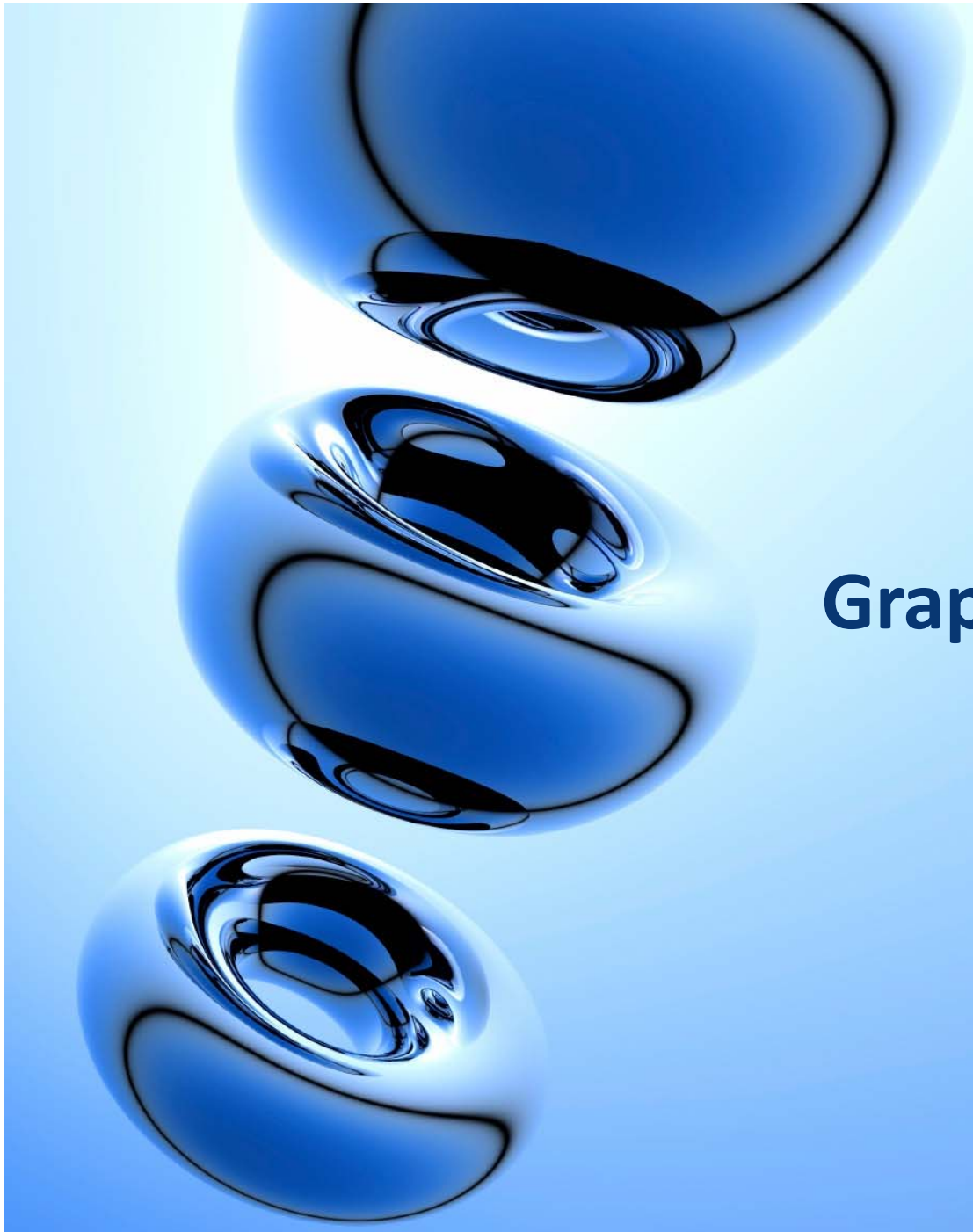

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Shaping the Future of
Drug Development

The Significance of Graphics in Early Phase Safety Reporting

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OVERVIEW

1. Goals in Phase I Studies
2. Data Checking
3. Reporting
4. Example Study
5. Summary

"WHAT" ARE THE GOALS IN PHASE I STUDIES?

