Addressing Data Challenges in Noncirrhotic Nonalcoholic Steatohepatitis (NASH) & Drug-Induced Liver Injury (DILI)

Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of NASH

Paul "Skip" Hayashi, MD, MPH
DILI Team Leader
FDA/CDER/OND/OII/DHN

Ruby Mehta, MD
Clinical Team Leader
FDA/CDER/OND/OII/DHN

Y. Veronica Pei, MD, MEd, MPH
Lieutenant Commander, U.S. Public Health Service
Associate Director of Biomedical Informatics
FDA/CDER/OND/ODES/DBIRBD/BIRRS

Objectives

- Identify data challenges in NASH clinical trials
- Identify data challenges in evaluation of suspected DILI
- Understand design principle and objectives of the NASH Technical Specifications Guidance
- Outline key aspects of the NASH Technical Specifications Guidance

NASH & DILI Disease Burden

Nonalcoholic Steatohepatitis (NASH)

- Estimated prevalence of NASH: 3-5%.
- Can progress to cirrhosis, liver failure and liver cancer
- No FDA-approved therapy
- Multiple drug development programs in treatment of NASH with liver fibrosis

Drug Induced Liver Injury (DILI)

- Uncommon but potentially lethal
- A frequent cause of acute liver failure in North America and Europe
- Main reason why drugs fail to achieve marketing authorization
- Major reason for post-marketing restrictions and withdrawals
- Difficult to diagnose and assess for post-marketing risk during drug development

Data Challenges to Evaluate Efficacy and Safety in Clinical Trials that Enroll Patients with Noncirrhotic NASH with Fibrosis

Pathology

- Adequacy of biopsy specimen
- Multiple evaluators (inter- and intra-observer variability)
- How to capture data for surrogate endpoints

Adjudication

- Criteria used
- By whom?
- How to indicate final accepted record

Imaging-based biomarkers

Inter- & Intra-Rater Agreement

- Number of central pathologists reading the slides
  - Training prior to trial initiation (anchor)
  - All pathologists read, screening and end-of-treatment in blinded manner
  - Submit pathologists' impression of scoring, i.e., staging and grading forms
  - Submit Joint Panel read scoring of all components in case of disagreement between pathologists' individual reads
- Degree of agreement
  - High
  - Low (problematic)
- Slides used for screening and end-of-treatment
- Glass slides versus digital slides
  - Data must be collected in prospective manner to perform percent agreement and CDRH should be consulted

Challenges in the Assessment of DILI Risk in Drug Development

Study Level Data

- Missing liver related data
- Liver related data found in different datasets
- Outliers
- Non-standardized data labeling

Case Level Data

- Missing pertinent clinical information
  - DILI onset date
  - Summary of evaluation testing
  - Outcomes and interventions

Study Level Data

Missing liver related data

- Liver enzymes, direct bilirubin, LDH, CPK, INR
- Local upper limit of normal values

Liver related data found in different datasets

- Liver tests found in efficacy dataset and missing from safety dataset

New data requested

- R-value = [ALT/ULN] ÷ [ALP/ULN]
- Liver injury onset date

Outlier values (e.g., bilirubin >1000 mg/dL)

DILI Case Level Data: What is in a good narrative?

