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NASH Now: Therapeutic Targets & the Competitive Clinical Trial Landscape

3nd Annual NASH Summit—Boston, MA

April 22-25, 2019

Boston, MA
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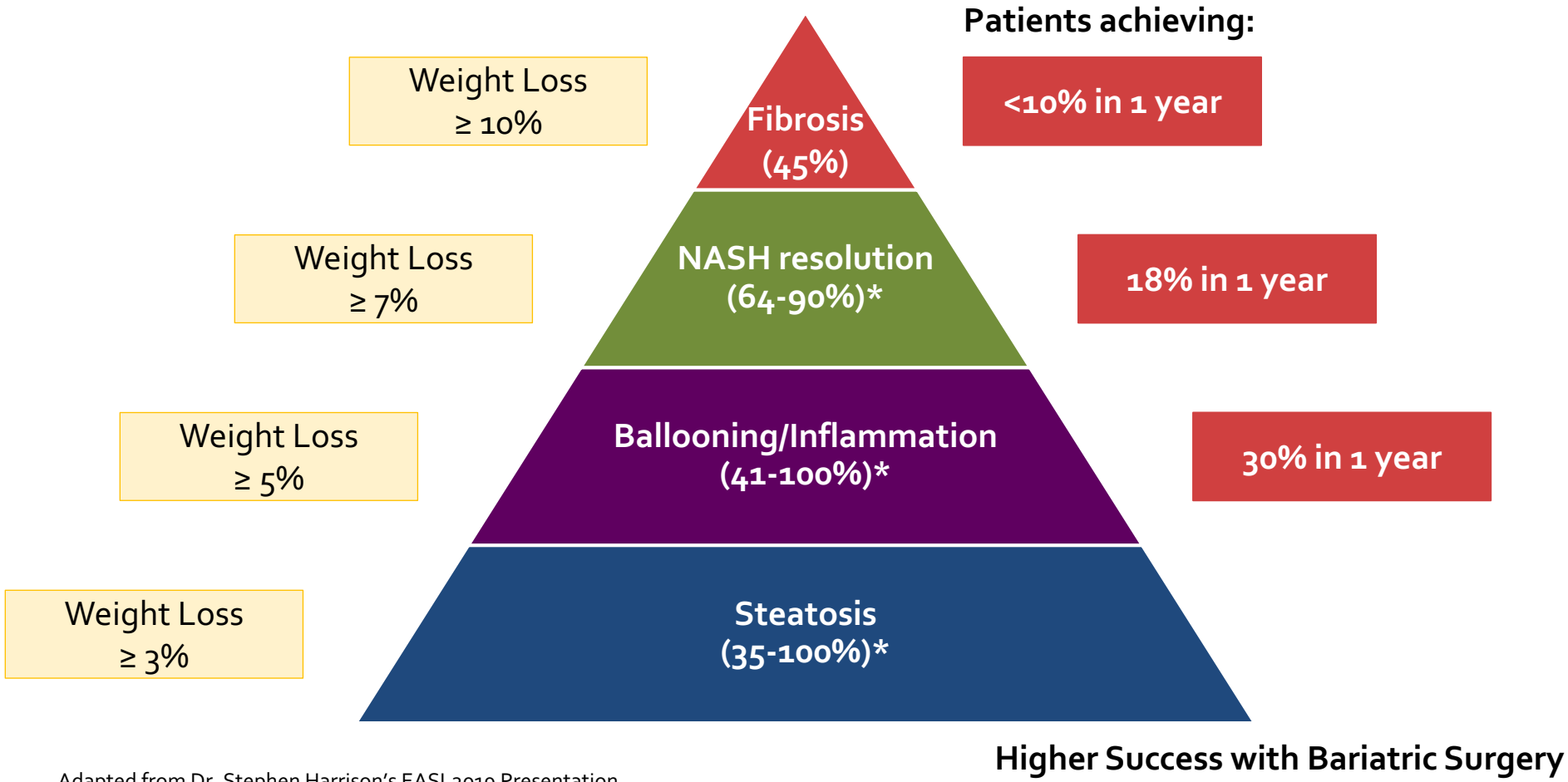
Foundation of Lifestyle Management for NASH: Weight Loss Pyramid

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

Adapted from Dr. Stephen Harrison's EASL2019 Presentation

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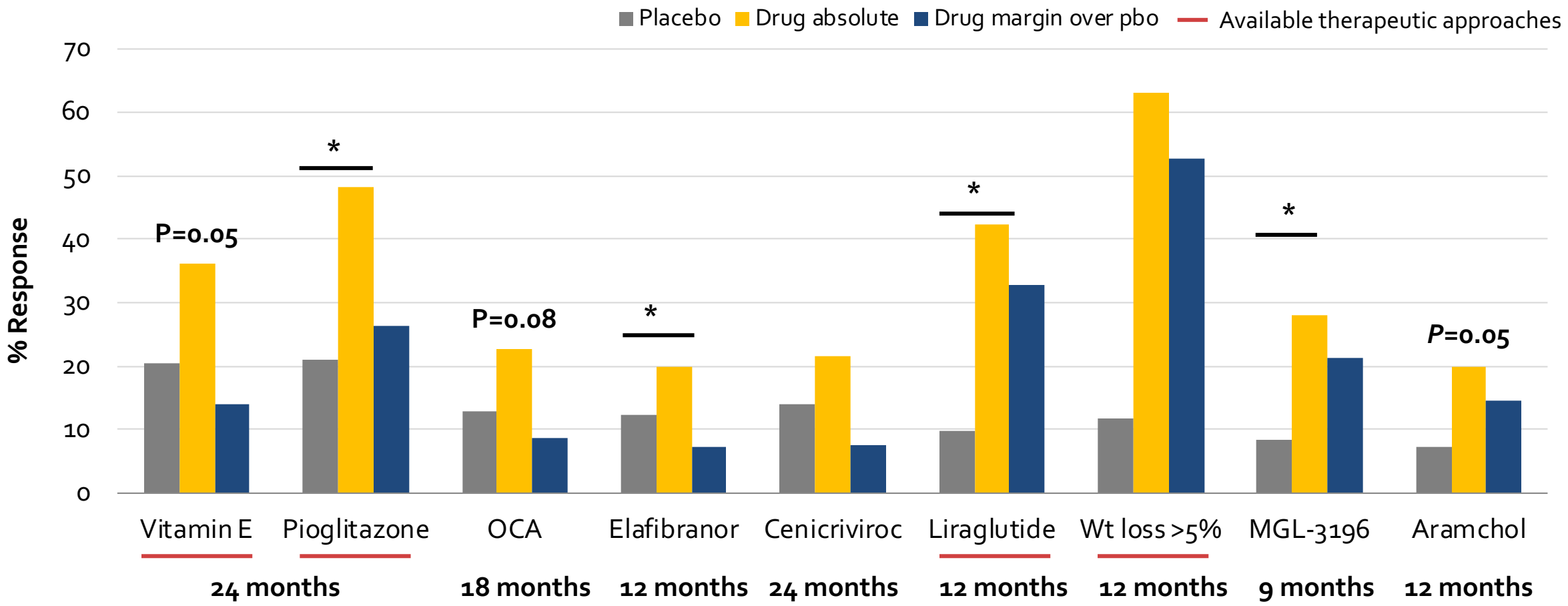
Foundation for Understanding Study Comparisons: NASH Resolution Comparison



Note: Some early studies (weight loss, vit E, pio, and lira) used criteria for NASH resolution such as non-nash or ballooning=0, without considering inflammation grade

