

Interactive Exploratory Analysis and Visualization for Late Phase Clinical Data

Sheng-Wei Wang and Casey Yang
Janssen R&D

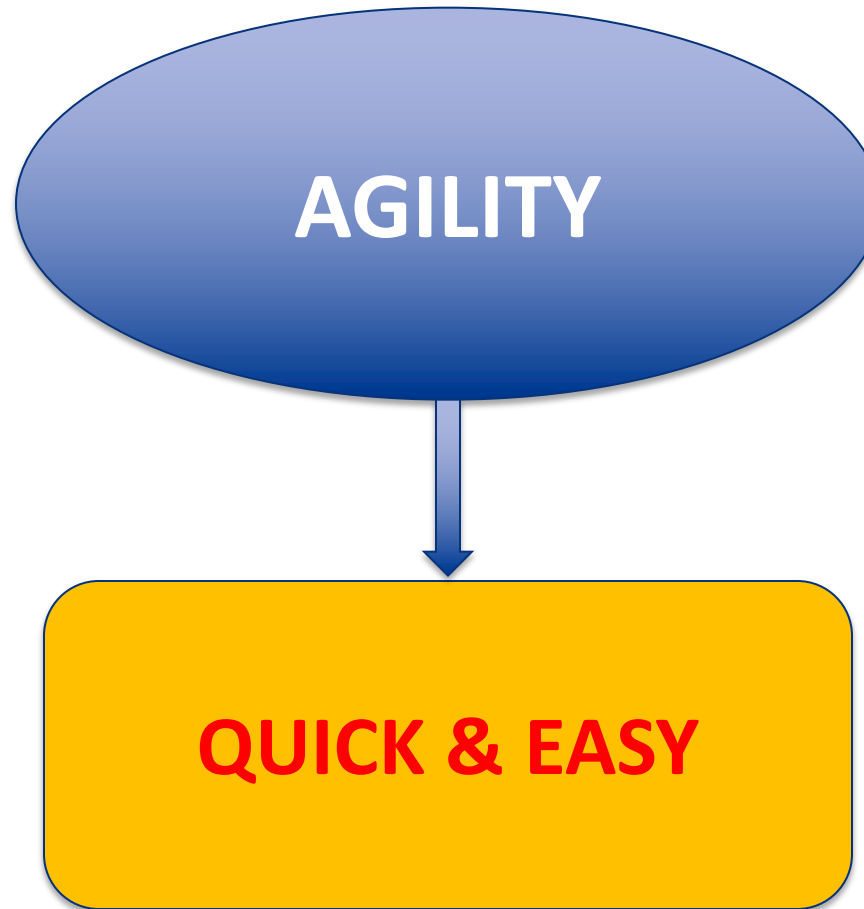
Acknowledgement: CVM (Lisa Lyons, Yingshan You, James Pan, Hsiaowei Deng, Wentao Lu, George Capuano, Pei-Ling Chu and Tao Sun), PDW (Sandy Lei)

Inspiration from Sir Winston Churchill

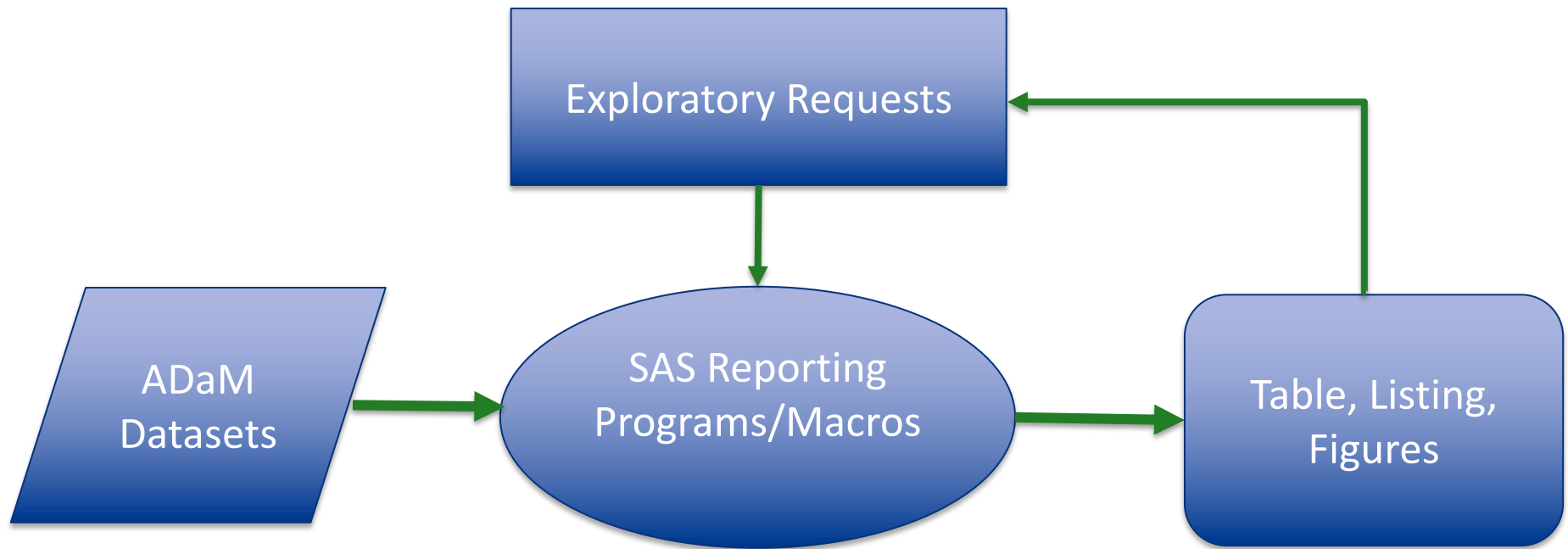
All the great things are simple, and
many can be expressed in a single
word: freedom, justice, honor, duty,
mercy, hope.

