Challenges with Histological System: Clinician Perspective

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DISCLOSURES

Scientific advisor or consultant for Akero, Alentis, Altimmune, Arrowhead, Axcella, Echosens, Enyo, Galectin, Genfit, Gilead, Hepagene, Hepion, HistoIndex, Intercept, Madrigal, Medpace, NGM Bio, Northsea, Novartis, Novo Nordisk, PathAI, Poxel, Sagimet, Terns, Viking.

Stock options: Akero, Cirius, Galectin, Genfit, Hepion, HistoIndex, PathAI, NGM Bio, Northsea.

Grant/Research support: Altimmune, Akero, Axcella, BMS, Cirius, CiVi Biopharma, Conatus, Corcept, Cymabay, Enyo, Galectin, Genentech, Genfit, Gilead, Hepion, Hepagene, Hightide, Ionis, Intercept, Madrigal, Metacrine, NGM Bio, Novartis, Novo Nordisk, Northsea, Pfizer, Sagimet, Viking.

1. What ? Is there a problem? **YES!**
2. So What? Why does it matter?
3. Now What ? How do we address this?

IS THERE A PROBLEM

HISTOLOGICAL ENDPOINT - CHALLENGES

Inter/intra observer variability

Sampling variability

Various central reading processes across programs

Different scoring systems

Core size, length, staining variability

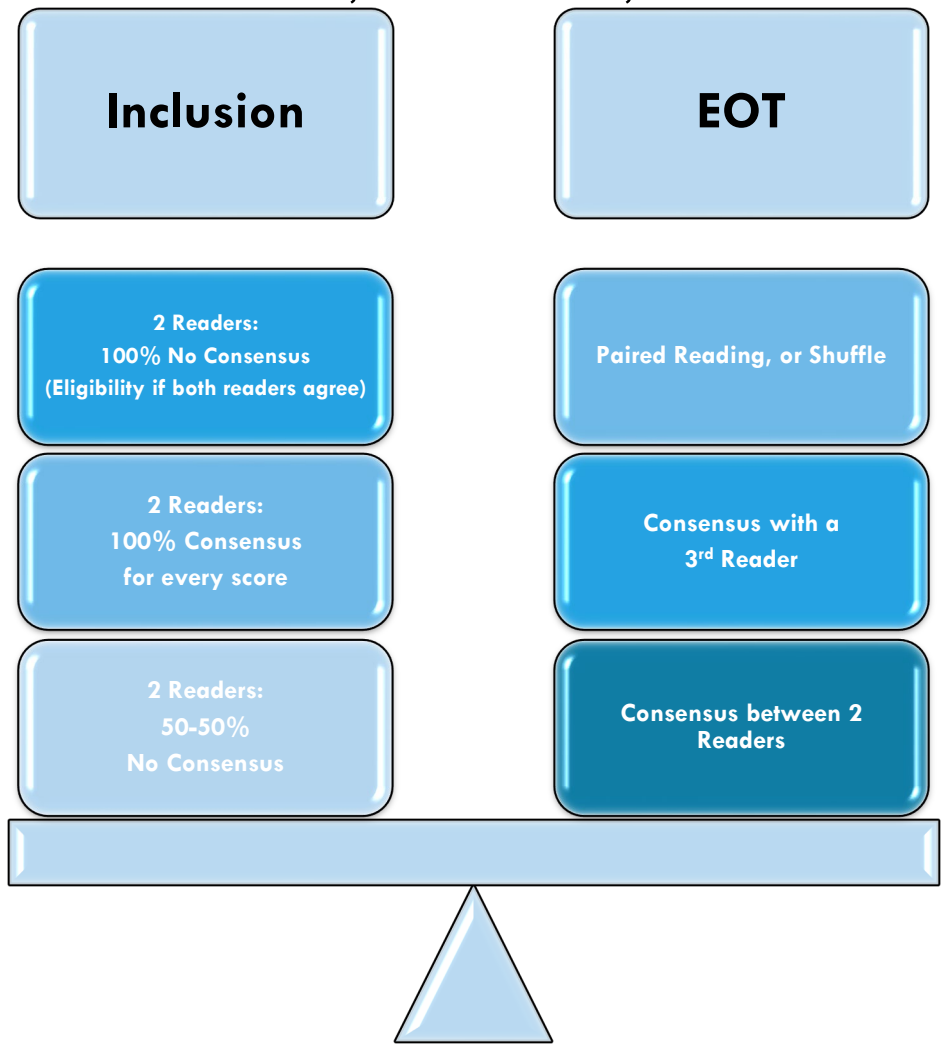
CENTRAL READING – NON STANDARDIZED METHODOLOGY

Screen Fail on Liver Biopsy Across Trials (Phase 2 & Phase 3)

From 33% to 65% SF

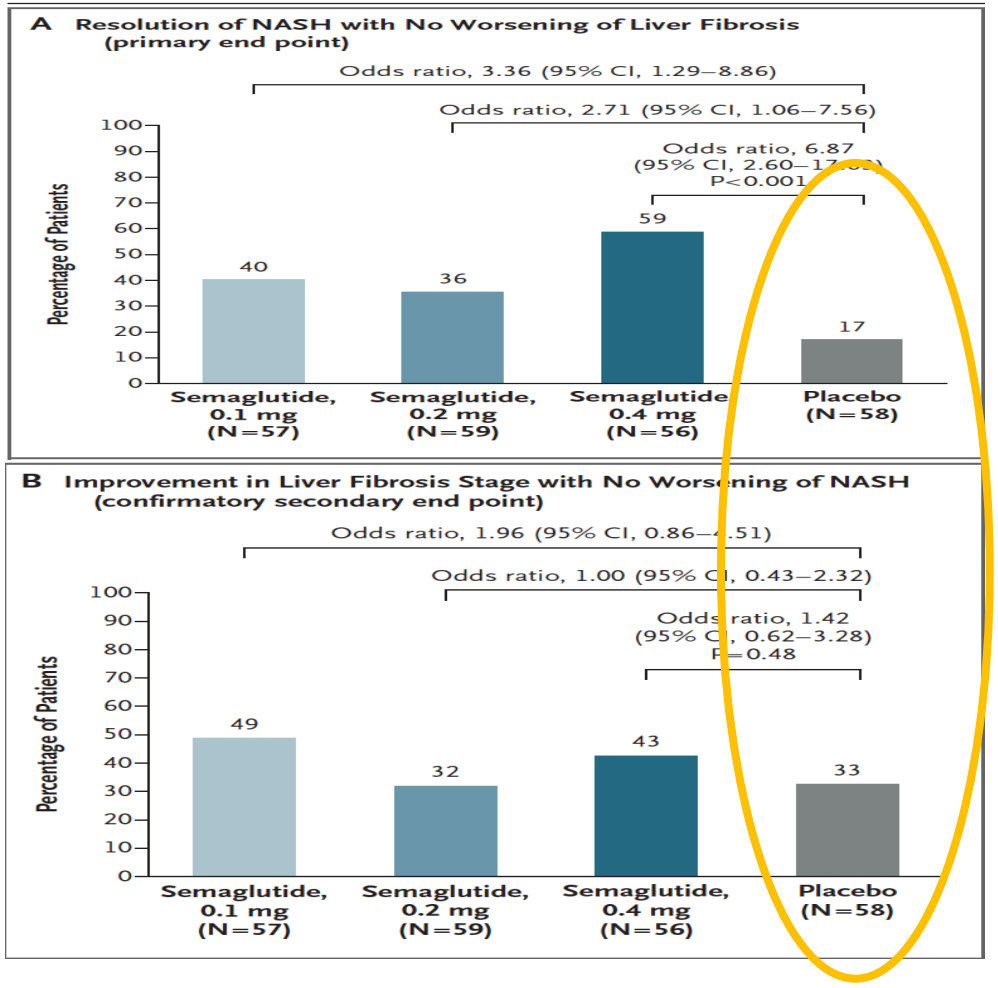
Need for improved reproducibility & standardization of central reading

Central Reading Methodology Differs Across Trials: 1 Reader, 2 Readers, 3 Readers



