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2023
KOREA
INTERCHANGE
SEOUL | 11-14 DECEMBER

Evaluating Safety, Quality and Traceability of Regulatory Submission Data

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Board of Director, CDISC
Dec 14, 2023

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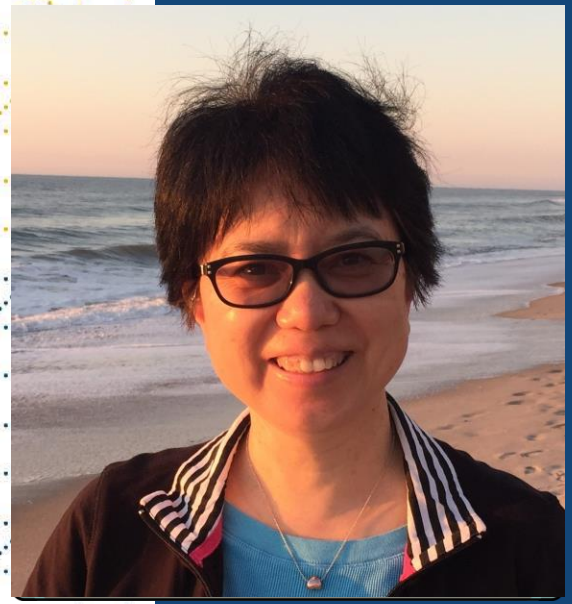
- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *{Please disclose any financial relationship or conflict of interest relevant to this presentation here OR}*
- *The author(s) have no real or apparent conflicts of interest to report.*



Meet the Speaker

Wenjun Bao

Title: Director

Organization: JMP Statistical Discovery, SAS Institute Inc.

Dr. Wenjun Bao is a Chief Scientist and Director of advanced analytics for JMP statistical Discovery, SAS Institute Inc. Before joining SAS, she was an Intramural Research Training Award (IRTA)Fellow at NIH (National Institutes of Health), a professor at Duke University, and a scientist at the US EPA (Environmental Protection Agency). She has rich experiences in clinical, bioinformatics, biochemistry, and molecular biology research. She has expertise in variety data analysis including AI/ML models in clinical trial and genomics data analysis and text mining with multiple publications in peer-reviewed journals. Dr. Bao has been a research grant review committee member for NIH since 2005 and a research adviser for scientists at universities and government agencies. Dr. Bao is a Board of Director for CDISC and an adjunct professor at Fudan University.

Standards Recognized by Regulatory Agencies

FDA Standards Trainings for Reviewers' Career Advancement

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 4655.3 Rev 3

POLICY AND PROCEDURES

OFFICE OF MANAGEMENT

Procedures for CDER Medical Officer Conversion to Career-Conditional

https://www.fda.gov/media/80047/download
4/25/2018

	6-9 Months	
	es (classroom or online)	
	CDER Review of Clinical Trials	OND: Office of New Drugs
	OND Ready, Set, Review	OTS: Office of Translational Sciences
	OND 2017 Clinical Review Template Introduction	OCS: Office of Computational Science
	OND The Road to Assessing Benefit and Risk	
	CDER MaPP 6010.3 Clinical Review Template Attachment B (Safety Review, p. 36 – print resource) http://inside.fda.gov:9003/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm080121.pdf	
	CDER Learn the Safety Dance	
	OTS MedDRA Training – I & II	Standard Terminology
	OCS Data standards training	Standard Data (CDISC)
	OCS JMP and JMP Clinical Training (multiple modules)	Standard Analysis Procedures
	FDA Library Electronic Resources	

Required Trainings

Japan Pharmaceuticals and Medical Devices Agency

Dr. Yuki Ando (PMDA)

Expected analyses in review teams

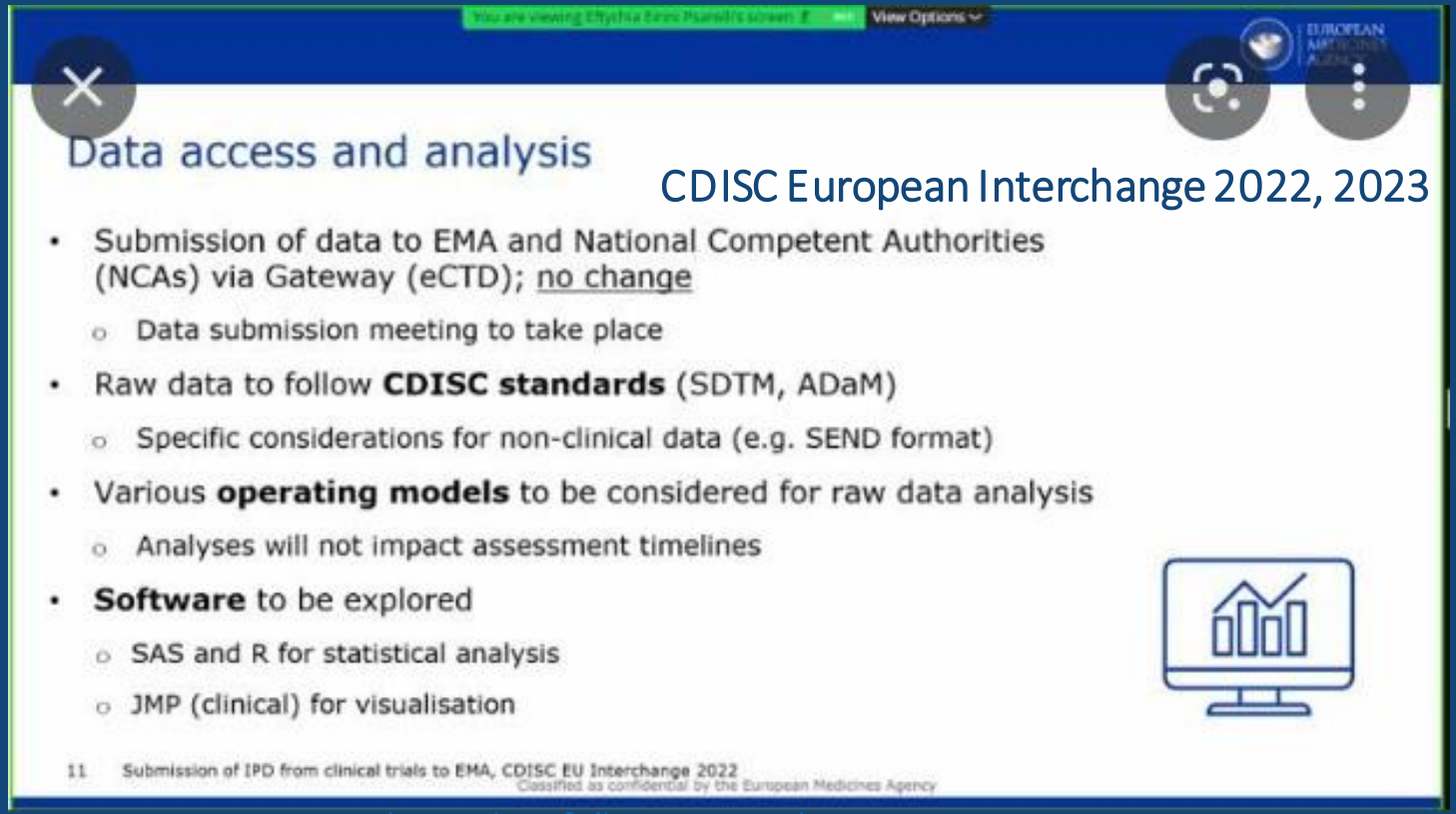
CDISC US Interchange, Nov. 2015

Common analyses to many clinical trials	• Distribution of patient demographics • Changes in laboratory data • Adverse events rates	STAT MEDICAL OTHERS Software: JMP Clinical, etc. Datasets: SDTM
General analyses for efficacy and safety data	• Simple analyses depending on the characteristics of evaluation variables – continuous/categorical/time-to-event)	STAT MEDICAL OTHERS Software: JMP, etc. Datasets: ADaM
Relatively complicated analyses	• Analyses with programing (innovative/complicated analyses) • Simulations	STAT MEDICAL OTHERS Software: SAS, etc. Datasets: SDTM, ADaM

https://www.pmda.go.jp/files/000208574.pdf

European Medicines Agency

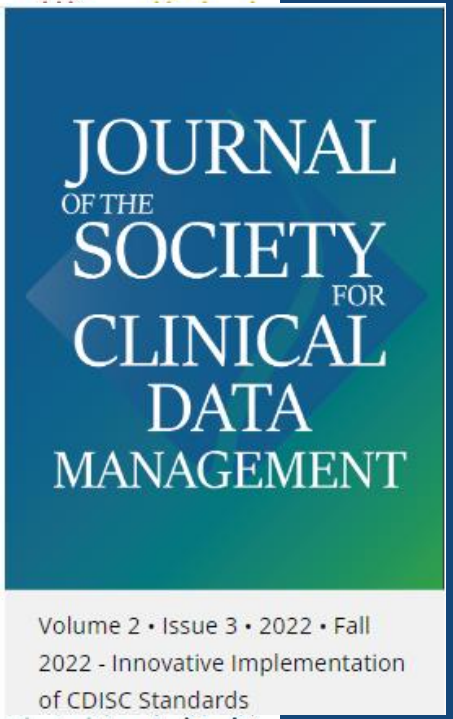
Dr. Eftychia Eirini Psarelli (EMA)



CDISC Special Issue in JSCDM

CDISC Special Issues

Rhonda Facile of CDISC led the effort



Electronic Submission and Utilization of CDISC Standardized Clinical Study Data in Japan

Yuki Ando

Developing Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH) Liver Fibrosis

Y. Veronica Pei , Vaishali Popat , Aaron Belowich and Chenoa Conley

Use of CDISC data in the Danish Medicines Agency

Claus Bang Pedersen , Zhiyi You and Jesper Kjær

https://www.jscdm.org/issue/9/info/

CDISC Special Issues

Rhonda Facile of CDISC led the effort

CDISC Enables Efficient Streamlining of Clinical Trial Safety Evaluation

Geoffrey Mann , Thomas J Pedersen , Rebecca Lyzinski , Anisa Scott , Andrew J Foglia , John Cromer , Meichen Dong , Nora Varga , Sam Gardner , Christopher J Kirchberg , Byron A Wingerd , Russell D Wolfinger and Wenjun Bao

Cite and download:

Mann, G. & Pedersen, T. J. & Lyzinski, R. & Scott, A. & Foglia, A. J. & Cromer, J. & Dong, M. & Varga, N. & Gardner, S. & Kirchberg, C. J. & Wingerd, B. A. & Wolfinger, R. D. & Bao, W., (2023) "CDISC Enables Efficient Streamlining of Clinical Trial Safety Evaluation", *Journal of the Society for Clinical Data Management* 3(1).

https://doi.org/10.47912/jscdm.169

CDISC Special Issues

Rhonda Facile of CDISC led the effort

In 2022, CDISC initiated a project with the Journal of the Society of Clinical Data Management (JSCDM) to create a library of peer-reviewed articles focused on the implementation of CDISC standards. More than 30 abstracts were received and, as of today, a total of 15 articles have been published and another four are nearing publication.

Prior to this effort there were few, if any, articles in the literature that directly dealt with implementing CDISC standards. To address this unmet need, Rhonda Facile, Vice President of Partnerships and Development at CDISC, led the effort to create the first CDISC special issue in JSCDM. A highlight of the first issue are articles from three different regulatory agencies: the U.S. Food and Drug Administration (FDA), Japan's Pharmaceutical and Medical Device Agency (PMDA), and the Danish Medicines Agency (DMA).

Many of my talented JMP colleagues who have made great contributions to the success of JMP Clinical are the co-authors of the paper. We are very grateful for the suggestions and editing provided by Rhonda Facile and Melissa Kirwin of CDISC, as well as Dr. Meredith Nahm Zozus, editor of the JSCDM.

https://community.jmp.com/t5/JMPer-Cable/CDISC-Enables-Efficient-Streamlining-of-Clinical-Trial-Safety/ba-p/677296

Standards Applied In FDA NDAs and CRs

Mann, G. & Pedersen, T. J. & Lyzinski, R. & Scott, A. & Foglia, A. J. & Cromer, J. & Dong, M. & Varga, N. & Gardner, S. & Kirchberg, C. J. & Wingerd, B. A. & Wolfinger, R. D. & Bao, W., (2023) "CDISC Enables Efficient Streamlining of Clinical Trial Safety Evaluation", *Journal of the Society for Clinical Data Management* 3(1).

https://doi.org/10.47912/jscdm.169

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FDA NDAs or CRs for Template for Drug Safety

Mydayis

5.2. Review of Safety

A 5.2.1. Safety Review Approach

B 5.2.2. Review of the Safety Database

C 5.2.3. Adequacy of Applicant's Clinical Safety Assessments

D 5.2.4. Safety Results

F 5.2.5. Analysis of Submission-Specific Safety Issues

E 5.2.6. Safety Analyses by Demographic Subgroups

5.2.7. Specific Safety Studies/Clinical Trials

F 5.2.8. Additional Safety Explorations

5.2.9. Integrated Assessment of Safety

NDA Mydayis 2019 https://www.fda.gov/media/142063/download

NDA: New Drug Application

CR: Clinical Review

A. Safety Review Approach

The Analysis Data Model (ADaM) and Study data Tabulation Model (SDTM) datasets were intact and evaluable using JMP programs for the clinical team and for evaluation by our Biometrics team.

Vyvanse https://www.fda.gov/media/151943/download

B. Review of Safety Database

Table 9: Study A1501001 Intravenous (IV) and Oral (PO) Treatment Exposures, Pediatric Subjects with EC and ICC, Ages 2 to <18 years old

Treatment Duration (days)	2 to <12 years old		12 to <18 years old		Overall	
	EC	ICC	EC	ICC	EC	ICC
Duration of IV treatment						
Mean	n=83	n=11	n=8	n=11	n=91	n=11
Median	9.00	10.0 (7.7)	8.5 (4.0)	n/a	8.0 (4.0)	10.0 (7.7)
Range	6	2-24	5-17	n/a	5-17	2-24
Duration of PO treatment						
Mean	n=2	n=6	n=5	n=8	n=7	n=14
Median	11 (1.7)	19.5 (13.8)	4.0 (2.6)	n/a	7.1 (5.0)	19.1 (13.6)
Range	11	13.2	3	n/a	8	13.2
Duration of IV + PO treatment	9.17	3-37	2-8	n/a	2-17	3-37
	n=2	n=11	n=5	n=8	n=7	n=19
Mean	18.5 (16.4)	17.2 (14.3)	12.4 (5.6)	n/a	16.1 (12.3)	17.2 (14.3)
Median	18.5	18	14	n/a	18	18
Range	16.32	9-42	8-18	n/a	8-32	9-42

Source: Trial A1501001 ADSL (AdAM) Data Set Table was created by the Clinical Reviewer using JMP software.

Vfend https://www.fda.gov/media/113616/download

C. Adequacy of Applicant's Clinical Safety Assessments

Demographics of Safety Database

Table 11: Treatment by age group in Study D1050326

Age Group	Lurasidone 20-80 mg Count	Lurasidone 20-80 mg Column %	Placebo Count	Placebo Column %	Count	% of Total
age >=6 and age <=12	38	21.7%	37	21.5%	75	21.61%
age >=13 and age <=17	137	78.3%	135	78.5%	272	78.39%
All	175	100.0%	172	100.0%	347	100.00%

Latuda https://www.fda.gov/media/103749/download

E. Safety Analyses by DM Subgroups

TEAEs & ARs by Age, Sex, Race, Ethnicity & location

Table 36: Treatment-Emergent Adverse Reactions Occurring in ≥2 Subjects in Any Subgroup Treated With Arazlo Lotion or Vehicle Lotion, by Age Group (ISS, Safety Analysis Set)

Preferred Term	Age 9 to <12 Years (N=26) Arazlo Lotion, n=14 n (%)	Age 9 to <12 Years (N=26) Vehicle Lotion, n=12 n (%)	Age ≥12 Years (N=1542) Arazlo Lotion, n=764 n (%)	Age ≥12 Years (N=1542) Vehicle Lotion, n=778 n (%)
Application site pain	1 (7.1)	0	40 (5.2)	2 (0.3)
Application site dryness	0	0	28 (3.7)	1 (0.1)
Combined PTs for application site: rash/dermatitis/erythema/hypersensitivity	1 (7.1)	0	24 (3.1)	0
Application site exfoliation	0	0	16 (2.1)	0
Application site pruritus	2 (14.3)	0	7 (0.9)	0
Application site irritation	0	0	6 (0.8)	0
Application site acne	0	0	1	2 (0.3)

Source: Adapted from ISS (Table 14.3.1.2.3.2. AH1) and Reviewer's JMP Clinical 7 Analysis. Adverse Events Distribution Report Results. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Adverse Events: AEREL='RELATED.' Treatment emergence determined using AE.ASTRTEM. MedDRA version 20.0. Abbreviations: ISS=integrated summary of safety, PT=preferred term.

COISC

Arazlo https://www.fda.gov/media/134644/download

G. information was verified by reviewers

Table 14: Enrollment by Country

Country	ABP 710 (N=279)	US-Remicade (N=279)	Total (N=558)
Australia	5 (1.8%)	4 (1.4%)	9 (1.6%)
Bulgaria	14 (5.0%)	11 (3.9%)	25 (4.5%)
Canada	2 (0.7%)	1 (0.4%)	3 (0.5%)
Czech Republic	52 (18.6%)	49 (17.6%)	101 (18.1%)
Germany	15 (5.4%)	11 (3.9%)	26 (4.7%)
Hungary	7 (2.5%)	14 (5.0%)	21 (3.8%)
Poland	125 (44.8%)	133 (47.7%)	258 (46.2%)
Spain	7 (2.5%)	4 (1.4%)	11 (2.0%)
United States	52 (18.6%)	52 (18.6%)	104 (18.6%)

Source: Study 20140111 CSR, Table 14-1.2.1; clinical reviewer verified using JMP and ADSL dataset by TRT01A.

