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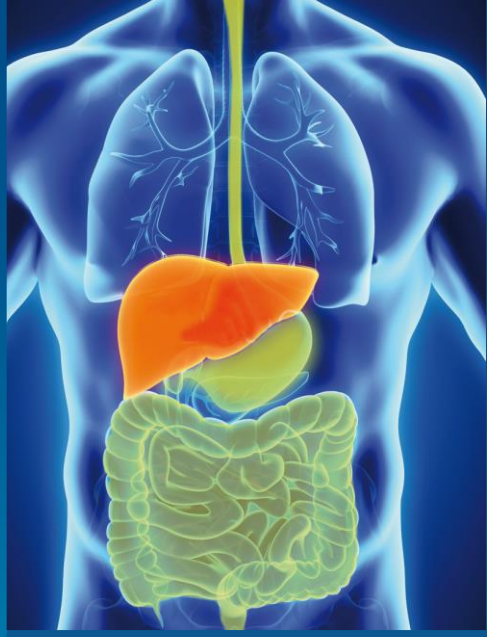

HEPCUP EASL: Immune-mediated and cholestatic Liver Diseases

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University Hospital Zürich

HEPCUP EASL 2025 – 21st May 2025


EASL CONGRESS
7–10 May 2025
Amsterdam, the Netherlands
Welcome to the Home of Hepatology!
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EASL CONGRESS
7-10 May 2025
Amsterdam, the Netherlands


YOUR LIVER
IS VITAL
It performs over 500 essential functions.
Step inside to discover its role and how to keep it healthy!
EASL


LIVER DISEASE
IS GRADUAL AND OFTEN GOES UNNOTICED
Many are diagnosed too late for treatment.
HELP!
Get your liver checked today, it can save your life!
EASL


LIVER DISEASE
CAN BE CAUSED BY:
Fat buildup
(obesity, diabetes, poor diet)
Toxins
(alcohol, drugs, chemicals)
Viral Infections
(hepatitis B & C)
Genetics
(hereditary conditions)
But 90% of cases are preventable.
Find out how!
EASL


FIBROSCAN
MobCenter
Hepatos
Hrvatsko društvo za bolesti jetre
Croatian Association For The Liver Diseases
info tel. 0800 400 405
www.hepatos.hr
InfoHep Center

Potential Conflicts of Interest

Subjective selection of abstracts from the EASL 2025

• Consultant / Advisor: Abbvie, Advanz, Alentis, AlphaSigma, AstraZenca, Avior, Bayer, BMS, CymaBay, Escient, Falk, Gilead, GSK, Intercept, Ipsen, Mirum, MSD, Novo Nordisk, Roche, Takeda

• Speaker: Abbvie, Advanz, AOP Orphan, Bayer, BMS, CymaBay, Falk, Gilead, GSK, Intercept, Ipsen, Johnson&Johnson, Medscape, Mirum, MSD, Newbridge, Novartis, Roche, Vertex Viofor.

• Unrestricted grants: Gilead, Intercept, Roche

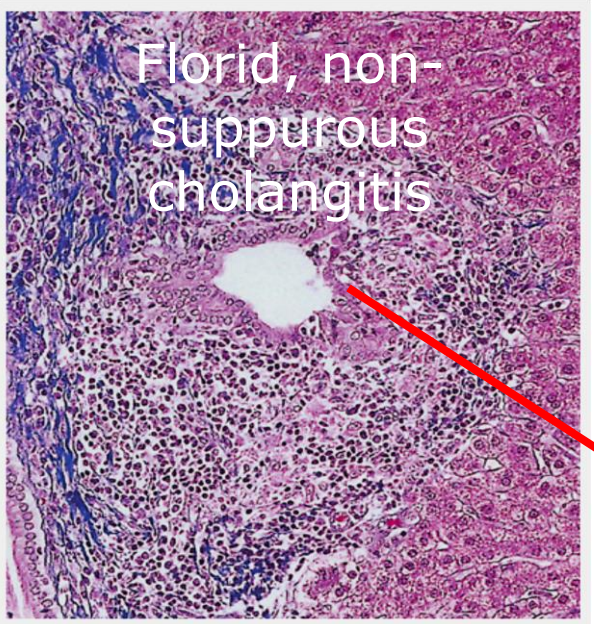
Outline

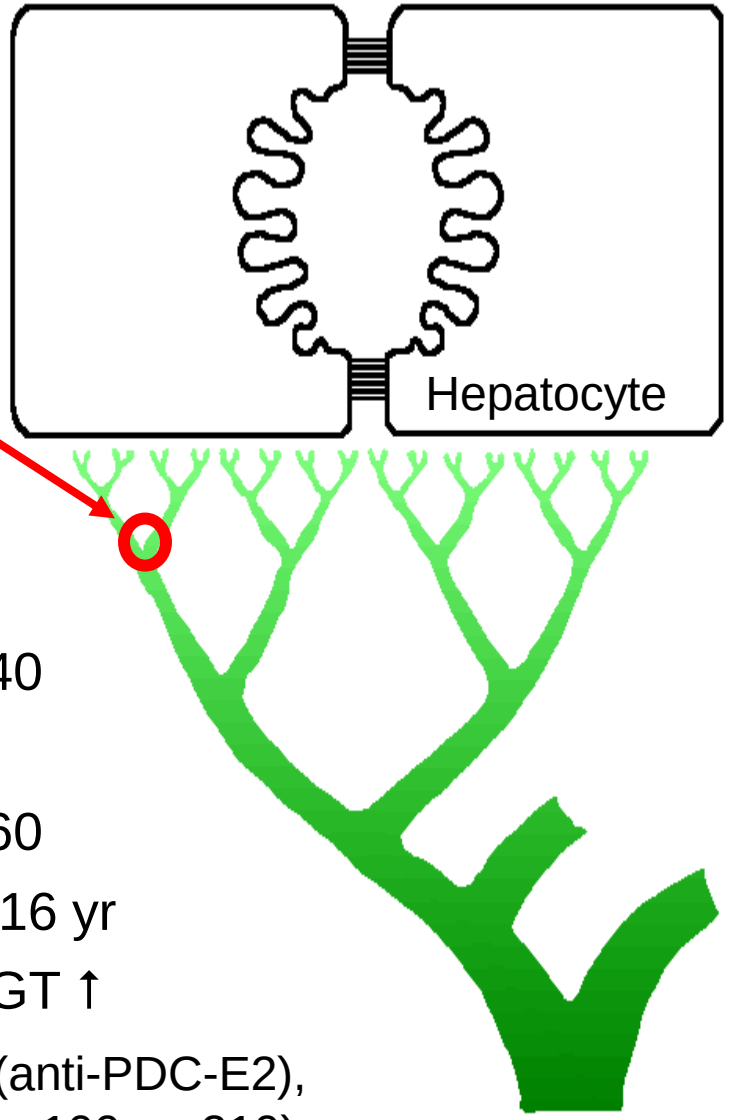
- **Primary Biliary Cholangitis**
- **Primary Sclerosing Cholangitis**
- **IgG4-related Diseases**
- **CF-associated Cholangiopathy**

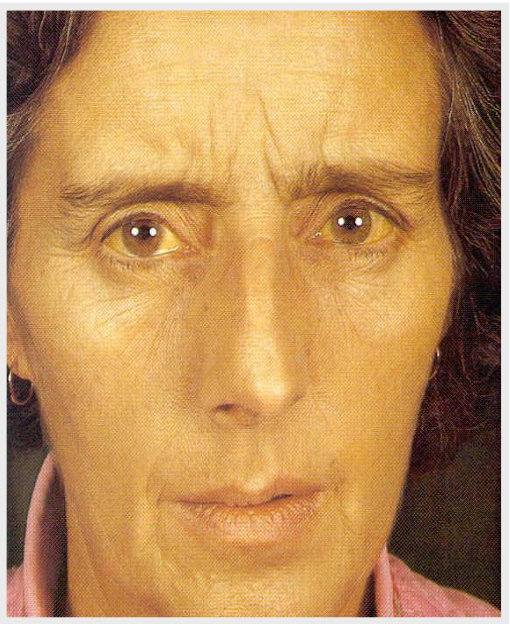
Outline

- **Primary Biliary Cholangitis**
- **Primary Sclerosing Cholangitis**
- **IgG4-related Diseases**
- **CF-associated Cholangiopathy**

Primary Biliary Cholangitis (PBC)
- Clinical Aspects -





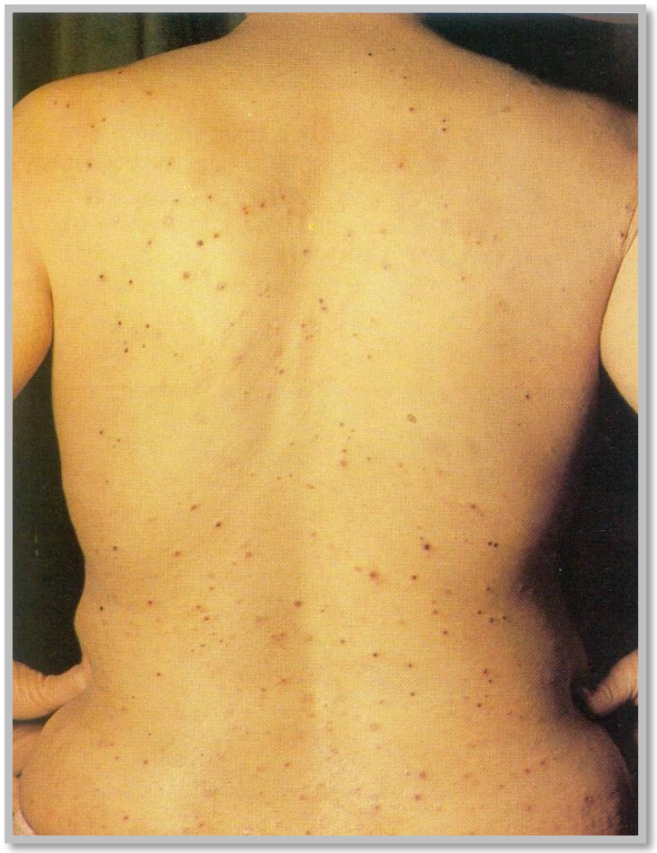


Sherlock and Summerfield 1979

Prevalence (per 100.000)	25 – 40
Gender (f : m)	9 : 1
Age of manifestation	40 – 60
Overall survival (w/o therapy)	7,5 – 16 yr
Laboratory findings	AP/ γGT ↑
Auto antibodies	AMA (anti-PDC-E2), ANA (sp100, gp210)

