Huidige en toekomstige behandelingsmethoden bij NAFLD

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- Wie te behandelen?
- Case finding en screening?
- Niet-pharmacologische behandeling
- Pharmacologische behandeling

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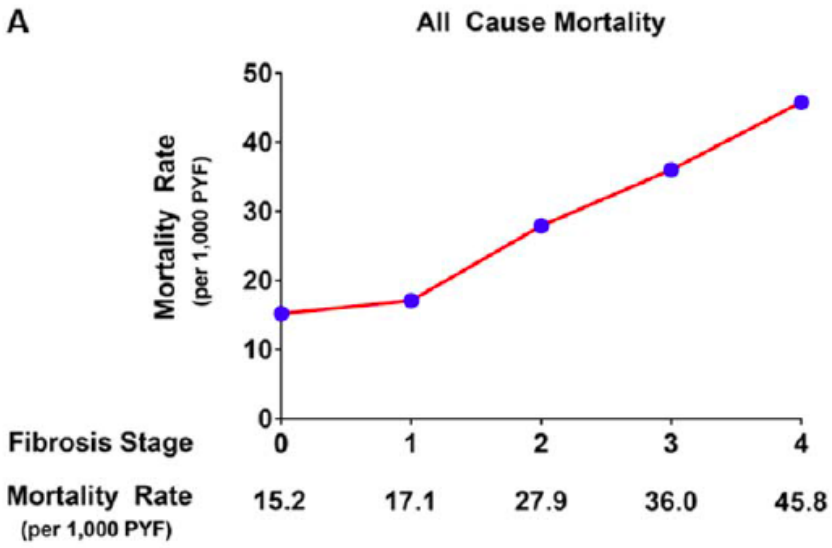
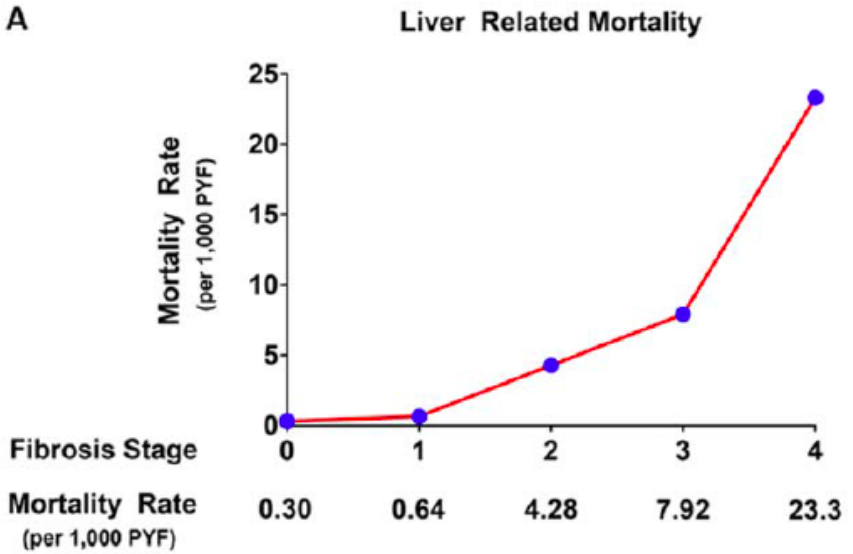
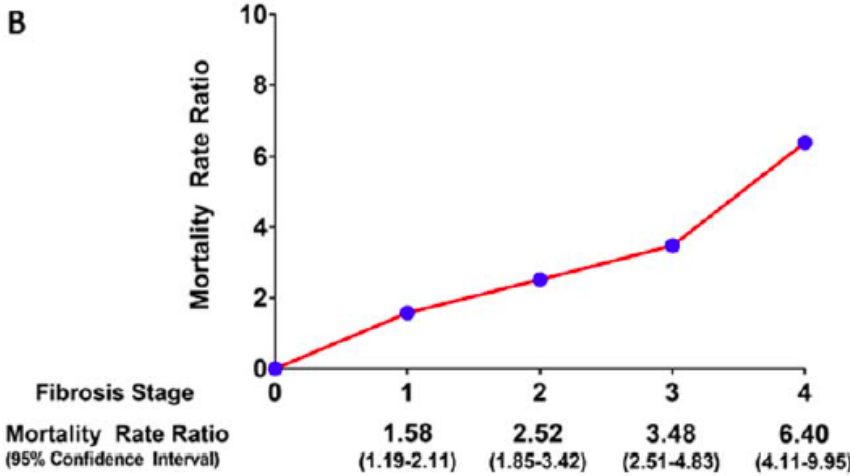
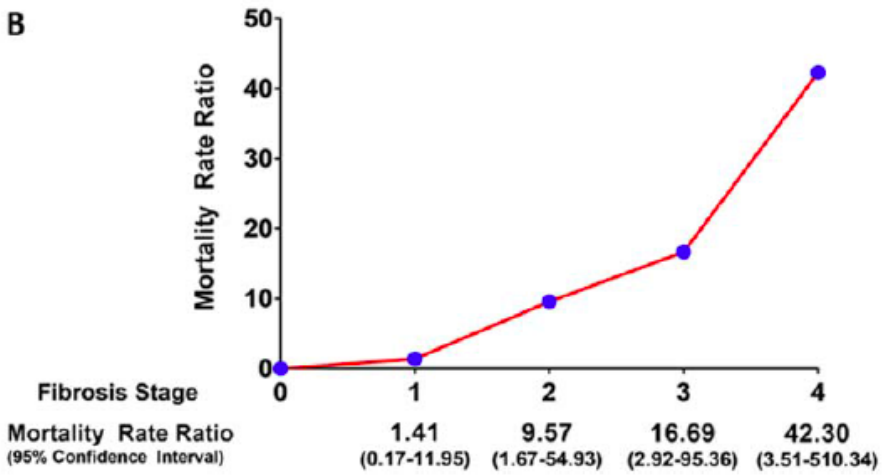

A
All Cause Mortality
Mortality Rate (per 1,000 PYF)
50
40
30
20
10
0
Fibrosis Stage
0 1 2 3 4
Mortality Rate (per 1,000 PYF)
15.2 17.1 27.9 36.0 45.8


A
Liver Related Mortality
Mortality Rate (per 1,000 PYF)
25
20
15
10
5
0
Fibrosis Stage
0 1 2 3 4
Mortality Rate (per 1,000 PYF)
0.30 0.64 4.28 7.92 23.3


B
Mortality Rate Ratio
10
8
6
4
2
0
Fibrosis Stage
0 1 2 3 4
Mortality Rate Ratio (95% Confidence Interval)
1.58 (1.19-2.11)
2.52 (1.85-3.42)
3.48 (2.51-4.83)
6.40 (4.11-9.95)

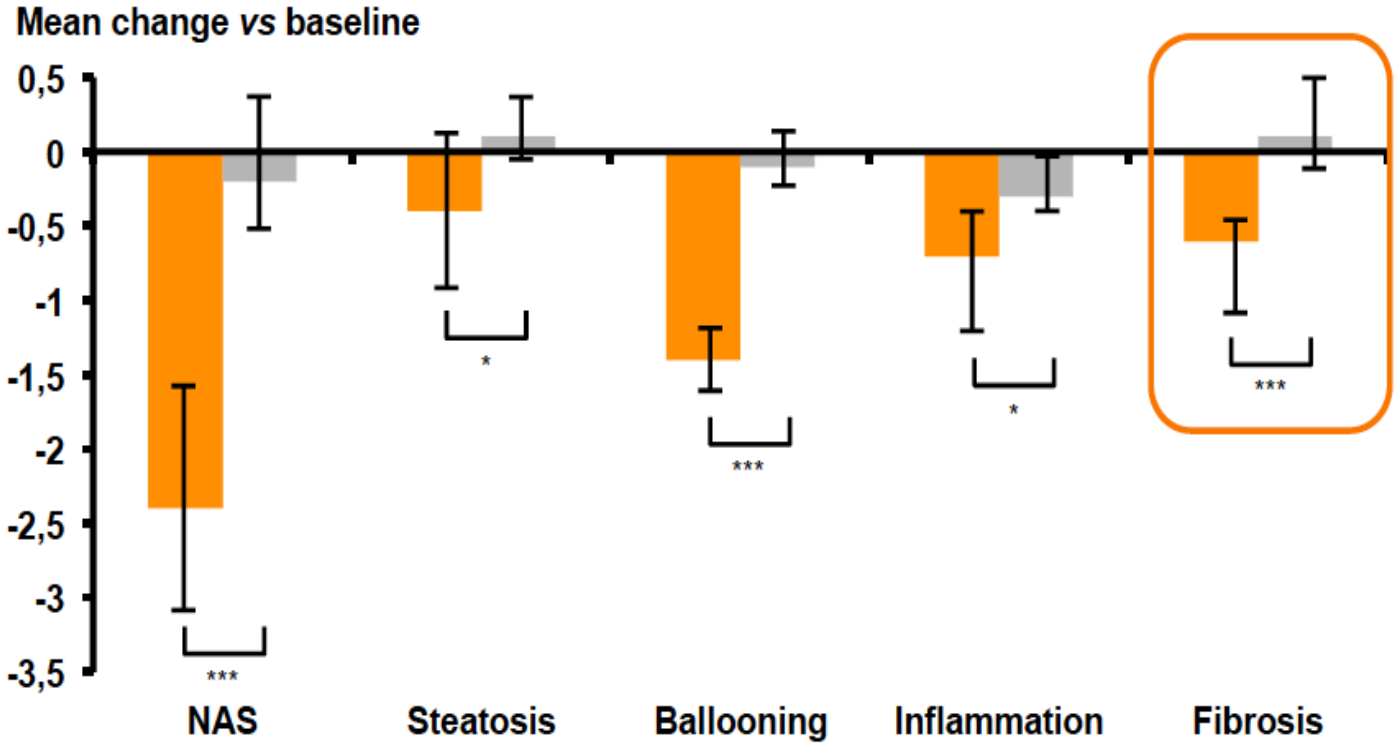

B
Mortality Rate Ratio
50
40
30
20
10
0
Fibrosis Stage
0 1 2 3 4
Mortality Rate Ratio (95% Confidence Interval)
1.41 (0.17-11.95)
9.57 (1.67-54.93)
16.69 (2.92-95.36)
42.30 (3.51-510.34)

		Final fibrosis stage					Total stages of fibrosis progressed	Person-years of follow-up evaluation	FPR (95% CI)	Time taken to progress by 1 stage (95% CI)
NAFLD (11 studies)										
		0	1	2	3	4				
Baseline fibrosis stage	0 (131)	79	28	13	7	4	+91	968	0.13 (0.07–0.18)	7.7 (5.5–14.8)
	1 (119)	26	44	32	15	2	+43	628.4	0.10 (0.04–0.16)	10.0 (6.2–25.0)
	2 (61)	9	17	14	13	8	−6	331.8	NA	-
	3 (34)	2	5	10	7	10	−16	153.4	NA	-
	4 (21)	0	0	1	6	14	−8	63.8	NA	-
	Overall (366)						+104	2145.4	NA	-
	Stage 0 plus stage 1 fibrosis (250)						+134	1596.4	0.12 (0.07–0.16)	8.3 (6.2–14.3)
NAFL (6 studies)										
		0	1	2	3	4				
Baseline fibrosis stage	0 (81)	52	16	8	4	1	+48	751.3	0.07 (0.02–0.11)	14.3 (9.1–50.0)
	1 (39)	6	13	14	6	0	+20	112.6	0.15 (-0.09 to 40)	NA
	2 (13)	2	3	5	2	1	−3	40.7	NA	-
	3 (0)	0	0	0	0	0	0	0	NA	-
	4 (0)	0	0	0	0	0	0	0	NA	-
	Overall (133)						+75	904.6	NA	-
	Stage 0 plus stage 1 fibrosis (120)						+68	863.9	0.09 (0.04–0.14)	11.1 (7.1–25.0)
NASH (7 studies)										
		0	1	2	3	4				
Baseline fibrosis stage	0 (21)	10	7	2	1	1	+18	115.5	0.14 (0.07–0.21)	7.1 (4.8–14.3)
	1 (49)	9	25	9	5	1	+13	396.6	0.08 (-0.01 to 0.17)	NA
	2 (25)	3	10	4	4	4	−4	222.3	NA	
	3 (16)	0	4	4	2	6	−6	95.8	NA	
	4 (5)	0	0	0	1	4	−1	12.6	NA	
	Overall (116)						+20	842.8	NA	
	Stage 0 plus stage 1 fibrosis (70)						+31	512.1	0.10 (0.03–0.17)	10.0 (5.9–33.3)

Who to treat?
Data & Controversies fueling the debate

- Fibrosis is the most important predictor of outcomes
  - Liver-related
  - Non-liver related
- NAFL progresses to advanced fibrosis
  - Annual progression rate slower than NASH

