PhUSE

PhUSE Computational Science Standard Analyses and Code Sharing Working Group

Script Discovery and Acquisition Project Team

Screen Shots of the Displays Created Using Scripts Contributed by the FDA

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1. Disclaimer

The opinions expressed in this document are those of the authors and do not necessarily represent the opinions of the Pharmaceuticals User Software Exchange (PhUSE), members' respective companies or organizations, or regulatory authorities. The content in this document should not be interpreted as a data standard and/or information required by regulatory authorities.

2. Notice of Current Edition

This edition of the "Screen Shots of the Displays Created Using Scripts Contributed by the FDA" white paper is a minor revision of the white paper originally titled as "Screen Shots of the Displays Created by JumpStart Programs".

3. Additions and/or Revisions

Date	Author	Version	Changes
2017-Mar-17	See Section 5	v1.0	First edition
2017-May-19	See Section 5	v1.1	Updated the title and purpose to more accurately reflect the purpose and use of the outputs of the analysis scripts provided by FDA.

4. Purpose

The purpose of this document is to show the displays associated with the scripts (SAS programs) contributed to the PhUSE Script Repository in 2016 by the Food and Drug Administration (FDA). These programs were developed by the Center for Drug Evaluation and Research's Office of Computational Science as tools to help reviewers with the analysis of sponsor-submitted study data in Clinical Data Interchange Standards Consortium-compliant study data tabulation model format.

The SAS programs encompass the following analysis panels:

- Adverse Events Analysis Panel, which provides users with different analyses to facilitate understanding of the adverse events present in the study and the frequency of their occurrence by treatment arm.

- Adverse Event Toxicity, which provides users with analyses of adverse events by toxicity grades and shows information on subjects experiencing adverse events corresponding to user-selected Medical Dictionary for Regulatory Activities (MedDRA) levels in the treatment and control arms.
- Adverse Events MedDRA Analysis Panel, which enables users to see events that occurred in the study according to their place in the MedDRA hierarchy and allows them to compare any two arms according to a number of statistics.
- Demographic Analysis Panel, which provides users with an overview of the number and percent of subjects that correspond to various variables in the demographics dataset.
- Disposition Analysis Panel, which details the number and percent of cases that correspond to the disposition dataset.
- Liver Lab Analysis Panel, which provides users with an overview of the number and percent of subjects who have predefined abnormalities in lab test values for alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase.

The displays provided here are not necessarily consistent with regulatory guidance documents or white papers created by the PhUSE Analysis and Display White Papers (ADW) Project Team. We do not recommend that sponsors create these tables and figures instead of those already in a sponsor's standards library or those that are recommended by the PhUSE ADW project team. Instead, these displays inform sponsors of what the FDA may see early in their review process. Updates or modifications to a sponsor's standards may be warranted if conceptual gaps are identified. However, sponsors may want to run the contributed programs to ensure the FDA will be able to run them without errors. The contributed programs were shared with the PhUSE Script Repository Discovery and Acquisition Project Team and the programs have been uploaded to the PhUSE Script Repository in GitHub [1].

If interested in ensuring the FDA will be able to run the programs without errors or in duplicating the displays, sponsors can start with and access the codes provided in the PhUSE Script Repository in GitHub by following these links:

- Index of all scripts: https://github.com/phuse-org/phuse-scripts/wiki/Simple-Index
- Index of FDA Analytical Scripts: https://github.com/phuse-org/phuse-scripts/wiki/Reviewed-Scripts.
- Once a script is tested, it will be in the tested/SAS folder

5. Acknowledgements

The primary contributors include Rebeka Revis, Hamning Tu, Mary Nilsson, Ted Peterson, and Bobbie Witczak. Thank you to Casie Polanco for editorial support. Thank you to all the original authors of the scripts and those involved with updates to the scripts over time.

6. Project Leader Contact Information

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7. References

1. Slain J, Tu H. CS07: Get a Jump Start on Clinical Data Analysis and Visualization with Standard Scripts. PhUSE Wiki. Available at: http://www.phusewiki.org/docs/Conference%202016%20CS%20Paper/CS07.pdf. Accessed 13 Feb 2017.

8. Appendices

8.1. AE Severity

Analysis 1: Adverse Events by Arm Greater than 2%

Adverse Events by Organ Class and Term

NDA/BLA: 12345
Study: 123
Analysis run date: 2015-03-11 11:22:04 AM

Where subject count is the number of subjects in the treatment arm experiencing at least one adverse event per organ class and term and greater than 2% of subjects in any arm experienced at least one adverse event

Body System or Organ Class	Dictionary-Derived Term	Placebo		Treatment		Total	
		N=577		N=575		N=1,152	
		Subject Count	%	Subject Count	%	Subject Count	%
Blood And Lymphatic System Disorders	Anaemia	31	5.4	48	8.3	79	6.9
Blood And Lymphatic System Disorders	Iron Deficiency Anaemia	15	2.6	5	0.9	20	1.7
Cardiac Disorders	Right Ventricular Failure	59	10.2	45	7.8	104	9.0
Cardiac Disorders	Palpitations	32	5.5	34	5.9	66	5.7
Cardiac Disorders	Atrial Fibrillation	11	1.9	12	2.1	23	2.0
Ear And Labyrinth Disorders	Vertigo	10	1.7	15	2.6	25	2.2
Endocrine Disorders	Hypothyroidism	12	2.1	8	1.4	20	1.7
Gastrointestinal Disorders	Diarrhoea	107	18.5	243	42.3	350	30.4
Gastrointestinal Disorders	Nausea	104	18.0	191	33.2	295	25.6
Gastrointestinal Disorders	Vomiting	50	8.7	103	17.9	153	13.3
Gastrointestinal Disorders	Abdominal Pain	32	5.5	48	8.3	80	6.9
Gastrointestinal Disorders	Abdominal Pain Upper	32	5.5	34	5.9	66	5.7
Gastrointestinal Disorders	Abdominal Distension	23	4.0	18	3.1	41	3.6
Gastrointestinal Disorders	Dyspepsia	14	2.4	24	4.2	38	3.3
Gastrointestinal Disorders	Abdominal Discomfort	14	2.4	21	3.7	35	3.0

Analysis 2: Serious Adverse Events by Arm

Serious Adverse Events by Organ Class and Term

NDA/BLA: 12345
Study: 123
Analysis run date: 2015-03-11 11:22:04 AM

Where subject count is the number of subjects in the treatment arm experiencing at least one serious adverse event per organ class and term

Body System or Organ Class	Dictionary-Derived Term	Placebo		Treatment		Total	
		N=577		N=575		N=1,152	
		Subject Count	%	Subject Count	%	Subject Count	%
Blood And Lymphatic System Disorders	Anaemia	3	0.5	5	0.9	8	0.7
Blood And Lymphatic System Disorders	Haemorrhagic Anaemia	0	0.0	1	0.2	1	0.1
Blood And Lymphatic System Disorders	Idiopathic Thrombocytopenic Purpura	0	0.0	1	0.2	1	0.1
Blood And Lymphatic System Disorders	Leukopenia	0	0.0	1	0.2	1	0.1
Blood And Lymphatic System Disorders	Neutropenia	1	0.2	0	0.0	1	0.1
Blood And Lymphatic System Disorders	Thrombocytopenia	0	0.0	1	0.2	1	0.1
Cardiac Disorders	Right Ventricular Failure	42	7.3	34	5.9	76	6.6
Cardiac Disorders	Atrial Fibrillation	4	0.7	7	1.2	11	1.0
Cardiac Disorders	Atrial Flutter	4	0.7	4	0.7	8	0.7
Cardiac Disorders	Acute Right Ventricular Failure	5	0.9	2	0.3	7	0.6
Cardiac Disorders	Cardiac Arrest	4	0.7	2	0.3	6	0.5
Cardiac Disorders	Supraventricular Tachycardia	4	0.7	1	0.2	5	0.4
Cardiac Disorders	Cardio-Respiratory Arrest	2	0.3	2	0.3	4	0.3
Cardiac Disorders	Cardiogenic Shock	2	0.3	2	0.3	4	0.3
Cardiac Disorders	Cardiopulmonary Failure	1	0.2	3	0.5	4	0.3

Analysis 3: Adverse Events by Severity and Arm

Adverse Events by Severity Level

NDA/BLA: 12345
Study: 123
Analysis run date: 2015-03-11 11:22:04 AM

Where the number in each column is the number of adverse events per treatment arm at the stated severity level.