Quzyttir https://www.fda.gov/media/133034/download

Avsola https://www.fda.gov/media/134460/download

5.2. Review of Safety.....

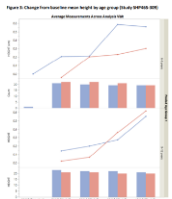
- A 5.2.1. Safety Review Approach .....
- B 5.2.2. Review of the Safety Database .....
- C 5.2.3. Adequacy of Applicant's Clinical Safety Assessments
- D 5.2.4. Safety Results.....
- F 5.2.5. Analysis of Submission-Specific Safety Issues.....
- E 5.2.6. Safety Analyses by Demographic Subgroups.....
- F 5.2.7. Specific Safety Studies/Clinical Trials .....
- F 5.2.8. Additional Safety Explorations.....
- 5.2.9. Integrated Assessment of Safety .....

5.3. Conclusions and Recommendations .....

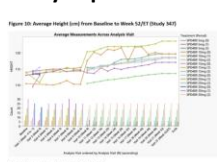
Mydayis https://www.fda.gov/media/142063/download

F. Specific Safety Studies/Clinical Trials & other assessments

F.1. Specific Safety Issues



F.2. Additional Safety Explorations



Vyvanse https://www.fda.gov/media/151943/download

Mydayis https://www.fda.gov/media/142063/download

D. Safety Results

D.1. Death and SAE

Participant: 101014
Randomized Arm: NIC .15
Investigator Name: 101B

Participant 101014 was a 74-year-old white female. Her medical history included focal deficit, headache, hypertension, vomiting, hypertension, allergies, diabetes mellitus, and other medical condition.]

The participant discontinued the trial on 21MAR1989 (Day 6) due to death.

Latuda https://www.fda.gov/media/103749/download

D.2. Discontinuations due to AEs

Table 30: Treatment-Emergent Adverse Reactions leading to Discontinuation, SGT-65-04 and SGT-65-05 Pooled (Safety Population)

Body System or Organ Class	Dictionary-Derived Term	Teqvayo Cream (N = 555), n (%) Count	%	Vehicle Cream (N = 277), n (%) Count	%
General disorders and administration site conditions	Application site pain	15	2.7%	-	-
	Application site pruritus	5	0.9%	-	-
	Application site exfoliation	3	0.5%	1	0.4%
	Application site dermatitis	4	0.7%	-	-

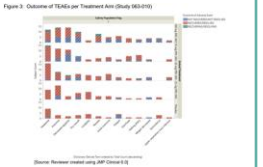
Twyneo https://www.fda.gov/media/151645/download

D.3. Treatment Emergent AEs and ARs

Table 14: TEAEs at least 2% and Greater than Placebo for all Treatment Arms

Study 063-010 Dictionary-Derived Term N=375	PRC-063 25mg N=77 Count	%	PRC-063 45mg N=73 Count	%	PRC-063 70mg N=73 Count	%	PRC-063 100mg N=100 Count	%	PRC-063 all doses N=297 Count	%	Placebo N=78 Count	%
Insomnia	13	16.9%	8	11.0%	12	16.4%	14	14.0%	47	12.5%	3	3.8%
Initial insomnia	3	3.9%	6	8.2%	4	5.5%	5	4.8%	18	4.8%	1	1.3%
Dry mouth	6	7.8%	6	8.2%	5	6.8%	10	12.5%	27	7.2%	3	3.8%
Nausea	3	3.9%	4	5.5%	3	4.1%	8	10.8%	18	4.8%	2	2.6%
Diarrhea	1	1.3%	2	2.7%	5	6.8%	5	5.4%	12	3.2%	1	1.3%
Decreased appetite	3	3.9%	5	6.8%	11	15.1%	14	18.9%	33	8.8%	2	2.6%
Feeling jittery	1	1.3%	2	2.7%	6	8.2%	3	4.1%	12	3.2%	1	1.3%
Weight decreased	2	2.6%	3	4.1%	2	2.7%	4	5.4%	11	2.9%	1	1.3%
Upper respiratory tract infection			3	4.1%	2	2.7%	2	2.7%	7	1.9%	1	1.3%

[Source: Reviewer created using JMP Clinical 6.0]



Adhansia XR https://www.fda.gov/media/124188/download

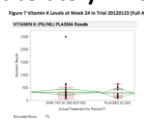
Table 25. FMQs with Events in ≥2% of Dasiglucagon Treated Subjects Over Entire Observation Period – Placebo-Controlled Pool

FMQ	0.6 mg Dasiglucagon n=116	Placebo n=53	1 mg GlucaGen n=43	RR*	95% CI
Nausea	66 (56.9%)	2 (3.8%)	23 (53.5%)	15.1	(3.8, 59.3)
Hypoglycemia	29 (25%)	7 (13.2%)	9 (20.9%)	1.9	(0.9, 4)
Vomiting	29 (25%)	1 (1.9%)	9 (20.9%)	13.3	(1.9, 94.7)
Headache	14 (12.1%)	2 (3.8%)	5 (11.6%)	3.2	(0.8, 13.6)
Infections	8 (6.9%)	4 (7.5%)	0 (0%)	0.9	(0.3, 2.9)
Diarrhea	6 (5.2%)	(0%)	1 (2.3%)	N/A	N/A
Injection Site Reactions	4 (3.4%)	2 (3.8%)	3 (7%)	0.9	(0.2, 4.8)

*RR= risk ratio (dasiglucagon versus placebo)
Source: Generated by reviewer in JMP with ADSL and ADAE datasets

Zegalogue https://www.fda.gov/media/147791/download

D.4. Laboratory Finding



Repatha https://www.fda.gov/media/154402/download

Clinical Trial Safety Review

1. Summary
   - A. Trial Summary: Study Flow Chart
   - B. Event Summary: Disposition of Participants
   - C. TEAE Summary: AEs Emerge or Worsen After Treatment

2. Review of Safety

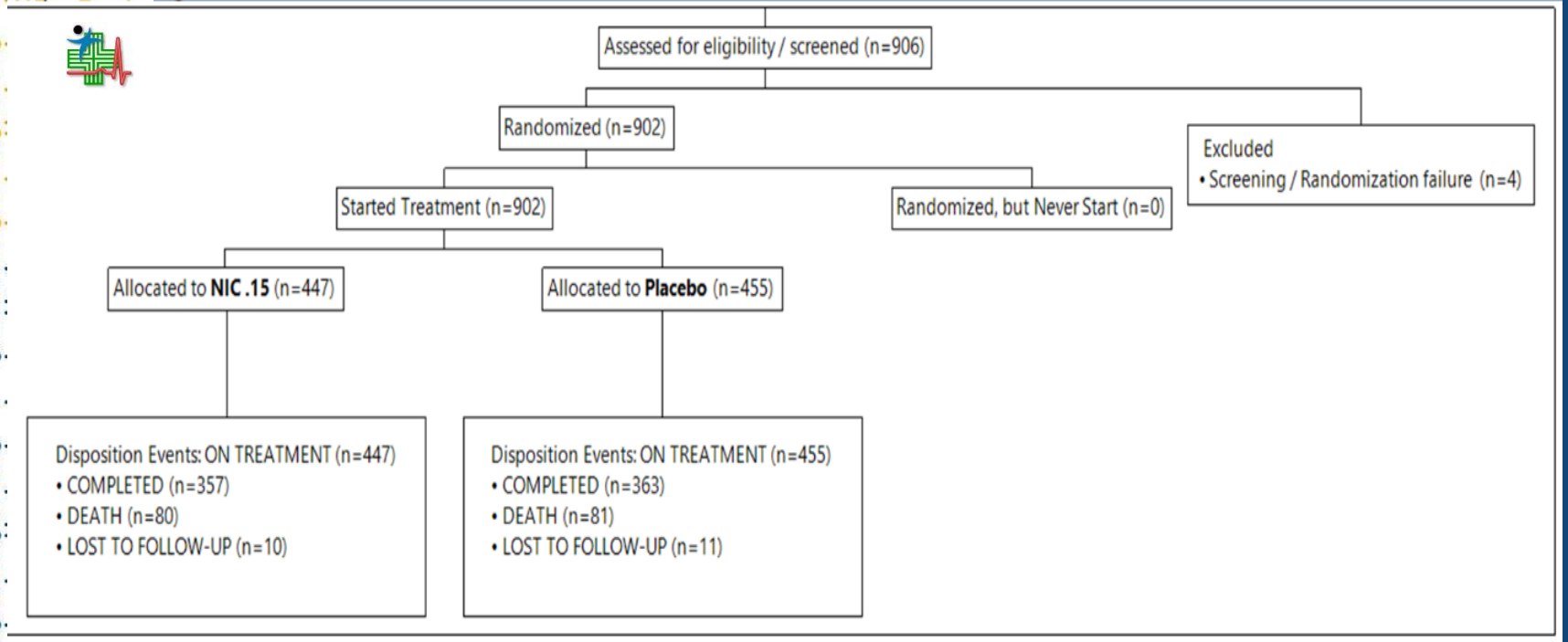
NDA Mydayis 2019 https://www.fda.gov/media/142063/download

Summary

A. Trial Summary: Study Flow Chart
B. Event Summary: Disposition of participants
C. TEAE Summary: AE emerge or worsen after treatment

Summary

Trial Summary: Study Flow Chart



CDISC: ADDS/DS, ADEX/EX and ADSL/DM; JMPC: Study Flow Diagram

Summary

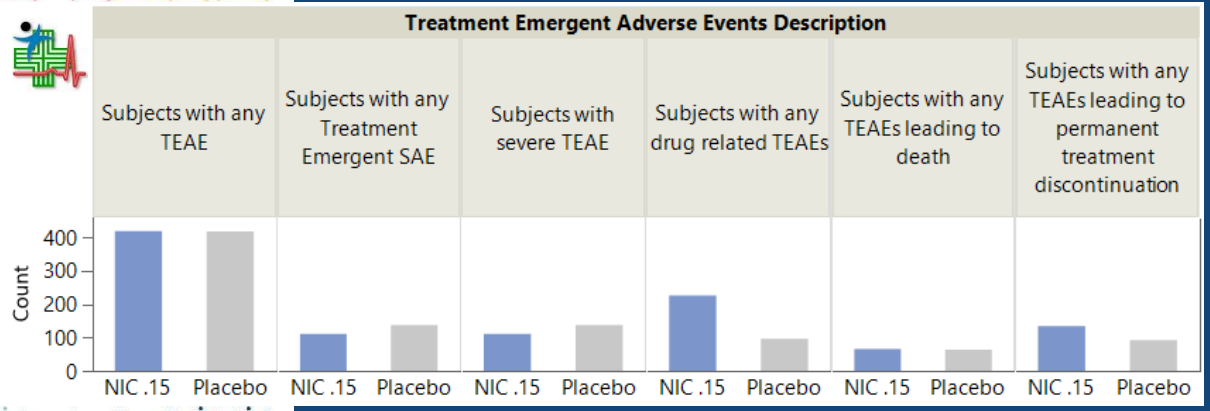
Event Summary: Disposition of Participants

	Planned Treatment for Period 01		
	NIC .15 (N = 447)	Placebo (N = 455)	Total (N = 902)
Category for Disposition Event/Standardized Disposition Term	**n (%)**	**n (%)**	**n (% of Total)**
DISPOSITION EVENT	447 (100.0)	455 (100.0)	902 (100.0)
COMPLETED	357 (79.9)	363 (79.8)	720 (79.8)
DEATH	80 (17.9)	81 (17.8)	161 (17.8)
LOST TO FOLLOW-UP	10 (2.2)	11 (2.4)	21 (2.3)
PROTOCOL MILESTONE	447 (100.0)	455 (100.0)	902 (100.0)
DATE OF SAH	447 (100.0)	455 (100.0)	902 (100.0)
RANDOMIZED	447 (100.0)	455 (100.0)	902 (100.0)
OTHER EVENT	367 (82.1)	374 (82.2)	741 (82.2)
RANDOMIZED	10 (2.2)	9 (2.0)	19 (2.1)
LOST TO FOLLOW-UP	15 (3.4)	10 (2.2)	25 (2.8)
RECOVERY	244 (54.6)	255 (56.0)	499 (55.3)
MODERATELY DISABLED	55 (12.3)	55 (12.1)	110 (12.2)
SEVERELY DISABLED	38 (8.5)	32 (7.0)	70 (7.8)
VEGETATIVE SURVIVAL	5 (1.1)	13 (2.9)	18 (2.0)
All	447 (100.0)	455 (100.0)	902 (100.0)

CDISC: ADDS/DS, ADSL/DM; JMPC: Event (DS) Distribution

Summary

Treatment Emergent Adverse Events Summary



Treatment Emergent Adverse Events Description	Planned Treatment for Period 01 NIC .15 (N = 447) n (%)	Placebo (N = 455) n (%)	Total (N = 902) n (% of Total)
Subjects with any TEAE	421 (94.2)	420 (92.3)	841 (93.2)
Subjects with any Treatment Emergent SAE	112 (25.1)	138 (30.3)	250 (27.7)
Subjects with severe TEAE	112 (25.1)	138 (30.3)	250 (27.7)
Subjects with any drug related TEAEs	227 (50.8)	97 (21.3)	324 (35.9)
Subjects with any TEAEs leading to death	67 (15.0)	64 (14.1)	131 (14.5)
Subjects with any TEAEs leading to permanent treatment discontinuation	135 (30.2)	93 (20.4)	228 (25.3)

CDISC Domain: ADAE/AE, ADSL/DM; JMPC: Treatment Emergent AEs Summary

Review of Safety

Review of Safety

A. Safety Review Approach

8.2.1. Safety Review Approach

Dupixent FDA

The 52-week safety and efficacy study (EFC14153) was evaluated for safety. Safety is also supported by findings from the open-label extension study (LTS14424) which enrolled subjects who participated in Study EFC14153. Study LTS14424 is reviewed separately in Section 8.2.7. The review tools used to conduct independent reviewer analyses included JMP Clinical, JMP, and the clinical investigator site selection tool.

NDA Dupixent 2021 https://www.fda.gov/media/155349/download

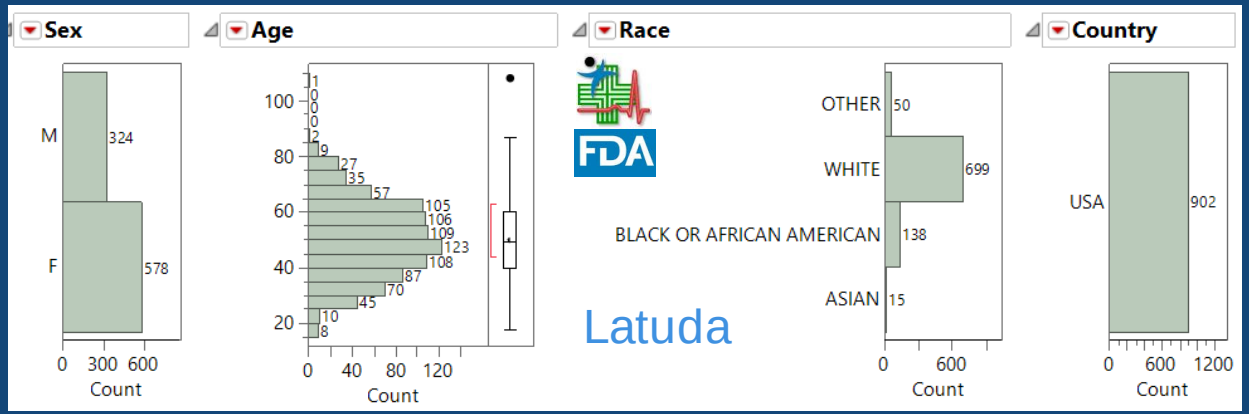
The Analysis Data Model (ADaM) and Study data Tabulation Model (SDTM) datasets were intact and evaluable using JMP programs for the clinical team and for evaluation by our Biometrics team.

Vyvanse FDA

NDA Vyvanse 2021 https://www.fda.gov/media/151943/download

Review of Safety

B. Review of Safety Database



CR Latuda 2018 https://www.fda.gov/media/103749/download

	Planned Treatment for Period 01		
	NIC .15 (N = 447)	Placebo (N = 455)	Total (N = 902)
Sex	**n (%)**	**n (%)**	**n (% of Total)**
F	281 (62.9)	297 (65.3)	578 (64.1)
M	166 (37.1)	158 (34.7)	324 (35.9)
Race	**n (%)**	**n (%)**	**n (% of Total)**
ASIAN	8 (1.8)	7 (1.5)	15 (1.7)
BLACK OR AFRICAN AMERICAN	78 (17.4)	60 (13.2)	138 (15.3)
WHITE	340 (76.1)	359 (78.9)	699 (77.5)
OTHER	21 (4.7)	29 (6.4)	50 (5.5)
Country	**n (%)**	**n (%)**	**n (% of Total)**
USA	447 (100.0)	455 (100.0)	902 (100.0)

	Planned Treatment for Period 01		
	NIC .15 (N = 447)	Placebo (N = 455)	Total (N = 902)
	Mean (Std Dev)	**Mean (Std Dev)**	**Mean (Std Dev)**
Age	49.7 (13.9)	50.2 (13.8)	50.0 (13.8)

CDISC: ADSL/DM; JMPC: Demographics Distribution

Number of Decimals to Display for Numeric Results
1
0 8

Review of Safety

B. Review of Safety Database

Table 8: Study A1501080 Intravenous (IV) and Oral (PO) Treatment Exposures, Pediatric Subjects with IA Ages 2 to <18 years old

Treatment Duration (days)	2 to <12 years old IA	12 to <18 years old IA	Overall
Duration of IV treatment			
	n=11	**n=20**	**n=31**
Mean (SD)	13.6 (10.3)	10.2 (4.7)	11.4 (7.2)
Median	8.0	8.5	8.0
Range	3-33	5-22	3-33
Duration of PO treatment			
	n=8	**n=14**	**n=22**
Mean (SD)	45 (34.3)	52.6 (24.7)	49.9 (28.0)
Median	55	59.5	59.5
Range	2-78	8-81	2-81
Duration of IV + PO treatment			
	n=8	**n=14**	**n=22**
Mean (SD)	59.4 (27.7)	62.4 (25.2)	61.3 (25.5)
Median	68.5	68.5	68.5
Range	18-85	19-90	18-90

Source: Trial A1501080. ADSL (AdAM) data set. Table was created by the Clinical Reviewer using JMP software.

Vfend

* Table directly Copied from CR

CR Vfend 2017 https://www.fda.gov/media/113616/download

CDISC Domain: ADSL/DM, ADEX/EX

Review of Safety

C. Adequacy of Applicant's Clinical Safety Assessments

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data quality issues were identified in the review of this supplemental BLA.

