
PARK CITY, UTAH • MARCH 11-13, 2021
NASH-TAG
CONFERENCE
2021

Seladelpar's Hold and Release: What Happened and What Did We learn?

Stephen Harrison, MD

Seladelpar

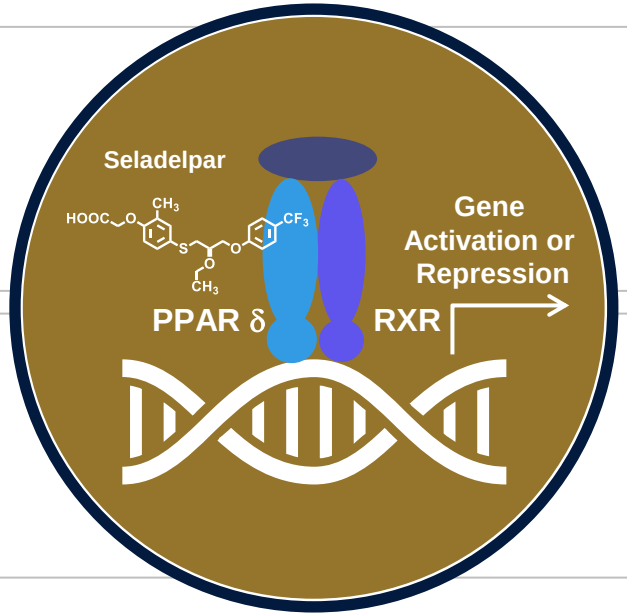
A potent and selective PPARδ agonist

DECREASE BILE ACIDS

- ↓ Cholesterol synthesis
- ↓ Bile acid synthesis (C4)
- ↑ Transport

HEPATOCYTE

CHOLANGIOCYTE



ANTI-INFLAMMATORY

- ↓ NFκB-dependent gene activation
- ↓ Inflammatory cytokines
- ↓ hs-C-Reactive Protein

KUPFFER CELL

MACROPHAGE

ANTI-FIBROTIC

- ↓ Profibrotic genes
- ↓ Stellate cell activation
- ↓ Collagen synthesis/deposition

STELLATE CELL

INCREASE LIPID METABOLISM

- ↓ Cholesterol/LDL-C
- ↑ Fatty acid oxidation
- ↑ Insulin sensitivity

HEPATOCYTE

MYOCYTE

ADIPOCYTE

ENTEROCYTE

Targets important cell types in liver disease

PPARδ, peroxisome proliferator-activated receptor delta.

Seladelpar Phase 2b Study in NASH

Paired liver biopsy 52-week study design: Liver fat ≥10%, NAS ≥4, F1 to F3, diabetes allowed