Body System or Organ Class	Dictionary-Derived Term	Placebo				Treatment				Total
		Mild	Moderate	Severe	Not Applicable	Mild	Moderate	Severe	Not Applicable	
Nervous System Disorders	Headache	162	71	12	0	306	256	82	0	889
General Disorders And Administration Site Cond	Disease Progression	81	226	155	3	52	163	130	1	811
Gastrointestinal Disorders	Diarrhoea	89	35	9	0	206	126	31	0	496
Gastrointestinal Disorders	Nausea	93	29	4	0	146	99	15	0	386
Respiratory, Thoracic And Mediastinal Disorders	Pulmonary Arterial Hypertension	7	85	126	0	8	43	86	0	355
Respiratory, Thoracic And Mediastinal Disorders	Dyspnoea	40	69	22	0	43	48	20	0	242
Infections And Infestations	Upper Respiratory Tract Infection	81	35	2	0	69	29	4	0	220
Musculoskeletal And Connective Tissue Disorde	Pain In Jaw	30	5	0	0	129	49	7	0	220
General Disorders And Administration Site Cond	Oedema Peripheral	72	46	9	0	46	36	6	0	215
Nervous System Disorders	Dizziness	73	26	1	0	74	30	3	0	207
Infections And Infestations	Nasopharyngitis	68	27	1	0	82	21	0	0	199
Musculoskeletal And Connective Tissue Disorde	Pain In Extremity	35	20	3	0	63	62	15	0	198
Gastrointestinal Disorders	Vomiting	30	20	4	0	59	74	10	0	197
Musculoskeletal And Connective Tissue Disorde	Myalgia	22	13	1	0	64	46	9	0	155
Respiratory, Thoracic And Mediastinal Disorders	Cough	46	33	3	0	47	18	0	0	147
Musculoskeletal And Connective Tissue Disorde	Arthralgia	32	21	3	0	28	49	4	0	137
Cardiac Disorders	Right Ventricular Failure	6	20	42	0	5	17	31	0	121

Analysis 4: Serious Adverse Events by Severity and Arm

Serious Adverse Events by Organ Class and Term

NDA/BLA: 12345
Study: 123
Analysis run date: 2015-03-11 11:22:04 AM

Where subject count is the number of subjects in the treatment arm experiencing at least one serious adverse event per organ class and term

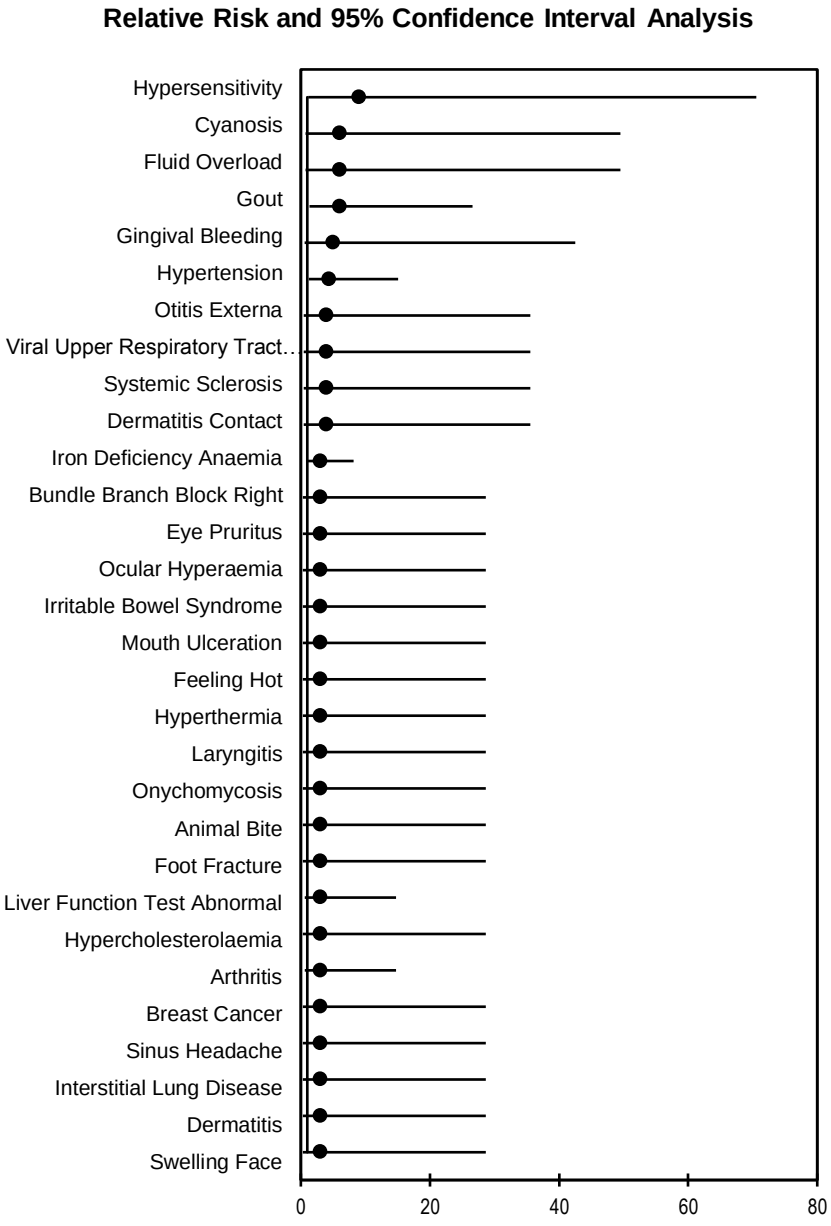
Body System or Organ Class	Dictionary-Derived Term	Placebo		Treatment		Total	
		N=577		N=575		N=1,152	
		Subject Count	%	Subject Count	%	Subject Count	%
Blood And Lymphatic System Disorders	Anaemia	3	0.5	5	0.9	8	0.7
Blood And Lymphatic System Disorders	Haemorrhagic Anaemia	0	0.0	1	0.2	1	0.1
Blood And Lymphatic System Disorders	Idiopathic Thrombocytopenic Purpura	0	0.0	1	0.2	1	0.1
Blood And Lymphatic System Disorders	Leukopenia	0	0.0	1	0.2	1	0.1
Blood And Lymphatic System Disorders	Neutropenia	1	0.2	0	0.0	1	0.1
Blood And Lymphatic System Disorders	Thrombocytopenia	0	0.0	1	0.2	1	0.1
Cardiac Disorders	Right Ventricular Failure	42	7.3	34	5.9	76	6.6
Cardiac Disorders	Atrial Fibrillation	4	0.7	7	1.2	11	1.0
Cardiac Disorders	Atrial Flutter	4	0.7	4	0.7	8	0.7
Cardiac Disorders	Acute Right Ventricular Failure	5	0.9	2	0.3	7	0.6
Cardiac Disorders	Cardiac Arrest	4	0.7	2	0.3	6	0.5
Cardiac Disorders	Supraventricular Tachycardia	4	0.7	1	0.2	5	0.4
Cardiac Disorders	Cardio-Respiratory Arrest	2	0.3	2	0.3	4	0.3
Cardiac Disorders	Cardiogenic Shock	2	0.3	2	0.3	4	0.3
Cardiac Disorders	Cardiopulmonary Failure	1	0.2	3	0.5	4	0.3

