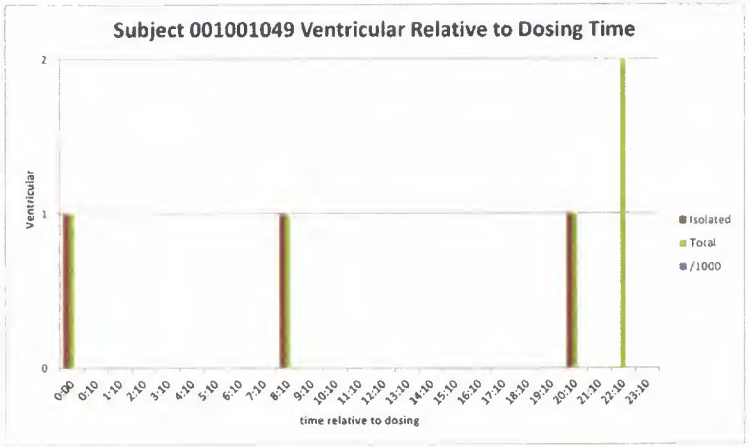
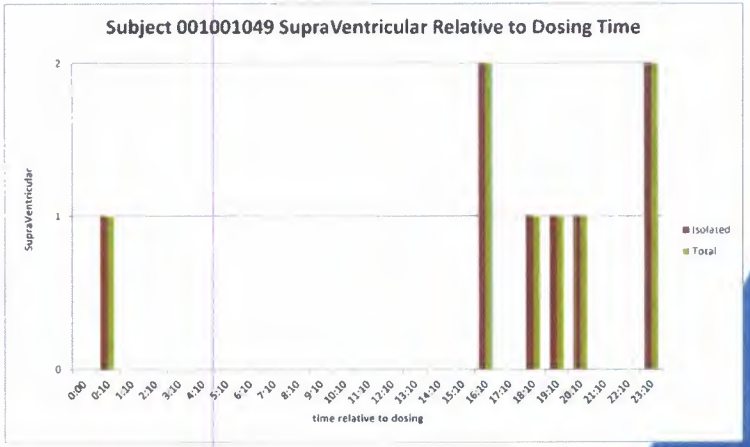
Subject 001001049 (0.5 mg)







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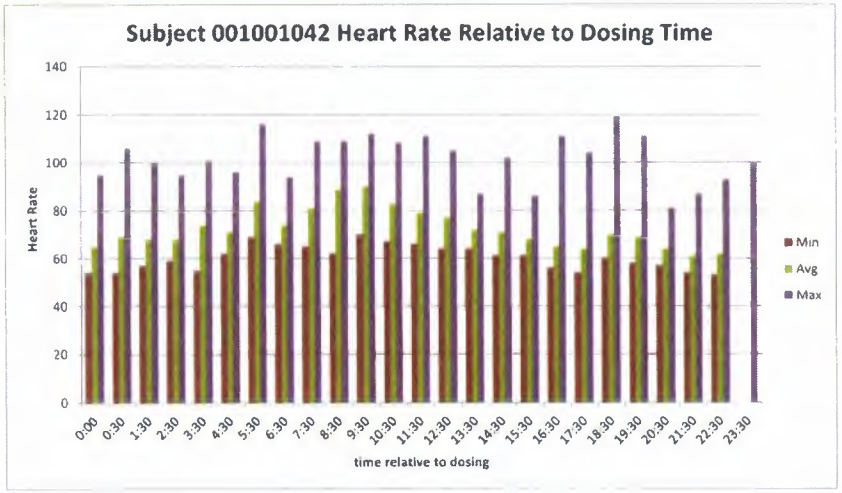
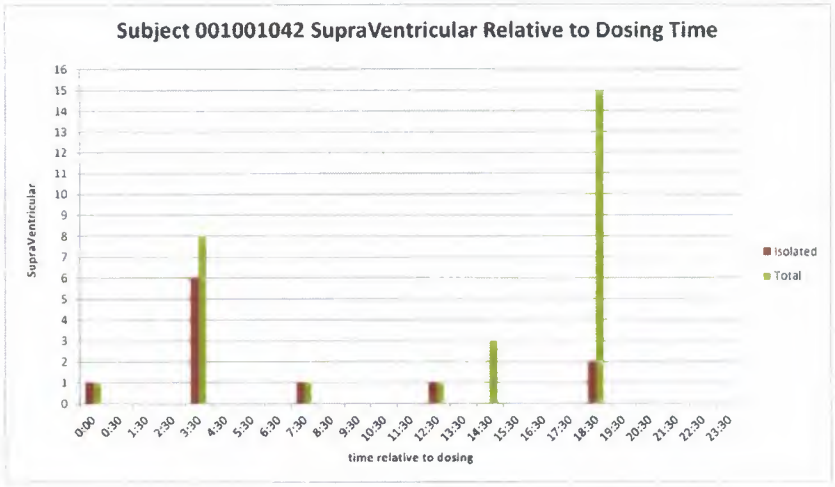
Subject 001001042 (0.5 mg)