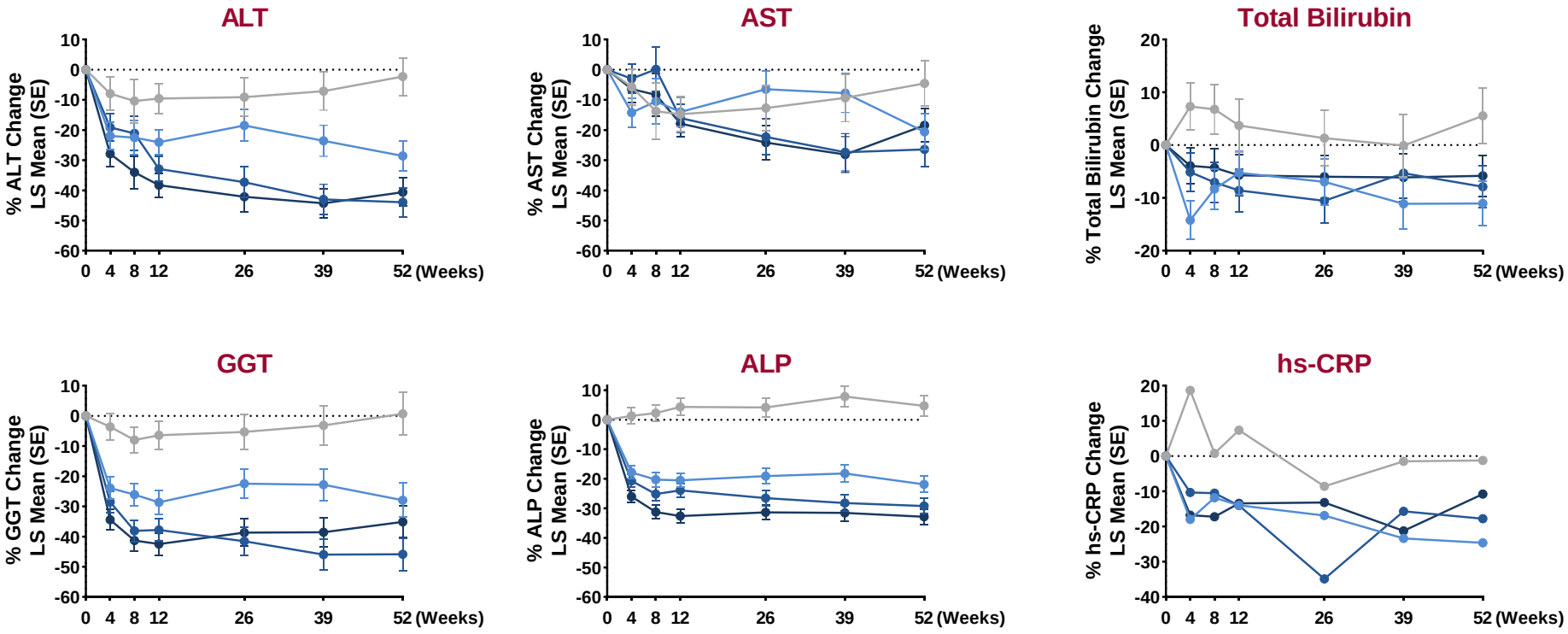
PRIMARY ENDPOINT
Change in Liver Fat Content
by MRI-PDFF

SECONDARY ENDPOINTS
Resolution of NASH
1-Stage Decrease
in Fibrosis

MRI-PDFF, magnetic resonance imaging proton-density-fat-fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score.

Seladelpar Effects on Liver Biochemistry in NASH Study

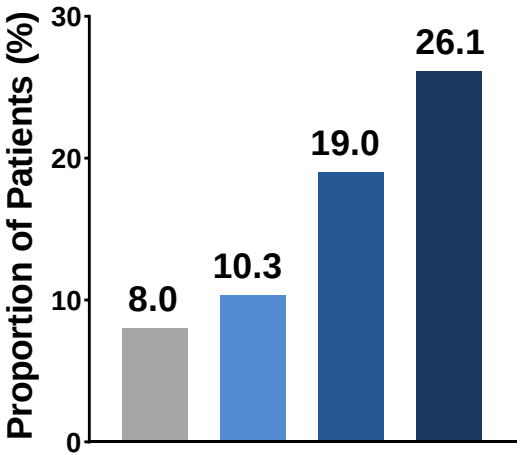
Dose-ordered and clinically meaningful improvements



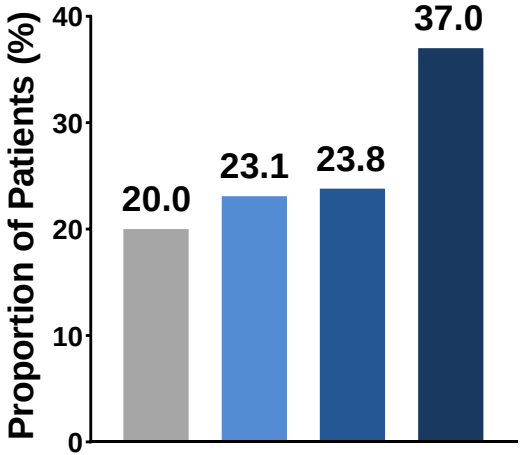
Seladelpar Liver Histology Response at Week 52/Early Termination