Analysis 5.1: Relative Risk

Placebo vs Treatment

Body System	Dictionary-Derived Term	Placebo Count	Placebo %	Treatment Count	Treatment %	Relative Risk	Lower 95% CI	Upper 95% CI
Immun	Hypersensitivity	9	1.6	1	0.2	9.0	(1.1,	70.6)
Card	Cyanosis	6	1.0	1	0.2	6.0	(0.7,	49.5)
Metab	Fluid Overload	6	1.0	1	0.2	6.0	(0.7,	49.5)
Metab	Gout	12	2.1	2	0.3	6.0	(1.3,	26.6)
Gastr	Gingival Bleeding	5	0.9	1	0.2	5.0	(0.6,	42.5)
Vasc	Hypertension	13	2.3	3	0.5	4.3	(1.2,	15.1)
Infec	Otitis Externa	4	0.7	1	0.2	4.0	(0.4,	35.6)
Infec	Viral Upper Respiratory Tract	4	0.7	1	0.2	4.0	(0.4,	35.6)
Musc	Systemic Sclerosis	4	0.7	1	0.2	4.0	(0.4,	35.6)
Skin	Dermatitis Contact	4	0.7	1	0.2	4.0	(0.4,	35.6)
Blood	Iron Deficiency Anaemia	15	2.6	5	0.9	3.0	(1.1,	8.2)
Card	Bundle Branch Block Right	3	0.5	1	0.2	3.0	(0.3,	28.7)
Eye	Eye Pruritus	3	0.5	1	0.2	3.0	(0.3,	28.7)
Eye	Ocular Hyperaemia	3	0.5	1	0.2	3.0	(0.3,	28.7)

Analysis 5.2: Relative Risk and 95% Interval Analysis

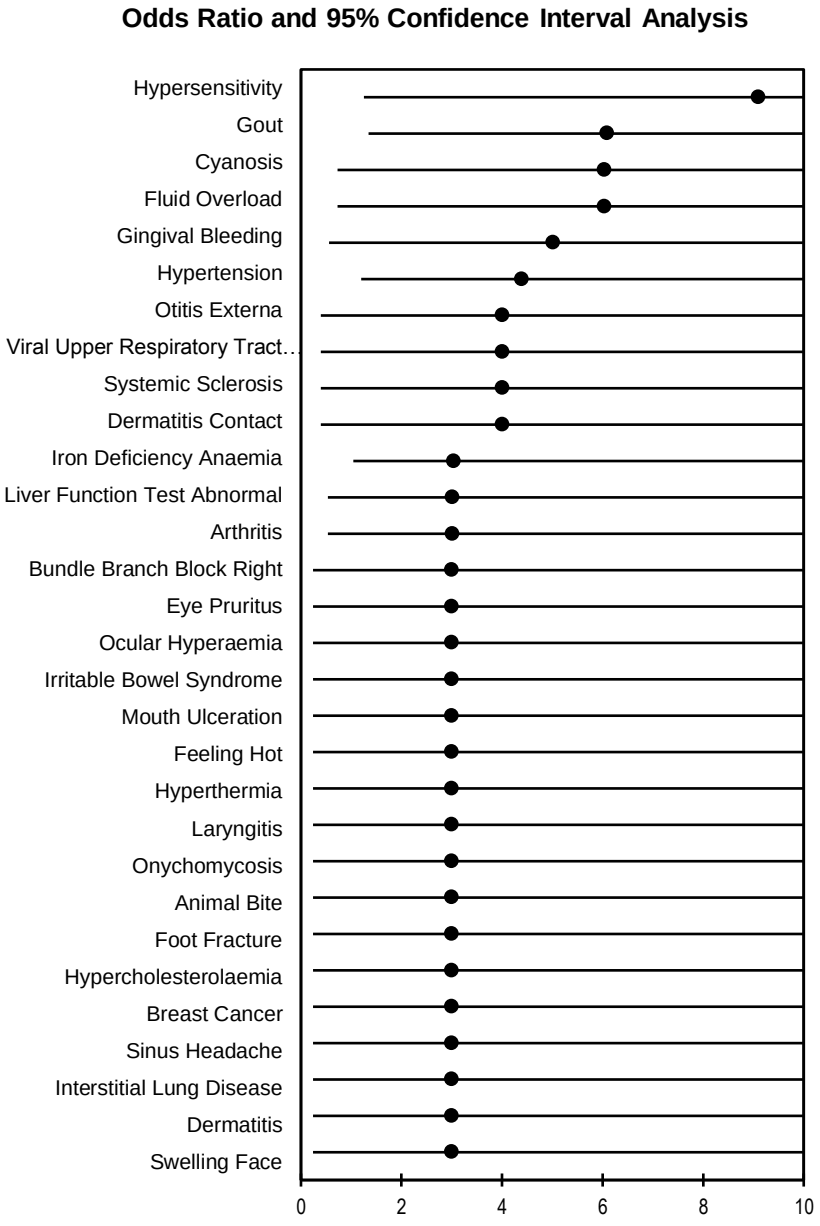


Analysis 6.1: Odds Ratio

Placebo vs Treatment

Body System	Dictionary-Derived Term	Placebo Count	Placebo %	Treatment Count	Treatment %	Odds Ratio	Lower 95% CI	Upper 95% CI
Immun	Hypersensitivity	9	1.6	1	0.2	9.1	(1.3,	399.3)
Metab	Gout	12	2.1	2	0.3	6.1	(1.3,	56.2)
Card	Cyanosis	6	1.0	1	0.2	6.0	(0.7,	277.9)
Metab	Fluid Overload	6	1.0	1	0.2	6.0	(0.7,	277.9)
Gastr	Gingival Bleeding	5	0.9	1	0.2	5.0	(0.6,	237.7)
Vasc	Hypertension	13	2.3	3	0.5	4.4	(1.2,	24.1)
Infec	Otitis Externa	4	0.7	1	0.2	4.0	(0.4,	197.7)
Infec	Viral Upper Respiratory Tract	4	0.7	1	0.2	4.0	(0.4,	197.7)
Musc	Systemic Sclerosis	4	0.7	1	0.2	4.0	(0.4,	197.7)
Skin	Dermatitis Contact	4	0.7	1	0.2	4.0	(0.4,	197.7)
Blood	Iron Deficiency Anaemia	15	2.6	5	0.9	3.0	(1.0,	10.8)
Inv	Liver Function Test Abnormal	6	1.0	2	0.3	3.0	(0.5,	30.6)
Musc	Arthritis	6	1.0	2	0.3	3.0	(0.5,	30.6)
Card	Bundle Branch Block Right	3	0.5	1	0.2	3.0	(0.2,	157.8)

Analysis 6.2: Odds Ratio and 95% Interval Analysis



8.2. AE Toxicity

Analysis 1: Toxicity Grade Summary

Toxicity Grade Summary

NDA/BLA: 12345
Study: 123
Analysis run date: 2015-01-16 2:06:12 PM

Where subject count is the number of subjects experiencing at least one adverse event at the stated toxicity grade using the maximum toxicity grade per subject

	Treatment N=254				Control N=239			
	All Grades		Grades 3/4/5		All Grades		Grades 3/4/5	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Total	251	98.8	172	67.7	233	97.5	144	60.3

NOTES:

1 This analysis uses the safety population and only counts adverse events that start between a subject's first exposure and 30 days after the subject's last exposure

Analysis 2: Preferred Term Analysis by Toxicity Grade (V1)