Symptoms
- Fatigue
- Pruritus
- Sicca syndrome
- Arthralgia
- …

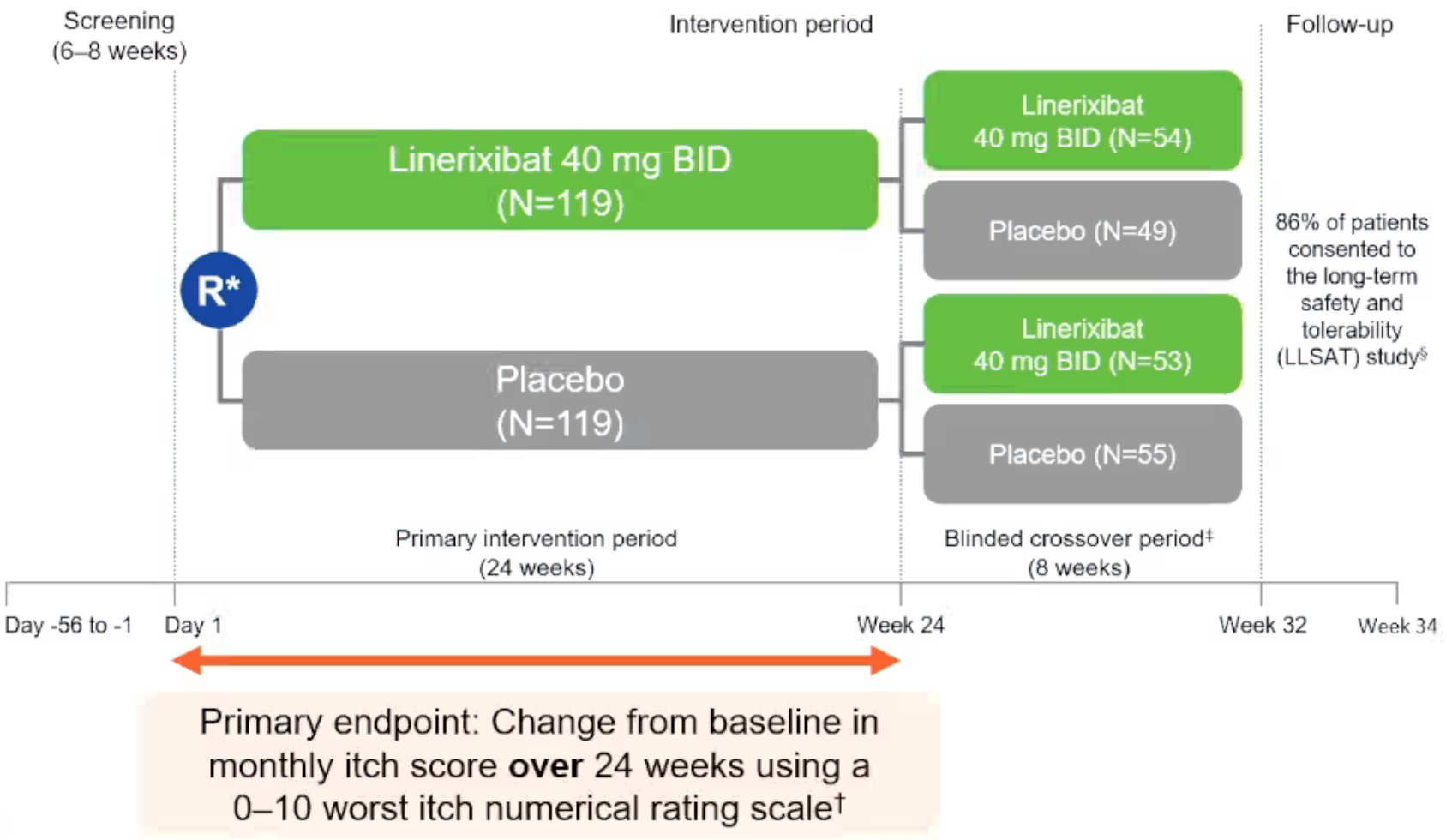
Pruritus in PBC



Sherlock and Summerfield, 1979

www.drug-rehab-headquarters.com /addiction-information; Drug and Alcohol rehab headquarters 2011

GLISTEN: Linerixibat for Pruritus in PBC
- Phase III Study; N=238 -



Eligibility criteria

- ✓ PBC
- ✓ Moderate-to-severe pruritus (WI-NRS ≥4)
- ✓ Concomitant medications for PBC and or pruritus were stable for 8 weeks before screening and during the study
- ✗ Treatment with obeticholic acid or other IBAT inhibitors
- ✗ Total bilirubin >2x ULN
- ✗ ALT >6x ULN

Stratification

- Pruritus severity
- Concomitant pruritus treatment

Key secondary endpoints

1. Change from baseline in pruritus **at** Week 2†
2. Change from baseline in sleep interference **over** 24 weeks#
3. Responders defined as achieving a ≥2-, ≥3- and ≥4-point reduction from baseline in pruritus **at** Week 24

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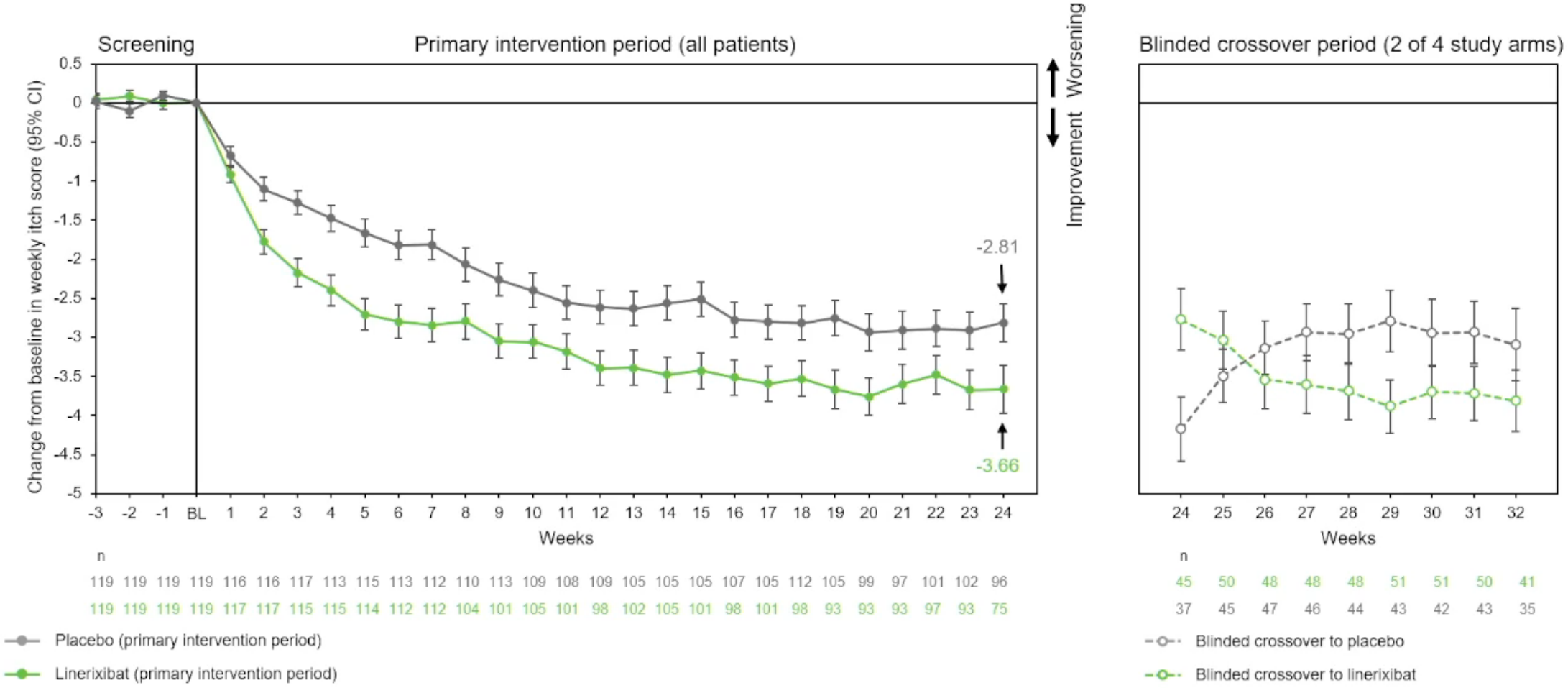
Hirschfield GM et al., EASL 2025; General Session, GS-011

GLISTEN: Linerixibat for Pruritus in PBC
- Phase III Study; N=238 -



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Hirschfield GM et al., EASL 2025; General Session, GS-011

GLISTEN: Linerixibat for Pruritus in PBC
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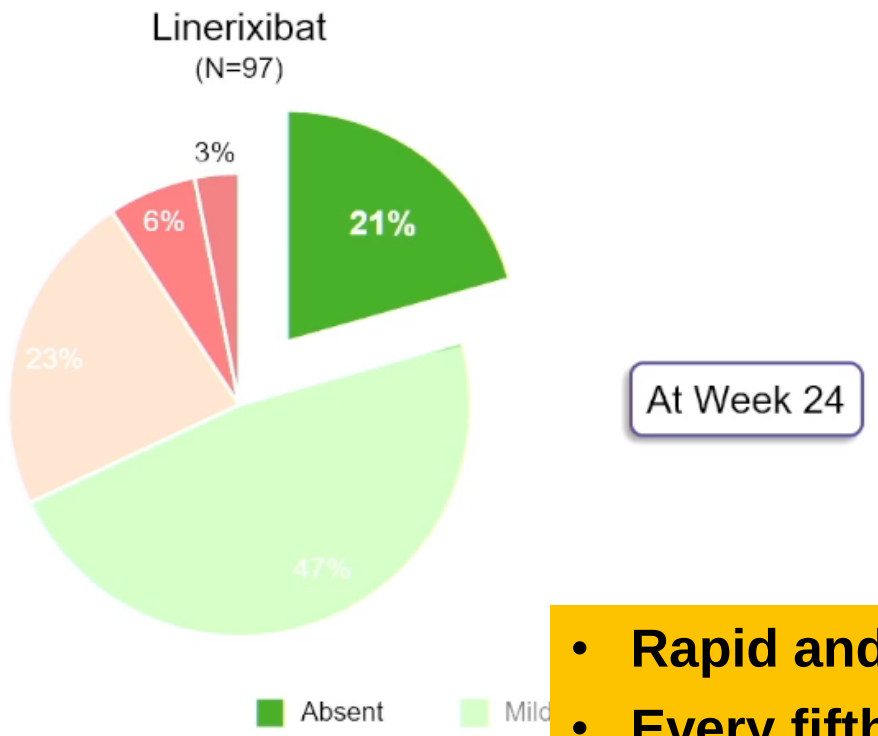

Secondary endpoint: change in P
Significant impro
(LS mean dif

- **Rapid and presistent improvement of pruritus**
- **Every fifth patient without pruritus after 6 months**
- **Improvement also for sleep**
- **AE: diarrhea (61%), GI-symptoms, ALT/AST**

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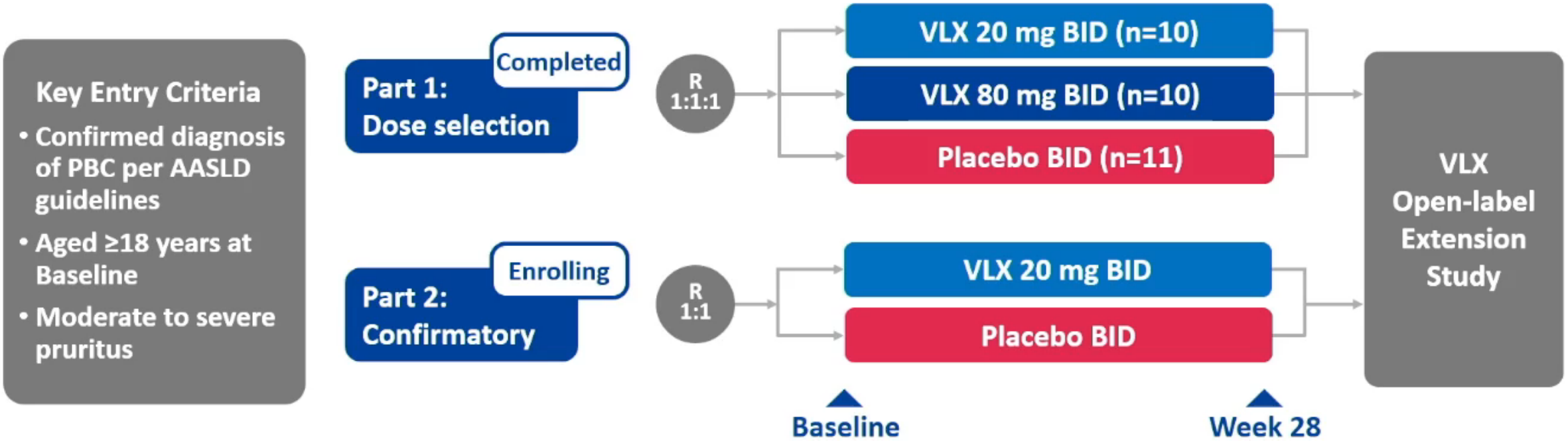
Hirschfield GM et al., EASL 2025; General Session, GS-011