THE PLACEBO EFFECT

Semaglutide



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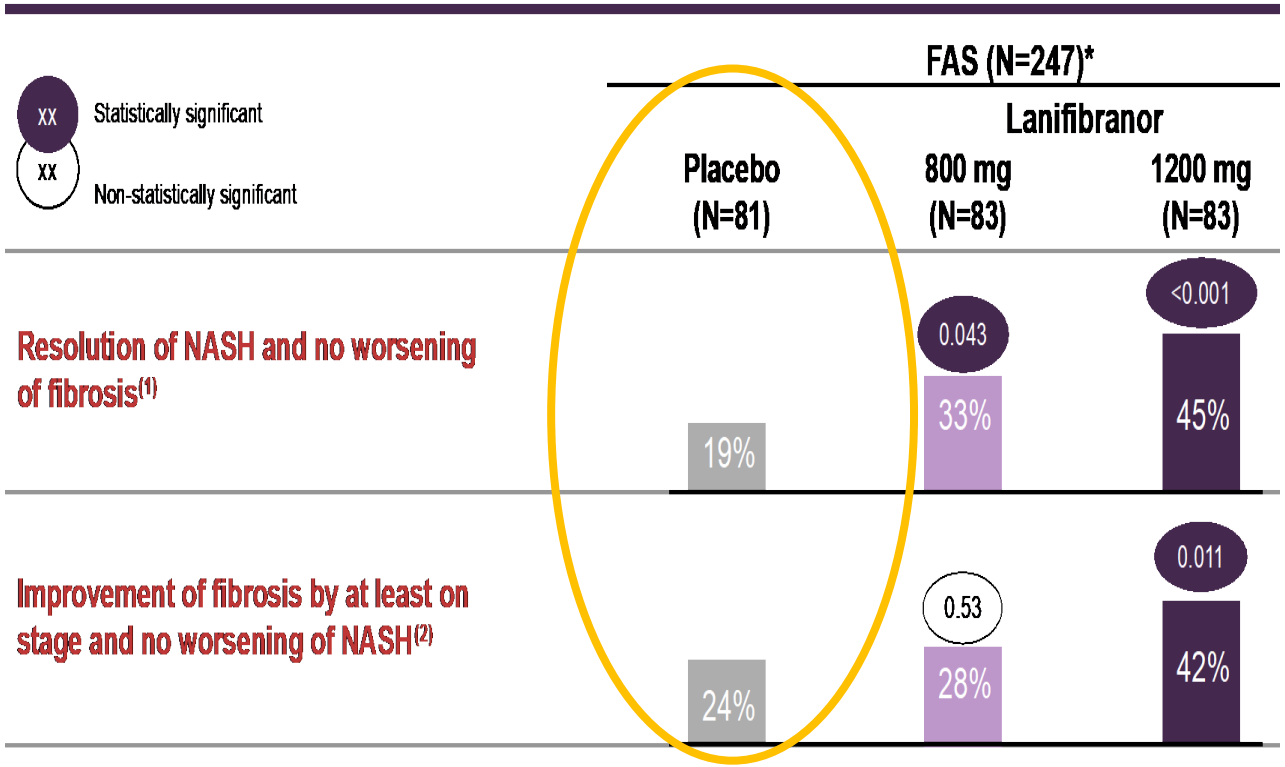

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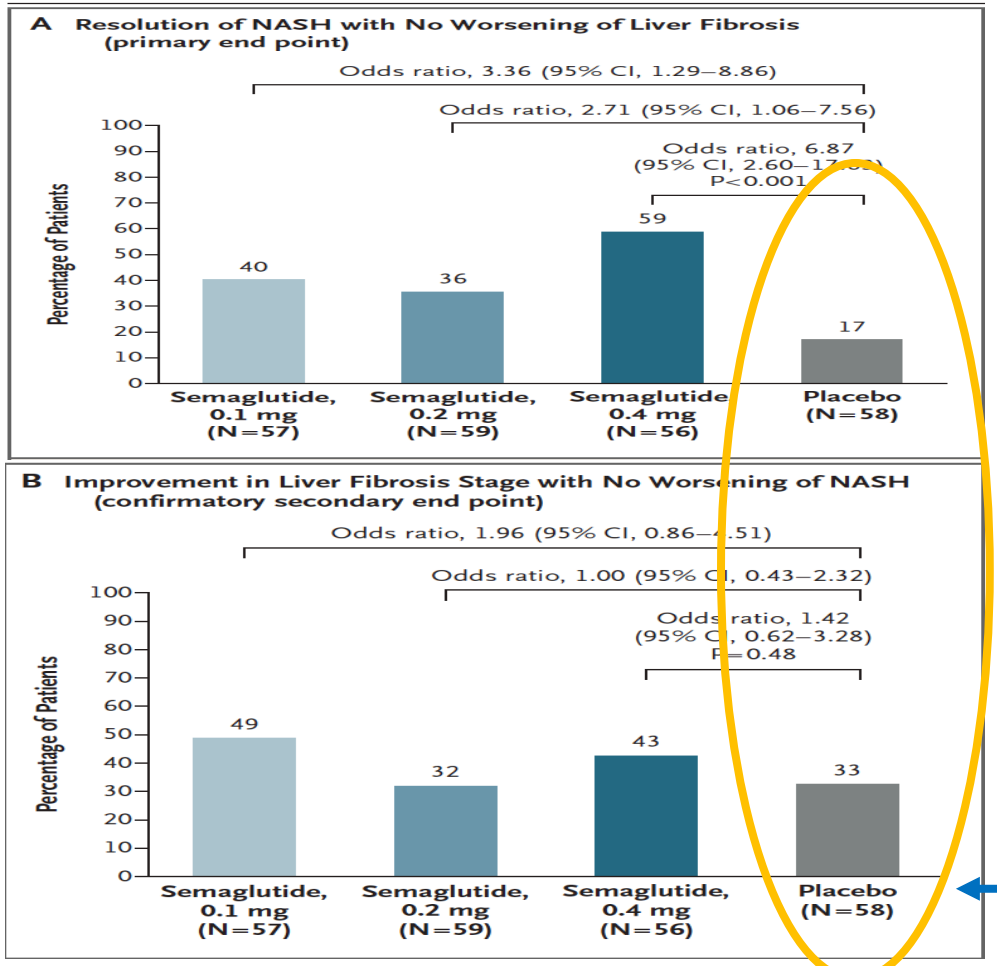

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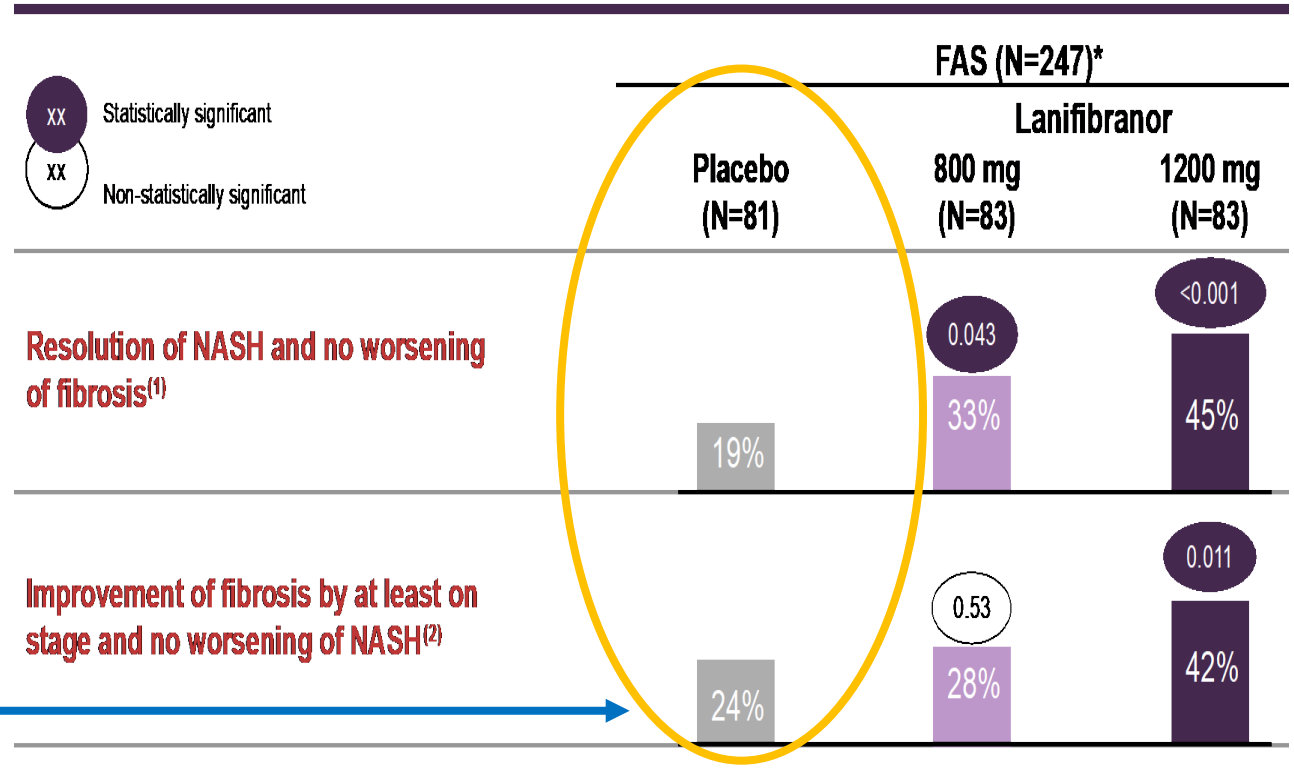