➔ Fibrosis is the target

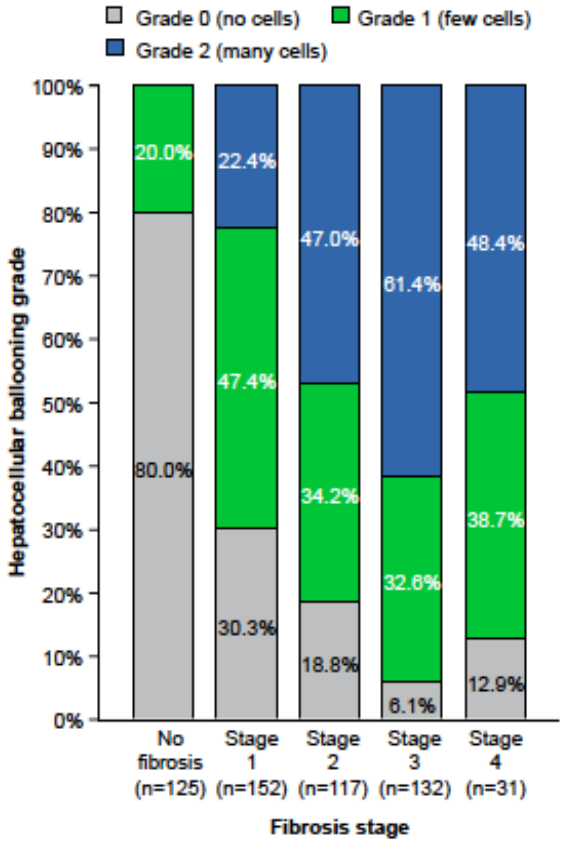


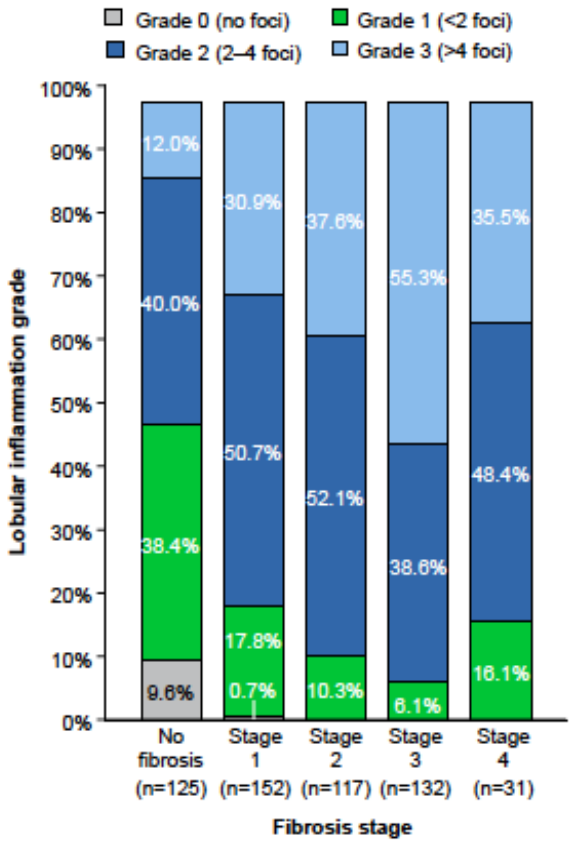
Patients who resolved NASH showed significant reduction in liver fibrosis while non-responders did not show any change from baseline

*p<0.05; ***p<0.001

Ratziu V, et al. Gastroenterology. 2016 Feb 11. pii: S0016-5085(16)00140-2

Association between fibrosis stage and hepatocellular ballooning and lobular inflammation grade





- Hepatocellular ballooning and lobular inflammation grade generally increased with increasing stages of fibrosis

	Correlation with fibrosis stage
Hepatocellular ballooning	r=0.60; p<0.001
Lobular inflammation	r=0.41; p<0.001
Portal inflammation	r=0.55; p<0.001
Steatosis	r=0.08; p=0.08

Ratziu et al. ILC 2017 LB-541

Characteristic	All patients (n = 108)	No progression of fibrosis (n = 63)	Progression of fibrosis (n = 45)	*p* value
Results at follow up biopsy				
BMI (kg/m^2)	34.9 ± 5.2	34.4 ± 4.7	35.6 ± 5.9	0.27*
T2DM	65%	51%	84%	<0.001
ALT (IU/L)	79 ± 66	82 ± 77	76 ± 48	0.63*
AST (IU/L)	57 ± 35	52 ± 34	63 ± 36	0.13*
GGT (IU/L)	148 ± 195	109 ± 143	202 ± 239	0.03*
Platelets (x10^9/L)	230 ± 62	248 ± 51	208 ± 69	0.001*
IgA (g/L)	3.26 ± 1.50	2.95 ± 1.32	3.7 ± 1.65	0.05*
IgG (g/L)	10.9 ± 3.1	11.2 ± 3.3	10.5 ± 2.7	0.4*
Ferritin	194 ± 218	199 ± 205	187 ± 237	0.81*
AST/ALT ratio	0.81 ± 0.30	0.74 ± 0.29	0.89 ± 0.29	0.01*
FIB-4 score	1.79 ± 1.39	1.36 ± 0.62	2.33 ± 1.69	0.001*
NAFLD score	-0.77 ± 1.38	-1.35 ± 1.08	-0.07 ± 1.40	<0.001*
NAS	4 (1-7)	3 (1-6)	5 (3-7)	<0.001
Fibrosis stage	2 (0-4)	1 (0-3)	3 (1-4)	<0.001^
0	23 (21%)	23 (37%)	0 (0%)	
1	19 (18%)	16 (25%)	4 (9%)	
2	19 (18%)	15 (24%)	4 (9%)	
3	33 (31%)	9 (14%)	24 (53%)	
4	13 (12%)	0 (0%)	13 (29%)	
Steatosis/NASH	25 (23%)/83 (77%)	21 (33%)/42 (67%)	0 (0%)/44 (100%)	<0.001#
Time between biopsy (yr)		6.7 ± 3.5	7.5 ± 5	0.35

McPherson *et al*. J Hep 2015

Who to treat?
Data & Controversies fueling the debate

- Fibrosis regression in trials associated with reduced disease activity
- Fibrosis progressors
  - NASH at second biopsy
  - Some signs of necro-inflammation at baseline
- NASH driver of disease

➔ NASH is the target

Treatment Indication

NASH

+

Some degree of activity

NAS ≥ 4

+

Some degree of fibrosis

F ≥ 2

Or

F1 + risk factors (NAS ≥ 5, DM2, obesity,…)

- Wie te behandelen?
- Case finding en screening?
- Niet-pharmacologische behandeling
- Pharmacologische behandeling

Casus

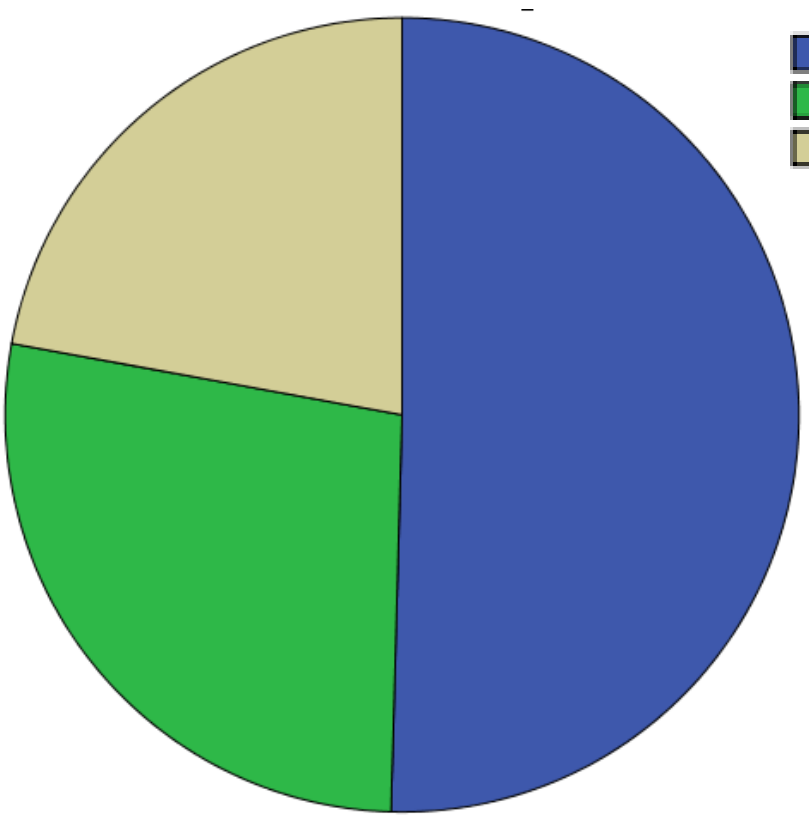
- Male, 48y
- L 1m68, G 85 kg, Waist 109 cm
- No medical history, does not smoke nor drink
- check-up 1y ago
  - Diagnosis T2DM -> metformin 500 mg/d
  - Diagnosis AHT -> amlodipin 5 mg/d
- Status praesens
  - AST 35 U/L, ALT 37 U/L, GGT 45 U/L, TRC 161x10e9/L, albumin 4.1 g/dL
  - US: grade 1 steatosis

Question 1

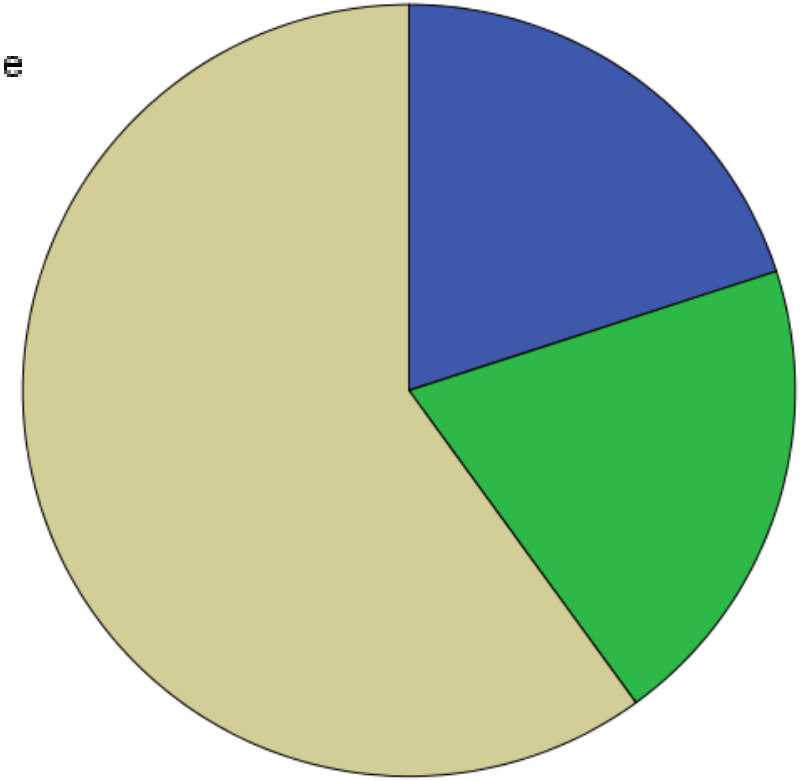
How do you interpret the transaminases (AST 35 U/L, ALT 37 U/L)?

1. Normal according to what I usually consider nomal/abnormal
2. Depends on local lab ULN
3. Normal as clearly < 40 U/L
4. Abnormal

ALT ≤ 40 U/L



ALT > 40 U/L



p<0.001

ALT cut-off values

- Male:
  - ALT 29-33 U/L
- Female
  - ALT 19-25 U/L

ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries

Paul Y. Kwo, MD, FACG, FAASLD[1], Stanley M. Cohen, MD, FACG, FAASLD[2] and Joseph K. Lim, MD, FACG, FAASLD[3]

Am J Gastroenterology 2016

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  - US: grade 1 steatosis

Would you consider this patient for further hepatological referral/biopsy?

1. No, I consider this to be NAFL
2. No, I consider this to be mild abnormalities requiring no further investigation
3. No, I would go for a fibroscan and then decide
4. Yes, I would consider this sufficient to warrant further investigation

- NAFLD Liver Fibrosis Score
  - Age, BMI, IFG/DM, AST/ALT, platelets, albumin
  - 0.269 -> indeterminate score
  - Cut-offs: -1.455 and 0.675
  - Adjust for age
  - High NPV

- Fibroscan 8.4 kPa

- Biopsy NASH with S2A3F3

Screening

WHO

- Elevated liver enzymes
- Obesity/metabolic syndrome
- Diabetes
- Cardiovascular event

HOW?