Dose-ordered increase in response rate for histological improvement*

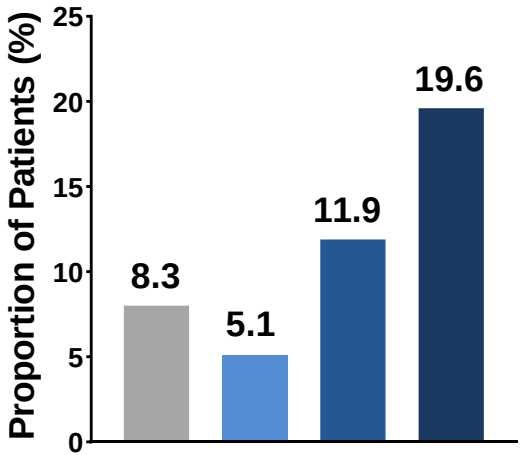
RESOLUTION OF NASH



FIBROSIS IMPROVEMENT



RESOLUTION OF NASH & FIBROSIS IMPROVEMENT



Placebo (n=19) 10 mg (n=33) 20 mg (n=40) 50 mg (n=40)

* None are significant versus placebo

Liver Biopsy Reading – Study Pathologists

- Single pathologist
- 307 screened, 181 randomized
- NAS, portal inflammation, and fibrosis scored

- Two pathologists
- ET reading initiated ≥ 9 months after last BL biopsy read
- Consensus reading until study was terminated
- Pathologists blinded only to treatment group
- No rescoring of BL biopsies
- NAS, portal inflammation, and fibrosis scored

NASH Histology “Unexpected” Findings

- **Blinded review of 52-week biopsies**
  - “Atypical” findings identified by study pathologists
  - Biochemistry improved or stable (ALT, AST, GGT, bilirubin)
  - No DILI signs or symptoms – rash, jaundice, eosinophilia, etc
  - No pattern of baseline demographics, concomitant medications or comorbidities
  - All seladelpar studies were discontinued and placed on hold

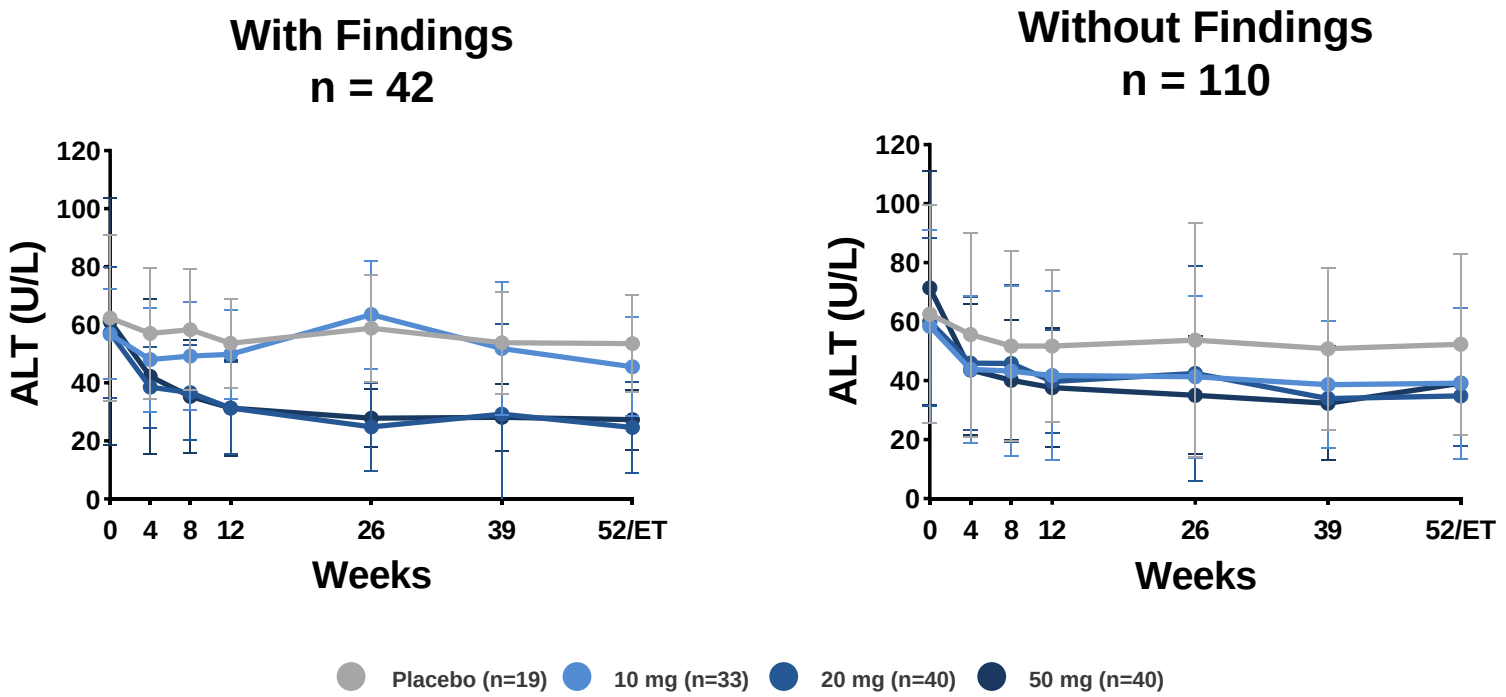
- **42 of 152 subjects with “atypical” findings**
  - Interface hepatitis with and without
    - Plasma cells/eosinophils
    - Bile duct injury
  - A few cases of what study pathologists described to be “vascular changes” or “PSVD-like lesions”
  - Other isolated findings (e.g., granuloma)

