WITH STANDARDS – UNLOCK THE POWER OF DATA

cdisc

2022
US
INTERCHANGE
26-27 OCTOBER | AUSTIN

Trace CDISC Application in FDA NDAs and CRs for Clinical Trial Safety

Wenjun Bao, Ph.D.
Chief Scientist and Director, JMP
Board of Director and C3C Member, CDISC

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.

Drug Safety

Standardized Requirements and Procedures

灵丹妙药磺胺

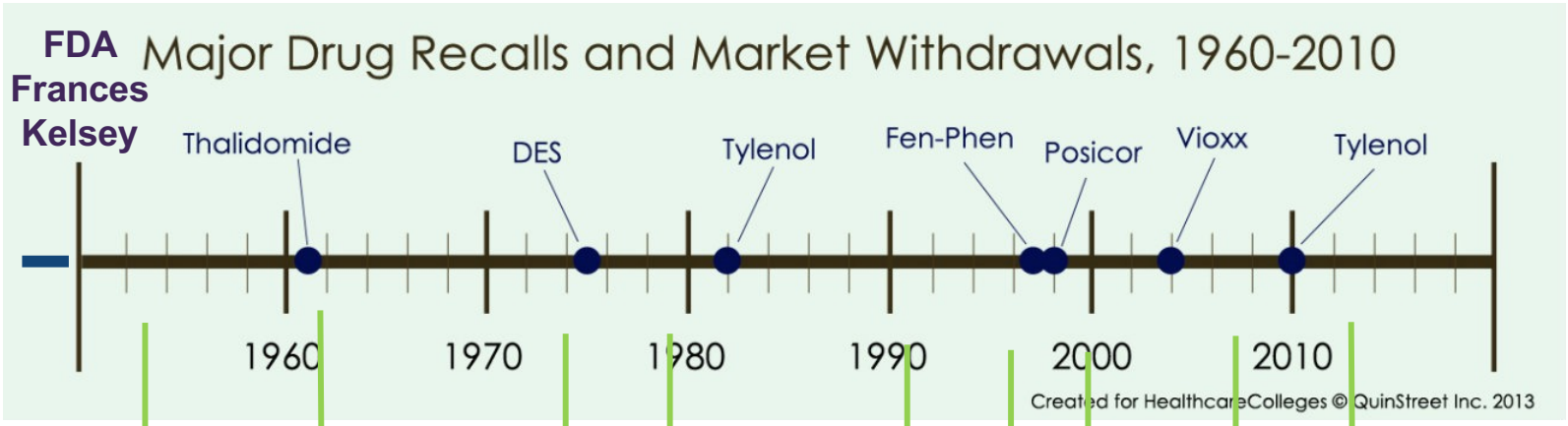
Elixir Sulfanilamide

1937

1938

Federal Food, Drug, and Cosmetic Act

FDA Frances Kelsey



1953

IRBs

1962

Kefauver-Harris Amendments FDA Regulation

1974

National Research Act

1979

The Belmont Report

1991

The Common Rule

1996

ICH GCP

2000

Clinical Trials.gov

2007

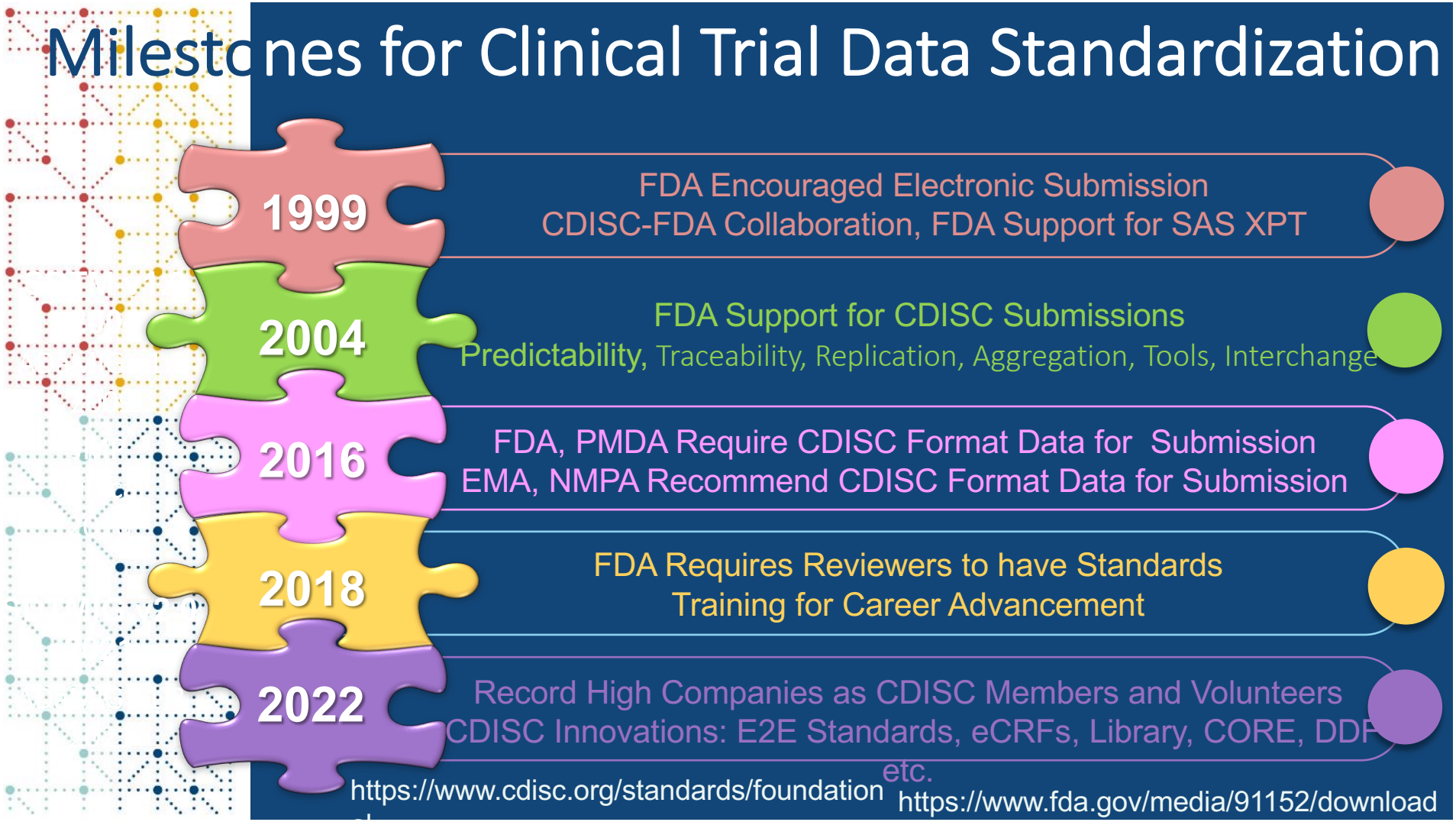
WHO ICTRP

2013

EMA Expands Trial Database

http://ictd2015.lillycoi.com

Milestones for Clinical Trial Data Standardization



PMDA JAPAN

Dr. Yuki Ando Nov. 2015

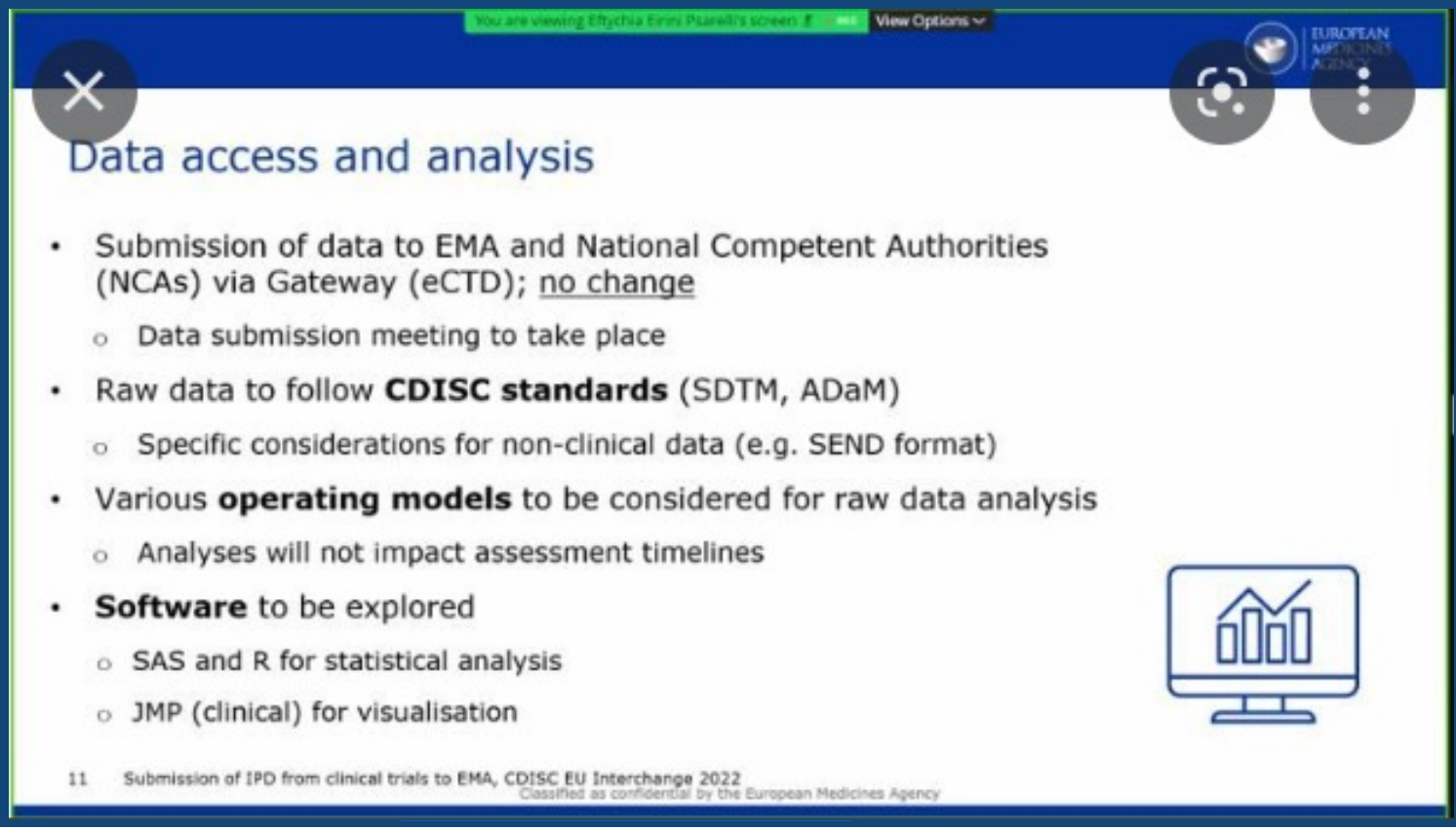
Expected analyses in review teams

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

EMA Europe

Dr. Eftychia Eirini Psarelli 2022



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

s (classroom or online)

	CDER Review of Clinical Trials
	OND Ready, Set, Review
	OND 2017 Clinical Review Template Introduction
	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
	OCS Data standards training
	OCS JMP and JMP Clinical Training (multiple modules)
	FDA Library Electronic Resources

Required Trainings

OND: Office of New Drugs

OTS: Office of Translational Sciences

OCS: Office of Computational Science

Standard Terminology

Standard Data (CDISC)

Standard Analysis Procedures

CDISC Special Issue

Dec. 2022:

Journal of the Society for Clinical Data Management

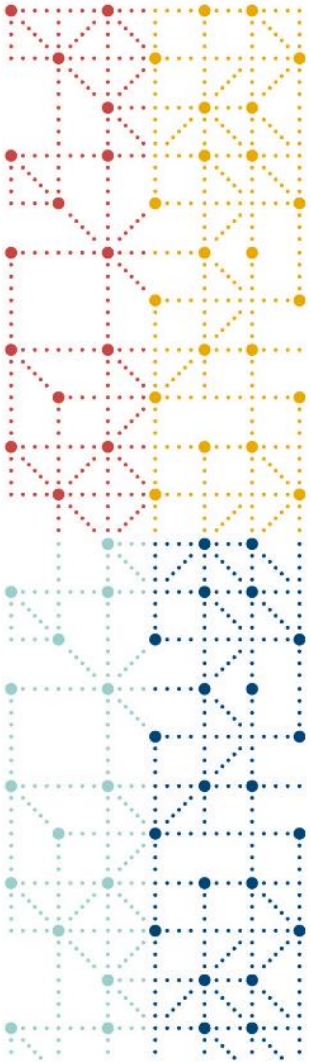
Papers in this issue

US FDA
Japan PMDA
Danish Medicines Agency

CDISC Enables Efficient Streamlining of Clinical Trial Safety Evaluation

Geoffrey Mann, Thomas J. Pedersen, Rebecca Lyzinski, Anisa Scott, John Cromer, Meichen Dong, Andrew J Foglia, Nora Varga, Sam Gardner, Christopher J. Kirchberg, Byron A. Wingerd, Russell D. Wolfinger*, Wenjun Bao*
