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NASH Now: Therapeutic Targets & the Competitive Clinical Trial Landscape

3nd Annual NASH Summit Europe—London, UK

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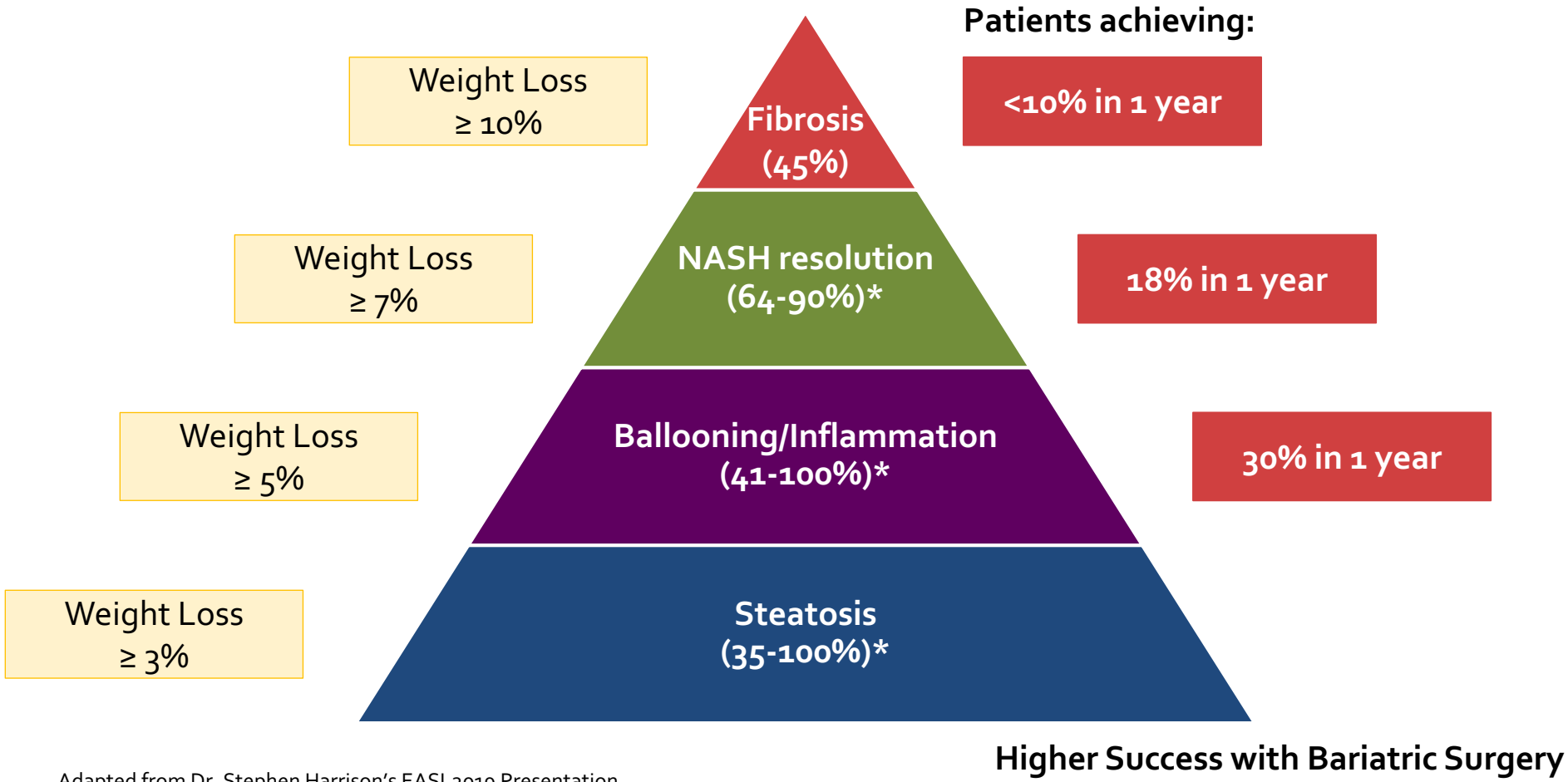
Disclosures

- Adjunct Professor of Medicine, University of Pennsylvania
- Consultant and acting Chief Medical Officer for Morphic Therapeutic (August 2018 to present)

Foundation of Lifestyle Management for NASH: Weight Loss Pyramid

Weight loss benefits steatosis, ballooning/inflammation, NASH resolution, & fibrosis



Adapted from Dr. Stephen Harrison's EASL2019 Presentation

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Currently Available Drugs for Treatment of NASH

Targeting insulin resistance				
Compound	**Mechanism of action**	**Trial**	**Primary endpoint(s)**	**AASLD recommendation as NASH treatment**
Metformin	Multiple	Multiple studies	Various	Not recommended
Pioglitazone	PPARγ agonist	PIVENS* Multiple studies	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in patients with biopsy-proven NASH
Liraglutide	GLP-1 receptor agonist	LEAN*	Resolution of NASH without fibrosis worsening	Premature to consider GLP-1 receptor agonists
Targeting Oxidative stress				
Compound	**Mechanism of action**	**Trial**	**Primary endpoint(s)**	**AASLD recommendation as NASH treatment**
Vitamin E	Antioxidant	PIVENS* TONIC*	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in non-diabetic adults with biopsy-proven NASH

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GLP-1 Agonist Therapy in NASH: LEAN Trial (Liraglutide; Novo Nordisk)*

	Liraglutide	Placebo	Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide *vs* placebo)	p value*
Primary outcome				
Number of patients with paired liver biopsies	23	22	..	..
Patients with resolution of non-alcoholic steatohepatitis	9 (39%)	2 (9%)	4·3 (1·0 to 17·7)	0·019
Changes from baseline in histopathological parameters				
Total NAFLD activity score				
Change in score	−1·3 (1·6)	−0·8 (1·2)	−0·5 (−1·3 to 0·3)	0·24
Patients with improvement	17 (74%)	14 (64%)	1·2 (0·8 to 1·7)	0·46
Hepatocyte ballooning score				
Mean change	−0·5 (0·7)	−0·2 (0·6)	−0·3 (−0·7 to 0·1)	0·15
Patients with improvement	14 (61%)	7 (32%)	1·9 (1·0 to 3·8)	0·05
Steatosis				
Change in score	−0·7 (0·8)	−0·4 (0·8)	−0·2 (−0·6 to 0·2)	0·32
Patients with improvement	19 (83%)	10 (45%)	1·8 (1·1 to 3·0)	0·009
Lobular inflammation				
Change in score	−0·2 (0·6)	−0·2 (0·5)	−0·01 (−0·3 to 0·3)	0·97
Patients with improvement	11 (48%)	12 (55%)	0·9 (0·5 to 1·6)	0·65
Kleiner fibrosis stage				
Change in score	−0·2 (0·8)	0·2 (1·0)	−0·4 (−0·8 to 0·1)	0·11
Patients with improvement	6 (26%)	3 (14%)	1·9 (0·5 to 6·7)	0·46†
Patients with worsening	2 (9%)	8 (36%)	0·2 (0·1 to 1·0)	0·04†

- Multiple GLP-1 agonism that are either on the market or in clinical development; few are being investigated in NASH
- Semaglutide: focus of Novo Nordisk NASH development
  - NCT02970942 "Investigation of Efficacy and Safety of Three Dose Levels of Subcutaneous Semaglutide Once Daily Versus Placebo in Subjects With Non-alcoholic Steatohepatitis" NASH (fibrosis stage 1, 2, 3), 320 subjects; 4 arms; Primary: NASH resolution [72 weeks]; 11/2019
  - NCT03987451 "A Research Study on How Semaglutide Works in People With Fatty Liver Disease and Liver Damage" NASH compensated cirrhosis; 69 subjects, 2 arms; Primary: MRE; 12/2020
  - NCT03987074 "Safety, Tolerability, and Efficacy of Monotherapy and Combination Regimens in Adults With Nonalcoholic Steatohepatitis (NASH)" NASH stage 2,3 fibrosis; 100 subjects; Sema + Fircocostat, Sema + Cilofexor, Sema + Firsocostat + Cilofexor; Primary safety; 6/2020
- GIP/GLP-1 agonists
- Glucagon/GLP-1 agonists

*Armstrong, et al. Lancet. 2016;387:679-690

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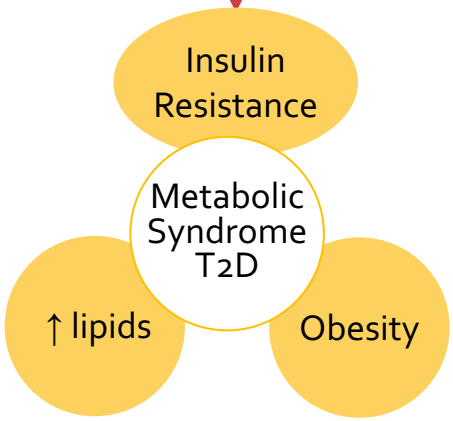
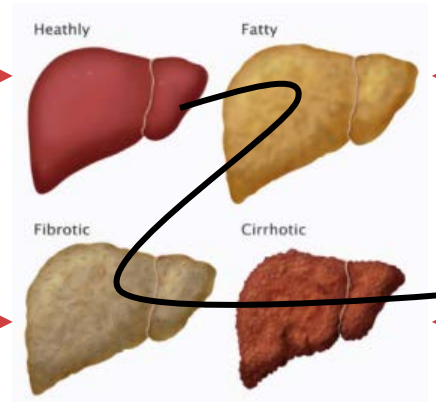
Categorization of NASH Development Assets