To assess the preliminary safety, tolerability, and pharmacokinetic profile of a drug

Estimate how large a dose can be given before unacceptable toxicity is experienced via dose escalation

Resulting dose decisions help to move trial into following phases

Safety is assessed through ECG, vital signs, and lab measurements

- Tables and figures for data issue checking and reporting

“HOW” TO ACHIEVE GOALS OF PHASE I STUDIES?

Data Checking

Reporting

"WHY" DO WE PERFORM DATA CHECKING?

Data checking is critical

- Make sure all necessary data is available for analysis
- Small samples in early phase studies, so errors in data can have huge effect on analyses
- Assumptions for models possibly not met if there are data errors

"HOW" DO WE PERFORM DATA CHECKING?

Done at the start of every study request

Frequency table for timepoints

- Checking for missing or extra timepoints against study flow chart

Boxplots to check for outliers

- Use of macro
- Identifies "farlow", "farhigh", "low", and "high" values

"WHY" DO WE REPORT?

Dose escalation meetings

- Decision on whether to continue dose escalation sequence according to protocol, change dose escalation sequence, or stop dosing

CSR Creation

- Section 12

"WHAT" DO WE REPORT?

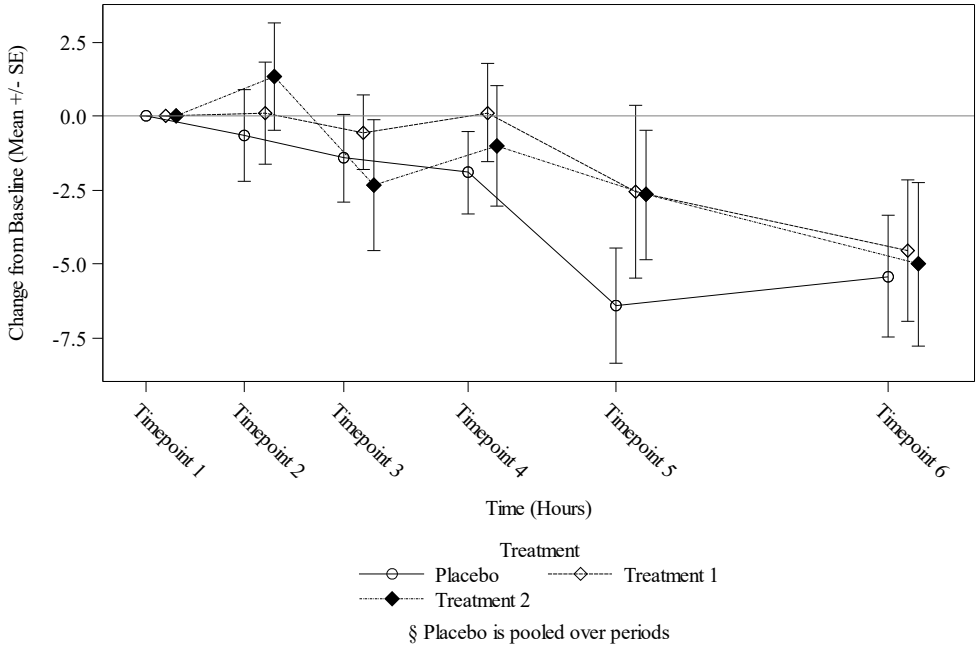
Table 1
<Drug> Summary for Safety <Domain> Data

Parameter (unit)
Part x
Panel x
Single Dose

Treatment	Time	Value			Change From Baseline †		
		N	Mean	SE	N	Mean	SE
Placebo §	Timepoint 1	x	xxx.xx	x.xx			
	Timepoint 2	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 3	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 4	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 5	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 6	x	xxx.xx	x.xx	x	xxx.xx	x.xx
Treatment 1	Timepoint 1	x	xxx.xx	x.xx			
	Timepoint 2	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 3	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 4	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 5	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 6	x	xxx.xx	x.xx	x	xxx.xx	x.xx
Treatment 2	Timepoint 1	x	xxx.xx	x.xx			
	Timepoint 2	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 3	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 4	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 5	x	xxx.xx	x.xx	x	xxx.xx	x.xx
	Timepoint 6	x	xxx.xx	x.xx	x	xxx.xx	x.xx

† Average of Timepoint 1 measurements serves as baseline; analysis performed on raw scale.
§ Placebo is pooled over periods.