JMP, SAS Institute Inc., Cary, NC 27513

FDA NDAs or CRs for Safety



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

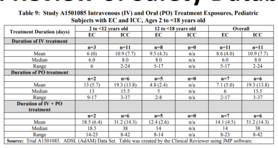
CR: Clinical Review

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



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

C. Adequacy of Applicant's Clinical Safety Assessments

Demographics of Safety Database

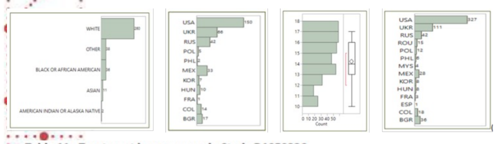


Table 11: Treatment by age group in Study D1050326

	Lurasidone 20-80 mg		Placebo			
Age Group	Count	Column %	Count	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)

	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

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

G. information was verified by reviewers

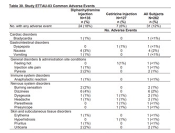


Table 14: Enrollment by Country

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.

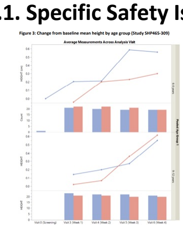
Quzyttir https://www.fda.gov/media/133034/download

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

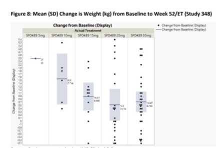
Mydayis https://www.fda.gov/media/142063/download

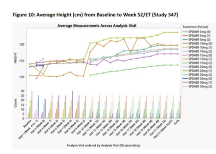
F. Specific Safety Studies/Clinical Trials & other assessments

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

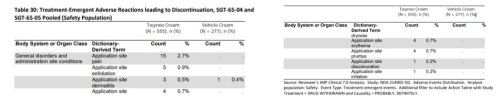
Participant: 101014
Randomized Arm: NIC .15
Investigator Name: 101B

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.

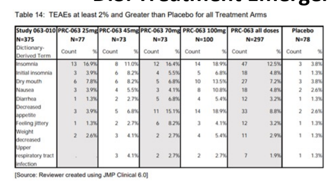
Latuda https://www.fda.gov/media/103749/download

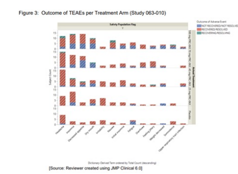
D.2. Discontinuations due to AEs



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

D.3. Treatment Emergent AEs and ARs





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

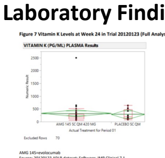
Table 25. FMQs with Events in ≥2% of Dasiglucagon Treated Subjects Over Entire Observation Period – Placebo-Controlled Pool

