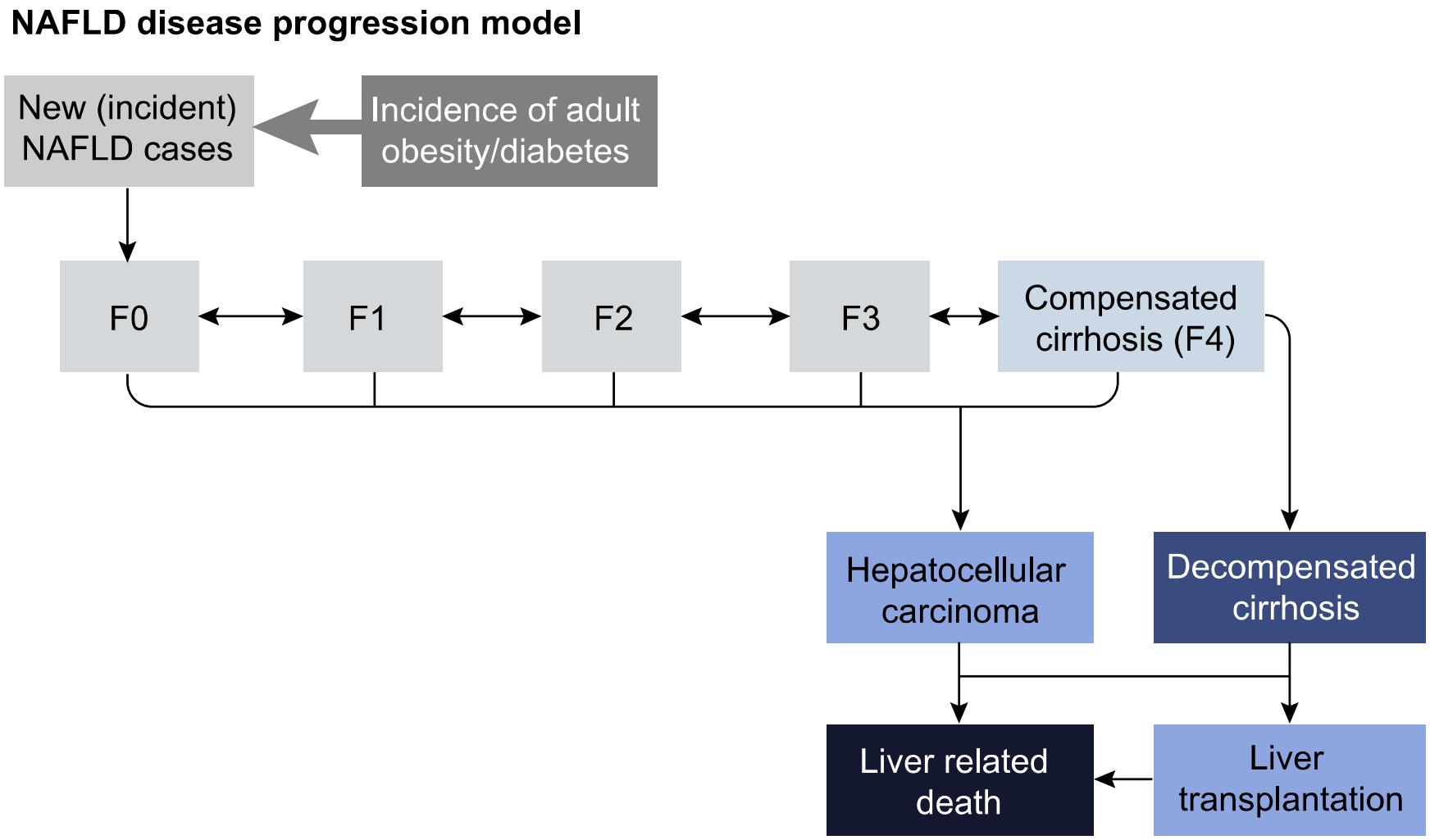
# Hígado graso no alcohólico

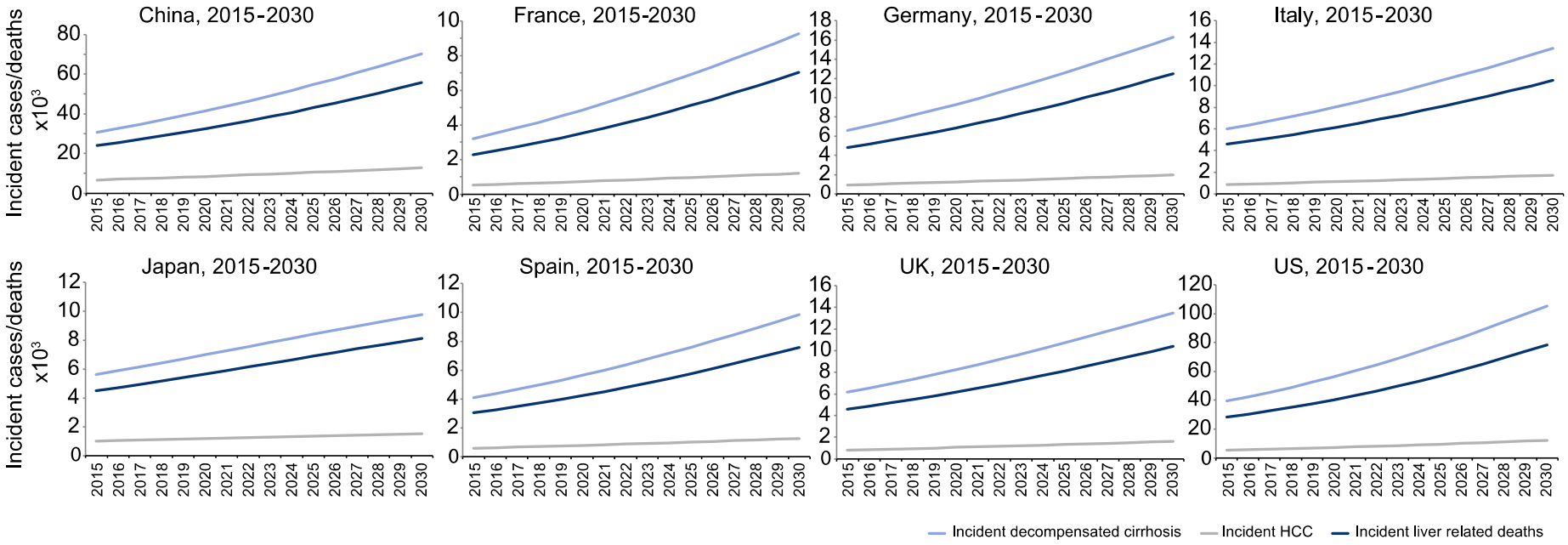
## Estudios Fase II-III

# Riesgo de Desarrollar NASH



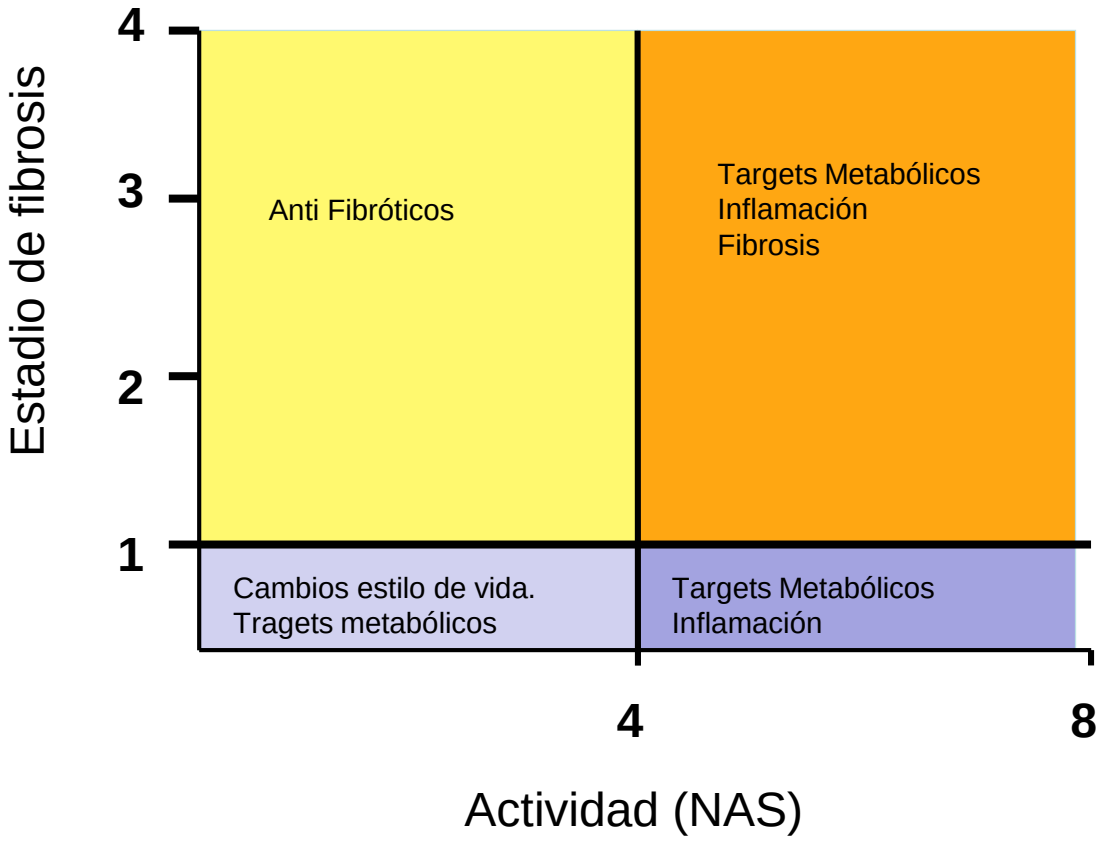

C Estes, et al. J hepatol 2018, vol 69:896-904