Adapted from Dr. Stephen Harrison's EASL2019 Presentation

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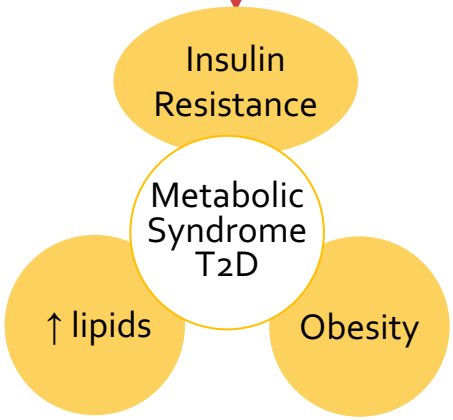
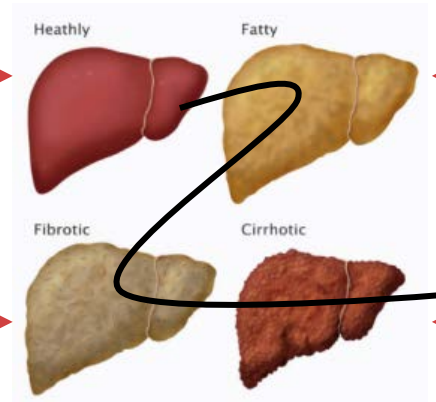
Categorization of NASH Development Assets

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

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

Modified/Expanded from EASL2019 Phenex Presentation

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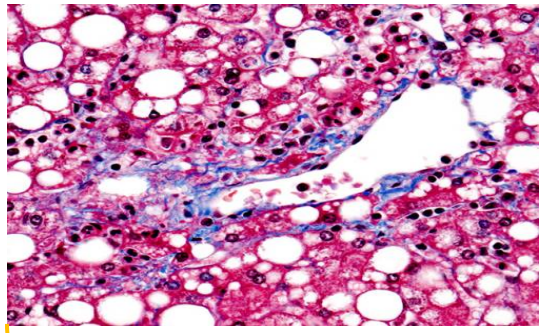
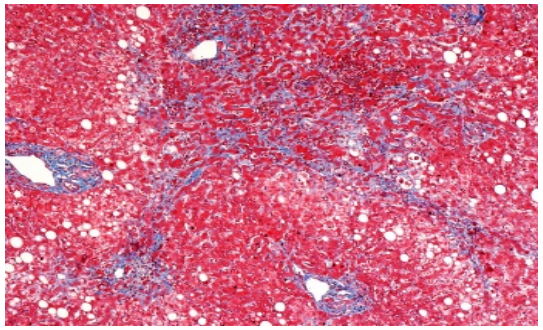
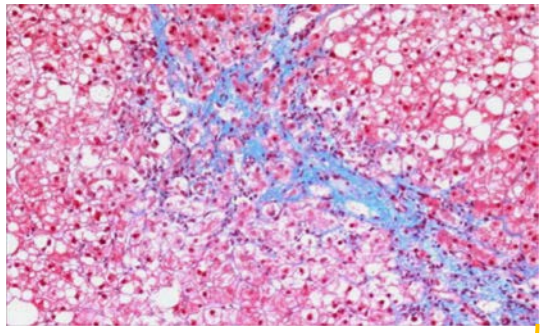
Advanced Phase (2 & 3) Monotherapy Programs in NASH

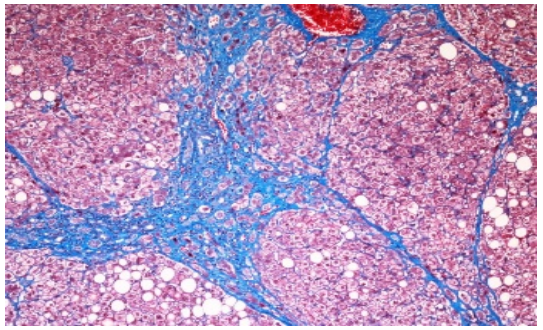
Phase 3 trials initiated & posted on clinicaltrials.gov

Stage 1	Stage 2	Stage 3	Stage 4









- Obeticholic Acid
  - Tropifexor/cilofexor/EDP-305/nidufexor
- Selonsertib
- Elafibranor (PPAR α/δ)
  - Seladelpar (PPAR δ)
  - Lanifibranor (PPAR α/δ/ɣ)
- Cenicriviroc
- Resmetrion
  - VK2809
- Pegbelfermin (FGF21)
  - BIO89-100, AKR-001

- Semaglutide (GLP-1)
- Firsocostat/PF-05221304
- NGM 282 (FGF19)
- NGM 313
- Volixibat (term)/Elobixibat
- MSDC-0602K
- Aramchol
- Namodenoson
- DUR-928
- IMM-124-E
- Emricasan*
- Simtuzumab*

- Obeticholic Acid
- Selonsertib**
- Simtuzumab*
- Emricasan*
- Belapectin (gal-3 inhibitor)*
- Pegbelfermin (FGF21)
- HSP47 inhibitor (HCV)

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

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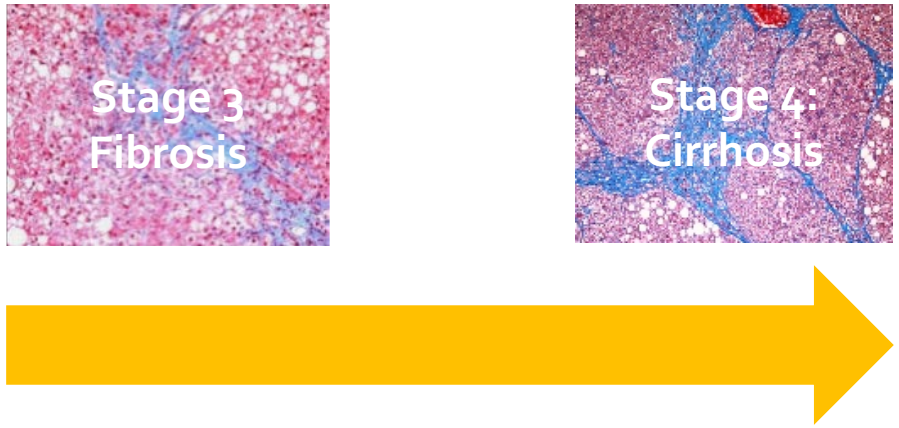
The Critical Cirrhosis Transition: Regulatory Endpoints for Pre-Cirrhotic NASH



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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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	Top line reported/ presented EASL
Selonsertib (Gilead)	ASK-1 inhibitor	3	STELLAR-3: NASH with F3 fibrosis Endpoints: Fibrosis; composite outcomes	Top line Q2 2019
Elafibranor (Genfit)	PPAR α/δ agonist	3	RESOLVE-IT: NASH with F1-3 fibrosis (2000 patients) Endpoints: Resolution; Composite outcomes	Q4 2019
Cenicriviroc (Allergan)	CCR2/5 inhibitor	3	AURORA: NASH with F2-3 fibrosis Endpoints: Fibrosis; composite outcomes	Q4 2020
Resmetrion (Madrigal)	THR β agonist	3	NASH with F2-3 fibrosis (n=2000) Endpoint: Resolution; Composite outcomes	Initiated Feb 2019 Top line: TBD