Targeted Metabolic
- Insulin sensitizers (GLP-1)
- FGF21/19
- SGLT-1 inhibitors
- KHK inhibitor
- PUFAs
- IBAT inhibitors
- DGAT-2 inhibitors

ROS stress reduction
- Vitamin E
- mTOT inhibitors

Anti-Steatosis
- ACC inhibitors
- SCD1 inhibitors
- FASN inhibitors
- Omega-3 fatty acid





Nuclear Hormone Receptors

Multifactorial Metabolic
- PPAR agonists
- FXR agonists
- THRβ agonists
- LXR agonists
- Mito pyruvate carrier modulators

Intestinal permeability
- Larazotide
- Lubiprostone

Anti-Inflammatory/Fibrotic
- CCR2/5 inhibitor
- ASK-1 inhibitors
- Caspase inhibitors
- Galectin-3 inhibitors
- 5-lipogenase inhibitors
- CB1 inhibitors
- A3AR antagonists
- LOXL2 inhibitors
- NOX1/4 inhibitors
- ROCK2 inhibitors
- αvβ6/1 integrin inhibitors

Modified/Expanded from EASL2019 Phenex Presentation

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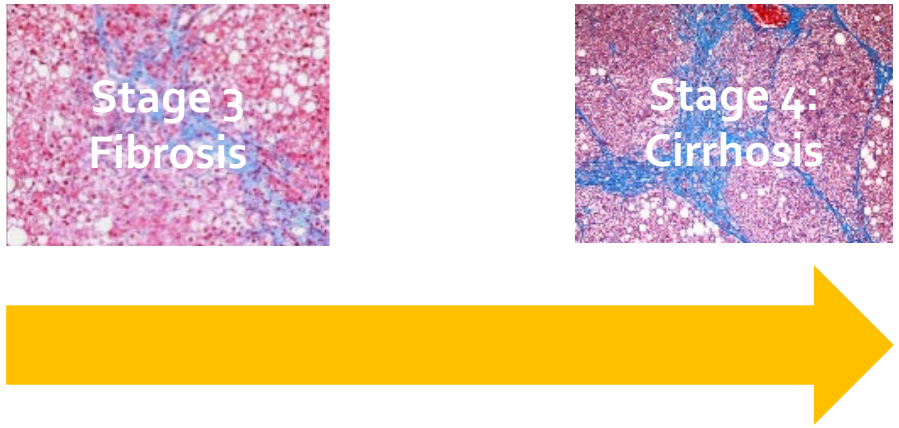
The Critical Cirrhosis Transition: Regulatory Endpoints for Pre-Cirrhotic NASH



Pre-cirrhotic NASH Endpoints	
Surrogates for Accelerated Approval (agreement with Agencies as part of Phase 3 clinical trials)	**Clinical Outcomes for Full Approval**
Fibrosis: Proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH	Reduced time to cirrhosis complications, including the ***progression to cirrhosis***
Resolution: Proportion of patients who achieve NASH resolution without worsening of liver fibrosis	

FDA: Fibrosis OR Resolution
EMA: Fibrosis And Resolution

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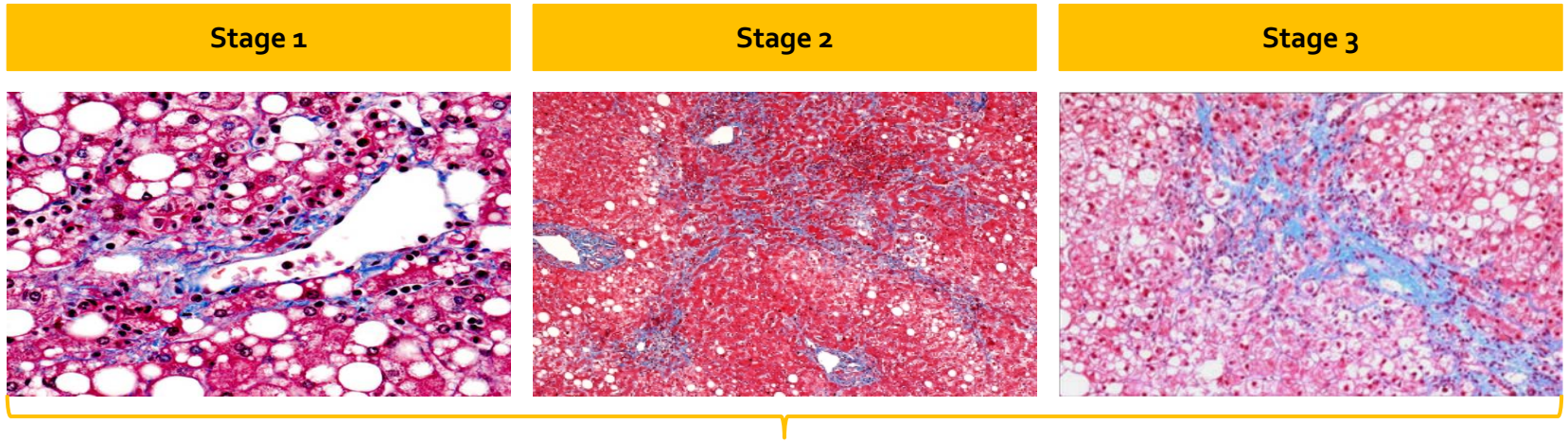
Advanced Phase Monotherapy Programs in Pre-Cirrhotic NASH



Phase 3 initiated/completed/posted

- Obeticholic Acid (FXR agonist) → Tropifexor/cilofexor/Nidufexor/EDP-305* (FXRs)
- Elafibranor (PPAR α/δ) → Seladelpar (PPAR δ)*/Lanifibranor (PPAR α/δ/ɣ))/PXL770 (deut pio)/Saroglitazar (PPARα/γ)
- Resmetrion (THRβ agonist) → VK2809 (THRβ agonist)
- Cenicriviroc (CCR2/5 inhibitor)
- Aramchol (SCD-1 inhibitor)
- MSDC-0602K (mito pyruvate carrier modulator)
- ~~Selonsertib (ASK-1 inhibitor) **~~

Phase 2 initiated/completed/posted

- Semaglutide (GLP-1 agonist)
- MEDI0382 (GLP-1/glucagon agonist)
- Firsocostat/PF-05221304 (ACC inhibitor)
- NGM 282 (FGF19 agonist)
- NGM 313 (KLB receptor agonist)
- Pegbelfermin (FGF21 agonist)
  - BIO89-100, AKR-001
- PF-06835919 (KHK inhibitor)
- Elobixibat (IBAT inhibitor)
- Namodenoson (A3 adenosine receptor agonist)
- IMM-124-E (bovine colostrum)
- CORT118335 (Glucocorticoid Receptor Modulators)
- Licoglifozin (SGLT2 inhibitor)
- Icosabutate (SCFA)
- AZD4017 (11-βhydroxysteroid dehydrogenase inh)
- CC-90001 (JNK inhibitor)
- TVB-2640 (fatty acid synthase inhibitor)
- ISIS 703802 (ANGPTL3 antisense)
- AZD4076 (microRNA-103/107)
- ~~Emricasan (Caspase inhibitor)*~~
- ~~Simtuzumab (LOXL-2 inhibitor)*~~

* *Failed primary endpoint in phase 2 trial*
** *Failed primary endpoint in phase 3 trial*

Combination therapies covered by other speakers during Summit

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Phase 3 Clinical Trials in Pre-Cirrhotic NASH*

Drug (Company)	MOA	Phase	Study Description	Data (estimate)
Obeticholic acid (Intercept)	FXR Agonist	3	REGENERATE: NASH with F2/F3 fib Endpoint: Fibrosis OR Resolution; Composite outcomes	Hit primary; NDA submitted
Elafibranor (Genfit)	PPAR α/δ agonist	3	RESOLVE-IT: NASH with F1-3 fibrosis (n=2000) Endpoints: Resolution [72 wks]; Composite outcomes	Recruit complete Dec 2021
Resmetriom (Madrigal)	THR β agonist	3	MAESTRO-NASH: NASH with F2-3 fibrosis (n=2000) Endpoint: Resolution [52 wks]; Composite outcomes	Recruiting June 2021
Cenicriviroc (Allergan)	CCR2/5 inhibitor	3	AURORA: NASH with F2-3 fibrosis (n=2000) Endpoints: Fibrosis [12 months); Composite outcomes	Recruiting Oct 2021
Aramchol (Galmed)	SCD1 inhibitor	3	ARMOR: NASH with F2/F3 fib (n=~2000) Endpoint: Fibrosis OR Resolution [52 wks]; Composite outcomes	Recruiting June 2022
MSDC-0602K (Cirius)	Mitochondrial pyruvate carrier modulator	3	NASH with fibrosis (n=3600) Endpoint: HbA1c [6 mo] and Resolution [12 mo] Composite hepatic and cardiac outcomes [31 mo]	Not yet recruiting December 2021
Selonsertib (Gilead)	ASK-1 inhibitor	3	STELLAR-3: NASH with F3 fibrosis Endpoints: Fibrosis; Composite outcomes	Failed primary Terminated**