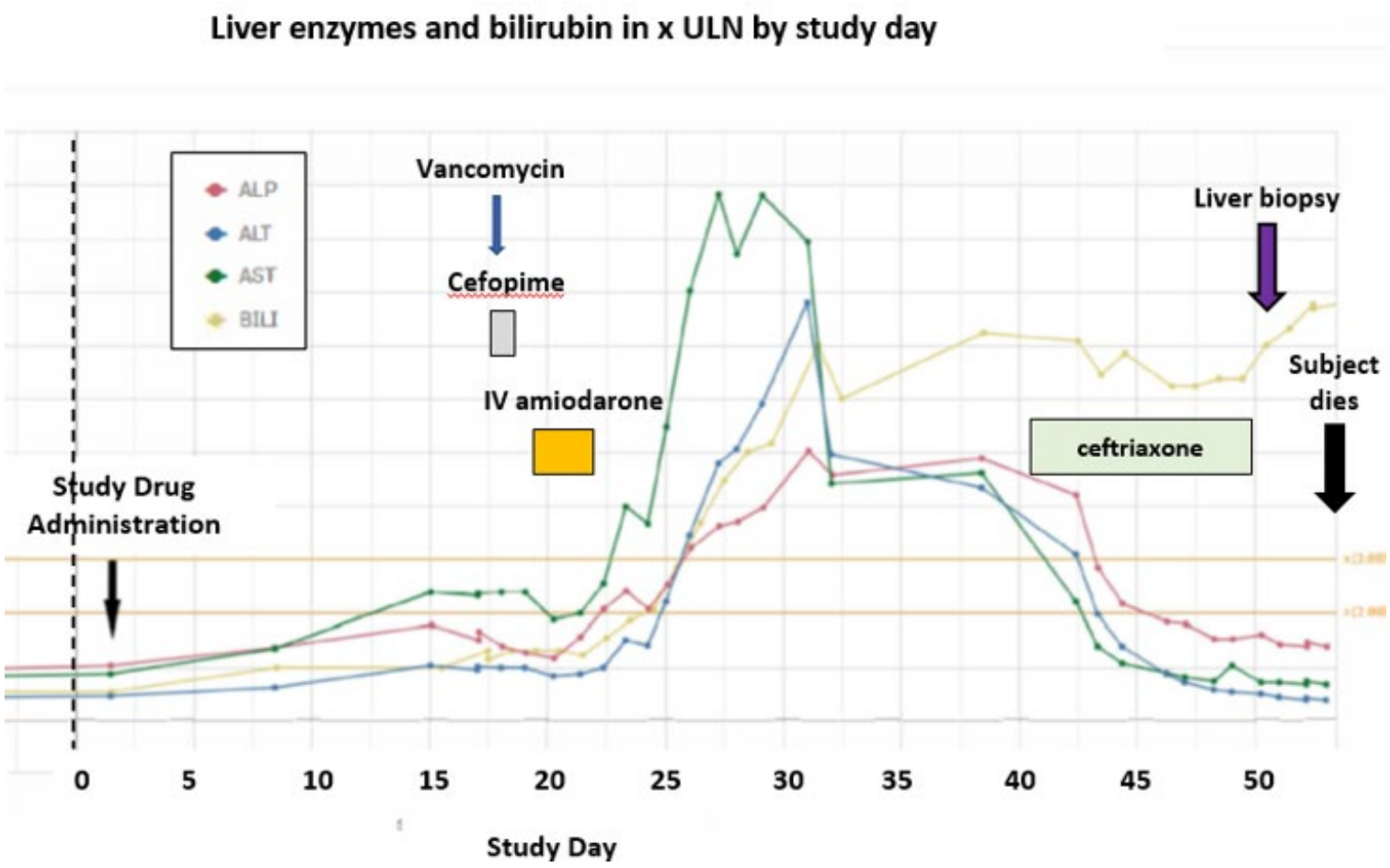
- Good baseline data
- Well documented time course
- Signs & symptoms

- Evaluation for alternative causes
  - Viral hepatitis A, B, C and E
  - Alcohol
  - *Bile duct obstruction (e.g., gallstones)*
  - *Concomitant medications*
  - Autoimmune hepatitis markers
  - Others:
    - Shock, sepsis, heat failure
    - Atypical viruses (CMV, EBV)
    - Liver biopsy data if available

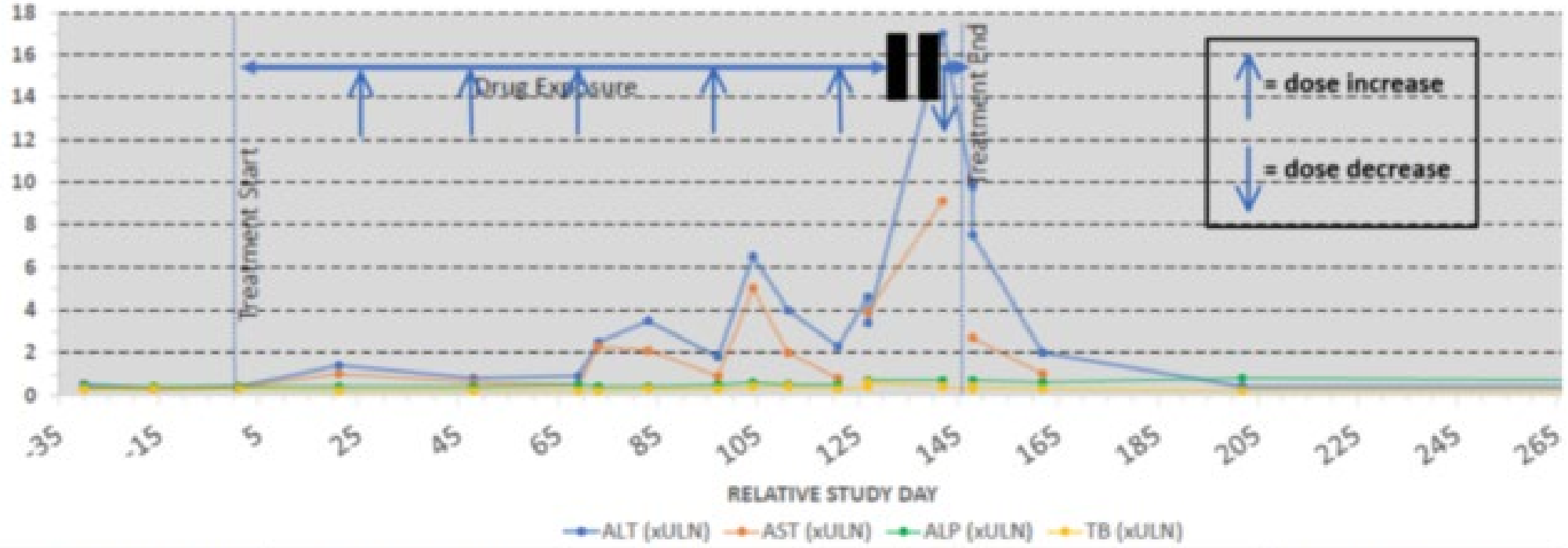
Tabular accounting of DILI evaluation testing

