

Corporate Presentation

March 2026

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This presentation contains certain forward-looking statements, with respect to GENFIT, including, but not limited to statements about our achievement of key milestones enabling us to receive payments under our license agreement with Ipsen, the successful commercialization of Iqirvo® (elafibranor), our achievement of the necessary objectives to obtain additional payments under the royalty financing agreement signed with HCRx, anticipated timing for study commencement and data readouts, in particular regarding our development programs for G1090N in the prevention and/or treatment of ACLF and for GNS561 in CCA, and development plans for our other pipeline programs, market estimates for the disease areas where we are pursuing R&D and our financial outlook including cash flow and cash burn projections. The use of certain words, such as "believe", "potential", "expect", "target", "may", "will", "should", "could", "if" and similar expressions, is intended to identify forward-looking statements. Although the Company believes its expectations are based on the current expectations and reasonable assumptions of the Company's management, these forward-looking statements are subject to numerous known and unknown risks and uncertainties, which could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking statements. These risks and uncertainties include, among others, the uncertainties inherent in research and development, including in relation to non-clinical and pre-clinical programs, reproducibility of preclinical results, the translation of animal model data to human biology, in relation to safety of drug candidates, cost of, progression of, and results from, our ongoing and planned clinical trials, patient recruitment, review and approvals by regulatory authorities in the United States, Europe and worldwide, of our drug and diagnostic candidates, pricing, approval and commercial success of elafibranor in the relevant jurisdictions, exchange rate fluctuations, and our continued ability to raise capital to fund our development, as well as those risks and uncertainties discussed or identified in the Company's public filings with the AMF, including those listed in Chapter 2 "Risk Factors and Internal Control" of the Company's 2024 Universal Registration Document filed on April 29, 2025 (no. 25-0331) with the Autorité des marchés financiers ("AMF"), which is available on GENFIT's website (www.genfit.fr) and the AMF's website (www.amf.org), and those discussed in the public documents and reports filed with the U.S. Securities and Exchange Commission ("SEC"), including the Company's 2024 Annual Report on Form 20-F filed with the SEC on April 29, 2025 and subsequent filings and reports filed with the AMF or SEC including the Half-Year Business and Financial Report at June 30, 2025 or otherwise made public, by the Company. In addition, even if the results, performance, financial position and liquidity of the Company and the development of the industry in which it operates are consistent with such forward-looking statements, they may not be predictive of results or developments in future periods. These forward-looking statements speak only as of the date of publication of this press release. Other than as required by applicable law, the Company does not undertake any obligation to update or revise any forward-looking information or statements, whether as a result of new information, future events or otherwise.

Strategic Highlights and Value Drivers

1

Iqirvo[®]: Strong commercial sales¹ trajectory in PBC

- Key contributing factor to GENFIT 's robust financial position
- US\$200M threshold exceeded already in the first full year of net sales

2

G1090N in ACLF: Safety profile and anti-inflammatory activity

- A promising investigational candidate for patients with ACLF and acute decompensation
- Solid foundation to progress into Phase 2 POC studies across the ACLF continuum

3

GNS561 in CCA: Safety profile and early antitumor activity

- Recommended Phase 2 doses expected for 1H26, Phase 2 initiation targeted for 2H26
- A potential to expand beyond CCA & to combine with other anticancer agents

4

Other R&D programs

- Continuum ACLF: SRT-015, CLM-022, VS-02-HE, *EViv*²
- UCD/OA: VS-01-HAC

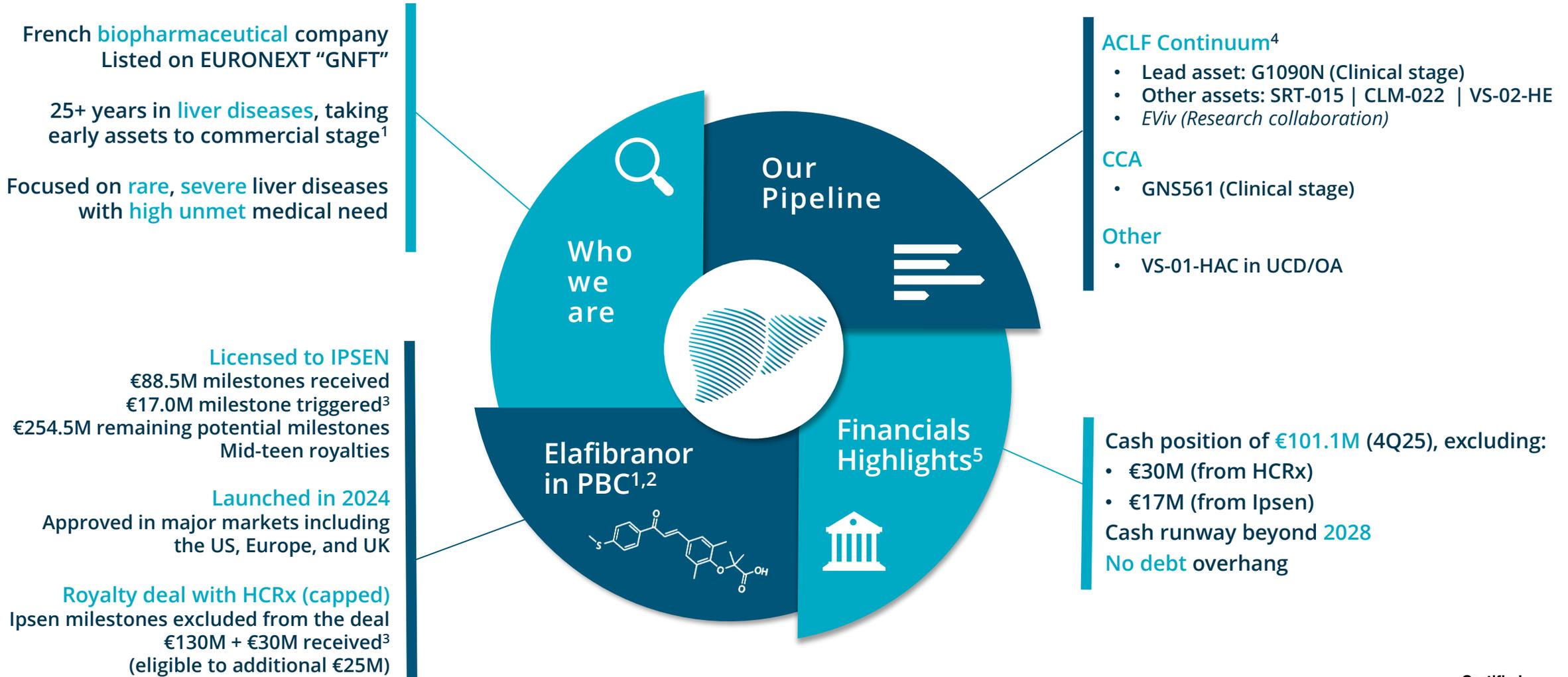
1. Who we are

2. *Iqirvo*[®]