NDA Dupilumab 2020 https://www.fda.gov/media/155349/download

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

[Do not insert text here]

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of data submitted is adequate to characterize the safety and efficacy of Twyneo cream and provides sufficient information to adequately label this product. There were no significant deficiencies discovered that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

NDA Twyneo 2020https://www.fda.gov/media/151645/download

* Statements directly Copied from NDAs

FDA NDA or CR Template: Review of Safety

NDA Latuda 2017 https://www.fda.gov/media/103749/download

Review of Safety

D. Safety Review: 1. Death and SAE

1. Compare between treatment and placebo groups
2. List the detail information about each subject

Participant: 101004
Randomized Arm: NIC .15
Investigator Name: 101A

AE Narrative

Participant 101004 was a 48-year-old white female. Her medical history included focal deficit, headache, loss of consciousness, vomiting, other medical condition, and allergies.

The participant discontinued the trial on 31JAN1988 (Day 4) due to death.

Serious Adverse Event (coded term): VASOCONSTRICTION
Drugs and Doses on Day of Event: Pre Treatment

On 28JAN1988 (Day 1) the participant experienced a vasoconstriction (severe) which was considered a serious adverse event (SAE). Though the event was considered serious, no reasons were provided on the case report form. At the time of the event, the participant had not yet started study medication. Trial medication had an action of drug withdrawn as a result of the event. It is not known from the case report form if therapeutic measures were administered to treat the event.

Adverse events that occurred within a +/- 3-day window of the onset of the SAE included brain oedema (mild), coma (severe), hydrocephalus (severe), hyperglycaemia (mild), hypotension (severe), intracranial pressure increased (severe), and subarachnoid haemorrhage (severe). Concomitant medications taken at the onset of the SAE included: docusate sodium, phenobarbital, potassium supplements, and ranitidine.

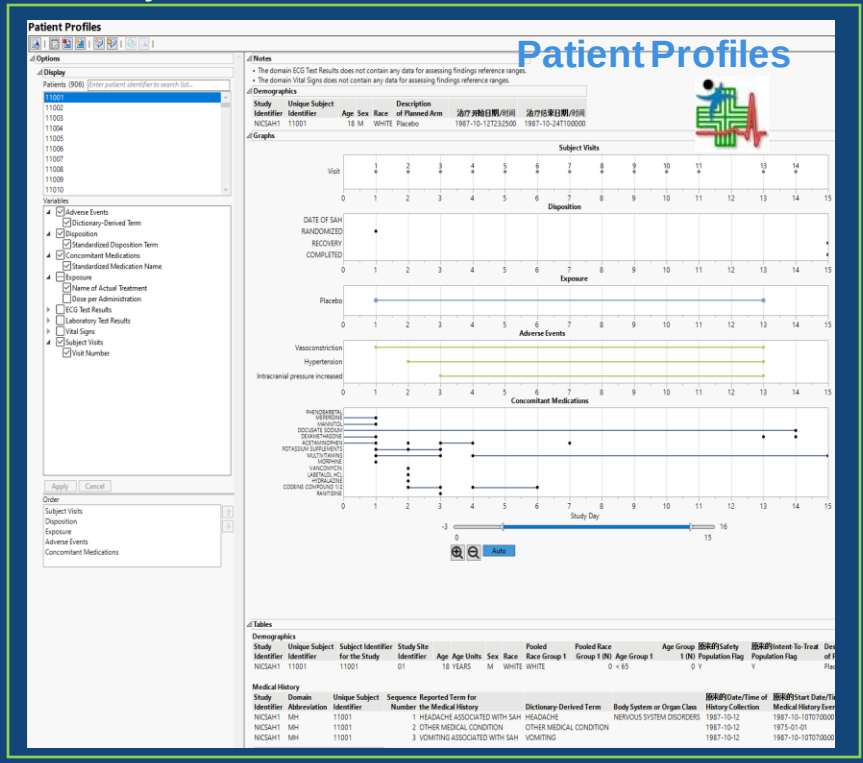
The investigator considered the AE to be not related to study medication. The event ended on 28JAN1988 (Day 1) with a final outcome of recovered/resolved.

Serious Adverse Event (coded term): HYDROCEPHALUS
Drugs and Doses on Day of Event: Pre Treatment

On 28JAN1988 (Day 1) the participant experienced a hydrocephalus (severe) which was considered a serious adverse event (SAE). Though the event was considered serious, no reasons were provided on the case report form. At the time of the event, the participant had not yet

CDISC:
All

JMPC:
Adverse Events
Narrative
Patient Profiles



AE Narrative

Description for Individual with SAE

Clinical Review
Nancy Dickinson, PharmD.
NDA 200603 S-029
Latuda (lurasidone)

8.3.2. Serious Adverse Events

Based on my analysis of the safety data in Study D1050326, there were six serious adverse events (SAEs) reported. Four (2.3%) were in the placebo arm and two (1.1% lurasidone treatment arm. The serious adverse events reported in the lurasi bipolar disorder and humerus fracture. In the placebo arm, the SAEs were p depression, , and spontaneous abortion. The psychiatric-related serious adv represent an exacerbation of the underlying psychiatric condition or may be efficacy of study drug, although the investigators did not all report them as SAEs occurred in the 10 to 12 year age group and the other four were in the to 17 years).

No additional treatment-emergent serious adverse events were reported in update of Study D1050326.

Narratives were created by reviewer using JMP Clinical:

1. Actual Arm: LURASIDONE 20-80 MG; Dose 20 mg/day

Serious Adverse Event (coded term [reported term]): BIPOLAR I DISORDER [I EPISODE]

SAE

Subject D1050326-0005-00003 was a 14-year-old African American male. His medical history included agitation (2013), indigestion (2013), initial onset of bipolar I disorder (2012), insomnia (2012), irritability (2012), headaches (2011), 314.01 ADHD (2006), and initial behavioral disturbance (2005).

DM, MH

The subject discontinued the trial on August 27, 2014, (Day 8) due to symptoms worsened. On Day 9 the subject experienced a bipolar I disorder [bipolar mixed episode] (moderate) which was considered a serious adverse event (SAE). Though the event was considered serious, no reasons were provided on the case report form.

Discontinuations Due to SAE

Concomitant medications taken at the onset of the SAE included: acetaminophen, lorazepam, risperidone, and valproic acid.

CM

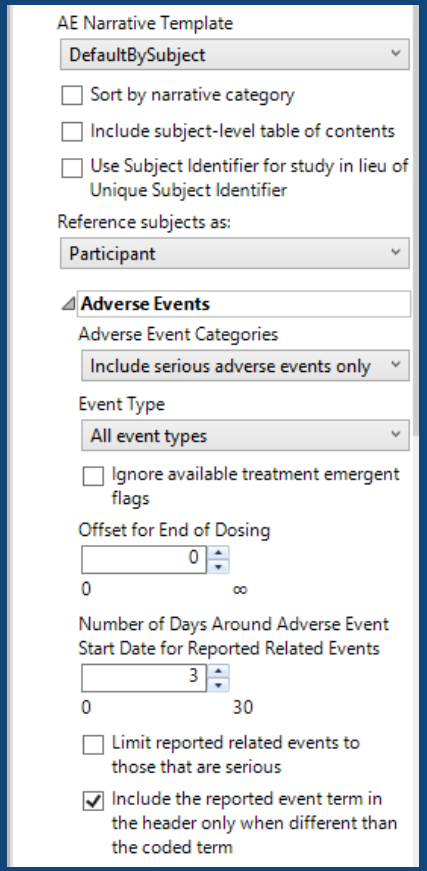
The investigator considered the AE to be unlikely related to study medication. The event ended on September 9, 2014, (Day 21) with a final outcome of recovered/resolved.

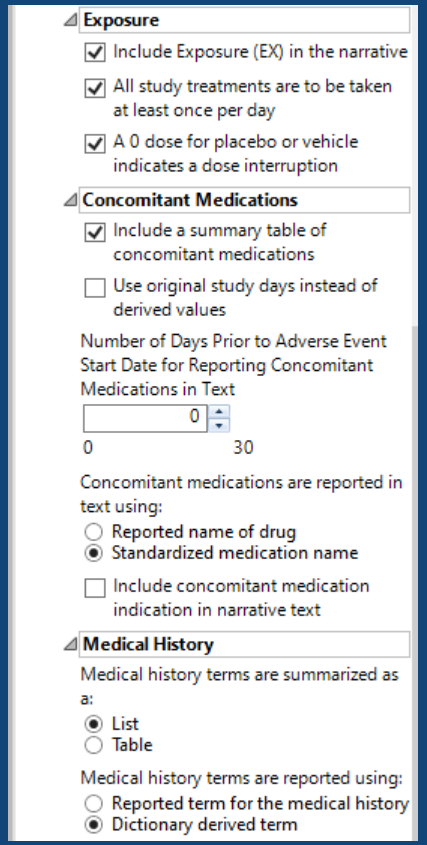
Outcome

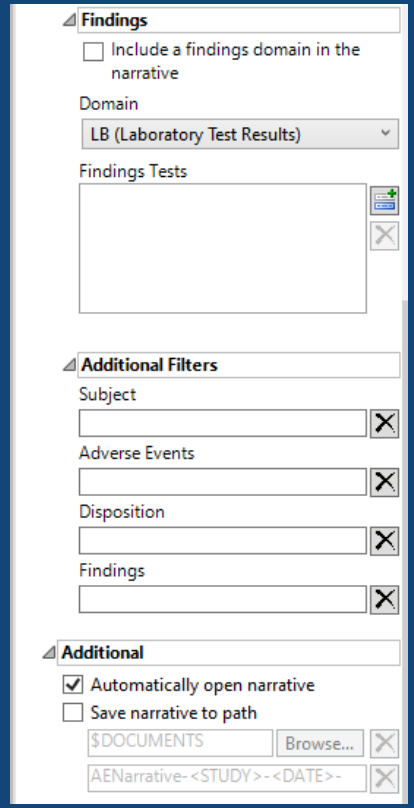
Reviewer's Comment: The bipolar mixed episode may have been due to the cyclical nature of bipolar I disorder.

NDA Latuda 2018
https://www.fda.gov/media/103749/download

AE Narrative Options







Review of Safety

D. Safety Review: 2. Discontinuations Due to AE

Twyneo

NDA 214902 Multi-disciplinary Review and Evaluation
Twyneo (tretinoin and benzoyl peroxide) cream, 0.1/3%

		Twyneo Cream (N = 555), n (%)		Vehicle Cream (N = 277), n (%)	
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**
	dryness				
	Application site erythema	4	0.7%	.	.
	Application site pruritus	4	0.7%	.	.
	Application site discolouration	1	0.2%	.	.
	Application site irritation	1	0.2%	.	.

Source: Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Action Takne with Study Treatment = DRUG WITHDRAWN and Causality = PROBABLY, DEFINITELY.

NDA Twyneo 2020 https://www.fda.gov/media/151645/download

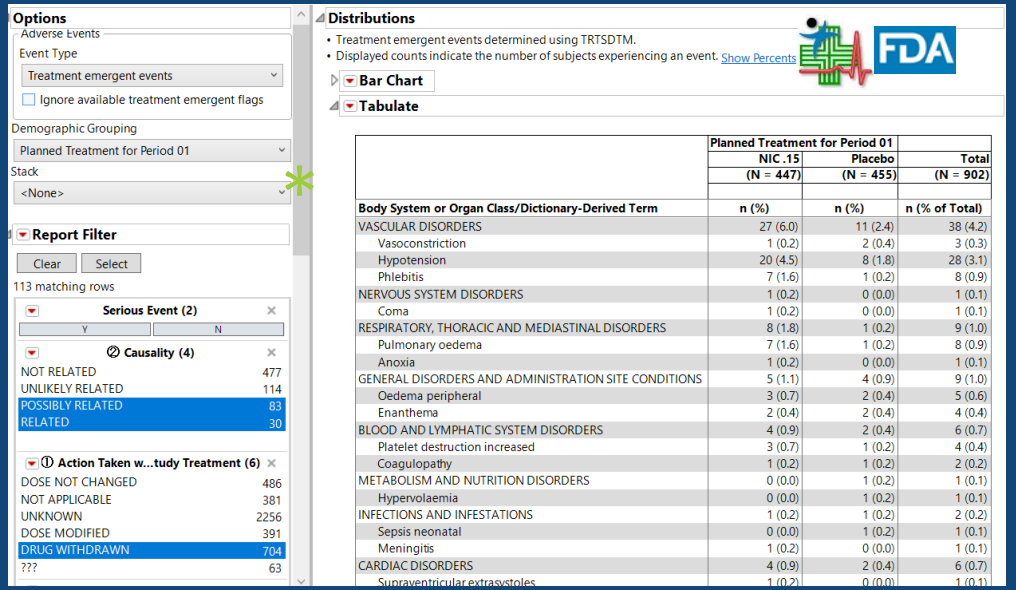
Review of Safety

D. Safety Review: 2. Discontinuations Due to AE

TRTSDTM

AEREL

AEACN



	Planned Treatment for Period 01		
	NIC .15 (N = 447)	Placebo (N = 455)	Total (N = 902)
Body System or Organ Class/Dictionary-Derived Term	n (%)	n (%)	n (% of Total)
VASCULAR DISORDERS	27 (6.0)	11 (2.4)	38 (4.2)
Vasoconstriction	1 (0.2)	2 (0.4)	3 (0.3)
Hypotension	20 (4.5)	8 (1.8)	28 (3.1)
Phlebitis	7 (1.6)	1 (0.2)	8 (0.9)
NERVOUS SYSTEM DISORDERS	1 (0.2)	0 (0.0)	1 (0.1)
Coma	1 (0.2)	0 (0.0)	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8 (1.8)	1 (0.2)	9 (1.0)
Pulmonary oedema	7 (1.6)	1 (0.2)	8 (0.9)
Anoxia	1 (0.2)	0 (0.0)	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (1.1)	4 (0.9)	9 (1.0)
Oedema peripheral	3 (0.7)	2 (0.4)	5 (0.6)
Enanthema	2 (0.4)	2 (0.4)	4 (0.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4 (0.9)	2 (0.4)	6 (0.7)
Platelet destruction increased	3 (0.7)	1 (0.2)	4 (0.4)
Coagulopathy	1 (0.2)	1 (0.2)	2 (0.2)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	1 (0.2)	1 (0.1)
Hypervolaemia	0 (0.0)	1 (0.2)	1 (0.1)
INFECTIONS AND INFESTATIONS	1 (0.2)	1 (0.2)	2 (0.2)
Sepsis neonatal	0 (0.0)	1 (0.2)	1 (0.1)
Meningitis	1 (0.2)	0 (0.0)	1 (0.1)
CARDIAC DISORDERS	4 (0.9)	2 (0.4)	6 (0.7)
Supraventricular extrasystoles	1 (0.2)	0 (0.0)	1 (0.1)

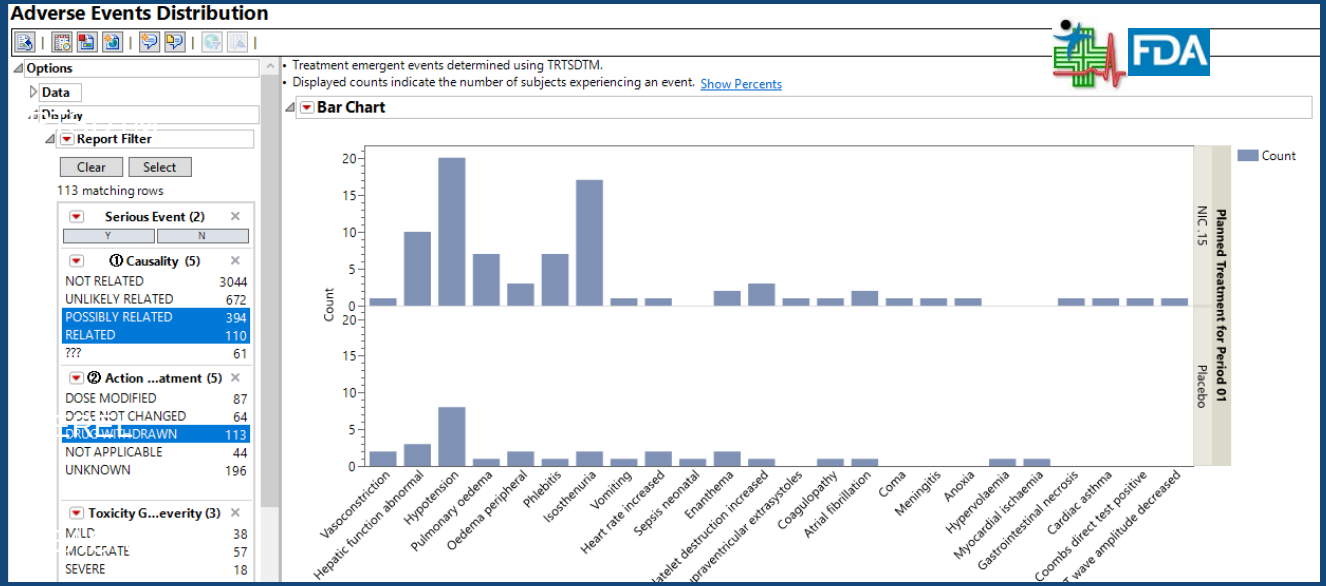
Source: Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Action Takne with Study Treatment = DRUG WITHDRAWN and Causality = PROBABLY, DEFINITELY.

NDA Twyneo 2020 https://www.fda.gov/media/151645/download

CDISC: ADAE/AE, ADSL/DM; JMPC: AE Distribution

Review of Safety

D. Safety Review: 2. Discontinuations Due to AE



Source: Reviewer's JMP Clinical 7.0 Analysis. Study: NDA 214902-ISS. Adverse Events Distribution. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Action Takne with Study Treatment = DRUG WITHDRAWN and Causality = PROBABLY, DEFINITELY.