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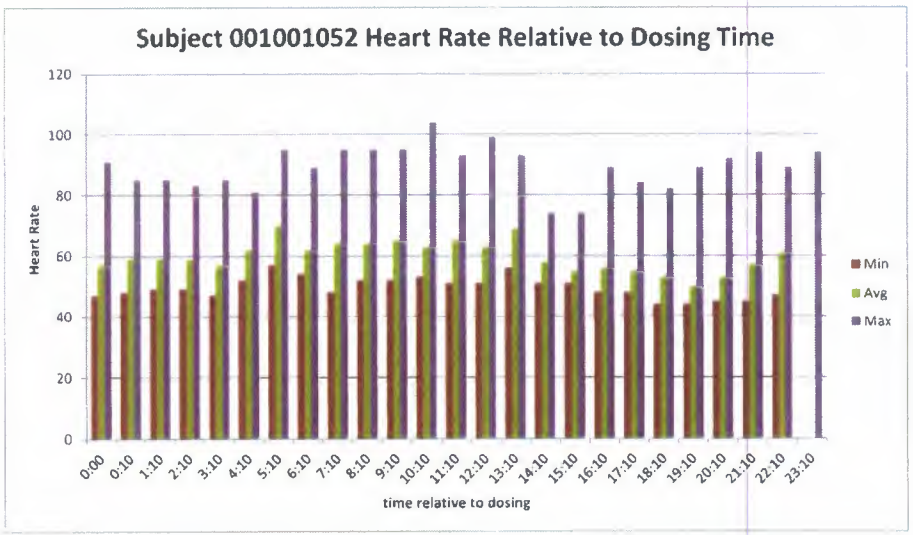
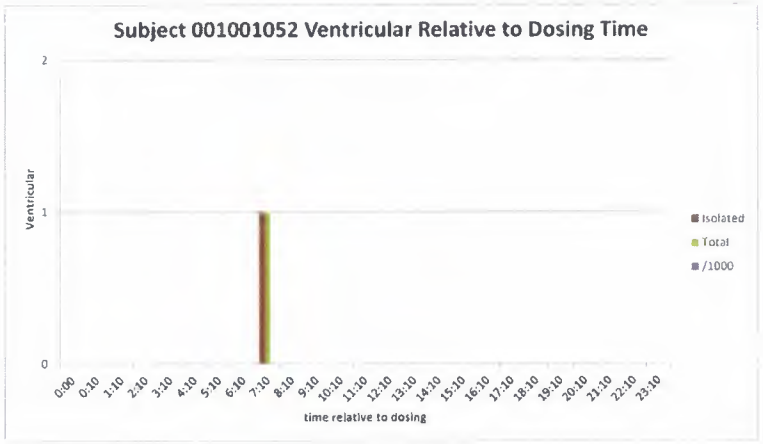
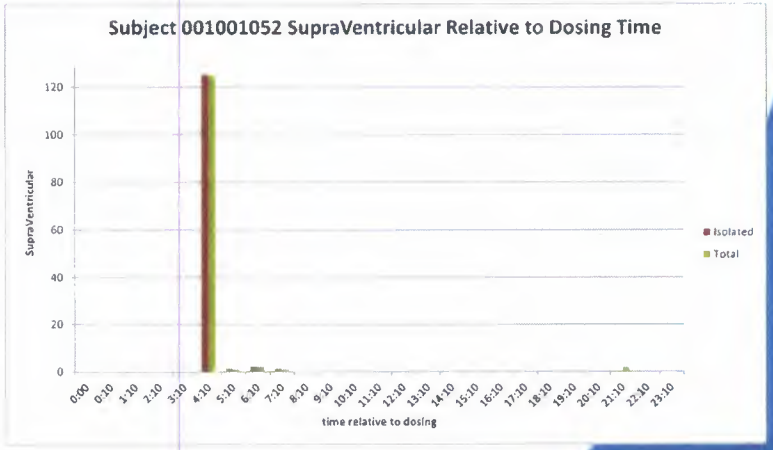
Subject 001001052 (0.5 mg)