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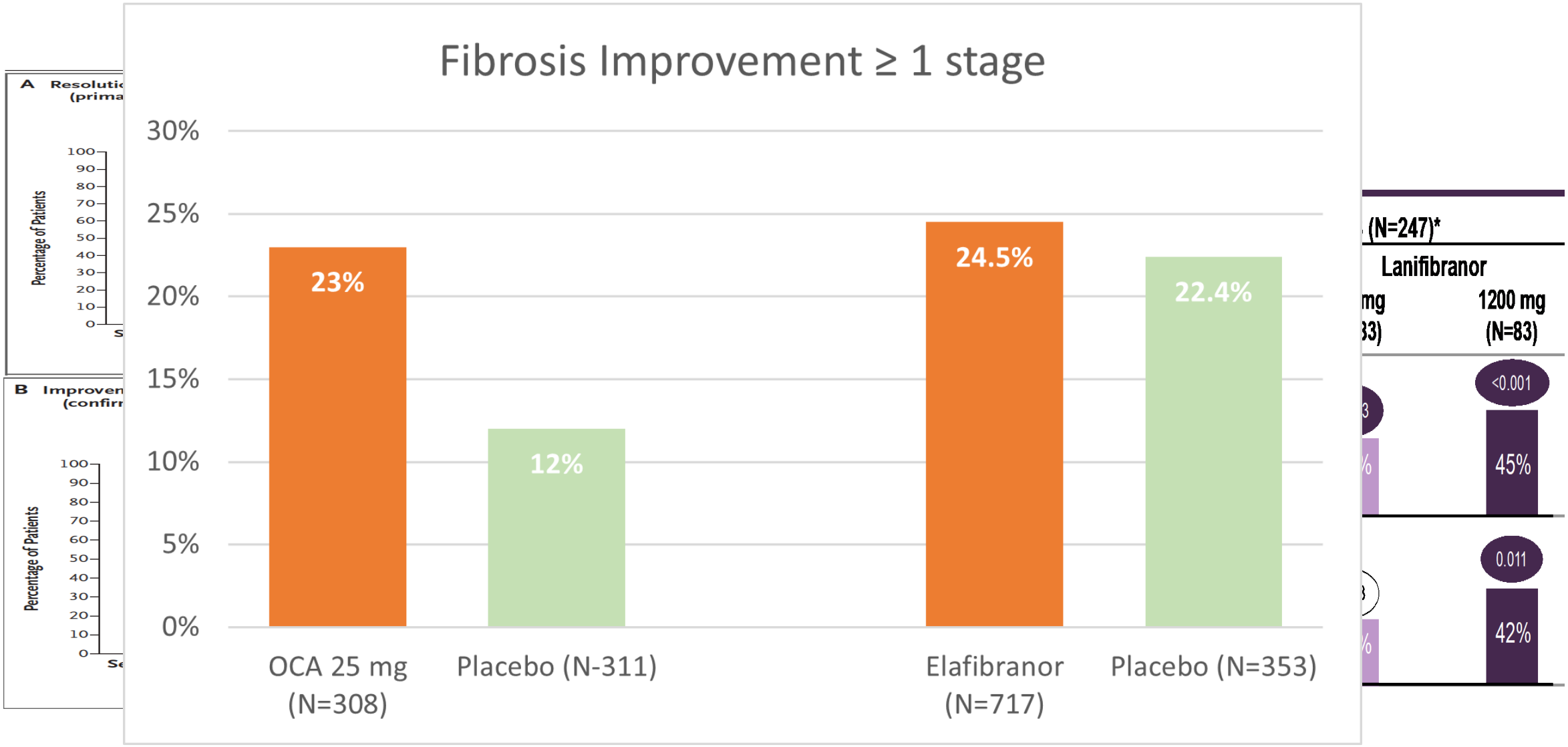
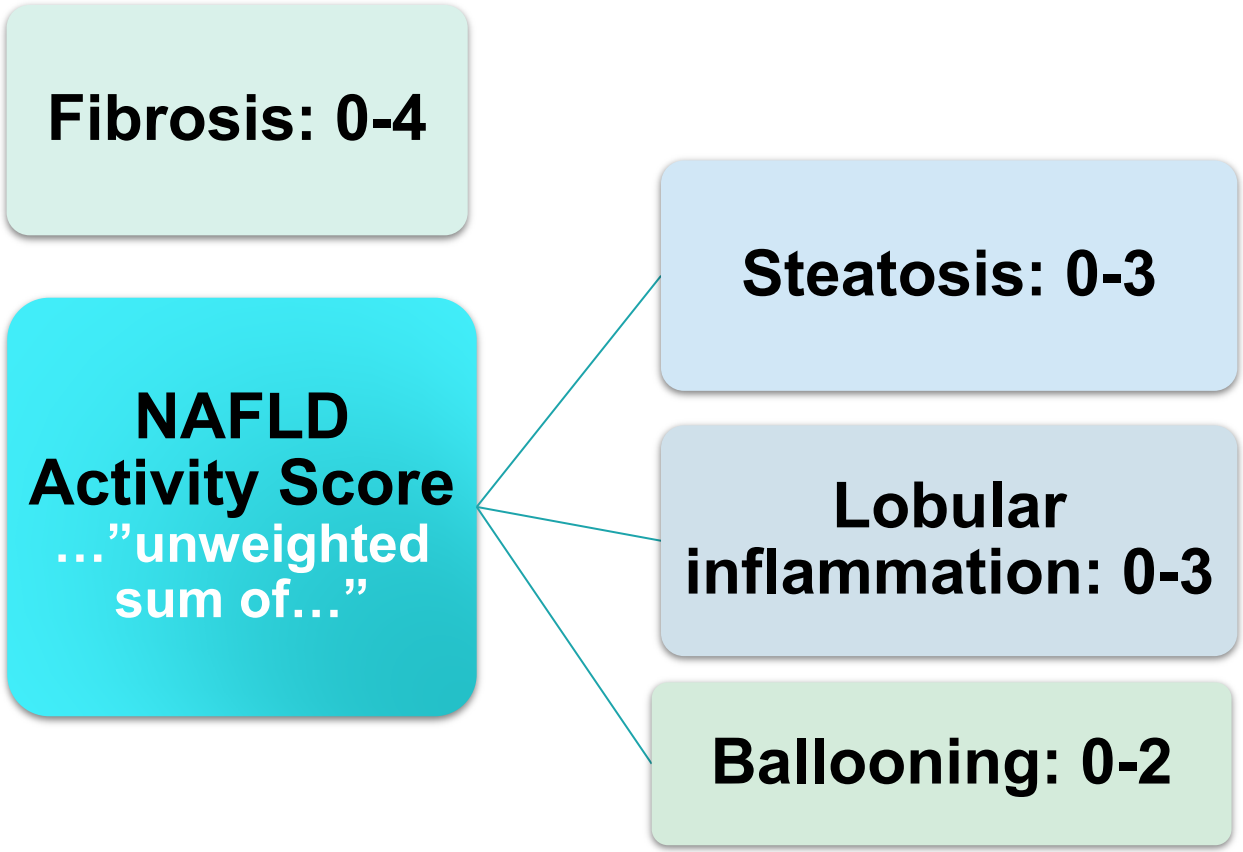