PLACEBO (N=25)	SELADELPAR 10 mg (N=39)	SELADELPAR 20 mg (N=42)	SELADELPAR 50 mg (N=46)
6/25 (24%)	8/39 (20.5%)	10/42 (23.8%)	18/46 (39.1%)

Seladelpar Phase 2b Study in NASH

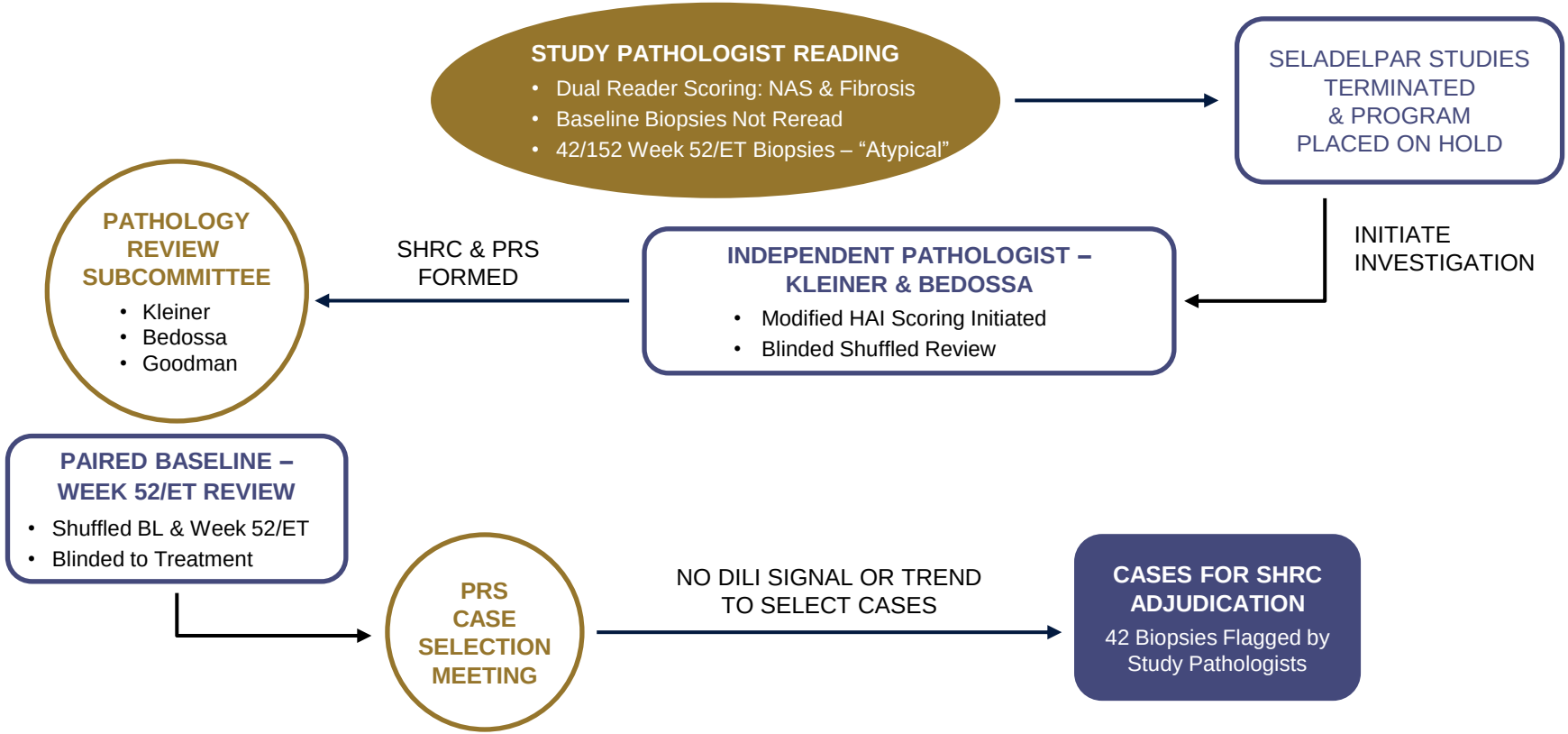
ALT levels with and without atypical findings