Test	Test done after injury onset	Date, study day & result
Hepatitis A IgM antibody	{Yes//No}	
Hepatitis B surface antigen	{Yes//No}	
Hepatitis B anti-HB core IgM antibody	{Yes//No}	
Hepatitis B DNA	{Yes//No}	
Hepatitis C antibody	{Yes//No}	
Hepatitis C RNA	{Yes//No}	
Hepatitis E IgM antibody	{Yes//No}	
ANA (anti-nuclear antibody)	{Yes//No}	
ASMA (anti-smooth muscle antibody)	{Yes//No}	
Immunoglobulin G (IgG) level	{Yes//No}	
CMV (cytomegalovirus) antibody IgM	{Yes//No}	
EBV (Epstein Barr Virus) heterophile antibody	{Yes//No}	
EBV capsid antibody IgM	{Yes//No}	
EBV early antigen IgG	{Yes//No}	
Abdominal or liver ultrasound	{Yes//No}	
Abdominal computerized tomography scan	{Yes//No}	
Abdominal magnetic resonance imaging	{Yes//No}	
MRCP or MRC (magnetic resonance cholangiopancreatography or MR cholangiography)	{Yes//No}	
Cholangiogram (ERCP* or percutaneous)	{Yes//No}	
Liver histology	{Yes//No}	

Standardized data facilitates line graphs
Competing drugs more easily identified



Standardized data facilitates line graphs
Dose-effect more easily identifiable



Total Daily Dose (mg)	Day Dose Level Started	Day Dose Level Completed	Dose Level When Interrupted	Reason for Interruption
300	1	20		
450	21	48		
600	48	69		
750	69	97		
900	97	121		
1050	121	126		
nterrupted	127	142	1050	Nausea, vomiting
450	143	146		

Addressing Data Challenges

DRAFT NASH Guidance

- Provides current FDA thinking & recommendations
- Drug development programs for the treatment of patients with noncirrhotic NASH fibrosis

