

Innovation and Regulatory Review

What is JumpStart?

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Disclosure

- No financial or commercial conflict of interest
- The opinions and information in this presentation are those of the presenter and do not represent the views and/or policies of the U.S. Food and Drug Administration

Outline

- Objectives
- Overview of JumpStart
- How JumpStart began
- Key benefits for reviewers
- Explanation of the JumpStart Service
 - Data Fitness Session
 - Exploratory Safety Session
- Questions

Objectives


- Explain how JumpStart facilitates the review process
- Describe how JumpStart fits into the review cycle
- Provide an overview of Data Fitness
- Provide an overview of Safety Findings

JumpStart Overview


- JumpStart is a **service** (not a tool) that supports NDA/BLA Review Teams' safety review early in the review process by providing:
 - An assessment of data quality and composition with interpretation to identify issues that may complicate safety review process
 - A large number of exploratory safety analyses to provide a basis for more thorough review
 - Reviewers with instruction for using a variety of analytical tools

JumpStart Service

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- [The Need for JumpStart](#)
- [How JumpStart Works](#)
- [JumpStart Testimonials](#)
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The JumpStart service is modernizing the drug review process—medical reviewers are using this service to quickly and thoroughly assess data from drug clinical trials, ensuring safe and effective products are approved for public use.

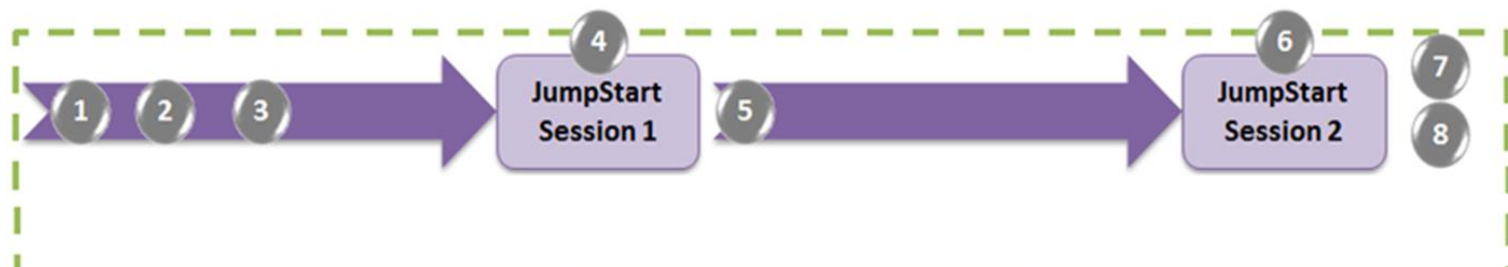
The Need for JumpStart

- Initiated in 2013 as “Modern Review Pilot”
 - Intended to “jumpstart” the review process
 - Involves running a series of study data analyses early in the review process
 - Pilot completed in 2013; since then nearly 100 sessions have been delivered to 17 review divisions