Winston Churchill

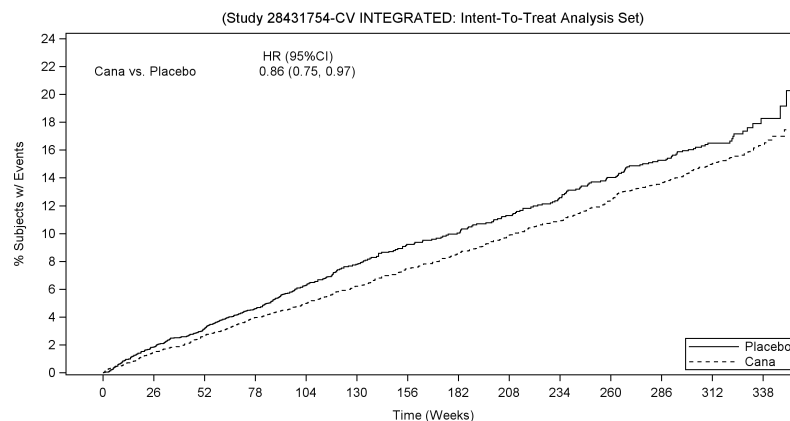
A Single Word for A Great Tool of Exploratory Analysis



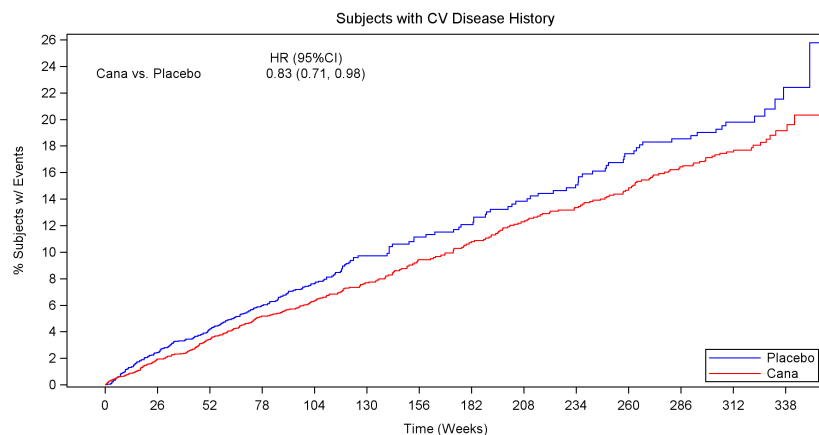
Exploratory Analysis Flow: Current Practice



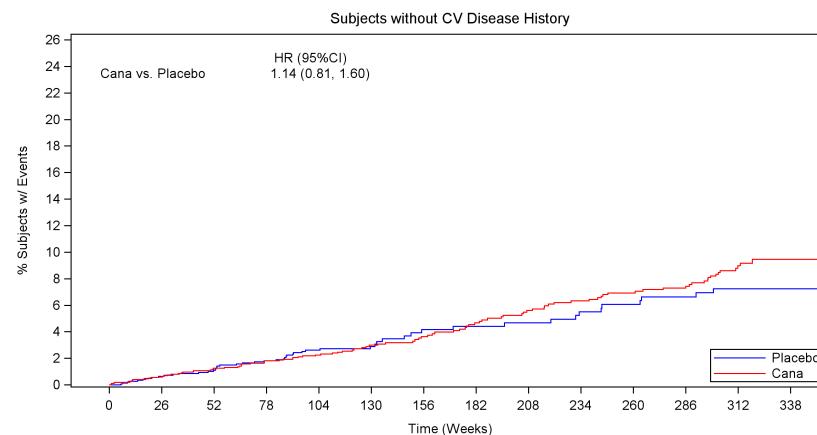
An Example of Exploratory Analysis: Kaplan-Meier Plot of MACE* by CV Disease History



Subjects	Time (weeks)													
	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216
Cana	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448



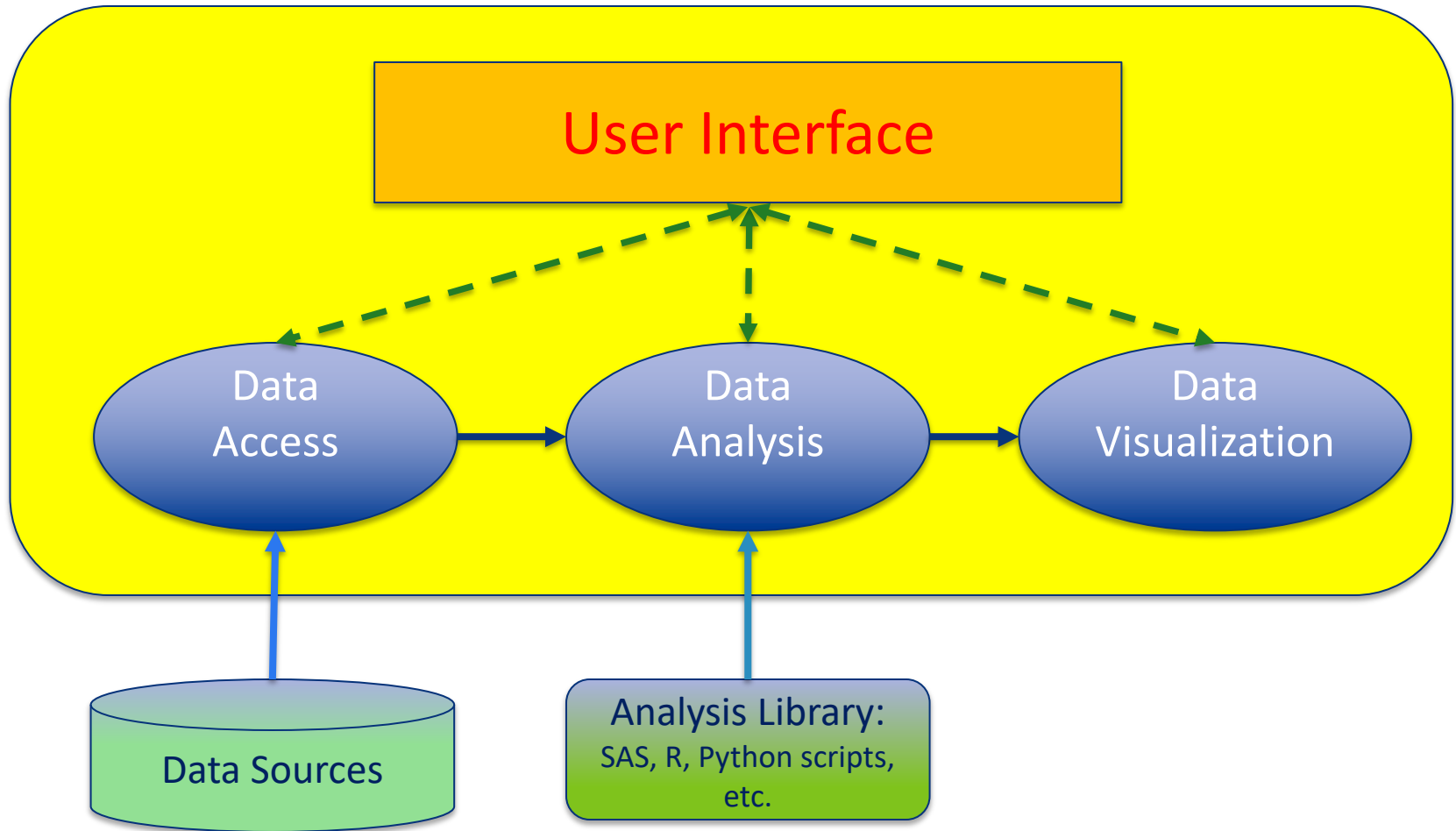
Subjects	Time (weeks)													
	2899	2662	2458	2243	1455	649	491	462	426	404	375	353	272	82
Placebo	3752	3453	3223	3010	2205	1344	1096	1045	984	944	892	843	647	189