* Includes trials that have been initiated and have information on trial posted on clinicaltrials.gov

** Continuing evaluation in combination clinical trial (ATLAS; NCT03449446)

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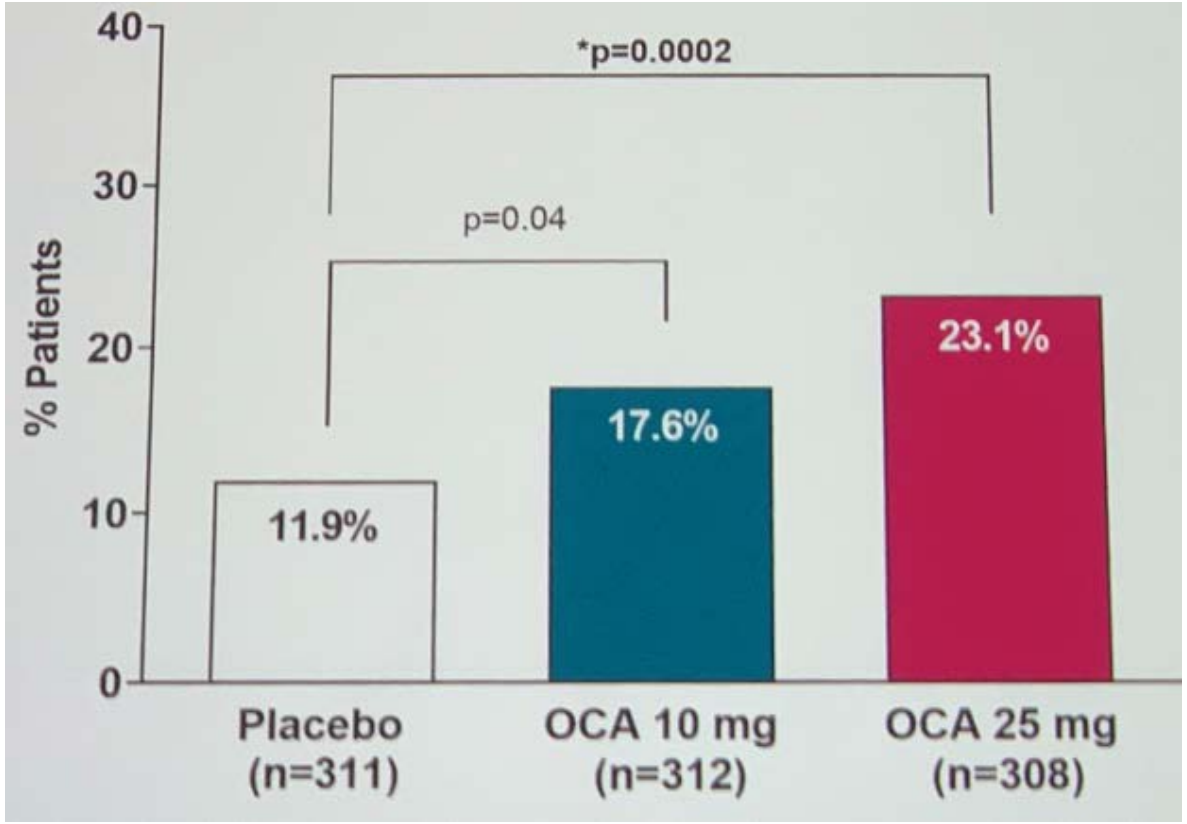
REGENERATE Results: Obeticholic acid in Pre-Cirrhotic NASH (Intercept)

Fibrosis improvement by ≥1 stage with no worsening of NASH (month 18 interim primary endpoint; ITT; n=931)



FXR agonist, modified bile acid

Regenerate Trial

- First positive phase 3 clinical trial in patients with NASH, fibrosis stage 2-3
- Magnitude of effect generally in line with expectations from phase 2 trial
- Secondary analyses all consistent with effect on fibrosis
- Resolution of NASH did not reach significance, but indication of effect
- LDLc & cholesterol increased, but returned to baseline by end of treatment
- AEs consistent with known OCA profile; 9% discontinued in 25mg OCA group due to pruritis; SAEs similar between groups
- *NDA submitted*

Data from EASL Presentation April 2019

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Elafibranor in Pre-Cirrhotic NASH (Genfit)

GOLDEN-505 phase 2 trial was basis for phase 3*

- No difference using protocol-defined primary endpoint
- There was significant difference between placebo and 120 mg elafibranor with new, more stringent, modified definition of NASH reversal
- Improvement in lipid parameters and glycemic control
- Safe and well tolerated

Table 3. Response Rate and Main Analyses for the Modified Definition of Response in Patients With bNAS ≥4 and Various Stages of Fibrosis at Baseline

Population	Selection, n	Treatment arm, n (%)			OR (95% CI)[a]	*P* value[a]
		Placebo	Elafibranor 80 mg	Elafibranor 120 mg		
All NAS ≥4	234[b]	76 (9)	83 (13)	75 (19)	3.52 (1.32–9.40)	.013
	202[c]	63 (11)	72 (15)	67 (21)	3.26 (1.17–9.02)	.024
NAS ≥4 with fibrosis (any stage)	204[b]	66 (11)	67 (15)	71 (20)	3.75 (1.39–10.12)	.009
	176[c]	55 (13)	58 (17)	63 (22)	3.22 (1.15–8.99)	.026
NAS ≥4 with moderate/advanced fibrosis (F2, F3)	118[b]	41 (7)	39 (10)	38 (13)	18.46 (4.80–70.96)	.0001
	99[c]	32 (9)	33 (12)	34 (15)	10.59 (2.52–44.50)	.002

[a]120 mg elafibranor vs placebo, direct treatment effect.
[b]All patients.
[c]Patients with end of trial liver biopsy.

PPARαδ agonist

RESOLVE-IT Phase 3 Trial

- Biopsy proven NASH with score of at least 1 in each component and NAS ≥4 and fibrosis scores of 1-3
- N=2000
- Placebo vs. elafibranor 120 mg daily
- Interim subpart H endpoint: Resolution of NASH at 72 weeks
- Clinical outcome composite ~4 years
- Anticipated interim results Q1 2020

* Ratziu, et al. Gastroenterology 2016;150:1147-1159

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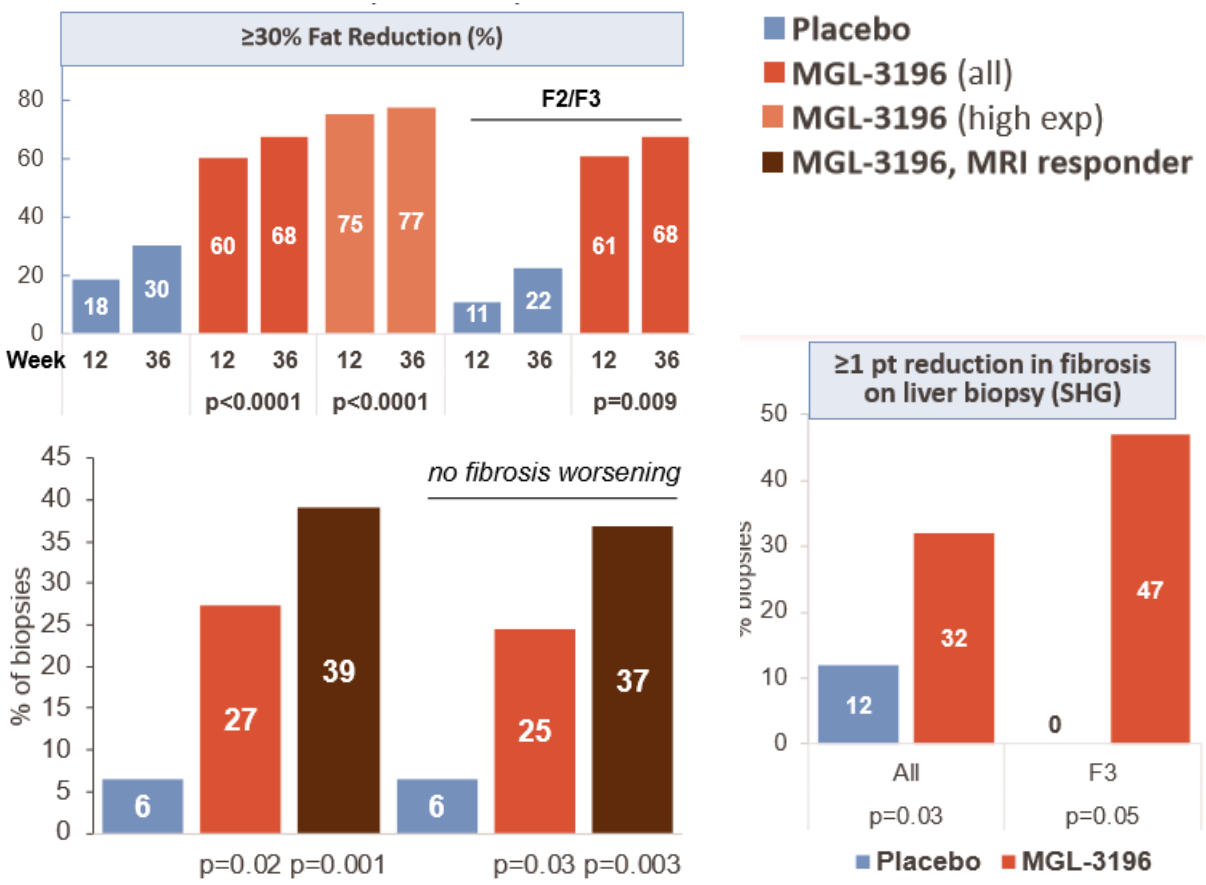
Resmetriom (MDL-3196) in Pre-Cirrhotic NASH (Madrigal)