Key Benefits for Reviewers

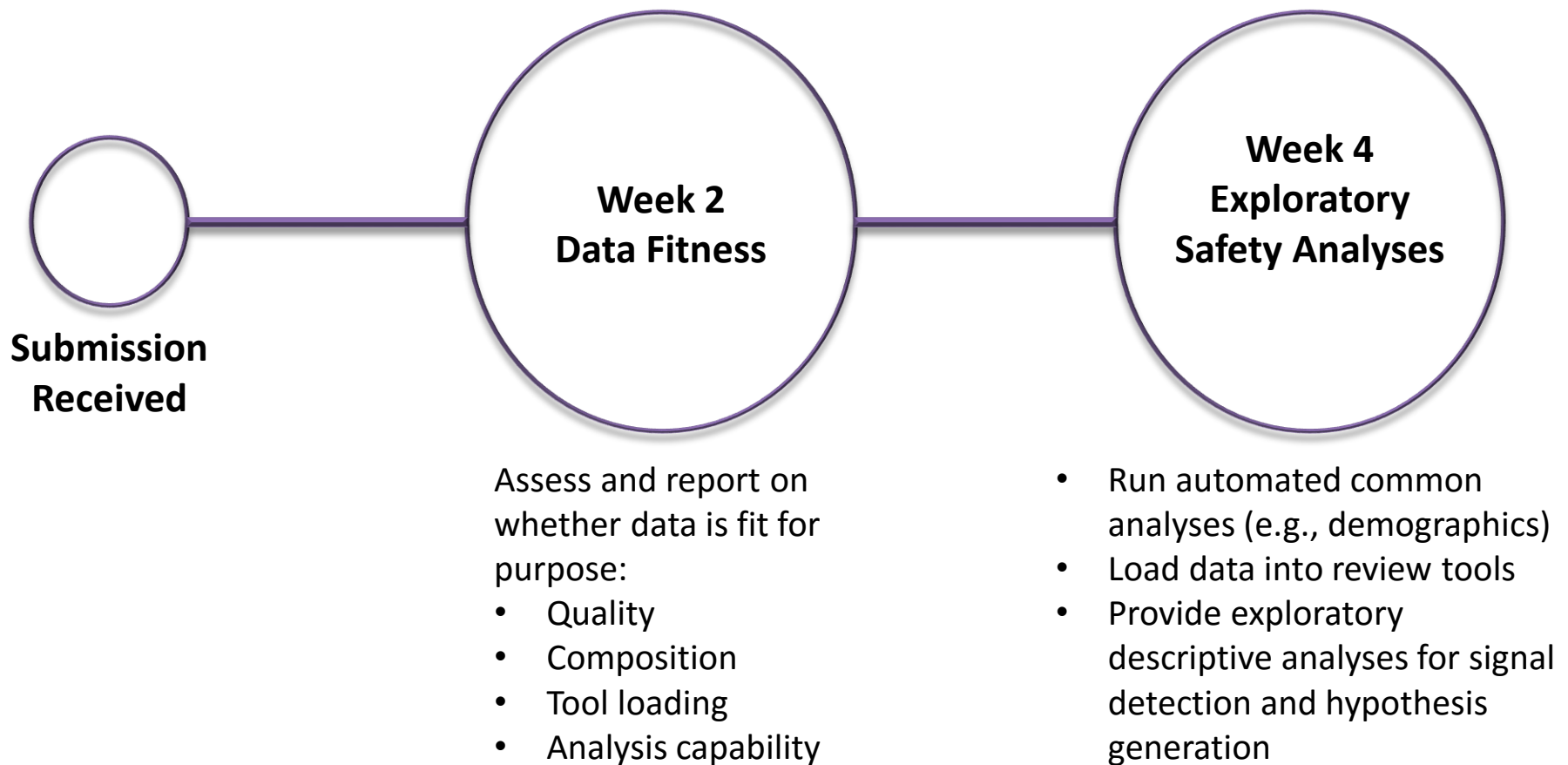
- Improves the review process
- Data fitness assessment addresses potential issues early in the review cycle
- Targeted exploratory safety analyses
- JumpStart work sessions encourage collaboration & communication
- Provides an opportunity for reviewers to take advantage of modern review tools & technologies

The JumpStart activities occur parallel to the 21st Century Review process



1 – Request Service	4 – Data Fitness Session	6 – Safety Analysis Session
2 – Receive Approval	5 – Output Table Delivery	7 – Updated Output Table
3 – Complete Parameter Form		8 – Complete Survey

