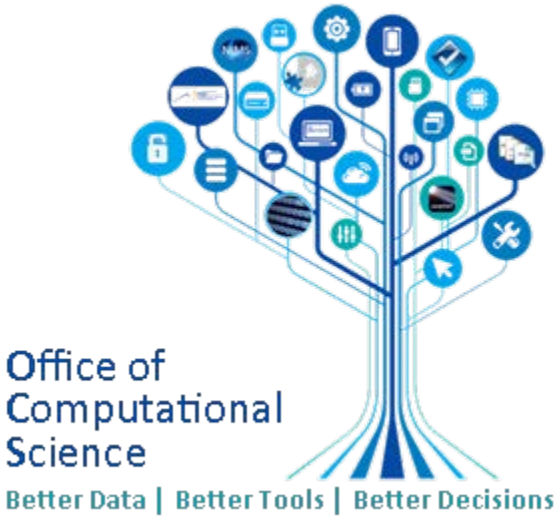
CDISC / PhUSE SEND Fit for Use Sponsor Pilot



Sponsor Submission Information

Sponsor:
Submission:
Type of Study: 4-Week Oral Toxicity Study in Beagle Dogs
Therapeutic Area: Cardiovascular
Date Received: August 3, 2016

OCS Feedback Section

SEND xpt File Feedback:
LB – data were collected on different days and VISITDY not provided to allow grouping

EG – Again, split collection days and repeat collections could not be grouped

PC – Missing values designated as “no result”. PC LLOQ is set = 1 in all records. It was unclear which samples were missing versus samples that were analyzed succesfully and found to be below or above the quantitation range. Providing units in PCSRESU is necessary to intrepret the LLOQ. Difficult to graph PC because VISITDY was not provided to allow the 24H timepoint to be grouped with the rest, and PCTPTNUM wasn’t provided in hours.

Dosages in TE and TX are missing a space – 30mg/kg/day

Trial Arm and Set Codes of “Control”, “Low”, “Intermediate”, “High” don’t provide much detail when we display them. Dosages would be more descriptive.

CL - "Refer to comment" is not a clinical observation.

Data Fitness Validation:
Reference the Data Fitness Analysis Report

SEND Analysis Tool:
Study Loaded

Define.xml Analysis:
Since this was a pilot, the Class value of “SPECIAL-PURPOSE” was corrected to “Special Purpose” to meet the define-1.0 standard and load to tools. Note that Class values have controlled terminology and “SPECIAL PURPOSE” with no hyphen is the CT. For other issues, see the Data Fitness Analysis Report.

Reviewer Feedback Section

Note: There are a team of reviewers conducting the analysis for the Fit for Use Pilot. If there is only feedback from one or two reviewers in a subsection of this document, there was concurrence from the other team members.

KickStart Service Analysis:

a. What sort of analysis was performed during the KickStart Service? – Please Explain?

The KickStart Service provides supplemental tables and visualizations of findings mentioned in the Study Report. Disposition, Body Weight graphs, clinical chemistry or hematology graphs, a table of clinical observations, pathology heat maps, and TK graphs are typically included. Other findings like tumors, organ weights, urinalysis, or death diagnosis are included if appropriate.

Study Data Reviewers Guide - SDRG Review:

a. Feedback on SDRG content: Please Explain?

Reviewer #1:
There were no major issues identified with the SDRG

b. Are the explanations for validation outcomes sufficient (i.e., warnings and errors section)?

Reviewer #6:
Explanations of warnings were understandable.

c. Is the content generally useful for the reviewer in understanding the SEND data? (is there too much or too little information)?

Reviewer #6:
The SDRG contained all required sections; the information was sufficient to interpret to SEND dataset.

Reviewer #3:
Agree

d. Does the "differences between report and dataset" section contain the right amount of information?