3. *Our lead assets*

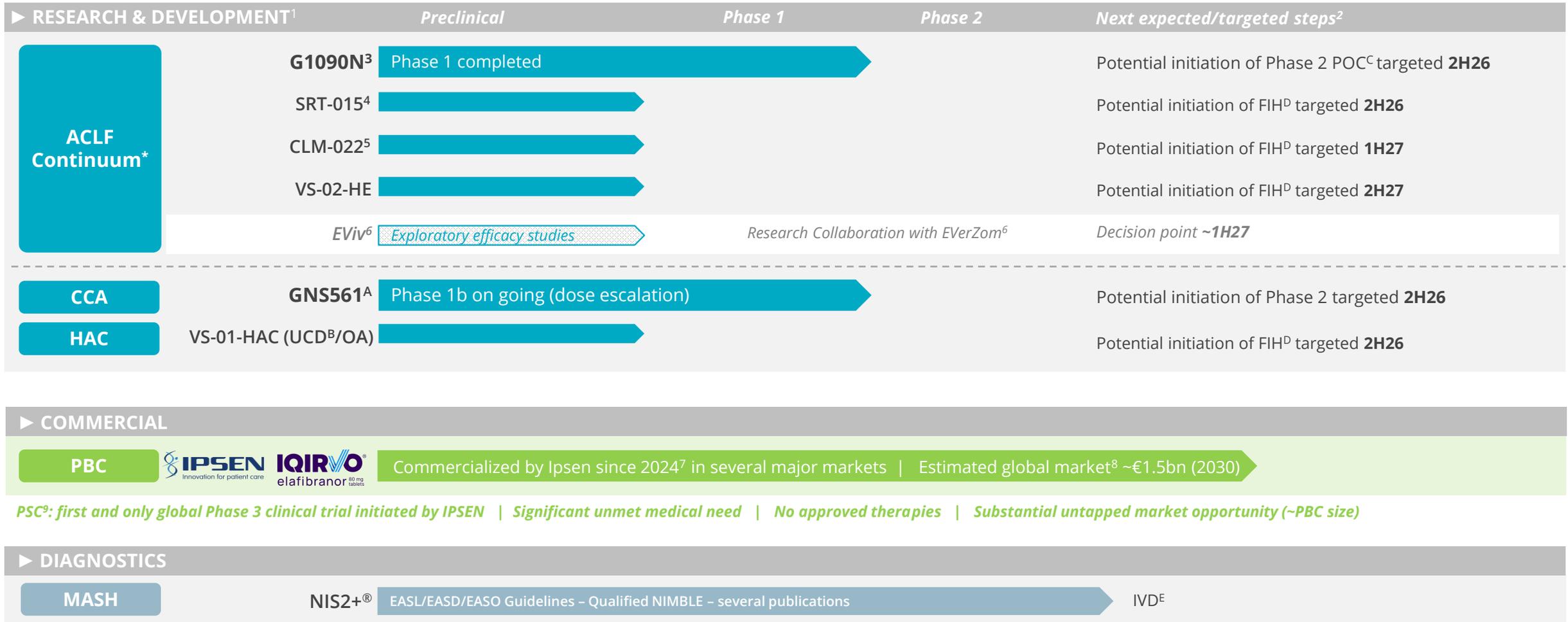
4. *Other programs*

Corporate Highlights



1. In-house from discovery to interim Phase 3 data readout, today commercialized by IPSEN - PR - Ipsen and GENFIT enter into exclusive licensing agreement for elafibranor, a Phase III asset evaluated in Primary Biliary Cholangitis, as part of a long-term global partnership
 2. Closing subject to approval by the 2025 OCEANE bondholders at upcoming bondholders meeting - PR - January 2025, 30 - GENFIT Announces Non-Dilutive Royalty Financing Agreement and Debt Overhang Resolution Plan | PR - GENFIT Reports First Quarter 2025 Financial Information
 3. PR - GENFIT to receive a €26.5 million milestone payment following the approval of pricing and reimbursement of Ipsen's Iqirvo® in Italy
 4. The ACLF pipeline covers a broad spectrum of conditions that patients with ACLF (Acute-on-Chronic Liver Failure) may experience, including Acute Decompensation (AD) or Hepatic Encephalopathy (HE). - PR - Research Collaboration with EverZom to Advance Exosome-based Regenerative Technology in ACLF
 5. PR - GENFIT Reports Third Quarter 2025 Financial Information and Provides a Corporate Update - PR - GENFIT Reports Fourth Quarter 2025 Financial Information and Provides a Corporate Update - This estimation is based on current assumptions and programs and does not include exceptional events. This estimation assumes (i) our expectation to receive significant future commercial milestone revenue pursuant to the license agreement with Ipsen and Ipsen meeting its sales-based thresholds and (ii) drawing down all additional installments under the Royalty Financing agreement with HCRx.

Pipeline



^A Orphan Drug Designation (ODD) FDA

^B Rare Pediatric Disease Designation FDA ; ODD FDA

^C POC = Proof of Concept ^D FIH = First-in-Human Study ^E IVD = In Vitro Diagnostic

* The ACLF pipeline covers a broad spectrum of conditions across a disease continuum including acute decompensation (AD) of liver cirrhosis, hepatic encephalopathy (HE), etc.

1. All drugs under development are investigational compounds that have not been reviewed nor been approved by a regulatory authority in targeted indications

2. Reflects management's anticipated timelines, which are subject to change | based on industry benchmark/average – PR: GENFIT Reports Full-Year 2024 Financial Results and Provides Corporate Update

3. Reformulation of Nitazoxanide (NTZ)

4. In-licensed from Seal Rock Therapeutics

5. In-licensed from Celloram

6. PR - Research Collaboration with EVerZom to Advance Exosome-based Regenerative Technology in ACLF

7. Out-licensed to Ipsen | US-FDA-accelerated-approval n | UE-EMA-approval | UK-MKRA-approval | Canada-approval; Potentially eligible for priority review voucher upon approval by the FDA

8. Global 2L PBC market estimated at ~€1.5bn (2030) – IPSEN - Investor presentation – June 2024

9. IPSEN 2025 Full-Year Financial Results - PR: GENFIT Reports Fourth Quarter 2025 Financial Information and Provides a Corporate Update

ACLF

Prevalence of ACLF
294,000 in 2021, US, EU4, UK
 ~**300,000** by 2036

Growing at Epidemic Rates
 +**26%** between 2006 and 2014¹

16 days
 Average length of **hospital stay**
(vs 7 days for cirrhotic patients)

\$52,000
 Average **cost** per hospitalization
 per patient in US

\$6.4Bn
 Estimated **annual cost burden** in US in 2021

~\$4Bn
 Potential **Market Opportunity**
 for grade 1-2 ACLF in US, EU4, UK by 2030

Oncology

Prevalence of CCA
20,000 to 30,000 for US, EU4, UK

~\$3.1Bn
 Market estimates for CCA
 for US, EU4, UK

Prevalence of iCCA 2L KRAS Mut.
~4,500-6,000 for US, EU4, UK, CN, JP

~€160-200M
 Peak annual sales opportunity in
 iCCA 2L KRAS Mut. for US, EU4, UK, CN, JP

Prevalence of hepatobiliary cancer
~85,000 for US, EU4, UK, CN, JP

Prevalence of liver/GI cancers
~450,000 for US, EU4, UK, CN, JP

UCD/OA

Prevalence
2,000 to 3,000
 for US, EU4, UK

~\$1.1Bn
 Market estimates
 for US, EU4, UK

1. Who we are

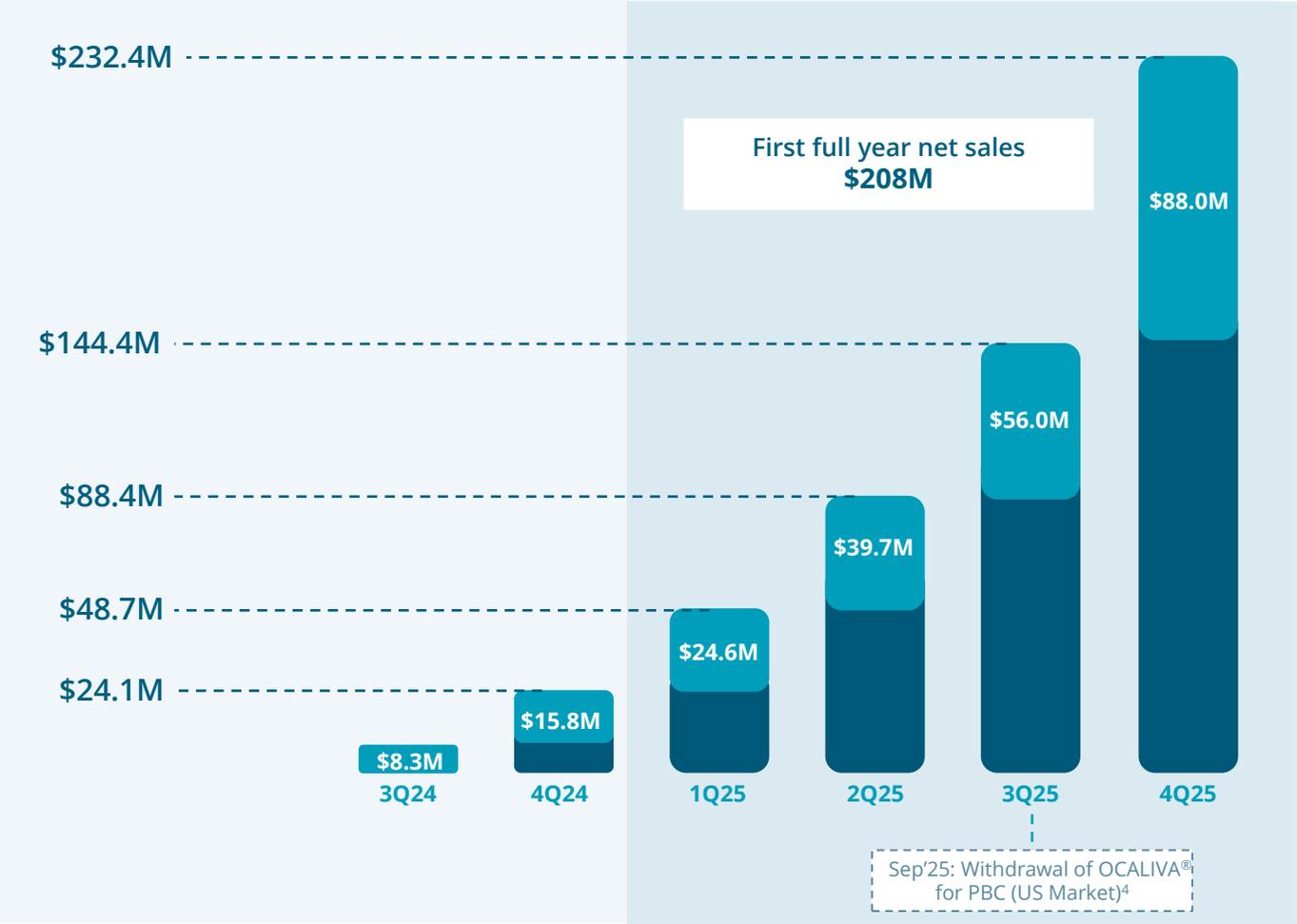
2. Iqirvo[®]

3. Our lead assets

4. Other programs

PBC: Solid Commercial Performance from Ipsen

Iqirvo® sales (global, quarterly) since commercial launch¹



Cumulative milestones payments received or triggered²
€105.5M

Cumulative royalties received³
€24.5M

Sales are reported in U.S. dollars (USD), while payments are made in euros (EUR). Currency conversion is performed in accordance with the contractually agreed exchange rate.
 1. Ipsen sales 1Q2025 | Ipsen 1H2025 | Ipsen sales 3Q25 | Ipsen FY2025
 2. €88.5M received + €17M expected in 1H26. FDA New Drug Application and EMA Marketing Authorization Application accepted | First commercial sale of Iqirvo® in the US | Reimbursement in a 3rd European country – Italy | \$200M threshold in its first full year of net sales
 3. GENFIT Announces Non-Dilutive Royalty Financing Agreement and Debt Overhang Resolution Plan | GENFIT Announces Completion of Non-dilutive Royalty Financing Agreement with HCRx and Results of Repurchase Offer to 2025 OCEANs holders PR: GENFIT Reports Fourth Quarter 2025 Financial Information and Provides a Corporate Update
 4. Intercept Announces Voluntary Withdrawal of OCALIVA® for Primary Biliary Cholangitis (PBC) from the US Market

PSC: On Going Phase 3 Launched by Ipsen

[Click here for details on this trial](#)
(Ipsen's 2025 Full-Year Results)



In February 2026, Ipsen confirmed the initiation of the first and only global Phase 3 clinical trial, addressing a significant unmet medical need, as no approved therapies currently exist for this severe and progressive disease.