JumpStart Sessions

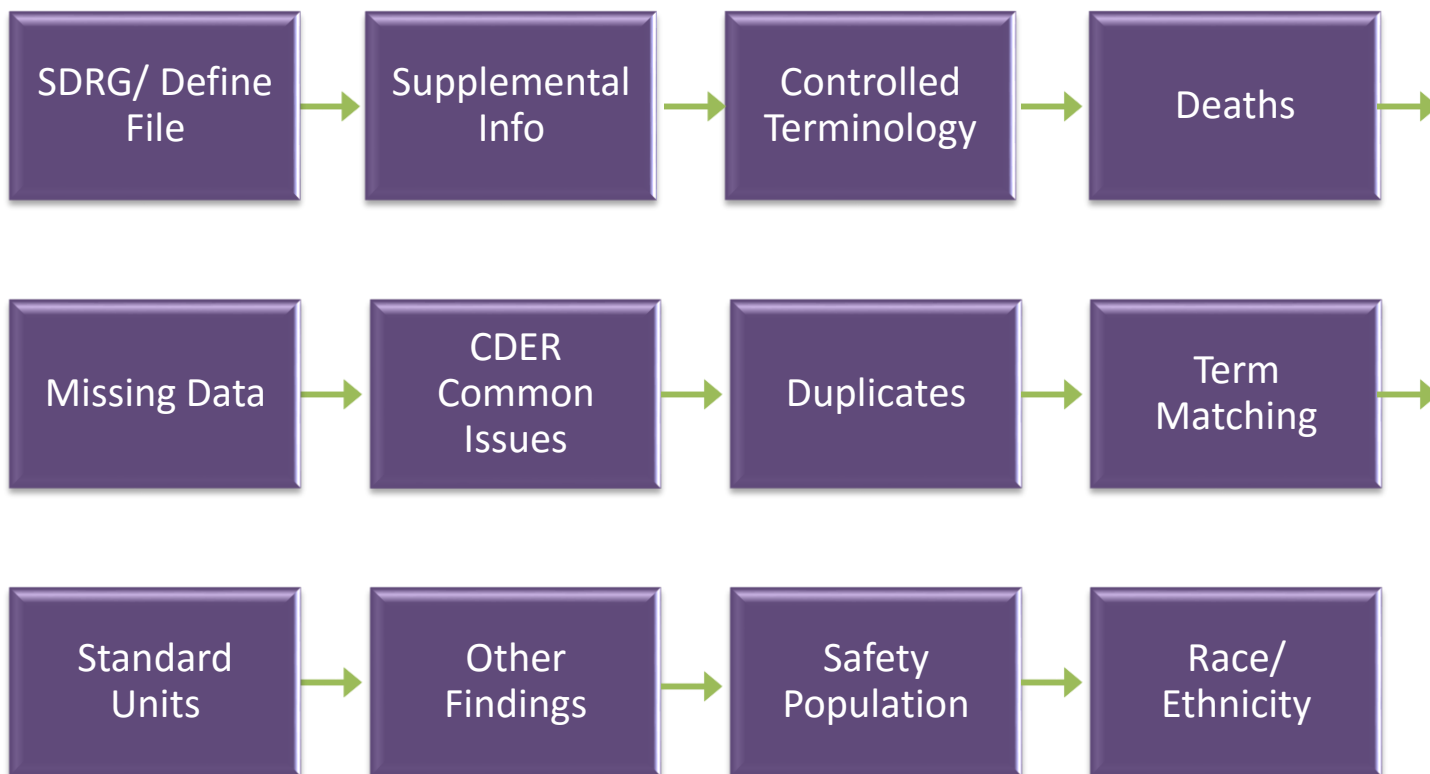


JumpStart utilizes a suite of tools to perform analyses relevant to the clinical review

Tool	Uses
DataFit	► Evaluates data fitness which focuses primarily on SDTM data
SAS Panels (e.g., MedDRA at a Glance)	► Provides standard analyses (e.g., Demographics, Disposition, Adverse Events, and Liver Labs)
MAED	► Runs Adverse Event analyses defined by analysis parameters/filters
Other tools that include patient profiles and analyses	► Provides an integrated safety analyses of safety data with pre-defined analyses

Tool	Uses
MedDRA Web-based Browser https://tools.meddra.org/wbb/	► Allows the user to view both the MedDRA hierarchy and the structure of Standardized MedDRA Queries (SMQs) for all versions of MedDRA.

Data Fitness Findings Discussion Flow



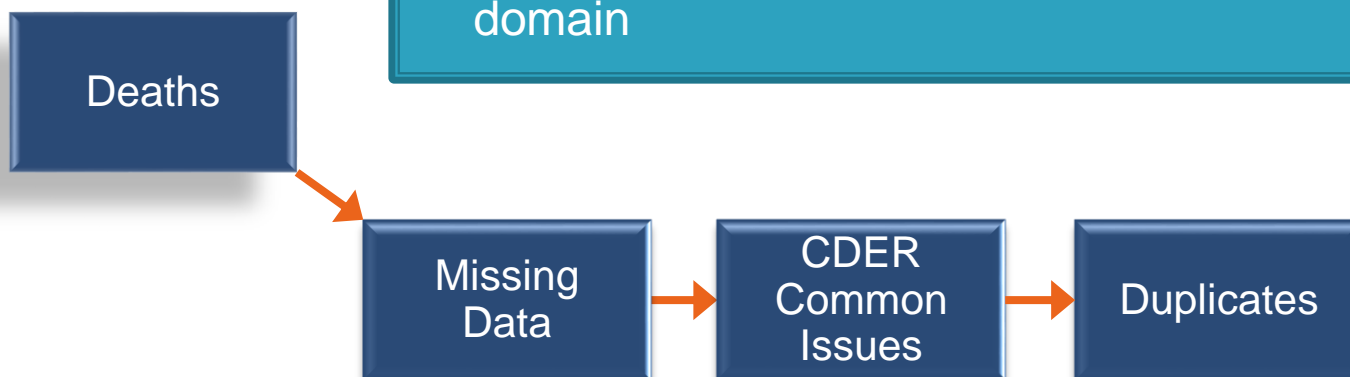
Deaths

Review Questions:

- ▶ How many deaths occurred during the study?
- ▶ Where is information about deaths located?
- ▶ Was the death information represented consistently across domains?