- Liver enzymes
- Scores
  - Routine parameters
  - ELF, Fibotest,...
- Fibroscan

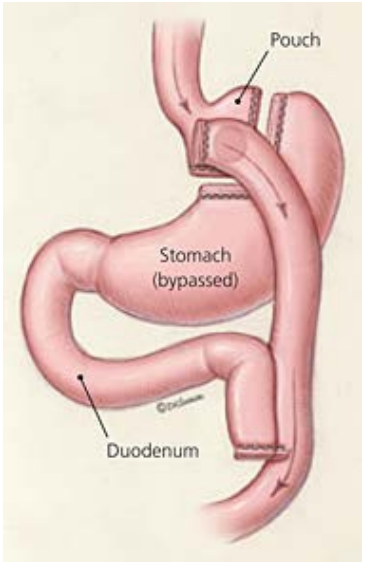
Guidelines

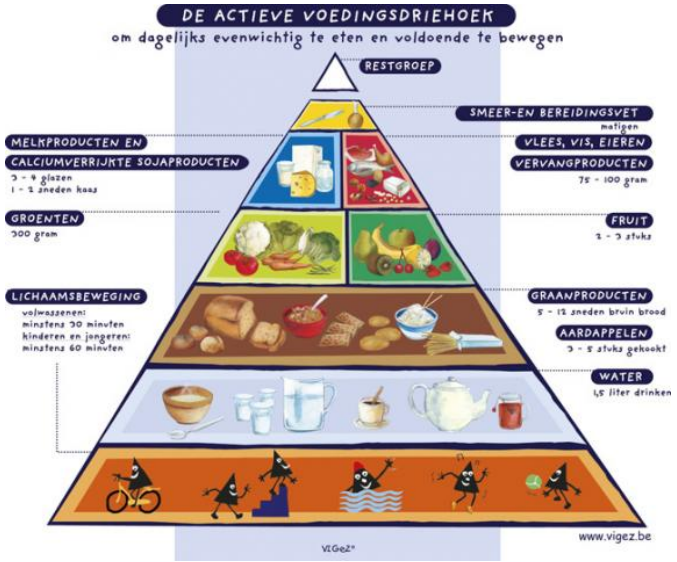
- Several proposals
- In preparation

- Wie te behandelen?
- Case finding en screening?
- Niet-pharmacologische behandeling
- Pharmacologische behandeling

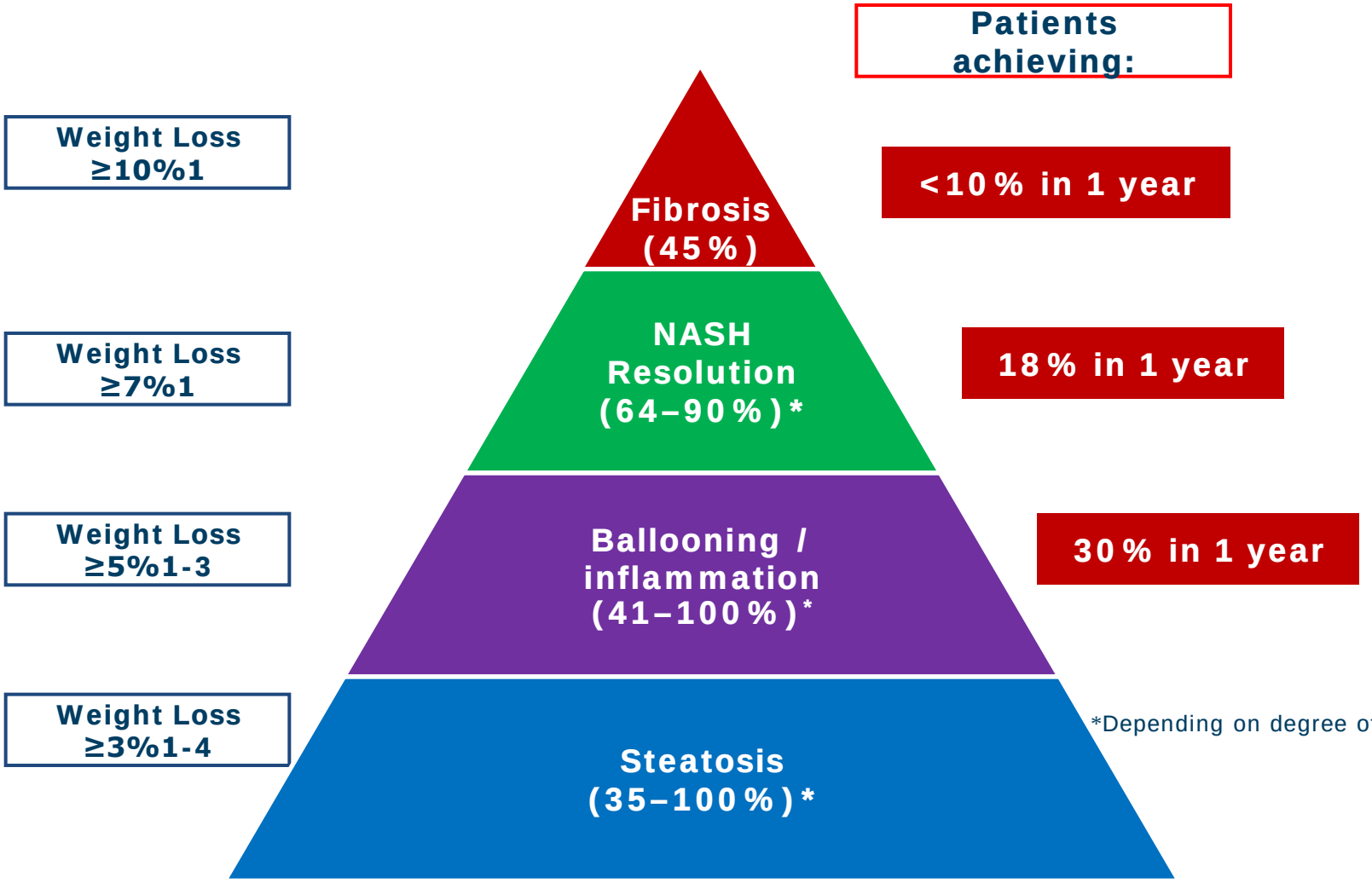
Life style modification and weight loss

- Weight reduction
  - Diet
  - Physical activity
  - Bariatric surgery ?





Weight loss pyramid



*Depending on degree of weight loss

Vilar-Gomez E, et al. Gastroenterology. 2015;149:367-78

- Wie te behandelen?
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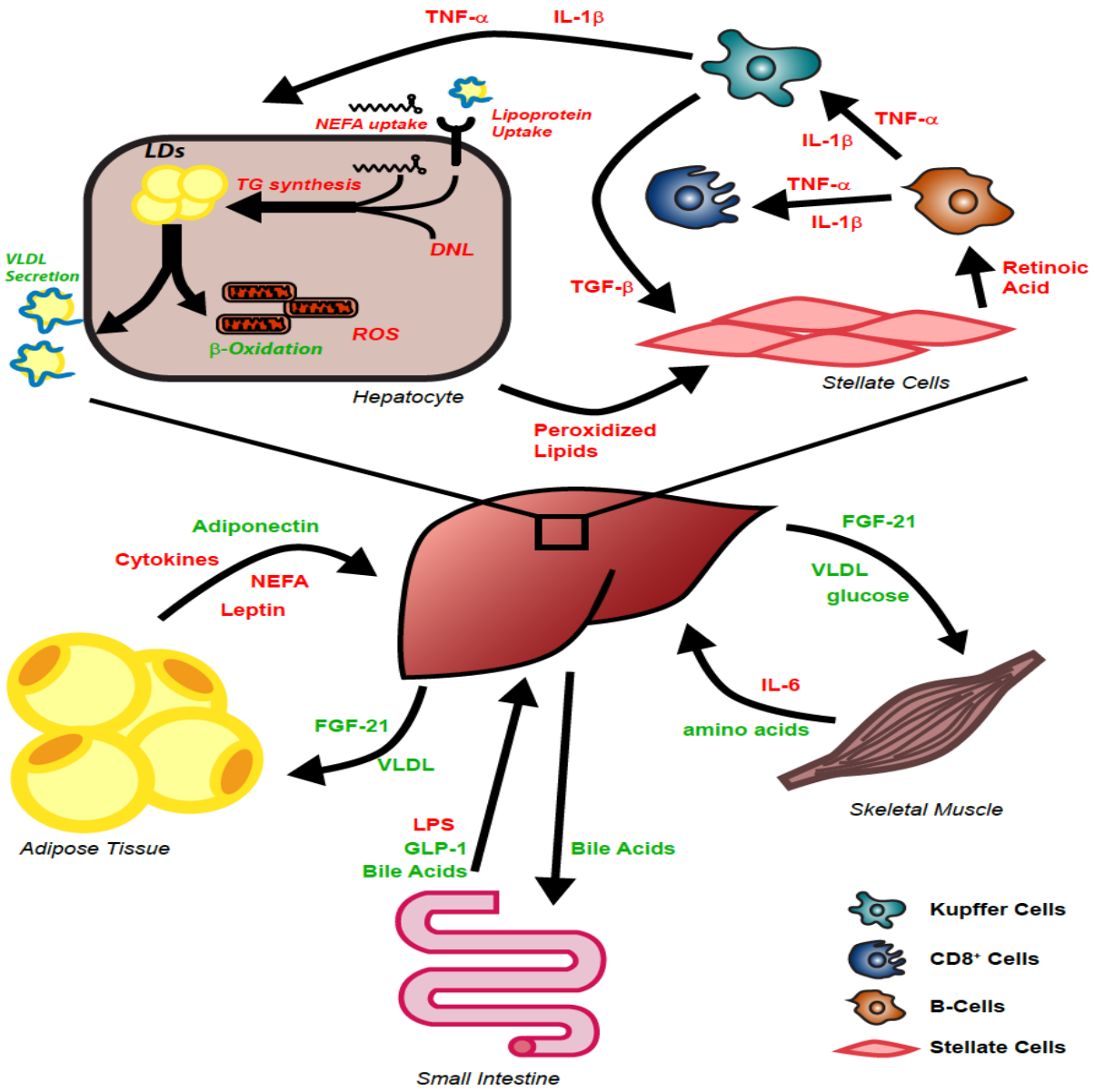


Haas, Francque & Staels. Ann Rev Physiol 2016

- Metformin
- Statins

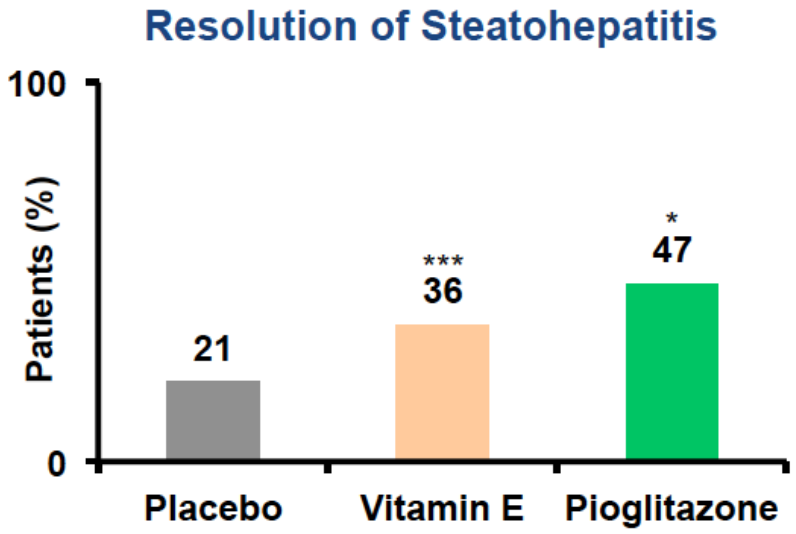
- Glitazones
- Vit E

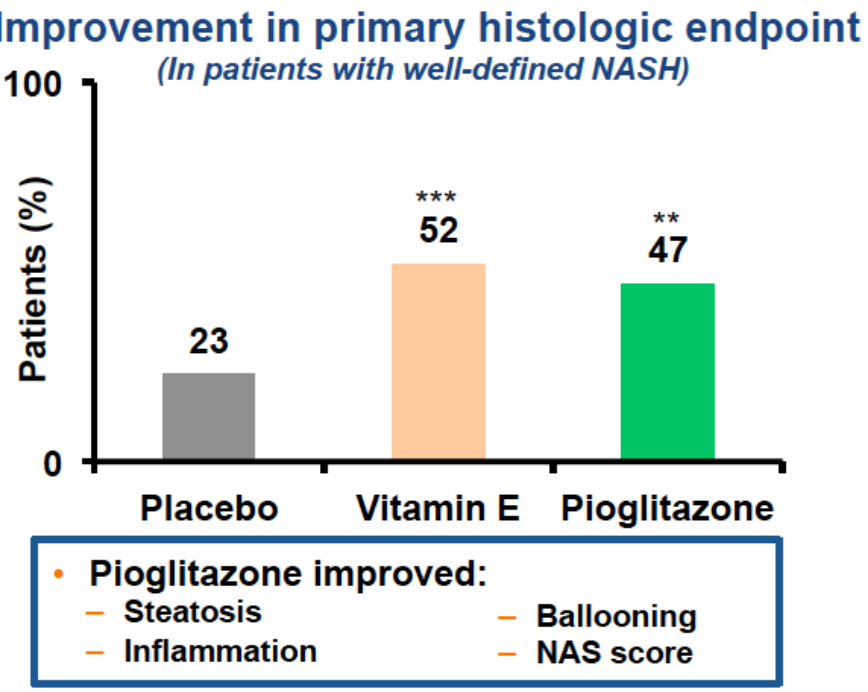
- Phase 3
  - Elafibranor
  - Obeticholic Acid
  - Selonsertib
  - Cenicriviroc

- Phase 2
  - GLP1-agonist
    - Liraglutide
    - Semaglutide
  - IVA3377
  - BI
  - Novartis
  - Gilead
  - ...