HISTOLOGY SCORING – NASH CRN



BUT

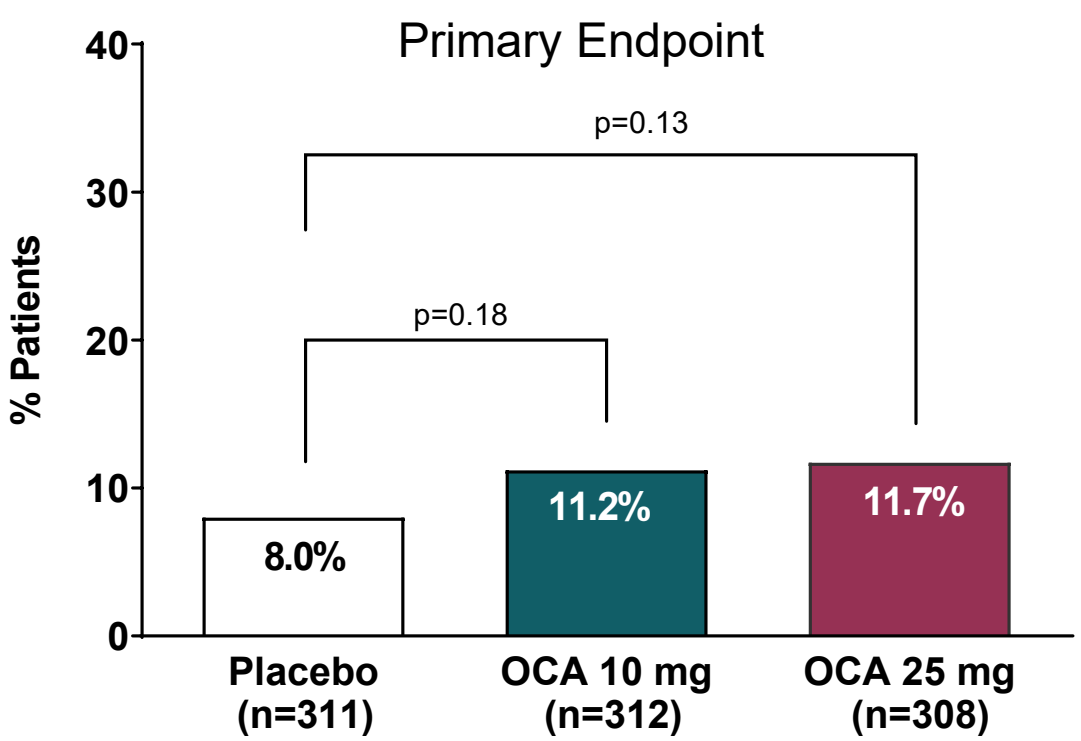
- Focus of paper on reader concordance
- No clear definitions for scoring
  - e.g. ballooning
    - 'None', 'few', 'many'
    - 3 balloon cells per High Power Fields *vs*
    - 3 balloon cells per 10 High Power Fields

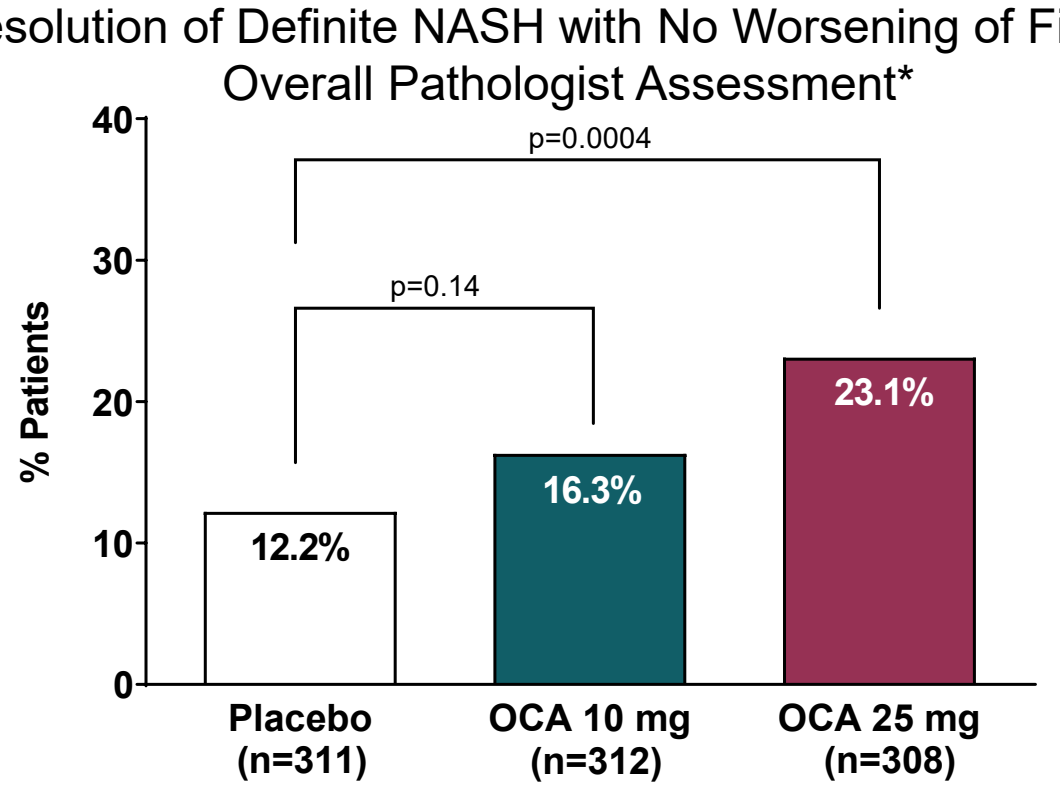
- Better suited for diagnosis than clinical trial use?

Kleiner et al for NASH CRN Hepatology 2005;41:1313-1321

REGENERATE PHASE 3 TRIAL

NASH Resolution with No Worsening of Fibrosis





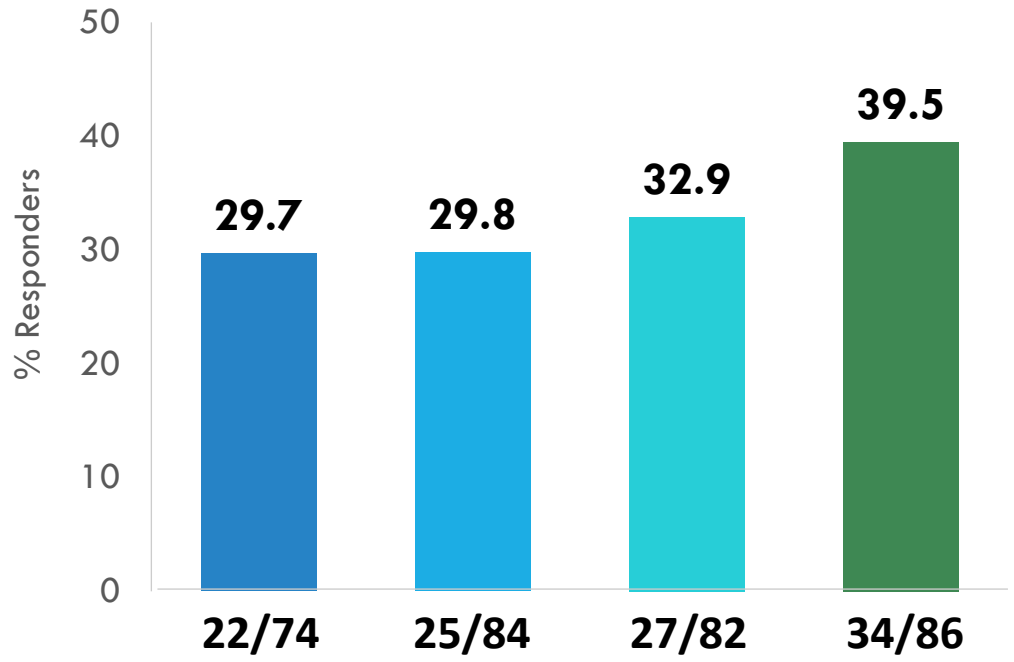
Primary endpoint definition:
(i) overall pathologist assessment of “no steatohepatitis,” and (ii) hepatocellular ballooning = 0 and lobular inflammation = 0 or 1, and (iii) no increase in fibrosis stage from baseline.
Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 interim analysis.
*Post-hoc analysis with endpoint defined as: (i) overall pathologist assessment of “no steatohepatitis,” and (ii) no increase in fibrosis stage from baseline.
P values are nominal. ITT population (N=931).