We provide a death summary for all studies that go through JumpStart. This highlights issues such as:

- DM death flags are not consistent with DS and AE records
- Potential death information located only in the CO domain



JumpStart: Deaths Report

171 subjects were found to have death information in the Demographics (DM) domain:

DOMAIN	USUBJID	RFSTDTC	RFENDTC	DTHDTC	DTHFL
DM	1000-077	2012-04-05	2012-07-11	2012-09-22	Y

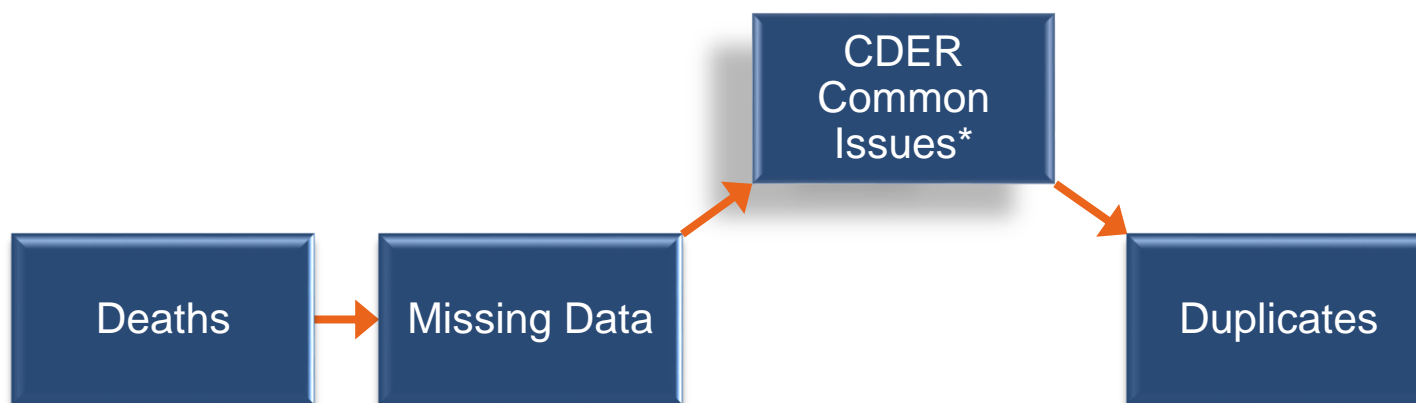
Additional information can be found in the Adverse Events (AE), Disposition (DS) and Death Details (DD) domains. Below is an example from the AE domain:

DOMAIN	USUBJID	AESEQ	AEDECOD	AEOUT	AESDTH	AESTDTC	AEENDTC	AESTDY	AEENDY
AE	1000-077	15	Brain oedema	FATAL	Y	2012-07-11	2012-08-20	27	85

CDER Common Issues

Review Questions:

- ▶ Did the applicant include key variables in the supplemental domains?
- ▶ Does the DM domain include start and end dates, an actual arm variable, a death flag, and a date of death variable?
- ▶ Does the DS domain contain the EPOCH variable?