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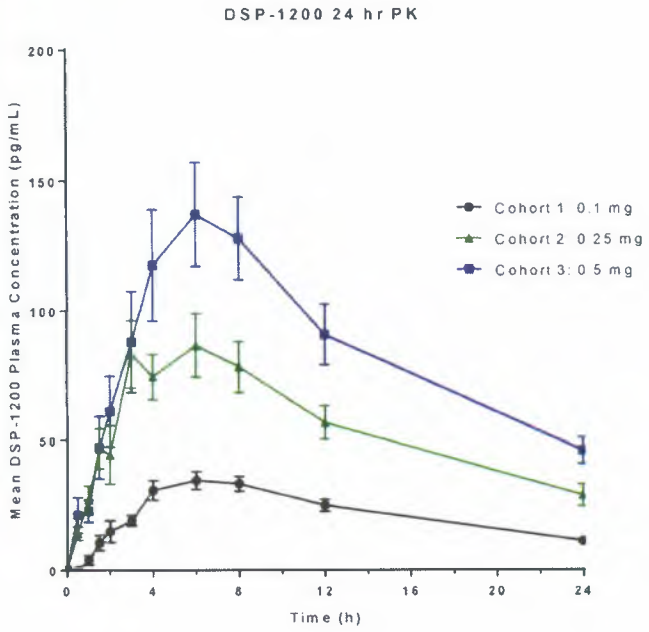
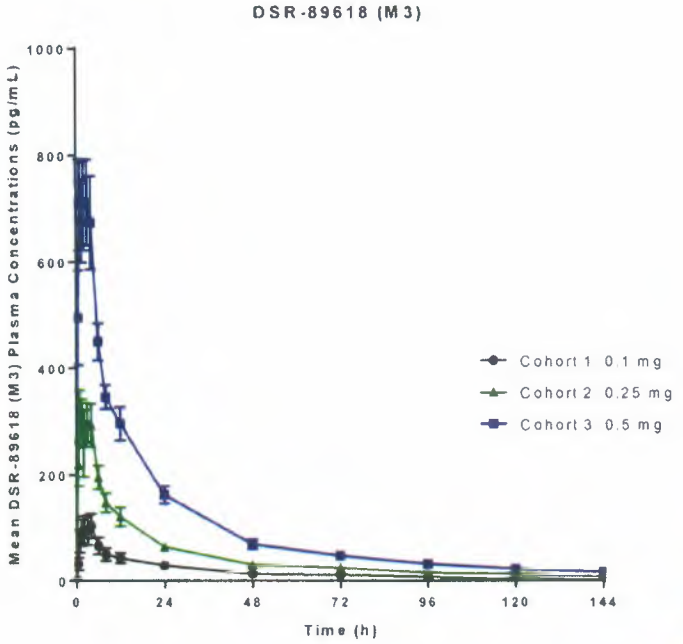
Mean Plasma DSP-1200 and M3 Concentration-time Profiles After Single Oral Dose Administration of 0.1, 0.25, and 0.50 mg DSP-1200