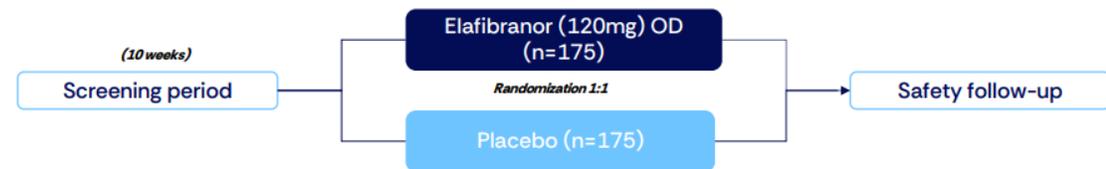
PSC represents a substantial untapped market opportunity, comparable in size to second line PBC.

Should Iqirvo® ultimately receive regulatory approval for this indication, GENFIT would be eligible for additional milestone payments as well as additional double-digit royalties.

Evaluating elafibranor in PSC

ELASCOPE: Phase III program initiated following positive Phase II data

- **Primary endpoint:** efficacy & safety of elafibranor (120mg) vs placebo based on time to first occurrence of clinical outcomes events
- **Secondary endpoints:** change from baseline in ALP, pruritus (WI-NRS) and fatigue (FACIT), alongside other exploratory endpoints



**No approved treatments
~40k patients in the U.S.
Transplant rates – 50% at 10 years**

Trial	Indication	Patients	Design	Primary Endpoint(s)	Status
Iqirvo ELASCOPE Phase III NCT07387549	PSC	350	Placebo or Iqirvo	Event-Free Survival	Not yet recruiting ¹

Acute-on-Chronic Liver Failure (ACLF)

Life-threatening worsening of pre-existing advanced chronic liver disease covering a broad spectrum of conditions across a disease continuum including acute decompensation (AD) of liver cirrhosis and hepatic encephalopathy (HE)

G1090N | SRT-015 | CLM-022 | VS-02-HE | *EViv*¹

Cholangiocarcinoma (CCA)

GNS561

1. *Who we are*
2. *Iqirvo*[®]
3. **Our lead assets**
4. *Other programs*

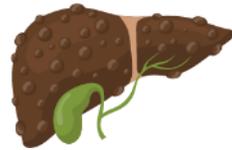
ACLF: A High Unmet Medical Need

CHRONIC PHASE

Chronic Liver Disease

Cirrhosis

= UNDERLYING CONDITION

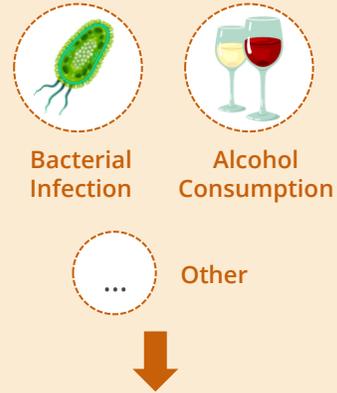


The liver is scarred but **still functioning** and people can live for **years** in this state **without noticeable symptoms**

ACUTE PHASE

Acute
Decompensation

= PRECIPITANT



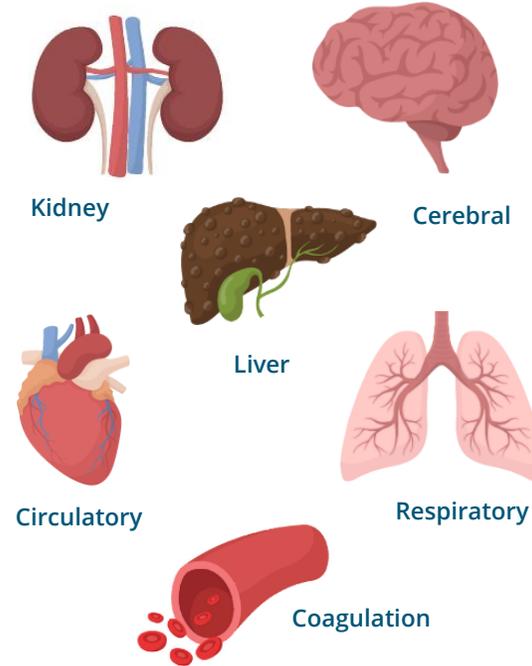
Liver function deteriorates and **serious complications** develop

- Ascites
- Hepatic encephalopathy
- Gastrointestinal bleeding

Urgent Hospitalisation

ACLF

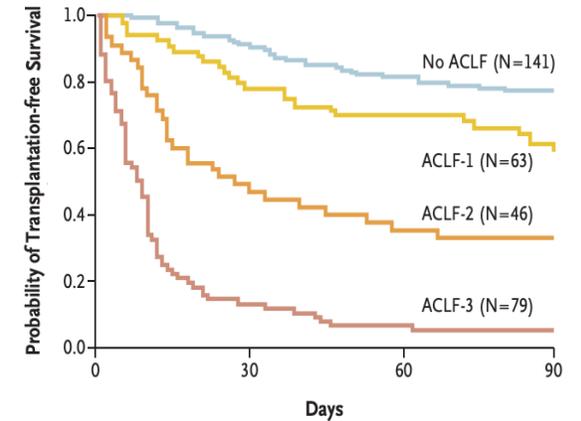
≥ 1 ORGAN DYSFUNCTIONS/FAILURES



Hospitalisation / Intensive Care Unit

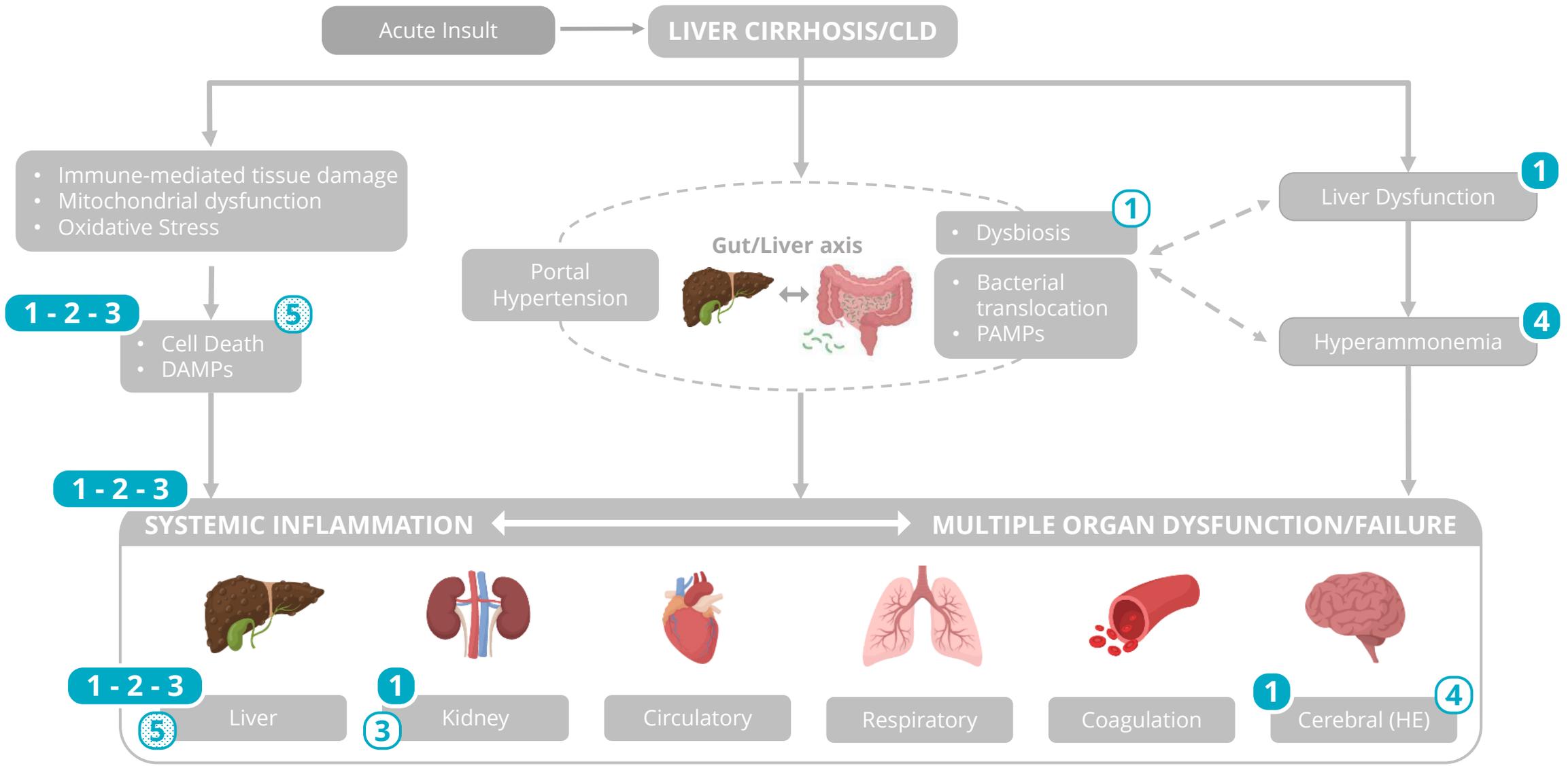
23-74% mortality at 28 days

▶ NO APPROVED DRUGS



Death

Our approach in ACLF: Targeting Multiple Pathways



ACLF: R&D Programs

We are developing a **diversified pipeline based on pathophysiology** to better address the **complexities** of the condition and improve **treatment outcomes**