AE Coding Report

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score	Record Count
ANXIETY ATTACK	Anxiety	Direct match to LLT	100	2
CLAMMINESS	Cold sweat	Direct match to LLT	100	1
DIZZINESS	Dizziness	Direct match to PT	100	1
HOARSENESS	Dysphonia	Direct match to LLT	100	1
NOSE BLEED	Epistaxis	Direct match to LLT	100	2
NOSEBLEED	Epistaxis	Direct match to LLT	100	3
FATIGUE	Fatigue	Direct match to PT	100	1
HEADACHE	Headache	Direct match to PT	100	10
NASAL CONGESTION	Nasal congestion	Direct match to PT	100	1
NASAL STUFFINESS	Nasal congestion	Direct match to LLT	100	1
NAUSEA	Nausea	Direct match to PT	100	1
NECK PAIN	Neck pain	Direct match to PT	100	1
SNEEZING	Sneezing	Direct match to PT	100	1
BLURRED VISION	Vision blurred	Direct match to LLT	100	1
NOSE BLEED (EPISTAXIS)	Epistaxis	Alternate spelling of LLT Nose bleeds	99	1
POST NASAL DRIP	Upper-airway cough syndrome	Alternate spelling of LLT Postnasal drip	99	1
CLAMMY/HOT	Cold sweat	Alternate spelling of LLT Clammy	96	1
SWELLING RIGHT LIP	Lip swelling	Alternate spelling of LLT Swelling of lips	94	1
BLEEDING OF THE NOSE	Epistaxis	Alternate spelling of LLT Bleeding nose	93	1
HEADACHE - FRONTAL, ETHMOID	Headache	Alternate spelling of LLT Headache aggravated	86	1
UNCONTROLLED HYPERTENSION WITH ARYTHMIAS	Hypertension	Alternate spelling of LLT Uncontrolled hypertension	85	1
MILD DIZZINESS	Dizziness	Partial word match to PT	80	1
ALLERGIC REACTION - RASH ON FACE, ARMS	Dermatitis allergic	Alternate spelling of LLT Allergic skin reaction	77	1
FACIAL PAIN S/P BALLOON SINUPLASTY	Facial pain	Alternate spelling of LLT Facial pain	77	1
FEELING OF "SAND IN EYES"	Foreign body sensation in eye	Partial word match to PT	11	1
MIGRAINE	Headache	Could not match	0	1
PATIENT SWALLOWED 4X3 PLEDGET DURING TREATMENT	Medication error	Could not match	0	1
INCREASED POST NASAL DRAINAGE	Rhinorrhoea	Could not match	0	1

Exploratory Safety Session

Adverse Event Exploration Flow



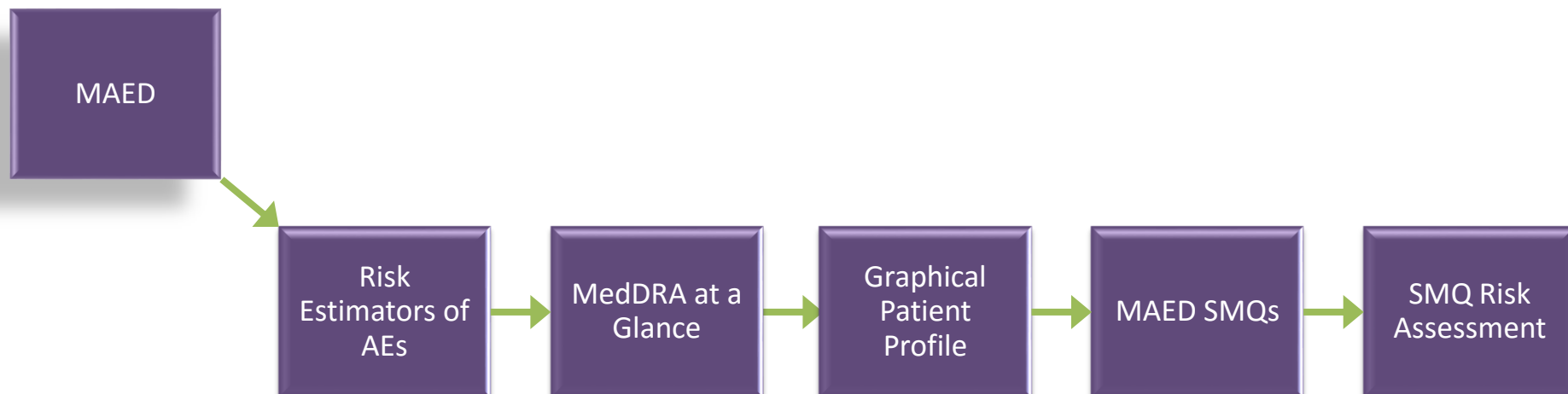
Review Questions:

- What are the most frequently occurring AEs?
- Which AEs occur more often in the treatment in relation to the comparator?
- Which AEs have the largest risk difference and/or relative risks?
- Are there worrisome AEs?

WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!