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

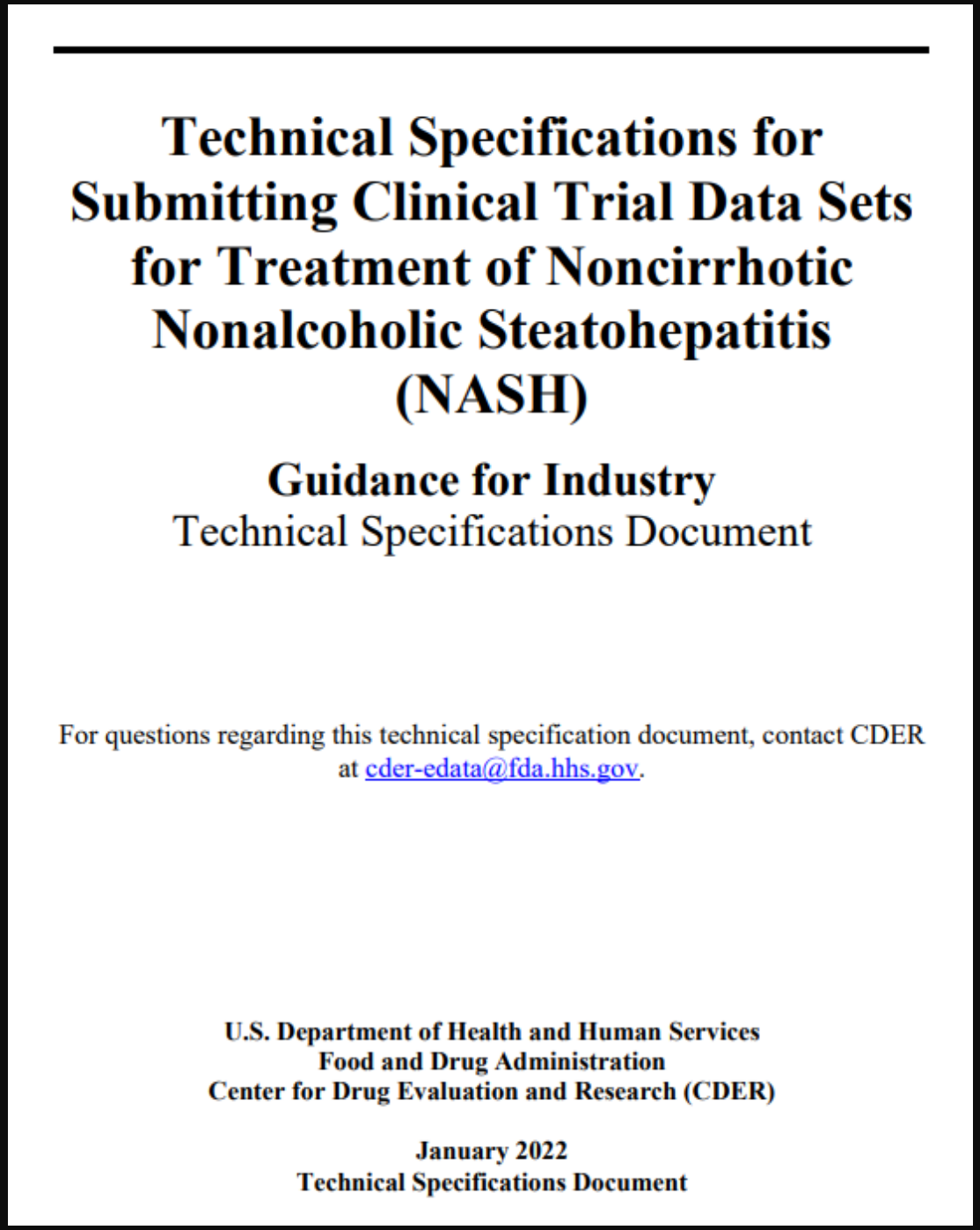
For questions regarding this draft document contact Evangela Covert 301-796-4075.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Design Principal

- Support DRAFT NASH Guidance
- Recommendations and specifications for content of the tabulated domains and analysis data sets
- Does not provide recommendations for clinical development

Available at https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.



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

Guidance for Industry

Technical Specifications Document

For questions regarding this technical specification document, contact CDER at cder-edata@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2022
Technical Specifications Document

Objective of Technical Specifications

1. Establish data specifications for submitting clinical trial data for NASH and DILI
2. Provide FDA with uniform data package for a more comprehensive and efficient review
3. Frameworks for data submission on efficacy and safety endpoints (e.g., progression to cirrhosis based on histology; DILI)
4. Opportunities for early dialog with FDA regarding data submission

Office of Drug Evaluation Science (ODES)

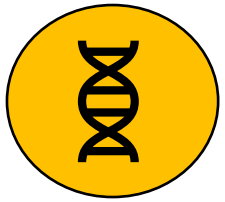
Biomedical Informatics and Regulatory Review Science (BIRRS)

Division of Hepatology and Nutrition

Office of Clinical Pharmacology

Office of Biostatistics

Office of Surveillance and Epidemiology



CDRH Office of Molecular Genetics & Pathology

Office of Strategic Programs

NASH-Specific Technical Specification Content

Study Data Tabulation Model (SDTM) Domains

- 9 Standard domains
  - Biospecimen Events (BE), Biospecimen Findings (BS), Microscopic Findings (MI), Laboratory (LB), Clinical Classifications and Disease Response (RS), Concomitant Medications (CM), Medical History (MH), Microbiology Specimens (MB), Substance Use (SU)
- 1 Supplemental domain
  - Supplemental Microscopic Findings (SUPPMI)
- 2 Custom domains
  - Imaging (ZG), Adjudication (ZG)

Analysis Data Model (ADaM) Data Sets

- Demographics (ADSL)
- Adverse Events (ADAE)
- Labs (ADLB)
- DILI (ADDILI)
- Microscopic Findings (ADMI)
- Non-Invasive Serum Biomarkers (ADRS)
- Time to Event (ADTTE)

What's in the SDTM Domains?