Change (Mean +/- SE) from Baseline for <Drug>
Summary for <Domain> Parameter
<Domain> Parameter= Param 1 Part= Part x Panel= Panel x



§ Placebo is pooled over periods

EXAMPLE STUDY

Phase I study for an acute treatment of migraine with or without aura

Study Objective: Assess the preliminary safety, tolerability and pharmacokinetic (PK) profile of drug after single and multiple dose administrations

Study Design: Randomized, double-blind, placebo-controlled dose study in healthy male subjects

EXAMPLE STUDY: STUDY DESIGN

Two Parts:

- Part I: Single rising oral doses in up to five periods with minimum of 7-days washout period between treatments periods

Panel	Period 1	Period 2	Period 3	Period 4	Period 5
A	40 mg	100 mg	200 mg	400 mg	40 mg w/food

- Part II: Four serial panels where subjects receive daily dose of drug for 10 consecutive days

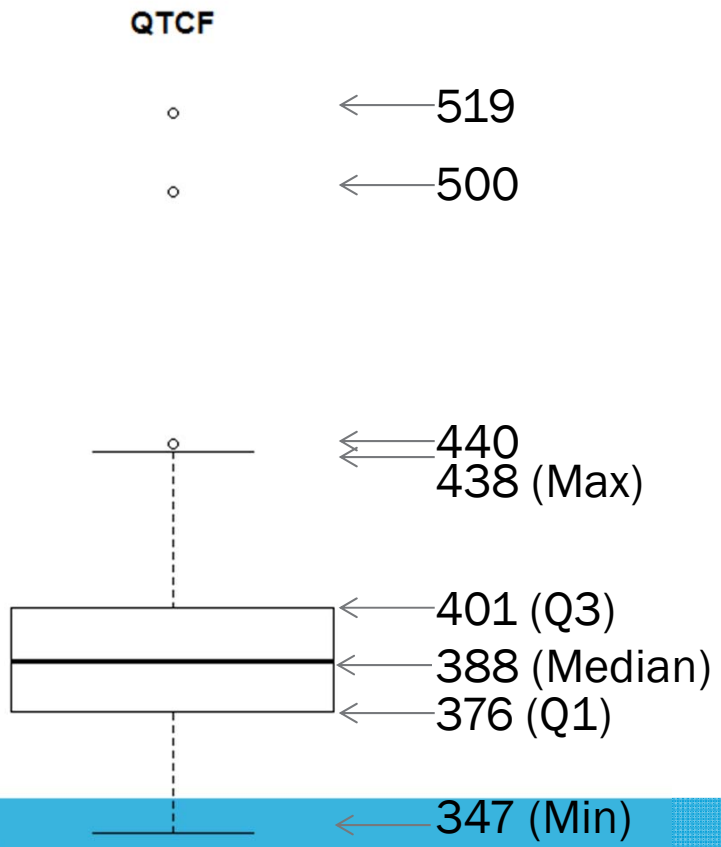
Panel	Dose Level			
B	50 mg			
C		100 mg		
D			200 mg	
E				400 mg

EXAMPLE STUDY: DATA CHECKING ECG

Procedures	Pre-study	Periods 1-5[i]																		Post-study[j]
		Pre-dose	0 hr	20 min	30 min	40 min	1 hr	1.5 hr	2 hr	3 hr	4 hr	6 hr	8 hr	10 hr	12 hr	16 hr	24 hr	48 hr	72 hr	
Study Informed Consent	X																			
Informed Consent for Future Biomedical Research[a]	X																			
Medical History	X																			
Blood for Future Biomedical Research[a]		X																		
Safety Evaluations																				
Physical Examination	X	X[b]															X			X
Height	X																			
Weight	X																			X
12-Lead Electrocardiogram (ECG) (Section 3.2.3)	X	X[c]			X		X		X		X						X			X
Heart Rate (HR)/Blood Pressure (BP) (Section 3.2.3)	X[d]	X[d]			X		X		X	X	X	X	X		X		X			X
Orthostatic Heart Rate (HR)/Blood Pressure (BP) (Section 3.2.3)	X	X					X		X		X						X			X
Oral / Tympanic Temperature	X	X															X			X
Respiratory Rate	X	X															X			X
Laboratory Safety Tests (Appendix 6.1 and 6.2)[e]	X	X															X			X[k]