Reviewer #6:
Fourteen differences between the study report and dataset were noted.
The following is a summary of the reported differences:

- Only urinalysis results collected on Day 29 were presented in the study report, while data collected on Days -5, -4, 24, 25, and 29 were presented in the LB domain.
- Ophthalmoscopy observations are located in the CL domain.
- QRS, PR and RR values were included in the EG domain but were not reported in the study report.
- ECG results collected on Day -5 and Day 25 for some animals were included with the Day -6 and Day 24 results, respectively, in the study report for mean data purposes, but included as separate days in the EG domain.
- Day -1 ECG results were flagged as baseline in the EG domain, but pre-treatment data recorded at different times was averaged for baseline values in the study report.
- Plasma concentrations were reported to 2 decimal points in the LB domain and 3 significant figures in the final report.
- Organ to Brain Weight Ratio and Organ to Body Weight Ratio are presented to 5 decimal points in the OM domain, but to <5 in the study report.
- Organ to Heart Weight Ratio is presented in the OM domain, but not in the final report.
- Plasma concentrations with a value of NR in the PC domain are reported as NQ in the study report; study report error.
- The terminology used in the study report was converted to SEND controlled terminology for the creation of the dataset.

Reviewer #3:
It is useful for the SDRG to point out these differences because the differences are apparent in the data visualizations.

- **Are there things that don't matter that are listed or vice versa?**

Reviewer #6:
Reporting of the errors in the study report under Section 6.2 is not necessary.

e. Is there something you wish was in the SDRG but isn't...or vice versa?

Reviewer #6:
No.

Submission PDF:(Please note: It is not the goal of this pilot to QA/QC the data in the PDF file)

a. Please note any discrepancies found with the PDF version of submission summary and/or individual tables?

Reviewer #6:
No discrepancies were noted between study report summary and the SEND Data Sets

Visualization Tools:

a. Did the data present in the visualization tools according to a reviewer's expectation? – Please Explain?

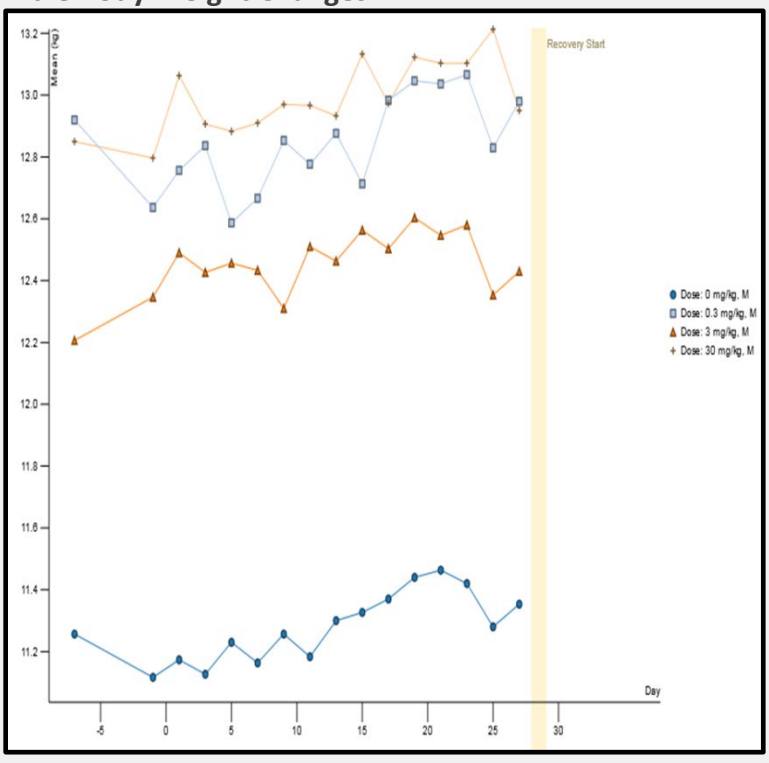
Reviewer #6:
Able to visualize body weight, clinical signs, disposition, ECG parameters, clinical chemistry, hematology, urinalysis, macroscopic and microscopic findings, and PK SEND data.

Reviewer #3:
"postdose" was split out and placed in CLLOC as noted in the SDRG. This does not seem correct since postdose is not a location.

b. Body Weight Graph? – Please Explain?

Reviewer #6:
Would also have been helpful to provide change in BW gain changes from Day 1 to Day 17.
The table below is a representative example of how body weight data is presented in our current visualization tool.