NDA Twyneo 2020 https://www.fda.gov/media/151645/download

CDISC: ADAE/AE, ADSL/DM; JMPC: AE Distribution

Review of Safety

D. Safety Review: 3. Common TEAEs

Table 25. FMQs with Events in ≥2% of Dasiglucagon Treated Subjects Over Entire Observation Period – Placebo-Controlled Pool

FMQ	0.6 mg Dasiglucagon n=116	Placebo n=53	1 mg GlucaGen n=43	RR*	95% CI
Nausea	66 (56.9%)	2 (3.8%)	23 (53.5%)	15.1	(3.8, 59.3)
Hypoglycemia	29 (25%)	7 (13.2%)	9 (20.9%)	1.9	(0.9, 4)
Vomiting	29 (25%)	1 (1.9%)	9 (20.9%)	13.3	(1.9, 94.7)
Headache	14 (12.1%)	2 (3.8%)	5 (11.6%)	3.2	(0.8, 13.6)
Infections	8 (6.9%)	4 (7.5%)	0 (0%)	0.9	(0.3, 2.9)
Diarrhea	6 (5.2%)	(0%)	1 (2.3%)	N/A	N/A
Injection Site Reactions	4 (3.4%)	2 (3.8%)	3 (7%)	0.9	(0.2, 4.8)

RR= risk ratio (dasiglucagon versus placebo)

Source: Generated by reviewer in JMP with ADSL and ADAE datasets

Zegalogue

VIRTUAL

Advancing Pre-Market Safety Analytics

SEPTEMBER 14, 2022

About this Virtual Meeting:

FDA and the Duke-Margolis Center for Health Policy will host a one-day virtual meeting focused on advancing pre-market safety analytics.

Due to lack of standardization of safety data analysis and visualization, inconsistencies exist in how adverse events are defined, categorized, analyzed, and presented in marketing applications. FDA led the development of two documents to facilitate review of safety data:

1. A standardized approach in grouping preferred terms known as the FDA Medical Queries (FMQ).
2. Standardized methods for visualization of safety data into tables and figures known as the Standard Safety Tables and Figures Integrated Guide (STF-IG).

The agency values feedback from external stakeholders and has made both documents available for public comment through an FDA-created docket.

Meeting Objective:

FDA will present its work and perspective on pre-market review of safety data. The FMQ and STF-IG will serve as a launch point for broader conversations on best practices and innovative approaches for advancing pre-market safety signal analytics.

CR Zegalogue 2020
https://www.fda.gov/media/147791/download

https://www.fda.gov/drugs/news-events-human-drugs/advancing-pre-market-safety-analytics-09142022

CDISC: ADAE/AE, ADSL/DM; JMPC: AE Distribution

Review of Safety

D. Safety Review: 3. Common TEAEs

Adhansia XR

Clinical Review
Nancy Dickinson, PharmD.
NDA 212038
Adhansia XR (methylphenidate HCL)

Table 14: TEAEs at least 2% and Greater than Placebo for all Treatment Arms

Study 063-010 N=375	PRC-063 25mg N=77		PRC-063 45mg N=73		PRC-063 70mg N=73		PRC-063 100mg N=100		PRC-063 all doses N=297		Placebo N=78	
Dictionary-Derived Term	Count	%	Count	%	Count	%	Count	%	Count	%	Count	%
Insomnia	13	16.9%	8	11.0%	12	16.4%	14	18.9%	47	12.5%	3	3.8%
Initial insomnia	3	3.9%	6	8.2%	4	5.5%	5	6.8%	18	4.8%	1	1.3%
Dry mouth	6	7.8%	6	8.2%	5	6.8%	10	13.5%	27	7.2%	3	3.8%
Nausea	3	3.9%	4	5.5%	3	4.1%	8	10.8%	18	4.8%	2	2.6%
Diarrhea	1	1.3%	2	2.7%	5	6.8%	4	5.4%	12	3.2%	1	1.3%
Decreased appetite	3	3.9%	5	6.8%	11	15.1%	14	18.9%	33	8.8%	2	2.6%
Feeling jittery	1	1.3%	2	2.7%	6	8.2%	3	4.1%	12	3.2%	1	1.3%
Weight decreased	2	2.6%	3	4.1%	2	2.7%	4	5.4%	11	2.9%	1	1.3%
Upper respiratory tract infection	.	.	3	4.1%	2	2.7%	2	2.7%	7	1.9%	1	1.3%

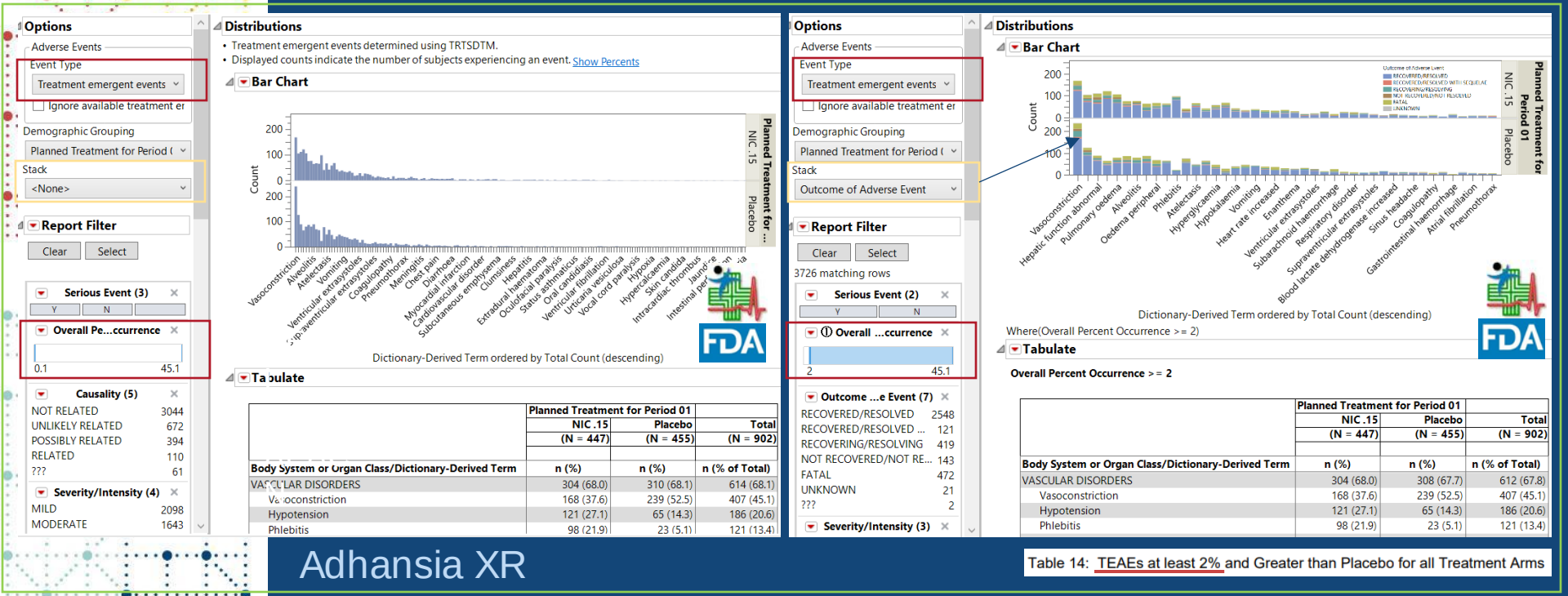
[Source: Reviewer created using JMP Clinical 6.0]

CR Adhansia XR 2019 https://www.fda.gov/media/124188/download

CDISC: ADAE/AE, ADSL/DM; JMPC: AE Distribution

Review of Safety

D. Safety Review: 3. Common TEAEs



Adhansia XR

Table 14: TEAEs at least 2% and Greater than Placebo for all Treatment Arms

CR Adhansia XR 2019 https://www.fda.gov/media/124188/download

CDISC: ADAE/AE, ADSL/DM; JMPC: AE Distribution

Review of Safety

D. Safety Review: 4. Significant AE

NDA/BLA Multi-disciplinary Review and Evaluation BLA 761055 S031
Dupixent (dupilumab)

Significant Adverse Events

Adverse events of special interest for Study EFC14153 that occurred more often in subjects on dupilumab compared to placebo are summarized in Table 22.

Table 24 AESI > Placebo (Safety Population)

Preferred Term	Placebo N=134 n (%)	Dupilumab 100 mg SC Q2W N=91 n (%)	Dupilumab 200mg SC Q2W N=180 n (%)	Dupilumab N=271 n (%)
Injection site reaction	18(13)	12(13)	36(20)	48(18)
Serious injection site reaction	0	0	2(1)	2(1)
Eosinophilia	1(1)	9(10)	9(5)	18(7)
Parasitic infection	1(1)	5(5)	2(1)	7(3)

AESI=adverse event of special interest ; Q2W= once every 2 weeks; SAE= serious adverse event; SC= subcutaneous
Source: Reviewer generated table in JMP

NDA Dupixent 2021
https://www.fda.gov/media/155349/download

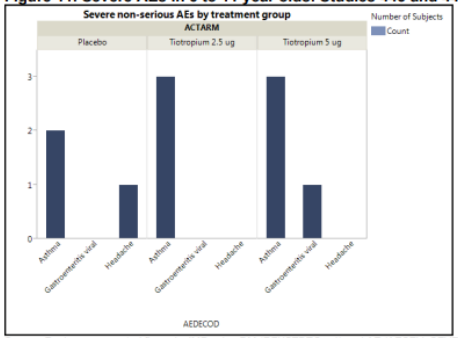
Clinical Review
Stacy Chin, MD
NDA 21-936 / S-007
Spiriva Respimat (tiotropium inhalation solution)

family emergency/death. In Study 446, dropouts due to an AE only occurred in the placebo group. Premature discontinuations coded as "other" were also due to moving away/changes in social situation.

7.3.4 Significant Adverse Events

Additional significant AEs that were categorized as severe and not already discussed in Sections 7.3.2 and 7.3.3 are shown in the figure below. The y-axis indicates number of subjects within each treatment arm; the x-axis indicates the severe, nonserious AE by MedDRA Preferred Term. Asthma was the most common, but the overall number of events was low and similar between treatment groups.

Figure 11. Severe AEs in 6 to 11 year olds: Studies 445 and 446

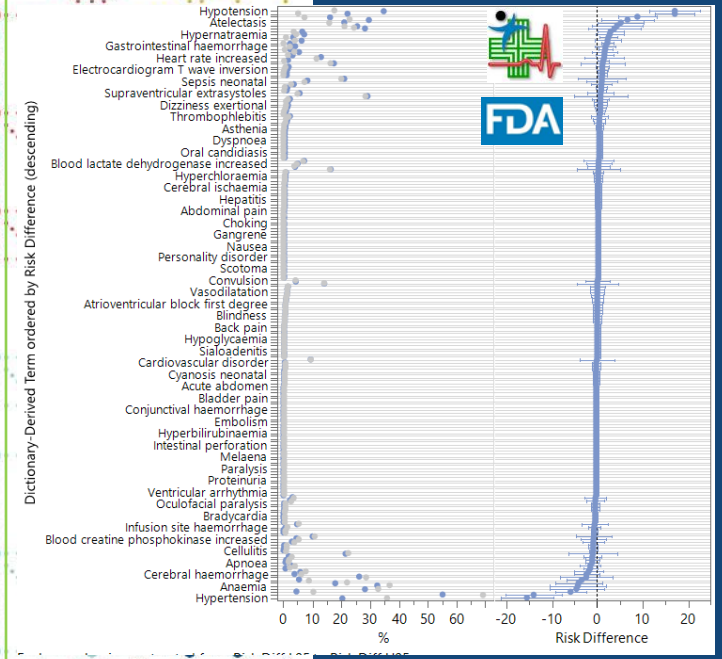


Source: Reviewer generated figure in JMP using DM (RFXSTDTC ≥ 1) and AE (AESEV=SEVERE, AESTDY ≥ 1, AESER=N) datasets

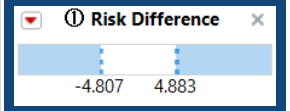
CR Spiriva Respimat. 2017
https://www.fda.gov/media/103941/download

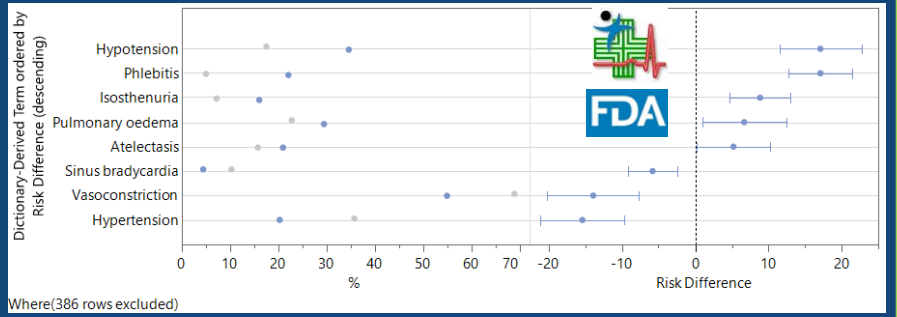
Review of Safety

D. Safety Review: 4. Significant AE



Dupixent





Dictionary-Derived Term	Planned Treatment for Period 01 NIC .15 (N = 447) n (%)	Placebo (N = 455) n (%)	Risk Difference for NIC .15 over Placebo Risk Difference (Risk Diff L95 , Risk Diff U95)
Atelectasis	94 (21.0)	72 (15.8)	5.2 (0.2 , 10.3)
Hypertension	91 (20.4)	163 (35.8)	-15.5 (-21.2 , -9.7)
Hypotension	155 (34.7)	80 (17.6)	17.1 (11.5 , 22.7)
Isosthenuria	72 (16.1)	33 (7.3)	8.9 (4.7 , 13.0)
Phlebitis	99 (22.1)	23 (5.1)	17.1 (12.7 , 21.4)
Pulmonary oedema	132 (29.5)	104 (22.9)	6.7 (0.9 , 12.4)
Sinus bradycardia	20 (4.5)	47 (10.3)	-5.9 (-9.2 , -2.5)
Vasoconstriction	246 (55.0)	314 (69.0)	-14.0 (-20.2 , -7.7)

NDA Dupixent 2021 https://www.fda.gov/media/155349/download

CDISC: ADAE/AE, ADSL/DM; JMPC: AE Risk Report; MedDRA

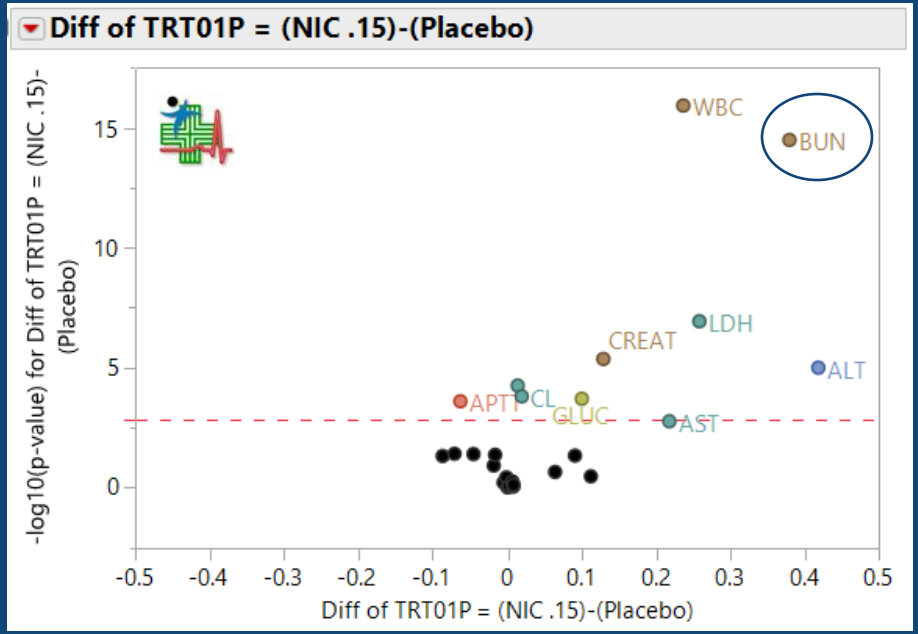
Review of Safety

D. Safety Review: 5a. Laboratory Findings

Comparison of Differences in Laboratory Measurement Values between Groups

Volcano Plot

BUN: Blood Urea Nitrogen

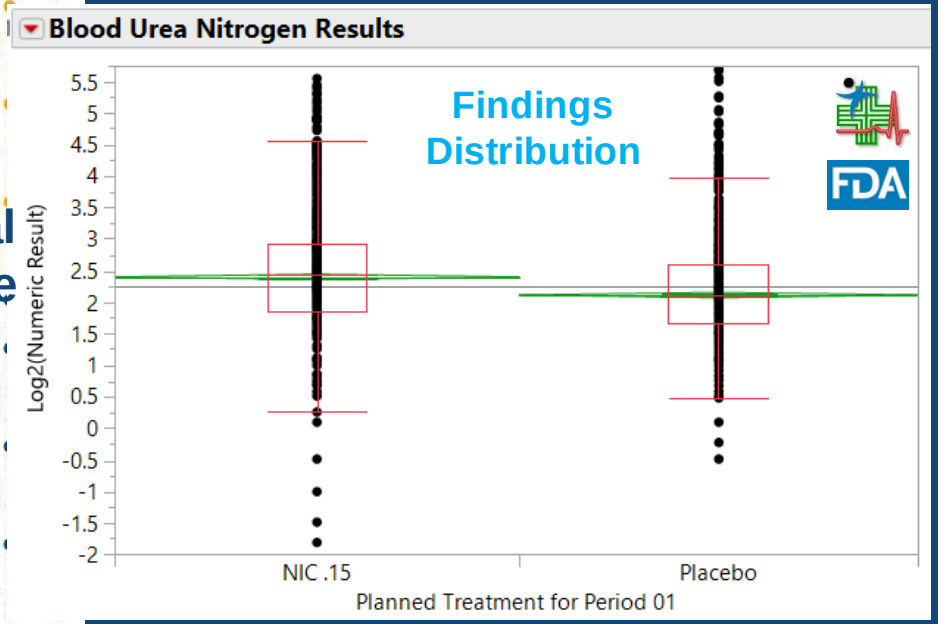


CDISC: ADLB/LB, ADSL/DM; JMPC: Finding ANOVA

Review of Safety

D. Safety Review: 5b. Laboratory Findings

Statistical difference for BUN



Oneway Anova

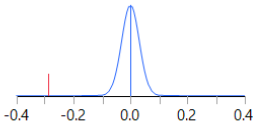
Summary of Fit

Rsquare	0.02816
Adj Rsquare	0.027839
Root Mean Square Error	0.845846
Mean of Response	2.26066
Observations (or Sum Wgts)	3032