EMMINENCE PHASE 2B TRIAL

Histological Improvement (2 point) in NAS with no Worsening of Fibrosis

Primary Analysis

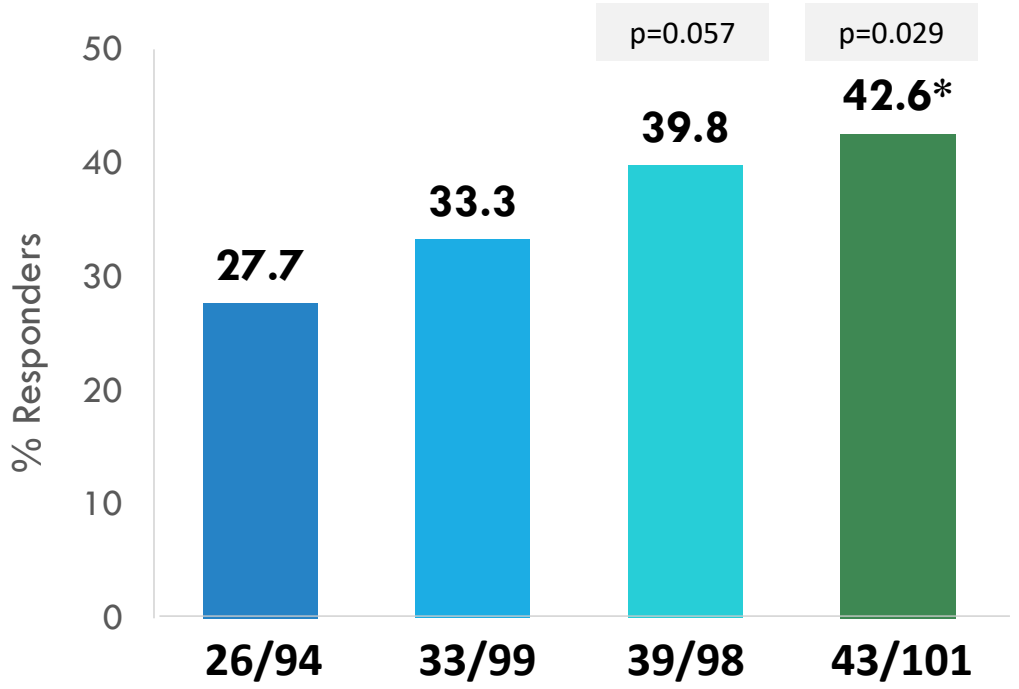
Re-Read, Observed Data



P value for dose as a linear predictor= 0.076

Post Hoc Analysis

Qualifying, Missing as non-responder



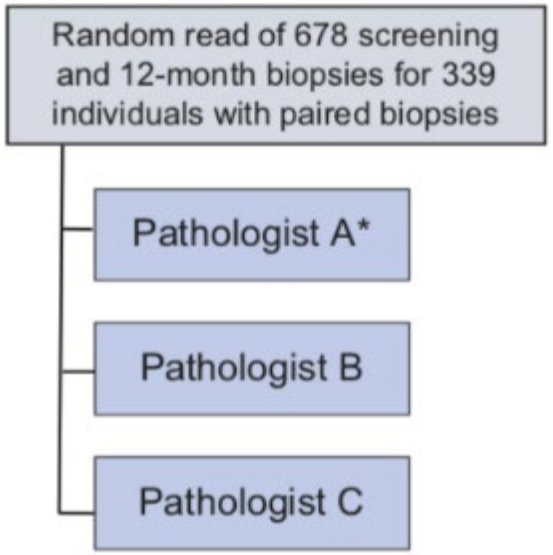
P value for dose as a linear predictor= 0.022

Placebo **62.5 mg** **125 mg** **250 mg**

The reduction in NAS must include at least a 1 point reduction in either ballooning or inflammation

SUBOPTIMAL RELIABILITY OF LIVER BIOPSY EVALUATION HAS IMPLICATIONS FOR RANDOMIZED CLINICAL TRIALS

EMMINENCE phase II study (insulin sensitizer: MSDC-0602K)
339 patients / 678 biopsies (digitized slides)



Overall inter-reader Comparison	Weighted κ
Inflammation	0.328
Ballooning	0.517
Steatosis	0.609
NAS	0.495
Fibrosis	0.484

Agreement between 3 pathologists ≈ 45% (inflammation, ballooning)
Agreement between 3 pathologists 12% for NAS and 69% for NASH diagnosis

- Full agreement for qualifying patients achieved in ≈ half of cases

More objective features ?

Davison BA J Hep 2020

INTEROBSERVER HISTOLOGY SCORING

EMMINENCE phase II study (insulin sensitizer: MSDC-0602K)

NASH Resolution with no worsening of fibrosis

Pathologist B

Pathologist A	No	Yes	N/E
No	64	9	2
Yes	8	16	1
N/E	0	0	0

Unweighted Kappa = 0.490

Pathologist C

Pathologist A	No	Yes	N/E
No	73	2	1
Yes	16	9	0
N/E	0	0	0

Unweighted Kappa = 0.382

Pathologist C

Pathologist B	No	Yes	N/E
No	69	3	0
Yes	18	7	0
N/E	2	1	1

Unweighted Kappa = 0.325

Davison B…. Dittrich H J Hepatol 2020; 73: 1322-1332

INTEROBSERVER HISTOLOGY SCORING

Table 3. Intra-reader reliability regarding NASH CRN Scores.

NASH CRN score	Intra-reader comparison	% Agreement*	% Agreement expected by chance*	Unweighted Kappa (95% CI)*	Weighted Kappa (95% CI)†	Weighted % agreement expected by chance†
NAS	Pathologist A - Qualifying *vs.* re-read of Screening (n = 389)	37.02	21.97	0.193 (0.133–0.253)	0.372 (0.318–0.427)	82.80
	Pathologist A - Qualifying *vs.* re-read of Screening (n = 200)	39.00	22.63	0.212 (0.127–0.296)	0.372 (0.294–0.449)	83.19
	Pathologist B - Individual *vs.* Paired Read of Screening (n = 200)	61.50	18.57	0.527 (0.443–0.611)	0.718 (0.656–0.779)	79.44
	Pathologist B - Individual *vs.* Paired Read of Screening and 12-Month (n = 400)	58.75	14.97	0.515 (0.457–0.572)	0.758 (0.721–0.794)	74.22
Fibrosis	Pathologist A - Qualifying *vs.* re-read of Screening (n = 389)	71.98	34.30	0.573 (0.510–0.637)	0.679 (0.625–0.733)	74.29
	Pathologist A - Qualifying *vs.* re-read of Screening (n = 200)	73.50	34.45	0.596 (0.509–0.683)	0.720 (0.654–0.787)	74.83
	Pathologist B - Individual *vs.* Paired Read of Screening (n = 200)	86.50	28.54	0.811 (0.746–0.877)	0.876 (0.832–0.921)	73.16
	Pathologist B - Individual *vs.* Paired Read of Screening and 12-Month (n = 400)	84.50	28.67	0.783 (0.734–0.832)	0.854 (0.819–0.890)	72.72

NASH, non-alcoholic steatohepatitis; NASH CRN, NASH Clinical Research Network.
Note: for n = 200, limited to those accessions re-read by Pathologist B.
*Unevaluable score considered as a response category.
†Using linear (Cicchetti-Allison) weights, omitting unevaluable responses and ignoring any correlation of visits within individuals.