Subjects	Time (weeks)													
	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	1445	1345	1273	1179	906	560	399	381	359	342	333	312	218	52
Cana	2038	1902	1796	1699	1407	1030	860	823	796	774	750	723	498	132

* Major Adverse Cardiovascular Events: CV death, nonfatal MI, nonfatal Stroke

Interactive Exploratory Analysis

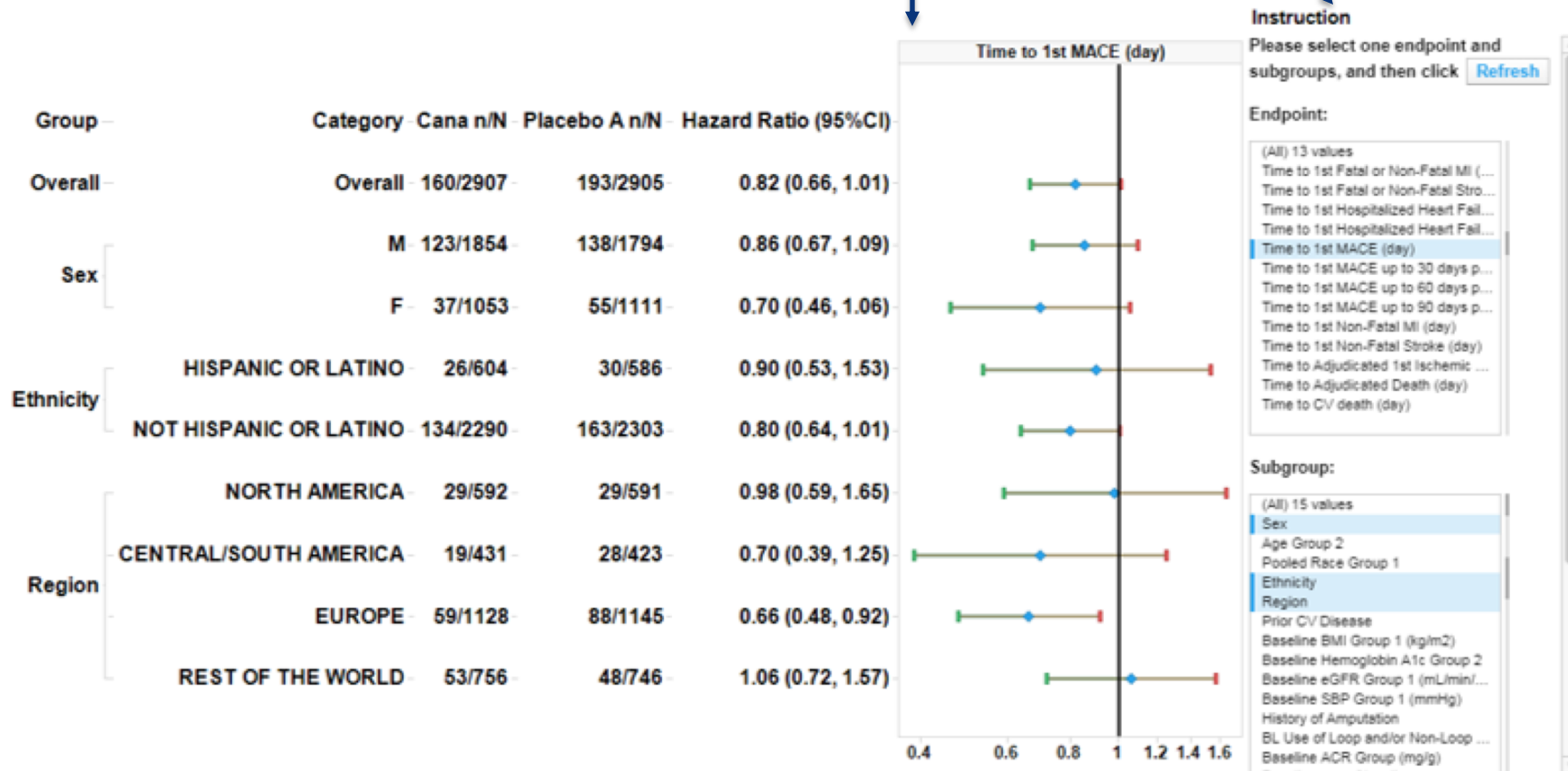


Interactive Exploratory Analysis Dashboard

- Agile exploration of analysis results
 - User interface of providing interactive inputs/specifications for analysis (point & click)
 - Dynamic visualization of analysis results
 - One Click Away
- Interactive data analytics and visualization tools:
 - TIBCO Spotfire
 - R/R-Shiny
 - Tableau
 - Qlik Sense
 - SAS Visual Analytics