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

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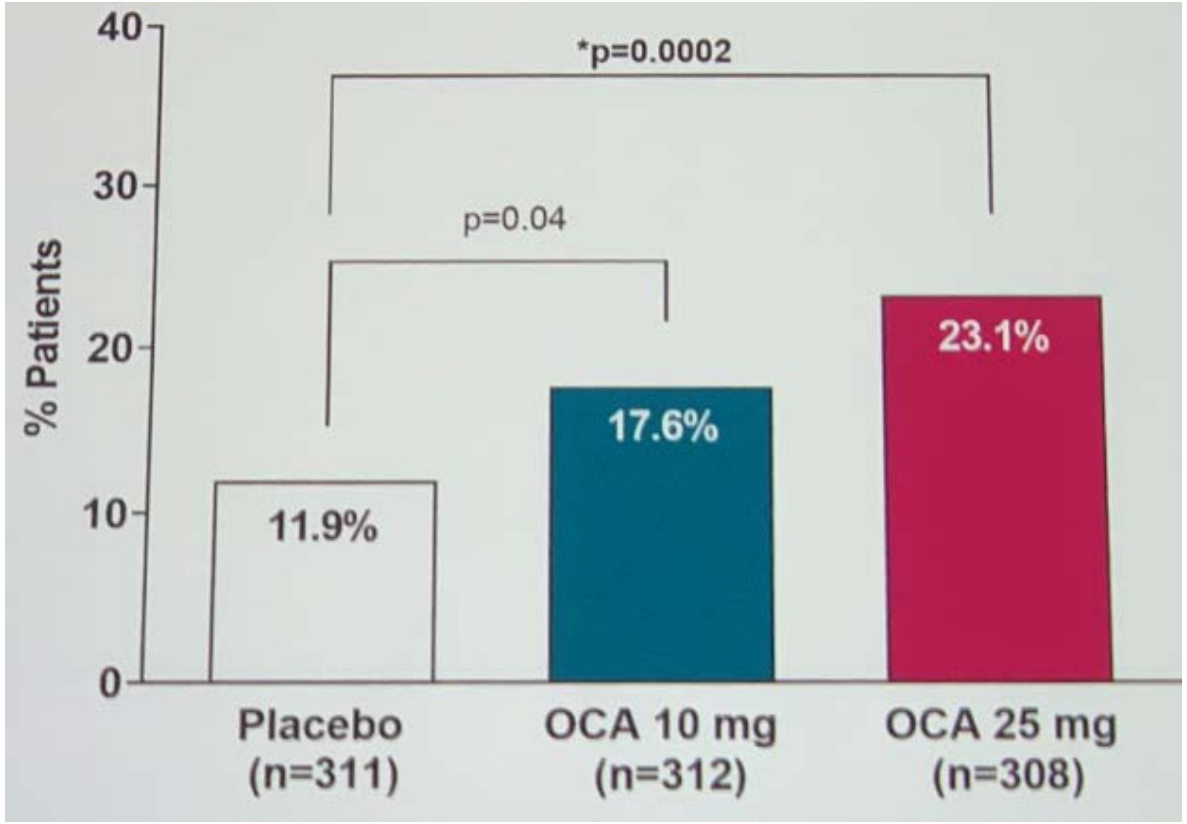
REGENERATE Results: Obeticholic acid in Pre-Cirrhotic NASH

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



- 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
- *GLASS HALF FULL*: Expect approval of OCA for NASH, but much room for efficacy improvement. Study ongoing for clinical outcomes.

EASL Presentation April 2019

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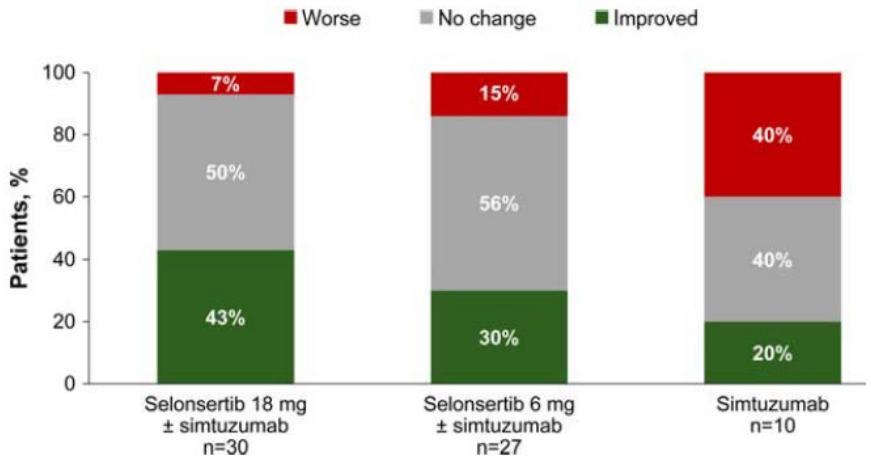
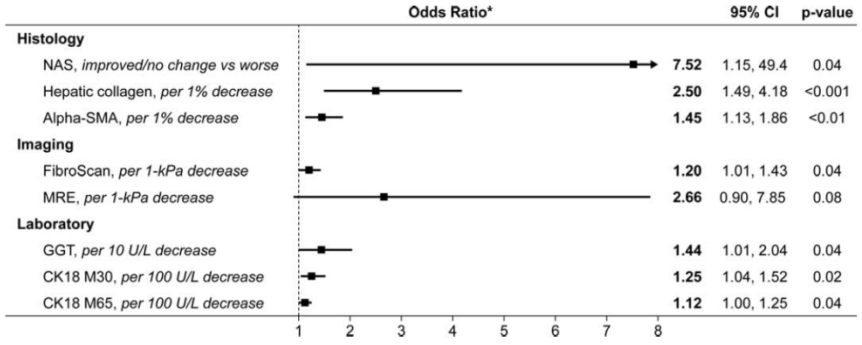
Selonsertib in Pre-Cirrhotic NASH

Phase 2 trial was basis for phase 3 (stage 2,3 fibrosis; 24 weeks)



Factors associated with fibrosis improvement



STELLAR3 Phase 3 Trial

- NASH with fibrosis stage 3 (bridging)
- N=808
- Placebo vs. selonsertib 6 and 18 mg daily
- Interim subpart H endpoint: Fibrosis reduction at week 48
- Event free survival at 240 weeks
- Anticipated interim data Q2 2019

Note: STELLAR4 failed primary endpoint in NASH cirrhosis
Loomba, et al. Hepatology 2018;67:549-559

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Elafibranor in Pre-Cirrhotic NASH

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.

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 end of 2019

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

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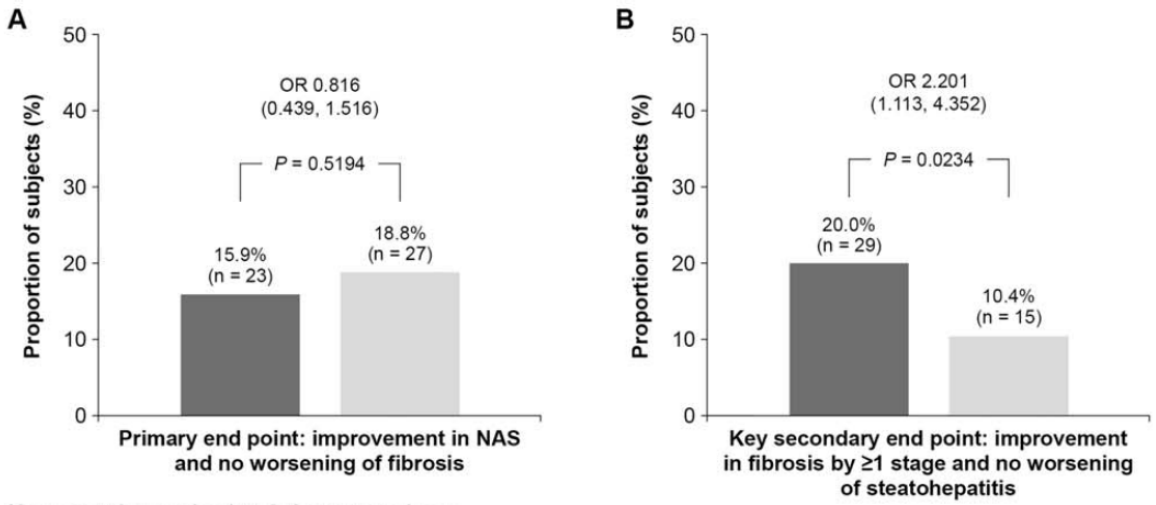
Cenicriviroc in Pre-Cirrhotic NASH

CENTAUR phase 2 trial was basis for phase 3

- Analysis after 1 year of therapy



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

- 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

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 2020?