Phase 2 trial was basis for phase 3 (stage 2,3 fibrosis; 36 weeks)



Thyroid hormone receptor β agonist

MAESTRO-NASH Phase 3 Trial

- NASH with fibrosis stage 1a, 1b, 2, 3 with NAS ≥4 and score of at least 1 in all 3 components
- N=2000
- Placebo vs. resmetrion 80-100 mg daily
- Interim subpart H endpoint: NASH resolution with at least 2-point reduction in NAS and no worsening of fibrosis at week 52
- Clinical outcome composite (up to 54 months)
- Anticipated interim data on 900 patients Q2 2021

Data taken from NASH-Tag 2019 Presentation

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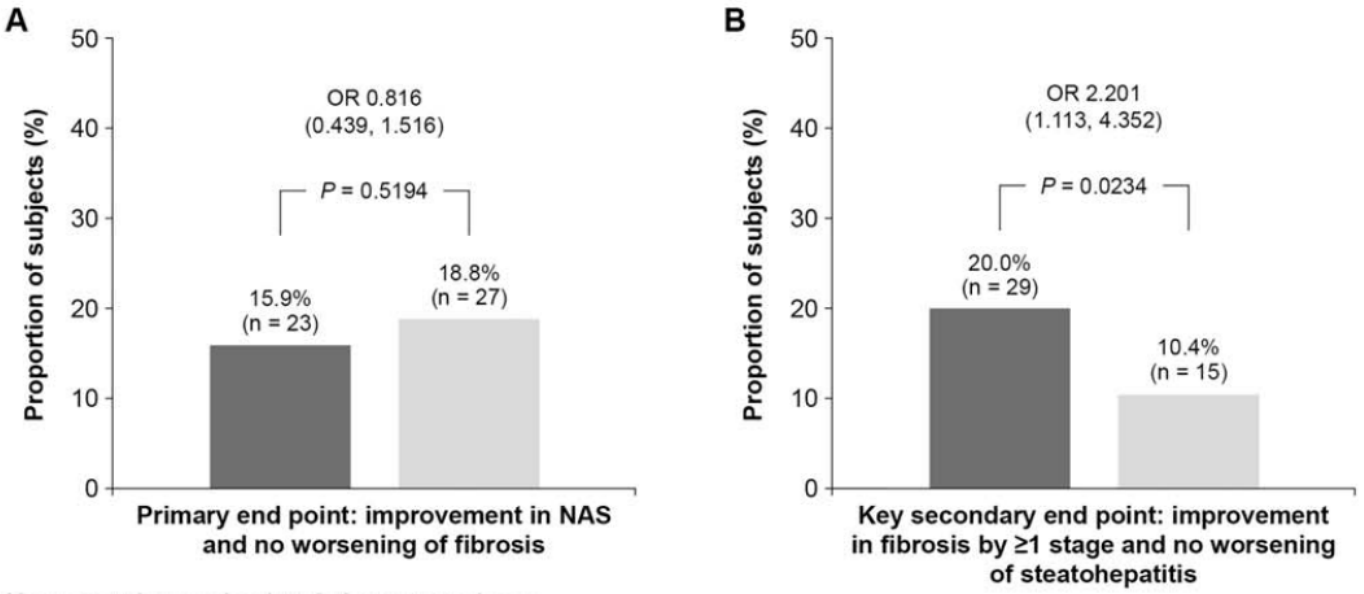
Cenicriviroc in Pre-Cirrhotic NASH (Allergan)

CENTAUR phase 2 trial was basis for phase 3

- Analysis after 1 year of therapy



- Analysis of the data after 2 years of treatment was not as strong
- The difference between placebo and treated was not different on the endpoint of a one stage reduction in fibrosis at 2 years

CCR2/CCR5 inhibitor

AURORA Phase 3 Trial

- NASH with fibrosis stage 2-3
- N=2000
- Placebo vs. cenicriviroc 150 mg daily
- Interim subpart H endpoint: Fibrosis reduction at 12 months
- Clinical outcome composite ~5 years
- Anticipated interim October 2021

Friedman, et al. Hepatology 2018;67:1754-1767

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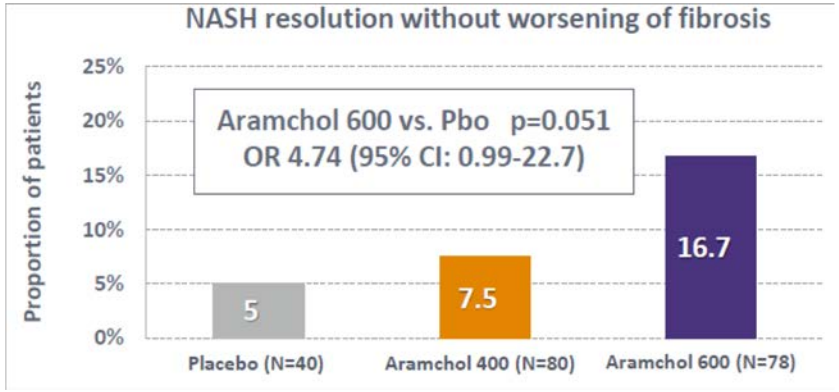
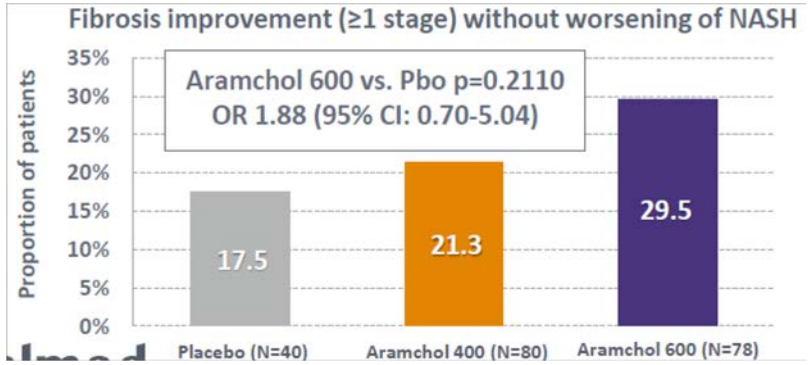
Aramchol in Pre-Cirrhotic NASH (Galmed)

ARREST phase 2 trial was basis for phase 3

- Significant reduction in HbA1c, AST, and ALT
- Numerical, non-significant reduction in progression to cirrhosis with high dose





Stearoyl-CoA desaturase (SCD-1) inhibitor

- Fatty acid bile acid conjugate
- Pre-clinical
  - Reduction in liver fat
  - Decrease fibrosis with effect on HSC's

ARMOR Phase 3 Trial

- NASH with NAS of ≥4 with ≥1 in each component
- Fibrosis stage 2-3
- N=2000
- Placebo vs. Aramchol 300 mg BID
- Interim subpart H endpoint: Fibrosis reduction or Resolution [52 weeks]
- Clinical outcome composite ~5 years
- Anticipated interim June 2022

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MSDC-0602K in Pre-Cirrhotic NASH (Cirius)

EMMINENCE phase 2 trial was basis for phase 3

- 12-month, 4 arm study in 402 subjects with NASH with NAS of ≥4 with ≥1 in each component and fibrosis stages 1-3
- Interim analysis showed statistically significant reductions in ALT and AST, measured from baseline at six months
- Statistically significant reductions in HbA1c and other measures of glycemic control and insulin resistance were observed
- Adverse event rate was similar across placebo and all doses

ALT (U/L)	Placebo (N = 78)	MSDC-0602K Dose		
		62.5 mg (N = 81)	125 mg (N = 84)	250 mg (N = 85)
Baseline mean (SD)	59.3 (34.31)	58.6 (35.14)	49.8 (25.81)	58.0 (31.71)
Month 6 mean (SD)	55.5 (33.40)	50.0 (30.94)	35.6 (24.02)	42.2 (36.07)
Placebo corrected LS mean (95% CI)[1,2]		-4.3 (-11.5, 2.9)	-14.3 (-21.6, -7.0)	-10.6 (-17.8, -3.5)
P-value, MSDC-0602K vs placebo		0.242	**0.000**	**0.004**