# Incidencia de Cirrosis, HCC y Muertes relacionadas a NASH

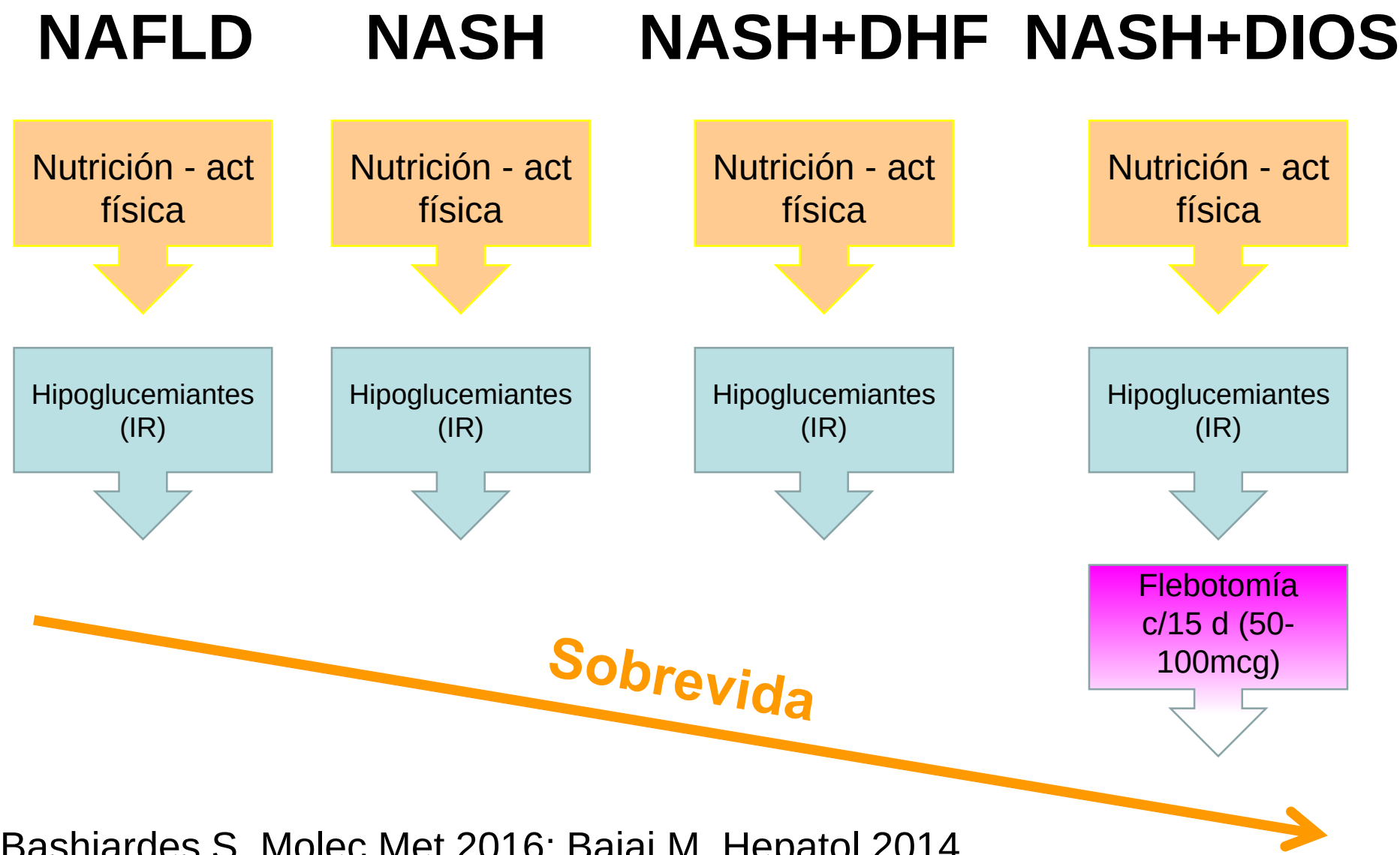



C Estes, et al. J hepatol 2018, vol 69:896-904

# Manejo Racional del Tratamiento del NASH



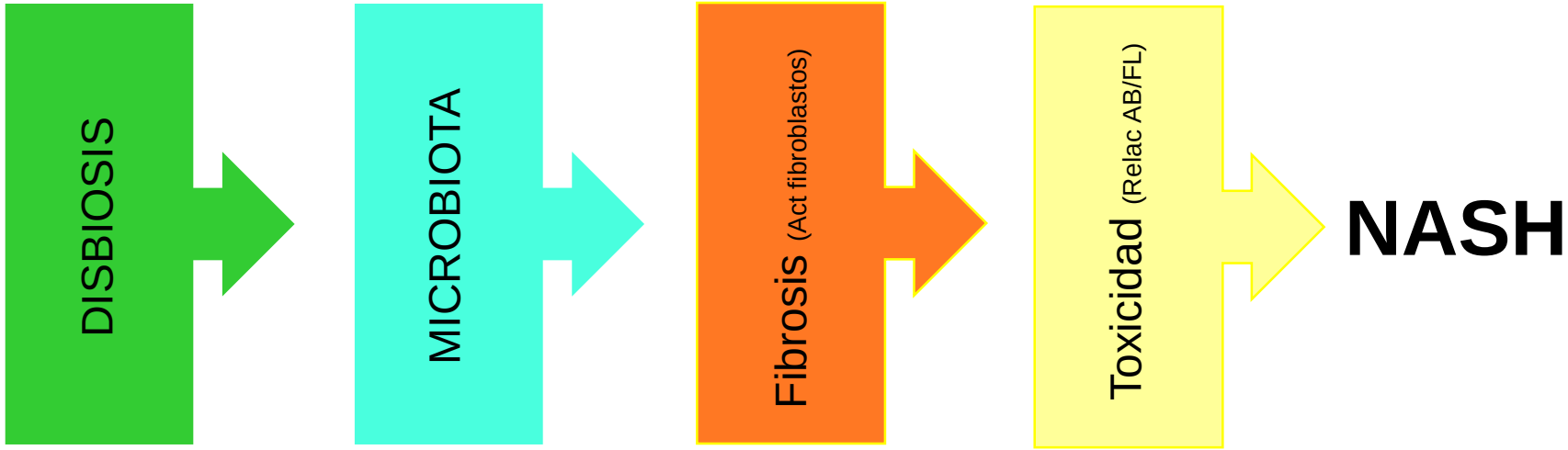
# Tratamiento General




Bashiardes S, Molec Met 2016; Bajaj M, Hepatol 2014.