ALT



Events Leading to SHRC Meetings

November 2019 — May 2020



Pathology Review Subcommittee

Case Selection Meeting – April 22

All biopsies (n=302, fully blinded)
Modified HAI Score
Bedossa & Kleiner

Liver Injury Assessment
Grading in 4 categories:

- **Interface Hepatitis**
- Bridging Necrosis
- Focal Necrosis/inflamm
- **Portal Inflammation**

Fibrosis staging – Ishak
Other

- **Bile duct injury**
- **Immune cells (Plasma cells & Eosinophils)**

Kleiner DE, Chalasani NP, Lee WM, et al; Drug-Induced Liver Injury Network (DILIN). Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology.* 2014;59(2):661-670.

Paired Baseline and Week 52/ET (n= 151, blinded to order)
Better, Same, Worse
Bedossa, Kleiner & Goodman

Interface Hepatitis
Portal Inflammation
Parenchymal Inflammation
Steatosis
Ballooning
Fibrosis
Plasma Cells
Eosinophils
Bile duct injury
Vascular Injury

Seladelpar Hepatotoxicity Review Committee (SHRC)

CLINICAL EXPERTS IN DRUG-INDUCED LIVER INJURY

Paul Watkins, MD – Chair
University of North Carolina, Chapel Hill

Willis Maddrey, MD
University of Texas Southwestern Medical Center

Neil Kaplowitz, MD
University of Southern California

LIVER PATHOLOGY EXPERTS* IN DRUG-INDUCED LIVER INJURY AND NASH

David Kleiner, MD, PhD
NIH and the Reference Pathologist for the Drug-Induced Liver Injury Network

Pierre Bedossa, MD, PhD
University Paris-Diderot, France, and CEO of LIVERPAT

Zachary Goodman, MD, PhD
Center for Liver Disease, Inova Healthcare Services

CLINICAL EXPERTS IN NASH AND CHOLESTATIC DISEASE

Michael Charlton, MD
University of Chicago

John Vierling, MD
Baylor College of Medicine

* Pathology Review Subcommittee (PRS)

Additional Biomarker Assessments

Evaluation as putative laboratory correlates of drug induced immune injury

BIOMARKERS	ASSAY
Immune Process Marker	IgG
	IgA
	IgM
Autoimmune Marker	Autoantibodies (ANA & AMA)
	Smooth muscle antibody, IgG titer
	Liver kidney microsome antibody, IgG
	Extractable nuclear antigen antibodies (SSA 52, SSA 60, SSB)
Inflammatory Markers Cell Death	10 cytokine & chemokine/ inflammatory markers
	Cytokeratin (CK18-M65)