HbA1c	Placebo	MSDC-0602K		
		62.5mg	125mg	250mg
Baseline (%)	6.83	7.09	6.90	6.97
Number of subjects	39	45	43	43
Placebo-corrected change from Baseline at 6 months		▼0.37	▼0.55	▼0.45
p-value		0.022	0.001	0.006

Mitochondrial pyruvate carrier modifier

- 2nd generation thiazolidinedione designed to modulate entry of pyruvate into mitochondria.
- Minimal direct agonism of PPARγ
- ↓ insulin resistance, ↓ *de novo* lipid synthesis, ↑ fatty acid oxidation and ↓ inflammation

Phase 3 Trial

- NASH with fibrosis; HbA1c >6%
- N=3600
- Placebo vs. 1 dose MSDC-0602K QD
- Primary:
  - Δ HbA1c in first 800 subjects [6 mo]
  - NASH Resolution first 1000 [12 mo]
- Secondary
  - Death, Hepatic or Cardiac events [31 mo]
- Not yet recruiting
- Anticipated primary December 2021

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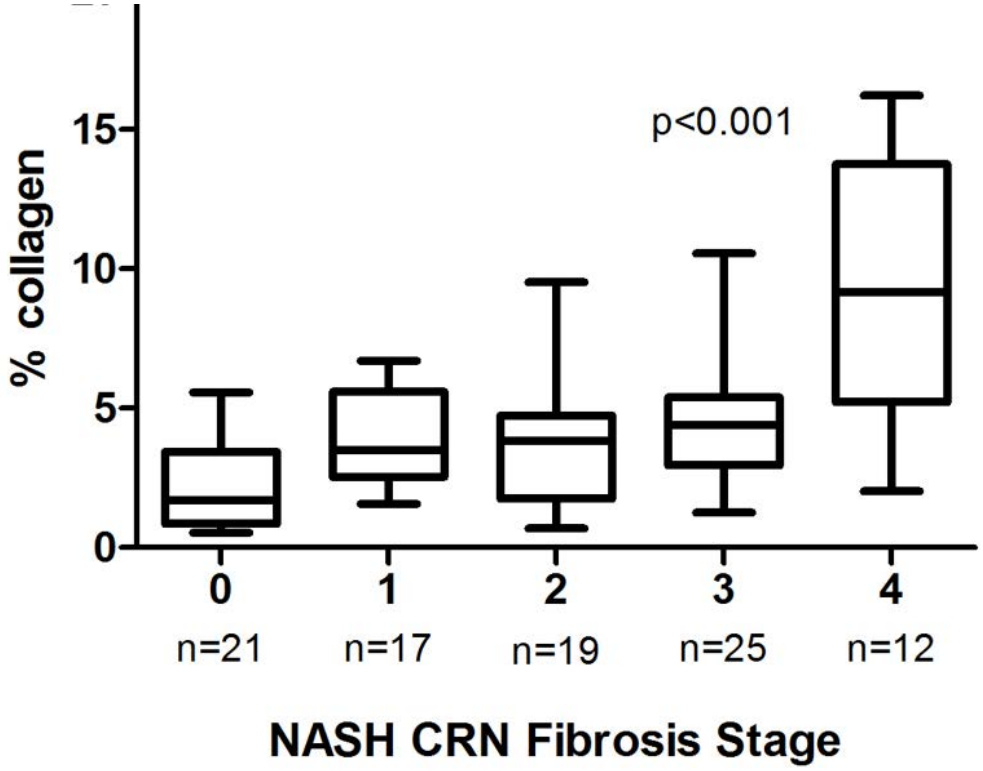
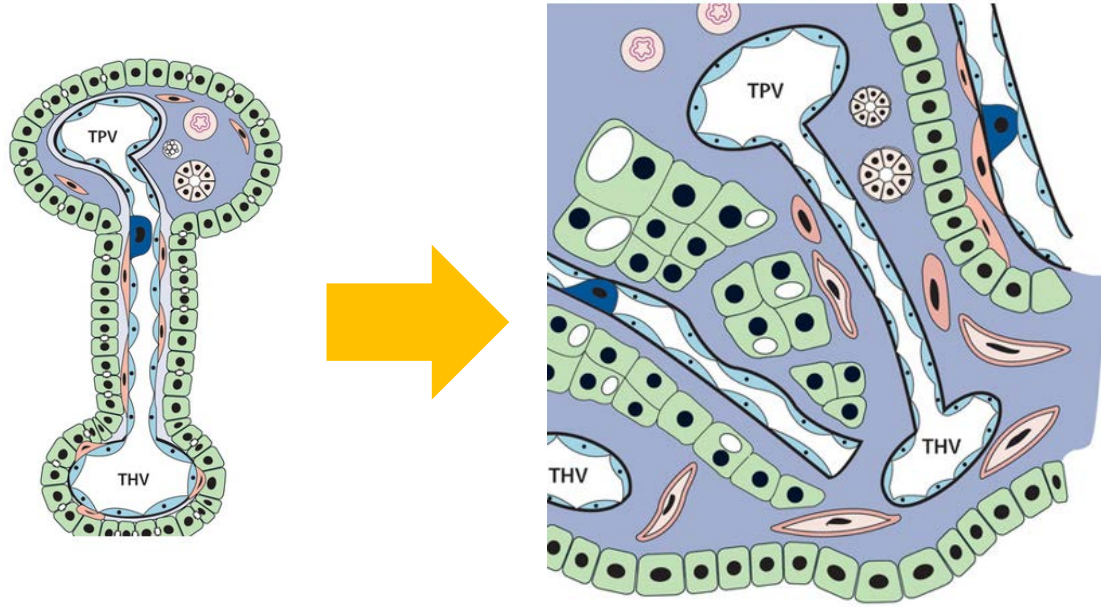
Fibrosis Continues to Accumulate in Cirrhosis and Distorts Liver Architecture

Amount of Fibrosis Covers Broad Range*



Distorted Architecture in Cirrhosis



Cirrhosis causes portal hypertension by increasing resistance to blood flow

- Structural Components
- Non-structural Components

* Data from Goodman, Harrison, and Traber

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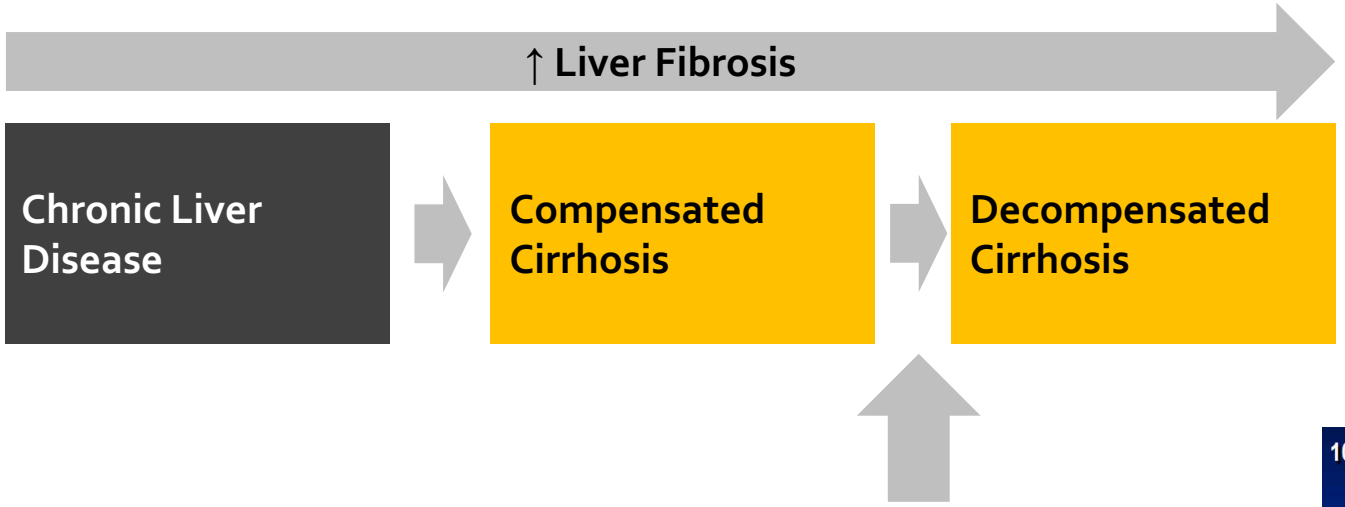
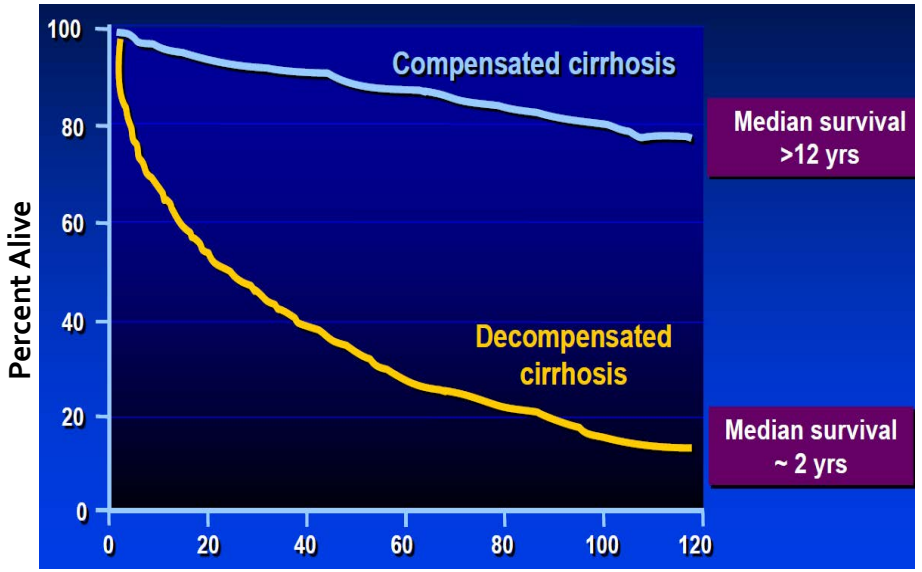
FDA Draft Guidance on Endpoints for Compensated NASH Cirrhosis*