Spotfire Analysis Dashboard Layout

- Analysis Panel: provide interactive instruction to conduct analysis
- Visualization area: display of the analysis results



Spotfire Use Case Demonstration: Survival Analysis

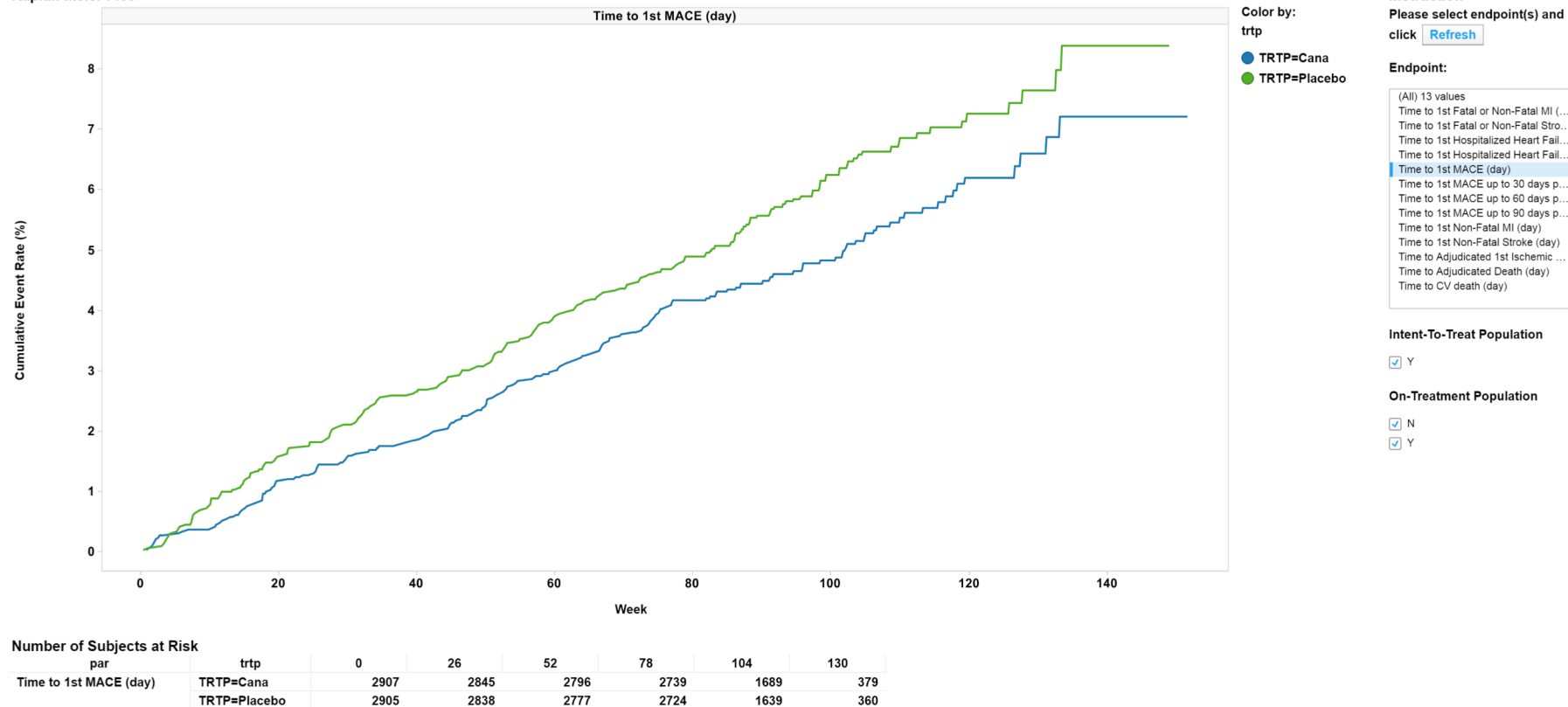
Using a Late Phase Clinical Trial data*

- Kaplan-Meier Plot
 - Interactive exploration across different endpoints by selecting
 - Parameter variable in the Time-To-Event Analysis Dataset
 - Option of selecting multiple parameters for displaying multiple K-M plots by trellis panel
- Forest Plot
 - Interactive exploration of Forest Plot across different subgroups for the selected endpoint
 - Customization of subgroups included in Forest Plot
 - Option of selecting different Tie methods in Cox Proportional Hazards model
 - Breslow, Efron, Exact

*Neal et al: Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes, N Engl J Med 2017; 377:644-657

Kaplan-Meier Plot of Primary Endpoint (MACE*)