Instructions for sorting data into appropriate domains

(e.g., biopsy findings belong in MI, hepatitis information in MB, etc.)

Instructions and variables to be collected and submitted for custom domains

Links to NCI/EVS controlled terminology & CDISC standards where applicable

Example codelists for custom domains

Instructions, sample tests, required/expected/permissible variables

What's in the ADaM Data Sets?

Standard ADaM Data Sets

(ADSL, ADAE, ADLB, ADTTE)

Custom ADaM data sets (ADRS, ADMI, ADDILI)

ADSL

Baseline variables

Flag individual subjects based on a condition of interest

ADAE

Request for sponsors to submit their own custom SMQs

ADLB

Flags to support DILI analysis – when are subjects hitting their peak, washout, etc.

ADTTE

Guidance for how to submit this dataset, but left parameters flexible to sponsors

Approach to Data for NASH Trials

BIOSPECIMEN
(E.G., HISTOPATHOLOGY)

BIOMARKERS

ADJUDICATION

DILI

Biospecimen-Related Domains

- Biospecimen Events (BE) Domain
- Biospecimen Findings (BS) Domain
- Microscopic Findings (MI) Domain
- Supplemental Microscopic Findings (SUPPMI) Domain

Biospecimen Events and Findings

Biospecimen Events (BE) Domain

- Anatomical location where the specimen was collected
- Events related to specimen e.g., collecting, extracting, freezing, thawing, etc.
- Collection event is linked to the BS domain

Biospecimen Findings (BS) Domain

- Information of specimen characteristic (e.g., biopsy length & diameter)

Microscopic Findings (MI) Domain

- Histopathological evaluation of liver biopsy
  - e.g., NAS, Fibrosis stage
- NAS and NASH CRN fibrosis can be recorded using:
  - ***Microscopic Findings Test Detail (MITSTDTL)***
  - ***Microscopic Findings Test Code (MITESTCD)***
  - ***Microscopic Findings Test Name (MITEST)***
- Capture observer details using the ***Evaluator (MIEVAL)*** and ***Evaluator ID (MIEVALID)*** variables
- Use of ***Accepted Record Flag (MIACPTFL)*** variable

Example of MI Domain

Recommended Test Codes, Tests, Test Details and Results

MITESTCD	MITEST	MITSTDTL	MIORRES
NASHIND	Histological Presence of NASH with Fibrosis Indicator		Yes, No
NAS	NAFLD Activity Score	STEATOSIS	0, 1, 2, 3
NAS	NAFLD Activity Score	LOBULAR INFLAMMATION	0, 1, 2, 3
NAS	NAFLD Activity Score	BALLOONING	0, 1, 2
NAS	NAFLD Activity Score	TOTAL SCORE	0, 1, 2, 3, 4, 5, 6, 7, 8
STEAT	Steatosis	STEATOSIS GRADE	<5%, 5-33%, >33-66%, >66%
STEAT	Steatosis	STEATOSIS LOCATION	Zone 3, Zone 1, Azonal, Panacinar
STEAT	Steatosis	MICROVESICULAR STEATOSIS	Present, Absent
FIBROSIS	Fibrosis	NASH CRN FIBROSIS STAGE	None, Mild zone3, Moderate zone 3, Portal/periportal, Zone 3 & Periportal, Bridging, Cirrhosis
INFLAM	Inflammation	LOBULAR INFLAMMATION	No foci, <2 foci, 2-4 foci, >4 foci
INFLAM	Inflammation	PORTAL INFLAMMATION	None to minimal, >Minimal
HCCINJ	Hepatocellular Injury	BALLOONING DEGENERATION	None, Few, Many
PTNUM	Number of Portal Tracts		

Supplemental Microscopic Findings (SUPPMI) Domain

- Assess the adequacy of biopsy sample(s) collected for analysis
- Link to : BS & MI domain

RDOMAIN	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
MI	Use these variables to link back to MI domain		MIOIQ	Overall Image Quality	Expected Values: Adequate, Not Adequate
MI			MIIMCND	Image Condition	e.g., Blurry Image, Cracked Slide, Multiple
MI			MIIMCND1	Image Condition 1	List Condition 1 if Multiple Conditions
MI			MIIMCND2	Image Condition 2	List Condition 2 if Multiple Conditions