Volixibat for Pruritus in PBC

- VINTAGE: Phase II Study; 26 weeks interim analysis -



Primary Endpoint

- Mean change in daily itch scores using the ItchRO[a] questionnaire from Baseline to Week 28

Select Secondary Endpoints[b]

- Incidence of AEs
- Change in sBA
- Change in HRQoL using PBC-40 and PROMIS

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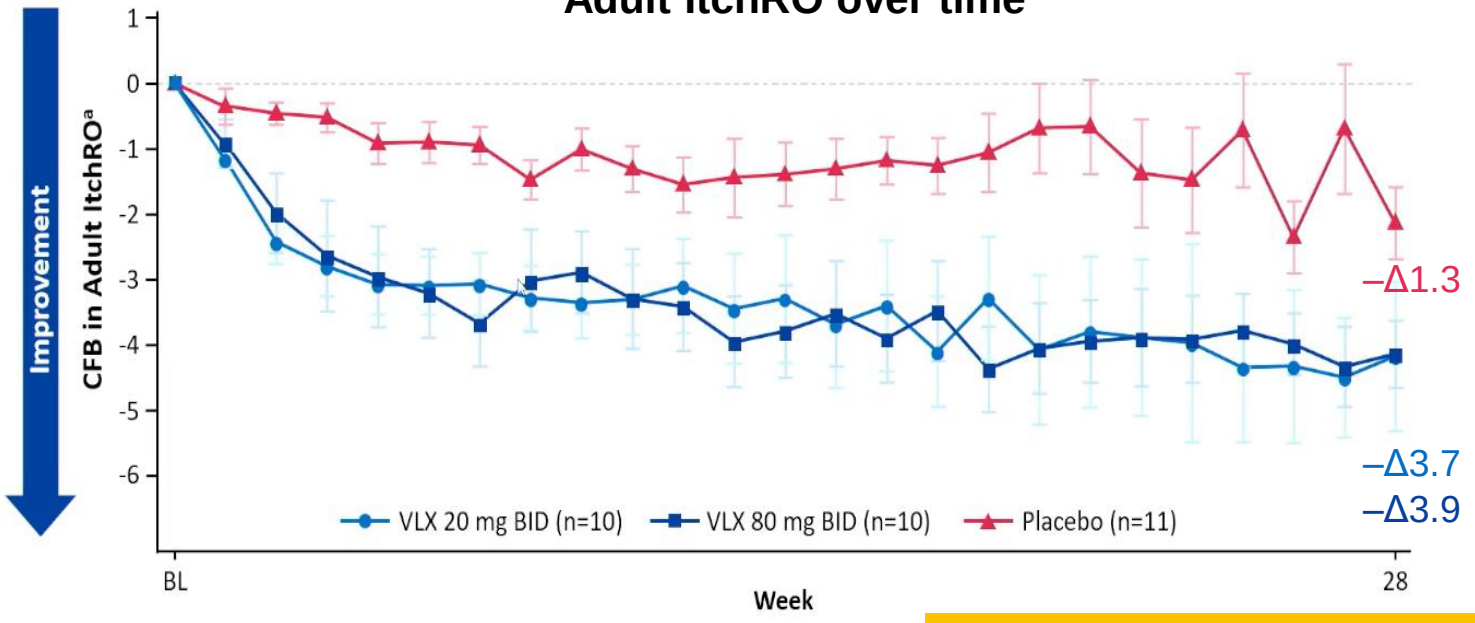
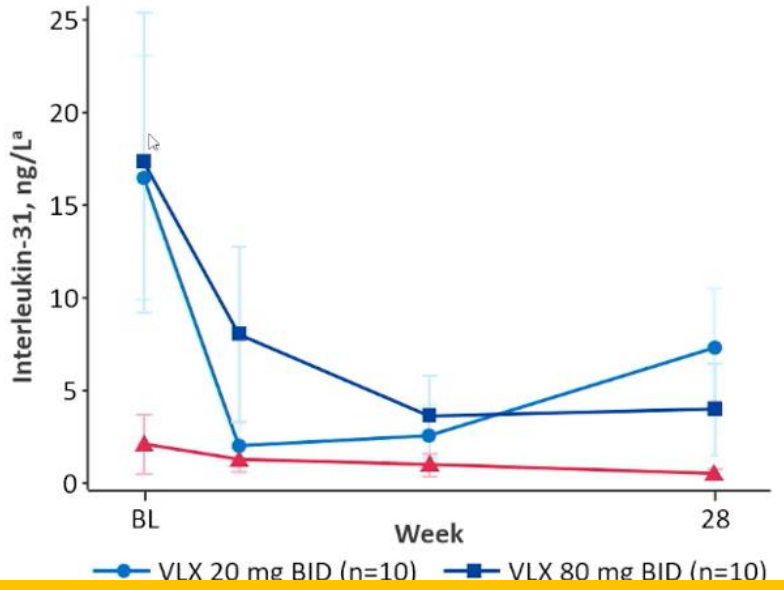
Henneghan M et al., EASL 2025; Parallel Session, OS-059

Volixibat for Pruritus in PBC
- VINTAGE: Phase II Study; 26 weeks interim analysis -

Adult ItchRO over time



IL-31 levels over time



- Most common TEAE: diarrhoea; reported in u
  volixibat
  - Severity = mild to moderate
  - Led to 1 discontinuation

- **No effect on cholestasis parameters, but TBS ↓**
- **Sleep and fatigue also improved**
- **20 and 80 mg equivalent effective → Phase IIb: 20 mg**
- **AE: diarrhea (77%), 1x discontinuation**
- **Confirmation with full patient count required**

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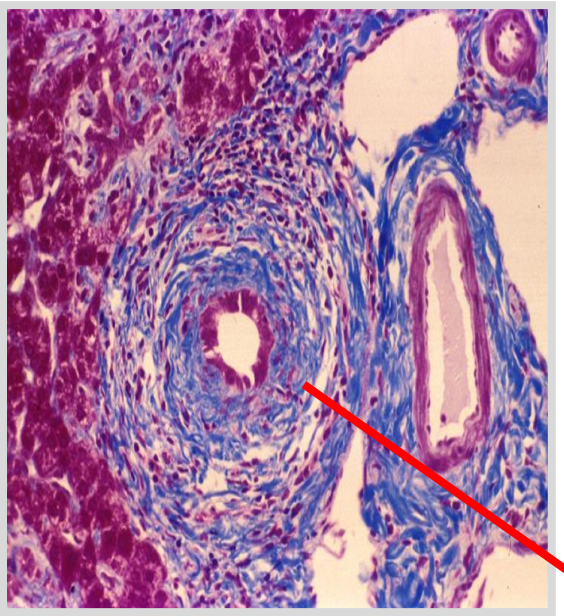
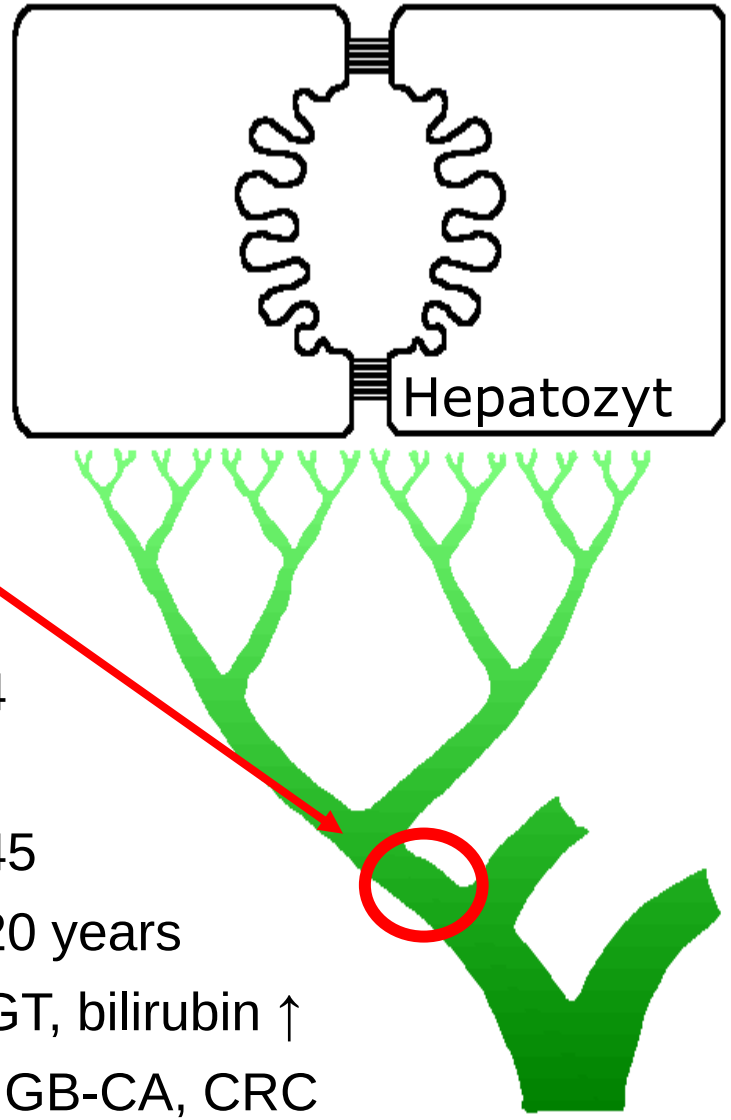
Henneghan M et al., EASL 2025; Parallel Session, OS-059

Outline

- Primary Biliary Cholangitis
- **Primary Sclerosing Cholangitis**
- IgG4-related Diseases
- CF-associated Cholangiopathy

Primary Sclerosing Cholangitis (PSC)
- Clinical Aspects -





www.drug-rehab-headquarters.com/addiction-information
Drug and Alcohol rehab headquarters 2011