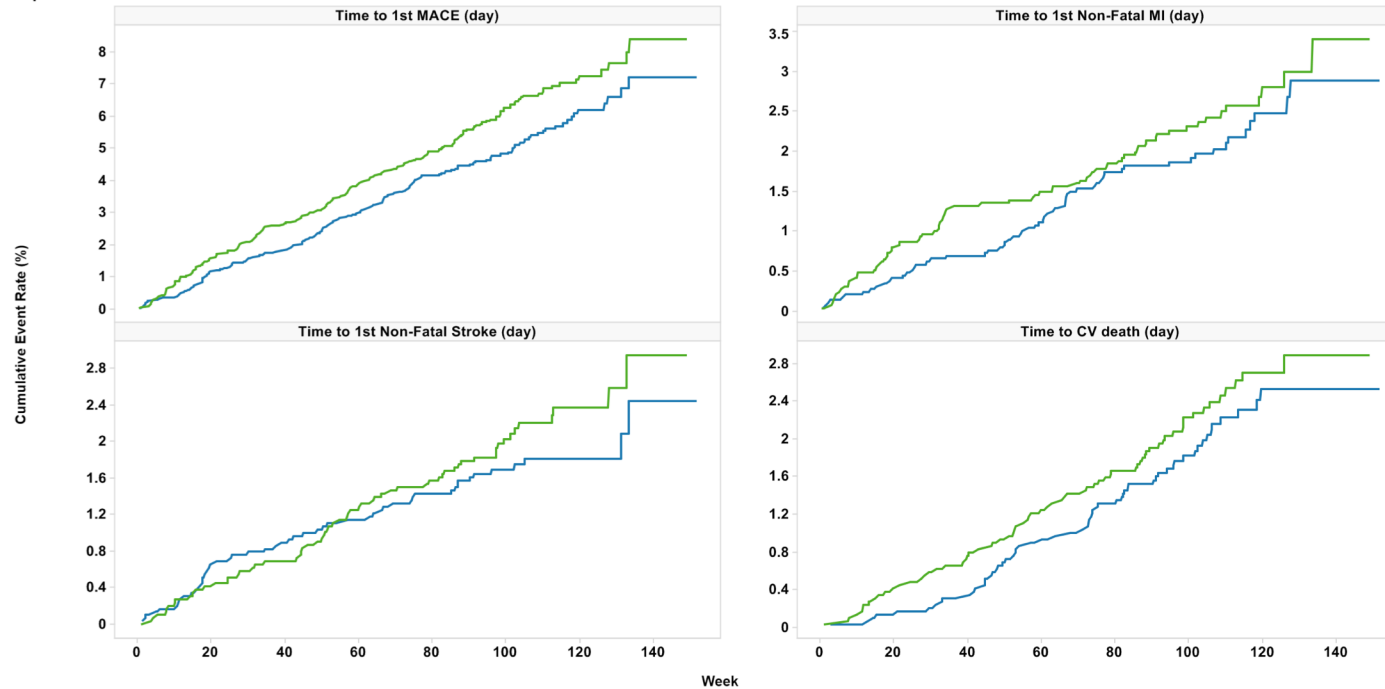
Kaplan-Meier Plot



*Major Adverse Cardiovascular Events: CV death, nonfatal MI, nonfatal Stroke

Kaplan-Meier Plot (Multi-Parameters)

Kaplan-Meier Plot



Color by:
trtp

● TRTP=Cana
● TRTP=Placebo

Instruction

Please select endpoint(s) and click [Refresh](#)

Endpoint:

(All) 13 values
 Time to 1st Fatal or Non-Fatal MI (...
 Time to 1st Fatal or Non-Fatal Stro...
 Time to 1st Hospitalized Heart Fail...
 Time to 1st Hospitalized Heart Fail...
 Time to 1st MACE (day)
 Time to 1st MACE up to 30 days p...
 Time to 1st MACE up to 60 days p...
 Time to 1st MACE up to 90 days p...
 Time to 1st Non-Fatal MI (day)
 Time to 1st Non-Fatal Stroke (day)
 Time to Adjudicated 1st Ischemic ...
 Time to Adjudicated Death (day)
 Time to CV death (day)