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Mean Plasma DSP-1200 and M3 PK Parameters*

DSP-1200 Plasma PK			
Dose (mg)	**C_{max} (pg/mL)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
0.1	**36.5**	6.33	**11.0**
0.25	**91.8**	4.50	**12.6**
0.5	**145**	6.00	**14.2**

M3 Plasma PK (Mean Data)			
Dose (mg)	**C_{max} (pg/mL)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
0.1	**107**	3.42	**37.2**
0.25	**347**	1.50	**51.7**
0.50	**771**	2.50	**53.7**

***calculations curtesy of Raju Poola**

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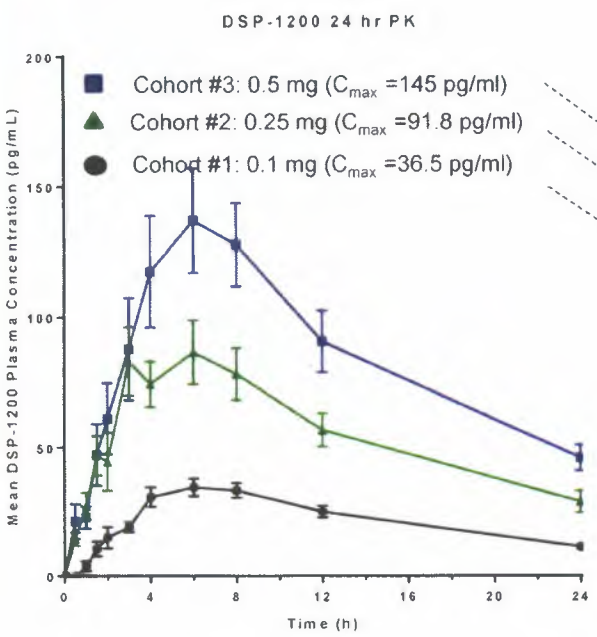
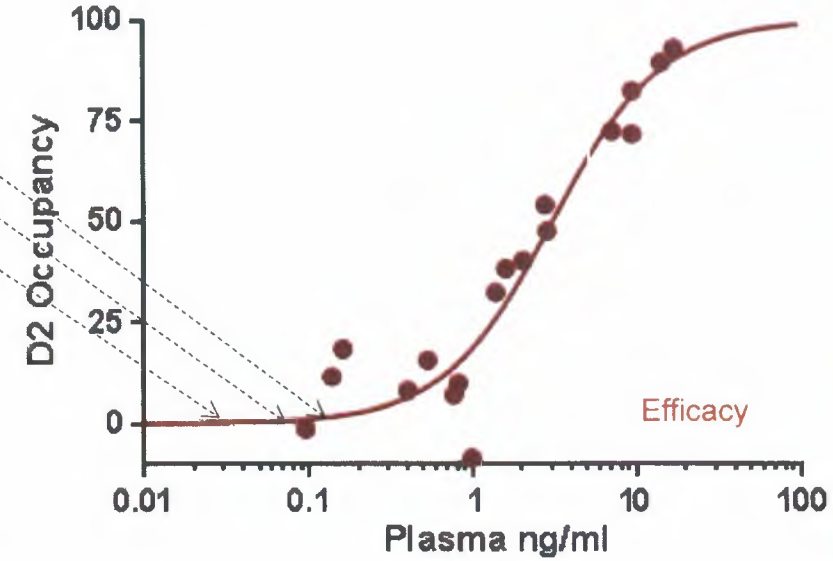
Projected D_2 receptor occupancy of DSP1200 (cohorts 1, 2, 3)





- Projected D_2 occupancies based on in vivo rodent occupancy (RO_{50} = 3.08 ng/ml)
- Assuming dose proportionality:
  - for cohort 9 (12 mg); D_2 occupancy will be ~ 45 % D_2 occupancy

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