G1090N

Oral

Anti-inflammatory and anti-bacterial

To reduce **cell death**, (systemic) **inflammation**, and **bacterial translocation**

Potential initiation of Phase 2 Proof-of-Concept targeted 2H26



SRT-015

Injectable

ASK1 inhibitor

To inhibit **apoptosis**, **inflammation** (liver-centric), and **fibrosis**

Potential initiation of First-in-human targeted 2H26

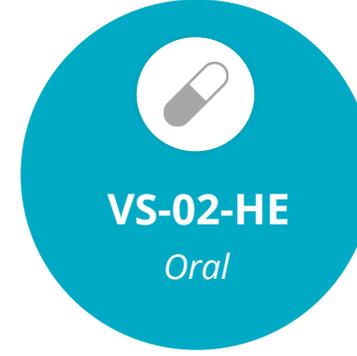


CLM-022

NLRP3 inflammasome inhibitor

To inhibit **inflammation** (systemic), and **cell death** (pyroptosis)

Potential initiation of First-in-human targeted 1H27



VS-02-HE

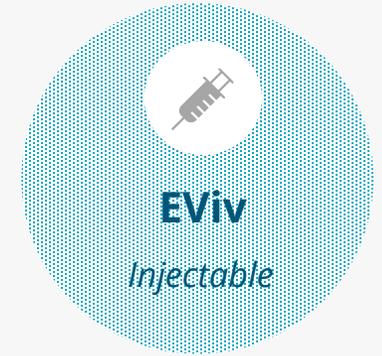
Oral

Urease inhibitor

To reduce **hyperammonemia**, stabilize blood ammonia and **prevent HE**

Potential initiation of First-in-human targeted 2H27

Research Collaboration with EVerZom¹



EViv

Injectable

Exosome Technology

Novel approach to **regenerative therapies**

Decision point ~1H27

Find details on these preclinical programs in section 4 – Other programs - slide 24

Reflects management's anticipated times, which are subject to change

1. PR EVerZom

Our Lead Asset in ACLF: G1090N

A Strong Scientific Rationale

G1090N
Anti-inflammatory



Findings to date:

- ✓ Decreases systemic inflammation in animal models, including in ACLF models
- ✓ Protects liver, kidney & brain in rat models of ACLF by decreasing tissue damage
- ✓ Protects mice from mortality in a model of sepsis induced by gut leakage (AASLD 2024 poster)
- ✓ Prevents cell death via anti-apoptotic and anti-necroptotic effects (EASL 2024 poster)
- ✓ Reduces PAMPs-induced inflammation (AASLD 2024 poster)

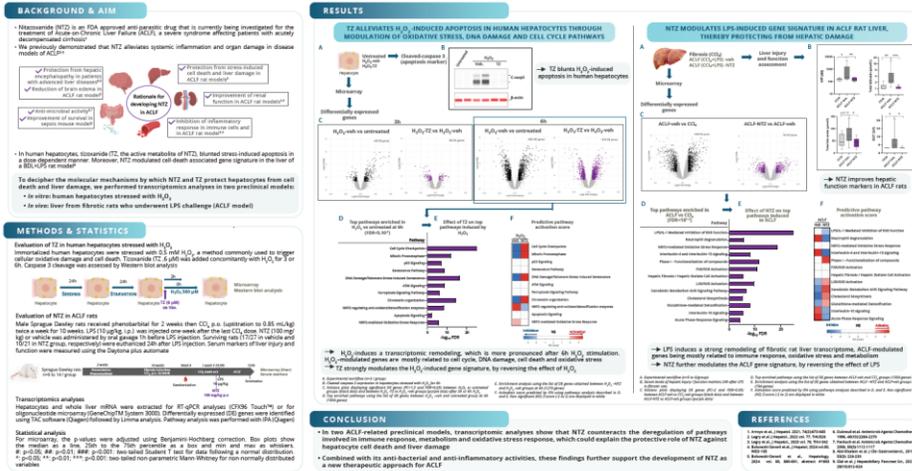
EASL 2025

NTZ ALLEVIATES STRESS-INDUCED HEPATOCYTE CELL DEATH THROUGH MODULATION OF OXIDATIVE STRESS AND DNA DAMAGE SIGNALING PATHWAYS IN ACLF MODELS

Marie Bobowski-Gerard¹, Nicolas Stramkovic Valentin¹, Sylvie Delacrique¹, Simon Debaecker¹, Nina S'Ervenste¹, Philippe Delattelle¹, Saïna Sayah Jeanne¹, Dean Hum¹, Vanessa Legry¹, Jérôme Eeckhoutte¹, Joan Clariá¹, Bart Staels¹

¹GENFIT SA, Louvain-la-Neuve, Belgium; ²CHU Lille and Institut Pasteur de Lille, U1011 EDD, Lille, France; ³Hospital Clinic IDIBAPS, Universitat de Barcelona, European Foundation for the Study of Chronic Liver Failure (EFCLF), Spain

THU-166



- ▶ TZ blunts the apoptotic response in hepatocytes
- ▶ NTZ counteracts the dysregulation of pathways involved in immune response, metabolism and oxidative stress in the liver of ACLF rats, in relation with its in vitro protective activity in hepatocytes

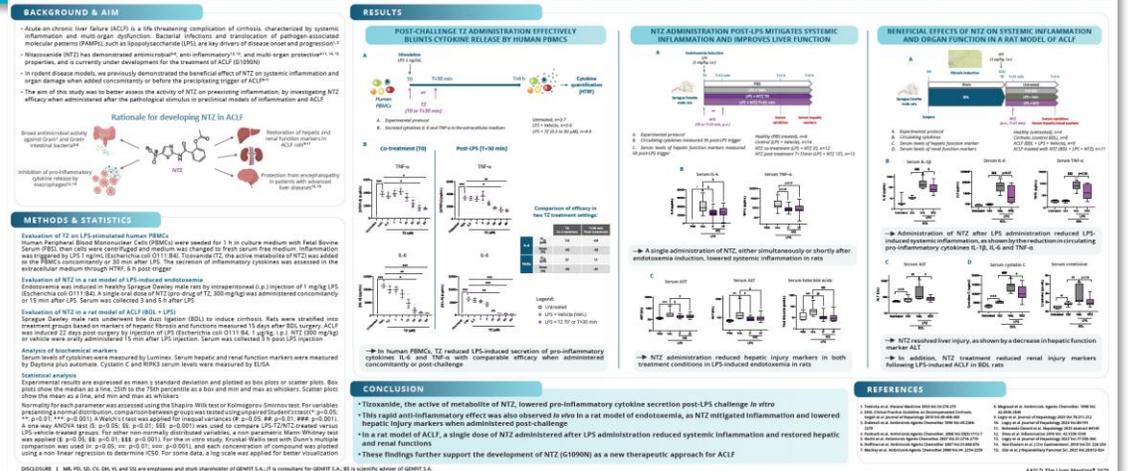
AASLD 2025

EFFICACY OF NITAZOXANIDE (NTZ) ON SYSTEMIC INFLAMMATION AND ORGAN FUNCTION IN DISEASE MODELS OF ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) WHEN ADMINISTERED POST-ACLF TRIGGER

Marie Bobowski-Gerard¹, Philippe Delattelle¹, Simon Debaecker¹, Camille Vanbèsien¹, Dean Hum¹, Vanessa Legry¹, Bart Staels¹, Jonel Trebicka¹, Saïna Sayah Jeanne¹

¹GENFIT SA, Louvain-la-Neuve, Belgium; ²CHU Lille and Institut Pasteur de Lille, U1011 EDD, Lille, France; ³Hospital de la Genética Universitat València, University Hospital Miquel Marqués, Valencia, Spain

4165



- ▶ TZ lowers pro-inflammatory cytokine secretion post-LPS challenge in PBMCs
- ▶ In a rat model of ACLF, a single dose of NTZ administered after LPS administration reduces systemic inflammation and restores hepatic and renal functions

▶ ▶ Combined with its anti-bacterial properties, all these findings further support the development of NTZ as a new therapeutic approach for ACLF ◀ ◀

G1090N: an investigational drug

G1090N: Reformulation of Nitazoxanide (NTZ); Tizoxanide (TZ): Active metabolite of NTZ | PAMPs = Pathogen-Associated Molecular Patterns