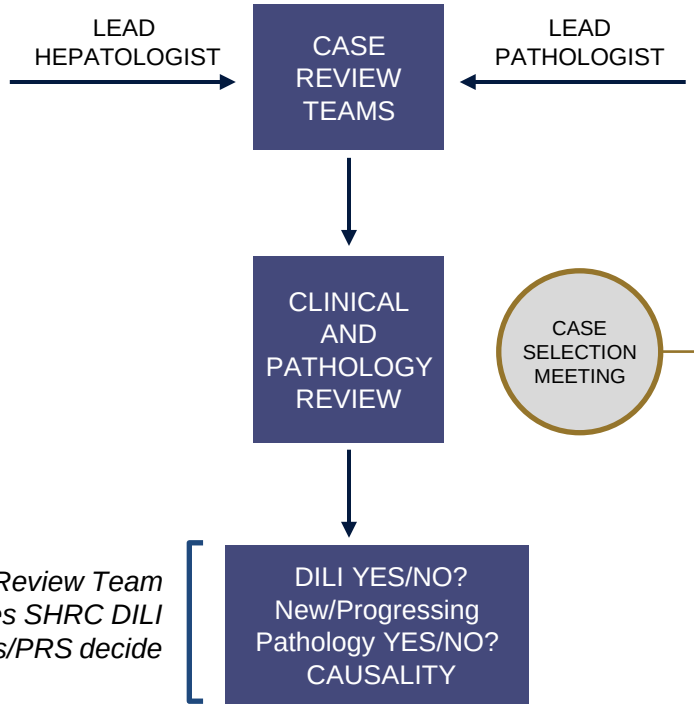
- Immunoglobulins were mostly normal, and changes were unremarkable
- ANA was often positive at baseline
- Tissue antibodies were sometimes positive at baseline
- Changes in detection of antibodies were uncommon without an evident association with atypical histology
- Inflammatory markers were largely unremarkable
- M65 (CK18) mostly decreased or remained the same.

Seladelpar Hepatotoxicity Review Committee

Case review and adjudication – April 27, 28, 30, and May 7, 2020

DILI CLINICAL HEPATOLOGISTS

- Paul Watkins (SHRC Chair)
- Willis Maddrey
- Neil Kaplowitz



Case Review Team proposes SHRC DILI Hepatologists/PRS decide

PATHOLOGY REVIEW SUBCOMMITTEE (PRS)

- Pierre Bedossa
- Zack Goodman
- David Kleiner

MODIFIED HAI SCORE (n=302)

Full blinding

- Pierre Bedossa
- David Kleiner

PRIOR INDEPENDENT PATHOLOGY REVIEWS

BETTER, SAME, WORSE (n=151 pairs)

Blinded for BL and Week 52/ET

- Pierre Bedossa
- David Kleiner
- Zack Goodman

SHRC Case Review Summary

- No cases of clinical/biochemical DILI (0 of 42)
- 69% (29 of 42) without evidence of new or progressive unexpected liver pathology
- 31% (13 of 42) with evidence of new or progressive unexpected liver pathology
  - No cases of highly likely or probable drug related (50% to 100%)
  - 1 case “possible” (25% to 49%)
  - 9 cases “unlikely” (<25%) – evenly distributed across treatment groups
  - 3 cases “not related” (0 to 10%)

Treatment	Not Related	Unlikely	Possible	Highly Likely	Probable
Placebo (n=25)	0	2	0	0	0
10 mg (n=39)	1	2	0	0	0
20 mg (n=42)	1	2†	0	0	0
50 mg (n=46)	1	3*	1‡	0	0

*One 50 mg case was a split decision – 3 votes Unlikely, 3 votes Not Related. †One 20 mg case was a split decision – 5 votes Unlikely, 1 vote Possible. ‡ Subject with long-standing lupus and diverticulitis prior to biopsy.

Seladelpar Hepatotoxicity Review Committee

Unanimous Consensus Statement – May 7, 2020

- The features noted by study pathologists at end of treatment were confirmed on this review. However, these did not differ qualitatively between baseline and end of treatment. We suspect these histologic features are underreported; however, in the experience of the pathology review subcommittee these features may be observed in patients with NASH.

- The panel unanimously concluded that the data in aggregate including the complete absence of clinical and biochemical evidence of drug-induced liver injury and the lack of significant differences in histologic features or their changes across the placebo and treatment groups do not support injury related to seladelpar.

- The panel also unanimously supported lifting of the clinical hold and the re-initiation of clinical development.

Summary

- Portal inflammation and interface hepatitis were common at baseline
  - Balance at baseline not controlled across treatment groups
  - Bile duct injury and immune cells also noted
  - Vascular injury perhaps pre-portal hypertension in advanced NASH with fibrosis?
- Bile duct injury and immune cells were noted but were more variable
- Changes in HAI grade were most often one grade
- Post hoc analysis did not establish significance of portal inflammation or interface
  - Hard to prove a negative, conclusions supported by:
    - Multiple reviewers
    - Different methods (HAI vs paired review)
    - Not dose ordered