Male Body Weight Changes



c. Histopath Table, Graphical and Tabular? – Please Explain?

Reviewer #6:

For macroscopic and microscopic findings, results seemed over-standardized in the SEND data. This is most notable for the macroscopic findings in the intestines, where the finding is only recorded in the SEND data as “AREA”. The finding would usually be reported as “Red area” but “red” was considered to be a modifier.

OCS Comment:

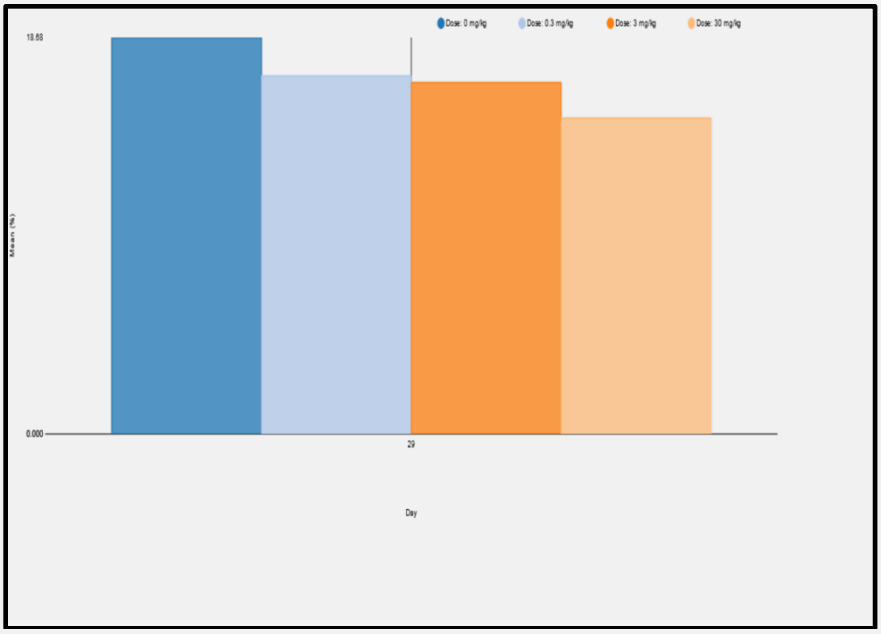
See the KickStart for a tabular display. In a larger study, using overly general terms in MASTRESC could unintentionally group unrelated findings.

The table and chart below are representative examples of how histopathology data and organ weight data are presented in our current visualization tool.

Male Microscopic Findings

Finding	Severity	M			
		Dose: 0 mg/kg	Dose: 0.3 mg/kg	Dose: 3 mg/kg	Dose: 30 mg/kg
GLAND, THYROID					
	#Examined	3	3	3	3
Hyperplasia	MILD				1 (33.3%)
Hyperplasia	Total				1 (33.3%)
STOMACH					
	#Examined	3	3	3	3
Hyperplasia	MILD		1 (33.3%)		
Hyperplasia	Total		1 (33.3%)		
TESTIS					
	#Examined	3	3	3	3
Hypospermatogenesis	MILD				1 (33.3%)
Hypospermatogenesis	Total				1 (33.3%)