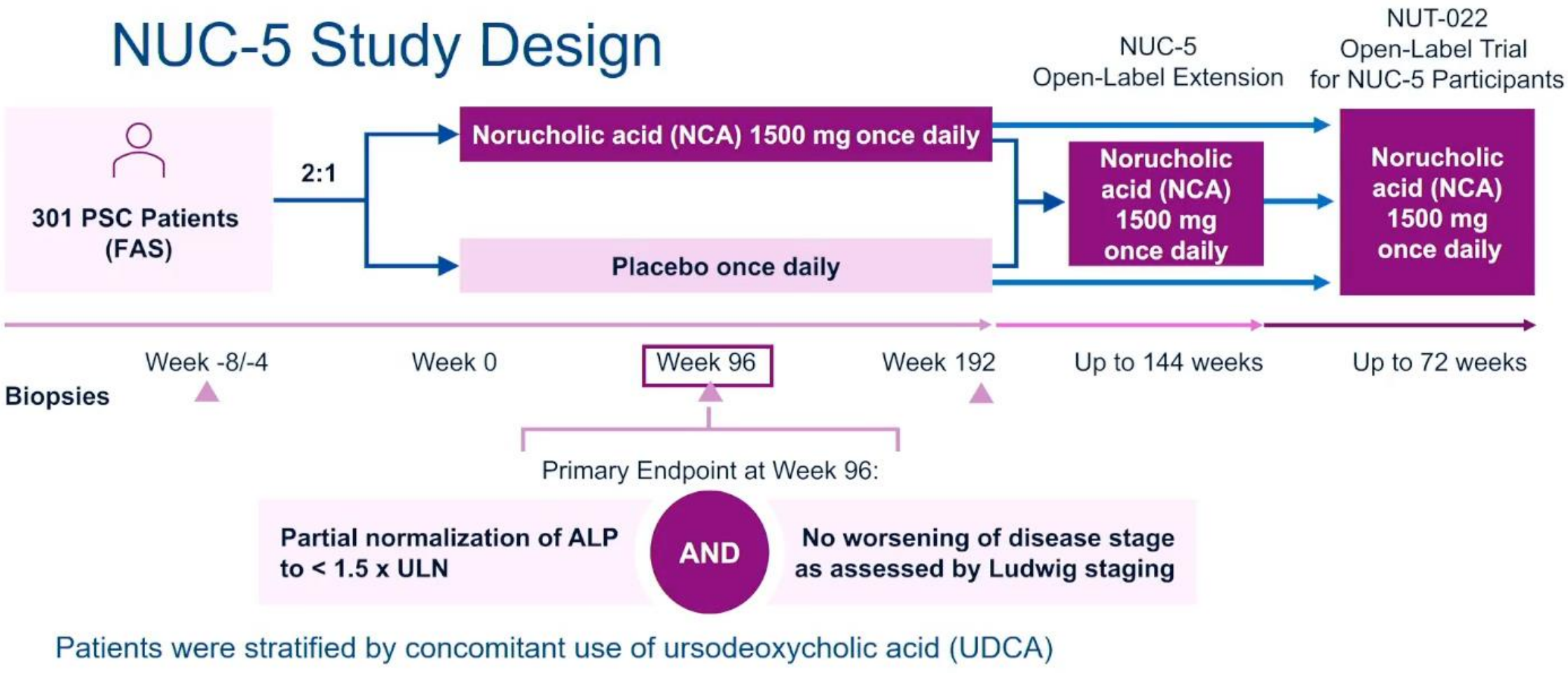
Prevalence (per 100.000)	9 – 14
Gender (f : m)	1 : 2
Age of manifestation	25 – 45
Surival	12 – 20 years
Laboratory pattern	AP, yGT, bilirubin ↑
Cancer risk	CCC, GB-CA, CRC

Symptom burden
- Pruritus
- Fatigue
- Jaundice
- Abdominal pain
- IBD-associated symptoms

Hirschfield GM et al., Lancet 2013;382:1587

NUC-5: Norucholic acid for PSC

- Phase III Study; N=301; IBD: 64%; UDCA: 78%; 96 week analysis -



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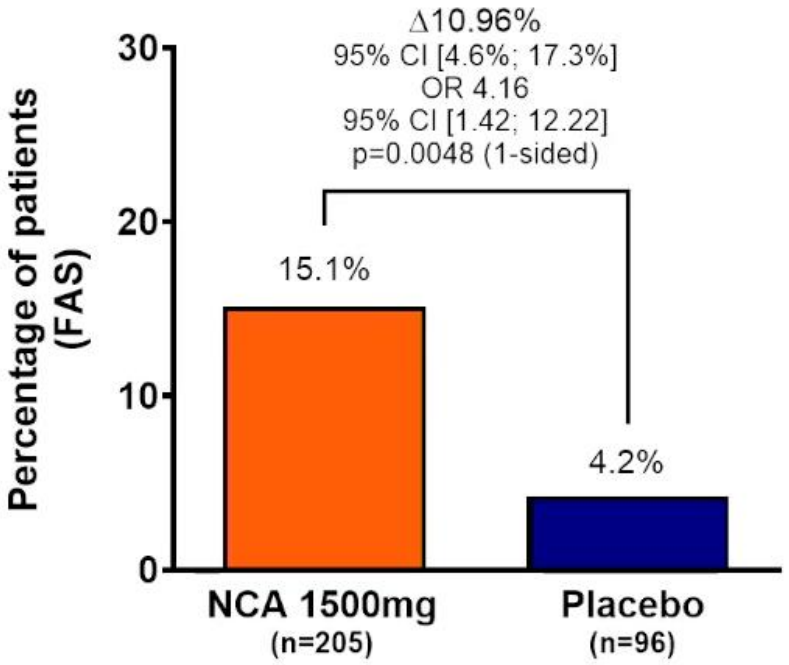
Trauner M et al., EASL 2025; Late Braker Session, LB-001

NUC-5: Norucholic acid for PSC

- Phase III Study; N=301; IBD: 64%; UDCA: 78%; 96 week analysis -

Results: Combined Primary Endpoint

Partial normalization of ALP to <1.5 x ULN and no worsening of Ludwig stage



- NCA was significantly superior to placebo in the combined primary endpoint
- Patients without second biopsy were evaluated as non-responders

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Trauner M et al., EASL 2025; Late Braker Session, LB-001

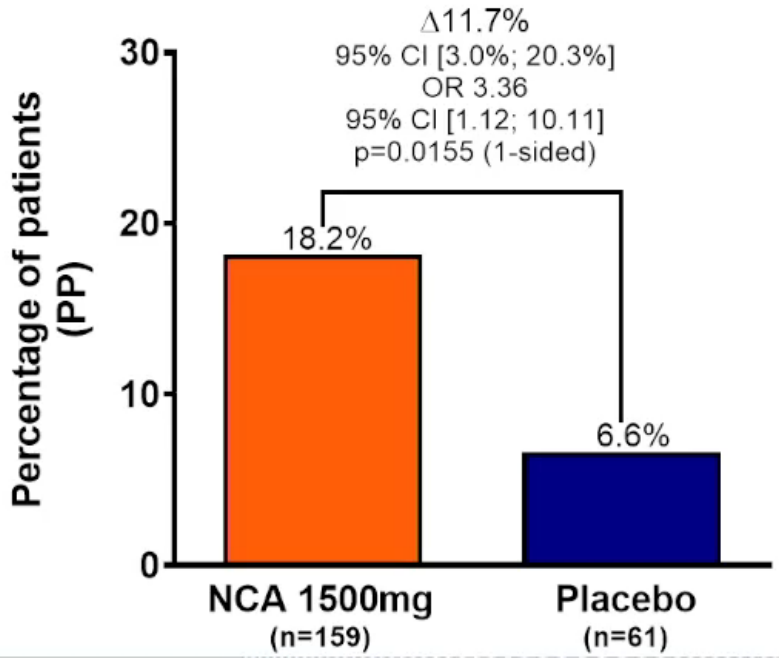
NUC-5: Norucholic acid for PSC

- Phase III Study; N=301; IBD: 64%; UDCA: 78%; 96 week analysis -

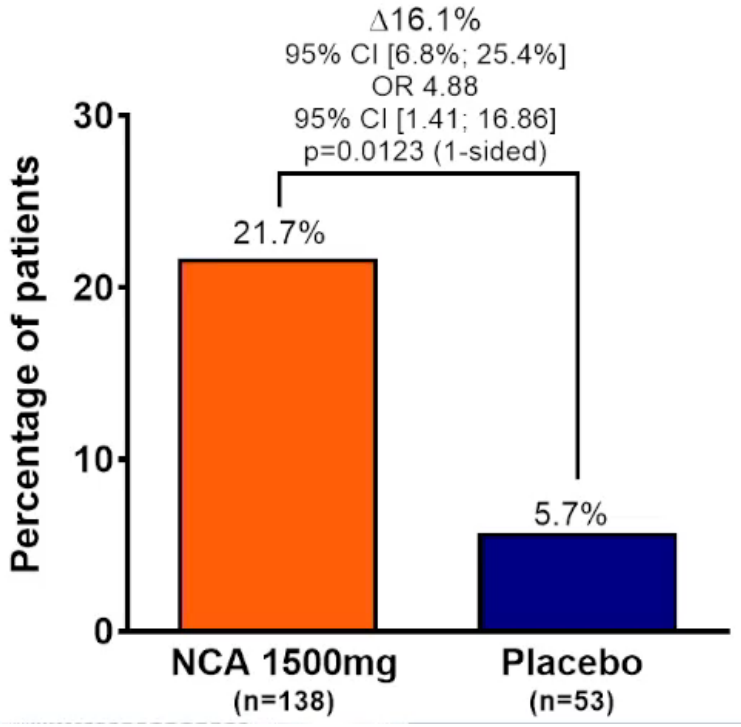
Combined Primary Endpoint

Partial normalization of ALP to <1.5 x ULN and no worsening of Ludwig stage

Per-protocol analysis



Patients with no missing values



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Trauner M et al., EASL 2025; Late Braker Session, LB-001

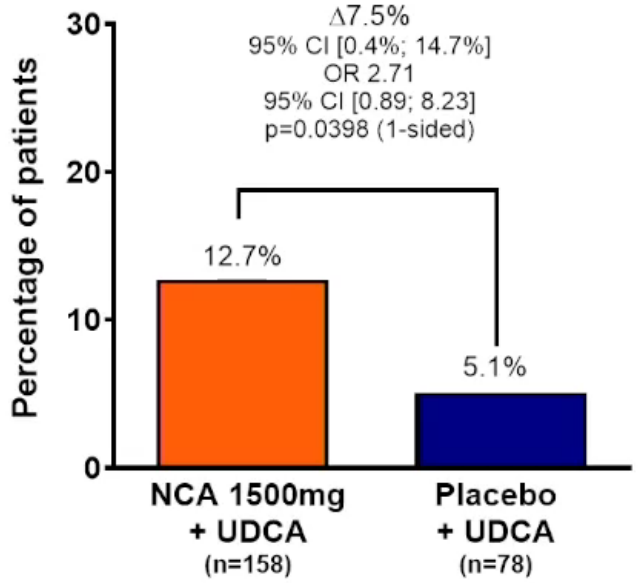
NUC-5: Norucholic acid for PSC

- Phase III Study; N=301; IBD: 64%; UDCA: 78%; 96 week analysis -

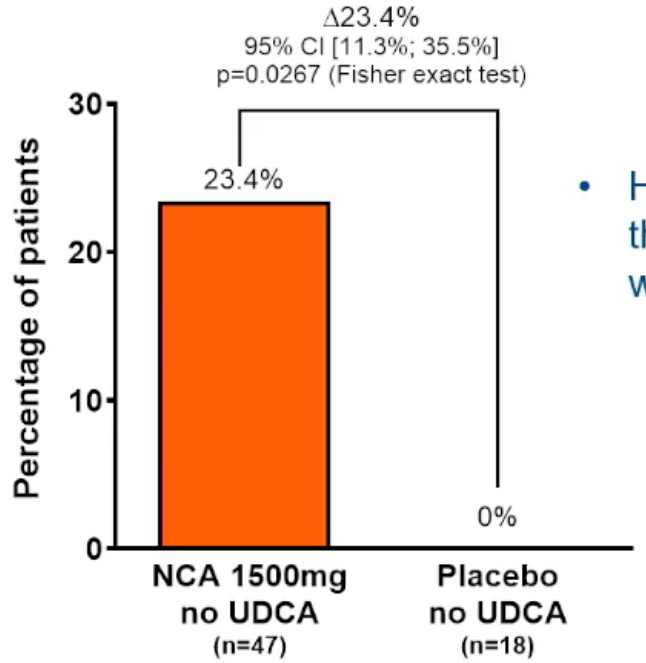
Subgroup Analysis

Partial normalization of ALP to <1.5 x ULN and no worsening of Ludwig stage

with concomitant UDCA



without concomitant UDCA



- Higher response rates for NCA than placebo both with and without concomitant UDCA