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

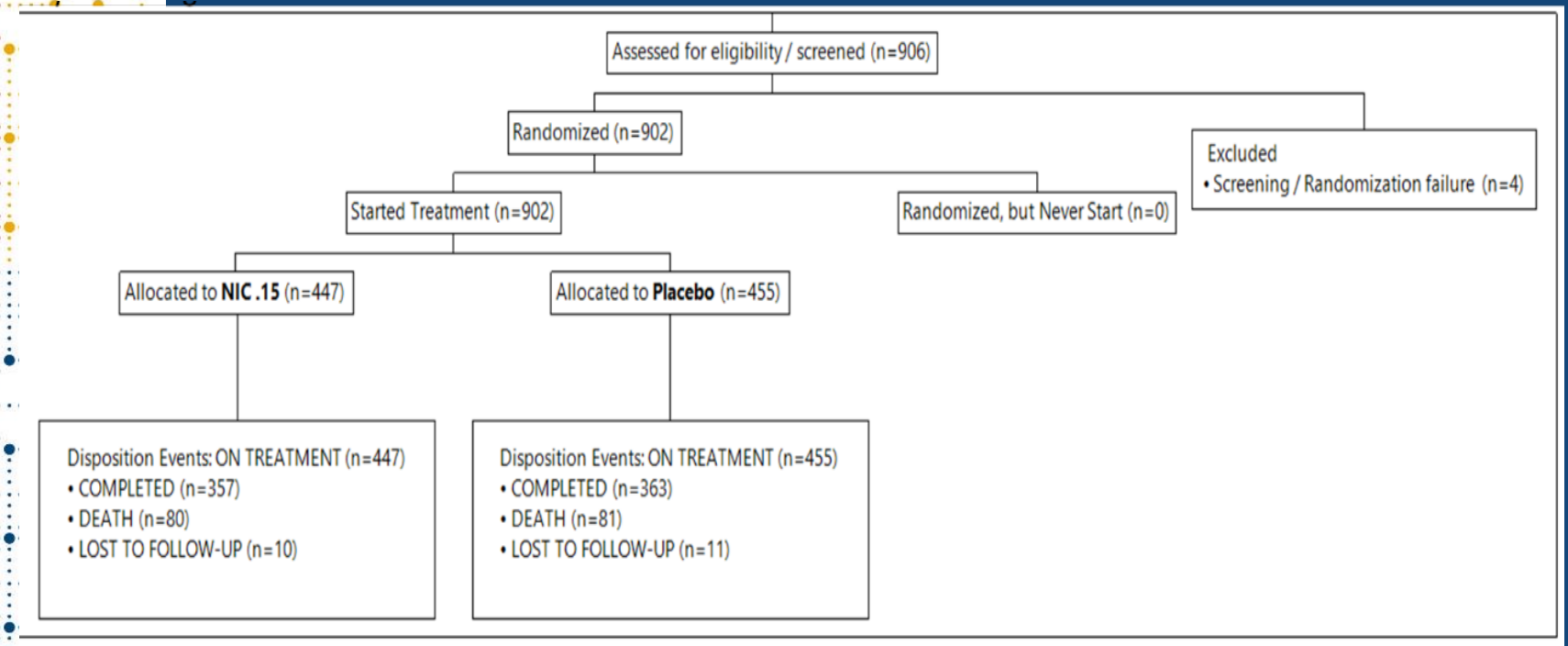
2. Review of Safety

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

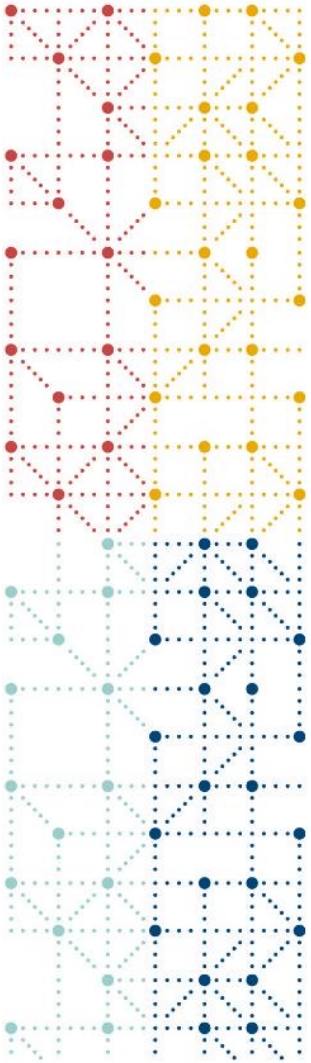
Summary

Summary

Trial Summary: Study Flow Chart



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



Summary

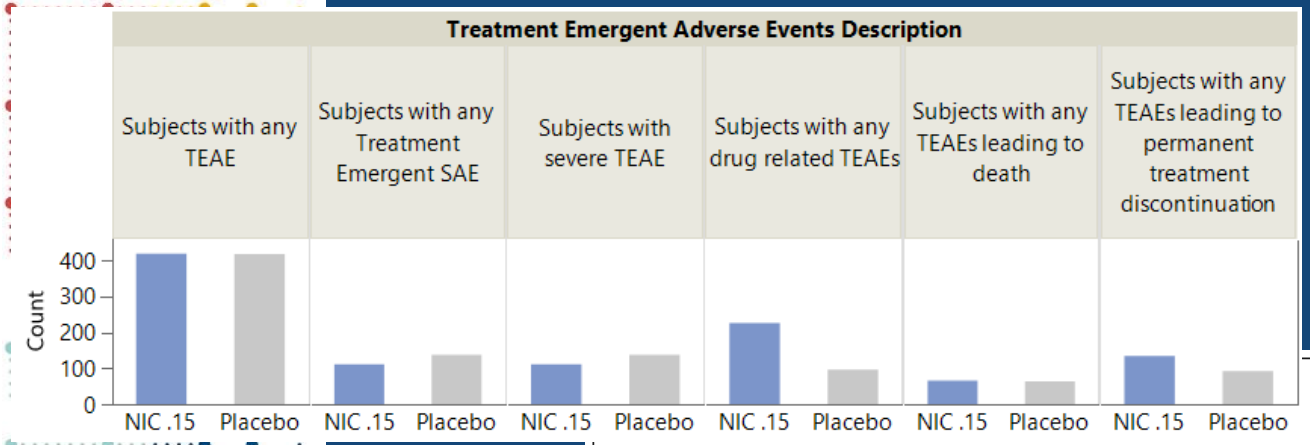
Event Summary: Disposition of Participants

	Planned Treatment for Period 01		
	NIC .15	Placebo	Total
	(N = 447)	(N = 455)	(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



	Planned Treatment for Period 01		
	NIC .15 (N = 447)	Placebo (N = 455)	Total (N = 902)
Treatment Emergent Adverse Events Description	**n (%)**	**n (%)**	**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

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.

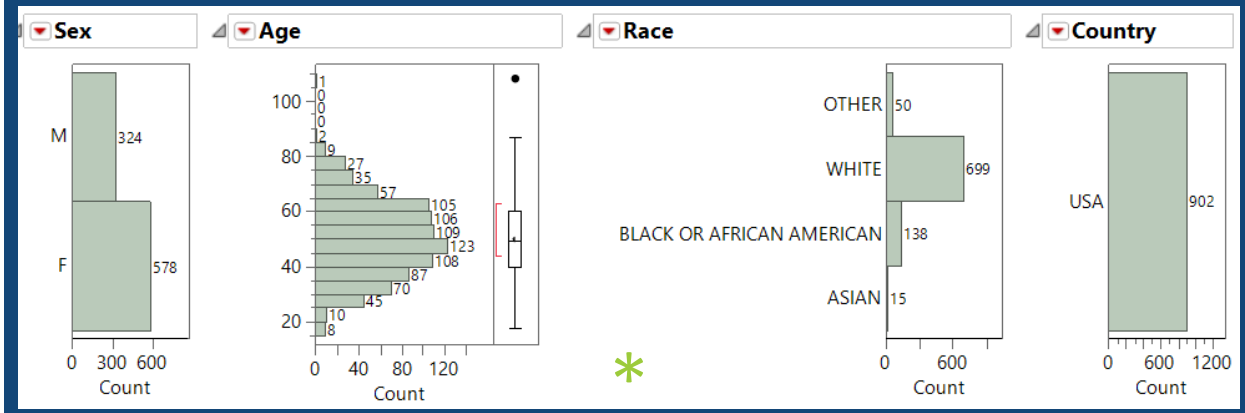
NDA Dupixent 2021 https://www.fda.gov/media/155349/download

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.

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

Review of Safety

B. Review of Safety Database



	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)

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)
	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.

* 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

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.