Obs	EGTPT	COUNT
1	DAY10 2 HR	32
2	DAY10 24 HR	32
3	DAY10 PREDOSE	32
4	DAY3 2 HR	32
5	DAY3 PREDOSE	32
6	DAY5 2 HR	32
7	DAY5 PREDOSE	32
8	DAY1 1 HR	40
9	DAY1 30 MIN	40
10	DAY1 4 HR	40
11	DAY1 2 HR	72
12	DAY1 24 HR	72
13	DAY1 PREDOSE REPEAT 1	72
14	DAY1 PREDOSE REPEAT 2	72
15	DAY1 PREDOSE REPEAT 3	72

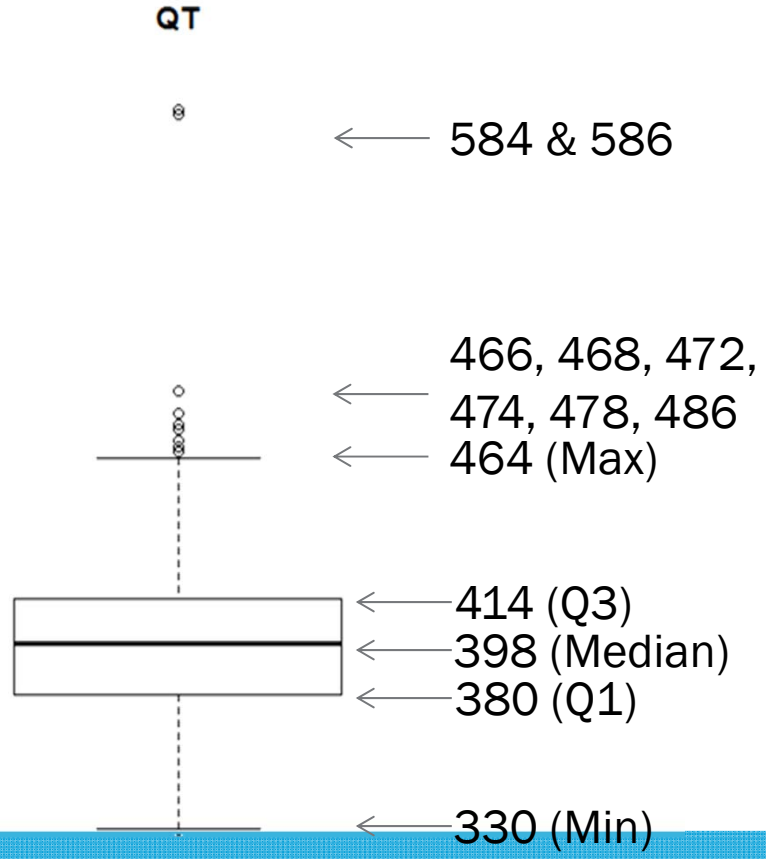
EXAMPLE STUDY: DATA CHECKING ECG



Obs	Statistics	Value	N_Obs
1	FARHIGH	500.000	1
2	FARHIGH	519.000	1
3	HIGH	440.000	1