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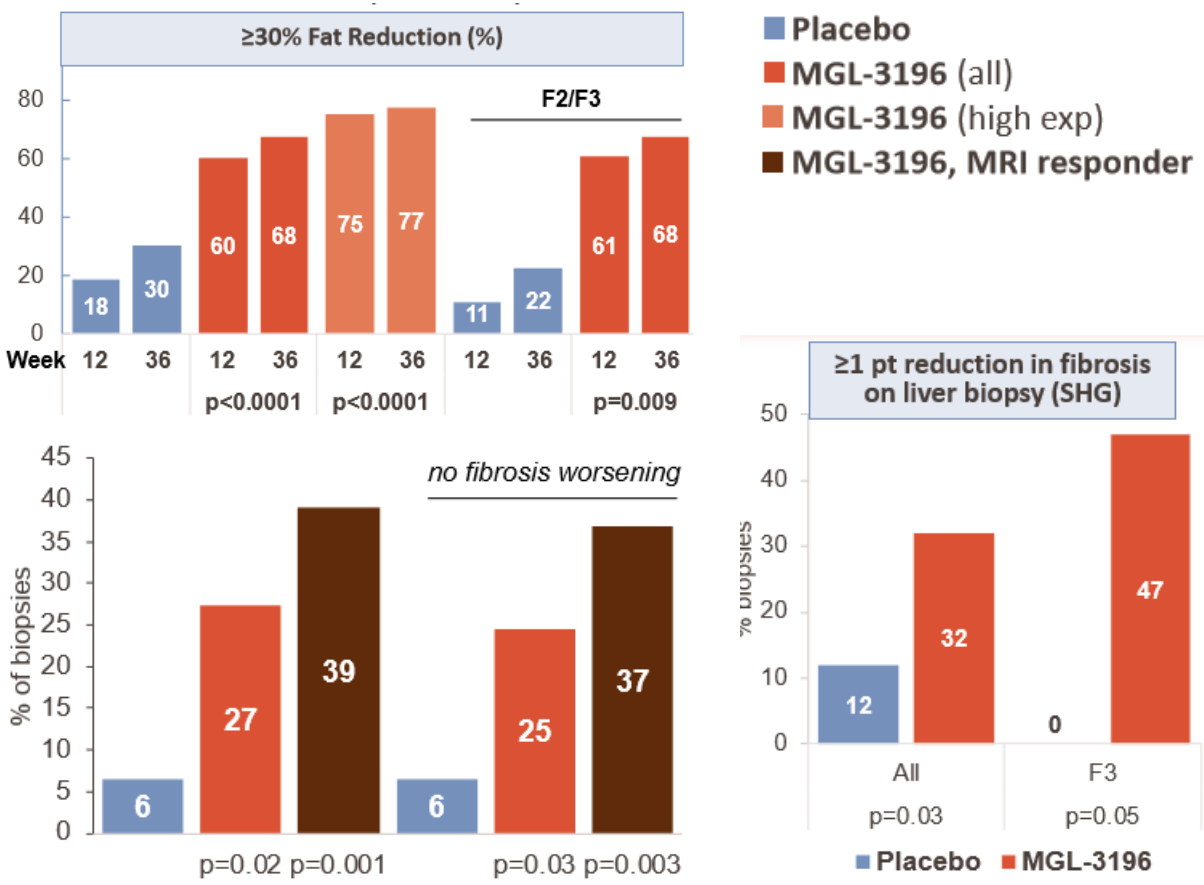
Resmetrion (MDL-3196) in Pre-Cirrhotic NASH

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



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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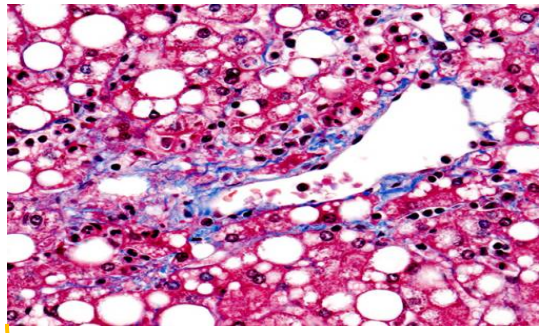
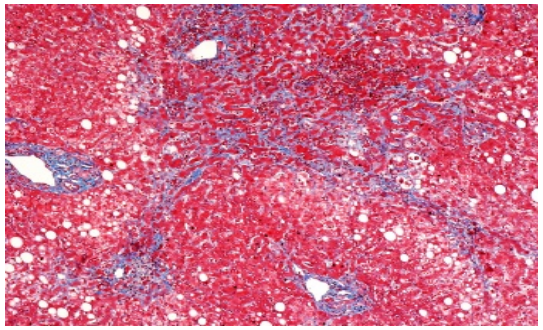
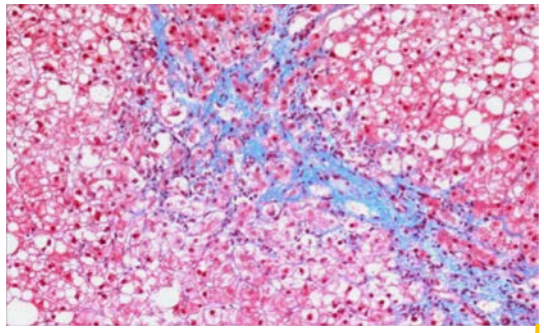
Advanced Phase (2 & 3) Monotherapy Programs in NASH

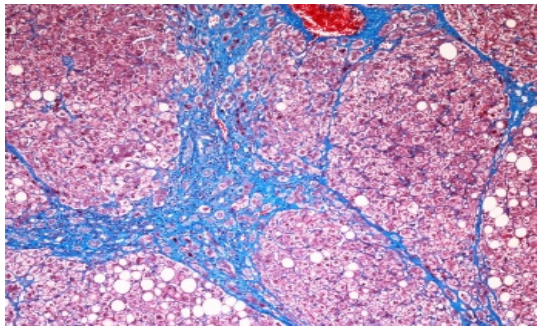
Phase 3 trials initiated & posted on clinicaltrials.gov

Stage 1	Stage 2	Stage 3	Stage 4









- Obeticholic Acid
  - Tropifexor/cilofexor/EDP-305/nidufexor
- Selonsertib
- Elafibranor (PPAR α/δ)
  - Seladelpar (PPAR δ)
  - Lanifibranor (PPAR α/δ/ɣ)
- Cenicriviroc
- Resmetrion
  - VK2809
- Pegbelfermin (FGF21)
  - BIO89-100, AKR-001

- Semaglutide (GLP-1)
- Firsocostat/PF-05221304
- NGM 282 (FGF19)
- NGM 313
- Volixibat (term)/Elobixibat
- MSDC-0602K
- Aramchol
- Namodenoson
- DUR-928
- IMM-124-E
- Emricasan*
- Simtuzumab*

- Obeticholic Acid
- Selonsertib**
- Simtuzumab*
- Emricasan*
- Belapectin (gal-3 inhibitor)*
- Pegbelfermin (FGF21)
- HSP47 inhibitor (HCV)