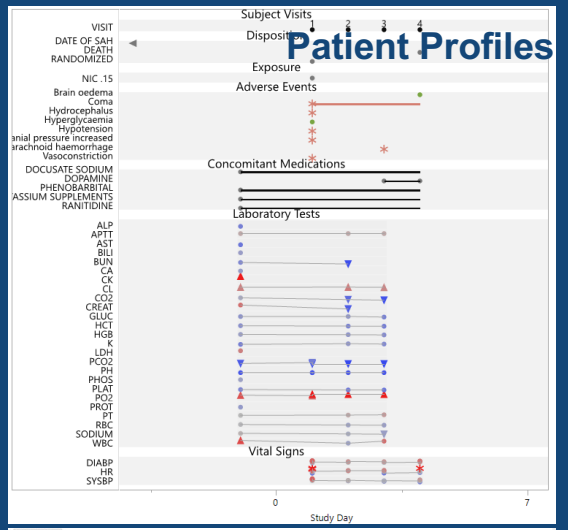
The investigator considered the AE to be not related to study medication. The event ended on 28JAN1988 (Day 1) with a final outcome of recovered/resolved.

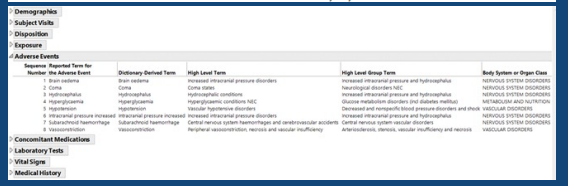
Serious Adverse Event (coded term): HYDROCEPHALUS
Drugs and Doses on Day of Event: Pre Treatment

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





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

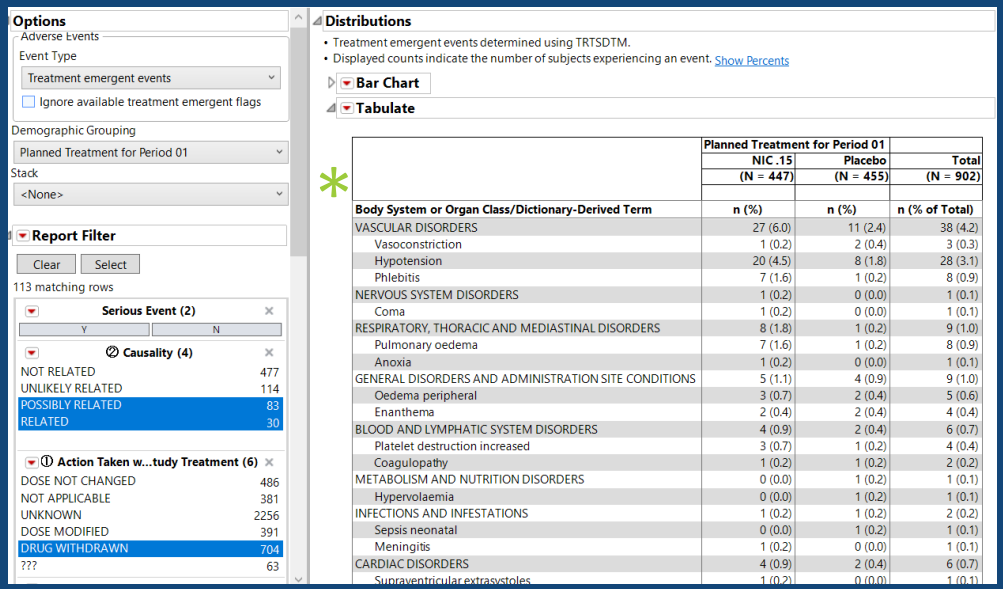
Review of Safety

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: 3. Common TEAEs

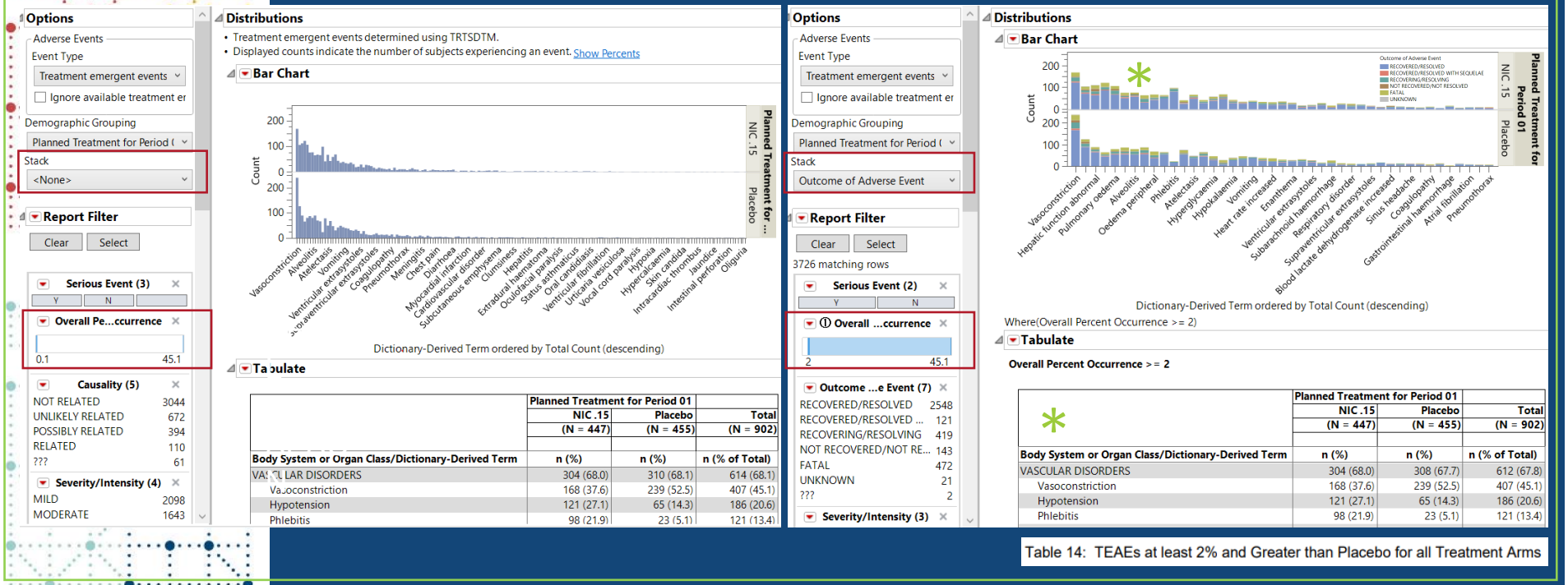


Table 14: TEAEs at least 2% and Greater than Placebo for all Treatment Arms

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: 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

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.

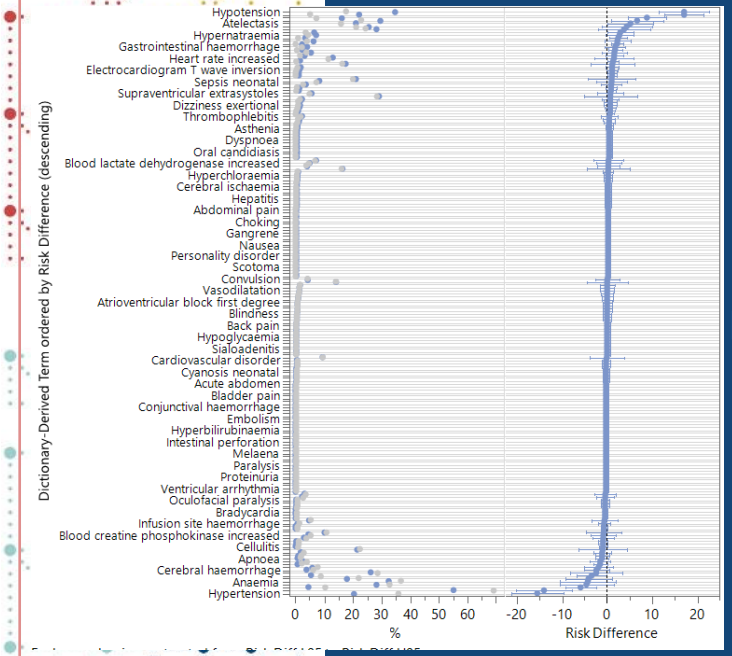
CR Zegalogue 2020
https://www.fda.gov/media/147791/download

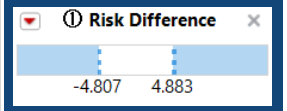
https://www.fda.gov/drugs/news-events-human-drugs/advancing-pre-market-safety-analytics-09142022