Davison B…. Dittrich H J Hepatol 2020; 73: 1322-1332

INTEROBSERVER HISTOLOGY SCORING

"*Kappas were poor for the diagnosis of NASH, its resolution and fibrosis improvement.*

Almost half of the patients would have been excluded from entry by 1 of the readers.

Poor reliability *allows improper entry, misclassification, and* ***diminishes treatment effect***".

Davison B…. Dittrich H J Hepatol 2020; 73: 1322-1332

COMPARISON OF ALPINE 2/3 DATA WITH COHORT 4 DATA

		Cohort 4 [1]		ALPINE 2/3			
		Placebo	1 mg	Placebo	0.3 mg	1 mg	3 mg
Non-invasive	Liver Fat Content	−13%	**−39%****	−15%	−25%	**−38%*****	−59%***
	ALT	−6%	**−49%*****	−8%	−25%*	**−40%*****	−51%***
	AST	+1%	**−33%****	−6%	−18%	**−30%****	−39%***
	C4	−38%	**−88%*****	−14%	−64%**	**−86%*****	−93%***
Histology	Fibrosis Improvement	18%	**38%**	19%	31%	**15%**	30%
	NASH Resolution	9%	**24%**	6%	11%	**18%***	22%*
	Both of Above	0%	**22%***	3%	11%	**9%**	14%*

***P<0.001, **P<0.01, *P<0.05 vs PBO

- In ALPINE 2/3, non-invasive data were robust and consistent with previous studies
- However, discrepancy appeared in histology data, and **fibrosis** endpoint in particular

1 Harrison et al., Gastroenterology. 2021;160:219-231; C4 values shown are median values

WHY DOES IT MATTER?

Screen fail rates on biopsy remain high

- Screen fails in Ph2b and Ph3 trials are costly
- Delays enrollment timelines- adding to cost

SCREEN FAILURE RATE IN TRIALS

High rates of ineligibility for participation in trials of new therapies in non-alcoholic steatohepatitis: a systematic review

Anna Roskilly[a], Jessica Shearer[a], Richard Parker[a] and Ian A. Rowe[a,b]

Background and aims: Non-alcoholic fatty liver disease is common and there are a number of treatments in development. Patients with non-alcoholic steatohepatitis (NASH) and significant fibrosis are thought to be the population most in need of treatment. Identification of this group requires liver biopsy. The aim of this study was to identify the proportion of patients screened for phase 2 randomised controlled trials who subsequently entered these studies.
Methods: Large, multicentre, phase 2 randomised controlled trials of pharmacological therapies for NASH were identified by systematic review. The pooled proportion of potential participants who entered the trials was estimated by meta-analysis. The reasons for trial ineligibility were separately extracted and analysed.
Results: Thirteen reports of 14 trials were included. Overall, there were 4014 screened individuals included in the quantitative analyses and 53% were subsequently enrolled in a trial. Considering trials in which the entry criteria matched the current paradigm for treatment, that is, the presence of NASH and significant fibrosis, only 35% of screened individuals were eligible for trial entry. More than half of ineligible individuals were excluded on the basis of liver histology most often due to insufficient disease activity with or without insufficient fibrosis.
Conclusion: The majority of patients considered at risk of NASH and fibrosis sufficient for treatment in randomised controlled trials are ineligible for trial entry. Most often, this is due to ineligible liver histology. These findings have implications for the design of future trials in NASH and for the applicability of treatments after licensing.
Eur J Gastroenterol Hepatol 32: 1023–1029

SCREEN FAILURE RATE IN TRIALS

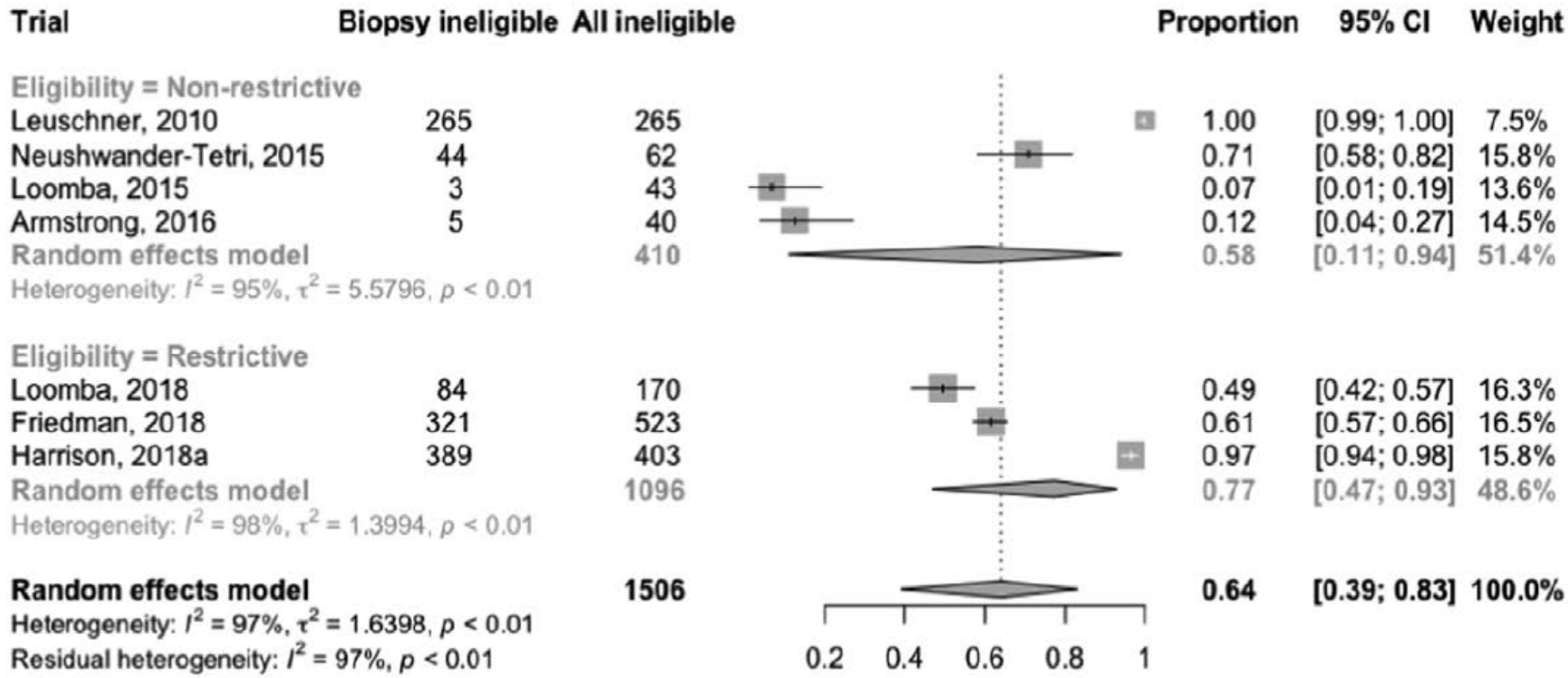
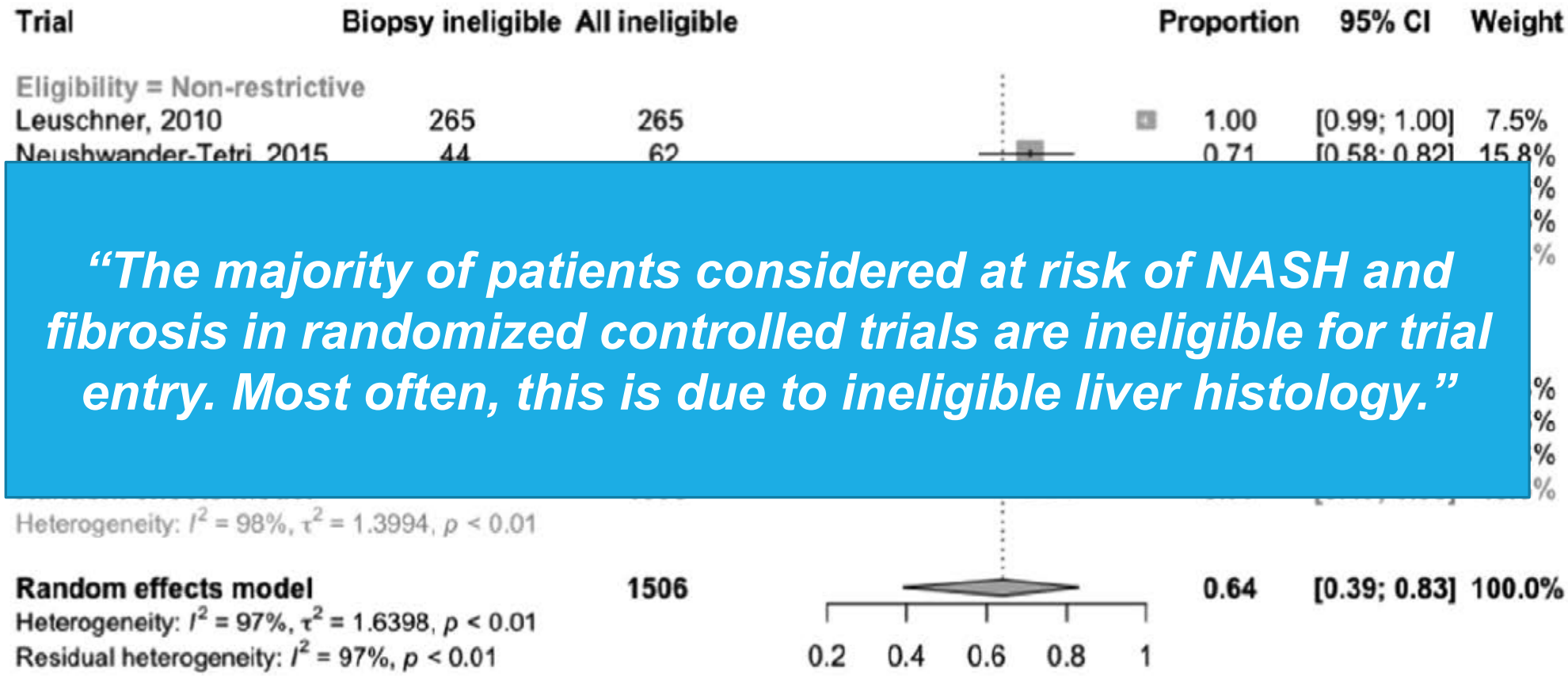