# Tratamiento Específico del NASH

## Esquemas terapéuticos




Metronidazol
Rifaximina
Minociclina
Neomicina

Probióticos
(lactobacilus)
Prebióticos
(Rifaximina)

Acido
Obeticólico

UDCA
nor UDCA
Metformina
Ac Obeticólico
Bezafibrato

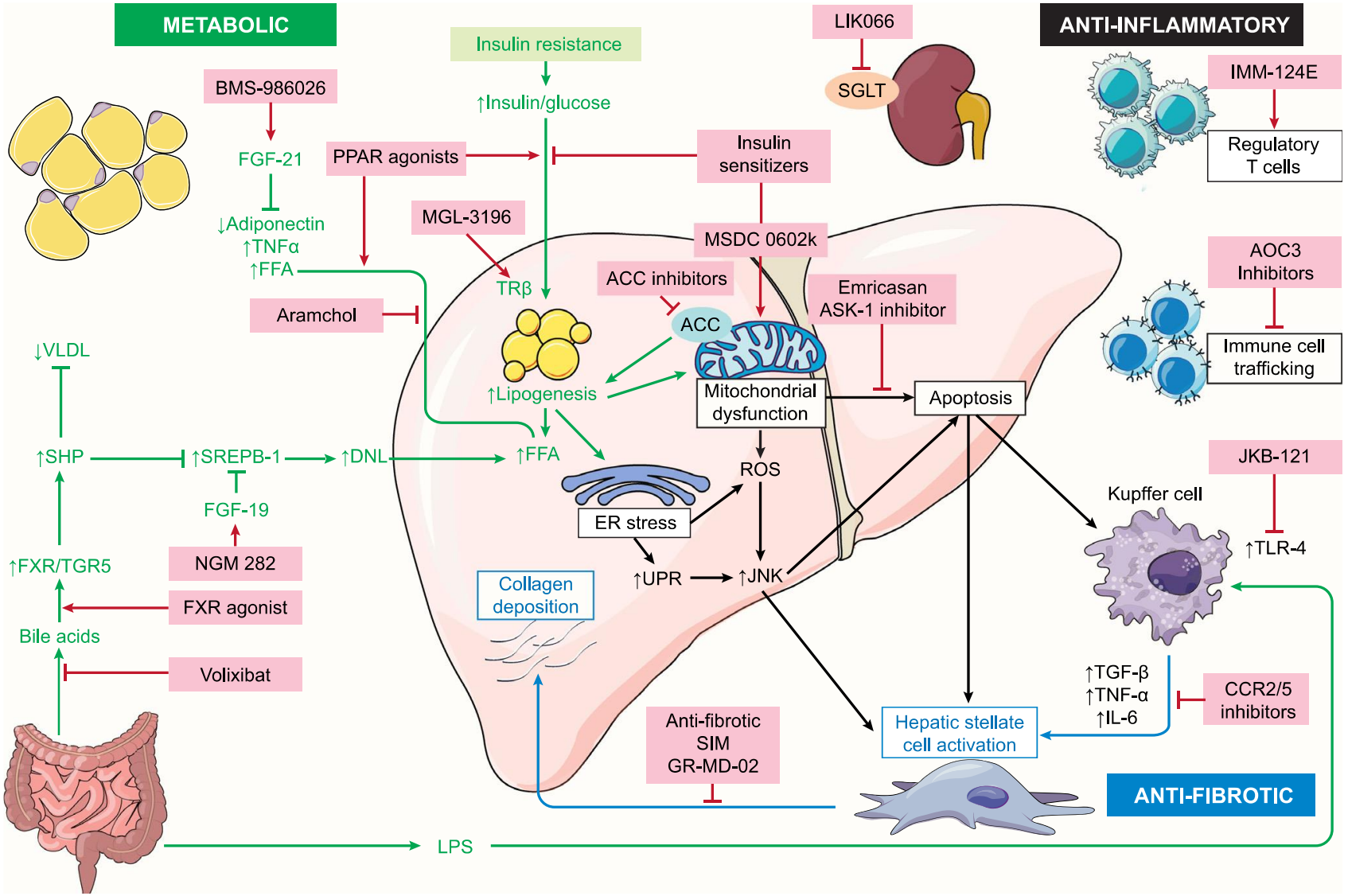
Bashiardes S, Molec Met 2016; Bajaj M, Hepatol 2014.

# Fármacos recomendados en NALFD

| | AGA/AALSLD (2012) | JSG/JSH (2014) | EASL/EASD/EAO (2016) | AASLD guidance (2017) |
|---|---|---|---|---|
| Vitamin E | First-line therapy for biopsy-proven NASH without diabetes and cirrhosis (800 mg/day) | Recommended | Not firmly recommended, but could be used | May be considered in biopsy-proven NASH without diabetes and cirrhosis (800 mg/day)<br>Discuss benefit and risk with patients |
| UDCA | Not recommended | Not recommended | Not mentioned in detail | Not recommended |
| Pioglitazone | Can be used in patients with biopsy-proven NASH | Recommended in NASH with insulin resistance | Not firmly recommended, but could be used | Can be used in patients with biopsy-proven NASH<br>Discuss benefit and risk with patients |
| Metformin | Not recommended as a specific treatment for NASH | Not recommended as a specific treatment for NASH | Insufficient evidence | Not recommended as a specific treatment for NASH |
| Liraglutide | Not mentioned | Not mentioned | Not mentioned | Premature as a specific treatment for NASH |
| ω3 fatty acid | May be considered in NAFLD with hypertriglyceridemia | Not mentioned | Reduced lipid in plasma and liver, but no evidence related to NASH | Not recommended as a specific treatment for NASH<br>May be considered in NAFLD with hypertriglyceridemia |
| Statin | Can be used to treat dyslipidemia | Recommended for hypercholesterolemia | Can be used to reduce LDL-C and prevent cardiovascular risk | Can be used to treat dyslipidemia<br>Should be avoided in decompensated cirrhosis |
| Pentoxifylline | Not mentioned | Recommended, but commercially unavailable in Japan | Not mentioned | Not mentioned |
| OCA | Not mentioned | Not mentioned | Not mentioned | Off-label use not recommended (approved for PBC in USA) |

Thuluvath P. Hepatol Int 2019

# Mecanismos de Acción de los Fármacos en NASH




Konerman M, et al. J Hepatol 2018 vol 68:362-375

# Diseño de estudios NAFLD-NASH

| | Focus | Timeline | Endpoints | Metabolic | Inflammatory | Fibrosis | Clinical |
|---|---|---|---|---|---|---|---|
| Phase IIa | · Proof of concept<br>· Short term safety<br>· Clarify target engagement | Truncated: 12-24 wk | Liver biopsy not required | Δ hepatic fat via MRI-PDFF or CAP | · Δ liver enzymes and other biomarkers<br>· Multiparametric MRI | · Δ biomarkers<br>· MRE, FS kPa | |
| Phase IIb | · Assess efficacy<br>· Safety and adverse events<br>· Therapeutic dosing | Intermediate: 24-72 wk | Paired liver biopsy | Δ hepatic fat via histology ± MRI-PDFF/CAP | · Δ inflammation and ballooning (NAS)<br>· Resolution of NASH w/o worsening of fibrosis<br>· Multiparametric MRI | · Δ fibrosis stage w/o worsening of NASH<br>· MRE, FS kPa | |
| Phase III | · Confirm efficacy<br>· Longer term safety and efficacy<br>· Clinical outcomes | Longer term: years | Paired liver biopsy | Δ hepatic fat via histology ± MRI-PDFF/CAP | · Δ inflammation and ballooning (NAS)<br>· Resolution of NASH w/o worsening of fibrosis<br>· Multiparametric MRI | · Δ fibrosis stage w/o worsening of NASH<br>· MRE, FS kPa | · Progression to cirrhosis<br>· Hepatic decompensation<br>· Overall mortality<br>· Liver-related mortality<br>· HCC<br>· Transplantation |

Harrison S. J Hepatol 2018

FLINT-J Trial
(Obeticolico)
INT-767
LMB763
GS9674
MGL-3196

EMMINENCE
(MSDC 0602K)
Pemafibrato
(K-877)
EVIDENCES II
(Saroglitazar)
GOLDEN 505
(Elafibranor)
NATIVE
(IVA337)