Biomarker: Laboratory (LB) Domain & Disease Response and Clinical Classifications (RS) Domain

- LB Domain:
  - Serum biomarkers relevant to NASH, liver fibrosis, or DILI (should be discussed with DHN)
  - Components used to derive a calculated serum biomarker
- RS Domain:
  - MELD Score
  - Child-Pugh Classification
  - West Haven Hepatic Encephalopathy Grade

Baselines

- Baseline values
- Baseline categorization of that value relative to ULN

ADSL Baseline Lab Characteristics			
Variable Name	**Variable Label**	**Type**	**Comments**
ALTBL	**Baseline ALT**	Num	ADLB.AVAL where ADLB.PARAMCD = 'ALT' and ADLB.DILIBLFL = 'Y'
ALTCAT	**Baseline ALT Category**	Text	Divide ADSL.ALTBL by LB.LBSTNRHI for the last pre-treatment record for ALT and set the category to one of the following: • If result is <= 1: <= 3 <=ULN • If result is >1 to <= 3: > ULN to <=3x ULN • If result is >3 to ≤5: >3x ULN to ≤5x ULN • If result is >5: >5x ULN
ALTCATN	**Baseline ALT Category (N)**	Integer	Numeric Representation of ALTCAT. "1" = "<=ULN", "2" = ">ULN to <=3x ULN", "3" = ">3x ULN to <=5x ULN", "4" = ">5x ULN"
ASTBL	**Baseline AST**	Num	ADLB.AVAL where ADLB.PARAMCD = 'AST' and ADLB.DILIBLFL = 'Y'
ASTCAT	**Baseline AST Category**	Text	Divide ADSL.ASTBL by LB.LBSTNRHI for the last pre-treatment record for AST and set the category to one of the following: • If result is <=1: <= ULN • If result is >1 to <=3: >ULN to <=3x ULN • If result is >3 to <=5: >3x ULN to <=5x ULN • If result is >5: >5x ULN
ASTCATN	**Baseline AST Category (N)**	Integer	Numeric Representation of ASTCAT. "1" = "<=ULN", "2" = ">ULN to <=3x ULN", "3" = ">3x ULN to <=5x ULN", "4" = ">5x ULN"
ALPBL	**Baseline ALP**	Num	ADLB.AVAL where ADLB.PARAMCD = 'ALP' and ADLB.DILIBLFL = 'Y'
ALPCAT	**Baseline ALP Category**	Text	Divide ADSL.ALPBL by LB.LBSTNRHI for the last pre-treatment record for ALP and set the category to one of the following: • If result is <=1: <= ULN • If result is >1 to <=2: > ULN to <=2x ULN • If result is >2: >2x ULN
ALPCATN	**Baseline ALP Category (N)**	Integer	Numeric Representation of ALPCAT. "1" = "<=ULN", "2" = ">ULN to <=2x ULN", "3" = ">2x ULN"
TBILIBL	**Baseline Total Bilirubin**	Num	ADLB.AVAL where ADLB.PARAMCD = 'BILI' and ADLB.DILIBLFL = 'Y'
TBILCAT	**Baseline Tot. Bilirubin Category**	Text	Set to "<=ULN" if ADSL.TBILIBL <= LBSTNRHI (for the last pre-treatment record in SDTM.LB where LBTESTCD = "BILI"); else set to ">ULN" if ADSL.TBILIBL > LBSTNRHI

Laboratory Analysis Data Set (ADLB)

Include all tests and records in the SDTM.LB domain

Dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review

Clearly indicate the units that the data was originally collected in if conversion of units

Imaging Results (ZI) Domain

- Custom domain
- Captures results of liver imaging (e.g., MRI or CT scan)
- Adopt the structure of a Findings Domain
  - Imaging Results Test (ZITEST)
  - Imaging Results Test Code (ZITESTCD)
  - Imaging Results Original Result (ZIORRES)

Esophagogastroduodenoscopy (EGD)

- EGD information: Procedures (PR) Domain
- Results of EGD: model ZI Domain, may consider GI Findings Domain in future

Adjudication (ZA) Domain

- Custom domain
- Events and/or clinical outcomes adjudicated by investigator(s) and/or committee(s) such as:
  - Liver-Related Death
  - Hepatic Decompensation Events
  - Major Adverse Cardiac Events (MACE)
  - DILI
- Follow the structure of a Findings About Events or Interventions (FA) Domain

Adjudication (ZA) Domain

- Examples of information stored:
  - Event assessment
  - Date of assessment
  - Adjudicator identifier
  - Accepted Record Flag