Intent-To-Treat Population

☒ Y

On-Treatment Population

☒ N

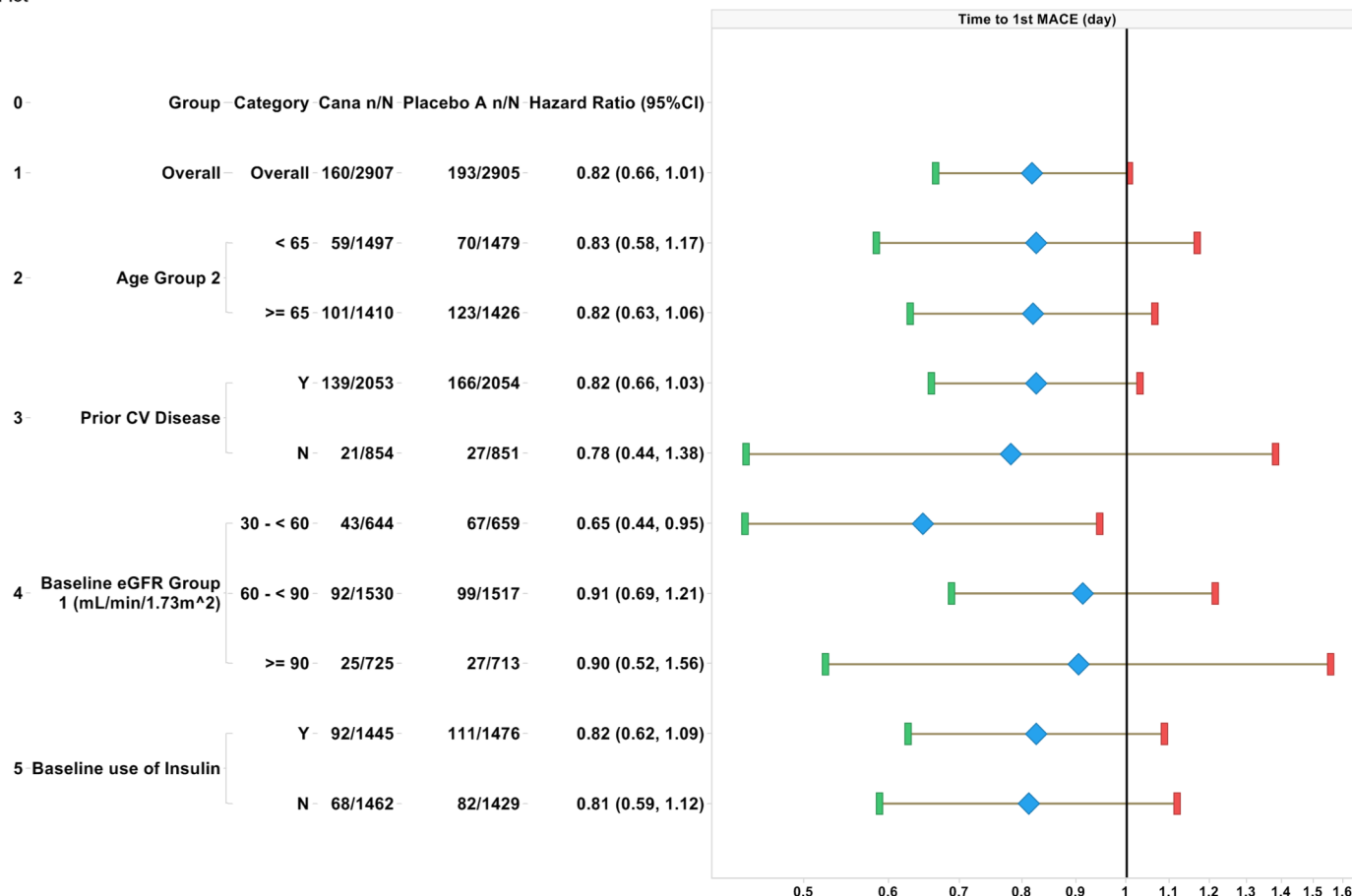
☒ Y

Number of Subjects at Risk

par	trtp	0	26	52	78	104	130
Time to 1st MACE (day)	TRTP=Cana	2907	2845	2796	2739	1689	379
	TRTP=Placebo	2905	2838	2777	2724	1639	360
Time to 1st Non-Fatal MI (day)	TRTP=Cana	2907	2866	2826	2775	1715	382
	TRTP=Placebo	2905	2852	2804	2763	1672	367
Time to 1st Non-Fatal Stroke (day)	TRTP=Cana	2907	2861	2818	2781	1717	387
	TRTP=Placebo	2905	2861	2811	2771	1677	370
Time to CV death (day)	TRTP=Cana	2907	2893	2864	2840	1765	398
	TRTP=Placebo	2905	2887	2859	2831	1730	387

Forest Plot of Primary Endpoint (MACE)

Forest Plot



Instruction

Please select one endpoint and subgroups, and then click [Refresh](#)

Endpoint:

(All) 13 values
 Time to 1st Fatal or Non-Fatal MI (...
 Time to 1st Fatal or Non-Fatal Stro...
 Time to 1st Hospitalized Heart Fail...
 Time to 1st Hospitalized Heart Fail...
 Time to 1st MACE (day)
 Time to 1st MACE up to 30 days p...
 Time to 1st MACE up to 60 days p...
 Time to 1st MACE up to 90 days p...
 Time to 1st Non-Fatal MI (day)
 Time to 1st Non-Fatal Stroke (day)
 Time to Adjudicated 1st Ischemic ...
 Time to Adjudicated Death (day)
 Time to CV death (day)

Subgroup:

(All) 15 values
 Sex
 Age Group 2
 Pooled Race Group 1
 Ethnicity
 Region
 Prior CV Disease
 Baseline BMI Group 1 (kg/m²)
 Baseline Hemoglobin A1c Group 2
 Baseline eGFR Group 1 (mL/min/...
 Baseline SBP Group 1 (mmHg)
 History of Amputation
 BL Use of Loop and/or Non-Loop ...
 Baseline ACR Group (mg/g)
 Baseline use of Insulin
 Diabetes History >= 10 Years

Ties for Cox PH Model

efron

Intent-To-Treat Population

☒ Y

On-Treatment Population

☒ N

☒ Y

Spotfire Use Case Demonstration: AE Summary Analysis

- Interactive AE summary analysis for special interest AEs
 - AE summary table by preferred term
 - AE attribute summary table (serious AE, leading to discontinuation, related to study drug, etc.)
 - AE occurrence summaries over time (bar chart)
- Dynamic inputs in the analysis panel
 - CQxxNAM (customized query name) variable
 - Search box tool for finding the CQ type requested
 - AE attributes (All, Serious AE, AE leading to drug discontinuation)

AE Summary Table by Preferred Term

AE Summary by Preferred Term for Renal Related

Dictionary_Derived_Term	Treatment					
	Placebo, n(%)	Rate(/1000pt-yrs)	Cana, n(%)	Rate(/1000pt-yrs)	IRD	95% C.I.
Total no. subjects with Special Interest AE	42/2903 (1.4)	7.75	41/2904 (1.4)	7.41	-0.34	(-3.64, 2.97)
Acute kidney injury	25/2903 (0.9)	4.61	15/2904 (0.5)	2.71	-1.90	(-4.23, 0.43)
Blood creatinine increased	5/2903 (0.2)	0.92	4/2904 (0.1)	0.72	-0.20	(-1.42, 1.02)
Glomerular filtration rate decreased	3/2903 (0.1)	0.55	6/2904 (0.2)	1.08	0.53	(-0.69, 1.75)
Nephropathy toxic	0	0.00	2/2904 (0.1)	0.36	0.36	
Renal failure	3/2903 (0.1)	0.55	5/2904 (0.2)	0.90	0.35	(-0.82, 1.52)
Renal impairment	7/2903 (0.2)	1.29	13/2904 (0.4)	2.35	1.06	(-0.63, 2.74)

Instruction

Please select CQNAM variable:

CQ12NAM

AE attribute selection:

All

Refresh

Search tool for CQ type and related CQNAM variable

CQ type:

Renal

(All) 48 values

Acute Renal Failure (Narrow)

Malignancy Renal Cell Cancer

Renal Related

CQNAM:

Type to search in list

(All) 1 values

CQ12NAM

AE Attribute Summary Table

Exposure Adjusted AE Summary for Renal Related

AE	Treatment			
	Placebo, n(%)	Rate/(1000pt-yrs)	Canva, n(%)	Rate/(1000pt-yrs)
Any Adverse Events	42 (1.4)	7.75	41 (1.4)	7.41
Adverse Events Leading to Discontinuation	10 (0.3)	1.84	16 (0.6)	2.89
Adverse Events Related to Study Drug	11 (0.4)	2.03	21 (0.7)	3.80
Adverse Events Related to Study Drug* and Leading to Discontinuation	6 (0.2)	1.11	11 (0.4)	1.99
Serious Adverse Events	19 (0.7)	3.51	12 (0.4)	2.17
Serious Adverse Events Leading to Discontinuation	2 (0.1)	0.37	4 (0.1)	0.72
Serious Adverse Events Related to Study Drug	2 (0.1)	0.37	4 (0.1)	0.72
Serious Adverse Events Related to Study Drug* and Leading to Discontinuation	1 (<0.1)	0.18	2 (0.1)	0.36
Death	1 (<0.1)	0.18	2 (0.1)	0.36

Instruction

Please select CQAM variable:

CQ12NAM

Refresh

Search tool for CQ type and related CQAM variable

CQ type:

Renal

(All) 48 values
Acute Renal Failure (Narrow)
Malignancy Renal Cell Cancer
Renal Related

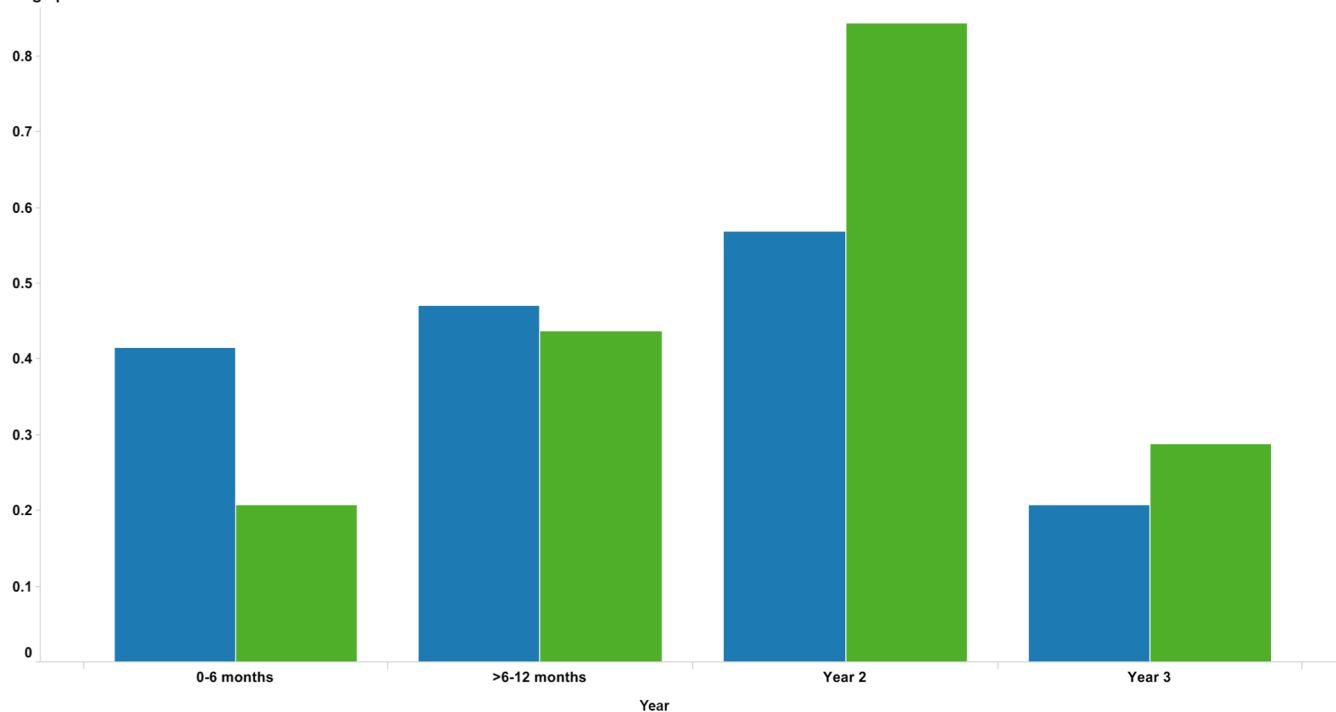
CQAM:

Type to search in list

(All) 1 values
CQ12NAM

Percentage of AE Occurrence Over Time

Percentage per Year



Color by:

TRT01P

● Cana

● Placebo

Instruction

Please select CQNAM:

CQ12NAM

CQ Type: Renal Related

Please select AE attribute:

All

Search tool for CQ Type and related CQNAM variable

re

(All) 48 values

- Acute Renal Failure (Narrow)
- Haemorrhage related
- Malignancy Renal Cell Cancer
- Proliferative retinopathy
- Renal Related
- Retinopathy Broad

Type to search in list

(All) 1 values

- CQ12NAM

On-Treatment Population:

☐ N

☒ Y

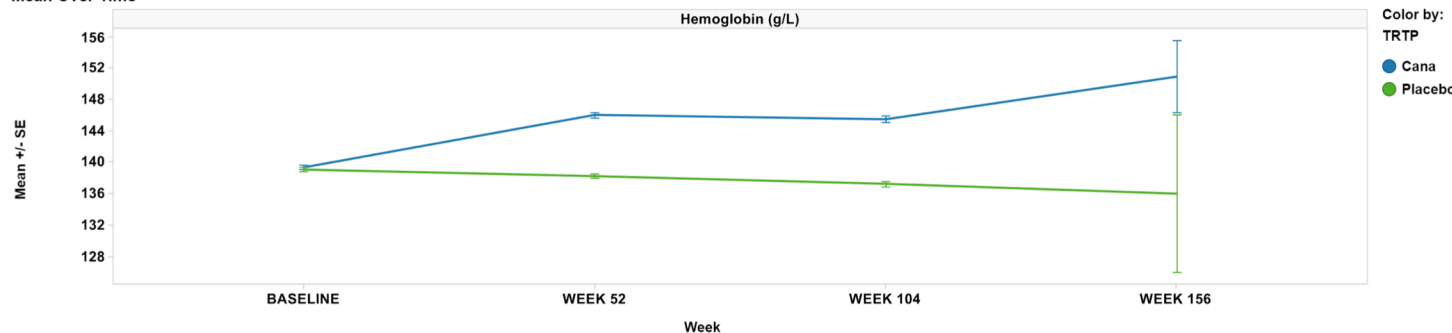
TRT01P	0-6 months			>6-12 months			Year 2			Year 3		
	n	N	%	n	N	%	n	N	%	n	N	%
Cana	12	2904	0.41 %	13	2771	0.47 %	15	2642	0.57 %	3	1454	0.21 %
Placebo	6	2903	0.21 %	12	2758	0.44 %	22	2612	0.84 %	4	1397	0.29 %