Secondary preferred terms excluded
 P-values should be used for ranking purposes only, not for determining statistical significance

SOC	Y 1 Weeks During			for Every 8 Weeks During			Group 2 (N = 168)			RD (per hundred)	RD CI (lower bound)
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)		
Blood and lymphatic system disorders	55	47	10.35	9	8	6.56	14	14	9.4	0.96	-4.5
Cardiac disorders	14	13	2.86	10	5	4.1	2	2	1.34	1.52	-0.88
Congenital, familial and genetic disorders	1	1	0.22	1	1	0.82	0	0	0	0.22	-0.21
Ear and labyrinth disorders	18	16	3.52	4	3	2.46	3	3	2.01	1.51	-1.31
Endocrine disorders	8	8	1.76	2	2	1.64	1	1	0.67	1.09	-0.69
Eye disorders	43	31	6.83	17	16	13.11	9	6	4.03	2.0	-1.12
Gastrointestinal disorders	338	168	37	70	43	36.25	108	54	36.24	0.76	-0.14
General disorders and administration site conditions	135	88	19.38	22	20	16.39	26	19	12.75	6.63	0.16
Hepatobiliary disorders	4	4	0.88	1	1	0.82	4	2	1.34	-0.46	-2.5
Immune system disorders	3	3	0.65	1	1	0.82	1	1	0.67	-0.61	-1.52
Infections and infestations	354	163	42.51	59	62	50.82	74	46	30.07	11.94	2.94
Injury, poisoning and procedural complications	53	35	7.71	11	9	7.38	3	3	2.01	5.7	2.36
Investigations	86	50	11.01	24	15	12.3	61	25	16.78	-5.77	-12.42
Metabolism and nutrition disorders	43	32	7.05	2	2	1.64	11	9	6.04	1.01	-3.48
Musculoskeletal and connective tissue disorders	166	101	22.25	47	28	22.95	30	22	14.77	7.48	0.62
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	4	0.88	4	4	3.28	2	1	0.67	0.21	-1.36
Nervous system disorders	204	97	21.37	44	28	22.95	59	28	16.79	2.57	-4.74
Pregnancy, puerperium and perinatal conditions	1	1	0.22	0	0	0	0	0	0	0.22	-0.21
Psychiatric disorders	47	36	7.93	10	10	8.2	8	6	4.03	3.9	-0.11
Renal and urinary disorders	14	11	2.42	6	3	2.46	6	2	1.34	1.08	-1.26
Reproductive system and breast disorders	11	10	2.2	6	5	4.1	2	2	1.34	0.86	-1.43
Respiratory, thoracic and mediastinal disorders	99	61	13.44	30	21	17.21	23	16	10.07	3.37	-2.39
Skin and subcutaneous tissue disorders	137	97	21.37	31	17	13.93	30	19	12.75	8.61	2.06



MAED: AE Incidence Table

	A	B	C	D	E	F	G	H
1	WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!							
2	Secondary preferred terms excluded.							
3	P-values should be used for ranking purposes only, not for determining statistical significance.							
5		Group 1 (Placebo			
6	SOC	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	RD (per hundred
7	Blood and lymphatic system disorders	32	26	2.5	5	5	1.13	1.37
8	Cardiac disorders	20	18	1.73	11	10	2.26	-0.53
9	Ear and labyrinth disorders	81	55	5.3	8	8	1.81	3.49
10	Endocrine disorders	6	5	0.48	1	1	0.23	0.26
11	Eye disorders	77	64	6.17	22	16	3.62	2.55
12	Gastrointestinal disorders	272	179	17.24	123	82	18.55	-1.31
13	General disorders and administration site conditions	325	235	22.64	61	51	11.54	11.1
14	Hepatobiliary disorders	4	4	0.39	0	0	0	0.39
15	Immune system disorders	6	5	0.48	6	6	1.36	-0.88
16	Infections and infestations	281	212	20.42	120	94	21.27	-0.84
17	Injury, poisoning and procedural complications	270	149	14.35	83	53	11.99	2.36
18	Investigations	131	103	9.92	38	32	7.24	2.68
19	Metabolism and nutrition disorders	69	61	5.88	16	15	3.39	2.48
20	Musculoskeletal and connective tissue disorders	155	121	11.66	57	45	10.18	1.48
21	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2	0.19	3	2	0.45	-0.26
22	Nervous system disorders	1094	528	50.87	252	137	31	19.87
23	Pregnancy, puerperium and perinatal conditions	1	1	0.1	0	0	0	0.1
24	Psychiatric disorders	261	159	15.32	80	55	12.44	2.87
25	Renal and urinary disorders	21	19	1.83	7	5	1.13	0.7
26	Reproductive system and breast disorders	25	22	2.12	6	6	1.36	0.76
27	Respiratory, thoracic and mediastinal disorders	86	68	6.55	50	39	8.82	-2.27
28	Skin and subcutaneous tissue disorders	103	82	7.9	40	31	7.01	0.89