G1090N
Anti-inflammatory



Oral

Key inclusion criteria

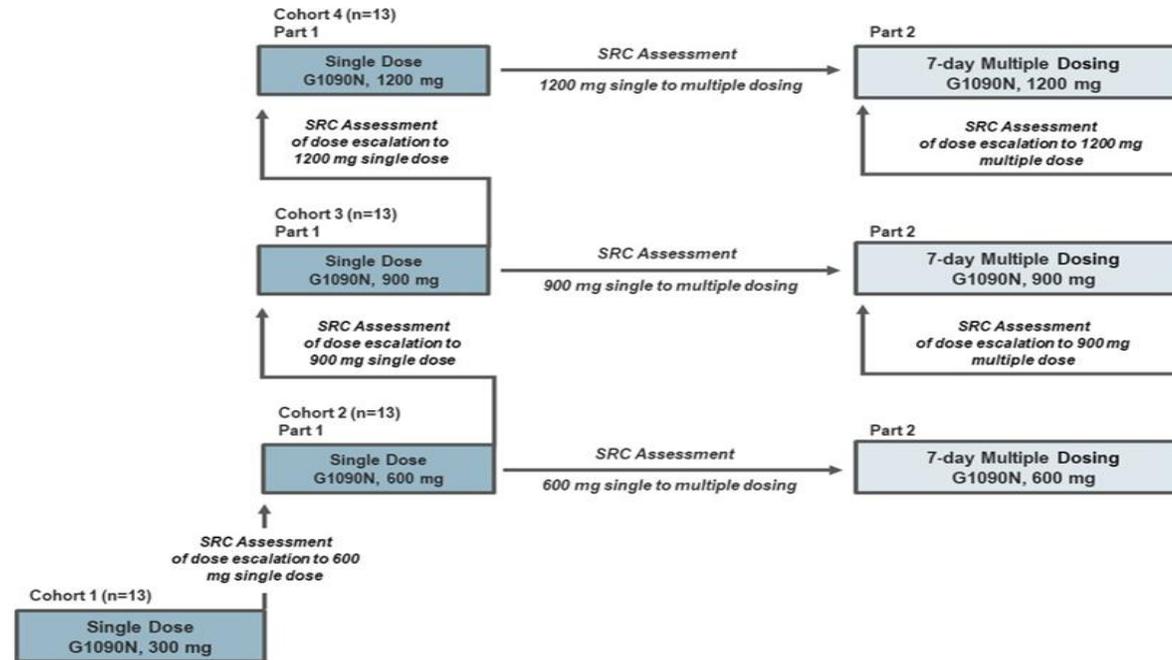
- **Healthy** Volunteers
- Normal liver and renal function

Key exclusion criteria

- **Significant medical history** or recent illness

N_{TOTAL}
=
52
PTS

A Phase 1 open-label study to assess pharmacokinetics, safety, and tolerability of G1090N in healthy subjects



n = number of subjects; PK = pharmacokinetic(s); SRC = Safety Review Committee.

Investigational drug G1090N is a promising therapy in ACLF due to:

- **major metabolite tizaxozanide targets major pathophysiological pathways** relevant in decompensated liver cirrhosis and ACLF
- shows **impact on systemic and tissue inflammation, cell death, apoptosis**

♦ **Primary endpoint:**
Pharmacokinetic parameters following single and multiple ascending dose administration

Secondary endpoints:
Safety and tolerability following single and multiple ascending dose administration

G1090N's Potential Recently Confirmed in the Clinic

G1090N

Anti-inflammatory



Oral



The safety profile observed in Phase 1 and the consistent biological activity evidenced in ex vivo assays represent a meaningful step in development. These findings position G1090N as a promising candidate for patients with AD and for patients with ACLF, a life-threatening condition with no approved therapies and significant unmet medical need. We are eager to see more patient data as the program moves forward, to confirm G1090N's safety and strengthen the case for its activity in patients with organ failure

Dr. Jacqueline O'Leary

MD at the UT Southwestern Medical Center, Dallas, TX (USA)



PRESS RELEASE

January 6, 2026

GENFIT: Favorable Phase 1 Safety Profile and Strong Anti-Inflammatory Activity for ACLF Lead Asset G1090N

- **Phase 1 results confirm investigational drug-candidate G1090N has a favorable safety and tolerability profile, supporting further clinical evaluation**
- **Compelling anti-inflammatory activity of G1090N was evidenced through functional ex vivo assays on blood samples from study participants and cirrhotic donors, showing inhibition of pro-inflammatory pathway**
- **Findings provide a solid foundation for advancing G1090N into Phase 2 proof-of-concept studies across the ACLF continuum**

Acute-On-Chronic Liver Failure (ACLF)

G1090N | SRT-015 | CLM-022 | VS-02-HE | EViv

Cholangiocarcinoma (CCA)

Malignancy of bile ducts. Without treatment <20% of patients survive 5 years from diagnosis¹. KRAS mutation is not addressed by current treatments.

GNS561

1. *Who we are*
2. *Iqirvo*[®]
3. **Our lead assets**
4. *Other programs*

CCA with KRAS Mutation: A High Unmet Medical Need

Rare and aggressive liver malignancy that develops in the bile ducts

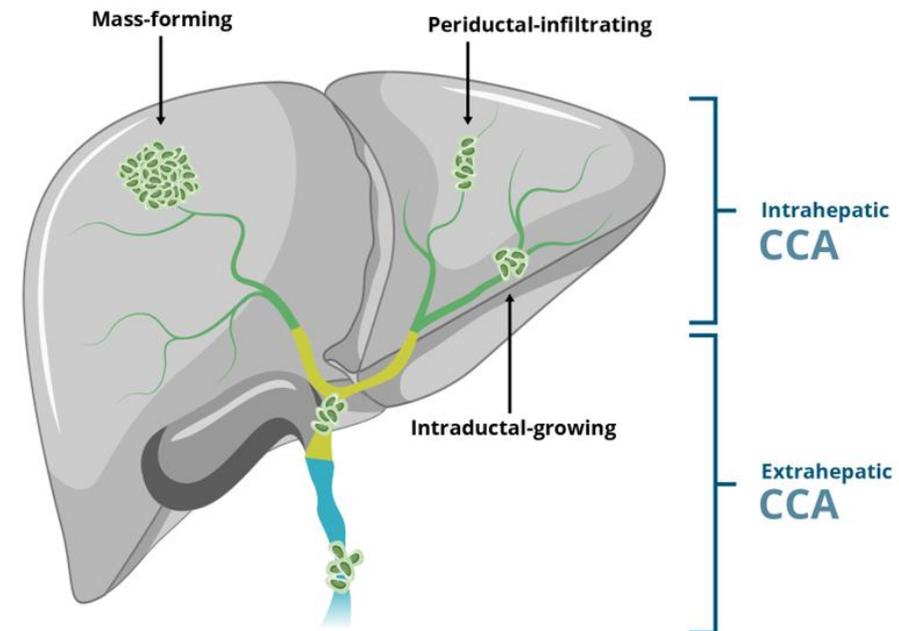
- As the cancer grows, it can **block the bile ducts** and lead to damage to the liver and other organs
- Without treatment **<20% of patients survive 5 years** from diagnosis¹

Unmet needs

- **Surgery** = primary treatment of CCA but **only 30%** of patients present with resectable tumors²
- First line and second line therapy = **survival is limited**²
- Rapid progression of the tumor until the **patient's death = 10–12 months** on current SoC³

~30% of patients with CCA harbor **KRAS mutations**⁴

- **one of the most common genes that might be mutated** or amplified resulting in the overactivation of some of these pathways⁵
- associate with **shorter survival**⁶
- KRAS mutation is **not addressed by current treatments** = **unmet needs** remain **very high** for these patients



Drawing: Adapted from Nature Reviews Gastroenterology & Hepatology volume 17, p. 557–588;

1. Lamarca et al. 2021 | 2. Jesus M. Banales et al. 2020, Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nature Reviews Gastroenterology & Hepatology volume 17, p. 557–588;

3. Banales et al., Cholangiocarcinoma 2026: status quo, unmet needs and priorities, Nat. Rev. Gastroenterol. Hepatol., 2025 | 4. Banales et al., Cholangiocarcinoma 2020: the next horizon in mechanisms and management, Nat Rev Gastroenterol Hepatol, 2020 | 5.