LEAN Study
(Liraglutide)
SUSTAIN-6
(Semaglutide)
SGLT2
(Canaglifozin)

MOZART
(Ezetimibe)
Pemafibrato Study
Aramchol Study
GS-0976

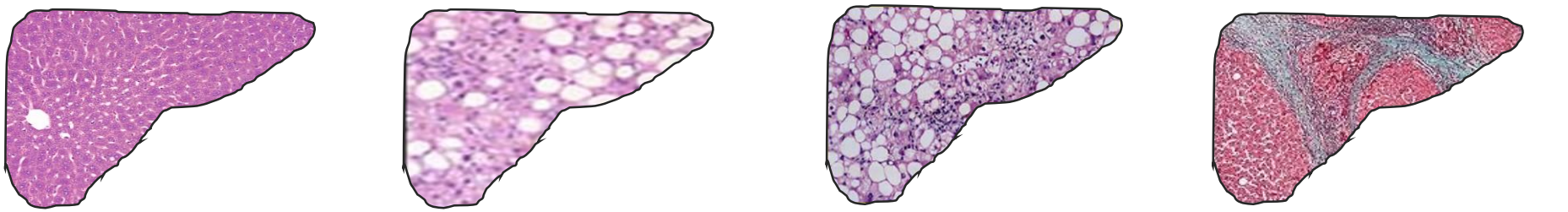
| Mechanism of action | Company (Product name) | Condition and stage | Primary endpoint(s) | N | Duration (wk) |
|---|---|---|---|---|---|
| FXR agonist non-bile acid | | | | | |
| | Novartis (LJN452) | NASH, stage 0–3, elevated ALT, OR PDFF >10%, obesity, DM2 | Adverse event profile, safety, improvement in ALT | 250 | 12 |
| | Novartis (LMB763) | NASH, stage 0–3, elevated ALT, OR PDFF >10%, obesity, DM2 | Adverse event profile, safety, improvement in ALT | 100 | 12 |
| FXR agonist non-bile acid + ACC inhibitor | | | | | |
| | Gilead (GS-9674) | MRE >2.5 kPa, PDFF >10% | Safety and tolerability | 140 | 24 |
| | Gilead (GS-976 + GS-9674) | MRE ≥NASH 2.88 kPa, PDFF ≥10%, OR MRE >4.67 kPa, not compensated, OR NASH, stage 2–3 | Safety and tolerability | 110 | 12 |
| PPAR-α/y agonist | | | | | |
| | Zydus (saroglitazar) | NAFLD stage 0–3, ALT >1.5 ULN | Percent change in ALT | 104 | 16 |
| PPAR-α/δ/y agonist | | | | | |
| | Inventiva Pharma (IVA337) | NASH, SAF fibrosis score <4 | Improvement in SAF without worsening fibrosis | 225 | 24 |
| GLP-1 analogue | | | | | |
| | Novo Nordisk (liraglutide) | NASH, fibrosis 1–4, compensated | Resolution of NASH without worsening of fibrosis | 52 | 48 |
| | Novo Nordisk (semaglutide) | NASH, stage 2–3 fibrosis | Resolution of NASH without worsening of fibrosis | 372 | 72 |
| ACCi | | | | | |
| | Gilead (GS-0976) | NAFLD OR NASH without cirrhosis | Safety and tolerability | 127 | 12 |
| | Pfizer (PF-05221304) | MRE ≥2.5 kPa, PDFF ≥8% NASH, stage 1–3 | Change in hepatic fat | 360 | 16 |
| FGF-19 agonist | | | | | |
| | NGM BIO (NGM282) | NASH, stage 1–3 | Change in hepatic fat | 140 | 12 |
| Recombinant FGF-21 | | | | | |
| | BMS (BMS986036) | NASH, stage 1–3 | Change in hepatic fat | 74 | 16 |
| TLR-4 antagonist | | | | | |
| | TAIWAN J (JKB-121) | NASH, stage 1–3 | Improvement in ALT and change in hepatic fat | 66 | 24 |
| Thyroid hormone receptor-B agonist | | | | | |
| | Madrigal (MGL-3196) | NASH, stage 1–3 | Change in hepatic fat | 125 | 36 |
| ASBT inhibitor | | | | | |
| | Shire (volixibat) | NASH, stage 0–3 | Improvement in NAS without fibrosis worsening | 266 | 48 |
| mTOT modulating insulin sensitizer | | | | | |
| | Cirius (MSDC 0602k) | NASH, stage 1–3 | Improvement in NAS without fibrosis worsening | 380 | 48 |
| Sodium glucose cotransporter 1 and 2 inhibitor | | | | | |
| | Novartis (LIK066) | NASH, stage 1–3 | Percent change in ALT | 110 | 12 |
| AOC3 inhibitor | | | | | |
| | Boehringer Ingelheim (BI 1467335) | NASH stage 1–3, OR MRE ≥3.64 kPa, PDFF ≥5% | Target enzyme activity relative to baseline in percent, 24 h post dose | 150 | Up to 16 |
| Induction of regulatory T cells | | | | | |
| | IMMURON (hyperimmune bovine colostrum) | NASH, stage 0–3 | Change in hepatic fat | 130 | 24 |

FXR ligando  PPAR-agonista  Anti-DBT  Hipolipemiantes

**Fase II Trials**

# Targets terapéuticos- fase II

**Hígado Normal** | **ESTEATOSIS** | **ESTEATOHEPATITIS** | **CIRROSIS**



| Insulino – Resistencia Metabolismo Lipídico | Lipotoxicidad Stress Oxidativo | Inflamación Activación Inmunológica | Apoptosis Necrosis celular | Fibrogénesis Turn Over Colágeno |
|---|---|---|---|---|

## METABOLISMO

Pioglitazona
Liraglutide
Semaglutide
GS-0976
PF-05221304
Aramchol
LIK066
BMS-986036
MGL-3196

Elafibranor
Amlexanox
Saroglitazar
MSDC-0602K
OCA
Tropifexor
LMB-763
Volixibat
NGM282
Amlexanox

## INFLAMACIÓN y MUERTE CELULAR

Pentoxifilina
Selonsertib

Selonsertib
Emricasan

**Disbiosis:**
IMM-124E(NCT02316717)
Solithromycin(NCT2510599)
JKB-121(NCT02442687)

## FIBROSIS

Cenicriviroc
Simtuzumab
GR-MD-02
Selonsertib + Simtuzumab
Tipelukast
Emricasan*
VAP1-inhibit
MT3995