GLITAZONES AND VITAMIN E

2 yr PIVENS trial pioglitazone or vit E in non-diabetic NASH





*p=0·05; **p<0·01; ***p<0·001 vs placebo

Sanyal AJ, et al. N Engl J Med. 2010;362:1675-85

Pharmacologic treatment in NASH
Current evidence

Vitamin E

- NASH without diabetes
- Insufficient evidence diabetics or cirrhotics
- Safety concern for long-term treatment

Pioglitazone

- NASH with or without diabetes
- Limited data in cirrhotics
- Side effects for long-term treatment

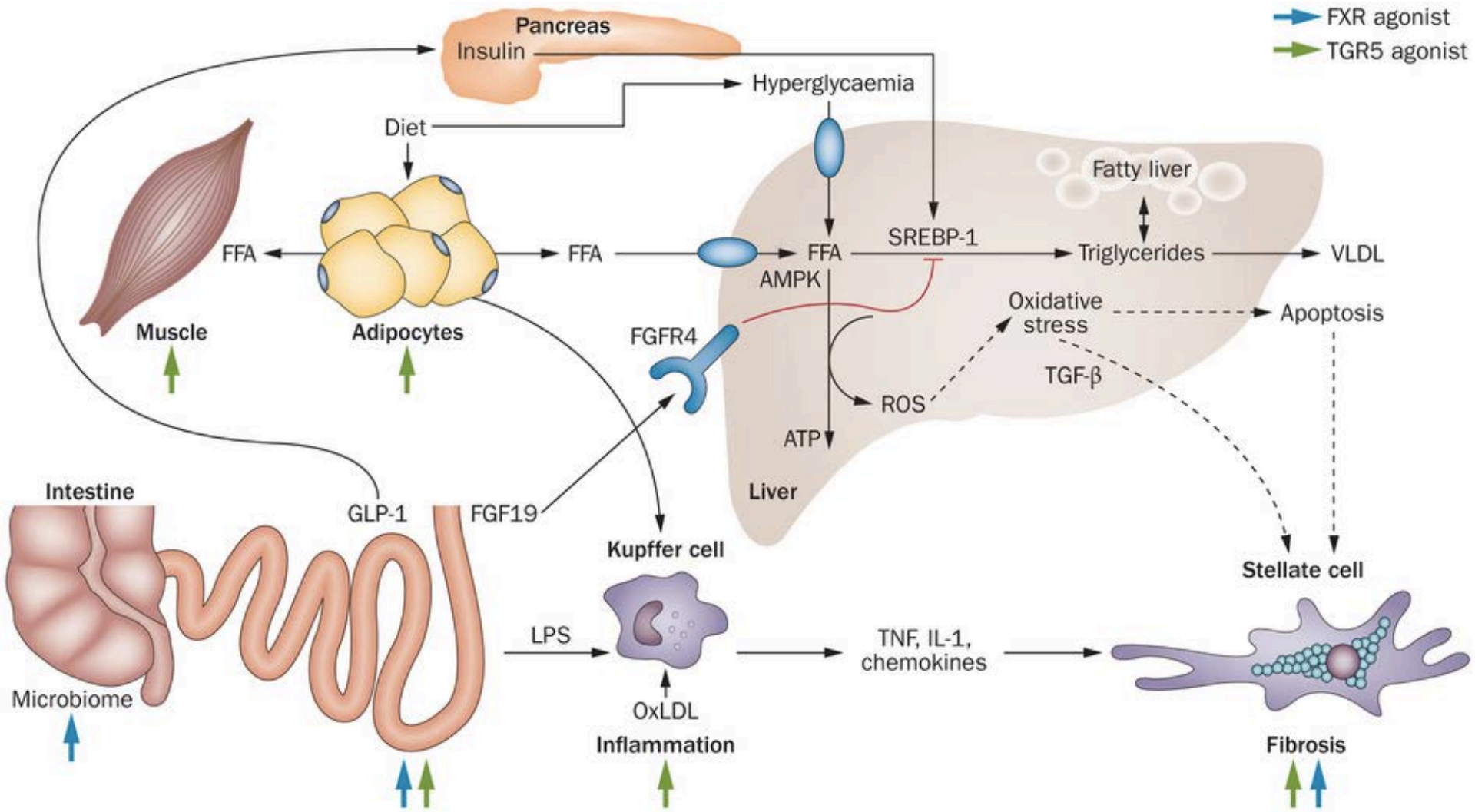
Rinella ME, et al. Gastroenterol Hepatol. 2014;10:219-27

Phase 3

- Subpart H
  - Conditional approval on surrogate endpoint
    - = histology
  - Final approval on clinical endpoint
    - = liver-related events
      - e.g. Progression to cirrhosis, decompensation,…

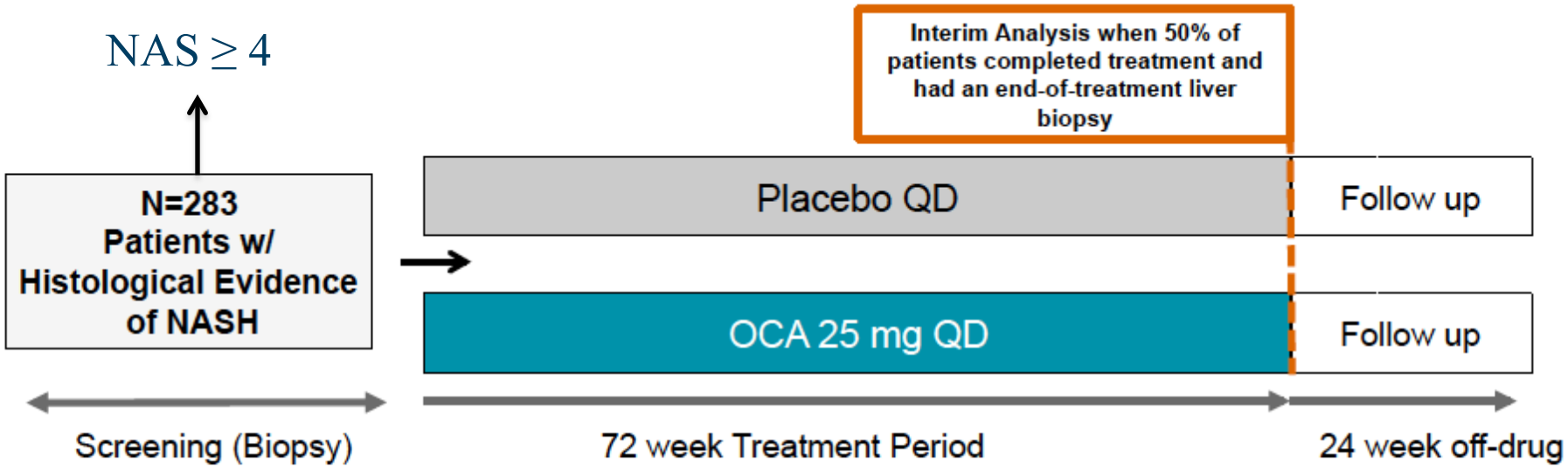
- Serial biopsies
- Long duration of trials
  - 72 weeks for interim analysis
  - Many years (4,5,6…?) for final analysis
- 2000 patients per study

FXR and TGR5



Schaap, Trauner, Jansen. Nat Rev Gastroenterology Hepatology 2013

FLINT trial: Obeticholic acid in non-cirrhotic NASH

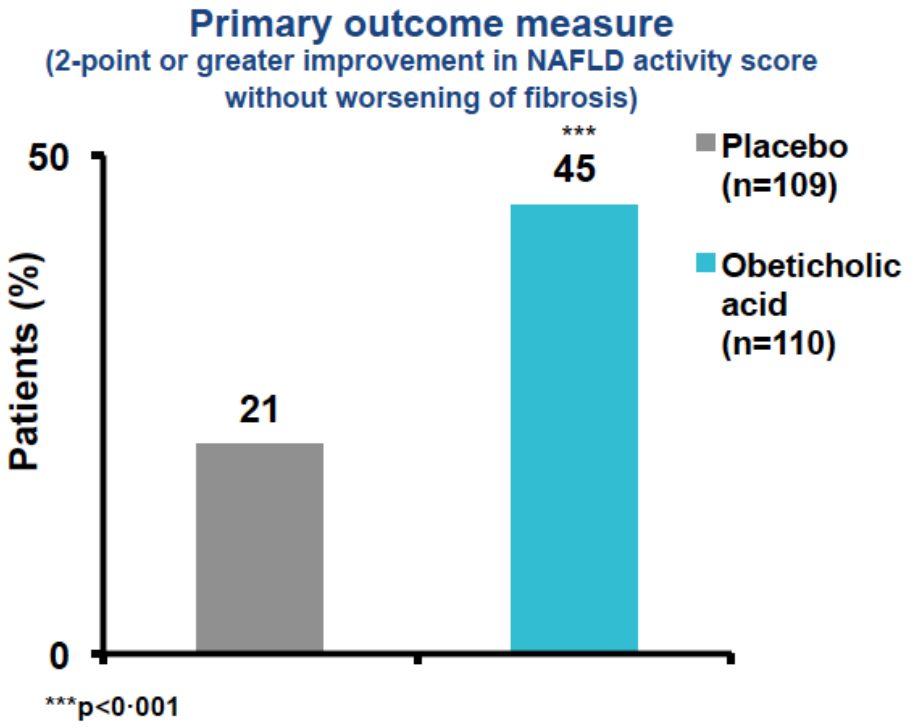


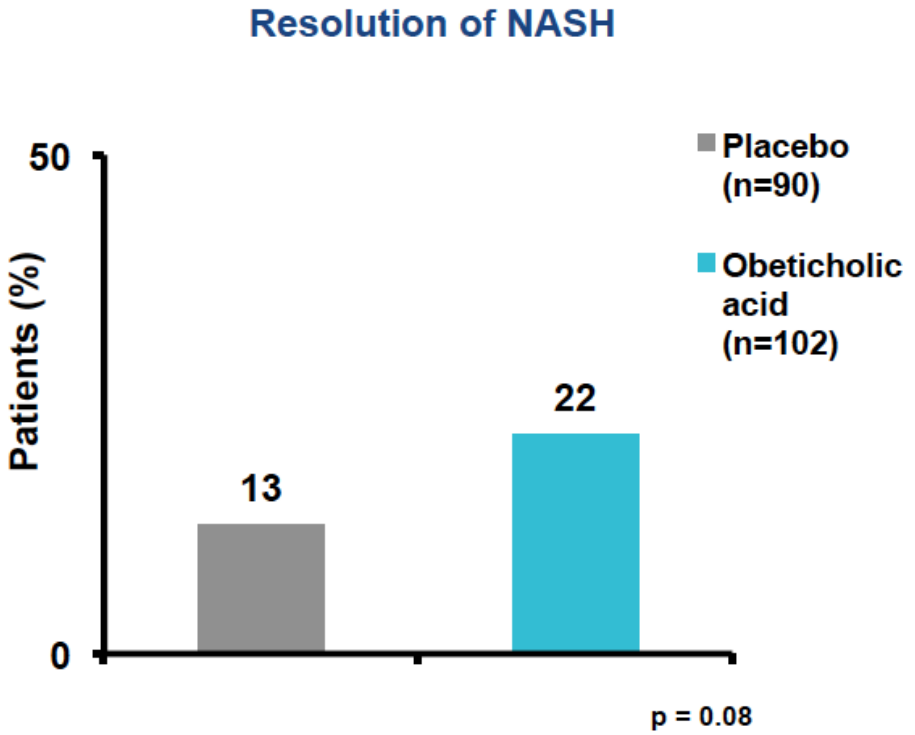
Primary endpoint: Histological improvement from baseline to 72 weeks of treatment; Improvement defined as:

- No worsening in fibrosis; and
- Decrease in NAS of ≥2 points

Neuschwander-Tetri Lancet 2014

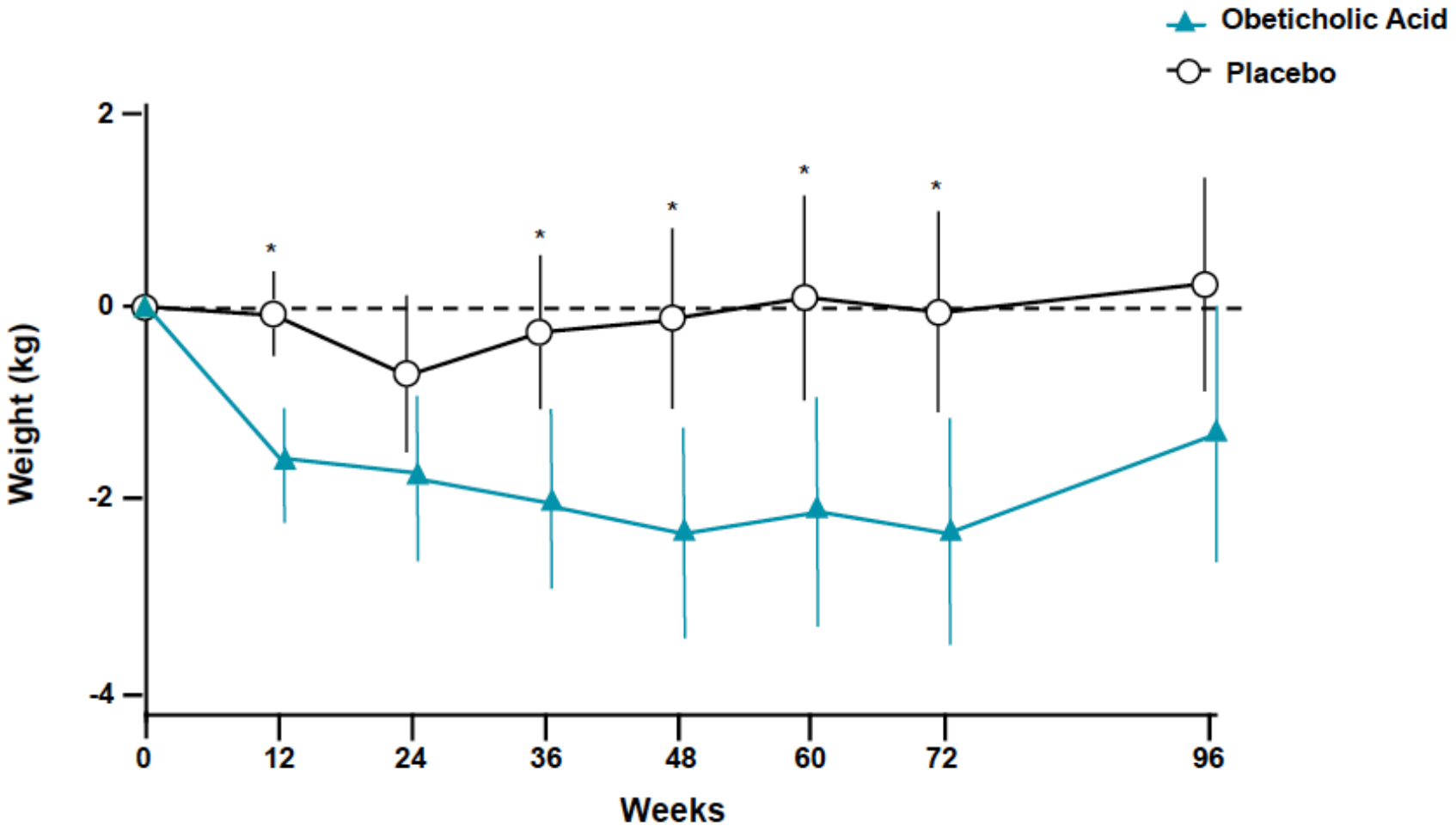
FLINT trial: OCA in non-cirrhotic NASH





Neuschwander-Tetri BA, et al. Lancet. 2015;385:956-65

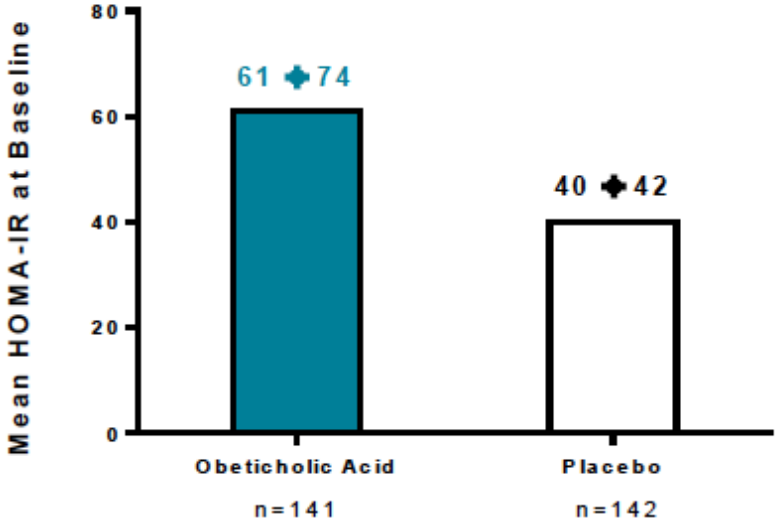
OCA effect on weight- FLINT trial



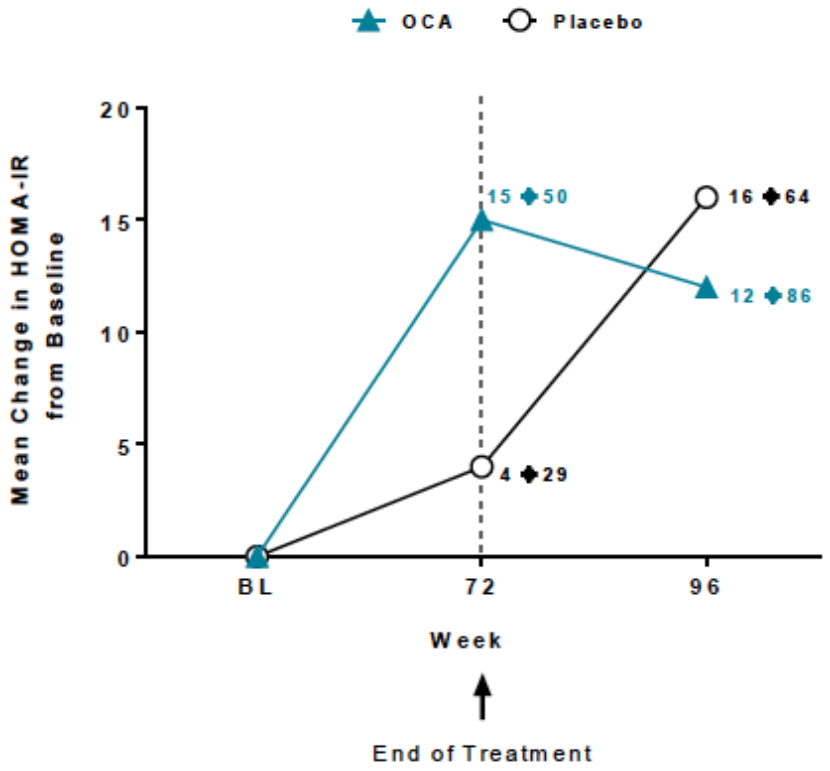
Neuschwander-Tetri Lancet 2014

OCA-Effect on HOMA-IR, FLINT trial

Baseline HOMA-IR*

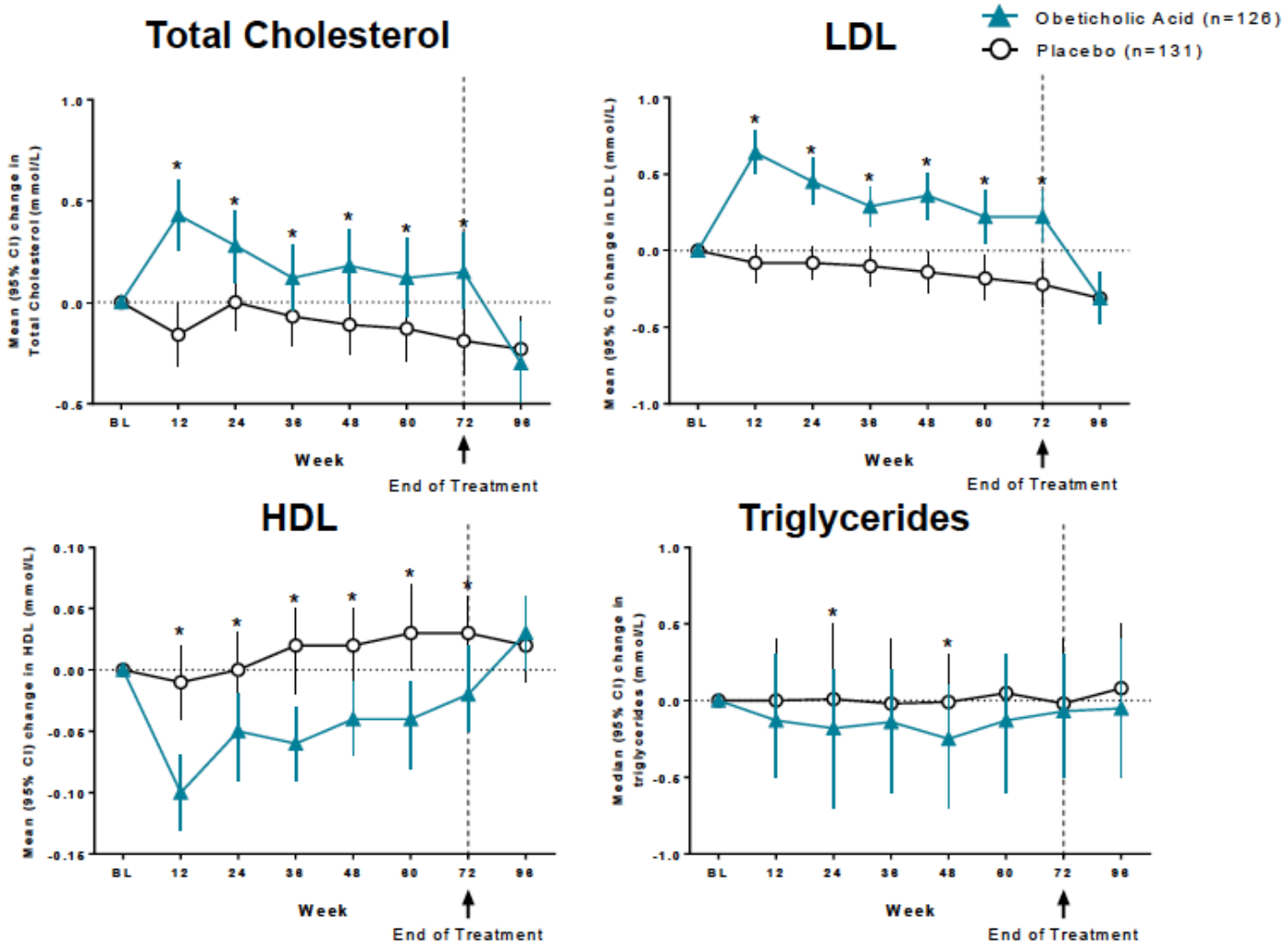


Changes in HOMA-IR* from Baseline



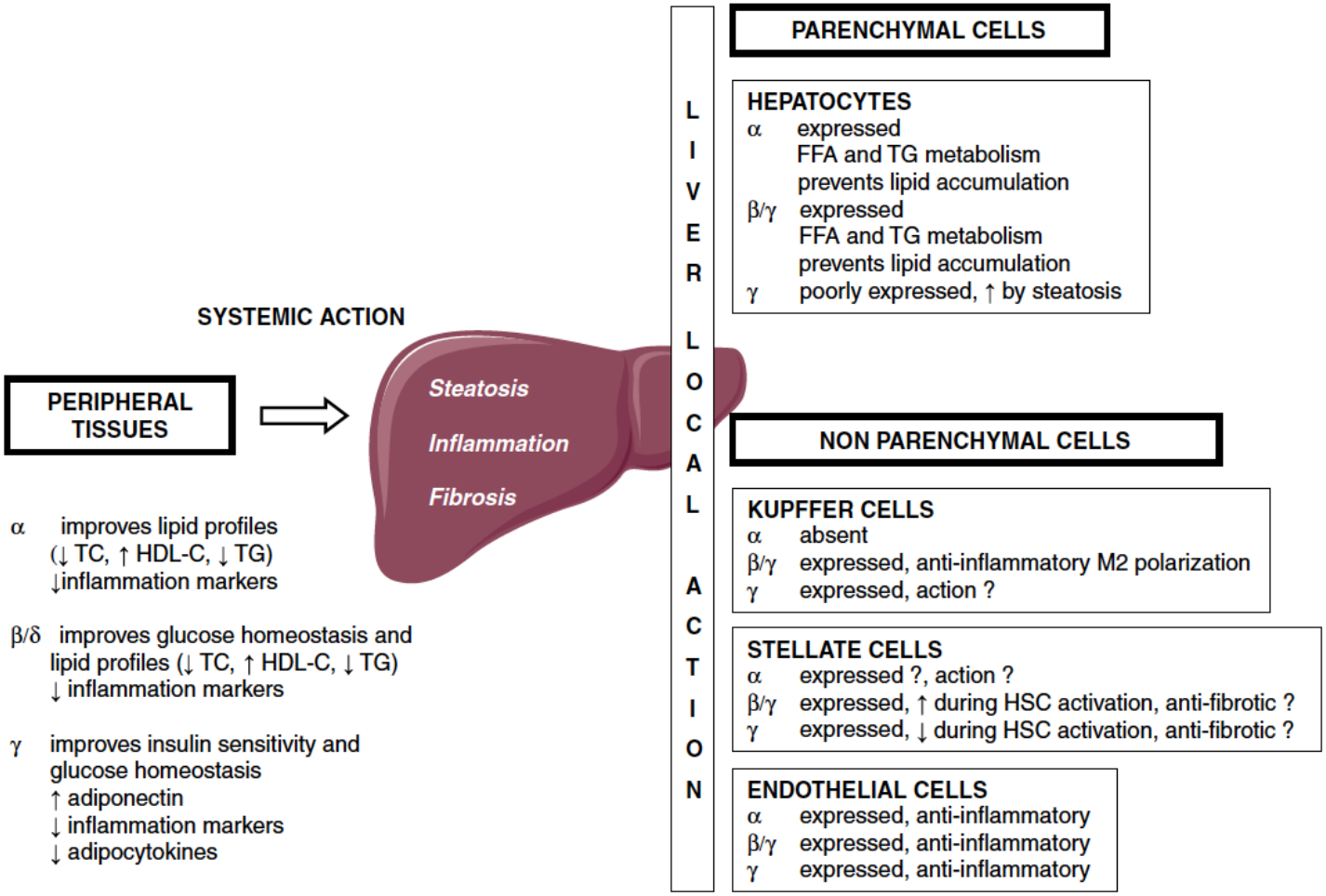
Neuschwander-Tetri Lancet 2014

OCA-Effect on lipids – FLINT trial



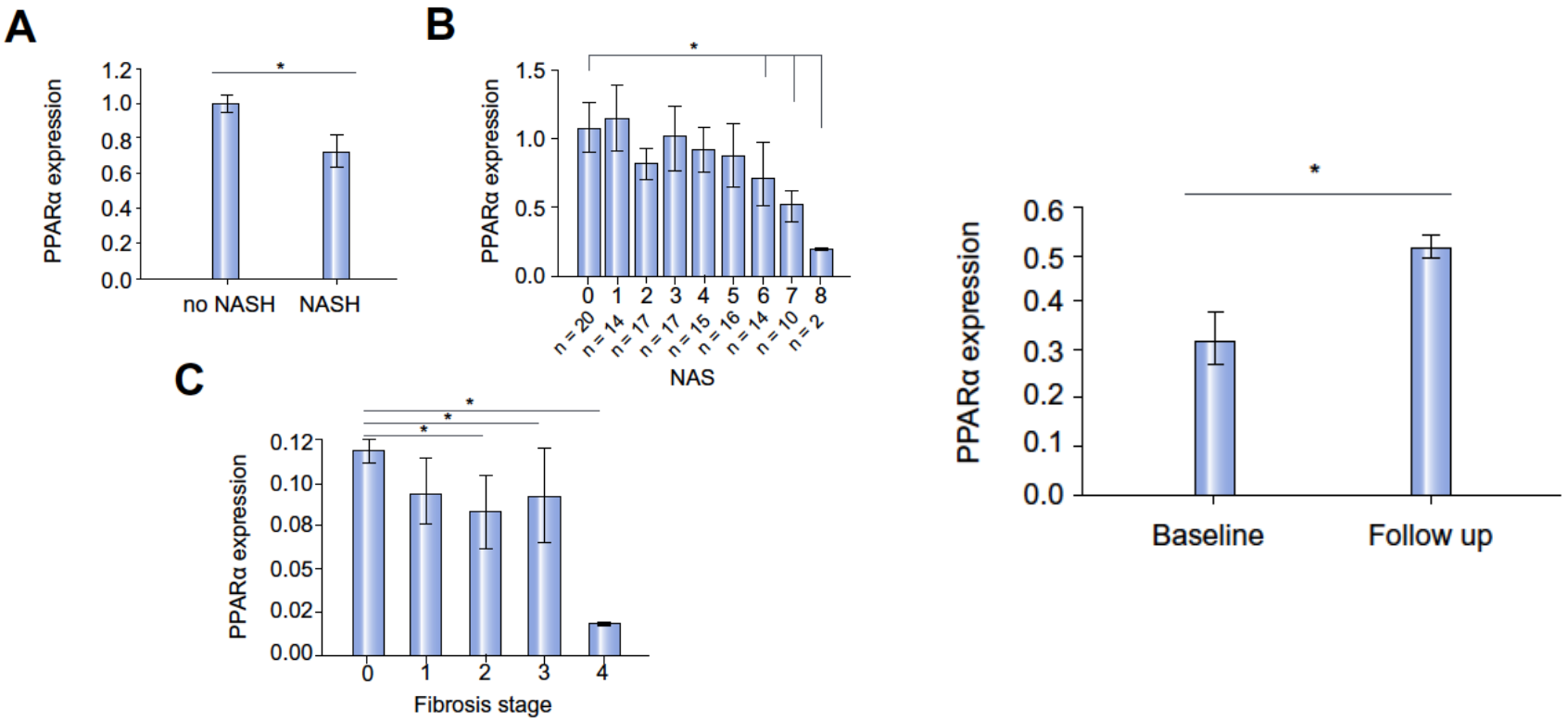
Neuschwander-Tetri Lancet 2014

GFT505/Elafibranor



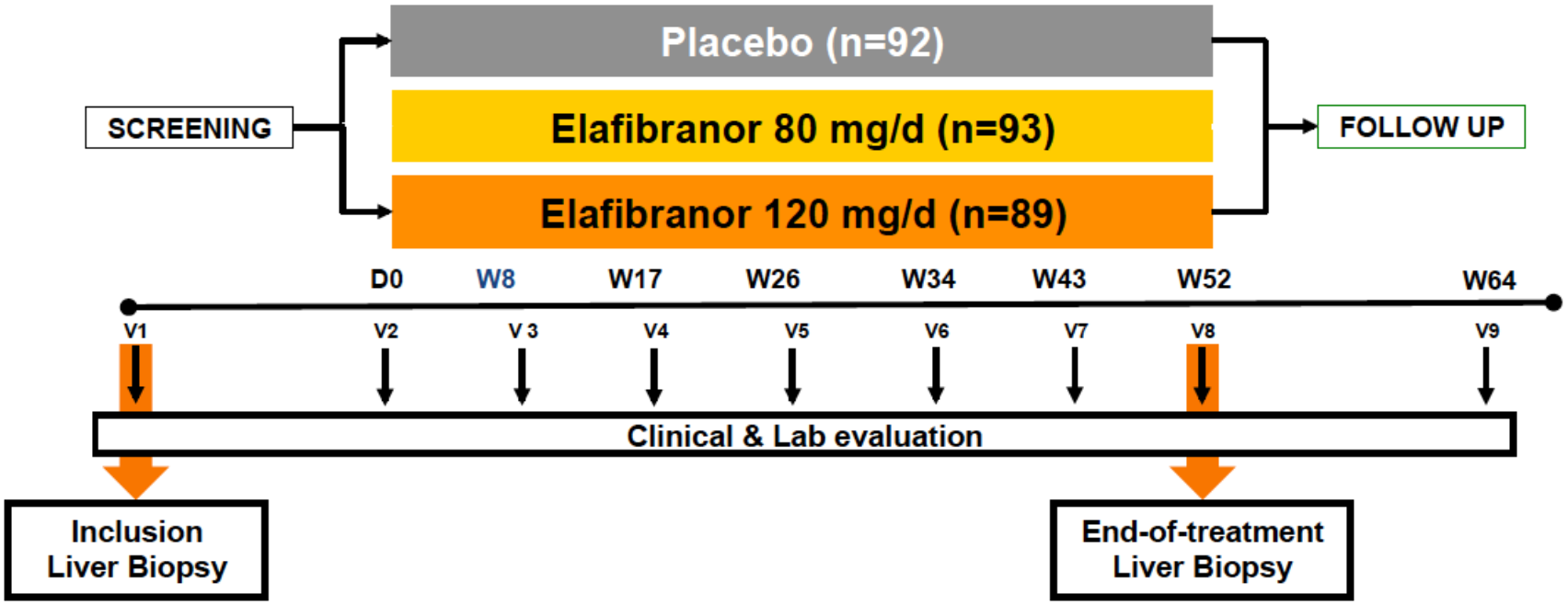
Tailleux *et al*, BBA, 2012

PPARα expression and NASH severity



Francque J Hep 2015

GOLDEN505 Elafibranor trial in NASH Design



First international trial in NASH: 56 sites (US + 8 European countries)

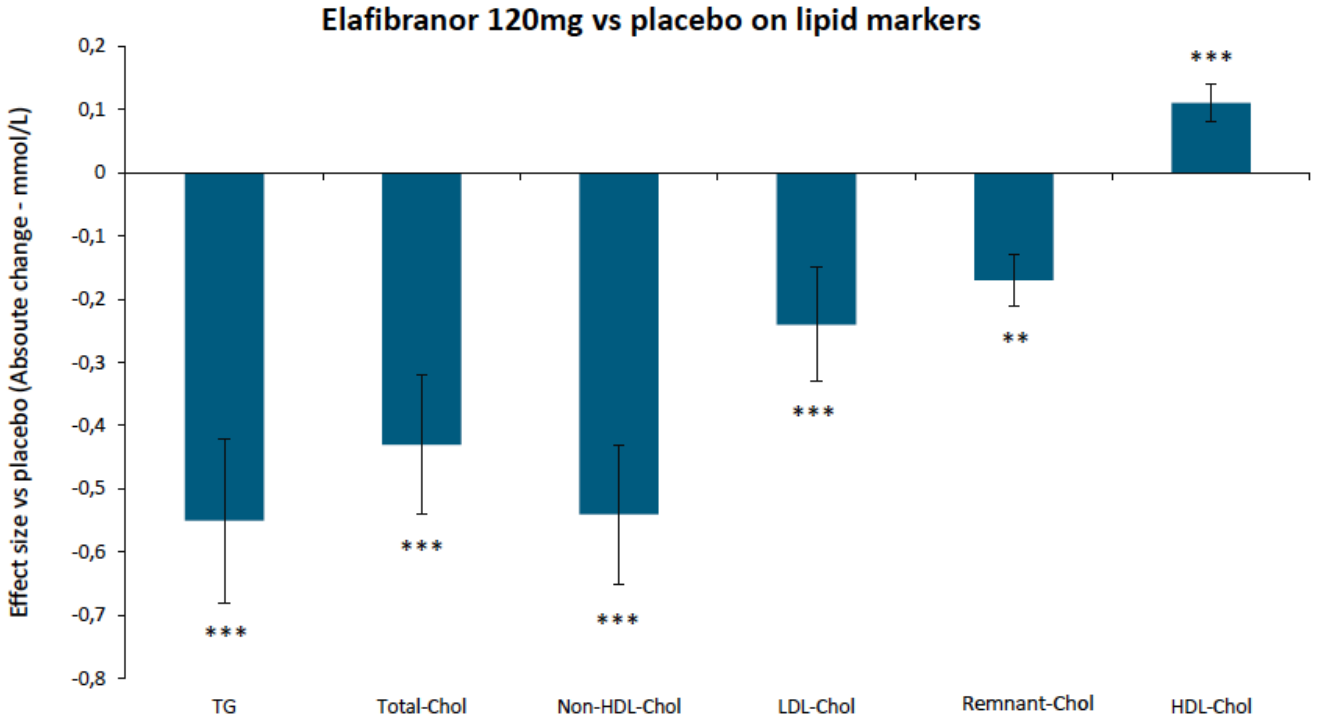