Surrogates for Accelerated Approval	Traditional Approval
FDA does not currently recognize any surrogate endpoints for accelerated approval under subpart H. Previously, the FDA did agree for phase 3 trials an endpoint of the proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH "Histological improvements in fibrosis can be proposed and justified; however, at present the relationship between histological changes in cirrhosis and clinical outcomes has not been characterized, and further, reversal of cirrhosis (e.g., fibrosis stage F4) may not be feasible. Because currently there is ***insufficient evidence to support the use of histological improvements as a surrogate endpoint*** that is reasonably likely to predict clinical benefit to support accelerated approval, in general, the FDA expects to evaluate drugs for the treatment of compensated NASH cirrhosis under the traditional approval pathway."	Endpoint: Effect of the investigational drug relative to placebo on the ***composite endpoint*** of time from randomization to the ***first of any one*** of the following outcome events: 1. Complication of ascites (bacterial peritonitis, diuretic-resistant ascites, hepato-pleural effusion, etc.) 2. Variceal hemorrhage 3. Hepatic encephalopathy 4. Worsening in the MELD score to ≤15 (this assumes the MELD at enrollment is ≤12) 5. Liver transplantation 6. Death from any cause

*Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment, Guidance for Industry, U.S. FDA, June 2019
Timeframe for comments on the draft guidance closed in August 2019

NASH Cirrhosis-Related Mortality Increases with Decompensation Events





D'Aminco et. Al., J Hepatol 2006;44:217 (Graphic borrowed from Dr. Guadalupe Garcia-Tso)

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Categorization of NASH Development Assets (Those Used in Cirrhosis Highlighted)

Targeted Metabolic
- Insulin sensitizers (GLP-1)
- FGF21/19
- SGLT-1 inhibitors
- KHK inhibitor
- PUFAs
- IBAT inhibitors
- DGAT-2 inhibitors

ROS stress reduction
- Vitamin E
- mTOT inhibitors

Anti-Steatosis
- ACC inhibitors
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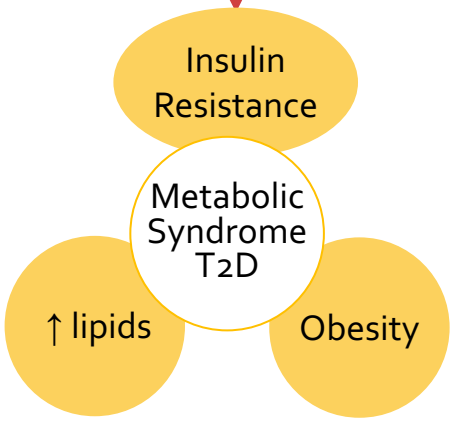
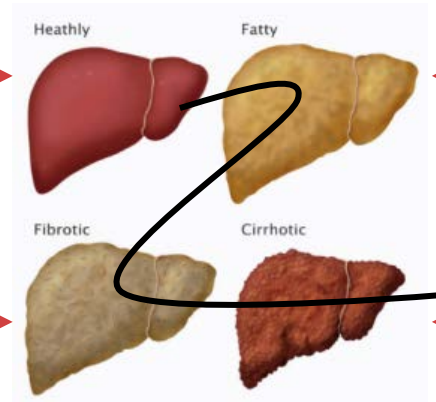
- FASN inhibitors
- Omega-3 fatty acid





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- PPAR agonists
- FXR agonists
- THRβ agonists
- LXR agonists

Intestinal permeability
- Larazotide
- Lubiprostone

Anti-Inflammatory/Fibrotic
- CCR2/5 inhibitor
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- Caspase inhibitors
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- 5-lipogenase inhibitors
- CB1 inhibitors
- A3AR antagonists
- LOXL2 inhibitors

Modified/Expanded from EASL2019 Phenex Presentation

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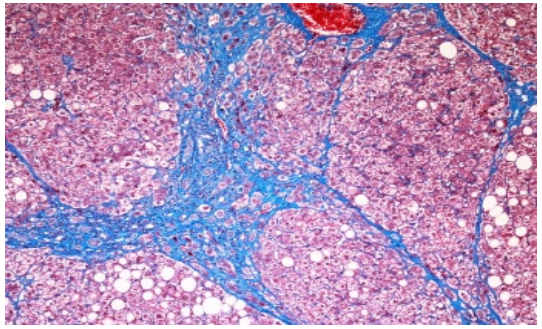
Advanced Phase (2 & 3) Monotherapy Programs in NASH Cirrhosis

Stage 4



Phase 3 initiated/completed/posted

- Obeticholic Acid
- ~~Selonsertib**~~
- ~~Simtuzumab*~~
- ~~Emricasan*~~

Phase 2 initiated/completed/posted

- Belapectin (gal-3 inhibitor)*
- Pegbelfermin (FGF21)

* Failed primary endpoint in phase 2 trial
** Failed primary endpoint in phase 3 trial

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Phase 3 and 2 Clinical Trials in NASH Cirrhosis Have Been Disappointing*

Drug (Company)	MOA	Phase	Study Description	Data	Status
Selonsertib (GILD)	ASK-1 inhibitor	3	STELLAR-4: Comp NASH cirrhosis EP: Fibrosis; composite outcomes	Failed primary	Also failed STELLAR3 (stage 3 NASH); ATLAS P2 combination trial ongoing
Obeticholic acid (ICPT)	FXR Agonist	3	REVERSE: Comp NASH cirrhosis EP: Fibrosis; composite outcomes	JUN 2021	Trial ongoing; In Aug 2019 increased patients from 540 to 900 and extended Rx 12 to 18 mo
Simtuzumab (GILD)	LOXL2 inhibitor	2	Comp NASH cirrhosis EP: Change in HVPG	Failed primary	Also failed in pre-cirrhotic NASH to improve fibrosis. Program discontinued
Belapectin (GALT)	Galectin-3 inhibitor	2	NASH-CX: Comp NASH cirrhosis EP: Change in HVPG	Failed primary	Post-hoc difference in HVPG without varices and reduced development of varices; no effect on fibrosis; P3 trial planned**
Emricasan (CNAT/Novartis)	Pan-caspase inhibitor	2 2	ENCORE-PH Change in HVPG ENCORE-LF Complications	Failed primary	Post-hoc analysis showed some effect in high HVPG sub-group; Currently not progressing
Pegbelfermin (BMS)	PEG-FGF21	2	Comp NASH cirrhosis EP: Fibrosis	JAN 2020	Completed trial enrollment

* Information on trial posted on clinicaltrials.gov or reported by company

** Not posted on clinicaltrials.gov

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Why Have NASH Cirrhosis Trials Failed?