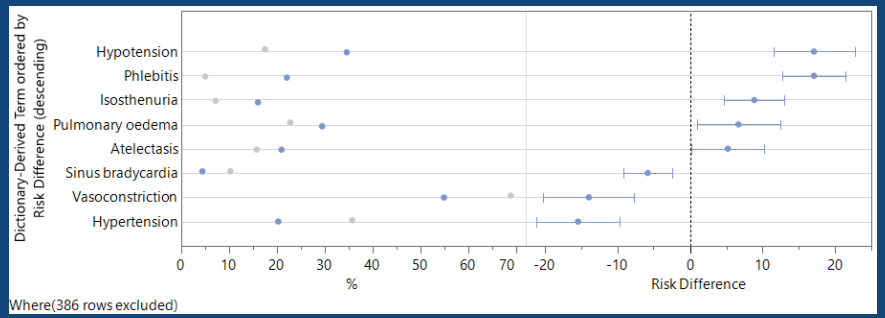
CDISC: ADAE/AE, ADSL/DM; JMPC: AE Distribution

Review of Safety

D. Safety Review: 4. Significant AE







*	Planned Treatment for Period 01		
	NIC .15 (N = 447)	Placebo (N = 455)	Risk Difference for NIC .15 over Placebo
Dictionary-Derived Term	**n (%)**	**n (%)**	**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

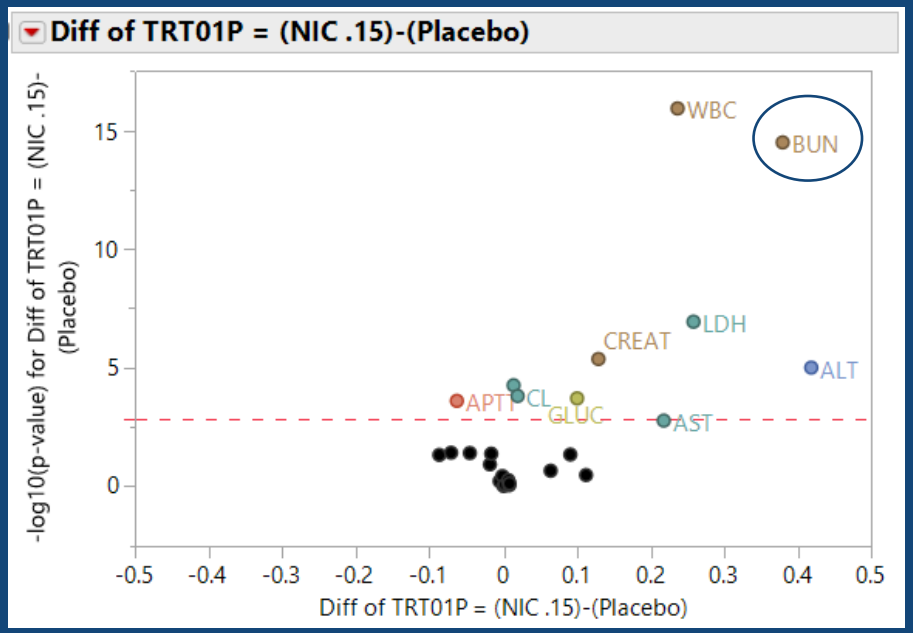
Review of Safety

D. Safety Review: 5a. Laboratory Findings

Comparison of Differences in Laboratory Measurement Values between Groups

Volcano Plot

BUN: Blood Urea Nitrogen

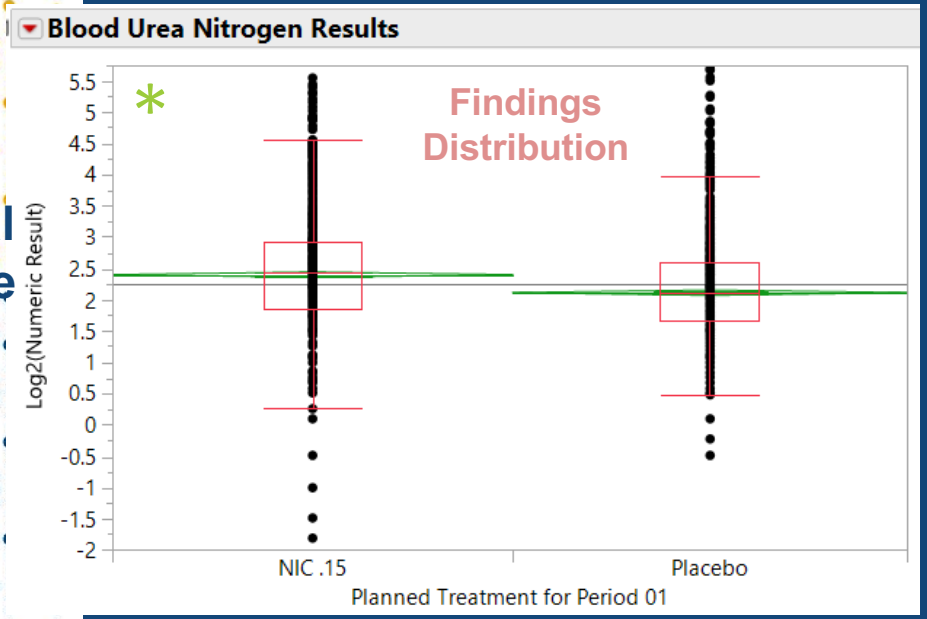


CDISC: ADLB/LB, ADSL/DM; JMPC: Finding ANOVA

Review of Safety

D. Safety Review: 5b. Laboratory Findings

Statistical difference for BUN



Oneway Anova

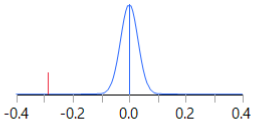
Summary of Fit

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

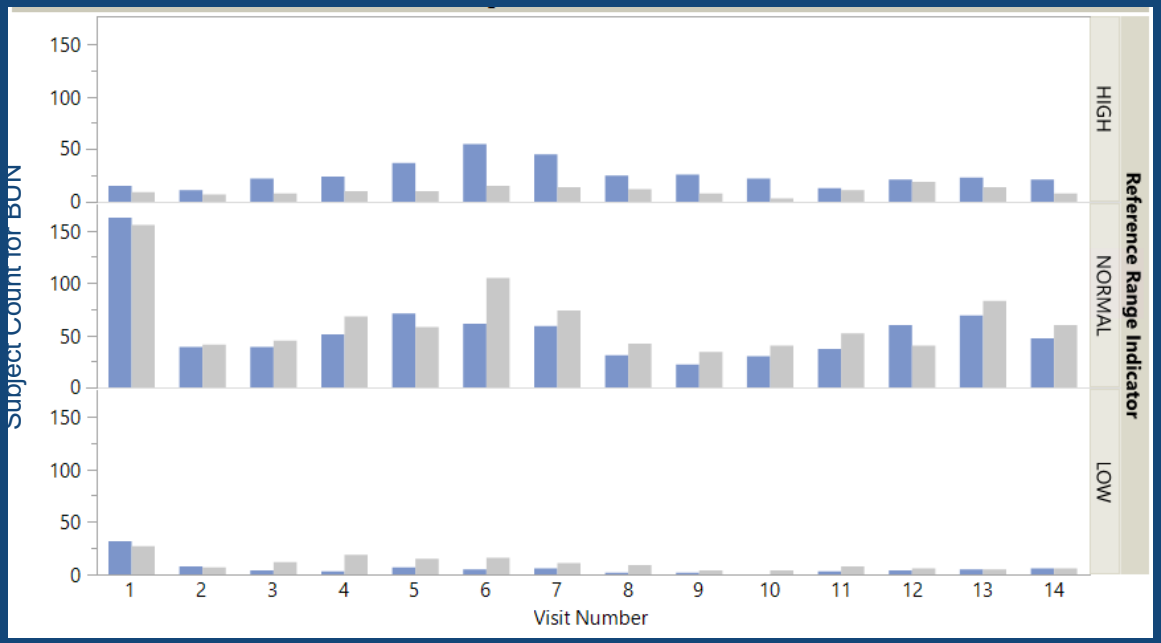
CR Repatha 2021 https://www.fda.gov/media/154402/download