Ratziu V, et al. Gastroenterology. 2016 Feb 11. pii: S0016-5085(16)00140-2

Elafibranor 120mg has significant effect vs placebo in both global and NAS≥4 populations

N	NAS	Placebo	**Elafibranor 120mg**	p-value	
274	All patients (FAS)	12%	19%	**0.045**	New Definition
234	NAS≥4	9%	**19%**	**0.013**	
204	NAS≥4 with fibrosis (any stage)	11%	**20%**	**0.009**	

Ratziu Gastroenterology 2016

Elafibranor improves CV risk factors: TG, Cholesterol, LDL-C, Remnant-C, HDL-C



The effect size vs placebo was calculated and expressed as LSMean±Standard Error.

** : p<0.01
*** : p<0.001

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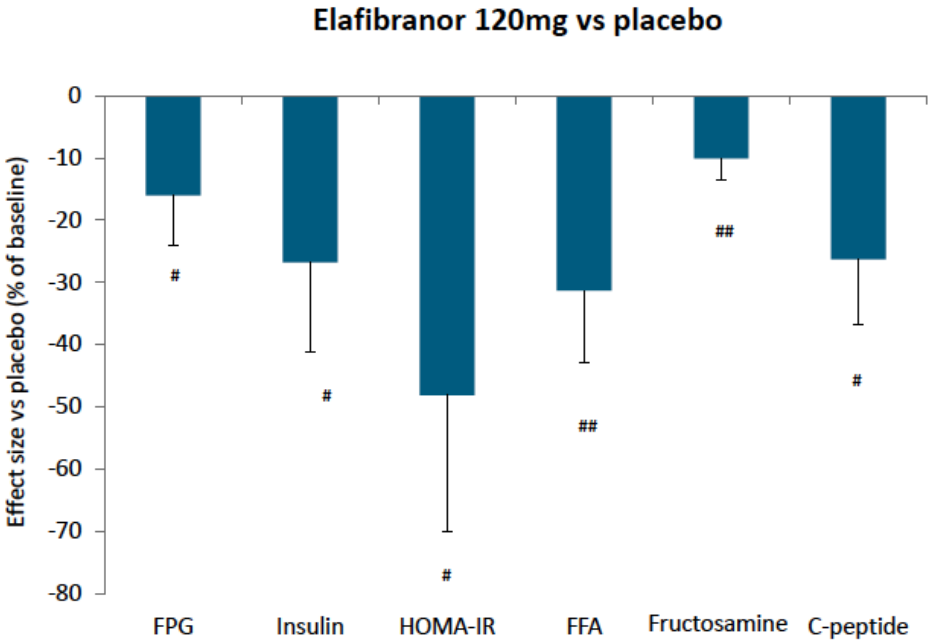
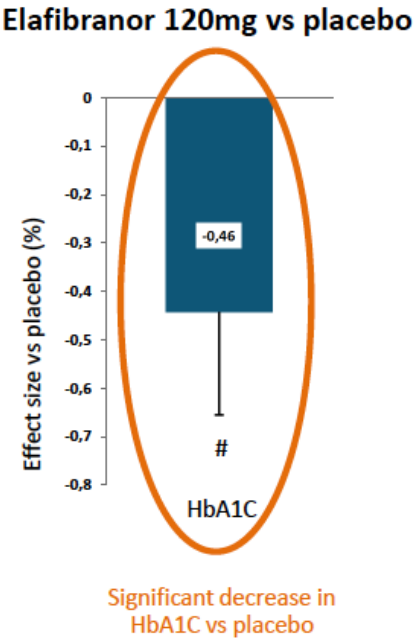
Elafibranor improves glucose homeostasis / insulin sensitivity in type 2 diabetic NASH patients





Significant decrease in HbA1C vs placebo

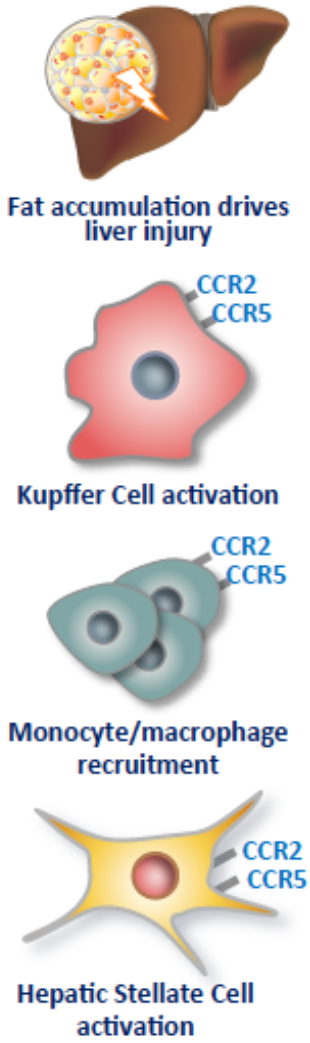
The effect size vs placebo was calculated and expressed as LSMean±Standard Error.