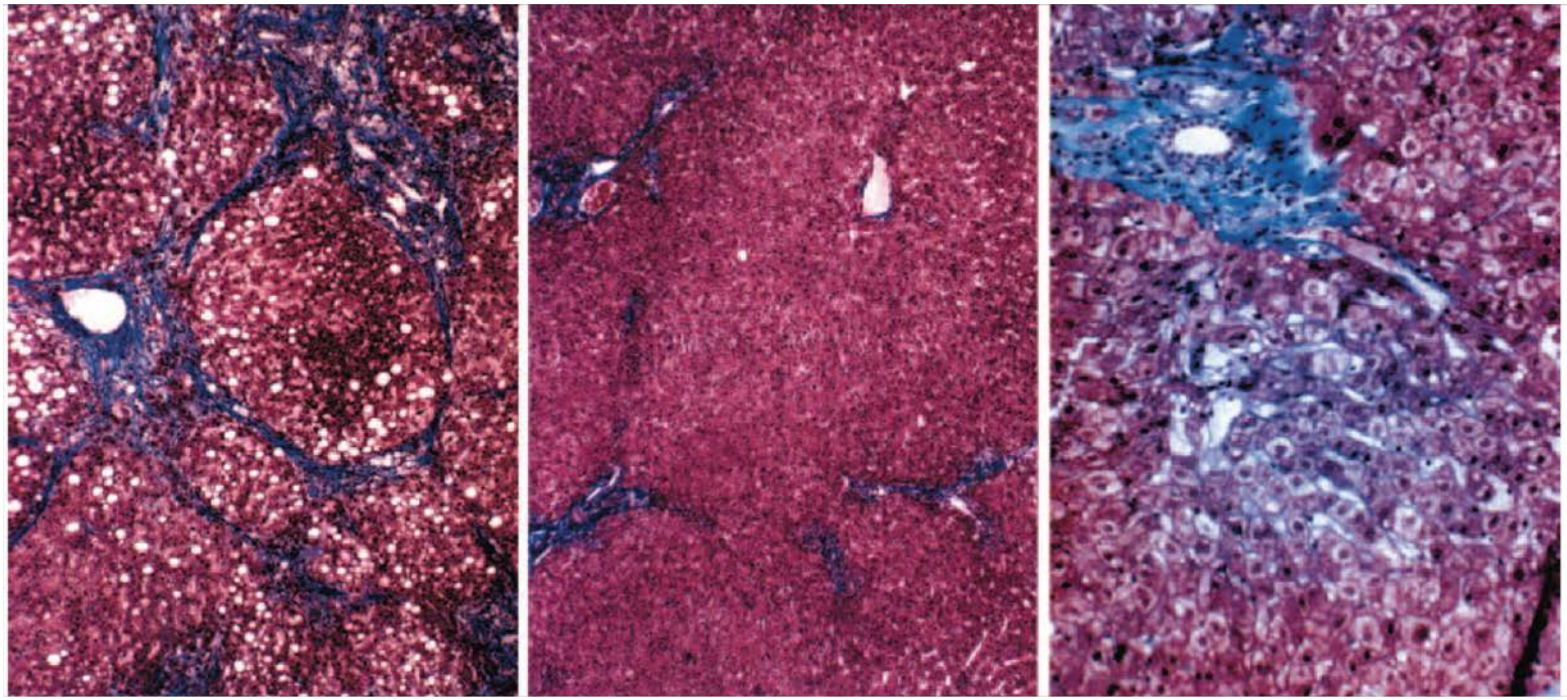
- Mechanism of Action?
  - Most drugs tested have anti-fibrogenic/anti-inflammatory activity. None with demonstrable pro-fibrolysis activity, although was a possible mechanism of simtuzumab.
- Adequacy of pre-clinical data?
  - Each of the drugs evaluated had effects on fibrosis in various rodent models of NASH and toxin-induced fibrosis. Indicates lack of good correlation of human results with animal models.
- Correct dosing in humans?
  - None of the drugs had adequate biomarkers of target engagement, particularly in determining pharmacodynamic activity in liver. Therefore, dose finding used indirect approaches, at best.
- Duration of therapy?
  - When the completed and ongoing trials were started, the conventional wisdom of opinion leaders that at least one year of therapy was required. Thus most of the trials included therapy for 1-2 years. Longer therapy may be required.
- ***Is there a need to combine anti-fibrotics with therapy addressing metabolic pathogenesis of NASH?***

Can Bariatric Surgery Reverse NASH Cirrhosis?

Month 0 (Surgery)
BMI 60
Wedge liver Biopsy
Ishak Stage 5 Fibrosis

Month 15
BMI 47
Wedge liver Biopsy
Ishak Stage 3 Fibrosis

Month 44
BMI 44
Needle liver biopsy
Ishak Stage 2 Fibrosis



Kral, et al. Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. Surgery 2005:135:48-58

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Approaches for Targeting Fibrosis in NASH Cirrhosis

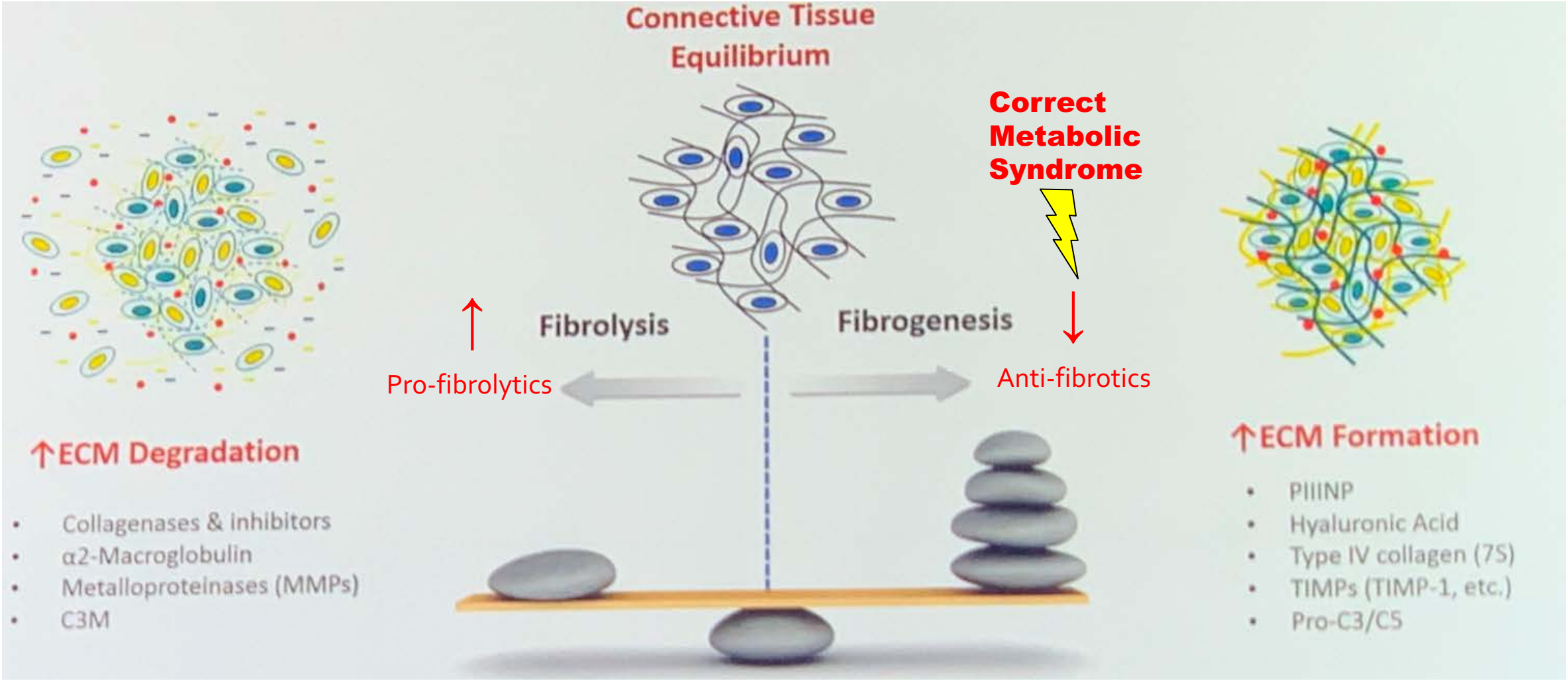

Figure from ILC-2019 Presentation by Dr. Quentin Anstee

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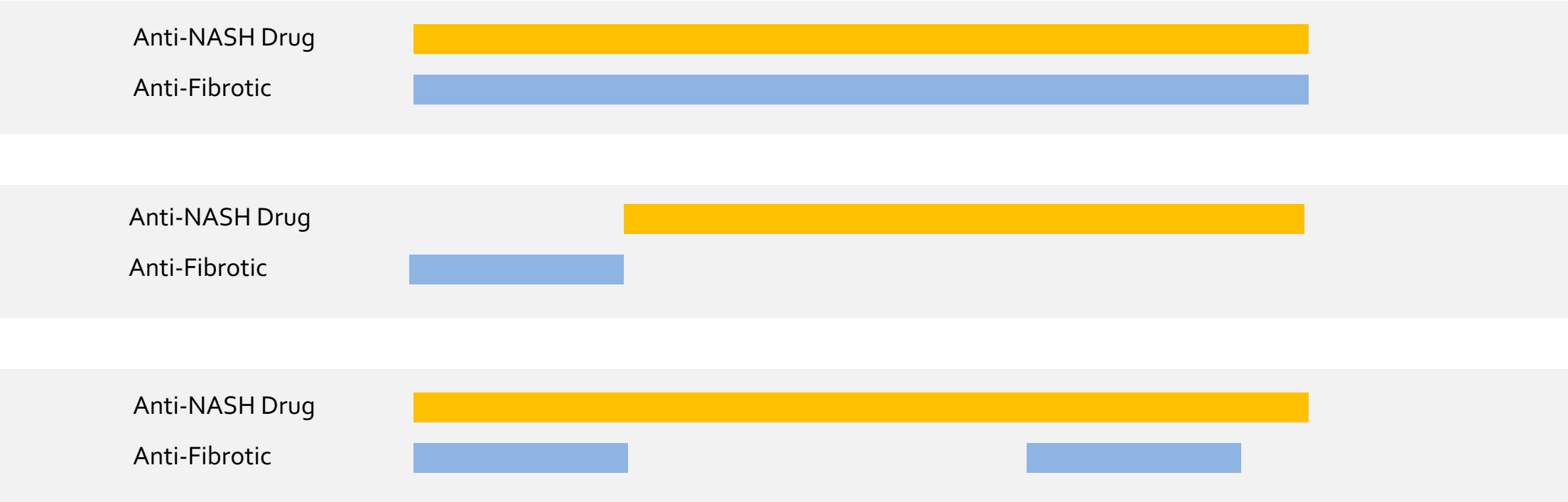
Potential Combination Approaches for Use of Anti-fibrotics in NASH Cirrhosis