Fitzwalter BE, Thorburn A. Recent insights into cell death and autophagy. FEBS J. 2015;282:4279–88. | 6. Signaling pathways involved in cholangiocarcinoma development and progression. Nature Reviews Gastroenterology & Hepatology volume 17, pages 557–588 (2020)

Rationale for Combining Anticancer Therapies and investigational drug GNS561, an Autophagy Inhibitor

GNS561
PPT1 inhibitor in
combination with
a MEK inhibitor



Oral

#1 Anticancer Therapies

Chemotherapeutic agents

MAP Kinase pathway targeted therapies

Immune checkpoint inhibitors
(anti-PD-1/PD-L1)

#2 GNS561

(Autophagy inhibitor)

By **entering the lysosomes and inhibiting PPT1**, GNS561 acts to block late-stage autophagy, which can lead to tumor cell death

Beneficial anti-cancer effects

- ▼ Cancer **cell survival**
- ▼ Tumor **growth**

Autophagy: tumor cell survival mechanism

- ▲ Cancer **cell survival**
- ▲ Tumor **growth**
- ▲ **Resistance** to treatment

Blocks cancer cell survival



Enabling simultaneous targeting of tumor growth and adaptive mechanisms of cancer cells

GNS561
PPT1 inhibitor in
combination with
a MEK inhibitor



Oral

A Phase 1b/2a open-label, multicenter study to evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of GNS561 in combination with trametinib in advanced KRAS mutated CCA after failure of standard-of-care first line therapy

✓ Key inclusion criteria

- Patients with **KRAS mutated CCA** who have **failed 1st line** treatment therapy

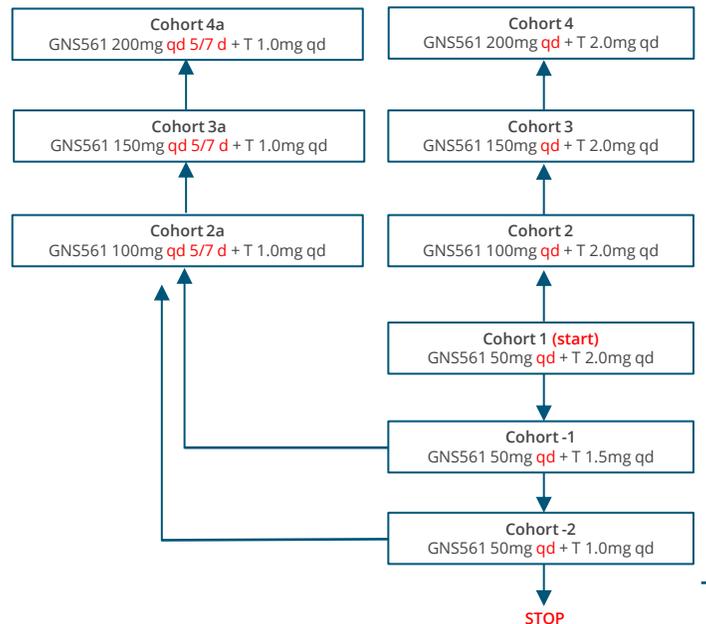
⊘ Key exclusion criteria

- **Prior** MEK or autophagy inhibitor **treatment**
- Uncontrolled **significant illness**
- Active **HBV/HCV**
- Hypersensitivity to **quinoline** derivatives / study drugs

Ongoing recruitment

N_{TOTAL}
=
74
PTS

PHASE 1b Dose finding



PHASE 2a POC Single arm N=50

Simon 2-stage



RP2DC

♦ **Primary endpoint:**
Efficacy - objective response rate

Secondary endpoints:
Efficacy - progression free survival ; Pharmacokinetics ; Pharmacodynamics ; Safety and tolerability

Phase 1b: Highly Encouraging Early Data

GNS561

PPT1 inhibitor in combination with a MEK inhibitor



Oral



Advanced KRAS-mutated cholangiocarcinoma remains a formidable clinical challenge, and the emerging activity seen in this initial study is encouraging. Because MEK inhibition alone has historically shown limited efficacy in this setting, the early signs of benefit with dual targeting of autophagy and MAPK signaling provide meaningful rationale for continued evaluation of this combination strategy

Dr. Mark Yarchoan

Associate Professor of Oncology at John Hopkins Medicine (Baltimore, MD, USA)
Principal investigator of the program



December 10, 2025

GENFIT: GNS561 Shows Promising Antitumor Activity in Combination Therapy

- **Highly encouraging early data from the ongoing Phase 1b study evaluating investigational drug GNS561 with a MEK inhibitor (MEKi) in KRAS mutated cholangiocarcinoma (CCA), positioning this novel combination as a potential new therapeutic approach for difficult-to-treat cancers:**
 - **No dose limiting toxicity reached to date, enabling recruitment of a third patient cohort**
 - **GNS561 and MEKi combination demonstrated disease stabilization in all evaluable patients with evidence of tumor shrinkage in a subset of patients, warranting further investigation**
 - **Recommended Phase 2 doses expected for 1H26**

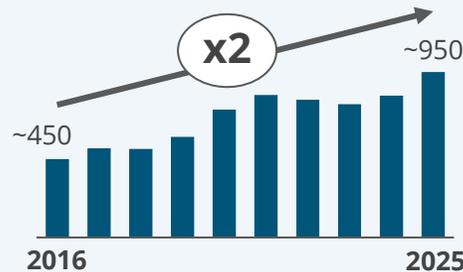
Moving Forward



- **Phase 1b dose escalation** will continue as planned to confirm activity signal
- **1H26** - Completion expected results will be used to establish recommended Phase 2 combination doses
- **2H26** - targeted Phase 2 initiation

Beyond CCA: a potential to explore the benefit of autophagy inhibition in other cancers

The number of **publications** implicating **autophagy** in **cancer treatment resistance** has **increased by ~10% each year** over the past 10 years^{1,2}



Rationale to expand GNS561 program into GI/liver tumors where:

- ✓ Autophagy plays a key role in resistance
- ✓ GNS561 has shown to accumulate the most
- ✓ There is a high incidence of MAPK alternations
- ✓ There is potential to combine with SoC (ICI, small molecules)



Hepatocellular carcinoma (HCC)



MSS colorectal cancer (CRC)



Pancreatic ductal adenocarcinoma (PDAC)



Gastro-pancreatic NET (GEP-NET)

~450,000 patients (in US, EU4+UK, and JP/CN)¹

Beyond MEKi: a potential to explore combinations with other anticancer agents

Anti-PD-1 | **RAFi**

Ex: Evidence already exists in HCC for GNS561 in combination with anti-PD-1 in a mouse model³

Acute-on-Chronic Liver Failure (ACLF)

Life-threatening worsening of pre-existing advanced chronic liver disease covering a broad spectrum of conditions across a disease continuum including acute decompensation (AD) of liver cirrhosis and hepatic encephalopathy (HE)

G1090N | **SRT-015** | **CLM-022** | **VS-02-HE** | **EViv¹**

Urea Cycle Disorders (UCD) & Organic Acidemias (OA)
VS-01-HAC

1. *Who we are*
2. *Iqirvo[®]*
3. *Our lead assets*
4. **Other programs**

SRT-015

SRT-015 ASK1 inhibitor



Findings to date:

- ✓ Decreases systemic inflammation in animal models, including in an ACLF model
- ✓ Protects mice from mortality in a model of sepsis induced by gut leakage
- ✓ Demonstrates efficacy when injected in mice with acute liver failure (AASLD24 poster)
- ✓ Shows anti-inflammatory and immuno-modulatory activities on human immune cells

EASL 2025



EFFICACY OF THE APOPTOSIS-SIGNAL-REGULATING KINASE 1 (ASK1) INHIBITOR SRT-015 IN *IN VIVO* AND *IN VITRO* PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPs)-INDUCED DISEASE MODELS

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¹INSITM SA, Genfit, France; ²INSITM SA, Genfit, Spain; ³INSITM SA, Genfit, Spain; ⁴INSITM SA, Genfit, Spain

THU-187

BACKGROUND & AIM

- Patients with liver cirrhosis have an increased risk of infection and are at high risk of death from sepsis. To reverse immune dysfunction, impaired liver function and altered gut microbiota and permeability.
- In these patients, immune dysfunction also results in a hyperinflammatory condition in the systemic circulation, as shown by elevation of circulating pro-inflammatory cytokines such as TNF α , IL-6, IL-1 β , IL-8, IL-10, IL-17, IL-22, IL-23, IL-27, IL-31, IL-33, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, IL-41, IL-42, IL-43, IL-44, IL-45, IL-46, IL-47, IL-48, IL-49, IL-50, IL-51, IL-52, IL-53, IL-54, IL-55, IL-56, IL-57, IL-58, IL-59, IL-60, IL-61, IL-62, IL-63, IL-64, IL-65, IL-66, IL-67, IL-68, IL-69, IL-70, IL-71, IL-72, IL-73, IL-74, IL-75, IL-76, IL-77, IL-78, IL-79, IL-80, IL-81, IL-82, IL-83, IL-84, IL-85, IL-86, IL-87, IL-88, IL-89, IL-90, IL-91, IL-92, IL-93, IL-94, IL-95, IL-96, IL-97, IL-98, IL-99, IL-100, IL-101, IL-102, IL-103, IL-104, IL-105, IL-106, IL-107, IL-108, IL-109, IL-110, IL-111, IL-112, IL-113, IL-114, IL-115, IL-116, IL-117, IL-118, IL-119, IL-120, IL-121, IL-122, IL-123, IL-124, IL-125, IL-126, IL-127, IL-128, IL-129, IL-130, IL-131, IL-132, IL-133, IL-134, 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RESULTS

SRT-015 IMPROVES SURVIVAL OF MICE WITH SEPSIS

SRT-015 REDUCES PRO-INFLAMMATORY CYTOKINE RELEASE INDUCED BY TLR ACTIVATION OF HUMAN WHOLE BLOOD

DOSE RESPONSE OF SRT-015 IN HUMAN WHOLE BLOOD AFTER TLR ACTIVATION

Table 1: Description of the human whole blood assays

Table 2: Effect of TLR agonists on the ex vivo assays

STATISTICS

CONCLUSION

REFERENCES

AASLD 2025



ASK1 INHIBITOR SRT-015 REDUCES SYSTEMIC INFLAMMATION WHILE PROMOTING IMMUNE HOST DEFENSE MECHANISMS IN PRECLINICAL *IN VITRO* AND *IN VIVO* MODELS RELATED TO ACLF

Vanessa Legry¹, Berta Romero-Gimaldos¹, Cristina López-Vicario¹, Bryan J. Contreras^{1,2}, Belén Sánchez-Rodríguez^{1,2}, Ophélie Hanot¹, Manon Clarisse¹, Simon Debacquer¹, Alba Díaz¹, Carla Montironi¹, Richard Moreau¹, Dean Hum¹, Bart Staels¹, Sakina Sayah Jeanne¹, Joan Clària^{1,2,3,4}

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BACKGROUND & AIM

- Acute on Chronic Liver Failure (ACLF) is characterized by multiple organ failures and high mortality. ACLF is closely associated with the presence of systemic inflammatory and impaired immune defense responses against pathogens, such as decreased neutrophil degradation and phagocytosis, as well as oxidative stress.
- Apoptosis signal-regulating kinase 1 (ASK1) is a key mediator of the inflammatory response, activated by reactive oxygen species (ROS) and other recognition of pathogen-associated molecular patterns (PAMPs). Its phosphorylation results in activation of p38 and p53 that regulate cell death and immune response.
- SRT-015 is a novel investigational ASK1 inhibitor. Preclinical studies have shown its anti-apoptotic and anti-inflammatory activities *in vitro*, as well as its ability to reduce liver injury and counteract systemic inflammation in acute liver failure models and improve survival in sepsis mice.
- The aim of this study was to investigate the effects of SRT-015 on systemic inflammation in a new model of ACLF that closely mimics the human condition, as well as on human leukocyte functions *in vitro*.