Spotfire Use Case Demonstration: Lab Summary Over Time

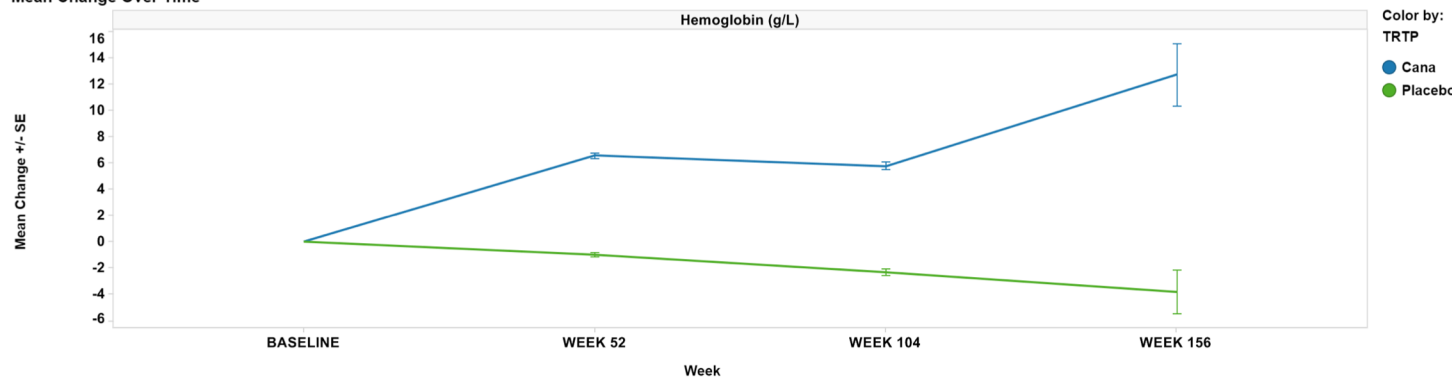
- Interactive exploration of lab summary (mean, mean change) over time across different lab tests through selecting
 - Lab category
 - Multiple plots of lab tests in the same category
 - Lab test
 - Search box tool for finding lab test requested
 - Analysis visits
 - Customization of analysis visits to be included in the plot
- Table of summary statistics (N, Mean, SD, Median, Min, Max, etc.) is automatically created for the lab tests selected in the over time plot

Mean and Mean Change Over Time for Hemoglobin (g/L)

Mean Over Time



Mean Change Over Time



Number of Subjects

PARAM	TRTP	BASELINE	WEEK 52	WEEK 104	WEEK 156
Hemoglobin (g/L)	Cana	2844	2528	1741	10
	Placebo	2838	2492	1685	5

Instruction

Please make the following selections:

Lab Category

- ☐ (All)
- ☐ Differentials
- ☐ Dipstick/Macroscopic
- ☐ HbA1c
- ☒ Hemogram
- ☐ Lipids
- ☐ Pregnancy Test
- ☐ RBC/WBC Morphology
- ☐ Sediment
- ☐ Serum Chemistry
- ☐ (None)

Lab Test

Type to search in list

(All) 5 values

Erythrocytes (x10E12/L)

Hematocrit (fraction)

Hemoglobin (g/L)

Leukocytes (x10E9/L)

Platelets (x10E9/L)

Analysis Visit, Week

- ☒ 0.00
- ☒ 13.00
- ☒ 26.00
- ☒ 52.00
- ☒ 78.00
- ☒ 104.00
- ☒ 130.00
- ☒ 156.00
- ☒ 9999.00
- ☒ (Empty)

On-Treatment Population

- ☐ N
- ☒ Y

Table of Summary Statistics Over Time for Hemoglobin (g/L)

Change From Baseline in Selected Lab Parameters Over Time

PARAM	TRTP	AVISIT	N	Mean	SD	Med	Min	Max	Base_Mean	Base_SD	N_chg	Mean_chg	L95_Mean_chg	U95_Mean_chg	SE_chg	SD_chg
Hemoglobin (g/L)	Cana	BASELINE	2844	139.317	13.9569	140.000	79.00	189.00			0					
		WEEK 52	2528	145.989	15.6982	147.000	55.00	194.00	139.411	13.8328	2528	6.578	6.1863	6.9704	0.2000	10.0577
		WEEK 104	1741	145.501	15.4871	147.000	90.00	203.00	139.724	13.5640	1741	5.777	5.2483	6.3060	0.2698	11.2580
		WEEK 156	10	150.900	14.5865	151.500	124.00	179.00	138.200	14.2267	10	12.700	8.0799	17.3201	2.3573	7.4543
	Placebo	BASELINE	2838	139.058	13.9295	139.000	92.00	193.00			0					
		WEEK 52	2492	138.193	14.5729	138.000	66.00	185.00	139.182	13.7661	2492	-0.989	-1.3571	-0.6213	0.1877	9.3705
		WEEK 104	1685	137.205	14.9299	137.000	80.00	202.00	139.509	13.8928	1685	-2.303	-2.7985	-1.8080	0.2527	10.3725
		WEEK 156	5	136.000	22.3942	127.000	115.00	162.00	139.800	23.1560	5	-3.800	-7.0443	-0.5557	1.6553	3.7014