Preferred Term Analysis by Toxicity Grade

NDA/BLA: 12345
Study: 123
Analysis run date: 2015-01-16 2:06:12 PM

Where subject count is the number of subjects experiencing at least one adverse event at the stated toxicity grade using the maximum toxicity grade per subject, organ class, and term

Body System or Organ Class	Dictionary-Derived Term	Treatment N=254				Control N=239			
		All Grades		Grades 3/4/5		All Grades		Grades 3/4/5	
		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Blood And Lymphatic System Disorders	Anaemia	27	10.6	4	1.6	17	7.1	4	1.7
Blood And Lymphatic System Disorders	Eosinophilia	1	0.4	0	0.0	1	0.4	0	0.0
Blood And Lymphatic System Disorders	Iron Deficiency Anaemia	1	0.4	0	0.0	0	0.0	0	0.0
Blood And Lymphatic System Disorders	Leukocytosis	1	0.4	0	0.0	0	0.0	0	0.0
Blood And Lymphatic System Disorders	Leukopenia	1	0.4	0	0.0	2	0.8	0	0.0
Blood And Lymphatic System Disorders	Lymphadenopathy	1	0.4	0	0.0	2	0.8	0	0.0
Blood And Lymphatic System Disorders	Lymphoid Tissue Hyperplasia	0	0.0	0	0.0	1	0.4	0	0.0
Blood And Lymphatic System Disorders	Lymphopenia	5	2.0	0	0.0	4	1.7	2	0.8
Blood And Lymphatic System Disorders	Microcytic Anaemia	0	0.0	0	0.0	1	0.4	0	0.0
Blood And Lymphatic System Disorders	Neutropenia	1	0.4	0	0.0	4	1.7	3	1.3
Blood And Lymphatic System Disorders	Normochromic Normocytic Anaemia	2	0.8	0	0.0	1	0.4	0	0.0
Blood And Lymphatic System Disorders	Thrombocytopenia	9	3.5	1	0.4	3	1.3	0	0.0
Cardiac Disorders	Acute Coronary Syndrome	1	0.4	1	0.4	0	0.0	0	0.0
Cardiac Disorders	Angina Pectoris	3	1.2	0	0.0	0	0.0	0	0.0

Analysis 3: Preferred Term Analysis by Toxicity Grade (V2)

Preferred Term Analysis by Toxicity Grade

NDA/BLA: 12345
Study: 123
Analysis run date: 2015-01-16 2:06:12 PM

Where subject count is the number of subjects experiencing at least one adverse event at the stated toxicity grade using the maximum toxicity grade per subject, organ class, and term

Adverse Event	Treatment N=254				Control N=239			
	All Grades		Grades 3/4/5		All Grades		Grades 3/4/5	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Blood And Lymphatic System Disorders								
Anaemia	27	10.6	4	1.6	17	7.1	4	1.7
Eosinophilia	1	0.4	0	0.0	1	0.4	0	0.0
Iron Deficiency Anaemia	1	0.4	0	0.0	0	0.0	0	0.0
Leukocytosis	1	0.4	0	0.0	0	0.0	0	0.0
Leukopenia	1	0.4	0	0.0	2	0.8	0	0.0
Lymphadenopathy	1	0.4	0	0.0	2	0.8	0	0.0
Lymphoid Tissue Hyperplasia	0	0.0	0	0.0	1	0.4	0	0.0
Lymphopenia	5	2.0	0	0.0	4	1.7	2	0.8
Microcytic Anaemia	0	0.0	0	0.0	1	0.4	0	0.0
Neutropenia	1	0.4	0	0.0	4	1.7	3	1.3
Normochromic Normocytic Anaemia	2	0.8	0	0.0	1	0.4	0	0.0
Thrombocytopenia	9	3.5	1	0.4	3	1.3	0	0.0

8.3. AE MedDRA Analysis Panel

Analysis 1: Two-Term MedDRA Analysis (V1)

Adverse Events Two-Term MedDRA Analysis
by System Organ Class and Preferred Term

NDA/BLA: 12345
Study: 123
Analysis run date: 2015-01-16 2:06:12 PM

Where subject count is the number of subjects experiencing at least one adverse event at the stated toxicity grade using the maximum toxicity grade per subject, system organ class, and preferred term

System Organ Class	Preferred Term	Treatment N=254				Control N=239				Risk Difference		
		All Grades				All Grades					Confidence Interval	
		Subject Count	%	% Lower CL	% Upper CL	Subject Count	%	% Lower CL	% Upper CL	Risk Difference	Lower CL	Upper CL
Blood and lymphatic system disorders	Anaemia	27	10.6	(7.12, 15.09)		17	7.1	(4.20, 11.14)		3.5	(-1.48, 8.52)	
Blood and lymphatic system disorders	Eosinophilia	1	0.4	(0.01, 2.17)		1	0.4	(0.01, 2.31)		0.0	(-1.15, 1.10)	
Blood and lymphatic system disorders	Iron deficiency anaemia	1	0.4	(0.01, 2.17)		0	0.0	(0.00, 1.53)		0.4	(-0.38, 1.16)	
Blood and lymphatic system disorders	Leukocytosis	1	0.4	(0.01, 2.17)		0	0.0	(0.00, 1.53)		0.4	(-0.38, 1.16)	
Blood and lymphatic system disorders	Leukopenia	1	0.4	(0.01, 2.17)		2	0.8	(0.10, 2.99)		-0.4	(-1.83, 0.94)	
Blood and lymphatic system disorders	Lymphadenopathy	1	0.4	(0.01, 2.17)		2	0.8	(0.10, 2.99)		-0.4	(-1.83, 0.94)	
Blood and lymphatic system disorders	Lymphoid tissue hyperplasia	0	0.0	(0.00, 1.44)		1	0.4	(0.01, 2.31)		-0.4	(-1.24, 0.40)	
Blood and lymphatic system disorders	Lymphopenia	5	2.0	(0.64, 4.53)		4	1.7	(0.46, 4.23)		0.3	(-2.06, 2.65)	
Blood and lymphatic system disorders	Microcytic anaemia	0	0.0	(0.00, 1.44)		1	0.4	(0.01, 2.31)		-0.4	(-1.24, 0.40)	
Blood and lymphatic system disorders	Neutropenia	1	0.4	(0.01, 2.17)		4	1.7	(0.46, 4.23)		-1.3	(-3.08, 0.52)	
Blood and lymphatic system disorders	Normochromic normocytic anaemia	2	0.8	(0.10, 2.82)		1	0.4	(0.01, 2.31)		0.4	(-0.99, 1.73)	
Blood and lymphatic system disorders	Thrombocytopenia	9	3.5	(1.63, 6.62)		3	1.3	(0.26, 3.62)		2.3	(-0.39, 4.96)	

Analysis 2: Two-Term MedDRA Analysis

Adverse Events Two-Term MedDRA Analysis
by System Organ Class and Preferred Term; Sorted by Relative Risk

NDA/BLA: 12345
Study: 123
Analysis run date: 2015-01-16 2:06:12 PM

Where subject count is the number of subjects experiencing at least one adverse event at the stated toxicity grade using the maximum toxicity grade per subject, system organ class, and preferred term