Pooled t Test

Placebo-NIC .15
Assuming equal variances

Difference	-0.28787	t Ratio	-9.36994
Std Err Dif	0.03072	DF	3030
Upper CL Dif	-0.22763	Prob > |t|	<.0001*
Lower CL Dif	-0.34811	Prob > t	1.0000
Confidence	0.95	Prob < t	<.0001*



Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Planned Treatment for Period 01	1	62.8139	62.8139	87.7957	<.0001*
Error	3030	2167.8289	0.7155		
C. Total	3031	2230.6428			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
NIC .15	1526	2.40365	0.02165	2.3612	2.4461
Placebo	1506	2.11577	0.02180	2.0730	2.1585

Std Error uses a pooled estimate of error variance

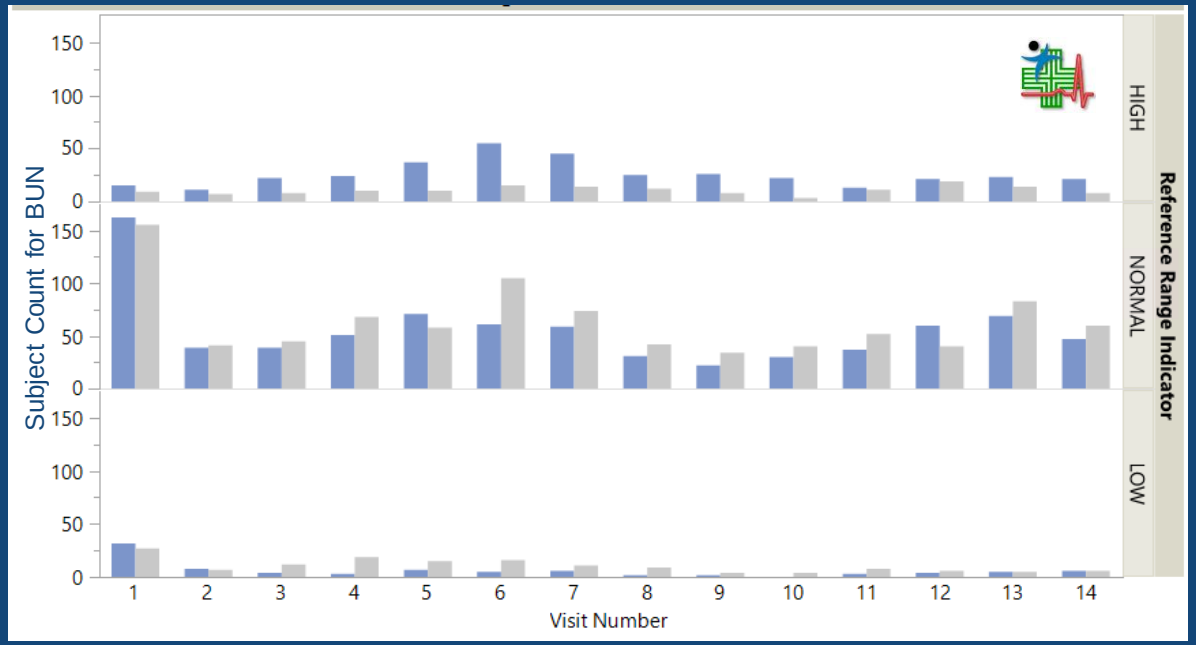
CR Repatha 2021 https://www.fda.gov/media/154402/download

CDISC: ADLB/LB, ADSL/DM; JMPC: Finding Distribution

Review of Safety

D. Safety Review: 5c. Laboratory Findings

Compare Treatment groups for Reference Range Indicator per Visit

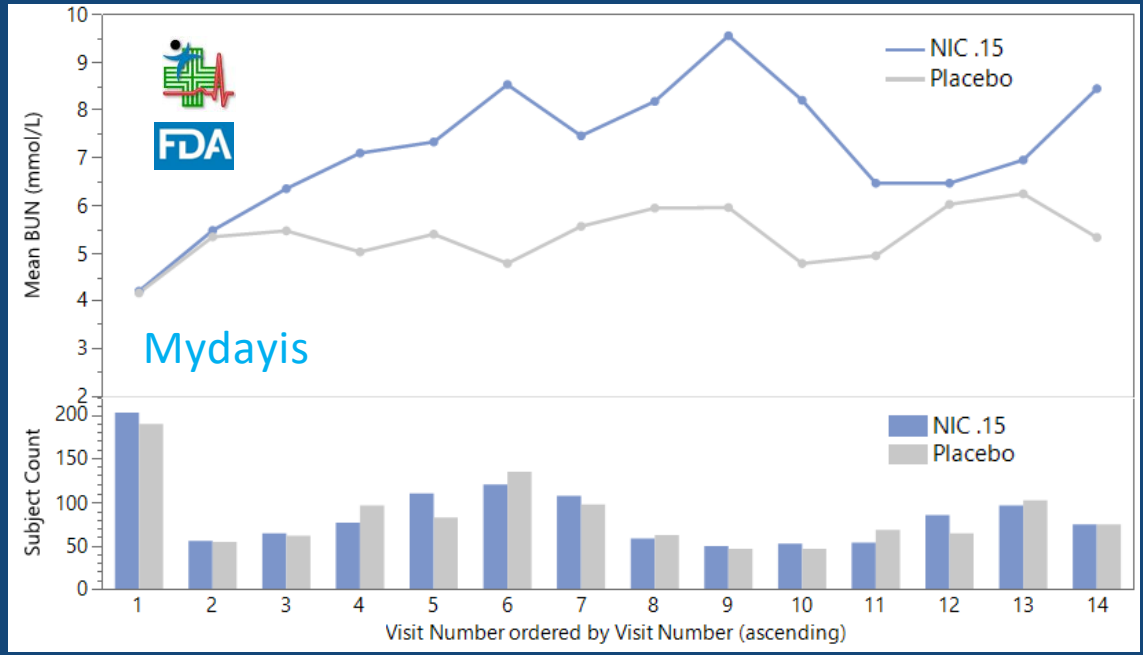


CDISC: ADLB/LB, ADSL/DM; JMPC: Finding Distribution

Review of Safety

D. Safety Review: 5d. Laboratory Findings

Compare Mean Measurement across Treatment Arms per Visit



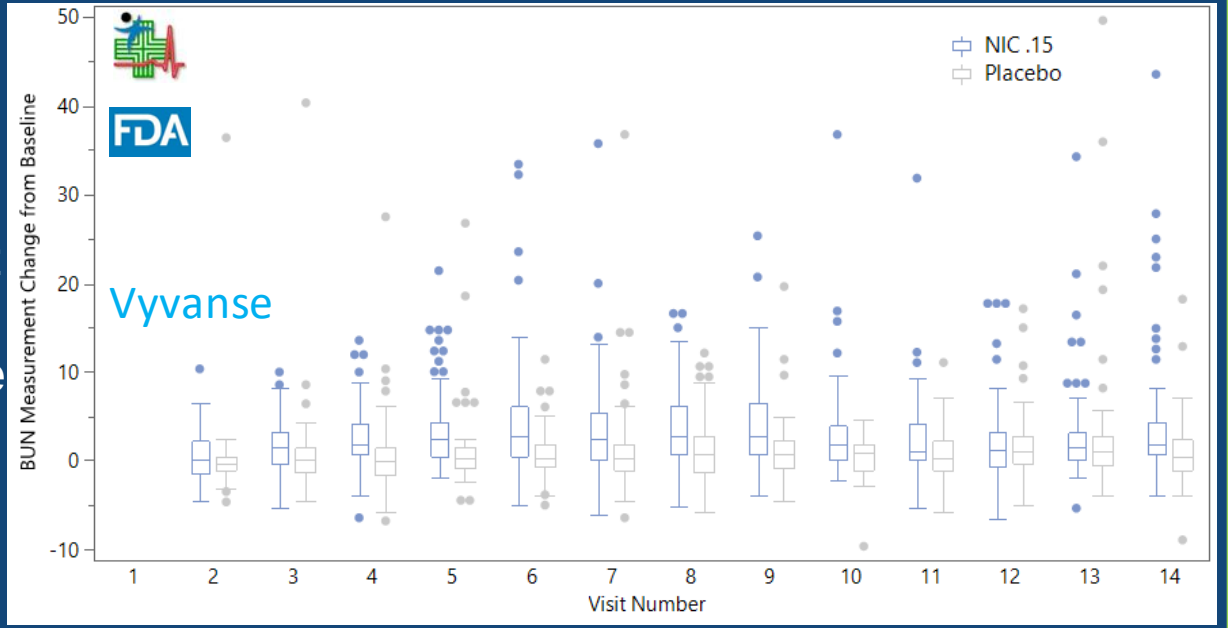
NDA Mydayis 2019 https://www.fda.gov/media/142063/download

CDISC: ADLB/LB, ADSL/DM; JMPC: Findings Time Trends

Review of Safety

D. Safety Review: 5e. Laboratory Findings

Compare Mean Measurement Changes from Baseline (V1) per Visit



NDA Vyvanse 2021 https://www.fda.gov/media/151943/download

CDISC: ADLB/LB, ADSL/DM; JMPC: Findings Box Plots

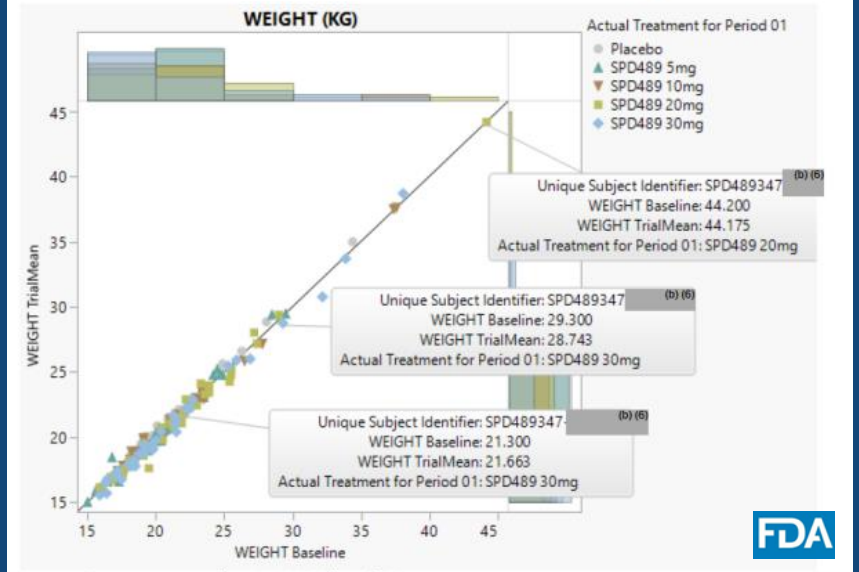
Review of Safety

D. Safety Review: 5f. Laboratory Findings

Zegalogue

Compare Mean Weights with Baseline Weight

Figure 4: Shift Plot of Patients Baseline and Mean Trial Weights (Study 347)



Source: Reviewer created using JMP Clinical 8.0

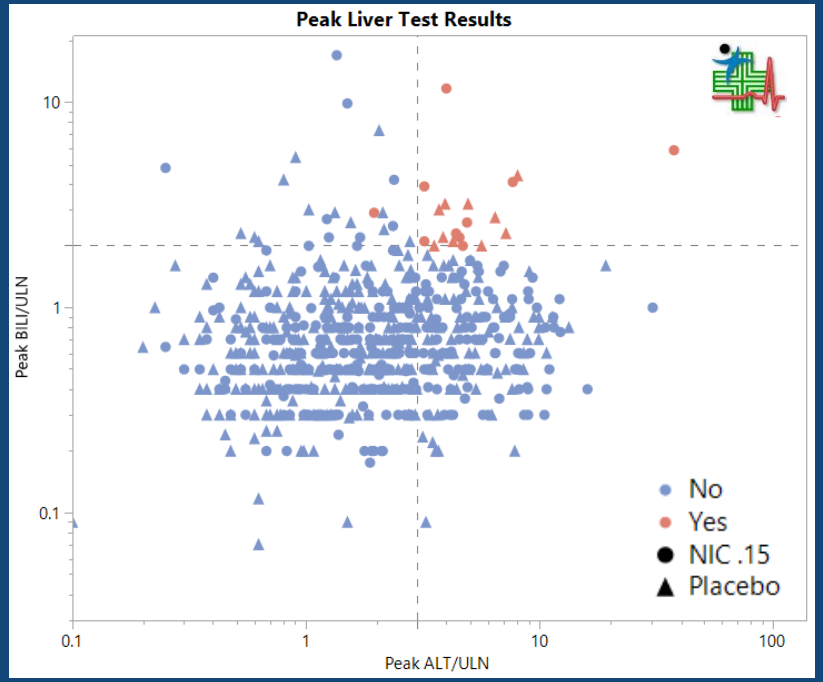
CR Zegalogue 2020 https://www.fda.gov/media/147791/download

CDISC: ADLB/LB, ADSL/DM; JMPC: Findings Shift Plot

Review of Safety

D. Safety Review: 5g. Laboratory Findings

Assess Drug-Induced Liver Injury



CDISC: ADLB/LB, ADSL/DM; JMPC: Hy's Law Screening

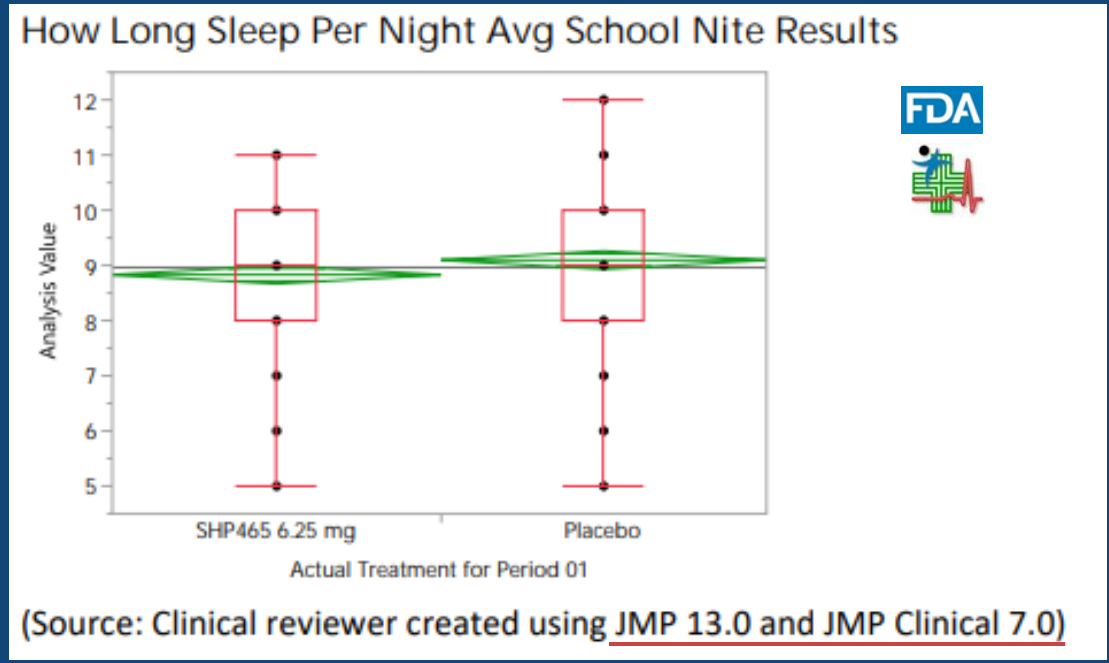
Review of Safety

E. Analysis of Submission – Specific Safety Issues

Mydayis

Mydayis was concerned about drug-induced Insomnia

Compare between groups for time to falling asleep and sleep length



(Source: Clinical reviewer created using JMP 13.0 and JMP Clinical 7.0)

NDA Mydayis 2019 https://www.fda.gov/media/142063/download

CDISC: ADLB/LB, ADSL/DM; JMPC: Finding Distribution

Review of Safety

F. Safety Analyses by Demographic Subgroups

Mydayis

Compare Arazlo Adverse Events Count and Percentage for Different Age Groups between Treatment and Placebo Groups

Table 36: Treatment-Emergent Adverse Reactions Occurring in ≥2 Subjects in Any Subgroup Treated With Arazlo Lotion or Vehicle Lotion, by Age Group (ISS, Safety Analysis Set)

	Age 9 to <12 Years (N=26)		Age ≥12 Years (N=1542)	
Preferred Term	**Arazlo Lotion, n=14 n (%)**	**Vehicle Lotion, n=12 n (%)**	**Arazlo Lotion, n=764 n (%)**	**Vehicle Lotion, n=778 n (%)**
Application site pain	1 (7.1)	0	40 (5.2)	2 (0.3)
Application site dryness	0	0	28 (3.7)	1 (0.1)
Combined PTs for application site: rash/dermatitis/erythema/hypersensitivity	1 (7.1)	0	24 (3.1)	0
Application site exfoliation	0	0	16 (2.1)	0
Application site pruritus	2 (14.3)	0	7 (0.9)	0
Application site irritation	0	0	6 (0.8)	0
Application site acne	0	0	1	2 (0.3)

Source: Adapted from ISS (Table 14.3.1.2.3.2. AH1) and Reviewer's JMP Clinical 7 Analysis. Adverse Events Distribution Report Results. Analysis population: Safety. Event Type: Treatment-emergent events. Additional filter to include Adverse Events: AEREL="RELATED." Treatment emergence determined using AE.AETRTEM. MedDRA version 20.0.
Abbreviations: ISS=integrated summary of safety, PT=preferred term