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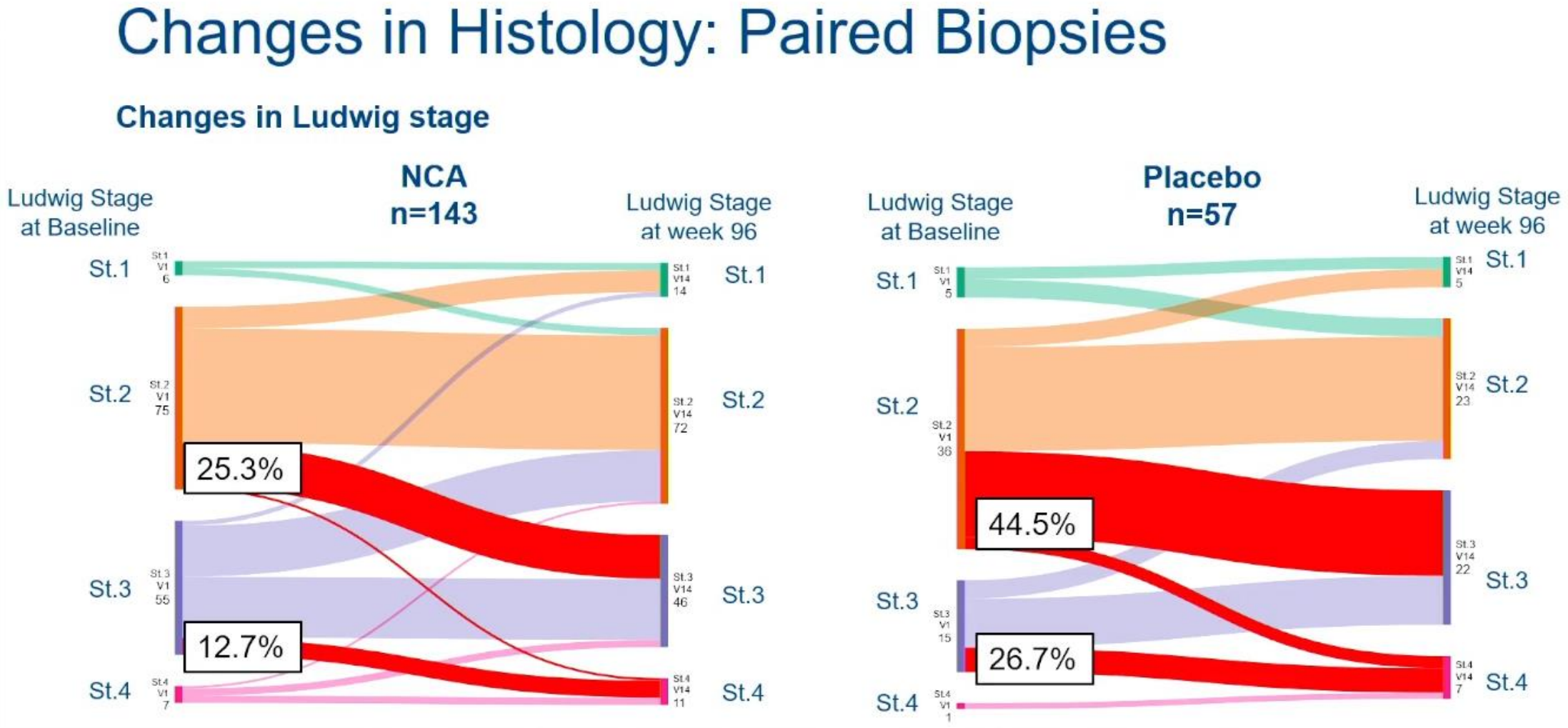
Trauner M et al., EASL 2025; Late Braker Session, LB-001

NUC-5: Norucholic acid for PSC

- Phase III Study; N=301; IBD: 64%; UDCA: 78%; 96 week analysis -



Trauner M et al., EASL 2025; Late Braker Session, LB-001

NUC-5: Norucholic acid for PSC

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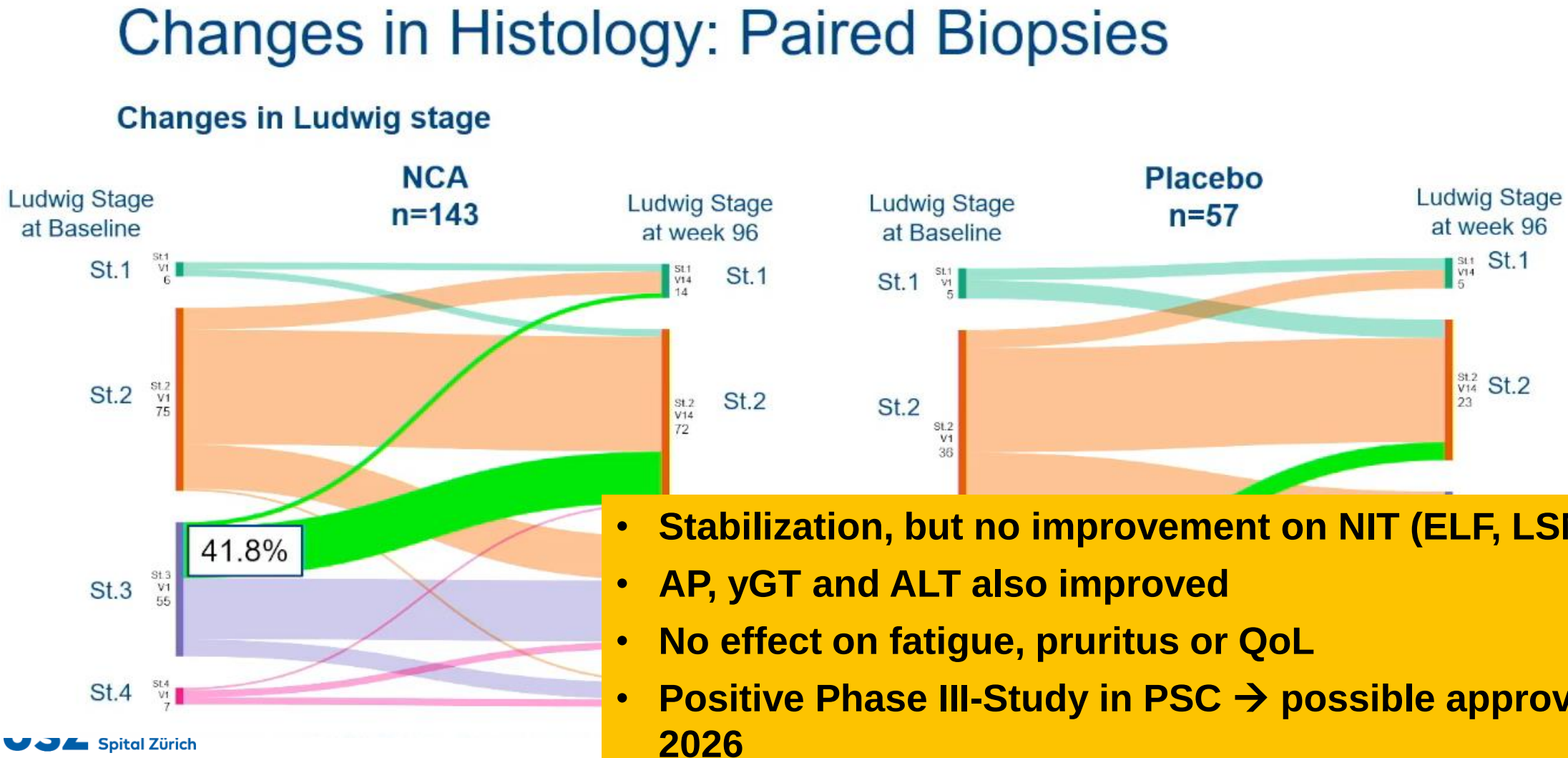
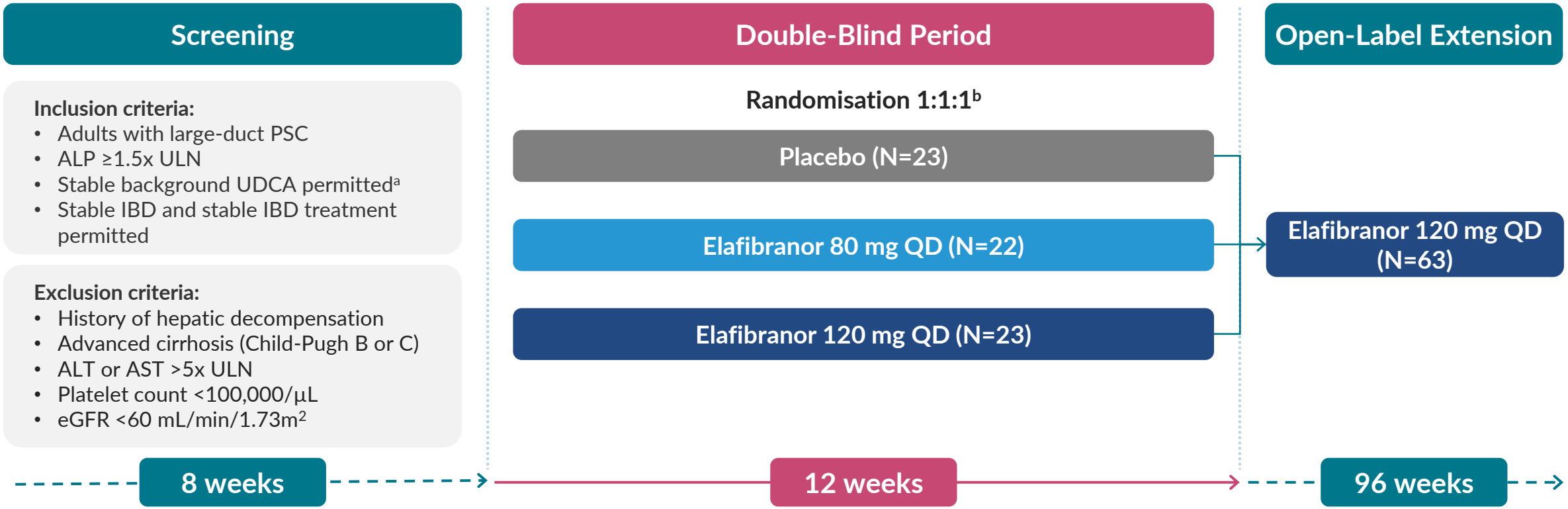


- **Stabilization, but no improvement on NIT (ELF, LSM)**
- **AP, yGT and ALT also improved**
- **No effect on fatigue, pruritus or QoL**
- **Positive Phase III-Study in PSC → possible approval in 2026**