Fig. 3. Forest plot of the proportion of screened individuals excluded following liver biopsy. Trials were stratified by restrictive eligibility criteria (defined as the presence of NASH and significant liver fibrosis falling short of cirrhosis). NASH, non-alcoholic steatohepatitis.

SCREEN FAILURE RATE IN TRIALS



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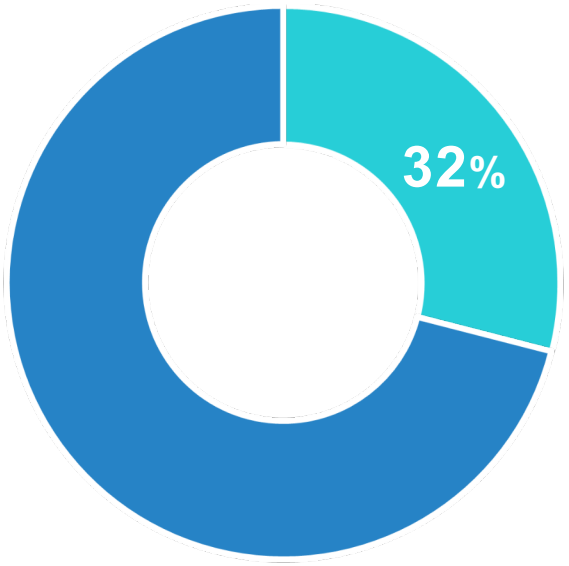
SCREEN FAILURE – AVERAGE FROM TRIALS

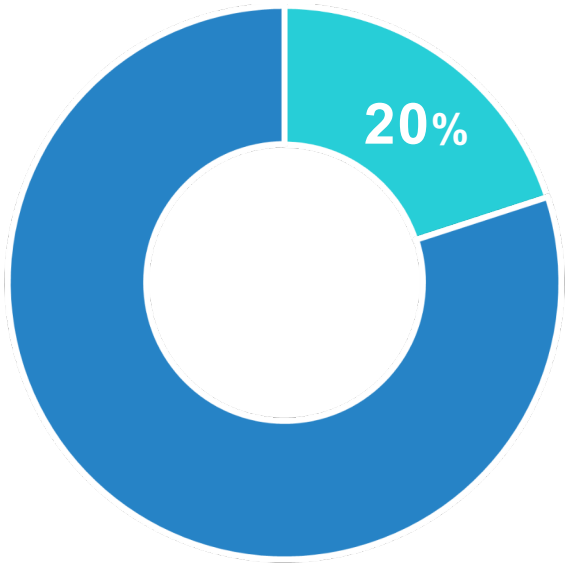
FAILED SCREENING LABS



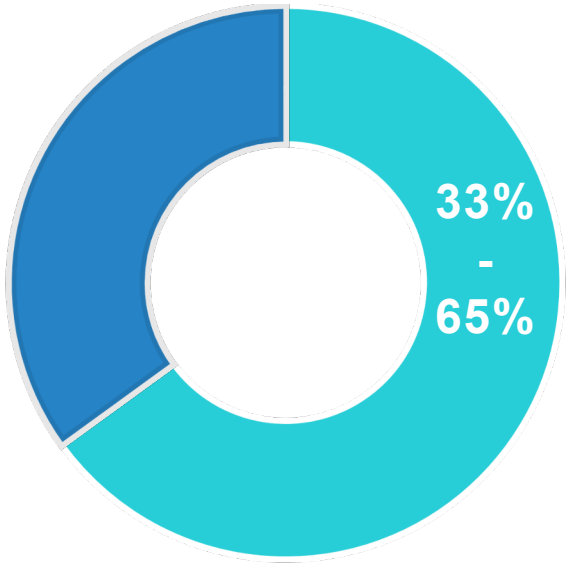
Top reasons for Lab SF:

- AST/ALT
- HbA1c
- Bilirubin
- eGFR

FAILED IMAGING QUALIFICATION



FAILED LIVER BIOPSY



Up to 65% SF on biopsy

- Lack of ballooning
- NAS < 4
- Lack of fibrosis

HOW CAN WE ADDRESS THE PROBLEM?

2022: NASH DRUG DEVELOPMENT FOCUS

Hit the Bull's Eye:

FDA Registration Histological Endpoint

"Because of the slow progression of NASH, the FDA recommends **liver histological improvements** as endpoints reasonably likely to predict clinical benefit to support accelerated approval."