NDA Arazlo 2019 https://www.fda.gov/media/142063/download

CDISC: ADAE/AE, ADSL/DM; JMPC: AE Distribution

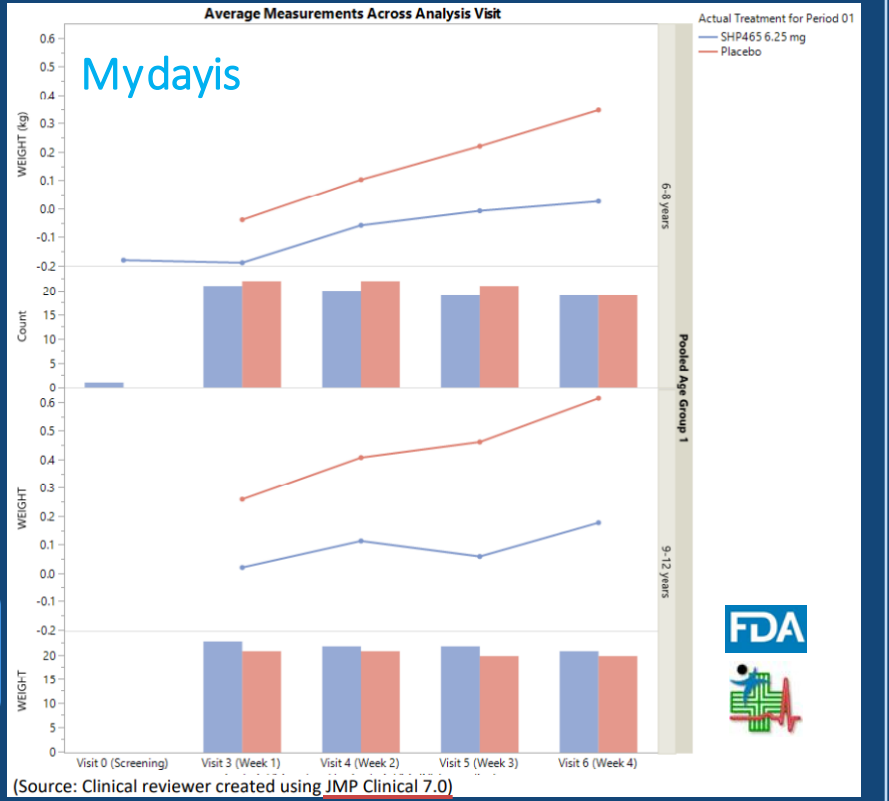
Review of Safety

F. Safety Analyses by Demographic Subgroups

Mydayis Affects on Weight and Height (Not Shown) Changes by Visits for Different Age Groups between Treatment and Placebo group

NDA Mydayis 2019
https://www.fda.gov/media/142063/download

CDISC: ADLB/LB, ADSL/DM;
JMPC: Findings Time Trends



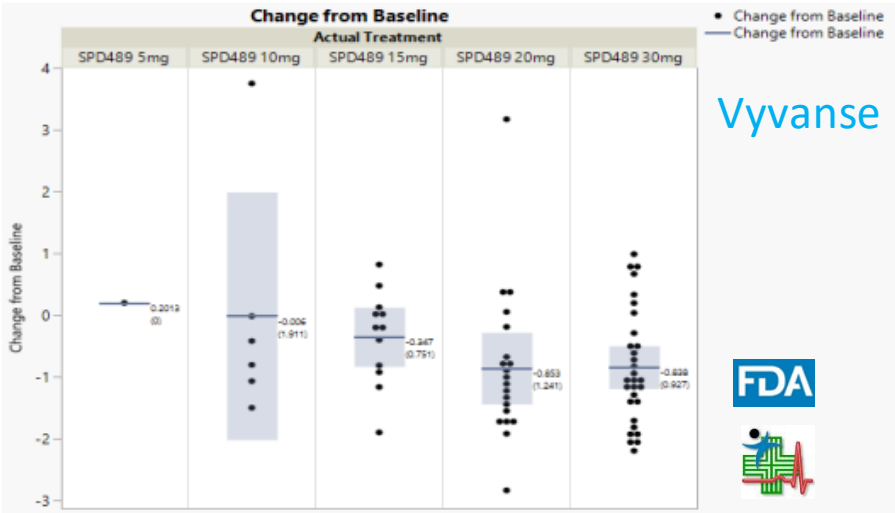
(Source: Clinical reviewer created using JMP Clinical 7.0)

Review of Safety

F. Specific Safety Studies/Clinical Trials and Additional Safety

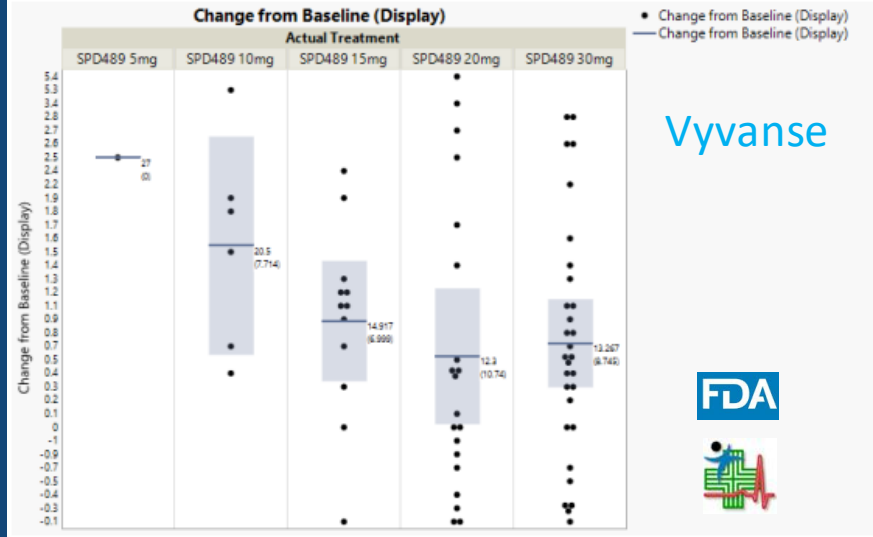
Changes in Weight and BWI According to Drug Dose to Address Concerns about the Effect of Vyvanse

Figure 7: Mean (SD) Change in BMI from Baseline to Week 52/ET (Study 348)



Source: Reviewer created using JMP Clinical 8.0.

Figure 8: Mean (SD) Change is Weight (kg) from Baseline to Week 52/ET (Study 348)



Source: Reviewer created using JMP Clinical 8.0.

NDA Vyvanse 2021 https://www.fda.gov/media/151943/download

CDISC: ADLB/LB, ADSL/DM; JMPC: Findings Box Plots

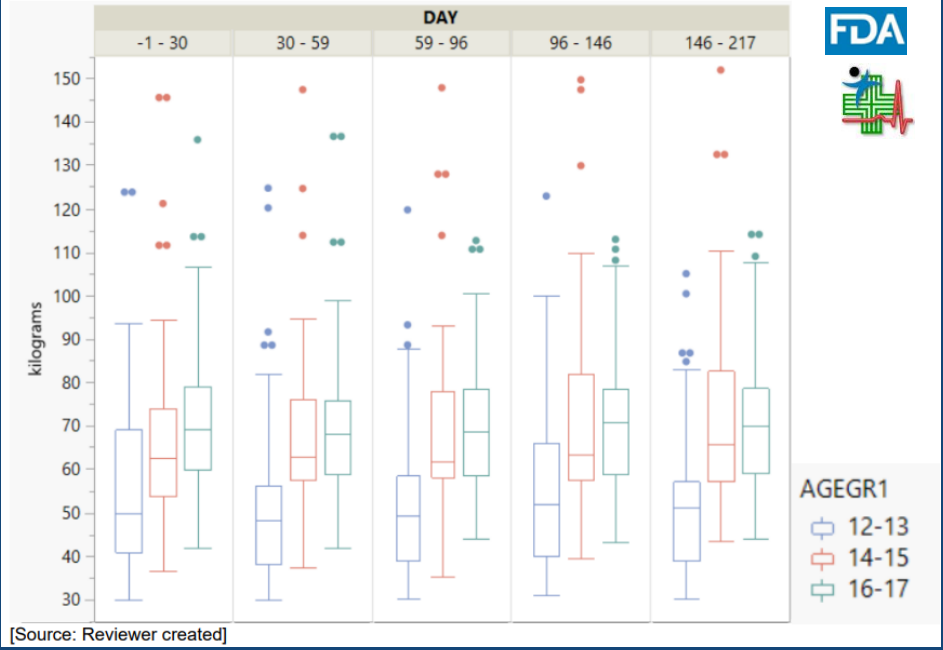
Review of Safety

F. Specific Safety Studies/Clinical Trials and Additional Safety

Adhansia XR

Average Weight by Age Group Over Time Address Concerns about the Effect of Adhansia XR

Figure 8: Average Weight by Age Group Over Time



[Source: Reviewer created]

CR Adhansia XR 2019https://www.fda.gov/media/124188/download

CDISC: ADLB/LB, ADSL/DM; JMPC: Findings Box Plots

Review of Safety

G. Verify Submitted Results for Demographic and Enrollment

Table 13. Demographic and Baseline Physical Characteristics in Study 20140108

Characteristic	ABP 710 (N=49)	EU-Remicade (N=49)	US-Remicade (N=50)
Sex [n (%)]			
Female	25 (51.0)	32 (65.3)	25 (50.0)
Male	24 (49.0)	17 (34.7)	25 (50.0)
Race [n (%)]			
White	35 (71.4)	34 (69.4)	34 (68.0)
Black or African American	0 (0.0)	1 (2.0)	0 (0.0)
Asian	12 (24.5)	13 (26.5)	13 (26.0)
Hawaiian or other Pacific Islander	1 (2.0)	0 (0.0)	0 (0.0)
Ethnicity [n (%)]			
Hispanic or Latino	4 (8.2)	2 (4.1)	1 (2.0)
Not Hispanic or Latino	45 (91.8)	47 (95.9)	49 (98.0)
Age (years)			
Mean (SD)	27.4 (6.0)	26.3 (5.7)	25.8 (5.8)
Median	28.0	25.0	24.0
Min, Max	18, 44	18, 43	18, 45
Age group [n (%)]			
< 65 years	49 (100)	49 (100)	50 (100)
≥ 65 years	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)			
Mean (SD)	69.0 (13.8)	64.6 (12.4)	71.2 (12.3)
Median	68.5	62.5	69.6
Min, Max	44.9, 154.0	44.8, 139.0	44.8, 139.0
Height (cm)			
Mean (SD)	171.8 (9.3)	167.3 (11.0)	171.7 (8.3)
Median	172.0	166.0	171.0
Min, Max	150.0, 192.0	150.0, 192.0	[illegible]
BMI (kg/m^2)			
Mean (SD)	23.2 (2.98)	22.9 (2.48)	[illegible]
Median	22.7	22.4	[illegible]
Min, Max	18.8, 29.6	18.6, 29.0	[illegible]

Source: Study 20140108 CSR, Table 10.4; clinical reviewer verified using JMP and ADSL dataset by TRT01A.

Avsola

Table 14: Enrollment by Country

Country	ABP 710 (N=279)	US-Remicade (N=279)	Total (N=558)
Australia	5 (1.8%)	4 (1.4%)	9 (1.6%)
Bulgaria	14 (5.0%)	11 (3.9%)	25 (4.5%)
Canada	2 (0.7%)	1 (0.4%)	3 (0.5%)
Czech Republic	52 (18.6%)	49 (17.6%)	101 (18.1%)
Germany	15 (5.4%)	11 (3.9%)	26 (4.7%)
Hungary	7 (2.5%)	14 (5.0%)	21 (3.8%)
Poland	125 (44.8%)	133 (47.7%)	258 (46.2%)
Spain	7 (2.5%)	4 (1.4%)	11 (2.0%)
United States	52 (18.6%)	52 (18.6%)	104 (18.6%)

Source: Study 20140111 CSR, Table 14-1.2.1; clinical reviewer verified using JMP and ADSL dataset by TRT01A.

BMDR Avsola 2018 https://www.fda.gov/media/134460/download

Review of Safety

G. Verify Submitted Results for Common Adverse Events

Quzyttir

Table 30. Study ETTAU-03 Common Adverse Events

	Diphenhydramine Injection N=135 n (%)	Cetirizine Injection N=127 n (%)	All Subjects N=262 n (%)
No. with any adverse event	24 (18%)	7 (6%)	31 (12%)
		No. Adverse Events	
Cardiac disorders			
Bradycardia	1 (1%)	0	
Gastrointestinal disorders			
Dyspepsia	0	1 (1%)	
Nausea	4 (3%)	0	
Vomiting	1 (1%)	0	

	Diphenhydramine Injection N=135 n (%)	Cetirizine Injection N=127 n (%)	All Subjects N=262 n (%)
General disorders & administration site conditions			
Feeling hot	0	1(1%)	1 (<1%)
Injection site pain	1 (1%)	0	1 (<1%)
Pyrexia	2 (2%)	0	2 (1%)
Immune system disorders			
Anaphylactic reaction	1 (1%)	0	1 (<1%)
Nervous system disorders			
Burning sensation	2 (2%)	0	2 (1%)
Dizziness	6 (4%)	0	6 (2%)
Dysgeusia	1 (1%)	1 (1%)	2 (1%)
Headache	1 (1%)	1 (1%)	2 (1%)
Paresthesia	0	1 (1%)	1 (<1%)
Presyncope	0	1 (1%)	1 (<1%)
Skin and subcutaneous tissue disorders			
Erythema	1 (1%)	0	1 (<1%)
Hyperhidrosis	0	1 (1%)	1 (<1%)
Pruritus	1 (1%)	0	1 (<1%)
Urticaria	2 (2%)	0	2 (1%)

Source: CSR ETTAU-03 Table 14.3.1 pg. 54 and Table 14.3.2 pg. 55 verified by Reviewer in JMP

NDA Quzyttir 2018 https://www.fda.gov/media/133034/download

FMQ and Standard Safety Tables and Figures

Medical Queries

- FMQ FDA
- AFMQ FDA
- SMQ MedDRA
- CMQ

FDA Medical Query (FMQ) and MedDRA (SMQ)

FMQ

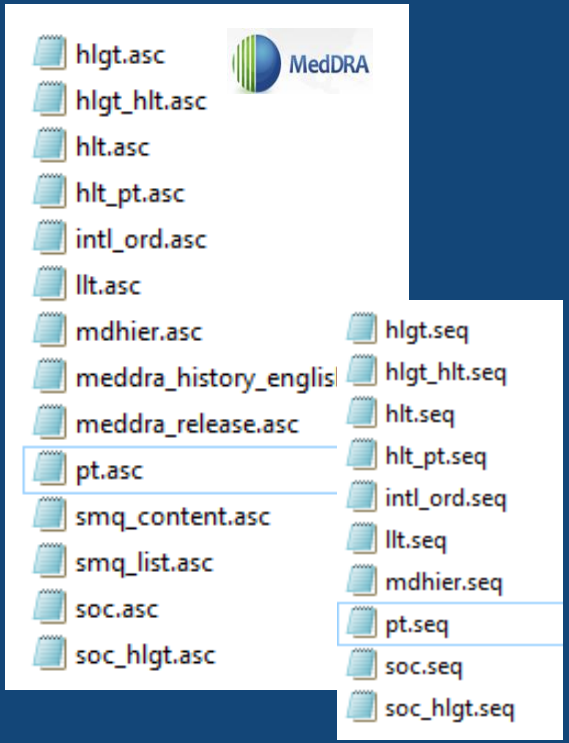
Differences

Format
Terminology
Grouping

English Only

Multiple Languages

SMQ

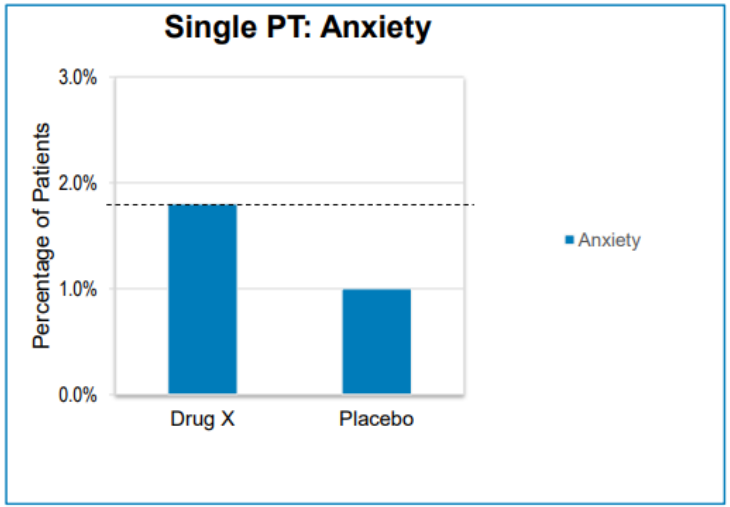


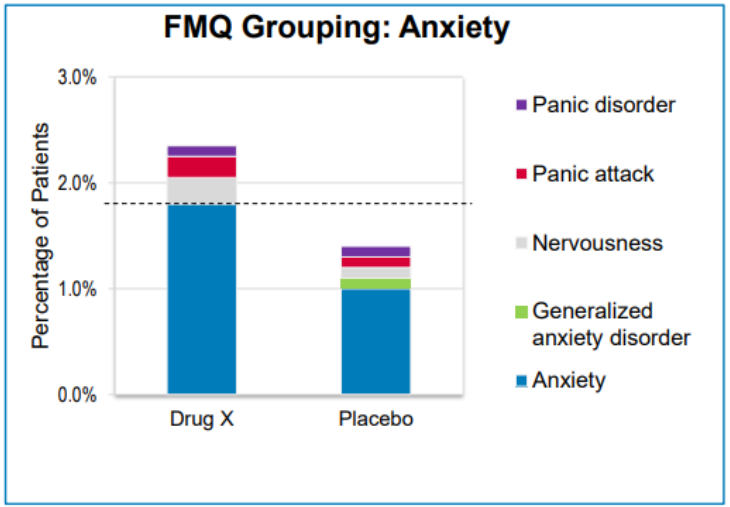
https://healthpolicy.duke.edu/sites/default/files/2022-09/Advancing%20Premarket%20Safety%20Analytics%20Final%20Slide%20Deck.pdf
https://dow nloads.regulations.gov/FDA-2022-N-1961-0001/attachment_1.xlsm

FDA Medical Query (FMQ)

Single PT Analysis vs. FMQ Grouping

- Using a 2% cut-off for an AE analysis, “Anxiety” doesn’t make the cut, but group these PTs, and a signal emerges at the 2% cut-off (no patient counted twice).