Adverse Event	Treatment N=254				Control N=239				Risk Difference			Relative Risk			Odds Ratio			P-value
	All Grades				All Grades					Confidence Interval			Confidence Interval			Confidence Interval		
	Subject Count	%	% Lower CL	% Upper CL	Subject Count	%	% Lower CL	% Upper CL	Risk Difference	Lower CL	Upper CL	*Relative Risk*	Lower CL	Upper CL	Odds Ratio	Lower CL	Upper CL	
Eye disorders																		
Retinal detachment	21	8.3	(5.19, 12.36)		0	0.0	(0.00, 1.53)		8.3	(4.88, 11.65)		40.5*	(2.47, 664.40)		44.1*	(2.66, 732.32)		0.00
Chorioretinopathy	30	11.8	(8.11, 16.43)		1	0.4	(0.01, 2.31)		11.4	(7.34, 15.45)		28.2	(3.88, 205.38)		31.9	(5.19, 1305.76)		0.00
Visual impairment	7	2.8	(1.12, 5.60)		0	0.0	(0.00, 1.53)		2.8	(0.74, 4.77)		14.1*	(0.81, 245.85)		14.5*	(0.82, 255.55)		0.02
Macular oedema	4	1.6	(0.43, 3.98)		0	0.0	(0.00, 1.53)		1.6	(0.04, 3.11)		8.5*	(0.46, 156.49)		8.6*	(0.46, 160.68)		0.12
Detachment of retinal pigment epithelium	8	3.1	(1.37, 6.11)		1	0.4	(0.01, 2.31)		2.7	(0.43, 5.03)		7.5	(0.95, 59.73)		7.7	(1.02, 344.85)		0.04
Vitreous floaters	6	2.4	(0.87, 5.07)		1	0.4	(0.01, 2.31)		1.9	(-0.10, 3.98)		5.6	(0.68, 46.55)		5.8	(0.69, 265.95)		0.12
Age-related macular degeneration	2	0.8	(0.10, 2.82)		0	0.0	(0.00, 1.53)		0.8	(-0.30, 1.87)		4.7*	(0.23, 97.52)		4.7*	(0.23, 99.29)		0.50
Diplopia	2	0.8	(0.10, 2.82)		0	0.0	(0.00, 1.53)		0.8	(-0.30, 1.87)		4.7*	(0.23, 97.52)		4.7*	(0.23, 99.29)		0.50
Orbital oedema	2	0.8	(0.10, 2.82)		0	0.0	(0.00, 1.53)		0.8	(-0.30, 1.87)		4.7*	(0.23, 97.52)		4.7*	(0.23, 99.29)		0.50
Retinopathy	2	0.8	(0.10, 2.82)		0	0.0	(0.00, 1.53)		0.8	(-0.30, 1.87)		4.7*	(0.23, 97.52)		4.7*	(0.23, 99.29)		0.50

8.4. Demographics

Analysis 1: Overview

Demographic Baseline Characteristics: Overview

NDA12345
Study: 123
Analysis run date: 2015-03-03 8:21:03 AM

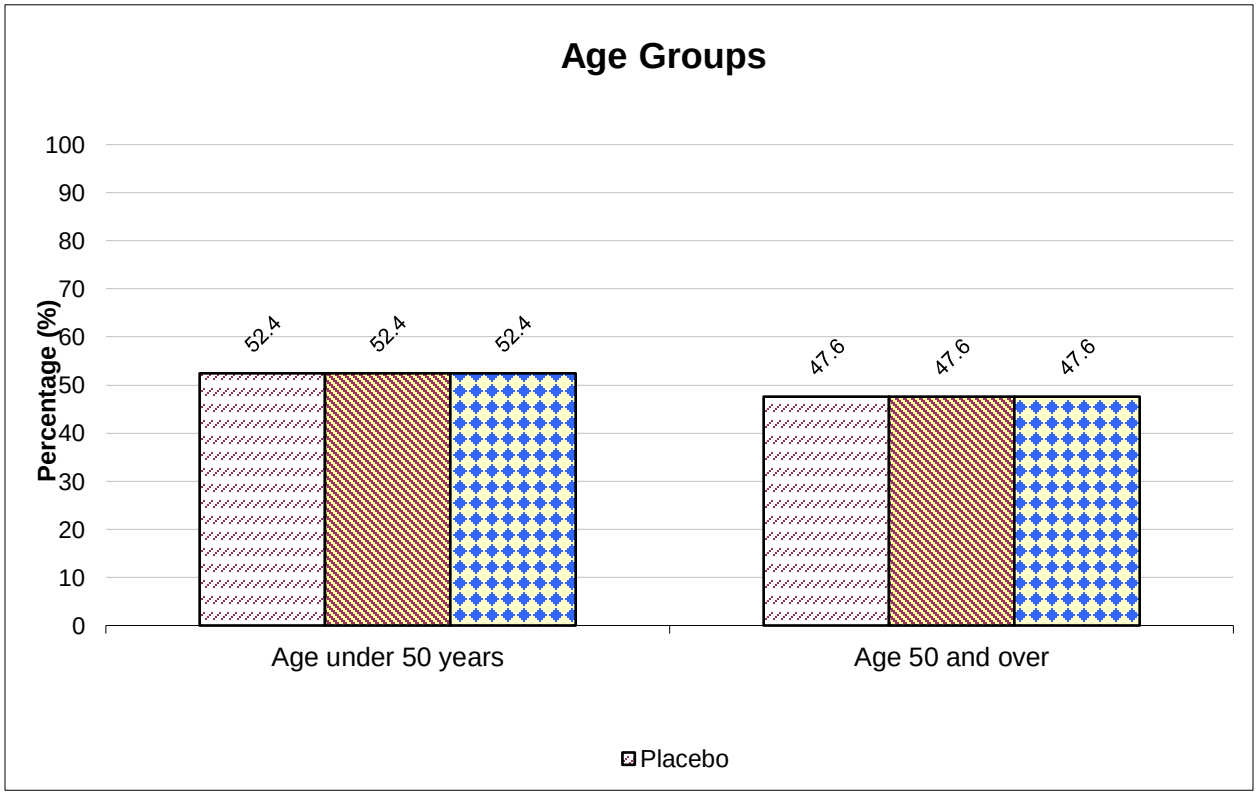
Demographic Baseline Characteristics		Placebo N=582		Treatment N=574		Overall N=1156	
Age	Mean (SE)	47.9 (15.6)		48.2 (15.2)		48.1 (15.4)	
	Min	18		18		18	
	Q1	35		37		36	
	Median	49		49		49	
	Q3	60		61		61	
	Max	80		78		80	
		Count	%	Count	%	Count	%
Age Group	Age under 50 years	305	52.4	301	52.4	606	52.4
	Age 50 and over	277	47.6	273	47.6	550	47.6
Sex	F	466	80.1	457	79.6	923	79.8
	M	116	19.9	117	20.4	233	20.2
Race	Asian	120	20.6	125	21.8	245	21.2
	Black Or African American	14	2.4	13	2.3	27	2.3
	Hispanic	63	10.8	51	8.9	114	9.9
	White	375	64.4	376	65.5	751	65.0
	Other	10	1.7	9	1.6	19	1.6
Ethnicity	Missing	582	100.0	574	100.0	1156	100.0

Analysis 2: Age Groups

Demographic Baseline Characteristics: Age Groups

NDA12345
Study: 123
Analysis run date: 2015-03-03 8:21:03 AM

Age Group	Placebo N=582		Treatment N=574		Overall N=1156	
	Count	%	Count	%	Count	%
Age under 50 years	305	52.4	301	52.4	606	52.4
Age 50 and over	277	47.6	273	47.6	550	47.6



Analysis 3: Age Groups by Disposition

Demographic Baseline Characteristics by Disposition Term: Age Groups

NDA12345
Study: 123
Analysis run date: 2015-03-03 8:21:03 AM

The Count column shows the count of subjects in each demographic group per arm whose last disposition event is the disposition term shown.
See the front page for further information. The % column shows the proportion of the demographic group in each arm that the count represents.