NASH Resolution

Resolution of steatohepatitis on overall histopathologic reading and no worsening of liver fibrosis

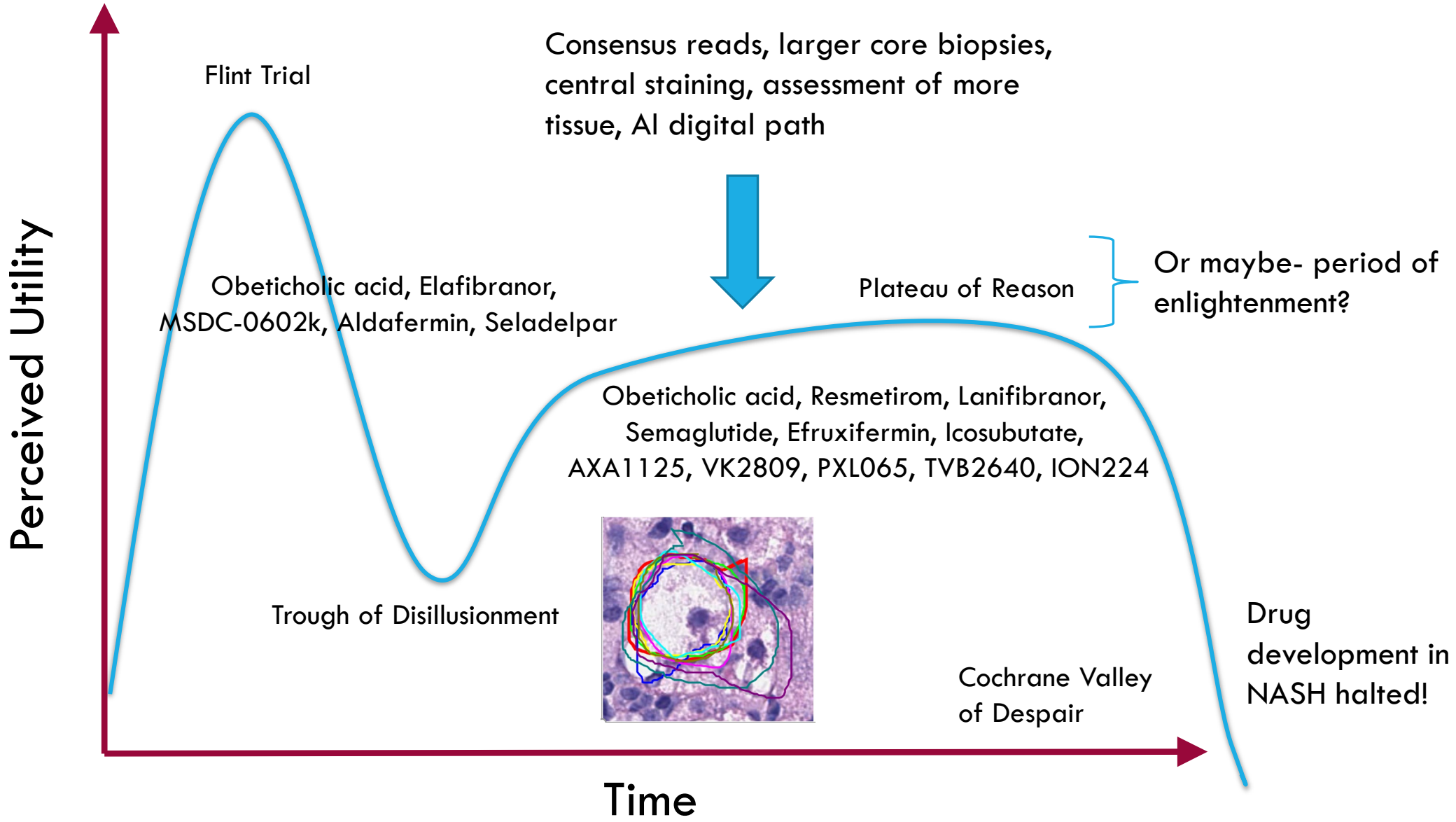
AND/OR

Fibrosis improvement

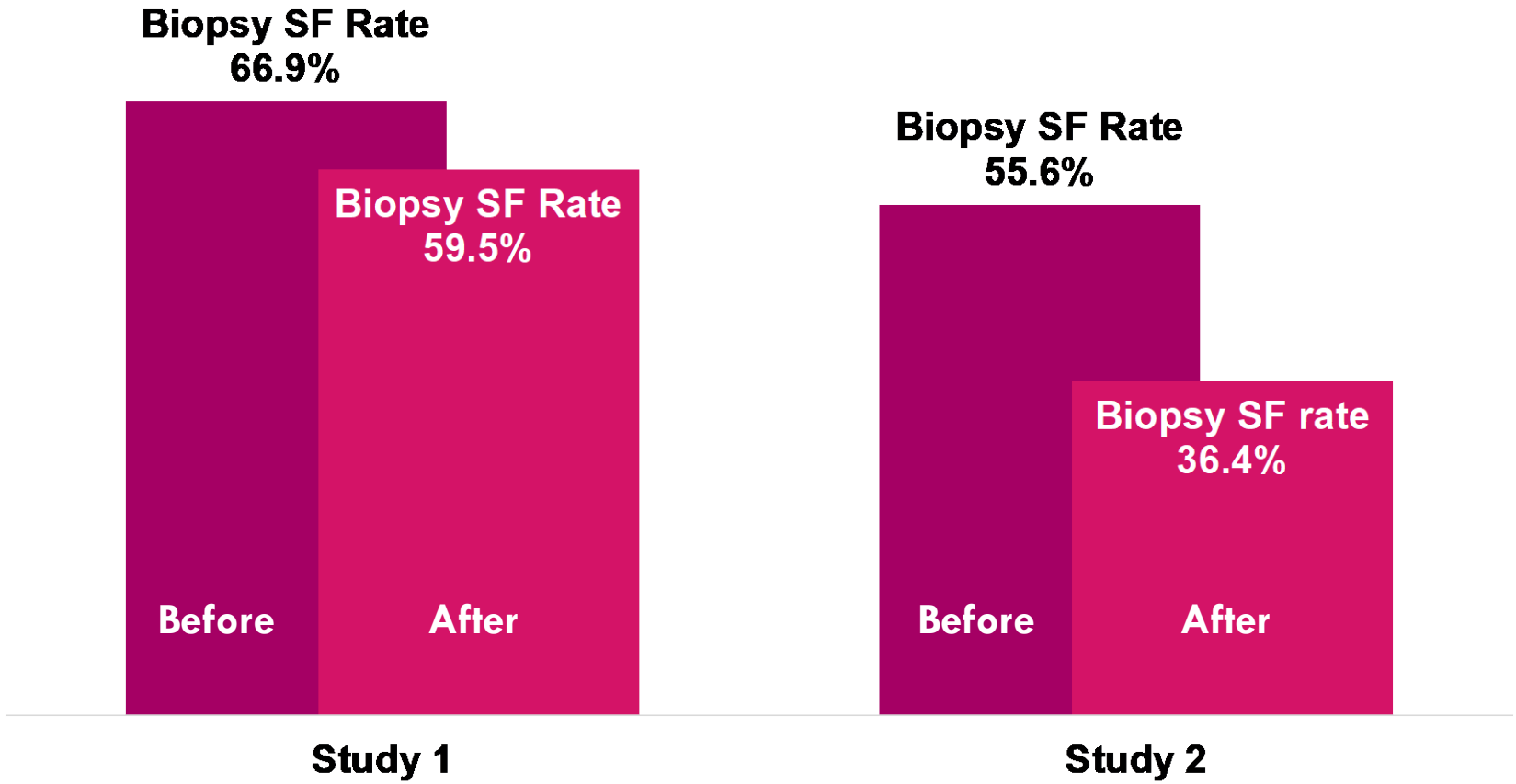
≥ 1 fibrosis stage and no worsening of steatohepatitis

FDA. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. December 2018.

CANEVHISTAL – MODEL OF HISTOPATHOLOGY IN NASH TRIALS



IMPACT OF BIOPSY READING PROCESS ON SCREEN FAILURE RATE



New reading process:
3 H&E vs 1

New reading process:
3 H&E vs 1 + Consensus Read

30 to 50% of "rescued" patients after biopsy re read

THOUGHTS ON IMPROVING HISTOLOGICAL ASSESSMENT

Histopathologic Requirement

- Look at more tissue (why only 1 H&E and 1 Trichrome)?
- Refine NASH diagnosis; Modify ordinal fibrosis scoring system?
- More than 1 pathologist- utilize panel review: 2 readers plus one adjudicator
- AI Digital pathology to augment ordinal scale pathology reads
- Consider using SAF instead of NASH CRN Histopathologic Interpretation

Focus on development of NITs linked to long term outcomes

- ELF, MRI-cT1, MRE, etc

Wrap up

- Grapes must be crushed to make wine
- Diamonds form under pressure
- Olives are pressed to release oil
- Seeds grow in darkness

Whenever you feel crushed, under pressure, pressed, or in darkness, you're in a powerful place of transformation

TRUST THE PROCESS