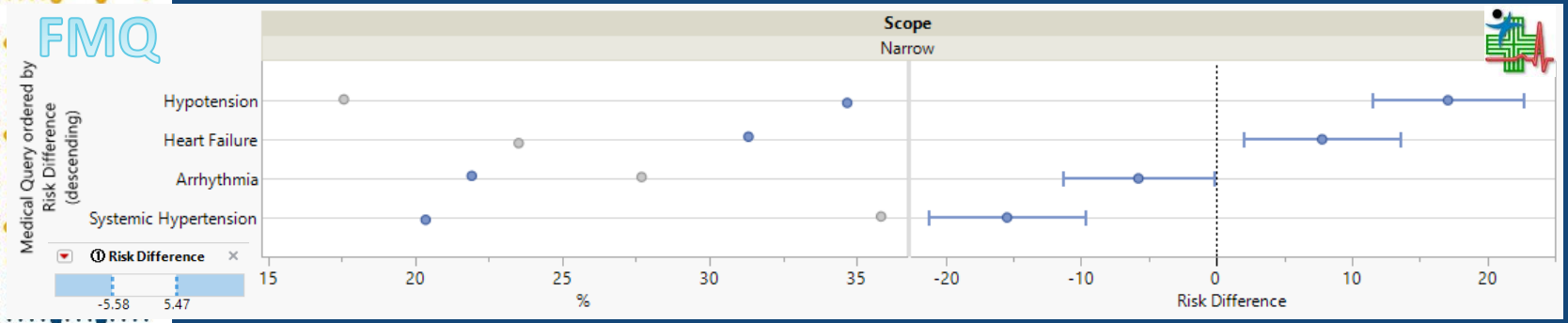


https://healthpolicy.duke.edu/sites/default/files/2022-09/Advancing%20Premarket%20Safety%20Analytics%20Final%20Slide%20Deck.pdf

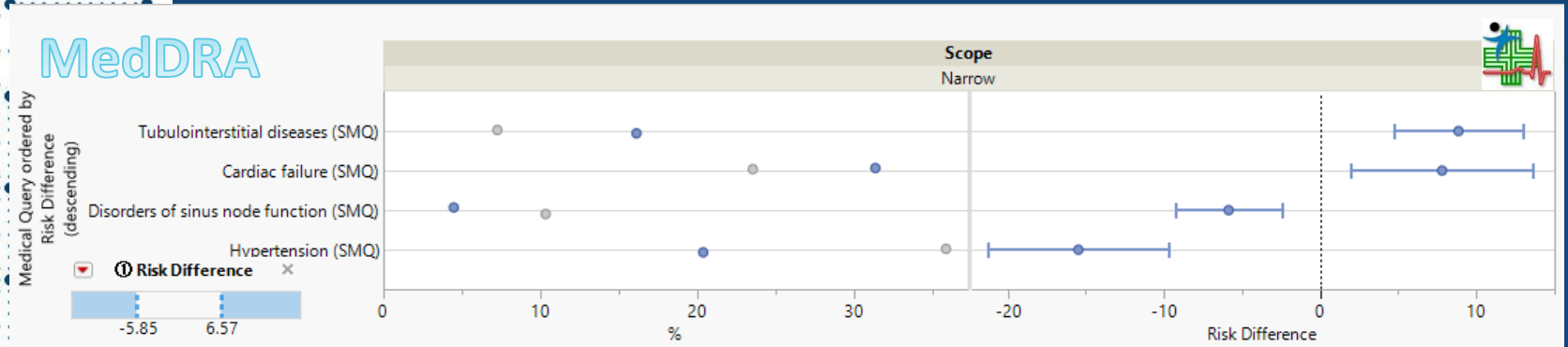
Nicardipine (Calcium Channel Blocker)

Treatment vs Placebo

FMQ

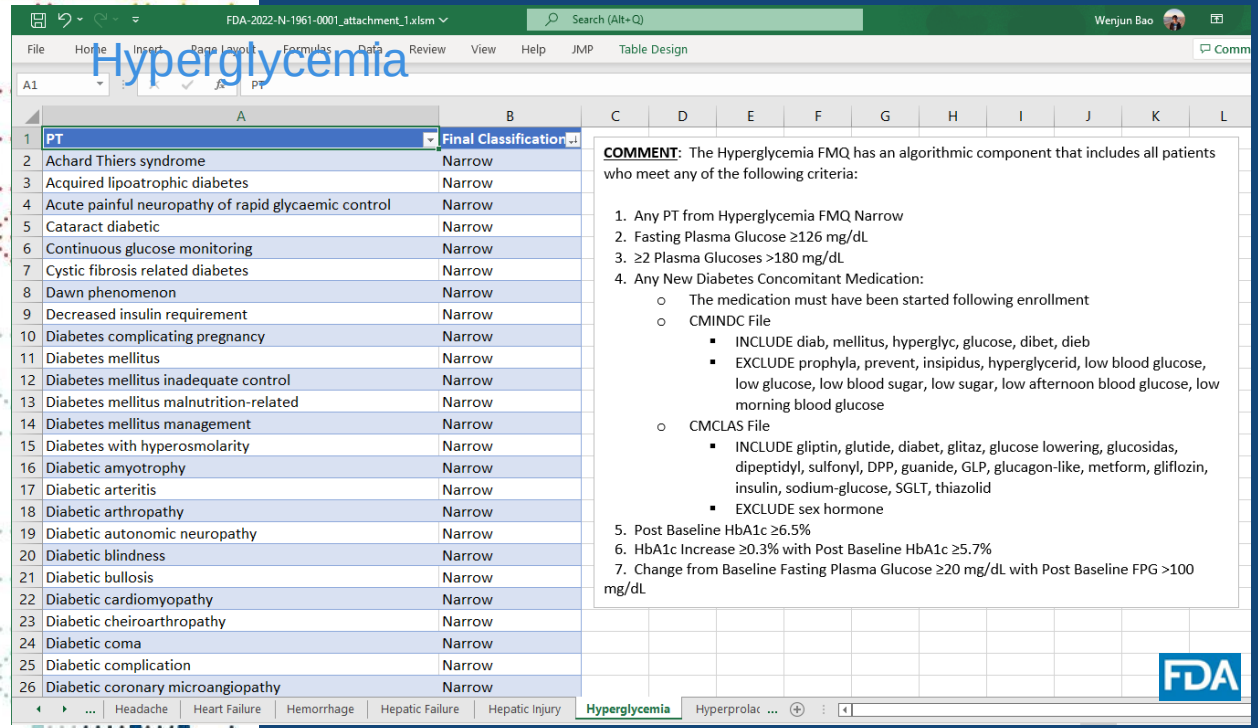


MedDRA



Algorithmic FDA Medical Query (AFMQ)

AE CM DM LB MH



	A	B
1	PT	Final Classification
2	Achard Thiers syndrome	Narrow
3	Acquired lipoatrophic diabetes	Narrow
4	Acute painful neuropathy of rapid glycaemic control	Narrow
5	Cataract diabetic	Narrow
6	Continuous glucose monitoring	Narrow
7	Cystic fibrosis related diabetes	Narrow
8	Dawn phenomenon	Narrow
9	Decreased insulin requirement	Narrow
10	Diabetes complicating pregnancy	Narrow
11	Diabetes mellitus	Narrow
12	Diabetes mellitus inadequate control	Narrow
13	Diabetes mellitus malnutrition-related	Narrow
14	Diabetes mellitus management	Narrow
15	Diabetes with hyperosmolarity	Narrow
16	Diabetic amyotrophy	Narrow
17	Diabetic arteritis	Narrow
18	Diabetic arthropathy	Narrow
19	Diabetic autonomic neuropathy	Narrow
20	Diabetic blindness	Narrow
21	Diabetic bullosis	Narrow
22	Diabetic cardiomyopathy	Narrow
23	Diabetic cheiroarthropathy	Narrow
24	Diabetic coma	Narrow
25	Diabetic complication	Narrow
26	Diabetic coronary microangiopathy	Narrow

All

Hyperglycemia
Hypoglycemia
Hypersensitivity
Rhabdomyolysis

Females

Abnormal Uterine Bleeding
Amenorrhea
Bacterial Vaginosis
Decreased Menstrual Bleeding
Excessive Menstrual Bleeding

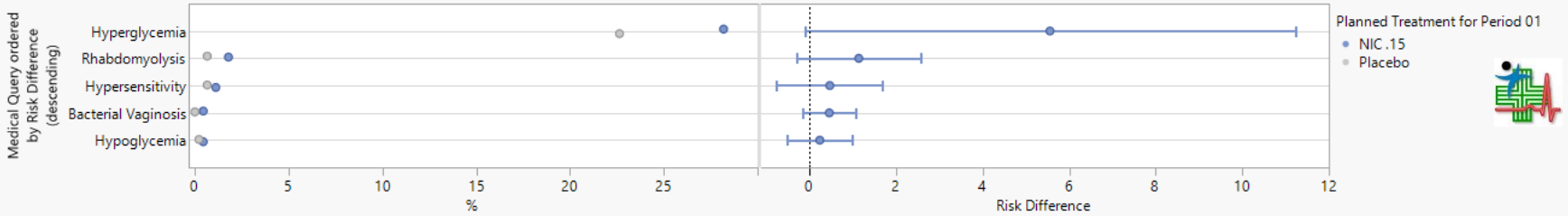
Males

Erectile Dysfunction
Gynecomastia

https://www.fda.gov/media/164639/download

Algorithmic FDA Medical Query (AFMQ)

Risk Plot



Each error bar is constructed from Risk Diff L95 to Risk Diff U95.

Algorithmic Medical Queries

Medical Query	NIC .15 (N = 447)	Placebo (N = 455)	Risk Difference for NIC .15 over Placebo
Hyperglycemia	126 (28.2)	103 (22.6)	5.6 (-0.1, 11.2)
Any PT from Hyperglycemia FMQ Narrow	114 (25.5)	96 (21.1)	4.4 (-1.1, 9.9)
≥2 Plasma Glucoses >180 mg/dL	42 (9.4)	28 (6.2)	3.2 (-0.2, 6.7)
Rhabdomyolysis	8 (1.8)	3 (0.7)	1.1 (-0.3, 2.6)
CPK >5 x ULN AND NO (CPK-MB/CPK >0.05 with start date within 3 days OR CPK >ULN at baseline)	8 (1.8)	3 (0.7)	1.1 (-0.3, 2.6)
Hypersensitivity	5 (1.1)	3 (0.7)	0.5 (-0.8, 1.7)
Non-algorithmic Narrow PTs	5 (1.1)	3 (0.7)	0.5 (-0.8, 1.7)
Bacterial Vaginosis	2 (0.4)	0 (0.0)	0.4 (-0.2, 1.1)
Biological females only	2 (0.4)	0 (0.0)	0.4 (-0.2, 1.1)
Hypoglycemia	2 (0.4)	1 (0.2)	0.2 (-0.5, 1.0)
Plasma Glucose <54 mg/dL	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Any Hypoglycemia FMQ Narrow Term	1 (0.2)	1 (0.2)	0.0 (-0.6, 0.6)

Custom Medical Query (CMQ)

3.2.9 Standardized MedDRA Query Variables

Standardized MedDRA Queries (SMQs; see https://www.meddra.org/standardised-meddra-queries)[4] are becoming increasingly common in clinical trial safety evaluations, particularly when known or suspected safety issues are associated with experimental compounds. In addition, customized queries (CQs) are often used to modify an SMQ or identify records of special interest. Table 3.2.9.1 lists variables used to identify SMQs and CQs, where *zz* is replaced with a zero-padded 2-digit integer (01-99) for each SMQ or CQ of interest. This ordering can be based on importance or some other producer-defined criteria. It is recommended that ordering be consistent across studies within a development program, but it is recognized that there may be situations where this is not possible or practical.

Table 3.2.9.1 Standardized MedDRA Query Variables

Variable Name	Variable Label	Type	Codelist	Controlled Terms	Core	SubClass ADVERSE EVENT Core	CDISC Notes
SMQzzNAM	SMQ zz Name	Char			Cond	Cond	The Standardized MedDRA Query name. Would be blank for terms that are not in the SMQ. Therefore this variable could be blank for all records if no terms within the study were included in the SMQ. Conditional on whether SMQ analysis is done
SMQzzCD	SMQ zz Code	Num			Perm	Perm	The standardized MedDRA queries number code
SMQzzSC	SMQ zz Scope	Char	BROAD, NARROW		Cond	Cond	The search strategy for SMQs can be narrow or broad. The preferred terms that are narrow in scope have high specificity for identifying events of interest, whereas the broad terms have high sensitivity. By definition, all narrow terms are also considered within the broad scope. Therefore, to summarize all broad terms, terms with either narrow ***or*** broad would be considered. Will be null for terms that do not meet the criteria. Conditional on whether SMQ analysis is done
SMQzzSCN	SMQ zz Scope (N)	Num	1, 2		Perm	Perm	Will be null for terms that do not meet the criteria
CQzzNAM	Customized Query zz Name	Char			Cond	Cond	The CQ name or name of the adverse event of special interest category based on a grouping of terms. Would be blank for terms that are not in the CQ. Conditional on whether CQ analysis is done Examples: "DERMATOLOGICAL EVENTS" "CARDIAC EVENTS", "IARS (INFUSION ASSOCIATED REACTIONS)"
ADECODy	Analysis Dictionary-Derived Term y	Char			Perm	Perm	The terms used for the analysis when combining multiple customized query or multiple standardized MedDRA queries and the original MedDRA dictionary terms under 1 variable Although designed for MedDRA queries, this variable could be used for other OCCDS analysis needs.

https://www.cdisc.org/system/files/members/standard/foundational/ADaM_OCCDS_Implementation_Guide%20v1.1.pdf

Custom Medical Query (CMQ)

ADAE - JMP Clinical

JMP Clinical File Edit Tables Rows Cols DOE Analyze Graph Tools View Window Help

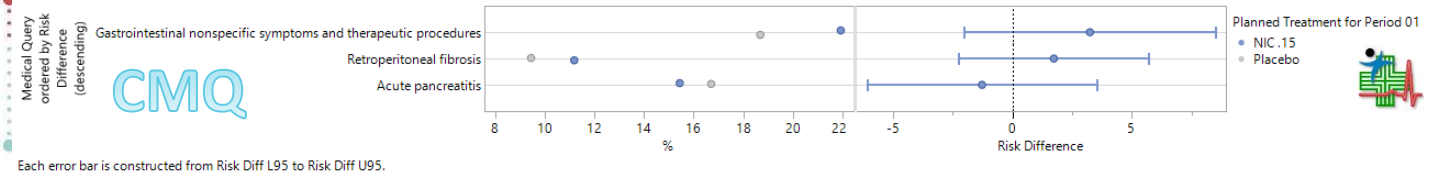
ADAE
Source

Columns (21/0)
STUDYID
DOMAIN
USUBJID

		AEHLGT	AEBODSYS	AESEV	AESER	AEACN	AEREL	AEOUT	AESTDTC	AEENDTC	AESTDY	AEENDY	CQ01NAM	CQ02NAM	CQ03NAM
1	rs	Body temperatur...	GENERAL DISOR...	MILD	N	DOSE NOT CHA...	NOT RELATED	RECOVERED/RES...	1988-01-25T12:0...	1988-01-31	5	11			
2	mi...	Gastrointestinal s...	GASTROINTESTI...	MILD	N	DOSE NOT CHA...	NOT RELATED	RECOVERED/RES...	1988-01-23T00:0...	1988-02-02	3	13	Acute pancreatitis	Gastrointestinal n...	
3	ory...	Lower respiratory...	RESPIRATORY, T...	MODERATE	N	UNKNOWN	NOT RELATED	RECOVERED/RES...	1988-01-31T05:0...	1988-02-06	6	12			
4	ic c...	Glucose metaboli...	METABOLISM AN...	MODERATE	N	UNKNOWN	NOT RELATED	RECOVERED/RES...	1988-01-26T00:0...	1988-02-05	1	11			
5	r fa...	Heart failures	RESPIRATORY, T...	MODERATE	N	UNKNOWN	NOT RELATED	RECOVERED/RES...	1988-01-29T06:0...	1988-02-03	4	9			
6	nyt...	Cardiac arrhythm...	CARDIAC DISOR...	MODERATE	N	UNKNOWN	NOT RELATED	RECOVERED/RES...	1988-01-26T00:0...	1988-02-05	1	11			
7	icr...	Increased intracr...	NERVOUS SYSTE...	MILD	N	UNKNOWN	NOT RELATED	RECOVERED/RES...	1988-01-31T00:0...	1988-01-31	4	4			
8		Neurological diso...	NERVOUS SYSTE...	SEVERE	Y	DRUG WITHDRA...	RELATED	RECOVERED/RES...	1988-01-28T16:1...	1988-01-31	1	4			
9	ic c...	Glucose metaboli...	METABOLISM AN...	MILD	N	DRUG WITHDRA...	NOT RELATED	RECOVERED/RES...	1988-01-28T00:0...	1988-01-28	1	1			
10	ten...	Decreased and n...	VASCULAR DISO...	SEVERE	Y	DRUG WITHDRA...	RELATED	RECOVERED/RES...	1988-01-28T00:0...	1988-01-28	1	1			
11	s s...	Central nervous s...	NERVOUS SYSTE...	SEVERE	Y	DRUG WITHDRA...	NOT RELATED	RECOVERED/RES...	1988-01-30T00:0...	1988-01-30	3	3			
13															
13															
13															
13															
13															
15															
13															
13															
13															
16															Retroperitoneal fi...
11														Gastrointestinal n...	
11															

Additional columns for CMQ

CMQ

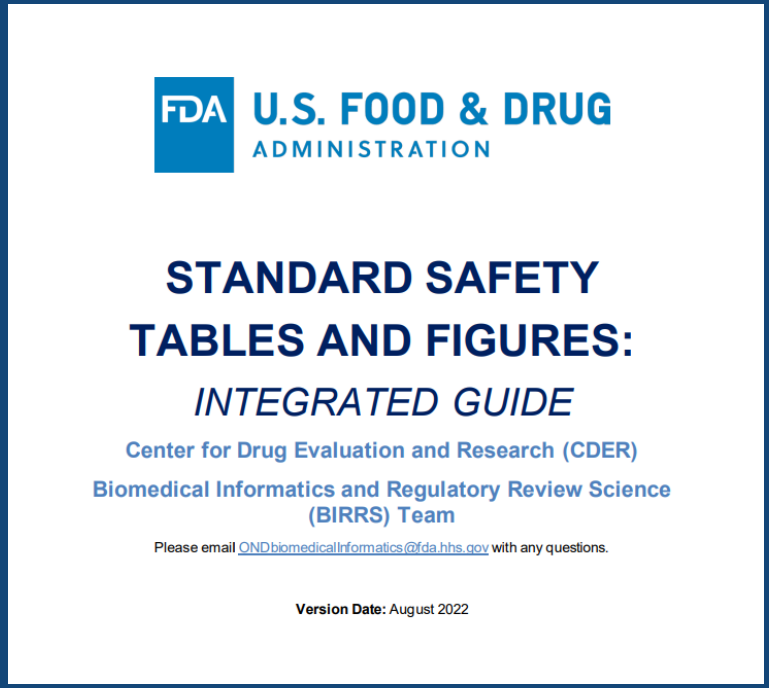


Each error bar is constructed from Risk Diff L95 to Risk Diff U95.