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

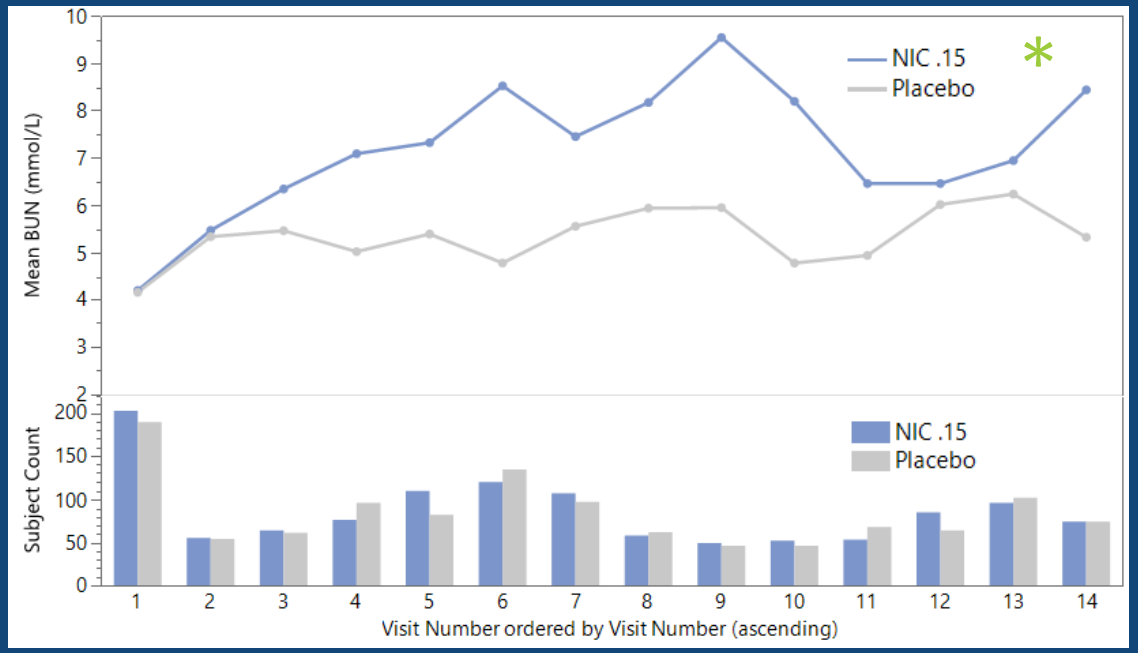


CDISC: ADLB/LB, ADSL/DM; JMPC: Finding Distribution

Review of Safety

D. Safety Review: 5d. Laboratory Findings

Compare Mean Measurement across Treatment Arms per Visit



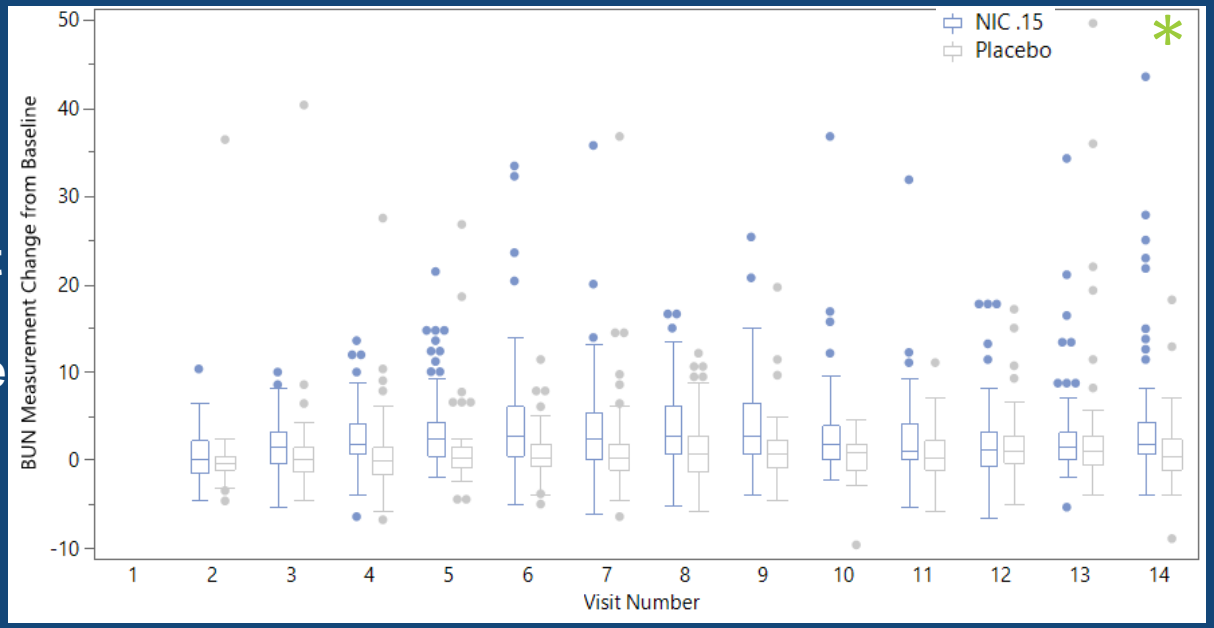
NDA Mydayis 2019 https://www.fda.gov/media/142063/download

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

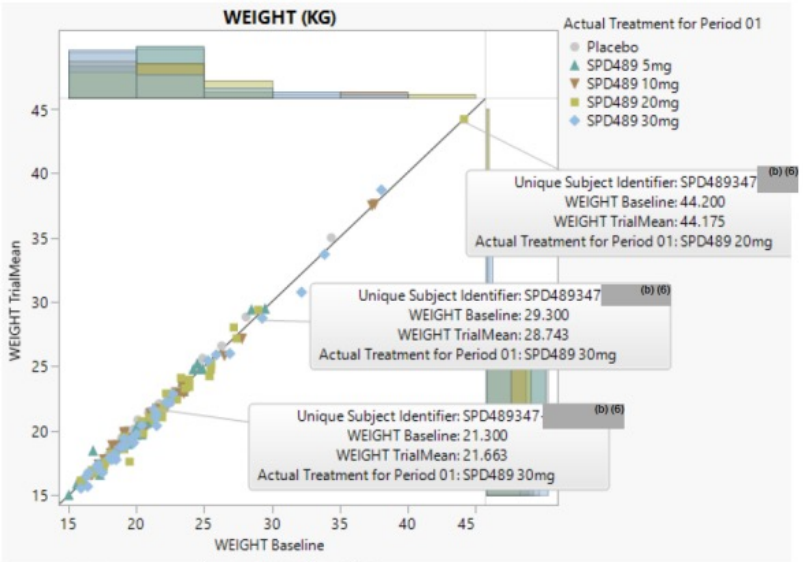
CDISC: ADLB/LB, ADSL/DM; JMPC: Findings Box Plots

Review of Safety

D. Safety Review: 5f. Laboratory Findings

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

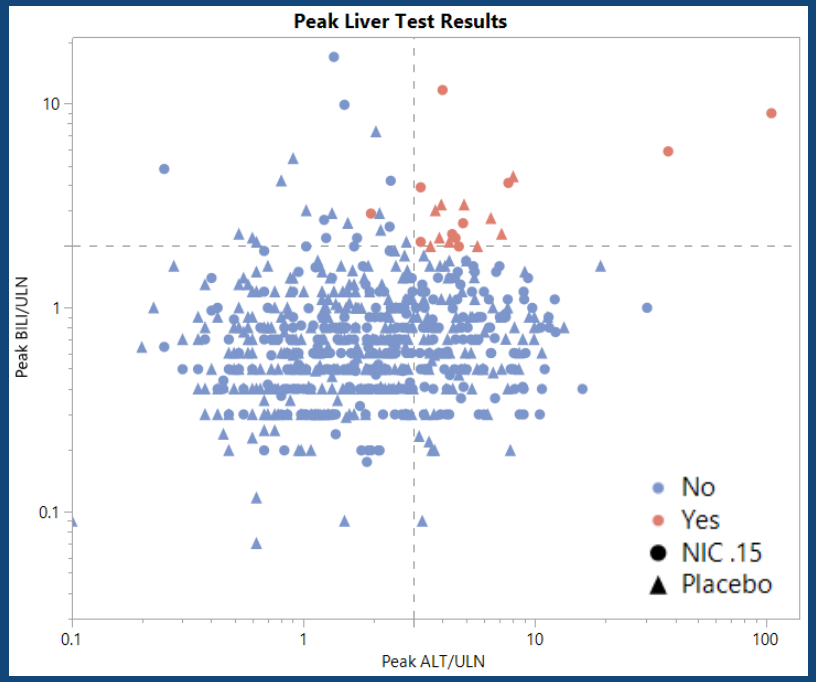
CR Zegalogue 2020 https://www.fda.gov/media/147791/download