Trauner M et al., EASL 2025; Late Braker Session, LB-001

ELMWOOD: Elafibranor for PSC

Phase II Study; N=68; AP: 369 U/L; IBD: 56%; UDCA: 71%; WI-NRS ≥ 4: 16%



Primary endpoint

Safety and tolerability of elafibranor 80 mg and 120 mg compared with placebo

Secondary endpoints

Change from baseline in biochemistries and non-invasive markers of fibrosis

Exploratory endpoints

Change in symptoms of PSC, including pruritus assessed by WI NRS

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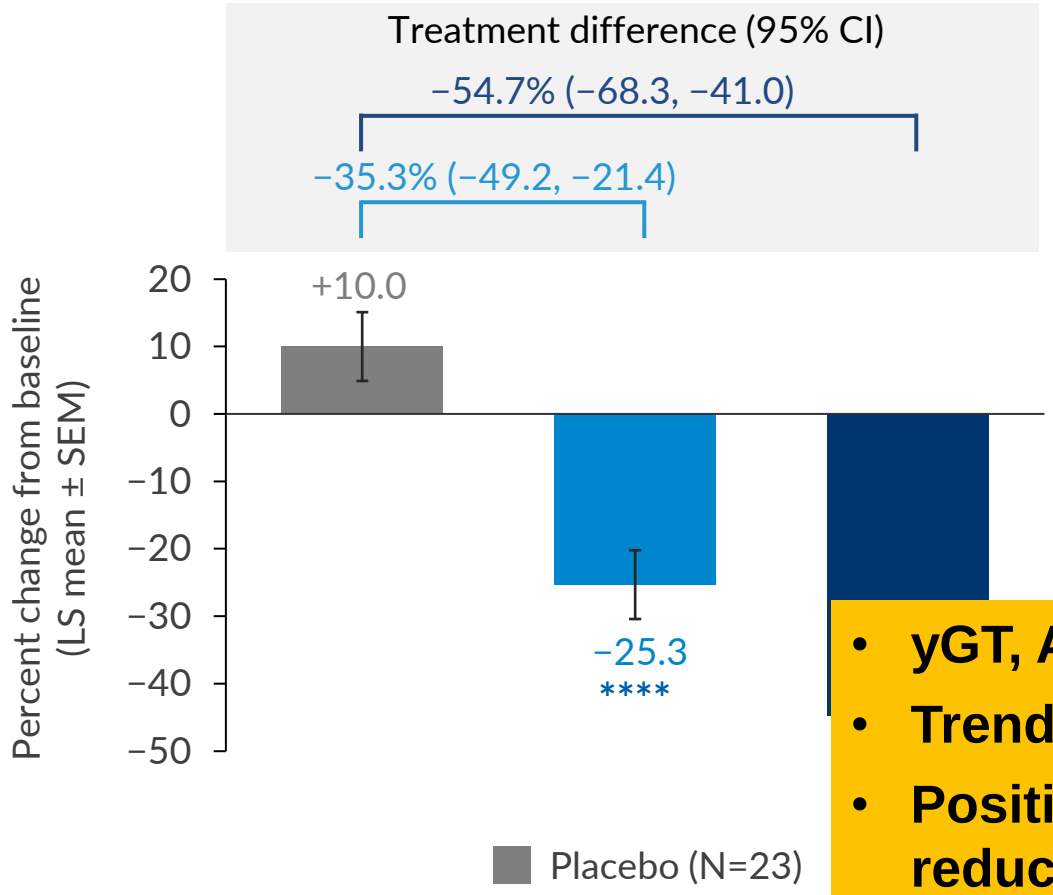
Levy C et al., EASL 2025; Parallel Session, OS-089

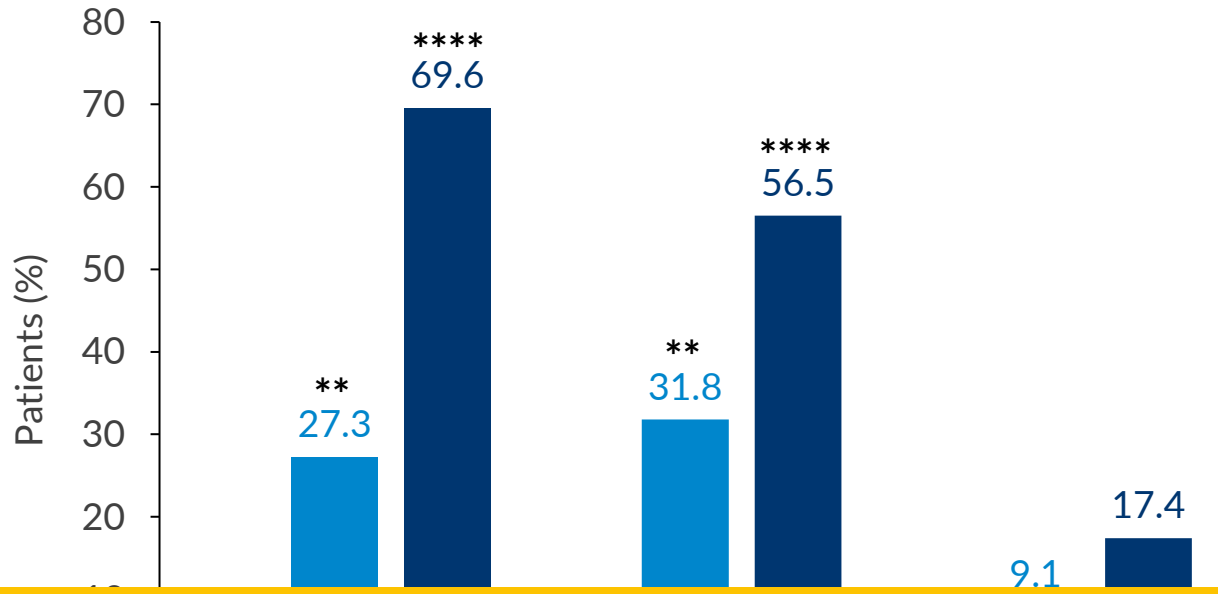
ELMWOOD: Elafibranor for PSC

Phase II Study; N=68; AP: 369 U/L; IBD: 56%; UDCA: 71%; WI-NRS ≥ 4: 16%

Relative change from baseline in ALP



ALP response according to threshold reductions



- **yGT, ALT and AST also improved**
- **Trend towards attenuated pruritus**
- **Positive Phase II-Study in PSC; But: relevance of AP reduction in PSC?**

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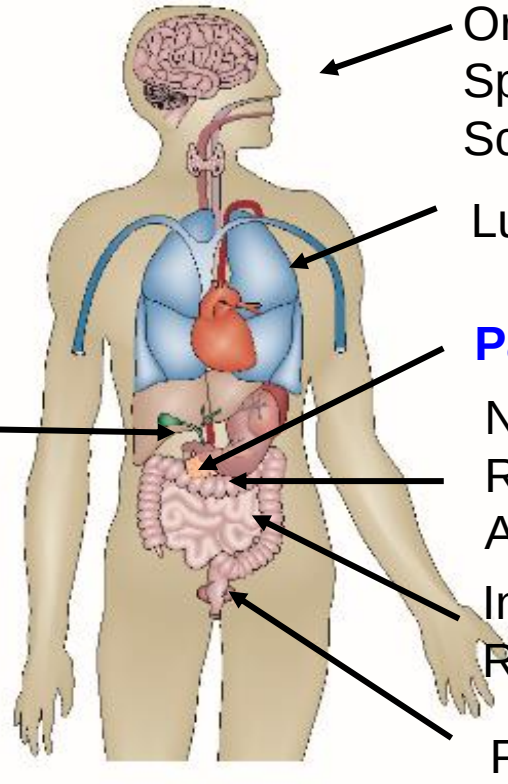
Levy C et al., EASL 2025; Parallel Session, OS-089

Outline

- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
- **IgG4-related Diseases**
- CF-associated Cholangiopathy

IgG4-related diseases (IgG4-RD)
- Clinical aspects -



Pachymeningen
Orbita, Hypophyse
Speichel- und Tränendrüsen
Schilddrüse

Lungen, Lymphknoten

Gallenwege:
- **IgG4-Cholangitis (IRC)**
  - Entzündlicher Pseudotumor
  - Biliäre Zirrhose
  - IgG4-Cholezystitis

Pankreas: Autoimmunpankreatitis Typ 1

Nieren und Ureteren
Retroperitoneum
Aorta

Intestinum,
Retroperitoneum

Prostata, Epididymis, Testis, Vagina

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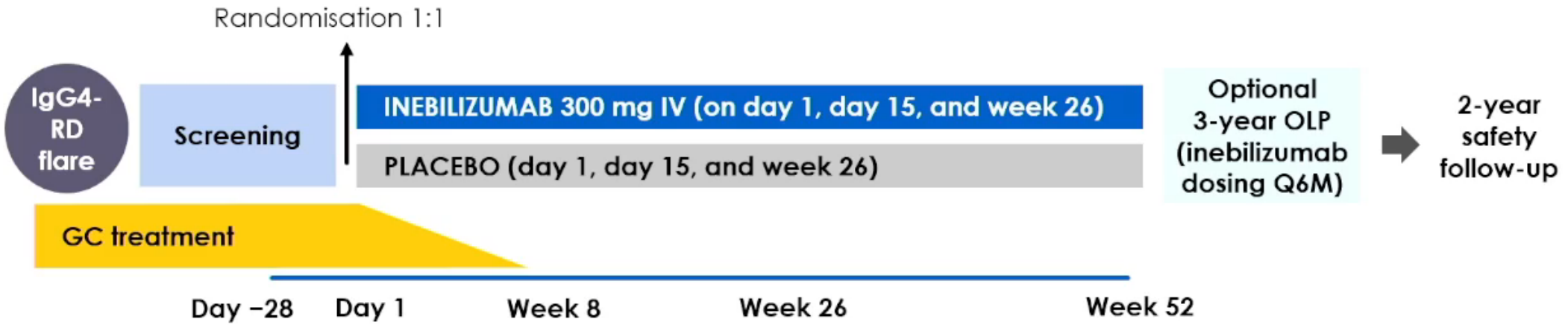
Yamamoto et al. Nature Rev Rheumatology 2014, modified
Löhr, Vujasinovic, Rosendahl, Stone, Beuers. Nat Rev Gastroenterol Hepatol 2022;19:184

Inebilizumab for IgG4-RD
- MITIGATE: Phase III-Study -



Key Eligibility Criteria

- Adult patients with an IgG4-RD diagnosis
- Meet 2019 ACR/EULAR classification criteria greater than or equal to 20 points
- History of at least two organs involved
- Experienced an active IgG4-RD flare requiring GC treatment during the screening period
- Discontinuation of all conventional immunosuppressive therapy for IgG4-RD prior to enrolment, with appropriate washout