 # : p<0.05
: p<0.01

Ratziu Gastroenterology 2016

Cenicriviroc (CVC)

- Oral, dual C-C chemokine receptor type 2 (CCR2) and type 5 (CCR5) antagonist with nanomolar potency
- Anti-inflammatory and antifibrotic activity observed in animal models
- Once-daily dose of 150 mg tablet
  - Long plasma half-life (30–40 hours)
- Favorable safety and tolerability profile
  - 600+ subjects treated in completed studies to date[2-3]
  - Well tolerated in cirrhotic subjects with mild to moderate hepatic impairment[3]



CVC MOA

Block overactive inflammatory signaling

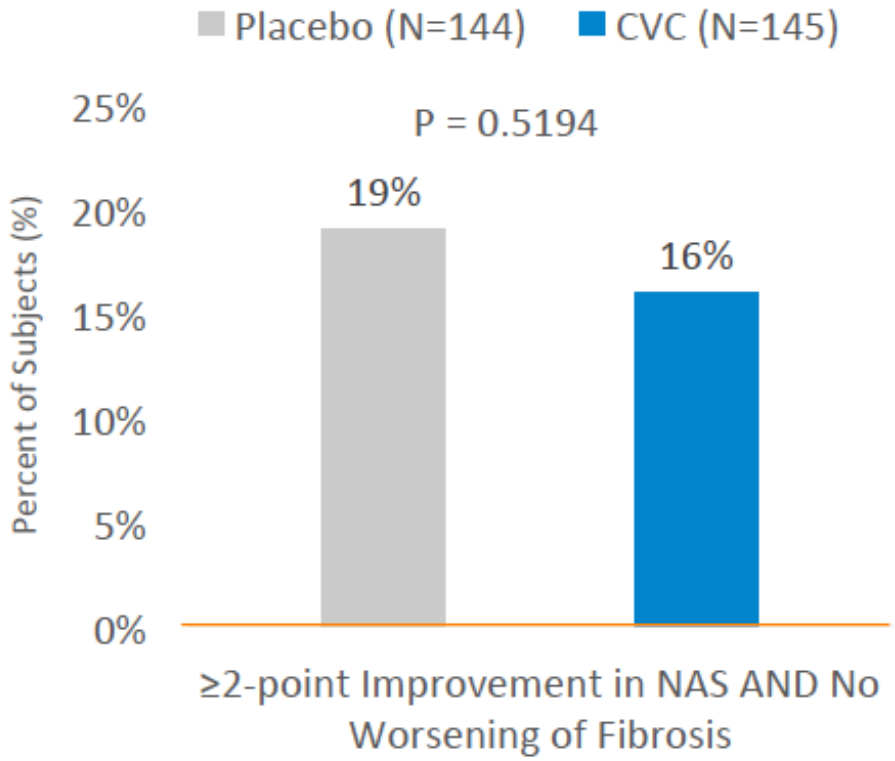
Disrupt signaling to activate stellate cells

1. Jalbert et al. Presented at CROI 2014; 2 Thompson et al. AIDS 2016; 3. Lefebvre et al. Clin Trans Sci 9 (2016) 139-148

MOA, mechanism of action

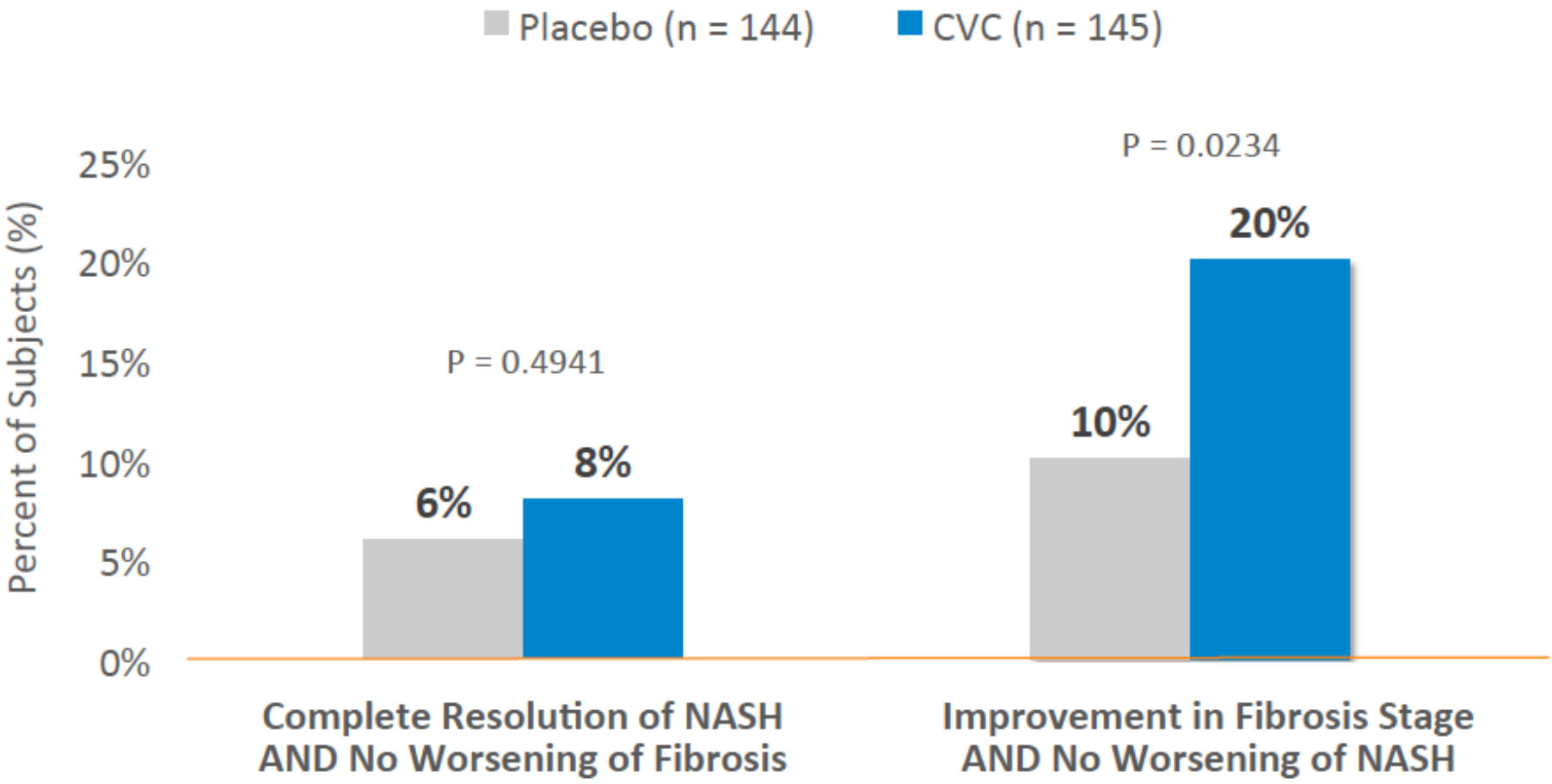
Results: Primary Endpoint (ITT)

- Primary endpoint: proportion of subjects with improvement in NAS by ≥ 2 points with at least a 1-point reduction in either lobular inflammation or hepatocellular ballooning AND with no concurrent worsening of fibrosis stage at Year 1



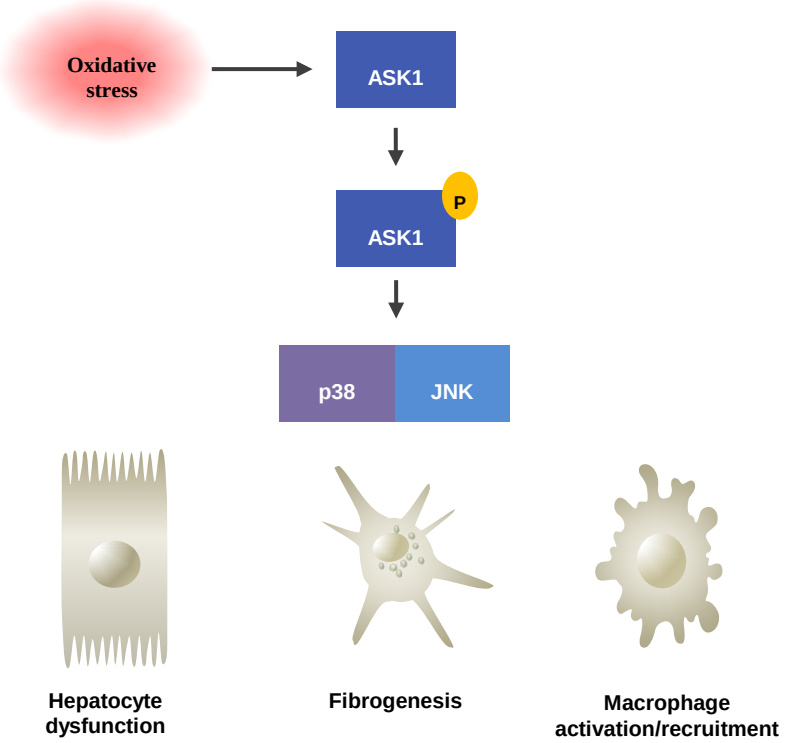
ITT, intent-to-treat (missing data counted as failure); CVC; cenicriviroc; NAS, NAFLD Activity Score

Results: Key Secondary Endpoints (ITT)



ITT, intent-to-treat (missing data counted as failure); CVC, cenicriviroc; NASH, nonalcoholic steatohepatitis

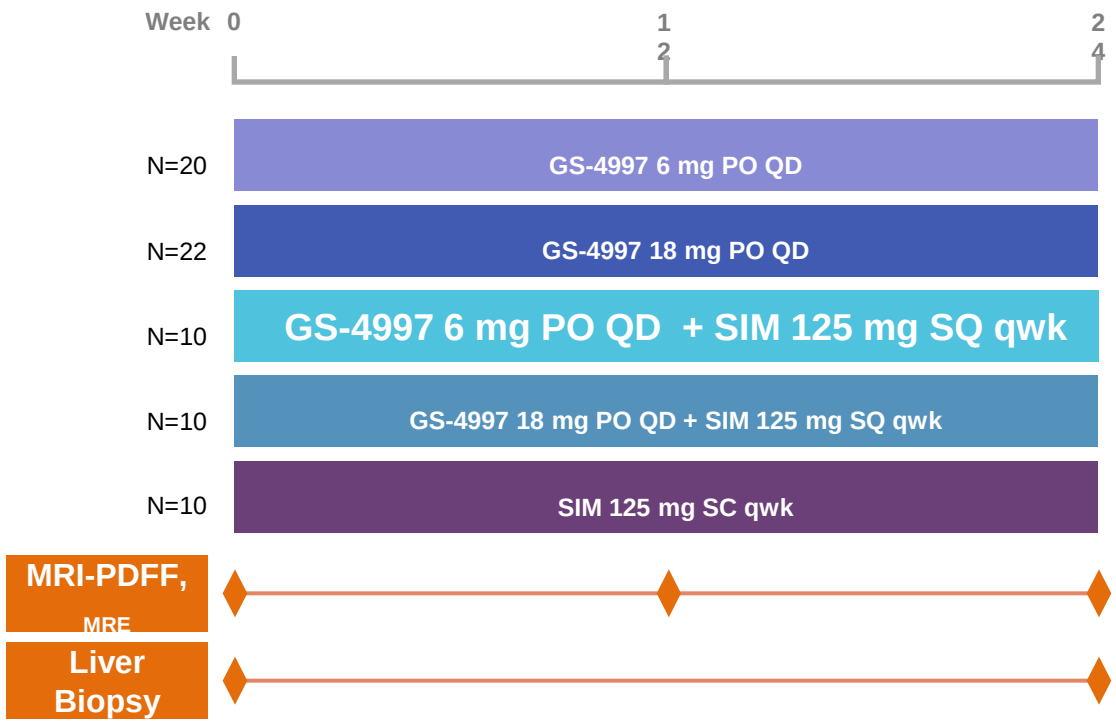
Rationale for ASK1 Inhibition in NASH



- ASK1 pathway activated in NASH and correlates with fibrosis stage
- In rodent models, ASK1 inhibition improves steatosis, inflammation and fibrosis
- GS-4997 (selonsertib) is a selective, potent (EC_{50} 10.8 nM), small molecule inhibitor of ASK1

Xiang, et al. J Hepatol 2016;64:1365–77
Zhao, et al. Gut 2014;63:1159–72
Huntzicker, et al. AASLD 2015 (#2149)
Budas, et al. AASLD 2016 (#1588).

Study Design

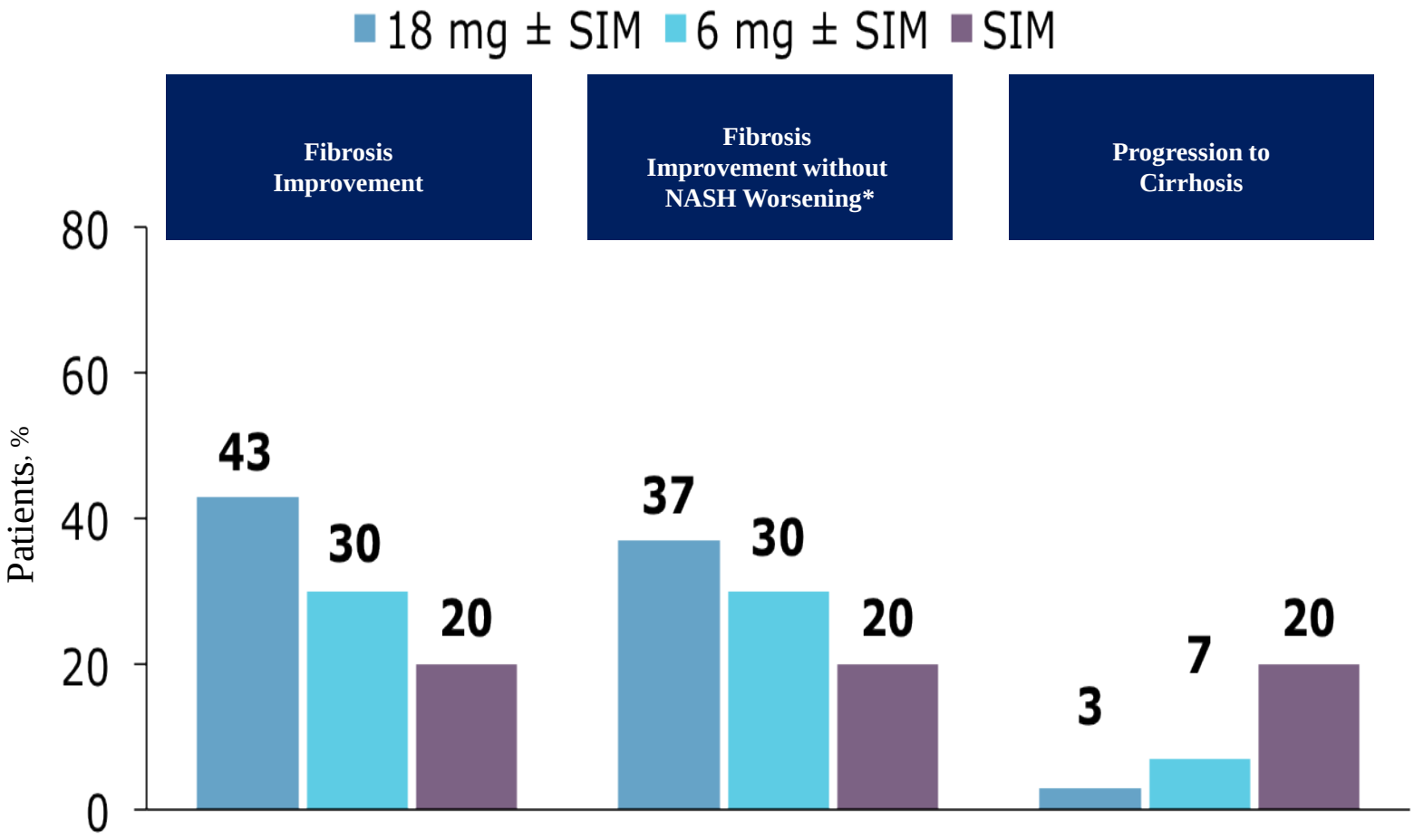


- Key inclusion criteria
  - Biopsy-proven NASH with NAS ≥5 (≥1 point for steatosis, lobular inflammation, hepatocellular ballooning)
  - F2-3 fibrosis
- 2:2:1:1:1 randomization (stratified by diabetes)