* Con HTP

Yomeda M, J Gastroenterol 2018.Chalasani N; Hepatology 2018

# Fármacos en Fase III

| Drug (Alias) | Mechanism | Study Name (ClinicalTrials.gov ID; Sponsor) | Target Completion Date* | Target Enrollment | Inclusion Criteria | | | Primary Outcome Measures |
|---|---|---|---|---|---|---|---|---|
| | | | | | NAS | Fibrosis Stage | Diagnosis | |
| Obeticholic acid (OCA) **(REGENERATE)** | FXR ligand | REGENERATE (NCT02548351; Intercept Pharmaceuticals, New York, NY, USA) | Oct 2021 | 2000 | ≥4, with ≥1 of each component of the score | F1–3† | Biopsy | • Histologic improvement - improvement in liver fibrosis and resolution of NASH at 18 months<br>• Composite outcome - death, MELD ≥15, cirrhosis, transplant, HCC, hospitalization, others at 6 years (est.) |
| Elafibranor (GFT505) **(RESOLVE-IT)** | PPAR-α/δ agonist | RESOLVE-IT (NCT02704403; Genfit, Loos, France) | Dec 2021 | 2000 | ≥4, with ≥1 of each component of the score | F1–3‡ | Biopsy | • Histologic improvement - resolution of NASH without worsening of fibrosis at 72 weeks<br>• Composite outcome - all-cause mortality, cirrhosis, "liver-related clinical outcomes" at 4 years (est.) |
| Selonsertib (GS-4997) | ASK-1 inhibitor | STELLAR-3 and STELLAR-4 (NCT03053050 and NCT03053063; Gilead Sciences, Foster City, CA, USA) | Jan 2020 | 800 (each) | – | F3 (STELLAR-3) F4 (STELLAR-4) | Biopsy | • Histologic improvement - ≥1 stage improvement in fibrosis without worsening of NASH at 48 weeks<br>• Event-free survival at 240 weeks |
| Cenicriviroc (CVC) **(AURORA)** | Dual CCR2/ CCR5 antagonist | AURORA (NCT03028740; Tobira Therapeutics, South San Francisco, CA, USA) | Jul 2019 | 2000 | – | F2–3 | Biopsy | • Histologic improvement - ≥1 stage improvement in fibrosis without worsening of NASH at 12 months<br>• Composite outcome - cirrhosis on histology, liver-related clinical outcomes, and all-cause mortality at 5 years (est.) |
| Liraglutide§ | GLP-1 analogue | CGH-LiNASH (NCT02654665; Changi General Hospital, Singapore) | Sep 2017 | 36 | – | – | Liver chemistries, ultrasound, ± biopsy | • Improvement in NASH at 12 months<br>• Reduction/normalization in aminotransferases, liver fat at 12 months |
| Metadoxine | Antioxidant (glutathione source) | (NCT02541045; Hospital General de Mexico, Mexico City, Mexico) | Aug 2018 | 108 | ≥3, with ≥1 of each component of the score | F0–2 | Biopsy | • Improvement in NAS at 6 months |
| Hydroxytyrosol and vitamin E¶ | Antioxidant | (NCT02842567; Bambino Gesù Hospital and Research Institute, Rome, Italy) | Apr 2017 | 80 | – | – | Biopsy | • Laboratory markers of inflammation and oxidative stress at 4 months<br>• Laboratory markers of metabolic syndrome at 4 months |

Connolly JJ, et al. J Clin Transl Hepatol. 2018 Sep 28;6(3):264-275.

# Resultados de Trabajos Fase III

| Drug (Alias) | Mechanism | Study Name[Ref] | Study Design | Population | Results |
|---|---|---|---|---|---|
| Obeticholic acid (OCA) **(REGENERATE)** | FXR ligand | FLINT[47] | Phase 2b U.S. multicenter, double-blind, RCT comparing obeticholic acid 25 mg daily to placebo for 72 weeks ($n$ = 283) | Adults with biopsy-proven, non-cirrhotic NASH with NAS ≥4, with ≥1 of each component of the score* | • Primary endpoint (improvement in NAS ≥2 points without worsening of fibrosis) met in 50/110 (45%) patients in the intervention arm vs. 23/109 (23%) patients in the placebo arm ($p < 0.001$)<br>• Fibrosis improved in 36/102 (35%) patients i the intervention arm vs. 19/98 (19%) patient in the placebo arm ($p = 0.004$) |
| Elafibranor (GFT505) **(RESOLVE-IT)** | PPAR-α/δ agonist | GOLDEN-505[52] | Phase 2b USA and Europe multicenter, double-blind, RCT comparing elafibranor 80 mg and 120 mg daily to placebo for 52 weeks ($n$ = 276) | Adults with biopsy-proven, non-cirrhotic NASH with NAS ≥3, with ≥1 of each component of the score* | • Protocol-defined primary outcome (reversal of NASH defined by the absence of at least 1 of steatosis, ballooning, and inflammation without progression to bridging fibrosis or cirrhosis) not significantly different between arms<br>• Modified definition of response (resolution o NASH as defined by disappearance of ballooning with disappearance or mild persistence of lobular inflammation and a pathologic diagnosis of steatosis ± mild inflammation and no worsening of fibrosis) met in 17/89 (19%) patients in the 120 mg arm vs. 11/92 (12%) in the placebo arm ($p = 0.045$)<br>• Fibrosis stage was significantly reduced in responders (based on the modified definition to 120 mg vs. non-responders |
| Selonsertib (GS-4997) **(AURORA)** | ASK-1 inhibitor | [54] | Phase 2 U.S. and Canada multicenter, open-label, RCT comparing selonsertib 6 mg and 18 mg daily ± simtuzumab to simtuzumab monotherapy for 24 weeks ($n$ = 72) | Adults with biopsy-proven F2–3 NASH with NAS ≥5 | • Fibrosis improved in 13/30 (43%) patients in the 18 mg ± simtuzumab arm vs. 8/27 (30%) patients in the 6 mg ± simtuzumab arm vs. 2/10 (20%) patients receiving simtuzumab monotherapy<br>• Mostly dose-dependent trends observed in ≥15% reduction in MRE stiffness, ≥30% reduction in MRI-PDFF, ≥2 point improvement in NAS, and less likely progression to cirrhosis |
| Cenicriviroc (CVC) | Dual CCR2/CCR5 antagonist | CENTAUR[58] | Phase 2b multinational multicenter, double-blind, RCT comparing cenicriviroc 150 mg daily to placebo for 2 years ($n$ = 289) | Adults with biopsy-proven F1–3 NASH with NAS ≥4 and diabetes or metabolic syndrome | • Pre-specified primary endpoint (≥2 point improvement in NAS [with ≥1-point reduction in lobular inflammation or ballooning] and no worsening of fibrosis) not met at 1 year interim analysis<br>• Fibrosis improved (without worsening of steatohepatitis) in 29/145 (20%) patients in the intervention arm vs. 15/144 (10%) patients in the placebo arm ($p = 0.023$), mos pronounced in subjects with higher disease activity and stage, at 1 year interim analysis |

*NAS (NAFLD activity score) scored as steatosis 0–3, ballooning 0–2, and lobular inflammation 0–3.

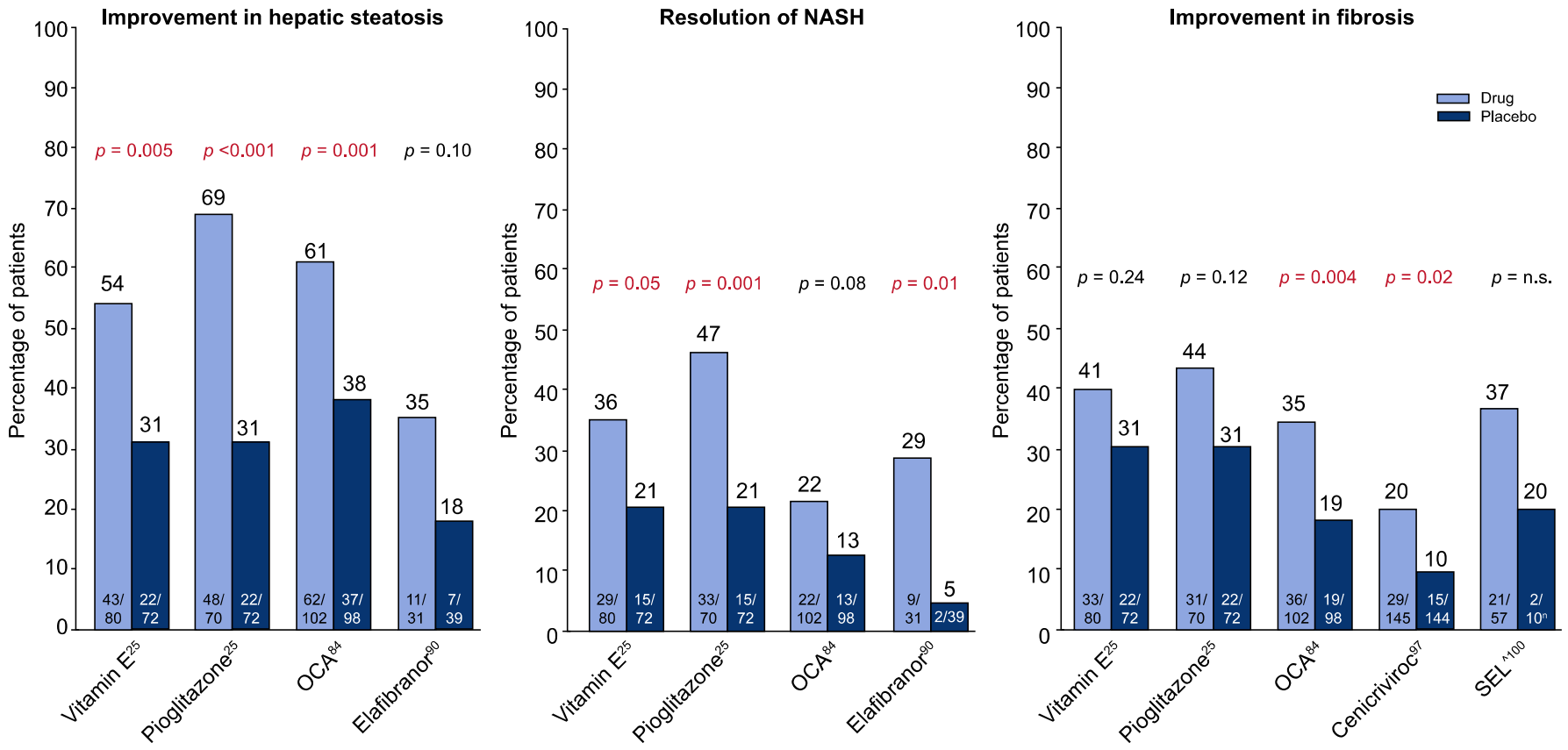
Connolly JJ, et al. J Clin Transl Hepatol. 2018 Sep 28;6(3):264-275.