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

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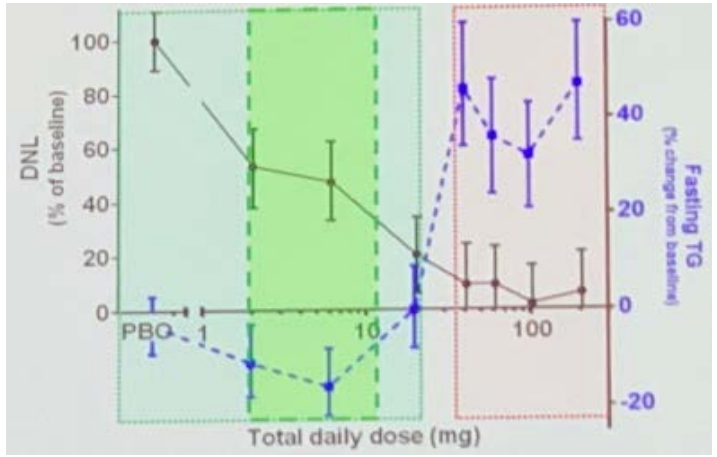
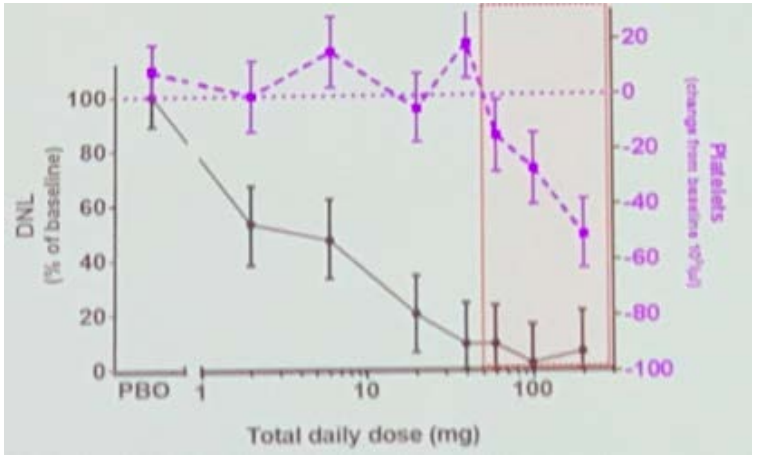
Acetyl-CoA Carboxylase inhibitors: Multiple Actions in NASH

PF-05221304 Phase 1:

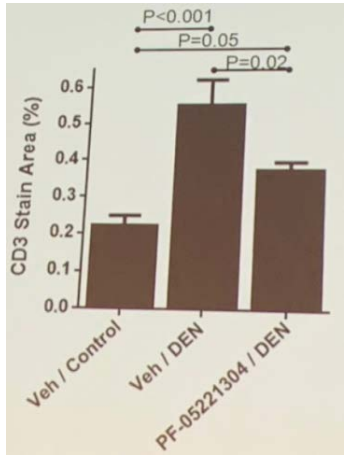
- ↓ de novo lipogenesis (DNL)
- ↑ serum TG at high doses
- ↓ platelets at high doses

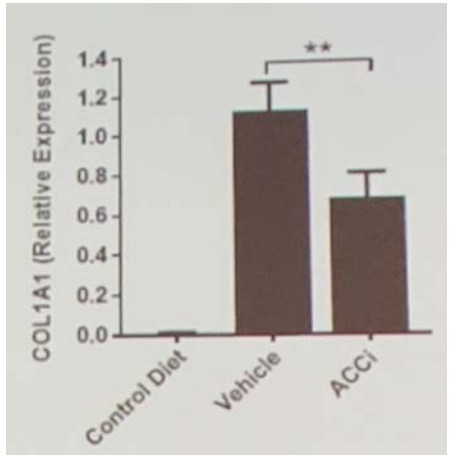


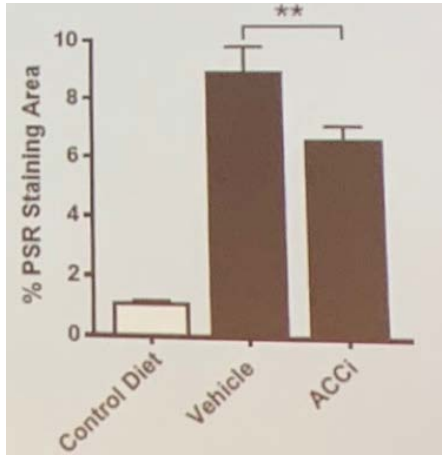


In cell culture and animal models:

- ↓ inflammatory cells
- ↓ fibrosis







Data taken from ILC-2019 Pfizer Presentations

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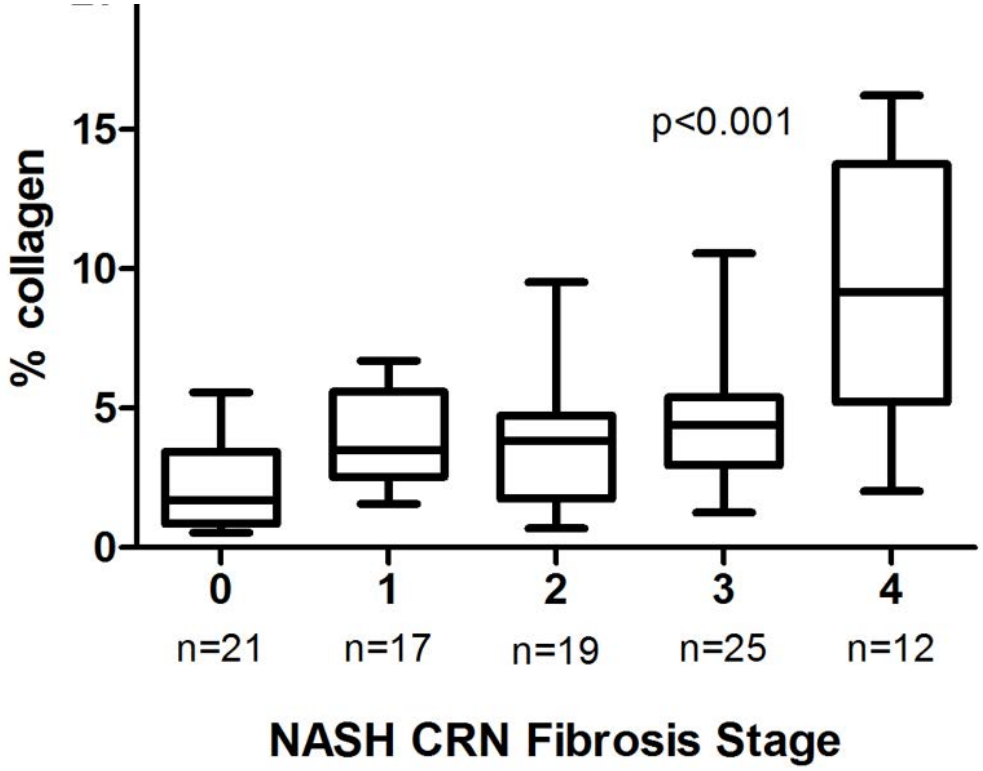
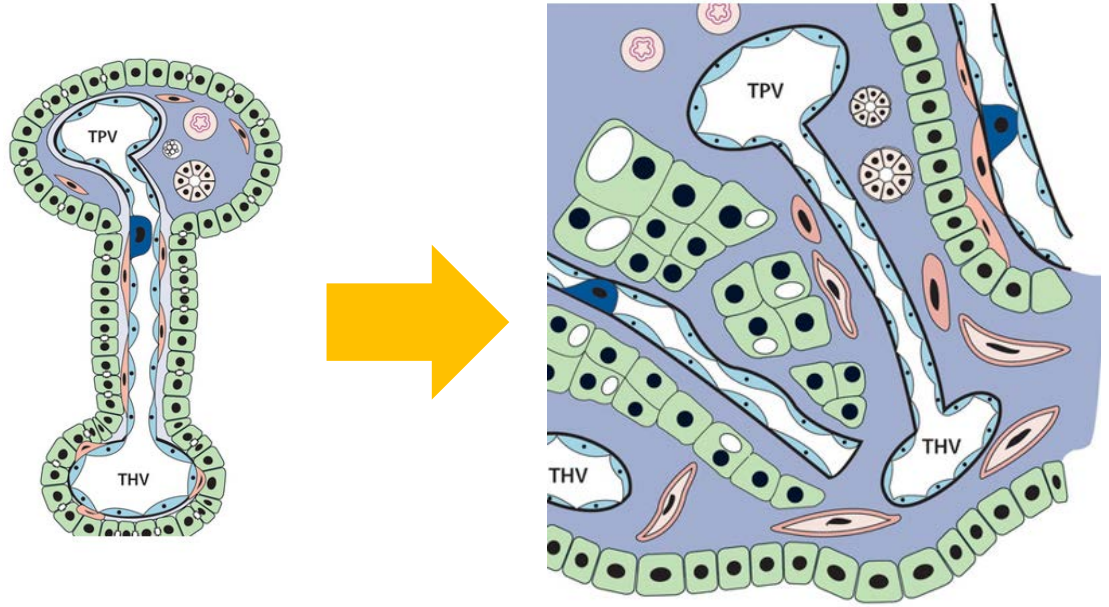
Cirrhosis Represents a Therapeutic Challenge