RESULTS

SRT-015 ALLEVIATES SYSTEMIC INFLAMMATION IN ACLF MICE

SRT-015 REDUCES LPS-INDUCED PRO-INFLAMMATORY CYTOKINE PRODUCTION FROM HUMAN BLOOD IMMUNE CELLS

EFFECT OF SRT-015 ON NEUTROPHIL FUNCTIONS

Table 1: Effect of SRT-015 on human whole blood cytokines

Table 2: Effect of SRT-015 on neutrophil functions

CONCLUSION

REFERENCES

- ▶ SRT-015 dose-dependently inhibits TNF- α , IL-6 and IL-1 β secretion in response to TLR2, TLR4 and TLR5 activation in human whole blood assay
- ▶ Improves survival in septic mice, one potential mechanism being through the regulation of innate immune response

- ▶ Improves the antibacterial function of neutrophils
- ▶ Decreases systemic inflammation in a preclinical model of ACLF

▶ ▶ These data support the development of investigational drug SRT-015 for the treatment of advanced liver disease and ACLF ◀ ◀

Next Step: Potential First-in-human trial could be initiated as early as 2H26



CLM-022 NLRP3 inflammasome inhibitor



Findings to date:

- ✓ Protects the liver in pre-clinical ALF models
- ✓ Protects mice from mortality induced by gut leakage-induced sepsis
- ✓ Dose-dependently inhibits IL-1 β secretion (AASLD 2024 poster)
- ✓ Shows potent inhibition of priming and activation steps of NLRP3 inflammasome

EASL
2025

CLM-022*, A DUAL INHIBITOR OF PRIMING AND ACTIVATION STEPS OF NLRP3 INFLAMMASOME, AS A POTENTIAL TREATMENT FOR ACUTE AND CHRONIC INFLAMMATORY LATE-STAGE LIVER DISEASES
Hana El Khalti*, Alexandra Caron*, Eudine Delecroix*, Victor Lanay*, Maryse Malysiak*, Valérie Daix*, Simon Debaecker*, Guillaume Vidal*, Dean Hum*, Bart Staels*, Sakina Sayah Jeanne*

BACKGROUND & AIM

- Inflammation is a common element in the pathogenesis of most chronic liver diseases leading to fibrosis, cirrhosis and liver failure. Due to the close connection with the intestine, the gut microbiota, the gut barrier, and the gut-derived pathogens (PAMPs), which activate resident immune cells, in addition to the hepatitis or other-related PAMPs, hepatic immune response and also contribute to liver disease progression (PAMPs), which are released from injured parenchyma and non-parenchymal cells (Kumar 2017).
- Inflammation is characterized by activation of innate immune cells, production of pro-inflammatory cytokines, and generation of reactive oxygen and nitrogen species. These events are regulated by inflammasomes which are composed of multiprotein complexes expressed in both parenchymal and non-parenchymal cells (Kumar 2017). NLRP3 inflammasome activation leads to the secretion of IL-1 β and IL-18 (Decker 2016).

RESULTS

CLM-022 INHIBITS THE NLRP3 PRIMING IN LPS-INDUCED PBMCs

CLM-022 IMPROVES HEPATIC FUNCTION IN APAP-INDUCED LIVER INJURY

CLM-022 INHIBITS PYROPTOSIS INDUCED BY INFLAMMASOME ACTIVATION IN WT BUT NOT IN NLRP3-KO THP-1 CELLS

CLM-022 IMPROVES HEPATIC FUNCTION AND REDUCES NLRP3 PROTEIN EXPRESSION IN APAP-INDUCED LIVER INJURY

CLM-022 INHIBITS SYSTEMIC INFLAMMATION AND PROTECTS THE LIVER IN RATS

CONCLUSION

REFERENCES

METHODS & STATISTICS

IN VIVO STUDIES

IN VITRO STUDIES

CONCLUSIONS

REFERENCES

AASLD
2025

EFFICACY OF CLM-022*, AN INHIBITOR OF THE NLRP3 INFLAMMASOME, IN IN VIVO AND IN VITRO PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPs)-INDUCED DISEASE MODELS
Guillaume Vidal*, Hana El Khalti*, Alexandra Caron*, Maryse Malysiak*, Valérie Daix*, Simon Debaecker*, Manon Clarisse*, Dean Hum*, Bart Staels*, Sakina Sayah Jeanne*

BACKGROUND & AIM

- Patients with liver cirrhosis are characterized by impaired gut barrier, more immune dysregulation, and increased gut permeability. These alterations drive the progression of gut-derived pathogen-associated molecular patterns (PAMPs) and immune danger-associated molecular patterns (DAMPs), which stimulate immune responses via receptors (TLRs and NLRs).
- Immune dysregulation and gut barrier dysfunction lead to a dysregulated inflammatory response and increased gut permeability. These alterations drive the progression of gut-derived pathogen-associated molecular patterns (PAMPs) and immune danger-associated molecular patterns (DAMPs), which stimulate immune responses via receptors (TLRs and NLRs). These events play a key role in the transition from acute inflammation to liver disease in chronic liver injury and cirrhosis. NLRP3 inflammasome activation is also highly susceptible to sepsis.
- CLM-022, an oral inhibitor of inflammasome priming and activation, has demonstrated hepatoprotective and immunomodulatory effects in pre-clinical models of acute liver injury and cirrhosis, as presented at the 2025 EASL International Liver Congress*

RESULTS

CLM-022 IMPROVES SURVIVAL IN A MOUSE MODEL OF CLP-INDUCED SEPSIS

CLM-022 REDUCES PRO-INFLAMMATORY CYTOKINE RELEASE IN HUMAN WHOLE BLOOD ASSAY

CONCLUSION

REFERENCES

METHODS

WHOLE BLOOD ASSAYS

IN VITRO STUDIES

IN VIVO STUDIES

CONCLUSIONS

REFERENCES

- ▶ CLM-022 inhibits NLRP3 inflammasome priming of LPS-induced human PBMCs
- ▶ Inhibition of IL-1 β production and pyroptosis by CLM-022 is lost in NLRP3-KO macrophages
- ▶ Oral CLM-022 provides hepatic protection in a model of acute liver injury in mice
- ▶ IV CLM-022 decreases cytokines levels and improves hepatic parameters in a rat endotoxemia model

- ▶ Improves survival in a mouse model of CLP-induced sepsis (40% vs 15% at day 7)
- ▶ Reduces the secretion of key pro-inflammatory cytokines in human whole blood assays at similar nanomolar IC50 values when administered either concomitantly with or following LPS stimulation

▶ ▶ These data support investigational drug CLM-022 as a potential treatment for inflammatory acute late-stage liver diseases ◀ ◀

Next Step: Pending further positive developments, potential First-in-human trial could be initiated in 1H27

VS-02-HE

VS-02-HE
Urease inhibitor

Hepatic Encephalopathy



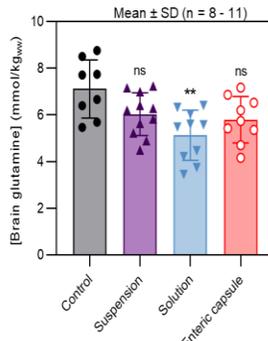
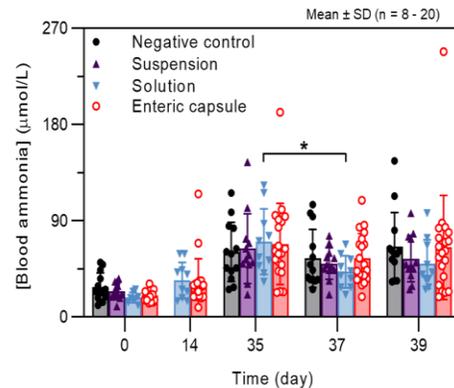
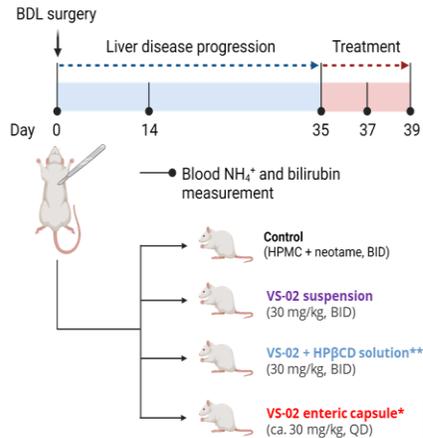
Oral