# Mecanismo de acción Fase III

| Drug name | Mechanism of action | Pharmaceutical company | Phase of clinical trial |
|---|---|---|---|
| Obeticholic Acid (OCA) | Farnesoid X receptor agonist | Intercept pharmaceuticals | 3 |
| Selonsertib | Apoptosis signal-regulating kinase-1 inhibitor | Gilead | 3 |
| Elafibranor | PPAR α/δ activator | Genfit | 3 |
| Cenicriviroc | CCR2/CCR5 antagonist | Allergan | 3 |

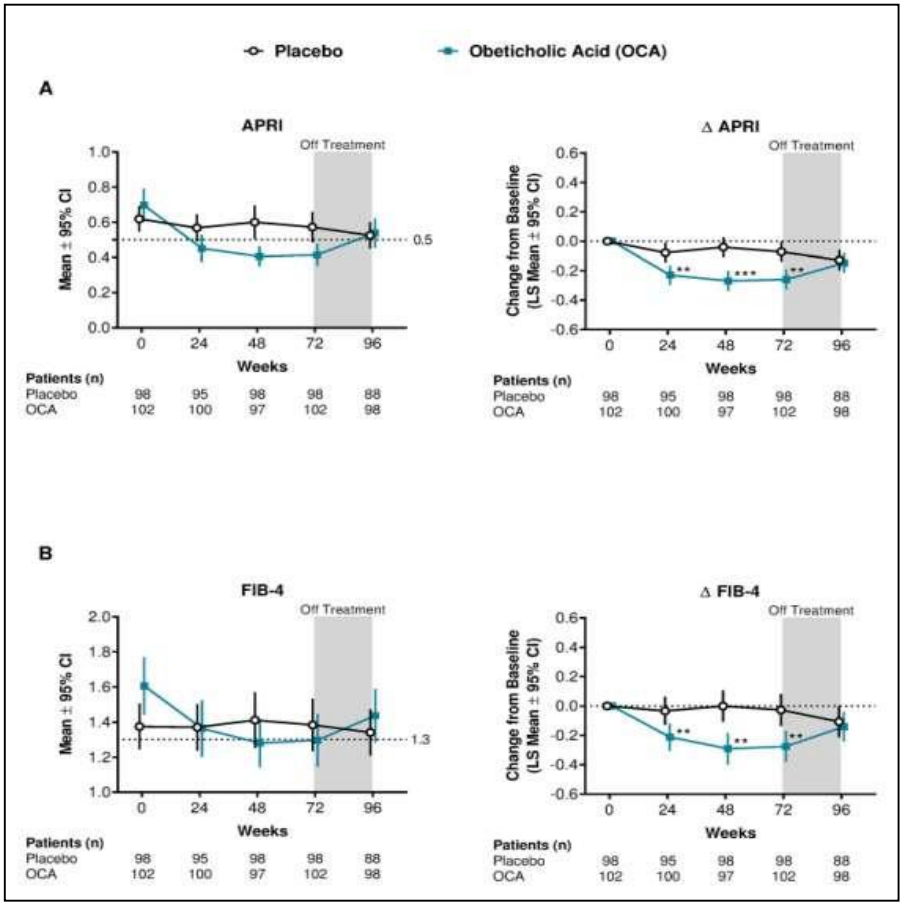
Thuluvath P. Hepatol Int 2019