FARHIGH values are values > 3*IQR + Q3, where IQR = Q3 – Q1

EXAMPLE STUDY: DATA CHECKING ECG



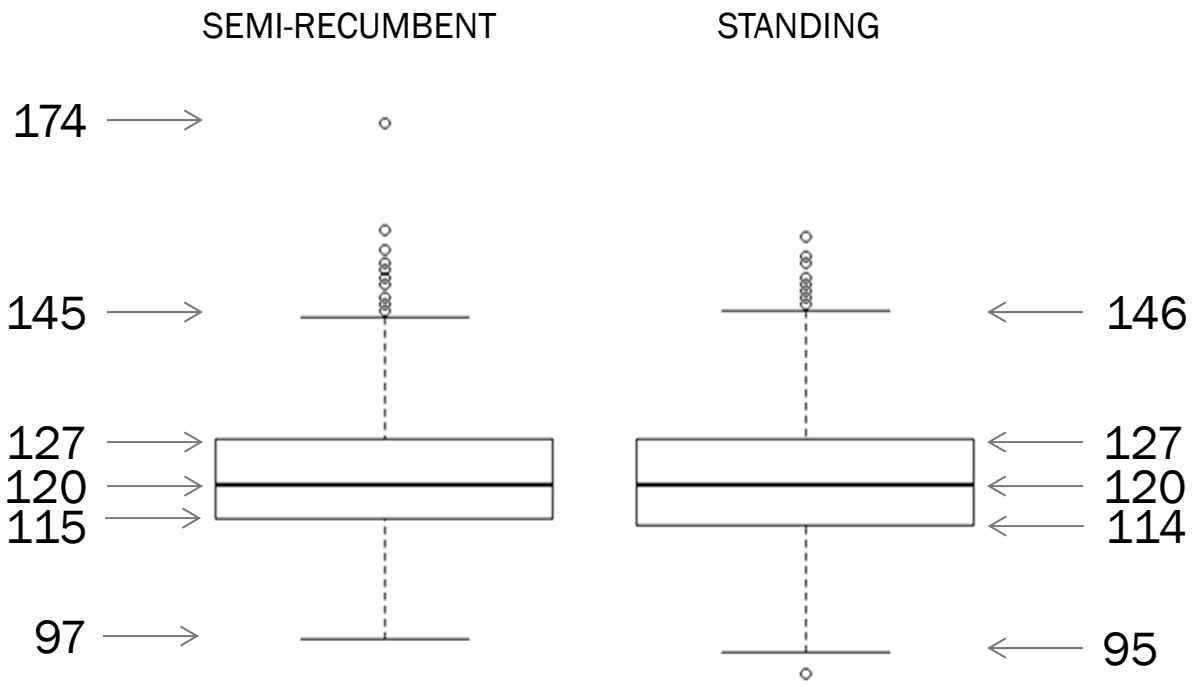
Obs	Statistics	Value	N_Obs
1	FARHIGH	584.000	1
2	FARHIGH	586.000	1
3	HIGH	466.000	3
4	HIGH	468.000	1
5	HIGH	472.000	1
6	HIGH	474.000	1
7	HIGH	478.000	1
8	HIGH	486.000	1

EXAMPLE STUDY: DATA CHECKING

ECG outliers identified by boxplots

ecg_parm	an_num	vt_num	PRSDTLTM	date	value	client comment
QT	21	7	DAY1 2 HR	2012-08-07T11:10	584	There were 2 unscheduled ECGs at 11:11 and 11:13 with QT of 410 and 422.
QT	38	7	DAY10 24 HR	2012-09-14T09:17	586	There was an unscheduled ECG at 9:19 with QT 414. For all of these, the protocol specifies that the average of the measurements will represent the QT value.
QTCF	21	7	DAY1 2 HR	2012-08-07T11:10	500	There was an unscheduled ECG at 9:19 with QTC Intv 377 msec
QTCF	38	7	DAY10 24 HR	2012-09-14T09:17	519	There were 2 unscheduled ECGs at 11:11 and 11:13 with QTC Intv 386 and 364 msec. There were 2 unscheduled ECGs at 11:11 and 11:13 with QTC Intv 386 and 364 msec.

EXAMPLE STUDY: DATA CHECKING VS



Obs	Statistics	Value	N_Obs
1	FARHIGH	174.00	1
2	FARLOW	62.00	1
3	HIGH	146.00	1
4	HIGH	147.00	4
5	HIGH	148.00	3
6	HIGH	149.00	2
7	HIGH	150.00	4
8	HIGH	151.00	4
9	HIGH	152.00	1
10	HIGH	153.00	3
11	HIGH	154.00	1
12	HIGH	155.00	1
13	HIGH	157.00	1
14	HIGH	158.00	1
15	LOW	92	1

FARLOW values are values < Q1 - 3*IQR, where IQR = Q3 – Q1

EXAMPLE STUDY: DATA CHECKING

VS and LB outliers identified by boxplots

domain	param	an_num	vt_num	bp_pst	prsdtltm	date	value	unit
VS	DIABP	3	5	Standing	DAY1 24 HR	2012-07-25T09:06	114	mmHg
VS	DIABP	5	4	Standing	DAY1 1 HR	2012-07-17T10:21	38	mmHg
VS	SYSBP	1	2	Semi-recum	DAY1 PREDOSE REPEAT 1	2012-06-19T08:27	174	mmHg
VS	SYSBP	5	4	Standing	DAY1 1 HR	2012-07-17T10:21	62	mmHg
LB	Eosinophils	6	4		DAY1 PREDOSE	2012-07-16T09:25	1.53	10[9]/L
LB	Alanine Aminotransferase	35	7		DAY10 24 HR	2012-09-14T09:10	1.319	microkat/L