Example Terminology for Adjudicated Events and Outcomes

ZAOBJ	ZATESTCD	ZATEST	ZAORRES
DILI	ADJDILI	DILI ADJUDICATION SCORE	1-6
	ADJDATE	EVALUATED EVENT ONSET DATE	Adjudicator's assessment of when the subject met event criteria
CARDIAC MACE	ADJCRIT	EVENT CRITERIA MET	Yes, No
	ADJDATE	EVALUATED EVENT ONSET DATE	Adjudicator's assessment of when the subject met event criteria
CARDIAC DEATH	ADJCRIT	EVENT CRITERIA MET	Yes, No
	ADJDATE	EVALUATED EVENT ONSET DATE	Date of Death
LIVER-RELATED DEATH	ADJCRIT	EVENT CRITERIA MET	Yes, No
	ADJDATE	EVALUATED EVENT ONSET DATE	Date of Death
CAUSE OF DEATH	ADJOUT	ADJUDICATION OUTCOME	Adjudicator's assessment of cause of death
	ADJDATE	EVALUATED EVENT ONSET DATE	Date of Death
HEPATIC DECOMPENSATION EVENT	ADJOUT	ADJUDICATION OUTCOME	HEPATIC ENCEPHALOPATHY, ASCITES, VARICEAL BLEED, SPONTANEOUS BACTERIAL PERITONITIS
	ADJDATE	EVALUATED EVENT ONSET DATE	Adjudicator's assessment of when the subject met event criteria

Approach to DILI Data Submission

Custom flags in the ADAE and ADLB

- Hepatic injury
- Potential DILI AE event
- Baseline lab for purposes of DILI evaluation

Derived parameters

- Calculated R value
- Ratio to ULN
- Ratio to baseline

Custom DILI Analysis Data Set (ADDILI)

DILI – ADAE Flags

- Potential DILI event
- Sponsor should create custom queries and accompanying flags: PT suggestive of hepatic injury within the MedDRA hierarchy
- Identify the earliest record within each hepatic injury flag
- Linking AE with lab DILI threshold (e.g., DILIAFL)

Variable Name	Variable Label	Type	Comments
HPxxFL	**Hepatic Injury xx Flag**	Char	Expected values: "Y" or null Sponsors should create Hepatic Injury Flag(s) to capture specific preferred terms within the MedDRA hierarchy. Sponsors should consult FDA regarding how many flags are required and how exactly to derive each flag.
HPFxxFL	**First Hepatic Injury xx Flag**	Char	Expected values: "Y" or null Create one additional flag for each HPxxFL flag created and flag the earliest (min ASTDY) on treatment (ASTDY >= 1) for each subject and record that fits the criteria. Otherwise, null
DILIFL	**Potential DILI Event Flag**	Char	Expected values: "Y" or null Flag the following Adverse Events as "Y": Fatigue, Nausea, Vomiting, Abdominal pain or tenderness, Fever, Rash, Pruritus, Jaundice/icterus, Altered mental status
DILIPFL	**Potential DILI Event Flag (30-days prior)**	Char	Expected values: "Y", "N" or null Null for records where DILIFL is null. For records with DILIFL = "Y": if the event occurs in the 30 days before a lab-identified DILI threshold met in the ADDILI data set, then "Y". Else, "N"
DILIAFL	**Potential DILI Event Flag (30-days after)**	Char	Expected values: "Y","N" or null Null for records where DILIFL is null. For records identified with DILIFL = "Y": if the event occurs in the 30 days after a lab-identified DILI threshold met in the ADDILI data set, then "Y". Else, "N"

DILI - ADLB

- Include unscheduled visits with liver-related lab results
- Example Flags:
  - DILI Baseline
  - DILI Onset
  - Peak value
  - Lab value ≤ 50% of peak increase