Primary endpoint: time to first treated flare

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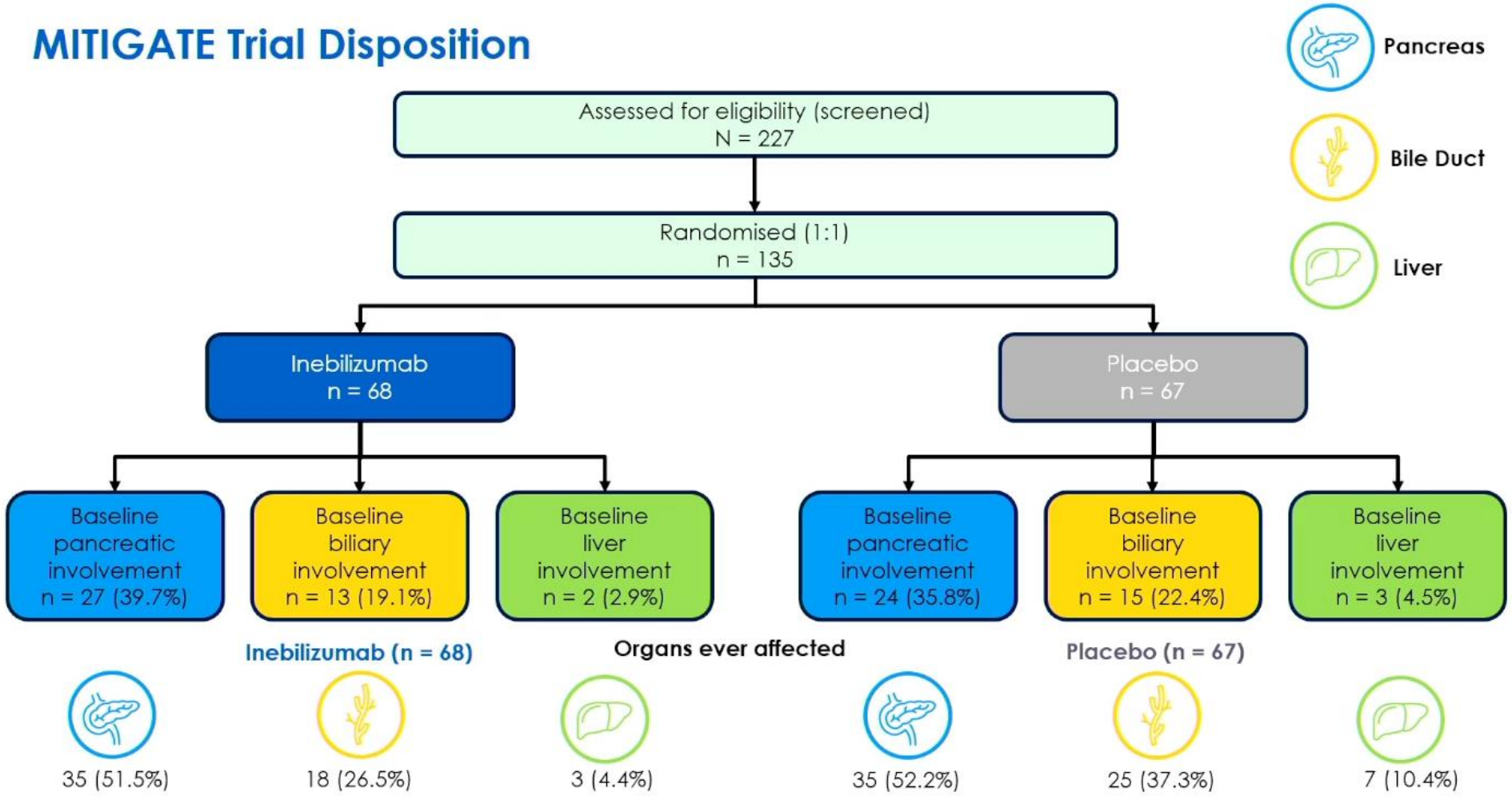
Culver E et al., EASL 2025; General Session, GS-002

Inebilizumab for IgG4-RD
- MITIGATE: Phase III-Study -



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Culver E et al., EASL 2025; General Session, GS-002

Inebilizumab for IgG4-RD
- MITIGATE: Phase III-Study -

Number of Participants With Flares

Overall trial population
Inebilizumab: 7/68 (10.3%)
Placebo: 40/67 (59.7%)
HR: 0.13 (95% CI: 0.06–0.28; *P* < 0.001)

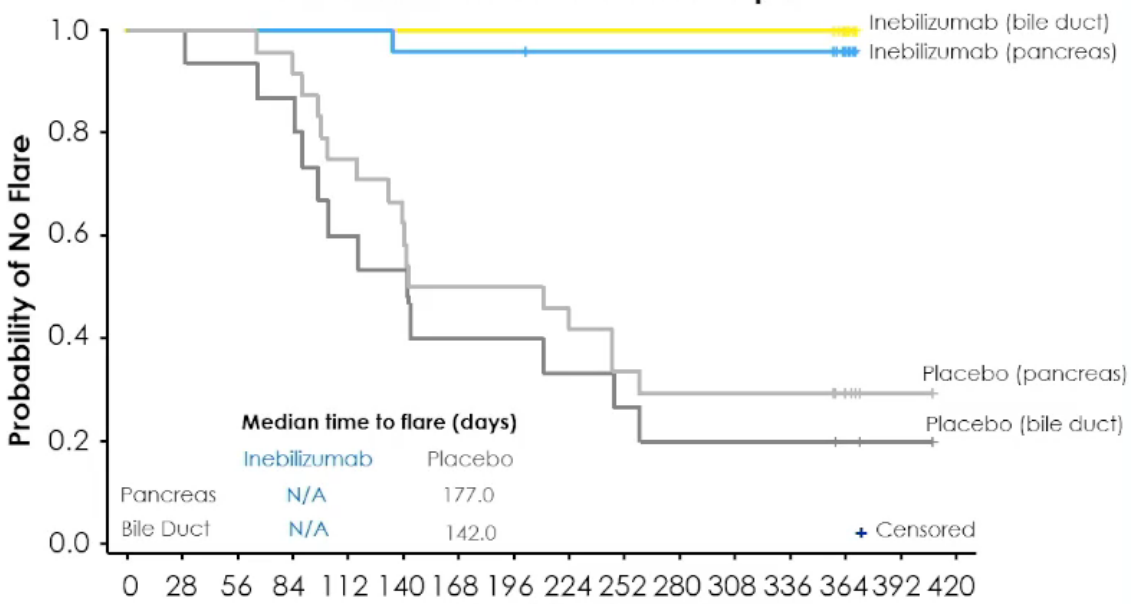
Pancreas
Inebilizumab: 1/27 (3.7%)
Placebo: 17/24 (70.8%)
HR: 0.03 (95% CI, 0.00–0.21; *P* < 0.001*)

Bile Duct
Inebilizumab: 0/13
Placebo: 12/15 (80.0%)
HR: 0.00 (95% CI: 0.00–N/A; *P* = 0.9945*)

Liver
Inebilizumab: 0/2
Placebo: 3/3 (100%)
HR: 0.00 (95% CI: 0.00–N/A; *P* = 0.9987*)

*P values are nominal.
CI, confidence interval; HR, hazard ratio; IgG4-RD, immunoglobulin G4–related dise
N/A, not applicable.
9

Time to the First Adjudicated IgG4-RD Flare in the Pancreas and Bile Duct Groups



- **First RCT using CD19 mAb in IgG4-RD**
- **Strong reduktion of flares and prednisone dose**
- **No safety signals**
- **Advantage over rituximab?**

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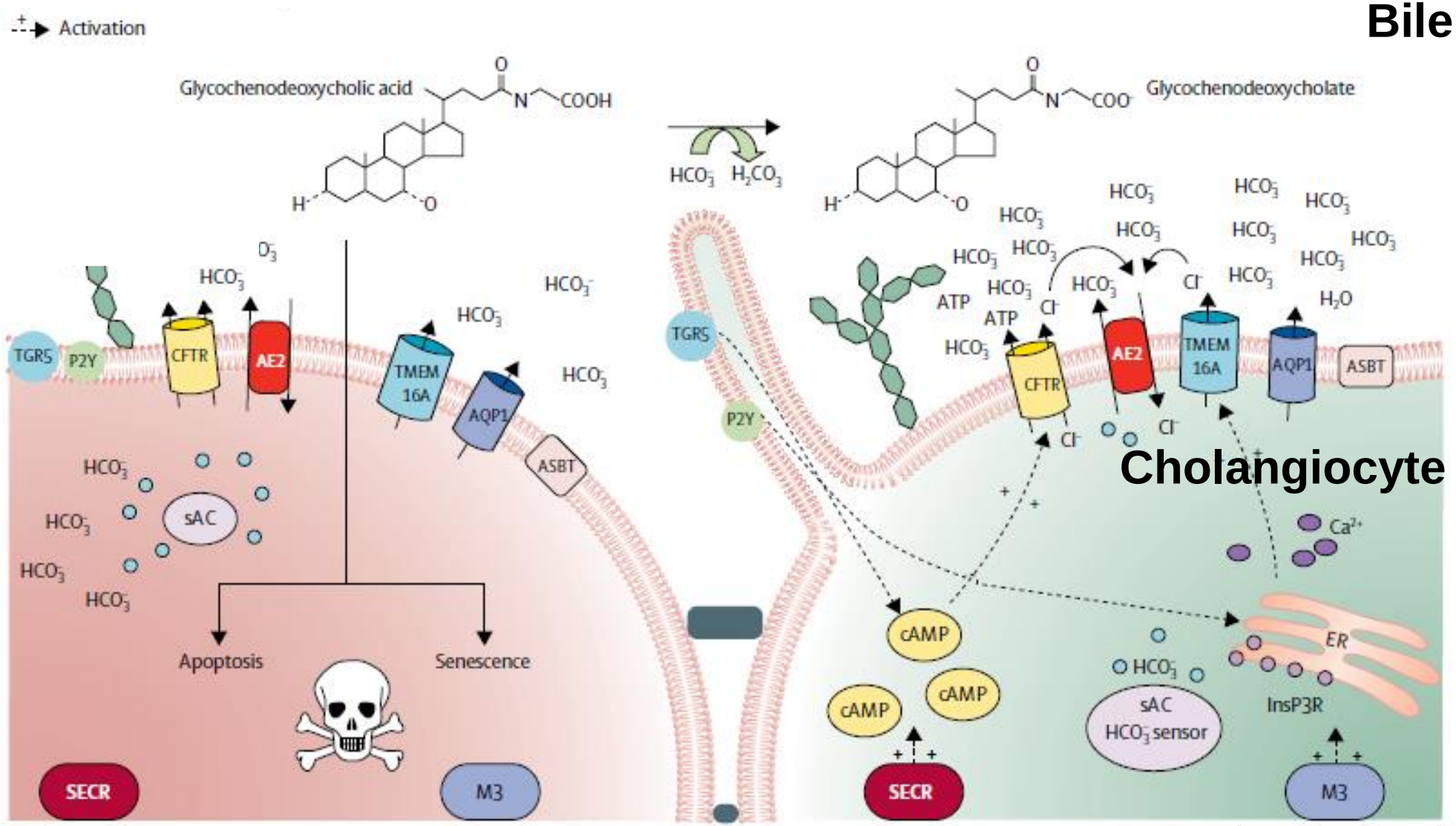
Culver E et al., EASL 2025; General Session, GS-002

Outline

- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
- IgG4-related Diseases
- **CF-associated Cholangiopathy**

The ‘Biliary HCO3- Umbrella‘ Hypothesis



[Lancet 2018;391:2547]