Combine anti-fibrotic with an anti-NASH Drug to address the underlying pathophysiology of the disorder



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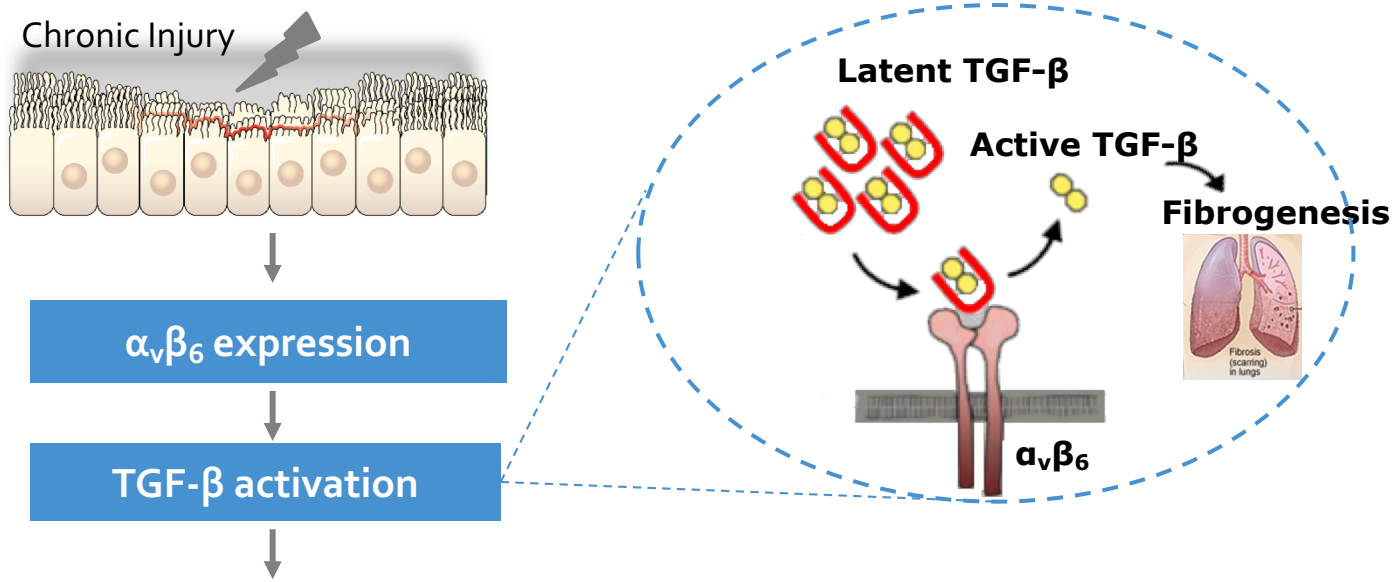
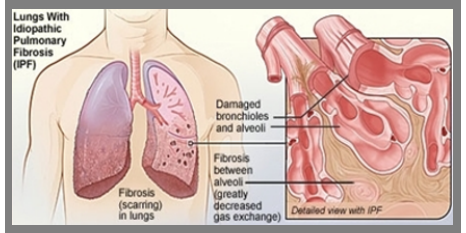
Potential for $\alpha_v\beta_6$ inhibition as Anti-fibrotic: Essential Upstream Activator of TGF-β Signaling

Provided by Drs Liangsu Wang and Min Lu, Morphic Therapeutic



Pulmonary Fibrosis

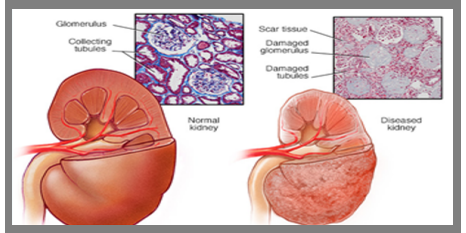


Idiopathic Pulmonary Fibrosis
Interstitial Lung Disease (Scleroderma-related, Arthritis-related)

Hepatic Fibrosis

Primary Sclerosing Cholangitis
Primary Biliary Cholangitis
Non-alcoholic Steatohepatitis
Liver Cirrhosis

Renal Fibrosis



Acute Kidney Injury
Chronic Kidney Diseases

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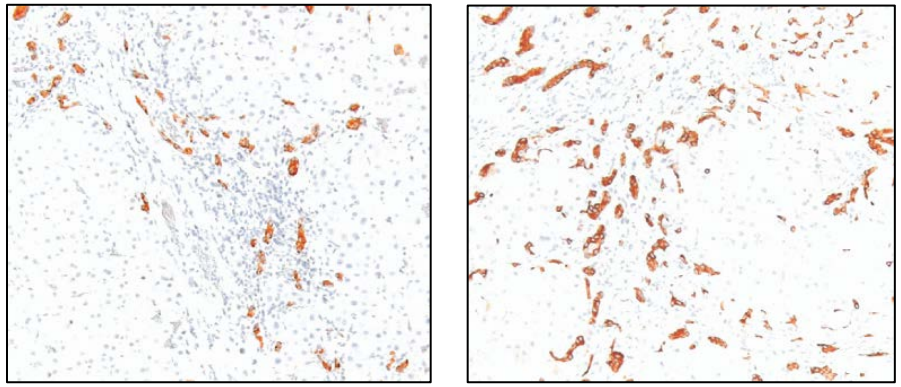
Integrin $\alpha_v\beta_6$ in Liver Fibrosis

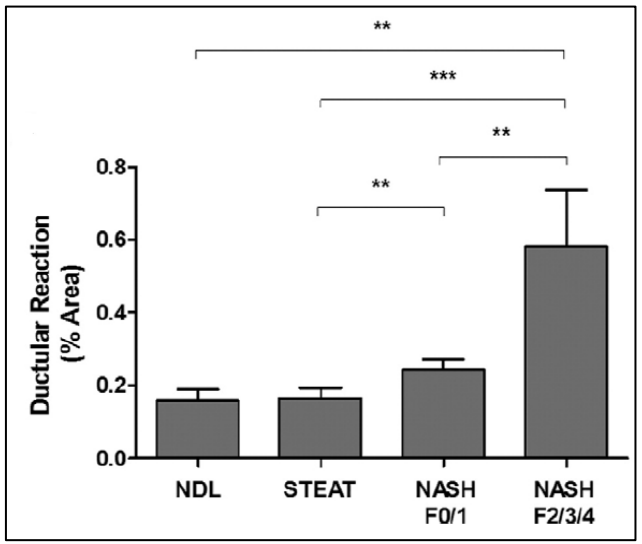
Provided by Drs Liangsu Wang and Min Lu, Morphic Therapeutic

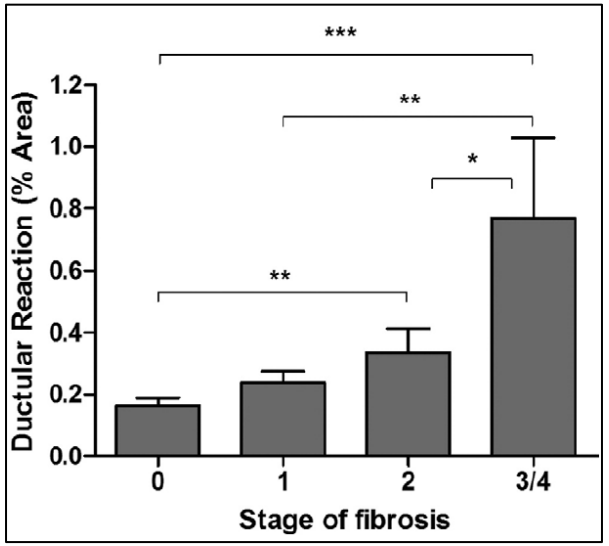
- $\alpha_v\beta_6$ has been shown to promotes ductular reaction (DR), fibrosis, and tumorigenesis in mice
- DR reported to be common in NASH fibrosis stage ≥2 by multiple studies
- DR, especially centrilobular DR, is a feature of progressive fibrosis
- $\alpha_v\beta_6$ may play a role in perpetuating NASH fibrosis through DR

Staining for Ductular Reactions



Ductular reaction seen in ≥ F2 and increases with stage of fibrosis





Richardson et al. GASTROENTEROLOGY 2007;133:80–90

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Summary of Drug Development in NASH

- Pre-cirrhotic NASH
  - Landscape will shift with agency evaluation and potential approval of obeticholic acid
  - Five additional promising agents in phase 3 clinical trials and many drugs in phase 2
  - Evaluations of combinations well underway and will continue to be major focus
- NASH Cirrhosis
  - Focus on compensated NASH cirrhosis with the objective of preventing decompensation events and subsequent liver transplant and liver-related mortality.
  - Results of clinical trials in NASH cirrhosis have been disappointing
  - Recent FDA guidance has indicated there are no acceptable surrogate endpoints and the traditional approval pathway must be used which is based on a composite endpoint of clinical outcomes.
  - Future investigation should focus on more specific and potent anti-fibrotics (e.g. anti-integrins), pro-fibrolytics, and combination with other drugs that affect the metabolic syndrome.

www.alacrita.com

Thank You!

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