Male Testes: Organ to Heart Weight Ratio



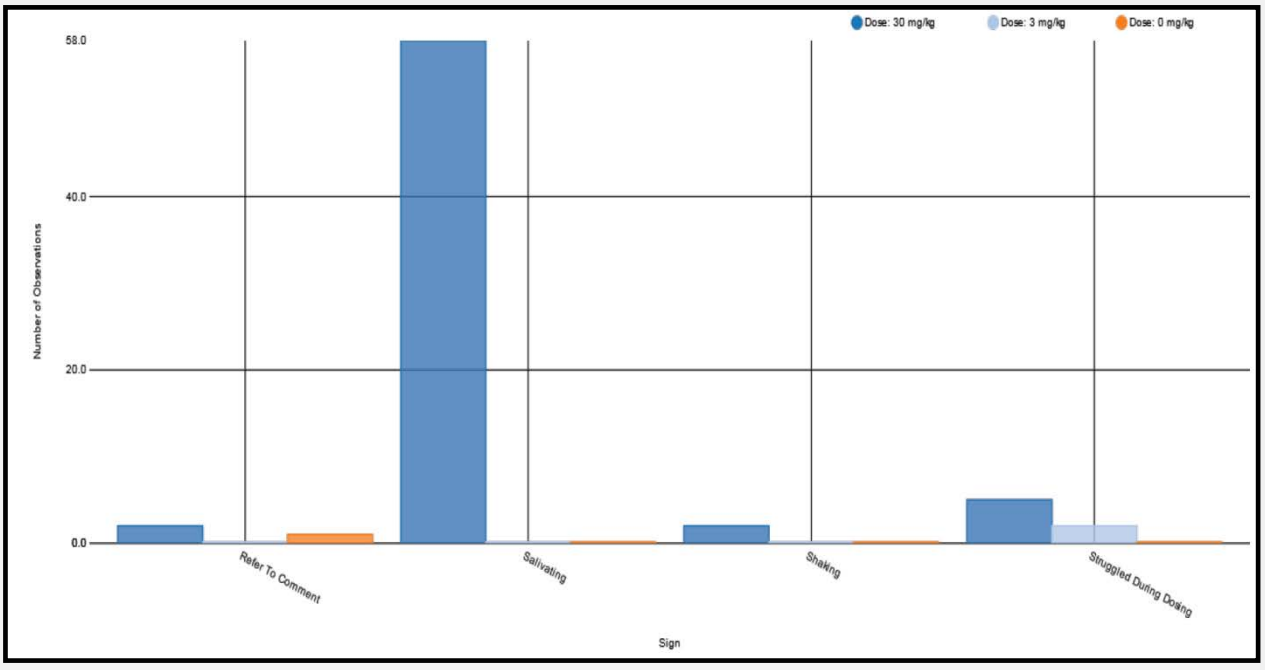
d. Clinical Observations? – Please Explain?

Reviewer #6:

The chart below is a representative example of how clinical observations data are presented in our current visualization tool.

"Refer to Comment", under the category "ophthalmology", is captured as a clinical sign for a male dosed at 30 mg/kg (STUDY-10); not sure what that is supposed to mean.

Male Clinical Observations



e. TK Information? – Please Explain?

Reviewer #6:

Able to view TK parameters for COMPOUND in tabular format for all dose groups.

Test	Day	Unit of the Standardized Result		Male			Female			
				Dose: 0.3 mg/kg	Dose: 3 mg/kg	Dose: 30 mg/kg	Dose: 0 mg/kg	Dose: 0.3 mg/kg	Dose: 3 mg/kg	Dose: 30 mg/kg
AUC All	1	h*ng/mL	MEAN	55.2	778.3	18130		17.18	1211	17130
		h*ng/mL	SD	±53.9	±635.2	±1986		±11.58	±1221	±5811
			N	3	3	3		3	3	3
AUC All	28	h*ng/mL	MEAN	21.47	668.7	27030		10.94	974.3	22200
		h*ng/mL	SD	±20.98	±402.2	±10800		±6.017	±589.5	±6580
			N	3	3	3		3	3	3
Max Conc	1	ng/mL	MEAN	87.53	760.7	6407		22.84	1407	9220
		ng/mL	SD	±82.63	±578.7	±2026		±17.91	±1213	±2711
			N	3	3	3		3	3	3
Max Conc	28	ng/mL	MEAN	27.7	731.7	11530		18.71	1158	11380
		ng/mL	SD	±22.46	±546.1	±3500		±11.11	±460.9	±4345
			N	3	3	3		3	3	3
Time of CMAX	1	h	MEAN	0.25	0.5	0.5833		0.6667	0.25	0.5833
		h	SD	±0	±0.433	±0.3819		±0.2887	±0	±0.3819
			N	3	3	3		3	3	3
Time of CMAX	28	h	MEAN	0.25	0.3333	0.6667		0.3333	0.25	0.5833
		h	SD	±0	±0.1443	±0.2887		±0.1443	±0	±0.3819
			N	3	3	3		3	3	3