About Hepatic Encephalopathy (HE)

- One of the **most common complications of liver cirrhosis and ACLF**
- A **central nervous system disorder** representing a diverse spectrum of neurologic symptoms
- **Excess ammonia** induces alteration of cell metabolism and can result in brain edema
- **> 45% of patients with cirrhosis** will experience **at least one episode of HE¹**
- HE is **largely underdiagnosed and undertreated** and is associated with poor quality of life

Findings to date:

- ✓ VS-02 lowers ammonia levels in an acute liver injury model
- ✓ VS-02 lowers ammonia & brain glutamine levels in a chronic liver disease model
- ✓ VS-02 demonstrates gut bacterial urease inhibitory activity



ISHEN 2025



GUT BACTERIAL UREASE INHIBITION BY VS-02 AS A POTENTIAL TREATMENT TO REDUCE HYPERAMMONEMIA AND PROTECT FROM HEPATIC ENCEPHALOPATHY (HE) IN CIRRHOSIS

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Sponsored by the: INSERM, CNRS, Univ. Sorbonne Paris, ICM, INSPI, UMR, INSERM

BACKGROUND & AIM

• Gut bacterial ureases, which convert urea into ammonia, contribute to systemic ammonia levels and thus represent a promising therapeutic target for reducing hyperammonemia and alleviating hepatic encephalopathy (HE).
• Hydroxamic acids (HAs) are potent urease inhibitors that have shown beneficial effects in preclinical models and patients with liver disease. Among them, *axohydroxamic acid* (AHA), *oxohydroxamic acid* (OHA), and *nicotinic hydroxamic acid* (NHA) are the only ones that have been clinically tested in liver disease patients. However, in studies conducted between 1970 and 1976, these encouraging results, none of these compounds, advanced in further development for HE, possibly due to insufficient potency or a failure to reach effective concentrations in the colon, the main site of bacterial urease activity.

• VS-02 is a hydroxamic acid derivative under development for the treatment of HE, formulated for colon targeted delivery to enhance local inhibitor concentration at the site of ammonia production while minimizing systemic exposure.

AIMS OF THE STUDY

- to evaluate the efficacy of VS-02 in reducing ammonia *in vivo*, in comparison to other hydroxamic acids (AHA and OHA)
- to characterize the pharmacokinetic (PK) profile of preclinical formulation of VS-02 following oral administration to identify the dose level achieving effective concentrations in the cecum, a primary site of bacterial urease activity in the rat gut

METHODS

In vivo urease activity assay in rat cecal content
Urease inhibitory activity of HAs was evaluated in pooled cecal content of male Sprague Dawley rats (n=3), diluted to 1% w/v, with 200 mM Na₂CO₃ (pH 8.5). After low speed centrifugation to remove debris, bacteria were incubated with 100 mM urea and an inhibitor for 30 min at 37°C. Ammonia levels were measured before (T0) and after incubation (T30) using a colorimetric urease activity assay kit (Sigma-Aldrich®).

PK study in rats

PK of VS-02 was studied in healthy male Sprague Dawley rats. Two groups of rats (n=2/group) received single oral doses of 30 mg/kg or 100 mg/kg VS-02 in gavage.

At pre-defined time points following dosing, rats were euthanized, and plasma, cecal contents, and feces were collected for quantification of VS-02 by the LC-MS/MS system (Sciex Triple Quad 6500+). PK parameters were calculated by non-compartmental analysis using Phoenix WinNonlin software (version 8.5.1).

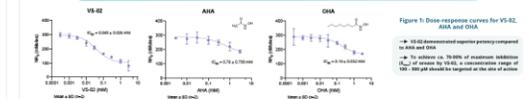
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Abstracts were submitted from 2024-2025

RESULTS

VS-02 DEMONSTRATES SUPERIOR UREASE INHIBITORY ACTIVITY COMPARED TO REFERENCE HYDROXAMIC ACIDS



PRECLINICAL FORMULATION OF VS-02 LEADS TO HIGH LOCAL EXPOSURE IN THE CECUM OF HEALTHY RATS

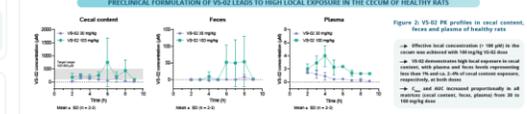


Table 1: PK parameters following oral administration of 30 or 100 mg/kg VS-02

Dose (mg/kg)	Matrix	Time (h)	C _{max} (µg/g)	C _{min} (µg/g)	AUC _{0-24h} (µg·h/g)	AUC _{0-24h} (Systemic or Feces) / AUC _{0-24h} (Cecal content)
30	Cecal content	0	158.3	5.28	597.2	19.9
	Feces	8	9.1	0.30	12.6	0.4
100	Cecal content	0	1.5	0.05	5.7	0.2
	Feces	8	32.3	0.32	19.4	1.0

PK parameters were calculated by non-compartmental analysis using Phoenix WinNonlin software (version 8.5.1).

CONCLUSION

- VS-02 demonstrated efficacy in a complex *in vivo* bacterial system, showing greater potency compared to HAs previously investigated in clinical trials
- Preclinical formulation of VS-02 enabled targeted delivery of the inhibitor in the cecum and minimized systemic exposure supporting its further assessment in an *in vivo* efficacy studies in animal models of HE
- Overall, these results support continued development of VS-02 as a potential treatment of HE in patients with cirrhosis

Abstract presented at ISHEN Conference 2025 | 5 - 8 October, 2025 | St Paulin, Quebec, Canada

- ▶ VS-02 shows greater potency in the inhibition of gut bacterial urease activity as compared to other HAs
- ▶ Preclinical formulation of VS-02 enables targeted delivery in the cecum and minimized systemic exposure

▶ ▶ These results support the development of VS-02 as a potential treatment of HE in patients with cirrhosis ◀ ◀

Next Step: Nonclinical studies and formulation development
Potential First-in-human trial could be initiated in 2H27



GENFIT Enters Research Collaboration with EVERZOM to Advance Exosome-based Regenerative Technology in ACLF

- **EVERZOM's investigational drug candidate EViv, developed to treat ACLF, using its proprietary exosome platform, represents a novel approach to regenerative therapies**
- **Pending successful *in vivo* proof-of-concept results, GENFIT has an exclusive option to take a license to drive EViv into clinical development**
- **Under this research collaboration, EVERZOM will contribute exosome expertise with associated bioproduction platform, while GENFIT will spearhead preclinical evaluation of EViv**

Acute-On-Chronic Liver Failure (ACLF)

G1090N | SRT-015 | CLM-022 | VS-02-HE | EViv

Urea Cycle Disorders (UCD) & Organic Acidemias (OA)

Ultra-rare disease: 1,900 HAC^{2,3,4} per year in children in US+EU4+UK. High mortality (75% at 5 years²). Survivors often have severe brain injuries. Neonatal RRT necessitates trained personnel, not available in non-specialized hospital, highly invasive. Delays timely critical medical care.

VS-01-HAC

1. *Who we are*
2. *Iqirvo[®]*
3. *Our lead assets*
4. **Other programs**

VS-01-HAC in UCD/OA

VS-01-HAC

Potential bridging therapy or first-line treatment



Peritoneal

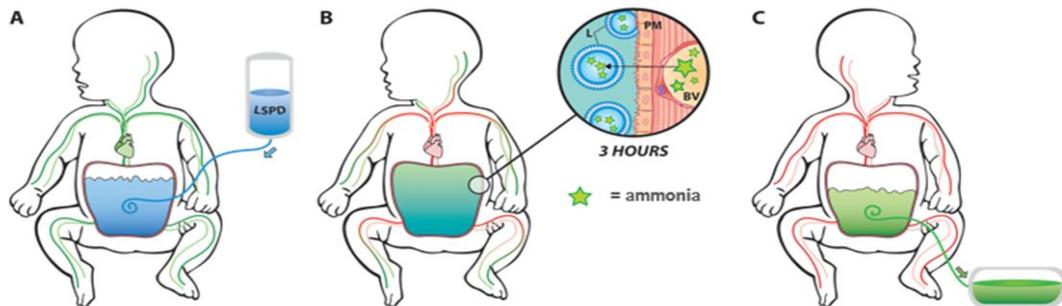
Findings to date:

✓ Preclinical proof of concept:

- VS-01 achieved robust ammonia clearance, ranging from 6.0 ± 2.8 mL/min on Day 1 to 9.5 ± 3.8 mL/min on Day 10^{1,2,3,4} in minipigs

✓ Clinical proof of concept:

- Ammonia clearance in adult patients with decompensated cirrhosis was markedly higher than that reported for conventional renal replacement therapy (RRT) modalities⁵



Optimal treatment setup

- Allows treatment onset without delay even outside of specialized centers
- Complementary to other therapeutical approaches

Promising data generated via ACLF program

- Efficient ammonia removal

Regulatory

- Orphan drug & rare pediatric disease designated (FDA)
- Potentially eligible for FDA priority review voucher upon approval

Next Step: Juvenile toxicology study ongoing with data expected early 1H26,
pharmacological validation in HA models expected in 1H26
Potential launch of First-in-human targeted 2H26