SOC
 HLGT
 HLT
 PT

MedDRA at a Glance

MedDRA at a Glance Comparison Analysis

Treatment arm:


Control arm:


Risk difference threshold (%):

Relative risk threshold:

Negative log p-value threshold:

Choose your arms and type in your thresholds in the yellow input cells
Look below to see which terms have signals; you may have to scroll down
The colors in the signal columns tell you about the signal:

 This term shows a signal



 A term above or below in MedDRA shows a signal

Level	System Organ Class	High-Level Group Term	High-Level Term	Preferred Term	DME	Signal	Signal At					Treatment:		Control:		Risk Difference	Relative Risk*	Cont Corr	Negative Log P-value	Sort Order
							SOC	HLGT	HLT	PT										
											Subject Count	%	Subject Count	%						
1	Gastrointestinal disorders										270	32.7	82	19.9	12.8	1.6		13.2		
2	Gastrointestinal disorders	Abdominal hernias and other abdominal wall conditions									3	0.4	0	0.0	0.4	3.5	*	0.6		
3	Gastrointestinal disorders	Abdominal hernias and other abdo	Abdominal hernias, site unspecified								0	0.0	0	0.0	0.0	0.5	*			
4	Gastrointestinal disorders	Abdominal hernias and other abdo	Abdominal hernias, site unspecified	Abdominal hernia							0	0.0	0	0.0	0.0	0.5	*			
3	Gastrointestinal disorders	Abdominal hernias and other abdo	Diaphragmatic hernias								3	0.4	0	0.0	0.4	3.5	*	0.6		
4	Gastrointestinal disorders	Abdominal hernias and other abdo	Diaphragmatic hernias	Hiatus hernia							3	0.4	0	0.0	0.4	3.5	*	0.6		
3	Gastrointestinal disorders	Abdominal hernias and other abdo	Umbilical hernias								0	0.0	0	0.0	0.0	0.5	*			
4	Gastrointestinal disorders	Abdominal hernias and other abdo	Umbilical hernias	Umbilical hernia							0	0.0	0	0.0	0.0	0.5	*			
2	Gastrointestinal disorders	Anal and rectal conditions NEC									1	0.1	1	0.2	-0.1	0.5		0.0		
3	Gastrointestinal disorders	Anal and rectal conditions NEC	Anal and rectal disorders NEC								1	0.1	1	0.2	-0.1	0.5		0.0		
4	Gastrointestinal disorders	Anal and rectal conditions NEC	Anal and rectal disorders NEC	Anal fissure							1	0.1	1	0.2	-0.1	0.5		0.0		
3	Gastrointestinal disorders	Anal and rectal conditions NEC	Anal and rectal signs and symptoms								1	0.1	0	0.0	0.1	1.5	*	0.0		
4	Gastrointestinal disorders	Anal and rectal conditions NEC	Anal and rectal signs and sympto	Anorectal discomfort							1	0.1	0	0.0	0.1	1.5	*	0.0		
2	Gastrointestinal disorders	Benign neoplasms gastrointestinal									2	0.2	1	0.2	0.0	1.0		0.0		
3	Gastrointestinal disorders	Benign neoplasms gastrointestinal	Benign neoplasms gastrointestinal (excl oral cavity)								2	0.2	1	0.2	0.0	1.0		0.0		
4	Gastrointestinal disorders	Benign neoplasms gastrointestinal	Benign neoplasms gastrointestinal	Colonic polyp							1	0.1	1	0.2	-0.1	0.5		0.0		
4	Gastrointestinal disorders	Benign neoplasms gastrointestinal	Benign neoplasms gastrointestinal	Gastric polyps							0	0.0	0	0.0	0.0	0.5	*			
4	Gastrointestinal disorders	Benign neoplasms gastrointestinal	Benign neoplasms gastrointestinal	Polyp colorectal							1	0.1	0	0.0	0.1	1.5	*	0.0		
2	Gastrointestinal disorders	Dental and gingival conditions									37	4.5	10	2.4	2.1	1.9		2.5		