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 and Harrison

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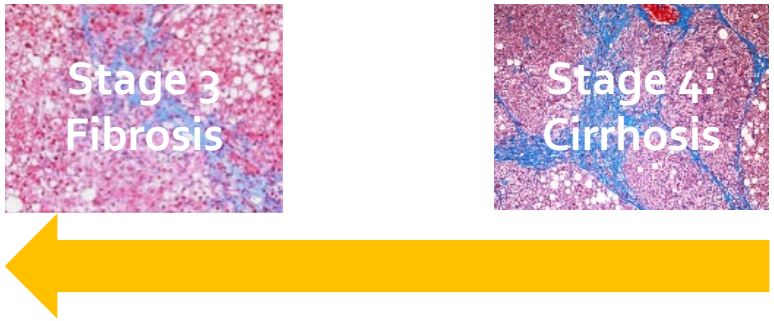
Endpoints for NASH Cirrhosis



NASH Cirrhosis Endpoints	
Surrogates for Accelerated Approval (agreement with Agencies as part of Phase 3 clinical trials)	**Clinical Outcomes for Full Approval**
Proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH	Reduced time to cirrhosis complications
The following are potential endpoints as there are no final phase 3 protocols	
Reduction in HVPG (endpoints will need to define threshold and degree of reduction in specific populations TBD)	Reduced time to cirrhosis complications
Reduced time to development of esophageal varices in patients with no varices at baseline	Reduced time to cirrhosis complications

Phase 3 and 2 Clinical Trials in NASH Cirrhosis*

Drug (Company)	MOA	Phase	Study Description	Data (estimate)
Selonsertib (GILD)	ASK-1 inhibitor	3	STELLAR-4: Compensated NASH cirrhosis Endpoints: Fibrosis; composite outcomes	Data reported 2/19 Failed primary
Obeticholic acid (ICPT)	FXR Agonist	3	REVERSE: Compensated NASH cirrhosis Endpoints: Fibrosis; composite outcomes	JUL 2020
Simtuzumab (GILD)	LOXL2 inhibitor	2	P2b multiple dose; compensated NASH cirrhosis Endpoints: Change in HVPG	Data reported 2017 Failed primary
Belapectin (GALT)	Galectin-3 inhibitor	2	NASH-CX: Compensated NASH cirrhosis Endpoints: Change in HVPG	Data reported 12/17 Failed primary
Emricasan (CNAT/Novartis)	Pan-caspase inhibitor	2 2	ENCORE-PH (severe portal HTN); Change in HVPG ENCORE-LF (decompensated cirrhosis); Complications	Data reported 11/19 Failed primary H2 2019
Pegbelfermin (BMS)	PEG-FGF21	2	P2b multiple dose; compensated NASH cirrhosis Endpoints: Fibrosis	JAN 2020

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

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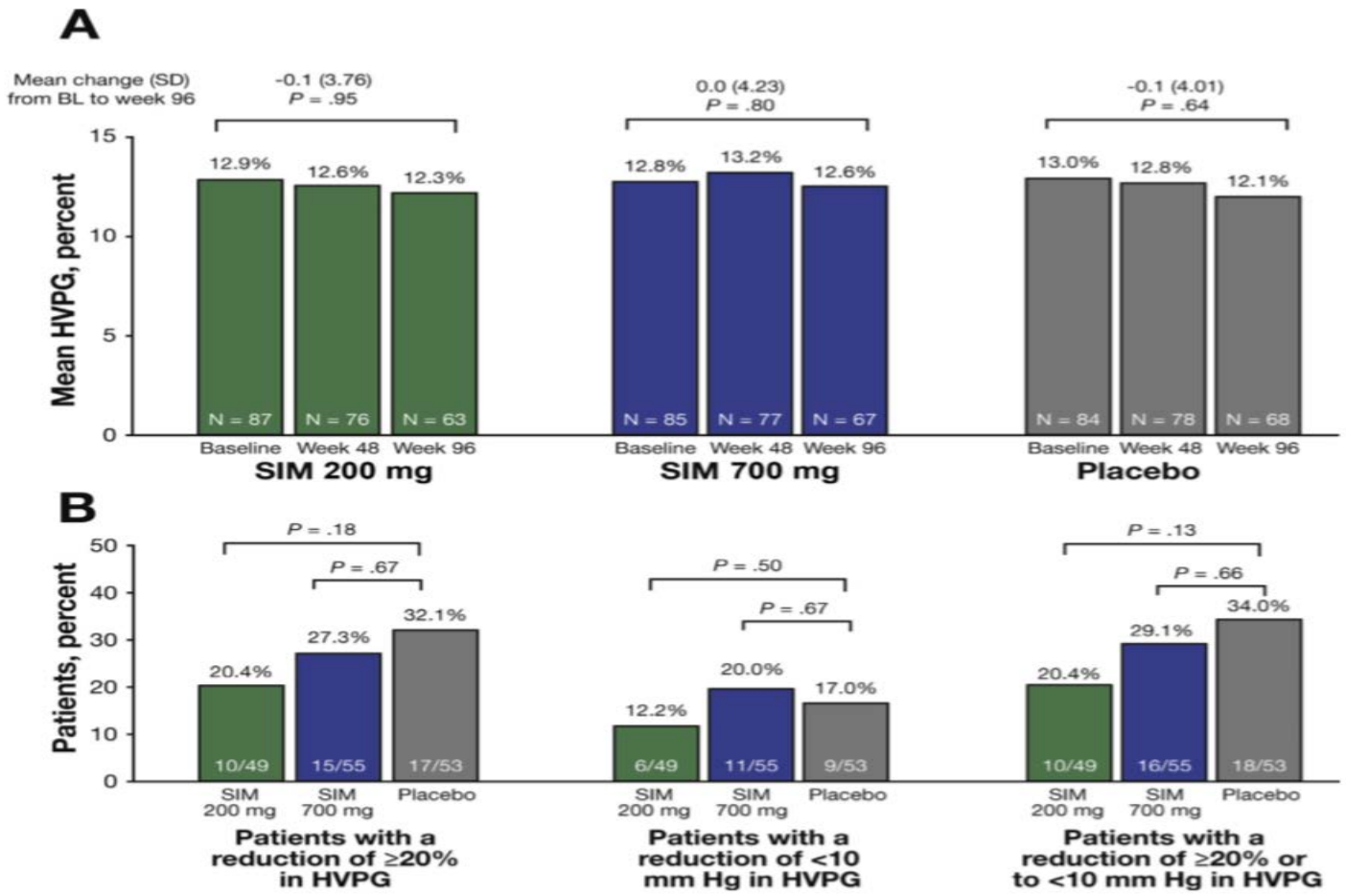
Phase 2b Results: Simtuzumab in Compensated NASH Cirrhosis



Large, randomized controlled clinical trial (n=258) evaluating two doses of SIM after 48 and 96 weeks of therapy

- 67% with clinically significant portal hypertension and 43% with esophageal varices
- Primary endpoint was change in HVPG at week 96
- No difference between placebo and treatment groups
- 32.1% of placebo group had ≥20% reduction in HVPG