Variable Name	Variable Label	Type	Comments
DILIFL	**Drug-Induced Liver Injury Flag**	Char	Expected Value: "Y" or null This flag should have "Y" for the following records: • ALT, AST, ALP, GGT, Total Bilirubin, Direct Bilirubin, INR records AND • The evaluable record for each test at each visit. If more than one record is collected at each visit, a derived record should be created with DTYPE = "AVERAGE". The average record should be flagged, and the individual records used to create the average record should not be flagged. Unscheduled visits may also be flagged as "Y". Else, null
DILIBLFL	**DILI Baseline Flag**	Char	Expected Value: "Y" or null For each subject and liver biochemistry parameter, flag the baseline record used for DILI analysis as "Y".
R2ANRHI	**Ratio to Analysis Range Upper Limit**	Num	Ratio to the upper limit of the analysis range. Equal to AVAL / ANRHI.
R2BASE	**Ratio to Baseline Value**	Num	Ratio to the baseline value. Equal to AVAL / BASE. If used for a given PARAM, should be populated for all post-baseline records of that PARAM regardless of whether that record is used for analysis.
PEAKFL	**DILI Peak Flag**	Char	Expected Values: "Y", "N" or null Null for all pre-treatment records and records where DILIFL = "N". If ANL02FL = "Y" and DILIFL = "Y", then "Y". Otherwise, "N"
REDUCEFL	**DILI Reduction Flag**	Char	Expected Values: "Y", "N" or null Null for all pre-treatment records and records where DILIFL = "N". Flag the first record after PEAKFL for each subject and parameter in which AVAL is equal to or less than 50% of the value of AVAL where PEAKFL = "Y"
ONSETFL	**DILI Lab Onset Flag**	Char	Expected Values: "Y" or null

Custom DILI Analysis Data Set (ADDILI)

Sponsor to seek agreement with DHN to established criteria for potential DILI

Custom Parameters

- Potential DILI (Y/N)
- Outcome of potential DILI (e.g., fatal, recovered/resolved etc.)
- Action taken (e.g., dose unchanged, drug interrupted)

Custom Variables

- Calculated R value
- Post-baseline max ratios (e.g., ALT/ULN or ALT/BL)
- Indicate components of DILI workup performed e.g., Hepatitis serology, alcohol intake, imaging etc.

Example of Recommended ADDILI Variables

Variable Name	Variable Label	Type	Comments
PARAM	Parameter	Char	Expected values: “Potential DILI” and “Outcome of Potential DILI”, “Action Taken from Potential DILI”
PARAMCD	Parameter Code	Char	• For PARAM = Potential DILI: “DILI” • For PARAM = Outcome of Potential DILI – Outcome: “OUTDILI” • For PARAM = Action Taken from Potential DILI= “ACNDILI”
AVAL	Analysis Value	Num	Expected Values: 1 or 0 Note: The criteria below are example criteria for evaluation of DILI. Sponsors may consult the FDA for appropriate criteria for their study. Example 1: PARAMCD = “DILI”: • If ALTULNMX >= 3 and TBALTMX >= 2 and ALPALTMX < 2, then 1 OR • If ASTULNMX >= 3 and TBASTMX >= 2 and ALPASTMX < 2, then 1 • Else 0 Example 2: PARAMCD = “DILI”: • If ALPULNMX >= 2 and TBALPMX >= 2, then 1 • Else 0
AVALC	Analysis Value (C)	Char	If AVAL = 1, then “Y”; if AVAL = 0, then “N” For PARAMCD = “OUTDILI” • Expected values: “FATAL”, “NOT RECOVERED/NOT RESOLVED”. “RECOVERED/RESOLVED”, “RECOVERED/RESOLVED WITH SEQUELAE”, “RECOVERING/RESOLVING”, “UNKNOWN” For PARAMCD = “ACNDILI”: • Expected values: “DOSE INCREASED”, “DOSE NOT CHANGED”, “DOSE RATE REDUCED”, “DOSE REDUCED”, “DRUG INTERRUPTED”, “DRUG WITHDRAWN”, “NOT APPLICABLE”, “UNKNOWN”

Additional SDTM Domains

Microbiology Specimens (MB) Domain:

- Include hepatitis serology test results (hepatitis A, B, C, and E)
- Data collection: baseline and during potential DILI assessments

Substance Use (SU) Domain:

- Quantify substance use
- Data collection: Baseline, scheduled visit, suspected DILI

Trial Summary (TS) Domain:

- Parameter to indicated use of NASH Tech Spec

How the NASH Tech Spec Facilitate Data Submission

1

Connection to appropriate existing controlled terminology

2

Guidance on new modeling strategy and/or controlled terminology where existing modeling inadequate

3

Creation of supplemental or custom domain(s) when more granular details may be required

Summary

- Outlines data specifications to support evaluation of efficacy and safety for NASH clinical trials
- Guidance for how to submit SDTM domains and ADaM data sets, but left parameters flexible to sponsors
- DILI evaluation related data elements can be generalizable to non-liver disease clinical trials
- Recommend early communication with DHN to define parameters, their derivations, custom parameters/data sets

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Questions

Email: ondbiomedicalinformatics@fda.hhs.gov

NASH Tech Spec Link