Standard Disposition Term	Age Group	Placebo N=582		Treatment N=574		Overall N=1156	
		Count	%	Count	%	Count	%
Completed	Age under 50 years	241	79.0	249	82.7	490	80.9
	Age 50 and over	208	75.1	201	73.6	409	74.4
Death	Age under 50 years	49	16.1	43	14.3	92	15.2
	Age 50 and over	56	20.2	57	20.9	113	20.5
Unknown	Age under 50 years	14	4.6	9	3.0	23	3.8
	Age 50 and over	13	4.7	15	5.5	28	5.1

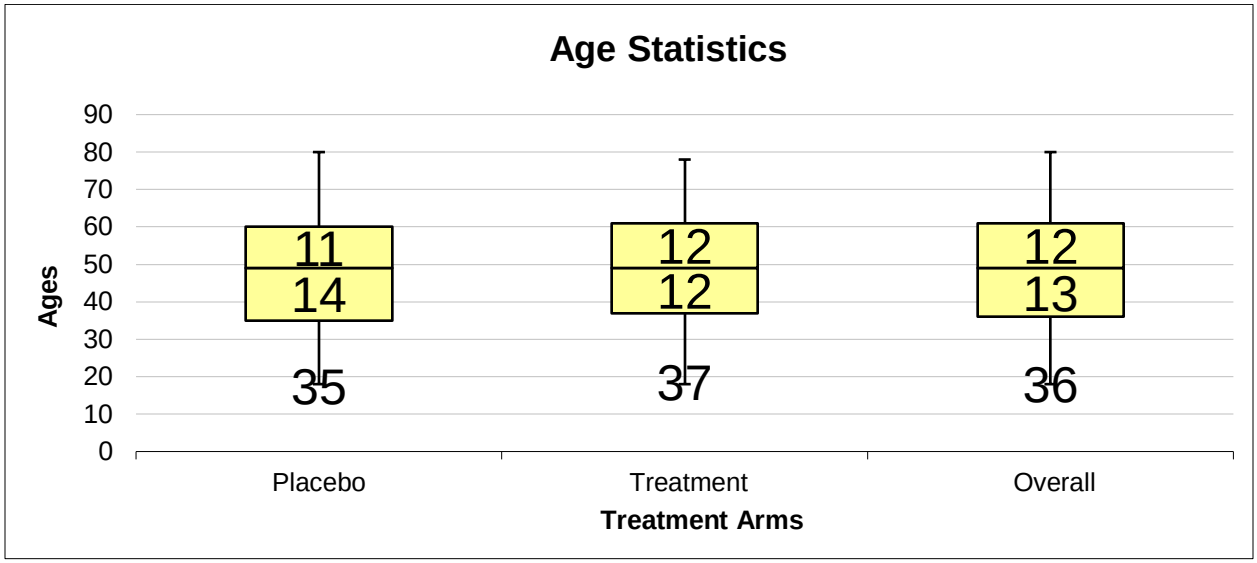
Analysis 4.1: Age Statistics - Table

Demographic Baseline Characteristics: Age Statistics

NDA12345
Study: 123
Analysis run date: 2015-03-03 8:21:03 AM

Age Statistic	Placebo N=582	Treatment N=574	Overall N=1156
Mean (SE)	47.9 (15.6)	48.2 (15.2)	48.1 (15.4)
Mode	36	40	54
Min	18	18	18
Q1	35	37	36
Median	49	49	49
Q3	60	61	61
Max	80	78	80

Analysis 4.2: Age Statistics - Figure



Analysis 5: Country and Site ID

Demographic Baseline Characteristics: Country and Site ID

NDA12345
Study: 123
Analysis run date: 2015-03-03 8:21:03 AM

Country	Site ID	Placebo N=582		Treatment N=574		Overall N=1156	
		Count	%	Count	%	Count	%
ARG	6004	3	0.5	3	0.5	6	0.5
	6005	3	0.5	3	0.5	6	0.5
	6001	4	0.7	2	0.3	6	0.5
	6006	2	0.3	1	0.2	3	0.3
	6008	1	0.2	1	0.2	2	0.2
	6007	1	0.2	0	0.0	1	0.1
AUS	1002	8	1.4	8	1.4	16	1.4
	1004	6	1.0	6	1.0	12	1.0
	1005	5	0.9	4	0.7	9	0.8
	1008	4	0.7	3	0.5	7	0.6
	1001	3	0.5	4	0.7	7	0.6
	1007	2	0.3	2	0.3	4	0.3
	1003	1	0.2	2	0.3	3	0.3
	1006	2	0.3	1	0.2	3	0.3
	1009	1	0.2	0	0.0	1	0.1

8.5. Disposition

Analysis 1: Disposition Events by Arm for All Subjects

Disposition Events by Arm for All Subjects

NDA12345
Study: 123
Analysis run date: 2015-01-05 11:59:07 AM

Category of Disposition Event	Subcategory of Disposition Event	Disposition Event	Treatment		Control	
			Subject Count	%	Subject Count	%
Protocol Milestone		Randomization	254	100.0	239	100.0
	Protocol	Informed Consent Obtained	254	100.0	239	100.0
		All Eligibility Criteria Met	241	94.9	226	94.6
		Not All Eligibility Criteria Met	13	5.1	13	5.4
Sample Collection Milestone	Rcr	Informed Consent Obtained	199	78.3	187	78.2
		Informed Consent Not Obtained	54	21.3	52	21.8
Disposition Event	Placebo Discontinuation	Progression Of Disease	75	29.5	129	54.0
	Protocol	Adverse Event	38	15.0	20	8.4
		Withdrawal By Subject	2	0.8	2	0.8
		Physician Decision	3	1.2	1	0.4
		Death	2	0.8	1	0.4
		Other	0	0.0	2	0.8
		Non-Compliance With Study Drug	1	0.4	1	0.4
		Non-Compliance	2	0.8	0	0.0
		Lost To Follow-Up	0	0.0	1	0.4

Analysis 2: Disposition Events by Arm for Exposed Subjects

Disposition Events by Arm for Exposed Subjects

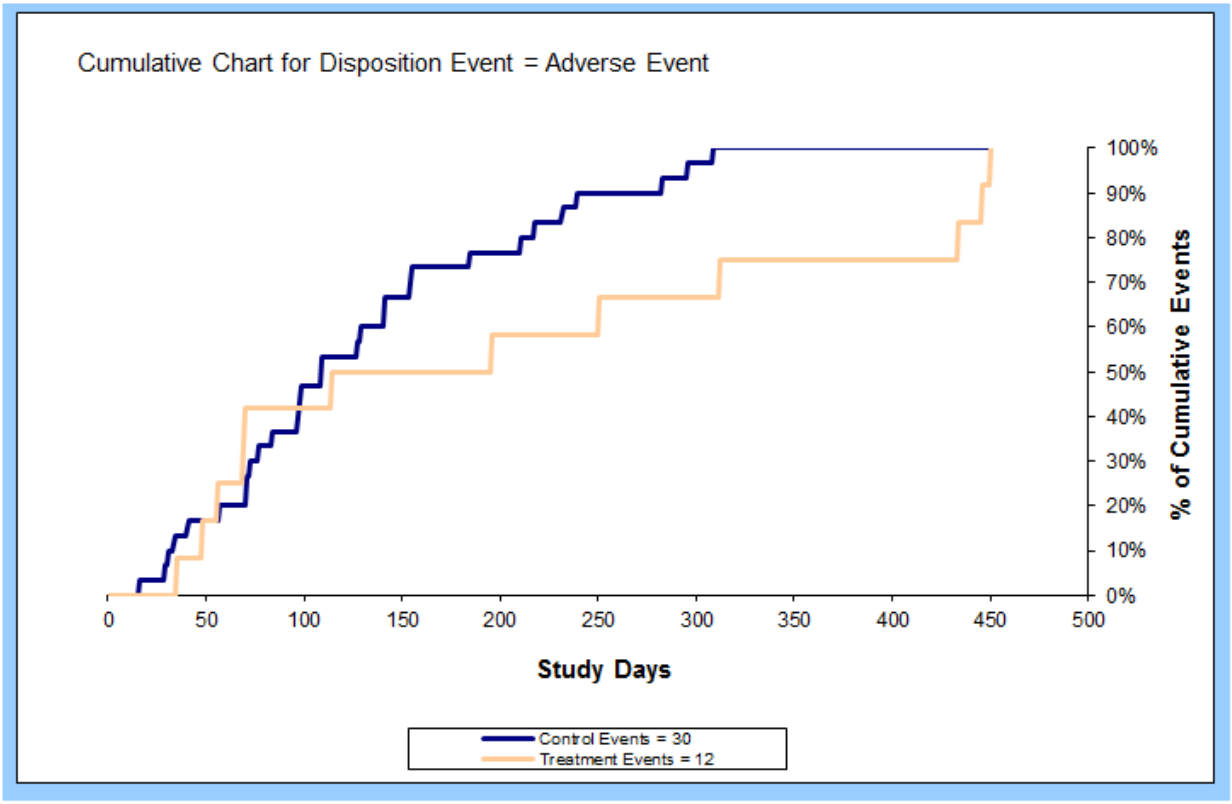
NDA12345
Study: 123
Analysis run date: 2015-01-05 11:59:07 AM