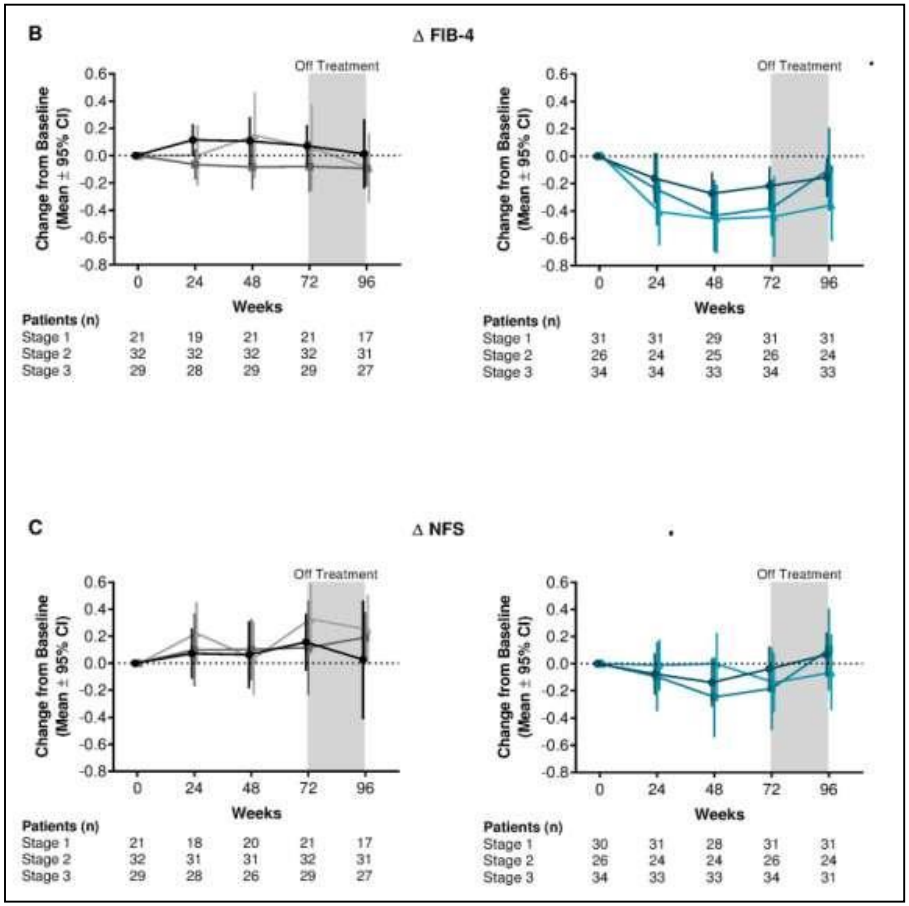
# Efecto Farmacológico en NASH




Konerman M, et al. J Hepatol 2018 vol 68:362-375

# OCA. Mejoría de Scores Clásicos

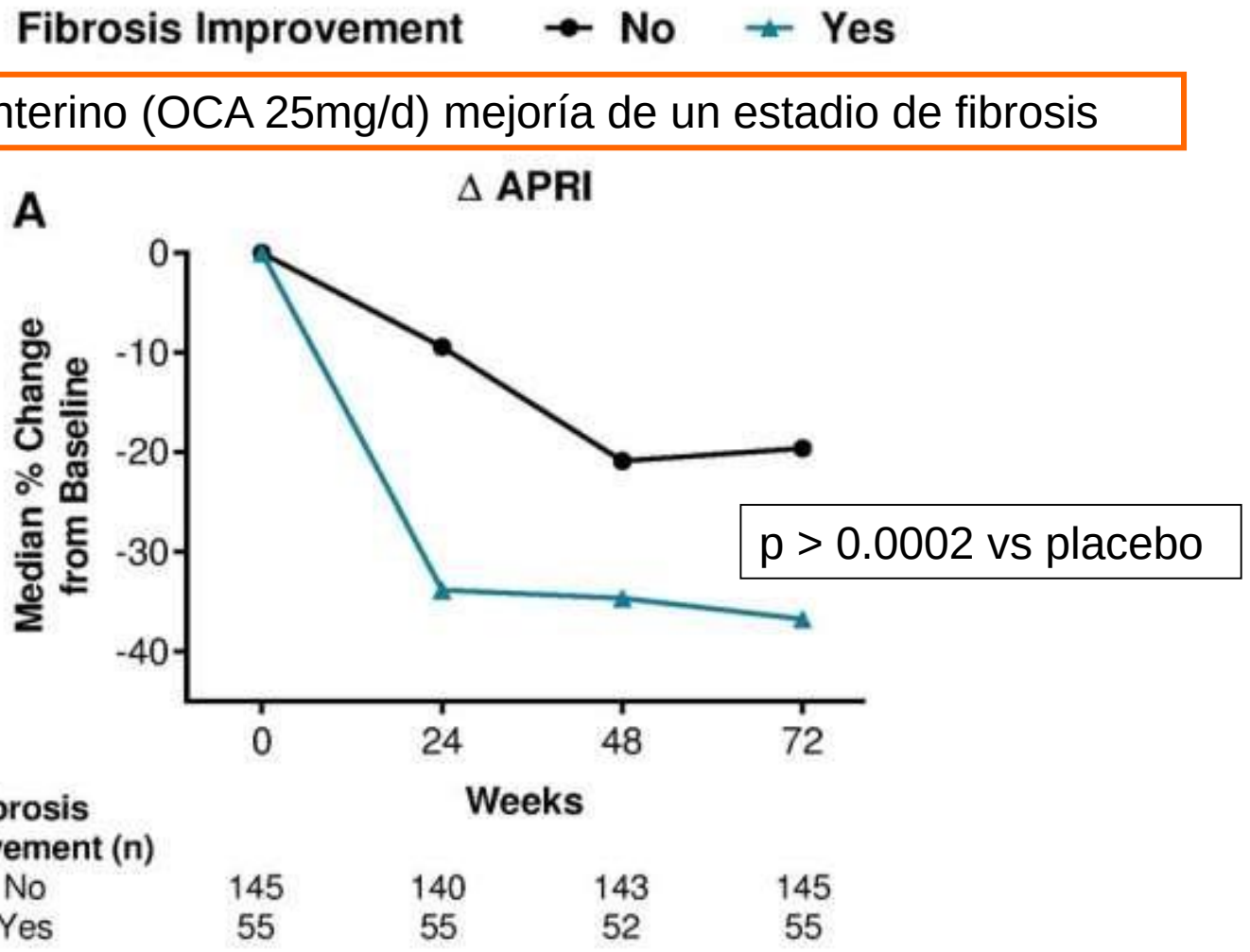



Sanyal AJ. Liver Int. 2018 Sep 25.

# OCA. Mejoría de Scores Clásicos

## REGENERATE TRIAL



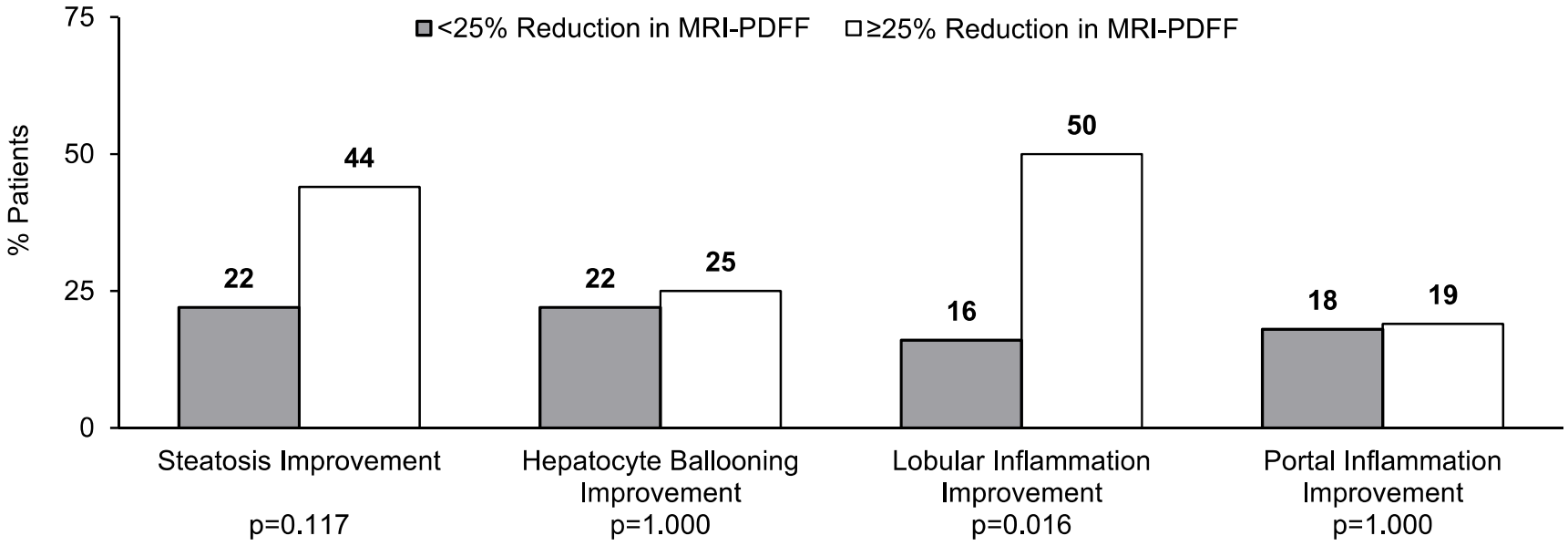

Análisis interino (OCA 25mg/d) mejoría de un estadio de fibrosis

p > 0.0002 vs placebo

Sanyal AJ. Liver Int. 2018. EASL19, Abstract.