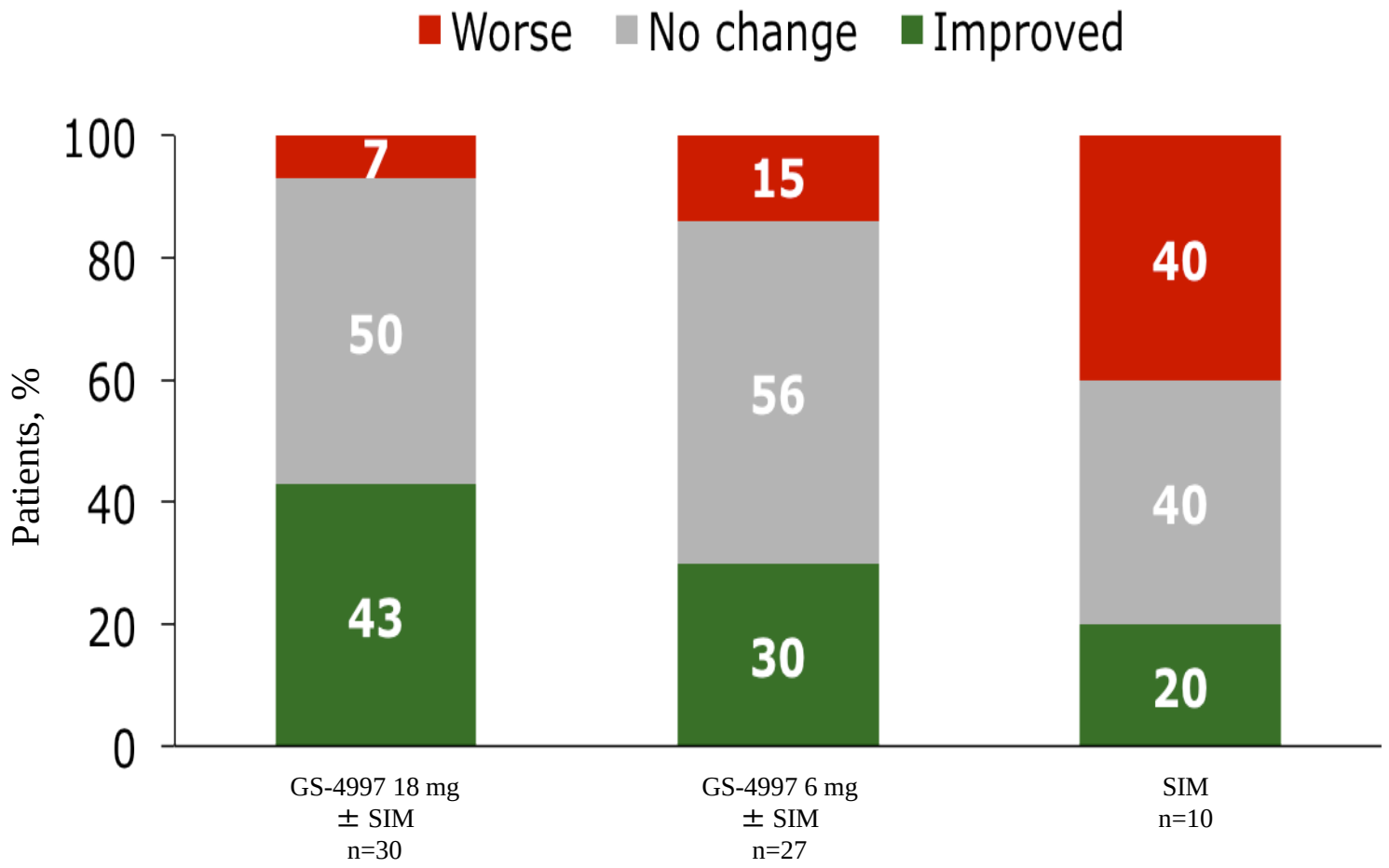
Results: Disposition

	GS-4997 18 mg ± SIM n=32	GS-4997 6 mg ± SIM n=30	SIM 125 mg n=10
Completed study treatment	30 (94)	27 (90)	10 (100)
Discontinued	2 (6)	3 (10)	0
Adverse event	2 (6)	1 (3)	0
Withdrew consent	0	1 (3)	0
Loss to follow-up	0	1 (3)	0
Baseline/Week 24 liver biopsies	30 (94)	27 (90)	10 (100)

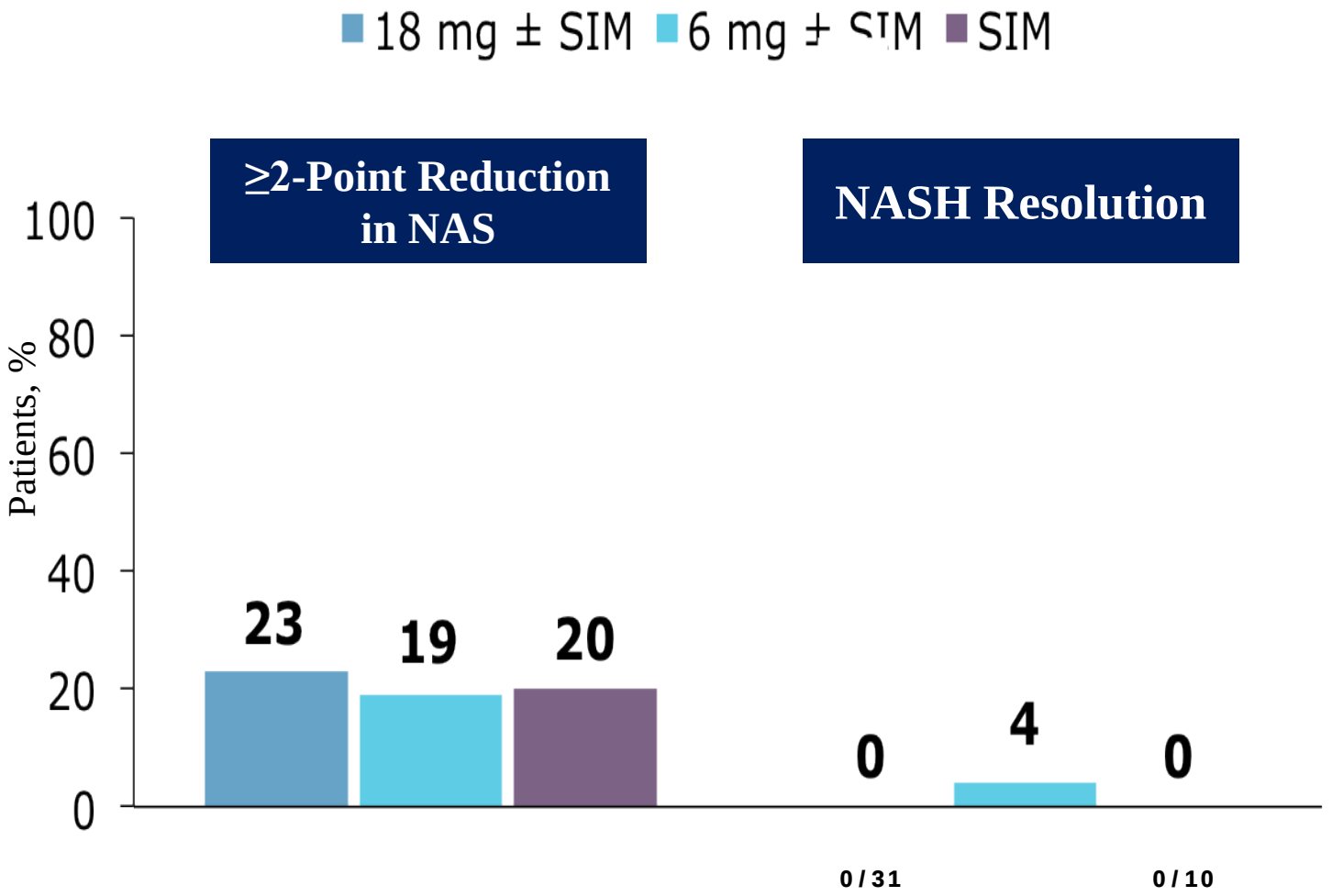
Results: Fibrosis Responses



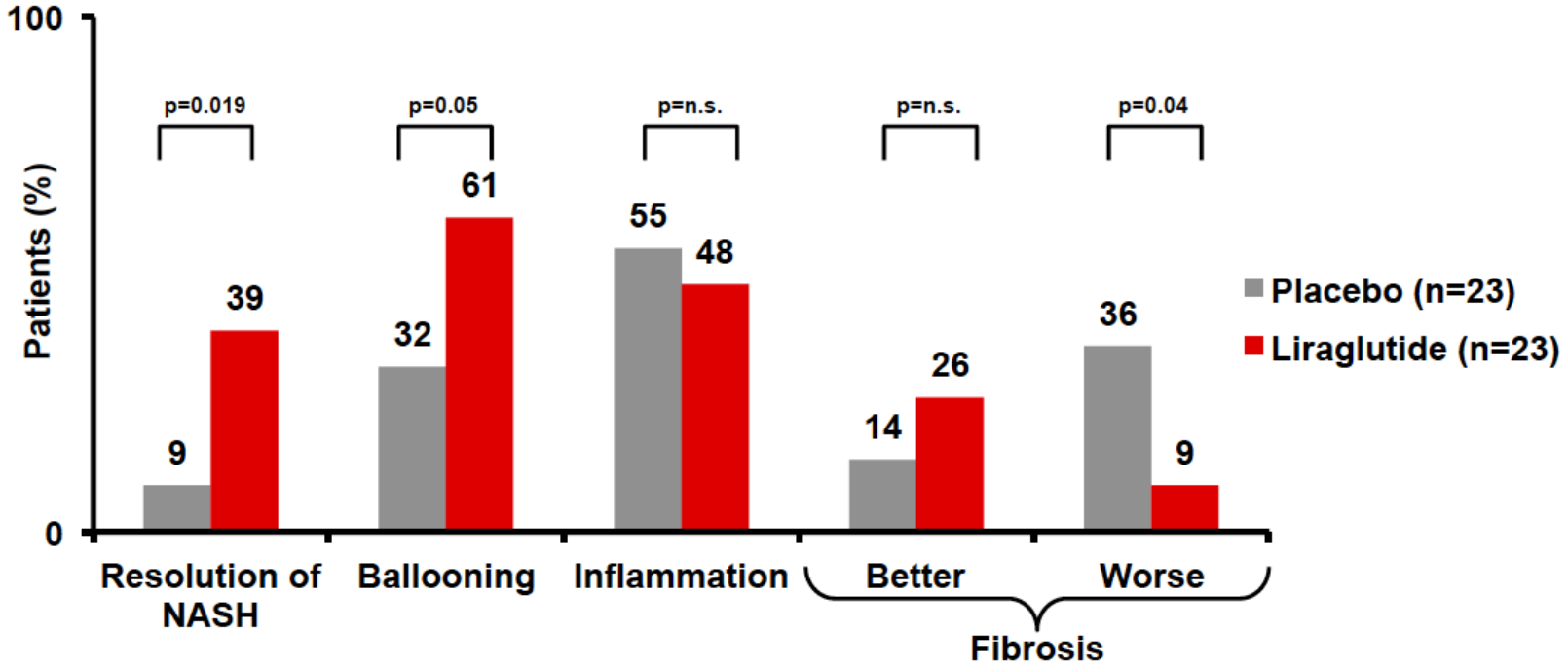
Results: Fibrosis Responses



Results: NAS Responses



1y LEAN liraglutide trial



Armstrong MJ, et al. Lancet. 2016;387:679-90

- IVA337
  - PPAR alpha-delta-gamma
- BI
- Gilead
- BMS
- ...

- Several MOA
  - FGF21, FGF19,...
- Combination therapy
  - Pre-clinical data
  - First demonstrate efficacy of individual compounds

Summary

- Who to treat:
  - NASH and some degree of fibrosis
  - Target activity vs. Fibrosis
- Screening warranted
  - Populations at risk
  - Screening strategies and flow charts
- Pharmacological treatment
  - Phase 3
  - Many in phase 2 with many MOA
  - Combination therapy?