Category of Disposition Event	Subcategory of Disposition Event	Disposition Event	Treatment		Control	
			Subject Count	%	Subject Count	%
Protocol Milestone	Missing	Randomization	254	100.0	239	100.0
	Protocol	Informed Consent Obtained	254	100.0	239	100.0
		All Eligibility Criteria Met	241	94.9	226	94.6
		Not All Eligibility Criteria Met	13	5.1	13	5.4
Sample Collection Milestone	Rcr	Informed Consent Obtained	199	78.3	187	78.2
		Informed Consent Not Obtained	54	21.3	52	21.8
Disposition Event	Placebo Discontinuation	Progression Of Disease	75	29.5	129	54.0
		Adverse Event	38	15.0	20	8.4
		Withdrawal By Subject	2	0.8	2	0.8
		Physician Decision	3	1.2	1	0.4
		Death	2	0.8	1	0.4
		Other	0	0.0	2	0.8
		Non-Compliance With Study Drug	1	0.4	1	0.4
		Non-Compliance	2	0.8	0	0.0

Analysis 3: Time to Disposition Event by Arm for All Subjects

Time to Disposition Event by Arm for All Subjects

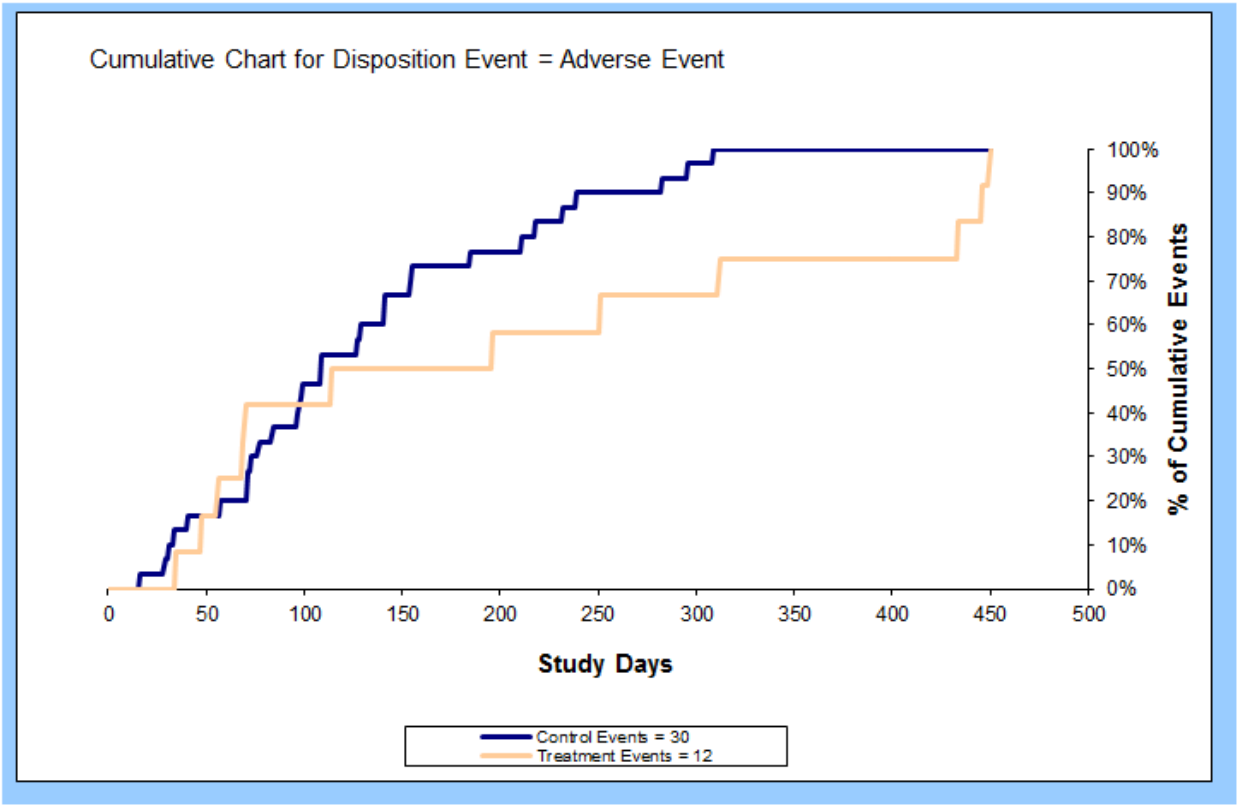
NDA/BLA: 123456
Study: ABC123
Analysis run date: 2015-12-02 8:52:04 AM
Subset where DSCAT = 'DISPOSITION EVENT' and DSSCAT = 'STUDY DRUG DISCONTINUATION'



Analysis 4: Time to Disposition Event by Arm for Exposed Subjects

Time to Disposition Event by Arm for Exposed Subjects

NDA/BLA: 123456
Study: ABC123
Analysis run date: 2015-12-02 8:52:04 AM
Subset where DSCAT = 'DISPOSITION EVENT' and DSSCAT = 'STUDY DRUG DISCONTINUATION'



8.6. Liver

Analysis 1: Liver Lab Tests Greater Than Upper Limit of Normal

Liver Lab Tests Greater Than Upper Limit of Normal

NDA/BLA: 12345
Study: 123
Analysis run date: 2011-04-07 1:13:08 PM

Liver Lab Test	Treatment N = 509			Control N = 253		
ALT ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	635	151	29.67	149	49	19.37
3x ULN	220	83	16.31	51	22	8.70
5x ULN	31	17	3.34	8	5	1.98
10x ULN	3	3	0.59	0	0	0.00
20x ULN	0	0	0.00	0	0	0.00
AST ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	819	181	35.56	178	65	25.69
3x ULN	270	88	17.29	74	30	11.86
5x ULN	47	28	5.50	16	12	4.74
10x ULN	5	5	0.98	1	1	0.40
20x ULN	1	1	0.20	0	0	0.00
ALP ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
2x ULN	673	107	21.02	170	51	20.16
3x ULN	340	64	12.57	59	25	9.88
5x ULN	98	29	5.70	10	7	2.77
10x ULN	17	8	1.57	2	1	0.40
20x ULN	0	0	0.00	0	0	0.00
TB ≥ ULN	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
1.5x ULN	47	26	5.11	28	20	7.91
2x ULN	20	15	2.95	16	11	4.35
3x ULN	8	7	1.38	6	5	1.98

Analysis 2.1: Combinations for Possible Hy's Law Cases at the Same Visit

Combinations for Possible Hy's Law Cases: At the Same Visit

Liver Lab Test At Same Visit	Treatment N = 509		
	Event Count	Subject Count	% of Subjects
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP normal	1	1	0.20
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP normal	0	0	0.00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP normal	0	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP > normal	22	11	2.16
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP > normal	10	6	1.18
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP > normal	3	2	0.39
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP missing	0	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP missing	0	0	0.00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP missing	0	0	0.00

Notes: All scores are post-baseline. Cases that have the lab combinations occurring at the same visit.