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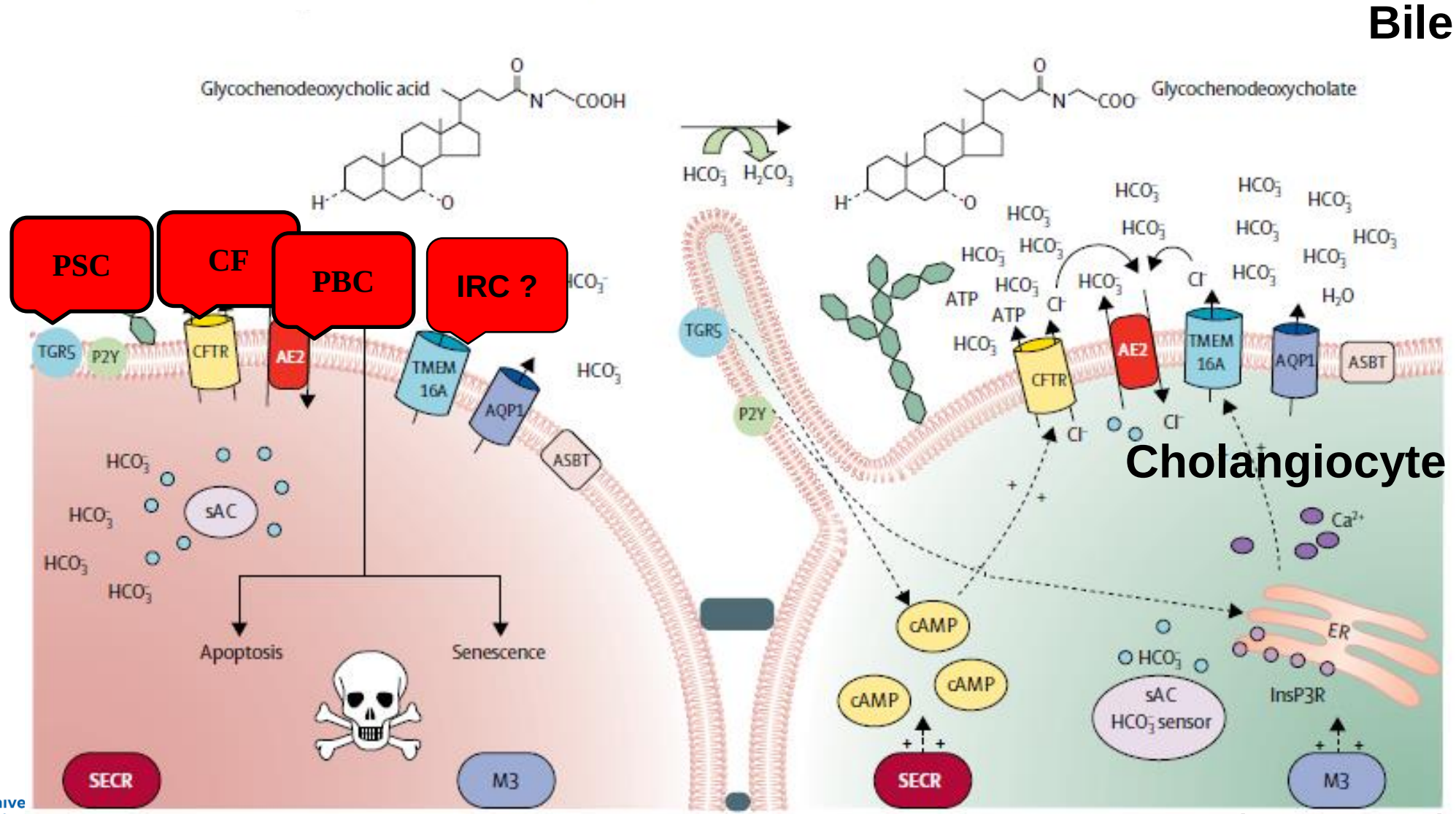
Beuers et al., Hepatology 2010;52:1489; Hohenester, Maillette de Buy Wenniger et al., Hepatology 2012;55:173; Chang et al., Hepatology 2016;64:522

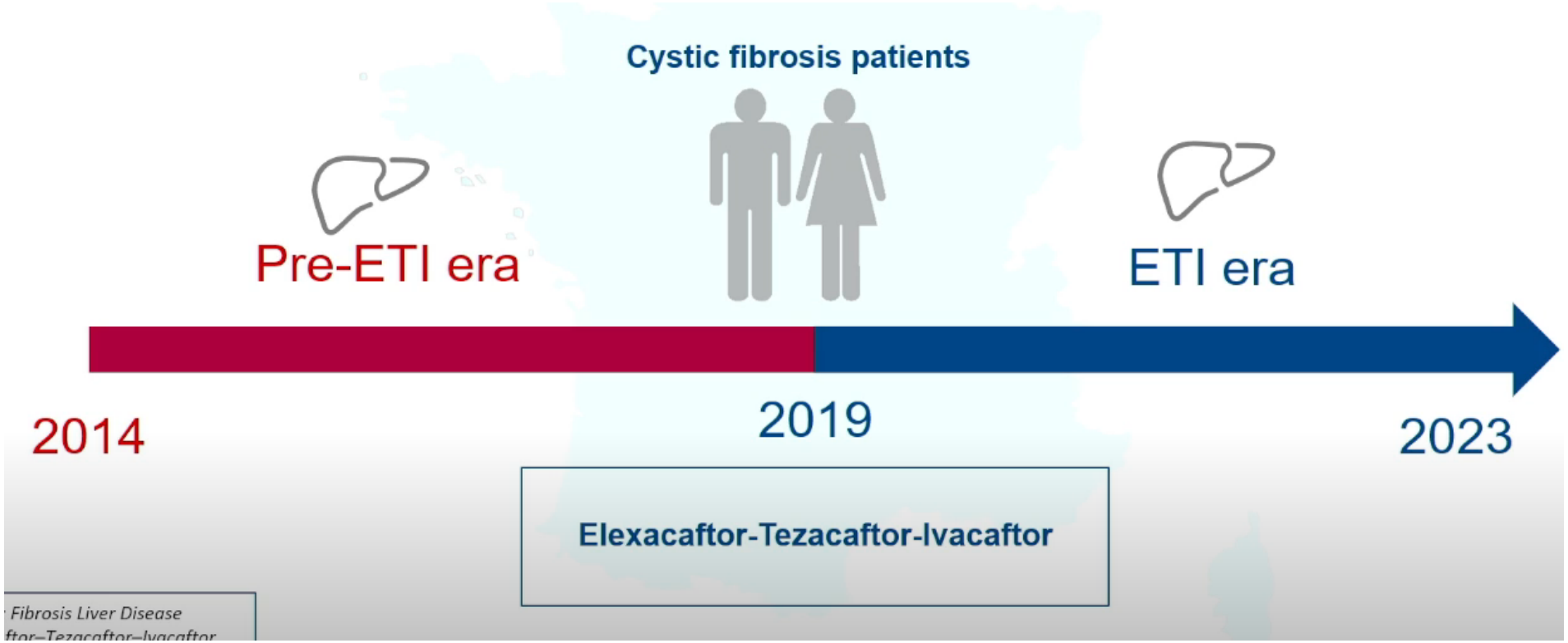
Defects in ‘Biliary HCO3- Umbrella‘ in cholangiopathies?



[Lancet 2018;391:2547]

Medina et al. Hepatology 1997: 25;12; Banales et al. Hepatology 2012;56:687; Reich et al. J Hepatol 2021;75:634

Effect of CFTR modulators on CF-ass. Cholangiopathy
- Elexacaftor-Tazacaftor-Ivacaftor (Tricafta) -



Incidence of progression of hepatobiliary disease: varices, variceal bleeding, decompensated cirrhosis, HCC, LTX, overall survival

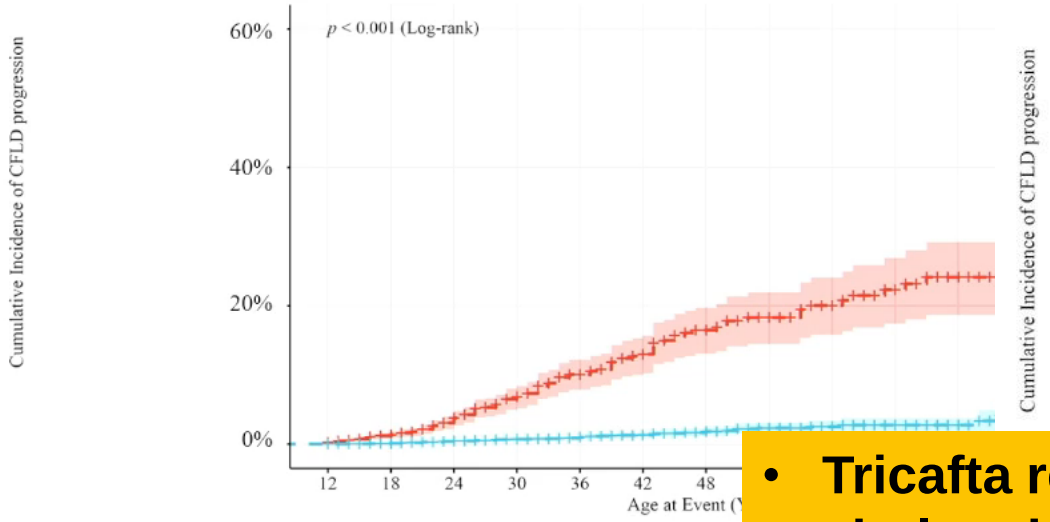
Mouliade C et al., EASL 2025; General Session, GS-008

Effect of CFTR modulators on CF-ass. Cholangiopathy
- Elexacaftor-Tazacaftor-Ivacaftor (Tricafta) -

After propensity score mating

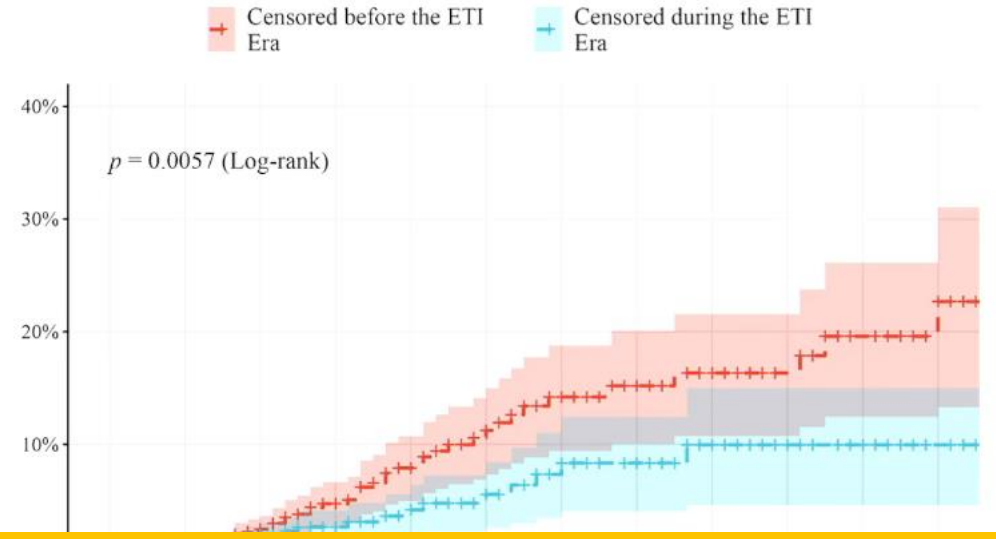
Counts, Incidence Rates (per 1,000 Person-Years), and Adjusted Incidence Rate Ratios for CFLD Progression

Event	Overall	Pre-ETI Era incidence	ETI Era incidence	Adjusted IRR
CFLD progression	191 (3.2)	130 (20.74)	61 (1.14)	0.07 (0.05–0.1



*Adjusted for age, sex, smoking, alcohol use disorders, liver and meta

sis Liver Disease
ezacaftor-Ivacaftor



- **Tricafta reduced incidence of progression of CF-ass. cholangiopathy**
- **Tricafta improved overall survival**
- **Association with improved lung function?**
- **No data on liver tests / NIT**

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Take Home Message – Autoimmune / Cholestasis

- **Linerixibat:** positive **Phase III-Study** GLISTEN in PBC patients with **strong reduction in pruritus** intensity, but high placebo effect.
- **Odevixibat:** positive interim analysis of **Phase II-Study** VINATGE in PBC patients with **strong reduction in pruritus** intensity
- **Norucholic acid (NAC):** positive **Phase III-Study** NUC-5 in **PSC** patients with stablization of disease (**histological** and biochemical)
- **Elafibranor:** positive **Phase II-Study** ELMWOOD in **PSC** patients with biochemical response
- **Inebilizumab:** positive **Phase III-Study in IgG4-RD** with complete **prevention of flares.**
- **Tricafta:** reduced progression of **CF-ass. cholangiopathy** and improved **overall survival.**