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

Review of Safety

D. Safety Review: 5g. Laboratory Findings

Assess Drug-Induced Liver Injury



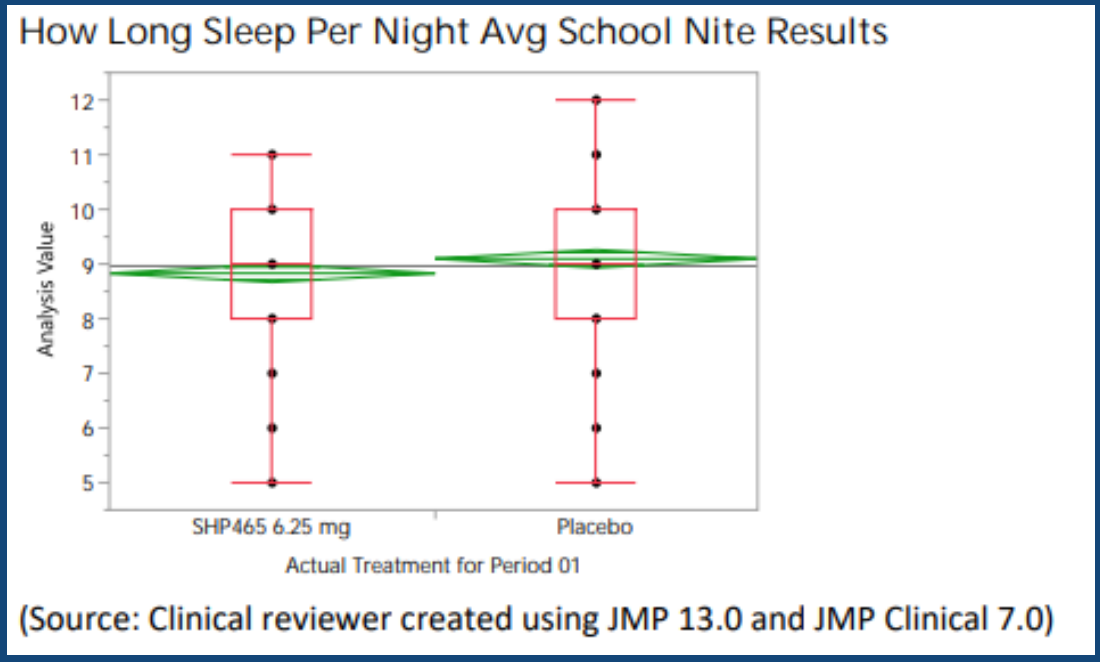
CDISC: ADLB/LB, ADSL/DM; JMPC: Hy's Law Screening

Review of Safety

E. Analysis of Submission – Specific Safety Issues

Mydayis 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

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

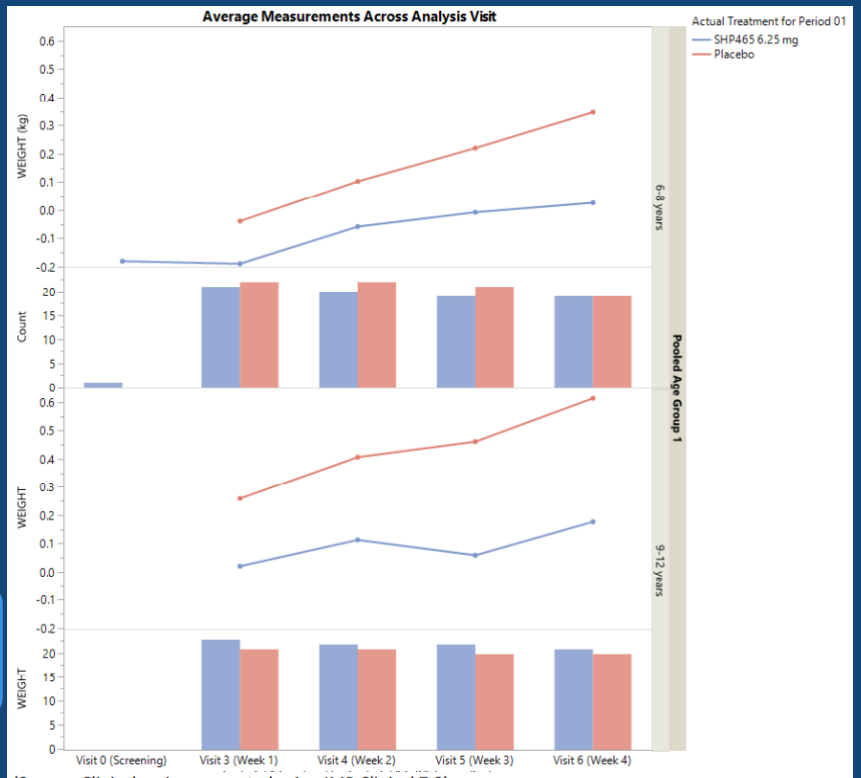
Review of Safety

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



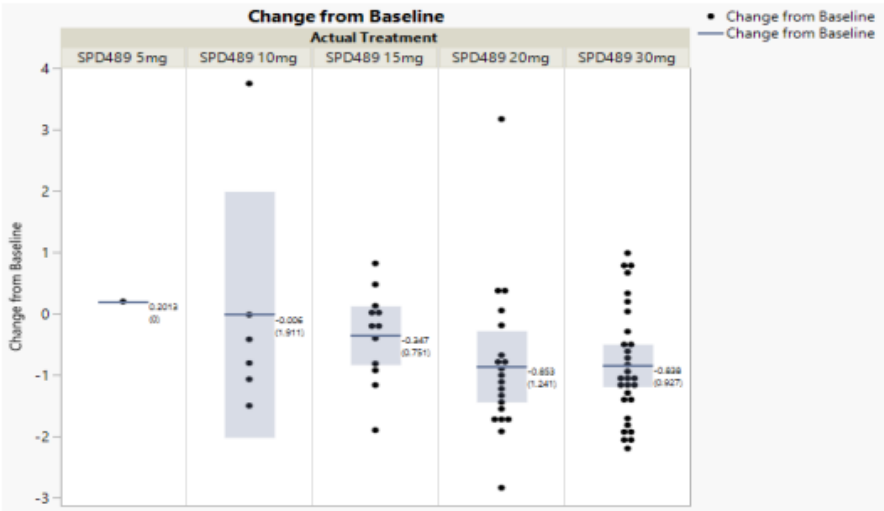
(Source: Clinical reviewer created using JMP Clinical 7.0)

Review of Safety

F. Specific Safety Studies/Clinical Trials and Additional Safety

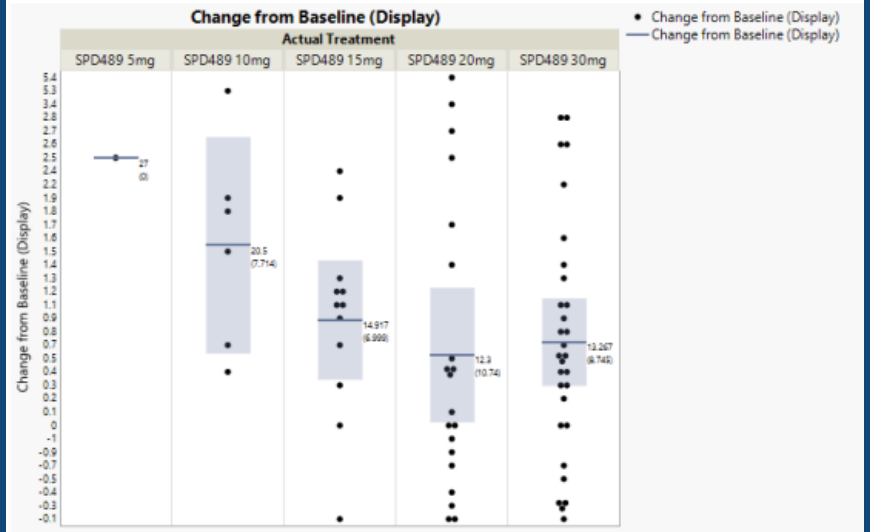
Changes in Weight and BWI According to Drug Dose to Address Concerns about the Effect of Vyvanse