# Selonsertib. Cambios Histológicos

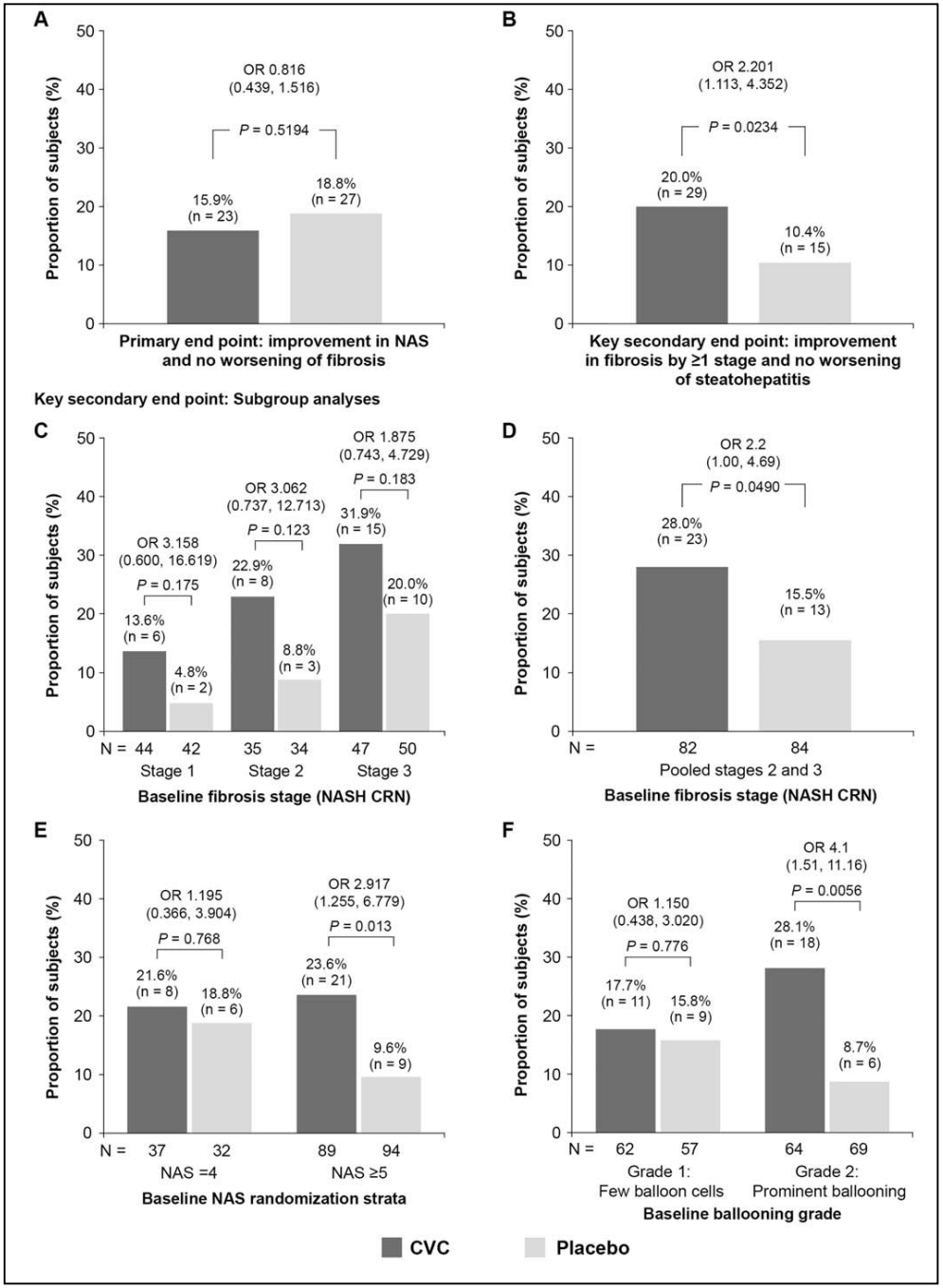
STELLAR-3 y STELLAR-4, suspendido en análisis interino por falla en end-point primario



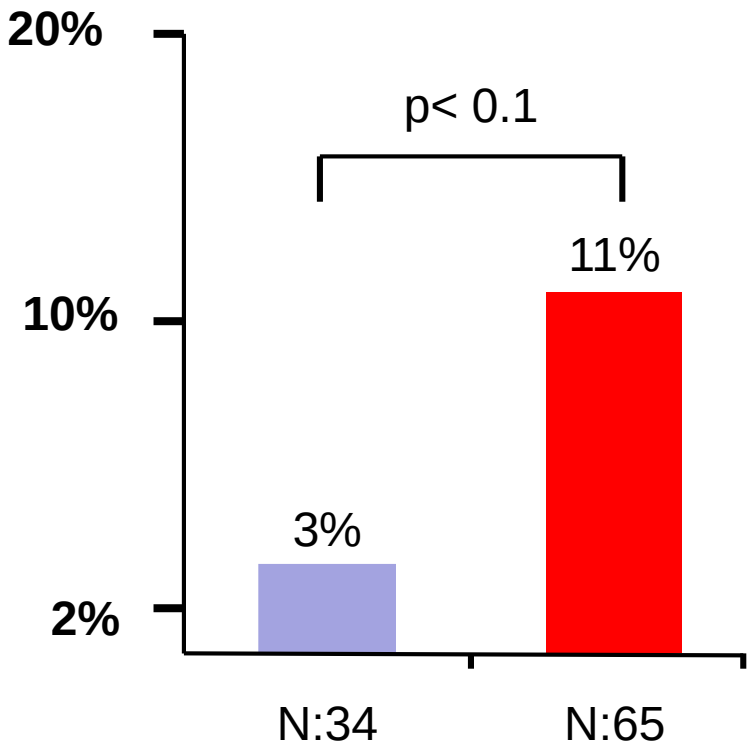

Jayakumar S, et al. J Hepatol. 2018. www.gilead.com/news-stellar-3, 2019.

# Cenicriviroc

Fase III-AURORA- Sep. 2020



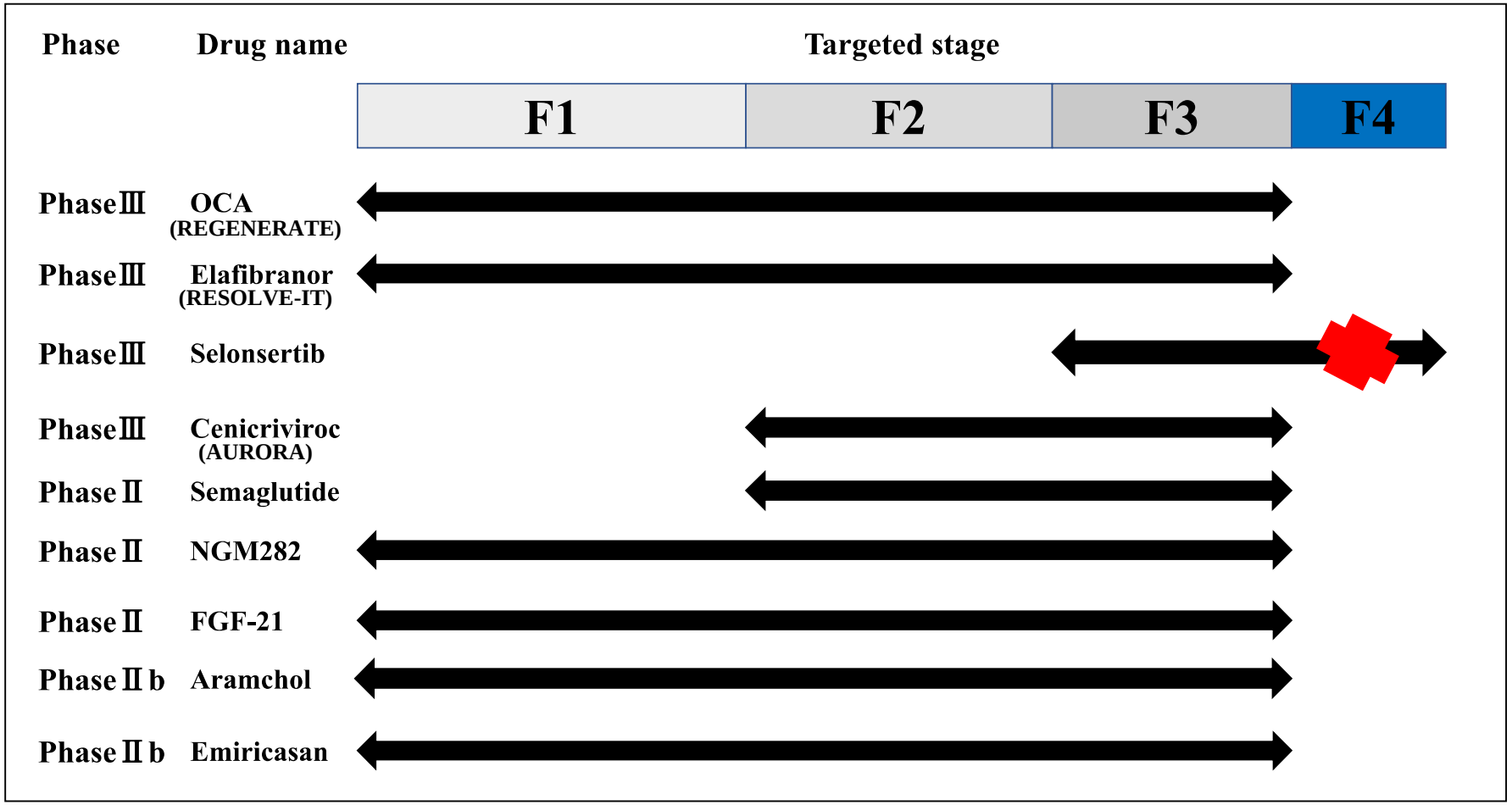

Mejoría del estadio de fibrosis ( >2) en el Fase II (CENTAUR)




Seguimiento a 2 años

Friedman SL, et al. Hepatology 2018.

# Antifibróticos Fase II y III




Yomeda M, J Gastroenterol 2018

# Tratamientos Futuros en NASH