EXAMPLE STUDY: ELEMENTS OF REPORT

1. ECG tables
2. ECG figures
3. Vital Signs tables
4. Vital Signs figures
5. Lab tables
6. Lab figures

EXAMPLE STUDY: REPORTING

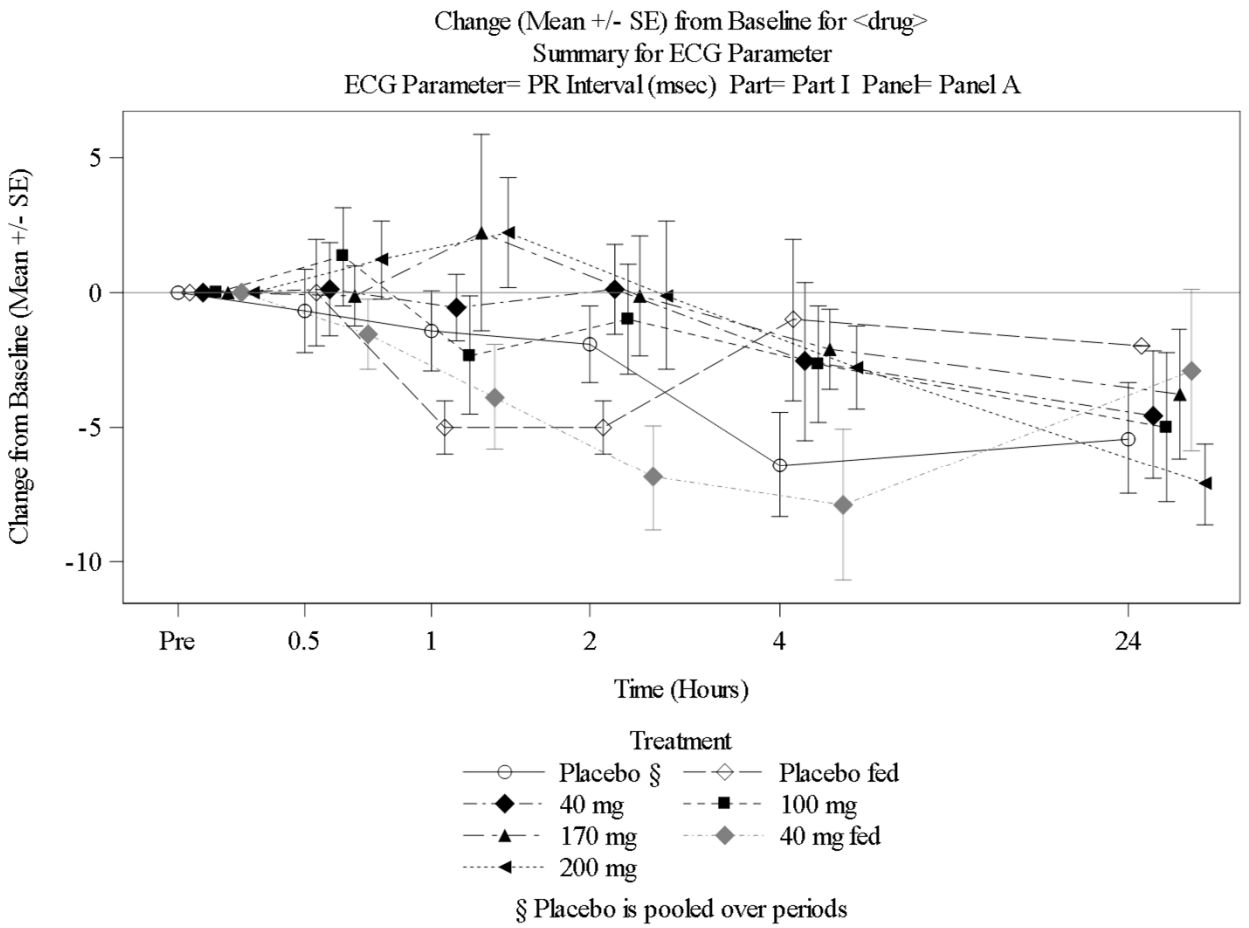
Treatment	Time	Value			Change From Baseline †		
		N ‡	Mean	SE	N ‡	Mean	SE
Placebo §	Predose	8	174.92	6.45			
	0.5 Hours	8	174.25	6.79	8	-0.67	1.53
	1 Hour	8	173.50	5.54	8	-1.42	1.48
	2 Hours	8	173.00	5.96	8	-1.92	1.40
	4 Hours	8	168.50	5.59	8	-6.42	1.95
	24 Hours	8	169.50	5.34	8	-5.42	2.06
Placebo fed	Predose	2	170.00	20.00			
	0.5 Hours	2	170.00	22.00	2	0.00	2.00
	1 Hour	2	165.00	21.00	2	-5.00	1.00
	2 Hours	2	165.00	19.00	2	-5.00	1.00
	4 Hours	2	169.00	23.00	2	-1.00	3.00
	24 Hours	2	168.00	20.00	2	-2.00	0.00
40 mg	Predose	6	174.89	5.95			
	0.5 Hours	6	175.00	4.81	6	0.11	1.72
	1 Hour	6	174.33	5.25	6	-0.56	1.26
	2 Hours	6	175.00	4.97	6	0.11	1.67
	4 Hours	6	172.33	4.96	6	-2.56	2.92
	24 Hours	6	170.33	5.12	6	-4.56	2.38
100 mg	Predose	6	175.67	7.62			
	0.5 Hours	6	177.00	8.18	6	1.33	1.81
	1 Hour	6	173.33	9.52	6	-2.33	2.20
	2 Hours	6	174.67	9.20	6	-1.00	2.03
	4 Hours	6	173.00	8.93	6	-2.67	2.17
	24 Hours	6	170.67	7.04	6	-5.00	2.77
170 mg	Predose	6	171.11	8.27			
	0.5 Hours	6	171.00	8.54	6	-0.11	1.12
	1 Hour	6	173.33	9.74	6	2.22	3.65
	2 Hours	6	171.00	9.74	6	-0.11	2.23
	4 Hours	6	169.00	9.64	6	-2.11	1.49
	24 Hours	6	167.33	7.86	6	-3.78	2.40