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

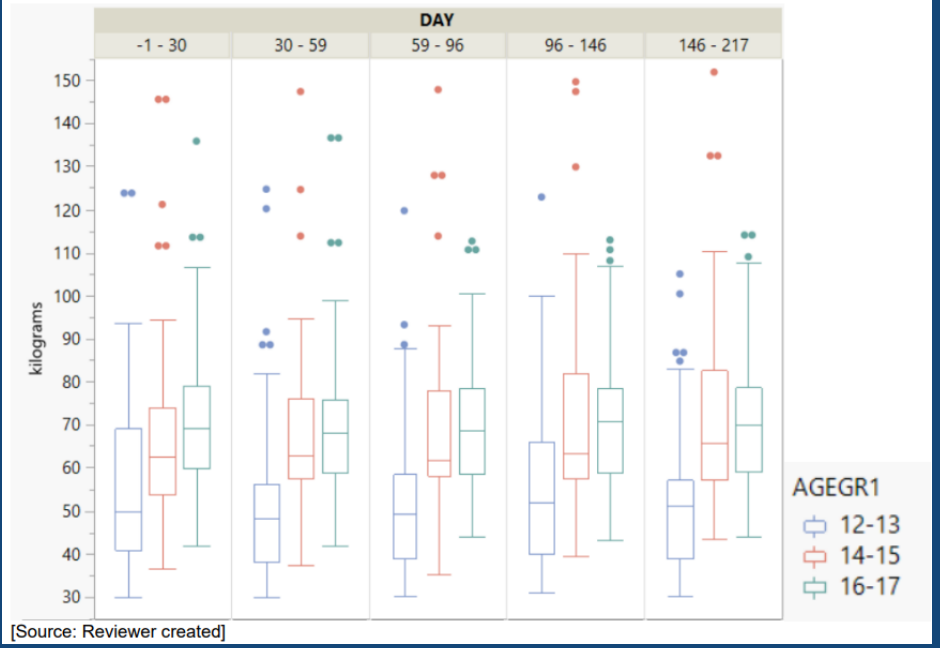
CDISC: ADLB/LB, ADSL/DM; JMPC: Findings Box Plots

Review of Safety

F. Specific Safety Studies/Clinical Trials and Additional Safety

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	151.0, 190.0
BMI (kg/m^2)			
Mean (SD)	23.2 (2.98)	22.9 (2.48)	24.0 (2.98)
Median	22.7	22.4	23.4
Min, Max	18.8, 29.6	18.6, 29.0	18.3, 29.4

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

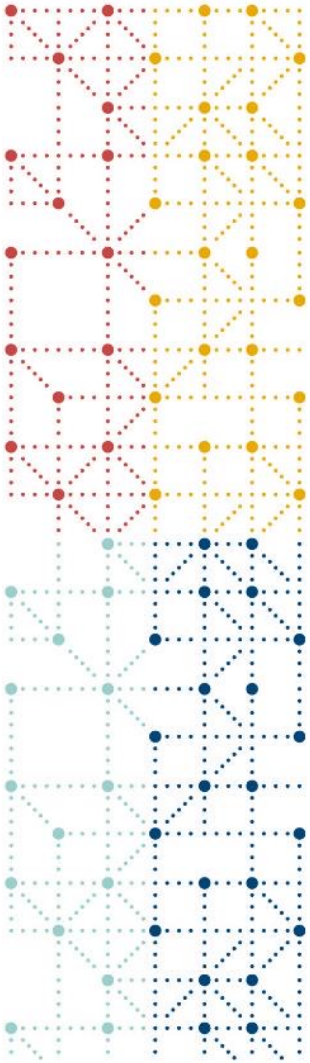
Table 30. Study ETTAU-03 Common Adverse Events

	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%)

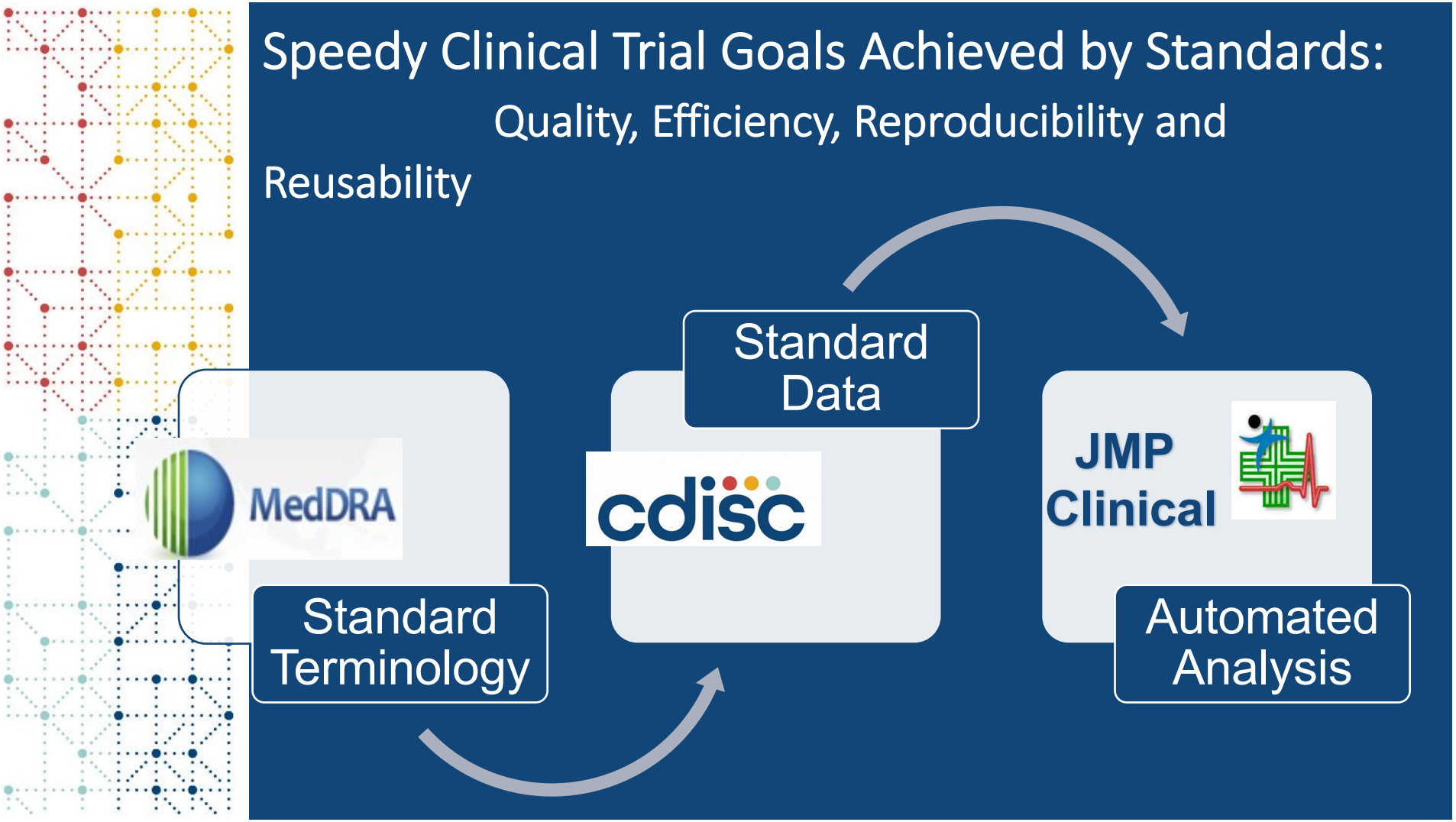
Source: CSR ETTAU-03 Table 14.3.1 pg. 54 and Table 14.3.2 pg. 55 verified by Reviewer in JMP

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



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 * were generated by JMP Clinical Sample Data that were similar to results in NDAs or CRs.
  - ✓ The results showed in ☐ were copied from NDA or CRS that were generated by FDA Reviewers.


Speedy Clinical Trial Goals Achieved by Standards:
Quality, Efficiency, Reproducibility and Reusability
MedDRA
Standard Terminology
cdisc
Standard Data
JMP Clinical
Automated Analysis

Thank You!

wenjun.bao@jmp.com