Harrison, et. al., Gastroenterology 2018;155:1140–1153

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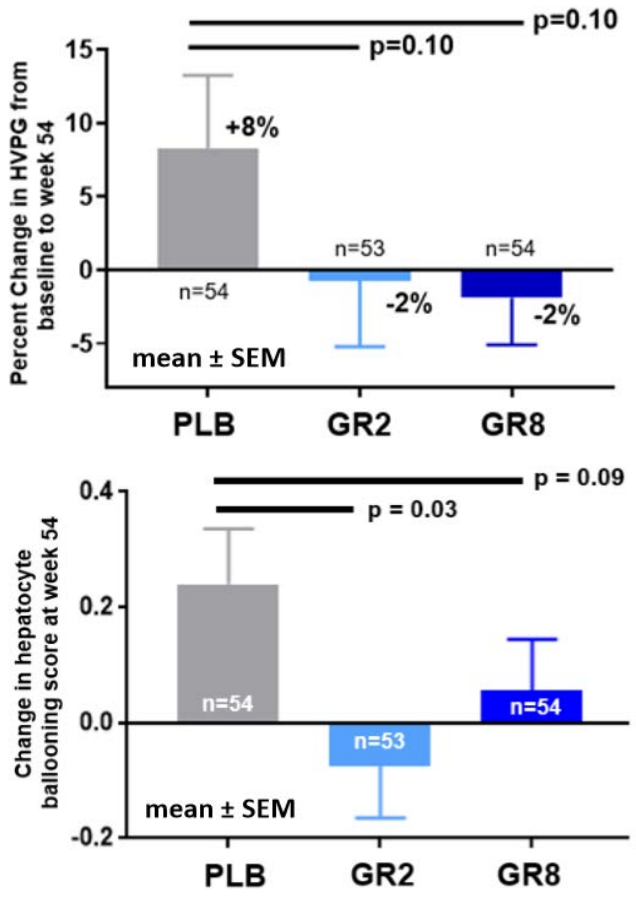
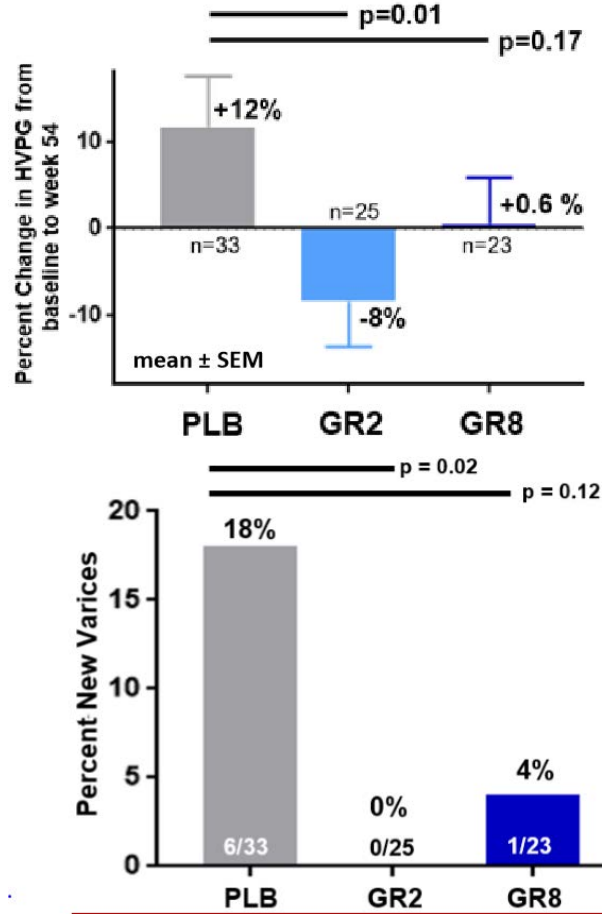
NASH-CX Results*: Belapectin (GR-MD-02) in Compensated NASH Cirrhosis

Total Patient Population (ITT)



No Varices (Post-hoc analysis)



- In total ITT population:
  - Missed primary of ΔHVPG at 54 weeks
  - Placebo had increase in hepatocyte ballooning which was significantly decreased in 2 mg/kg group
  - No differences fibrosis on liver biopsy or serum biomarkers
- In post-hoc analysis, patients without varices at baseline had:
  - Significant ΔHVPG in 2 mg/kg group
  - Lower incidence of varices development
  - Ballooning and fibrosis assessment not reported for no varices subgroup
- Subgroup results require repetition in study designed to study patients without varices.
- Company indicates it plans to initiate phase 3 with 2 years of treatment in patients without varices. Protocol is being finalized with target of start in fall 2019**.

* Naga Chalasani, EASL2018 Presentation
** Company Presentation March 2019

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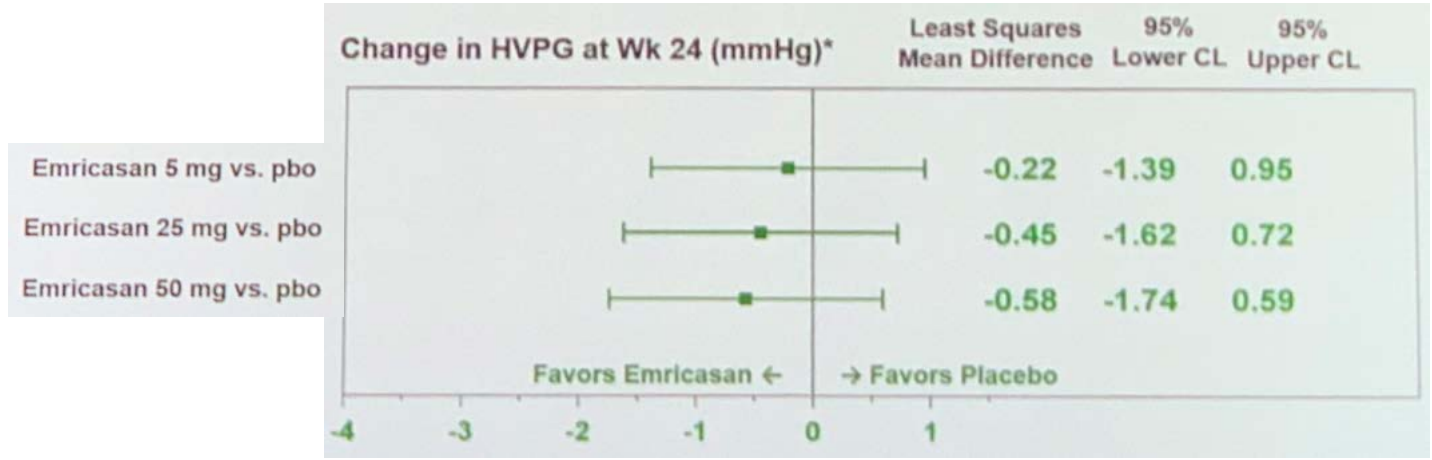
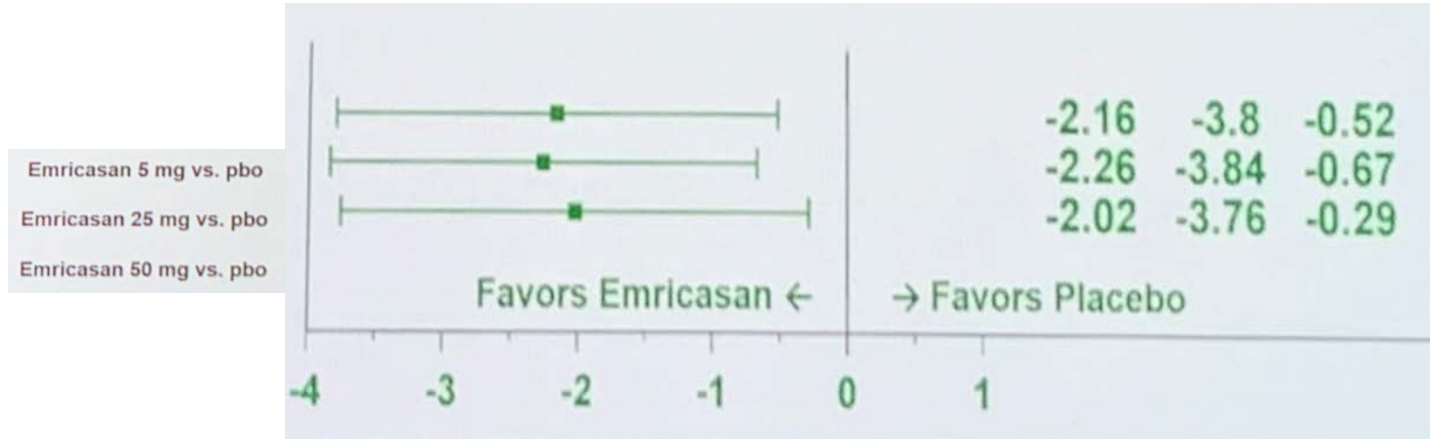
ENCORE-PH Clinical Trial Results in NASH Cirrhosis with HVPG ≥12 mmHg