AE by Toxicity by Grade can be displayed via a separate SAS panel

MAED: SMQ, Custom MedDRA Queries

1	WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!							
2	* after SMQ name indicates SMQ with narrow terms only. Broad search will yield the same results.							
3	Number in parenthesis before SMQ name represents SMQ level.							
4	P-values should be used for ranking purposes only, not for determining statistical significance.							
6		Group 1			Placebo			
7	SMQ (Narrow Search)	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	RD (per hundred)
8	(1) Hostility/aggression	47	31	2.99	4	3	0.68	2.31
9	(2) Vestibular disorders	64	40	3.85	4	4	0.9	2.95
10	(1) Hearing and vestibular disorders	74	48	4.62	5	5	1.13	3.49
11	(1) Biliary disorders	4	4	0.39	0	0	0	0.39
12	(2) Functional, inflammatory and gallstone related biliary disorders	4	4	0.39	0	0	0	0.39
13	(1) Hyponatraemia/SIADH	12	9	0.87	1	1	0.23	0.64
14	(2) Hearing impairment	10	9	0.87	1	1	0.23	0.64
15	(1) Torsade de pointes/QT prolongation	3	3	0.29	0	0	0	0.29
16	(1) Shock	3	3	0.29	0	0	0	0.29
17	(2) Torsade de pointes, shock-associated conditions	3	3	0.29	0	0	0	0.29
18	(3) Gallbladder related disorders *	3	3	0.29	0	0	0	0.29
19	(3) Gallstone related disorders *	3	3	0.29	0	0	0	0.29
20	(1) Dyslipidaemia *	19	18	1.73	3	3	0.68	1.06
21	(1) Ischaemic heart disease	2	2	0.19	0	0	0	0.19
22	(2) Other ischaemic heart disease	2	2	0.19	0	0	0	0.19
23	(1) Drug abuse, dependence and withdrawal	2	2	0.19	0	0	0	0.19
24	(2) Drug abuse	2	2	0.19	0	0	0	0.19
25	(1) Haemodynamic oedema, effusions and fluid overload *	16	14	1.35	4	3	0.68	0.67
26	(1) Hepatic disorders	16	12	1.16	3	3	0.68	0.48
27	(2) Drug related hepatic disorders - comprehensive search	16	12	1.16	3	3	0.68	0.48
28	(3) Liver related investigations, signs and symptoms	16	12	1.16	3	3	0.68	0.48

 Broad SMQ
  Narrow SMQ

Liver / Hy's Law Analyses

Liver Lab Tests Greater Than Upper Limit of Normal

Liver Lab Test			
ALT ≥ ULN	Event Count	Subject Count	% of Subjects
2x ULN	406	107	52.45
3x ULN	163	71	34.80
5x ULN	42	28	13.73
10x ULN	7	6	2.94
20x ULN	1	1	0.49
AST ≥ ULN	Event Count	Subject Count	% of Subjects
2x ULN	183	78	38.24
3x ULN	64	39	19.12
5x ULN	17	11	5.39
10x ULN	4	1	0.49
20x ULN	0	0	0.00
ALP ≥ ULN	Event Count	Subject Count	% of Subjects
2x ULN	35	13	6.37
3x ULN	15	7	3.43
5x ULN	10	3	1.47
10x ULN	3	1	0.49
20x ULN	0	0	0.00
TB ≥ ULN	Event Count	Subject Count	% of Subjects
1.5x ULN	56	16	7.84
2x ULN	24	12	5.88
3x ULN	12	7	3.43

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

Liver Lab Test At Same Visit			
	Event Count	Subject Count	% of Subjects
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN & ALP normal	1	1	0.49
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	9	3	1.47
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN & ALP > normal	7	3	1.47
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN & ALP > normal	6	2	0.98
Total Subjects	0	3	1.47
ALT or AST ≥ 3 ULN, TB ≥ 1.5 ULN	10	3	1.47
ALT or AST ≥ 3 ULN, TB ≥ 2 ULN	7	3	1.47
ALT or AST ≥ 5 ULN, TB ≥ 3 ULN	6	2	0.98
Total Subjects	0	3	1.47

Summary

- JumpStart facilitates the review process
 - Data Fitness provides assessment of data quality and composition
 - Targeted exploratory safety analyses orient and guide the application's safety assessment