Medical Queries and Terms

Medical Query	NIC .15 (N = 447)	Placebo (N = 455)	Risk Difference for NIC .15 over Placebo
Gastrointestinal nonspecific symptoms and therapeutic procedures	98 (21.9)	85 (18.7)	3.2 (-2.0, 8.5)
Cardiac failure congestive	24 (5.4)	17 (3.7)	1.6 (-1.1, 4.4)
Diarrhoea	6 (1.3)	2 (0.4)	0.9 (-0.3, 2.1)
Chest pain	7 (1.6)	4 (0.9)	0.7 (-0.7, 2.1)
Constipation	2 (0.4)	1 (0.2)	0.2 (-0.5, 1.0)
Abdominal pain	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Ecchymosis	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Nausea	1 (0.2)	0 (0.0)	0.2 (-0.2, 0.7)
Vomiting	63 (14.1)	64 (14.1)	0.0 (-4.5, 4.6)
Abdominal distension	1 (0.2)	1 (0.2)	0.0 (-0.6, 0.6)
Hyperhidrosis	0 (0.0)	1 (0.2)	-0.2 (-0.6, 0.2)
Hypovolaemia	0 (0.0)	3 (0.7)	-0.7 (-1.4, 0.1)
Retroperitoneal fibrosis	50 (11.2)	43 (9.5)	1.7 (-2.2, 5.7)
Sepsis neonatal	37 (8.3)	33 (7.3)	1.0 (-2.5, 4.5)
Pulmonary embolism	4 (0.9)	1 (0.2)	0.7 (-0.3, 1.6)

Standard Figures and Tables



U.S. FOOD & DRUG ADMINISTRATION

STANDARD SAFETY TABLES AND FIGURES:

INTEGRATED GUIDE

Center for Drug Evaluation and Research (CDER)

Biomedical Informatics and Regulatory Review Science (BIRRS) Team

Please email ONDbiomedicalInformatics@fda.hhs.gov with any questions.

Version Date: August 2022

https://www.regulations.gov/document/FDA-2022-N-1961-0046

Following FDA Integrated Guide

Table 14. Patients With Adverse Events[1] by System Organ Class and FDA Medical Query, Safety Population, Pooled Analyses[2]

System Organ Class[4] FMQ	Narrow FMQs: Drug Name N = XXX n (%)	Narrow FMQs: Active Control N = XXX n (%)	Narrow FMQs: Placebo N = XXX n (%)	Narrow FMQs: Risk Difference (%) (95% CI)[3]	Broad FMQs: Drug Name N = XXX n (%)	Broad FMQs: Active Control N = XXX n (%)	Broad FMQs: Placebo N = XXX n (%)	Broad FMQs: Risk Difference (%) (95% CI)[3]
SOC1								
FMQ1	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ2	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)
FMQ3	n (%)	n (%)	n (%)	X (Y, Z)	n (%)	n (%)	n (%)	X (Y, Z)

Narrow Medical Queries and Terms

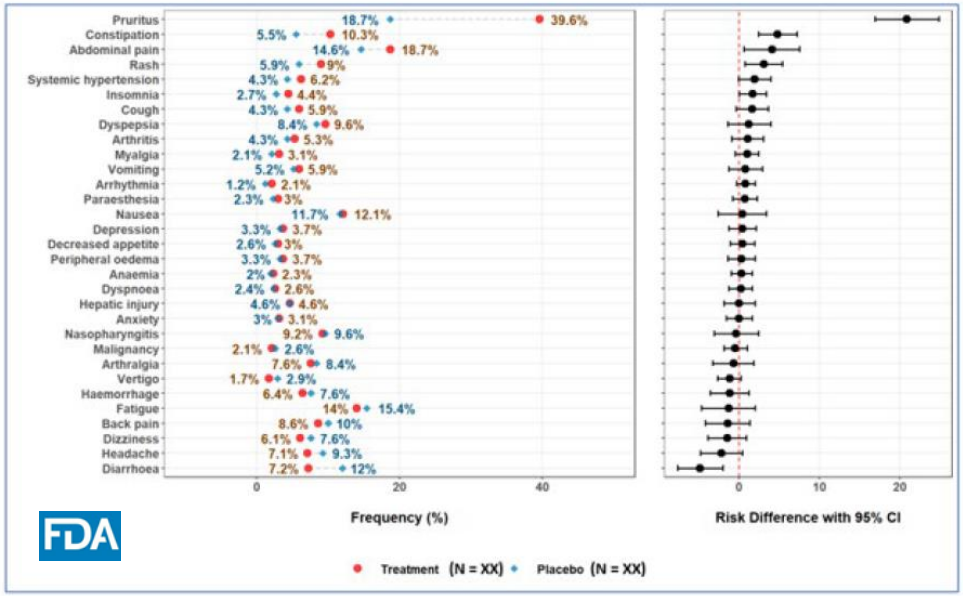
Medical Query	NIC .15 (N = 447)	Placebo (N = 455)	Risk Difference for NIC .15 over Placebo
Hypotension	155 (34.7)	80 (17.6)	17.1 (11.5, 22.7)
Hypotension	155 (34.7)	80 (17.6)	17.1 (11.5, 22.7)
Heart Failure	140 (31.3)	107 (23.5)	7.8 (2.0, 13.6)
Pulmonary oedema	132 (29.5)	104 (22.9)	6.7 (0.9, 12.4)
Cardiac failure congestive	24 (5.4)	17 (3.7)	1.6 (-1.1, 4.4)
Hyperglycemia	114 (25.5)	96 (21.1)	4.4 (-1.1, 9.9)
Hyperglycaemia	114 (25.5)	96 (21.1)	4.4 (-1.1, 9.9)

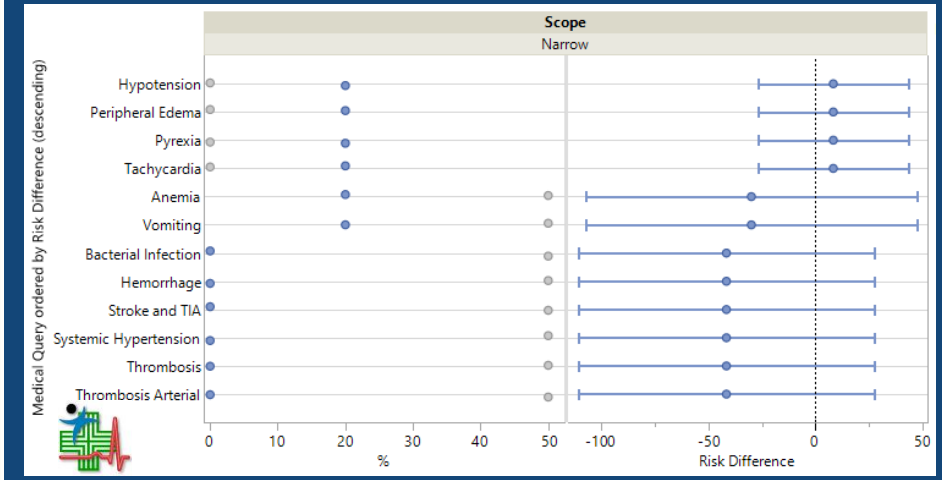
Broad Medical Queries and Terms

Medical Query	NIC .15 (N = 447)	Placebo (N = 455)	Risk Difference for NIC .15 over Placebo
Fall	158 (35.3)	83 (18.2)	17.1 (11.4, 22.8)
*Hypotension	155 (34.7)	80 (17.6)	17.1 (11.5, 22.7)
*Dizziness exertional	7 (1.6)	4 (0.9)	0.7 (-0.7, 2.1)
Syncope	155 (34.7)	80 (17.6)	17.1 (11.5, 22.7)
*Hypotension	155 (34.7)	80 (17.6)	17.1 (11.5, 22.7)
*Hypotension	155 (34.7)	83 (18.2)	16.4 (10.8, 22.1)
*Hypotension	155 (34.7)	80 (17.6)	17.1 (11.5, 22.7)
*Hypovolaemia	0 (0.0)	3 (0.7)	-0.7 (-1.4, 0.1)
Heart Failure	178 (39.8)	152 (33.4)	6.4 (0.1, 12.7)
Pulmonary oedema	132 (29.5)	104 (22.9)	6.7 (0.9, 12.4)

Following FDA Integrated Guide

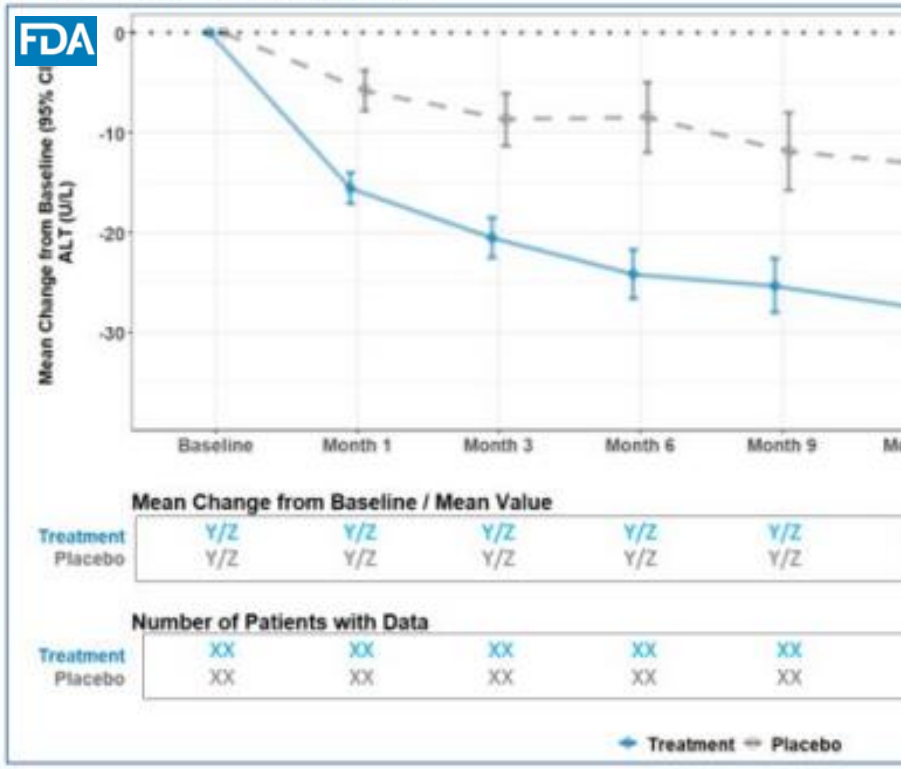
Figure 5. Patients With Adverse Events[1] ≥X% in Any Treatment Arm by FDA Medical Query (Narrow), Safety Population, Trial X

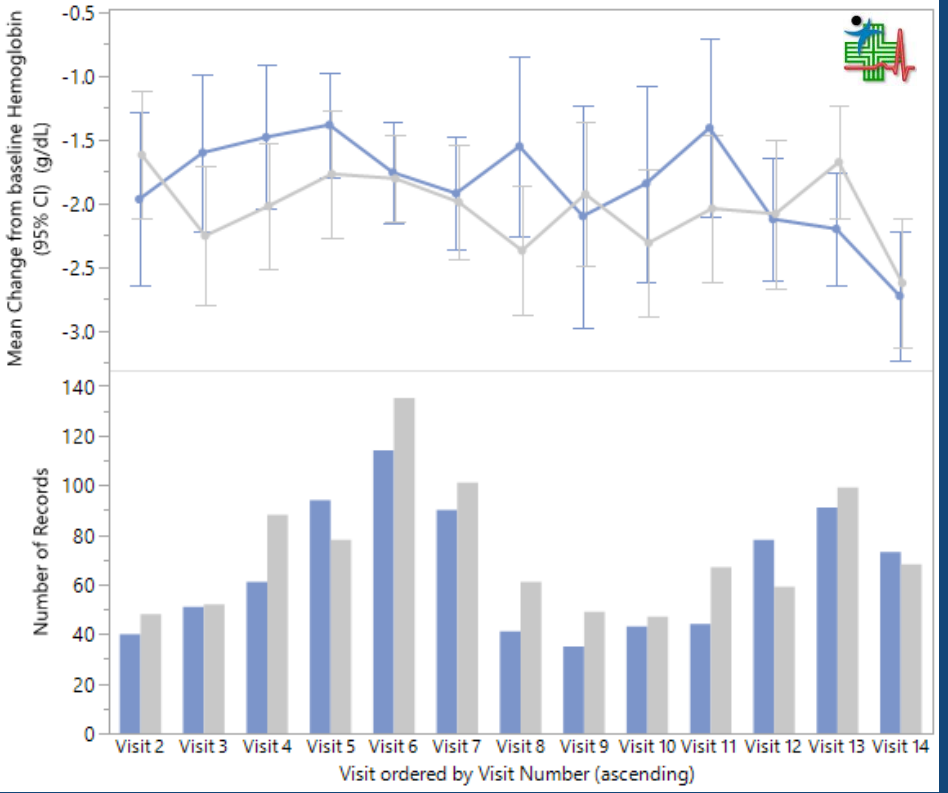




Following FDA Integrated Guide

Figure 8. Mean Laboratory (Liver Biochemistry) Data Change From Baseline Over Time, Safety Population, Pooled Analyses



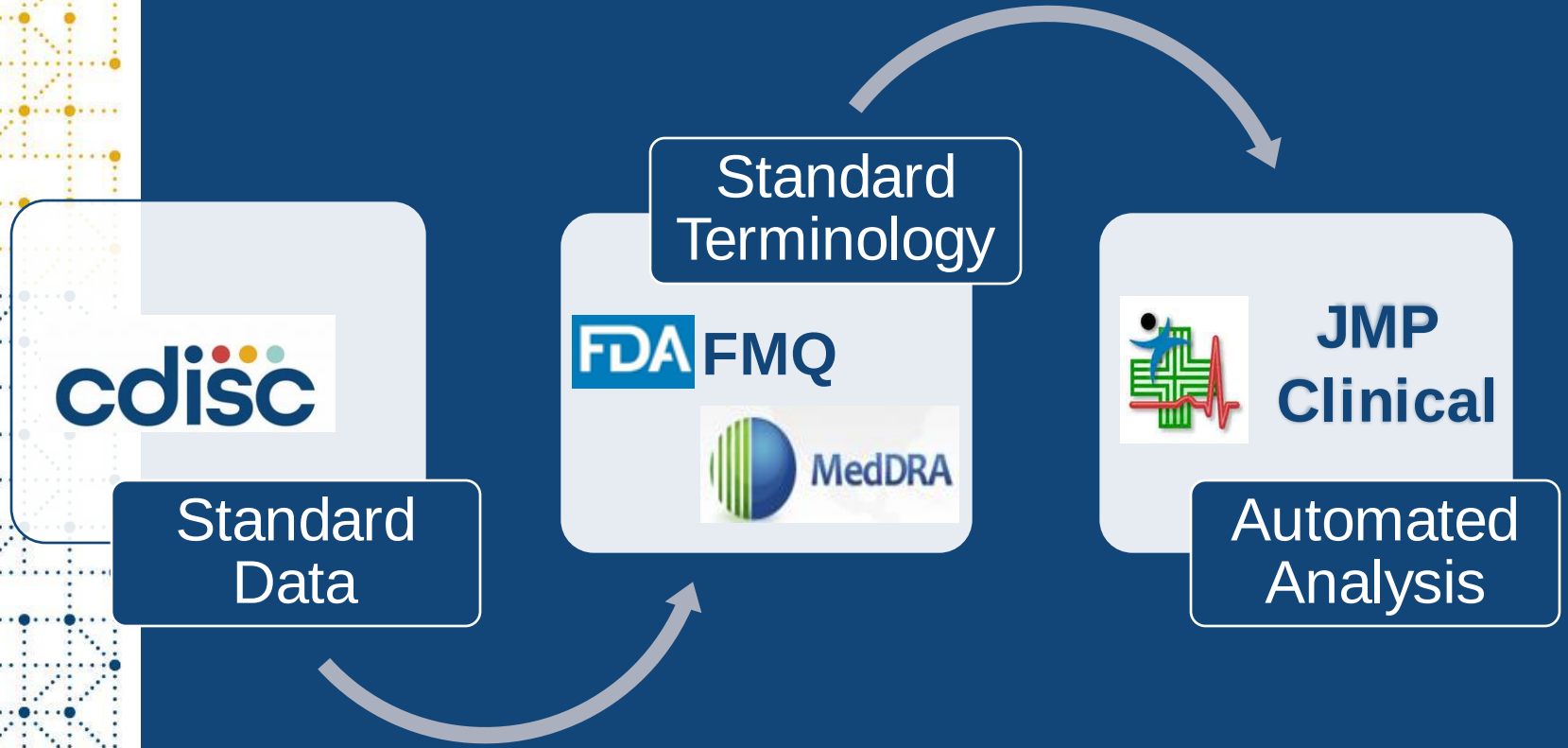


Discussion:

- CDISC offers foundation for streamlining reviewing clinical trial data.
- FDA NDAs and CRs have the standard templates to follow.
- FDA NDAs and CRs show the usage of CDISC data as JMP Clinical requires Data in CDISC Format, ADaM first, then SDTM.
- All the FDA NDAs and CRs referred here are public available.
- The analysis results in this talk were generated by JMP Clinical:
  - ✓ The results showed in ☐ with FDA were copied directly from NDA or CRS that were generated by FDA Reviewers.
  - ✓ The results showed in ☐ with FDA were generated by JMP Clinical Nicardipine Sample Data that were similar to results in NDAs or CRs.

Speedy Clinical Trial Goals Achieved by Standards

Quality, Efficiency, Reproducibility and Reusability



Thank You!!

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