Overall, no significant change in HVPG at week 24 with emricasan versus placebo



Subgroup Analysis: Compensated cirrhosis with baseline HVPG ≥16 mmHg had a significant decrease in HVPG at end of treatment



Guadelupe Garcia-Tso, EASL2019 Presentation

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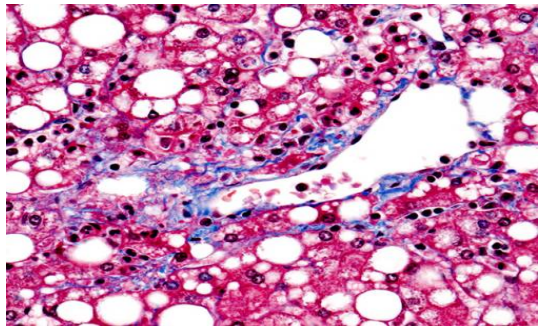
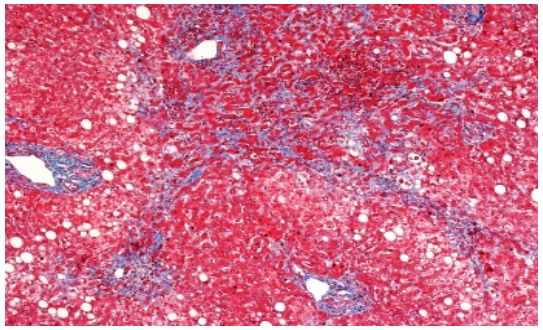
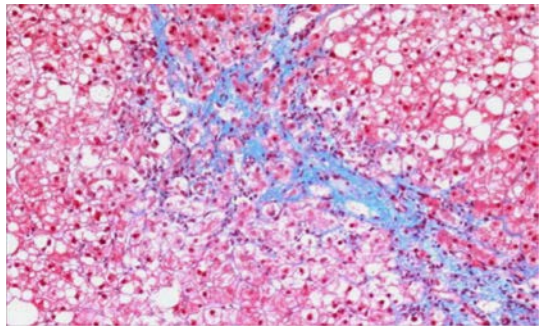
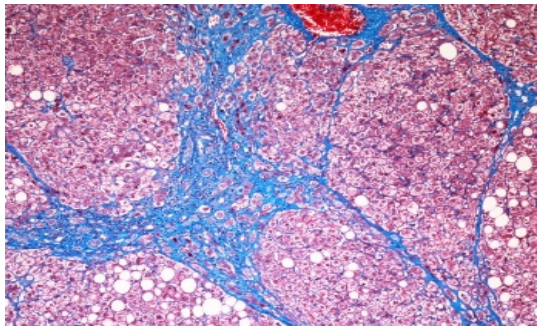
Summary of Late Stage NASH Monotherapy Programs

Phase 2 trials

Phase 3 trials initiated & posted on clinicaltrials.gov

Stage 1	Stage 2	Stage 3	Stage 4
			
▪ Obeticholic Acid ▪ Selonsertib ▪ Elafibranor (PPAR α/δ) ▪ Cenicriviroc ▪ Resmetrion			▪ Obeticholic Acid ▪ Selonsertib** ▪ Simtuzumab* ▪ Emricasan* ▪ Belapectin (gal-3 inhibitor)* ▪ Pegbelfermin (FGF21)

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

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Equilibrium of ECM Turnover: Addressing Cirrhosis Will Require Drugs That Increase ECM Degradation

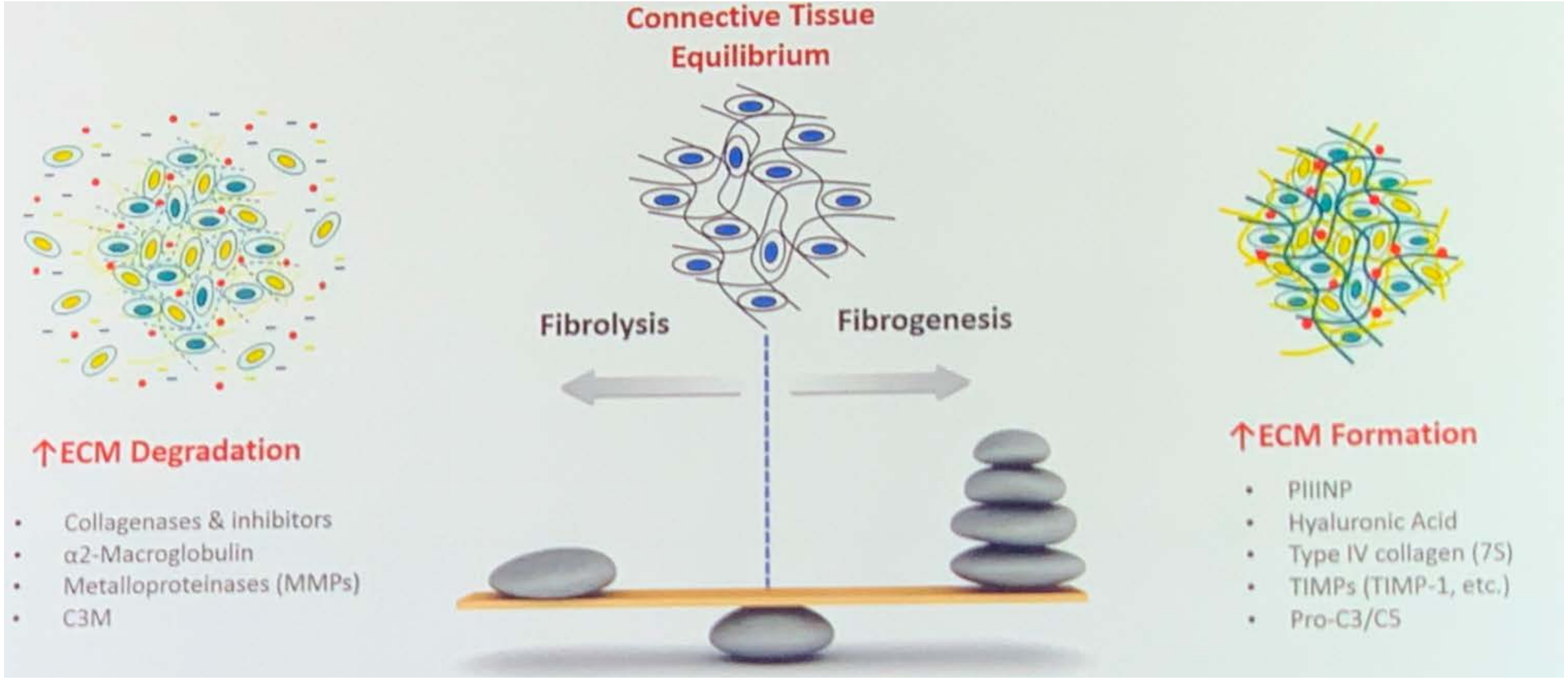

Figure from ILC-2019 Presentation by Dr. Quentin Anstee

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Thank You!

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