Analysis 2.2: Combinations for Possible Hy's Law Cases at Any Time during the Study

Combinations for Possible Hy's Law Cases: At Any Time During the Study

Liver Lab Test Any Time During Study	Treatment N = 509		Control N = 253	
	Subject Count	% of Subjects	Subject Count	% of Subjects
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP normal	6	1.18	2	0.79
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP normal	5	0.98	2	0.79
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP normal	2	0.39	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP > normal	15	2.95	10	3.95
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP > normal	9	1.77	6	2.37
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP > normal	3	0.59	2	0.79
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP missing	0	0.00	0	0.00
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP missing	0	0.00	0	0.00
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP missing	0	0.00	0	0.00

Notes: All scores are post-baseline. Subjects that have the lab combinations occurring at any point during the study.

Analysis 2.3: Combinations for Possible Hy's Law Cases Patients at Any Time during the Study

Combinations for Possible Hy's Law Cases Patients: At Any Time During the Study

Unique Subject ID	Treatment Arm
ABC-001	Treatment 1
ABC-002	Treatment 2
ABC-003	Treatment 1
ABC-004	Treatment 2

Analysis 3: Baseline Lab Tests – Maximum vs Baseline

Maximum Post-Baseline Lab Tests vs Baseline Lab Tests

NDA/BLA: 12345
Study: 123
Analysis run date: 2011-04-07 1:13:05 PM

ALT Baseline / ALT Maximum	Treatment N = 609									
	ALT < 2x ULN		2x ≤ ALT < 5x ULN		5x ≤ ALT < 10x ULN		10x ≤ ALT < 20x ULN		ALT ≥ 20x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
ALT < 2x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2x ≤ ALT < 5x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5x ≤ ALT < 10x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ ALT < 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
ALT ≥ 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

AST Baseline / AST Maximum	Treatment N = 609									
	AST < 2x ULN		2x ≤ AST < 5x ULN		5x ≤ AST < 10x ULN		10x ≤ AST < 20x ULN		AST ≥ 20x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
AST < 2x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2x ≤ AST < 5x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5x ≤ AST < 10x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ AST < 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
AST ≥ 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

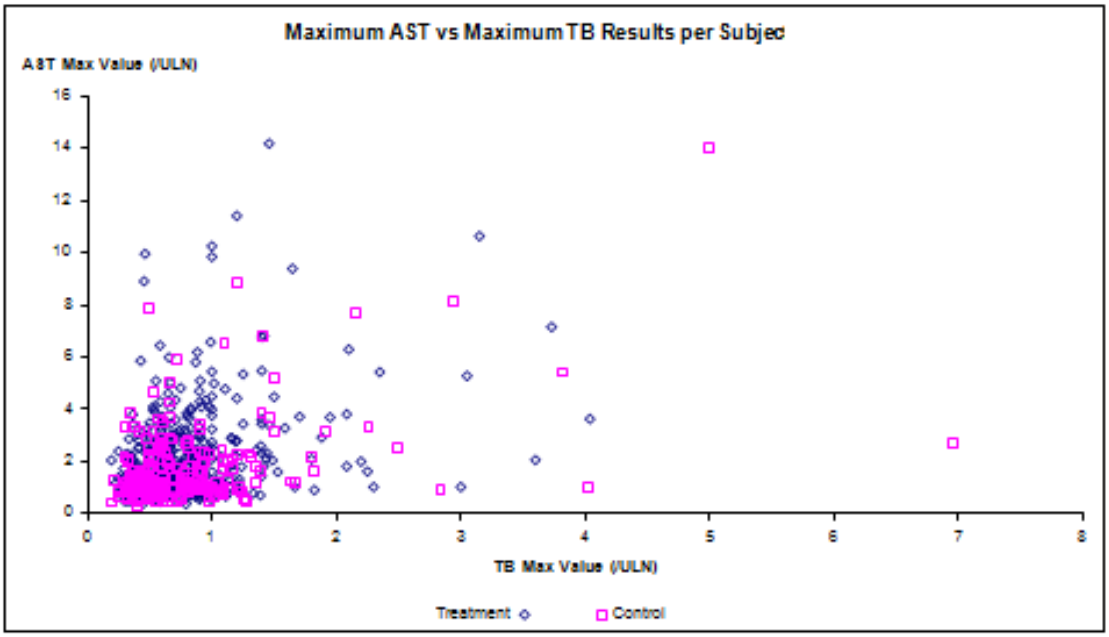
ALP Baseline / ALP Maximum	Treatment N = 609									
	ALP < 2x ULN		2x ≤ ALP < 5x ULN		5x ≤ ALP < 10x ULN		10x ≤ ALP < 20x ULN		ALP ≥ 20x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
ALP < 2x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2x ≤ ALP < 5x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5x ≤ ALP < 10x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ ALP < 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
ALP ≥ 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

TB Baseline / TB Maximum	Treatment N = 609									
	TB < 2x ULN		2x ≤ TB < 5x ULN		5x ≤ TB < 10x ULN		10x ≤ TB < 20x ULN		TB ≥ 20x ULN	
	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
TB < 2x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2x ≤ TB < 5x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5x ≤ TB < 10x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
10x ≤ TB < 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
TB ≥ 20x ULN	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Analysis 4: Maximum AST/ALT vs Maximum TB Lab Test Results per Subject Charts

Maximum AST and ALT vs Maximum TB Lab Test Results per Subject Charts

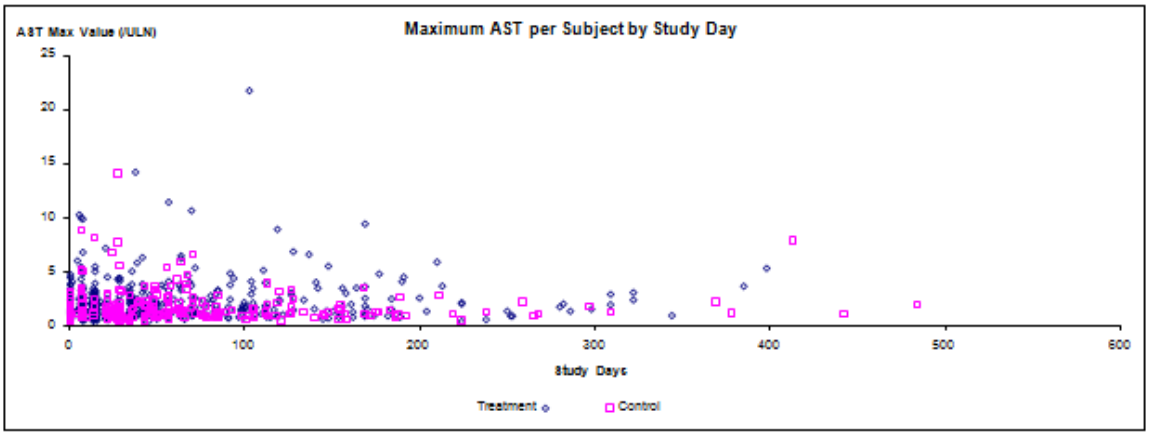
NDA/BLA: 12345
Study: 123
Analysis run date: 2011-04-27 11:29:20 PM



Analysis 5: Maximum Lab Test Results per Subject by Study Day

Maximum Lab Test Results per Subject by Study Day

NDA/BLA: 12345
Study: 123
Analysis run date: 2011-04-27 11:29:30 PM



Notes: All scores are post-baseline. The first occurrence of the maximum value is used.