† Average of predose measurements serves as baseline; analysis performed on raw scale.
‡ Actual sample sizes are provided.
§ Placebo is pooled over periods.

Treatment	Time	Value			Change From Baseline †		
		N ‡	Mean	SE	N ‡	Mean	SE
40 mg fed	Predose	6	174.22	5.22			
	0.5 Hours	6	172.67	6.25	6	-1.56	1.32
	1 Hour	6	170.33	4.63	6	-3.89	1.94
	2 Hours	6	167.33	6.32	6	-6.89	1.94
	4 Hours	6	166.33	7.58	6	-7.89	2.82
	24 Hours	6	171.33	5.79	6	-2.89	2.98
200 mg	Predose	6	178.78	7.77			
	0.5 Hours	6	180.00	8.59	6	1.22	1.44
	1 Hour	6	181.00	6.67	6	2.22	2.03
	2 Hours	6	178.67	9.90	6	-0.11	2.76
	4 Hours	6	176.00	7.64	6	-2.78	1.53
	24 Hours	6	171.67	7.51	6	-7.11	1.51

† Average of predose measurements serves as baseline; analysis performed on raw scale.
‡ Actual sample sizes are provided.
§ Placebo is pooled over periods.

ECG Parameter = PR Interval (msec)
Part = Part I
Panel = Panel A


Change (Mean +/- SE) from Baseline for <drug>
Summary for ECG Parameter
ECG Parameter= PR Interval (msec) Part= Part I Panel= Panel A
Change from Baseline (Mean +/- SE)
5
0
-5
-10
Pre
0.5
1
2
4
24
Time (Hours)
Treatment
Placebo §
Placebo fed
40 mg
100 mg
170 mg
40 mg fed
200 mg
§ Placebo is pooled over periods

SUMMARY

Figures are useful in early phase safety reporting at the data issue checking stage as well as the reporting stage

- Easily identify possible outliers
  - Quickly report issues to Sponsor for decision making
- Easily display trends for change in baseline
  - Quickly provide evidence to continue with scheduled dosage increase or if adjustment is necessary

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Thank you!
Questions?