

# Corporate Presentation

February 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](http://www.genfit.fr)) and the AMF's website ([www.amf.org](http://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<sup>®</sup>: Strong commercial sales<sup>1</sup> trajectory in PBC

- Key contributing factor to GENFIT 's robust financial position
- Next update by IPSEN: February 12, 2026

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

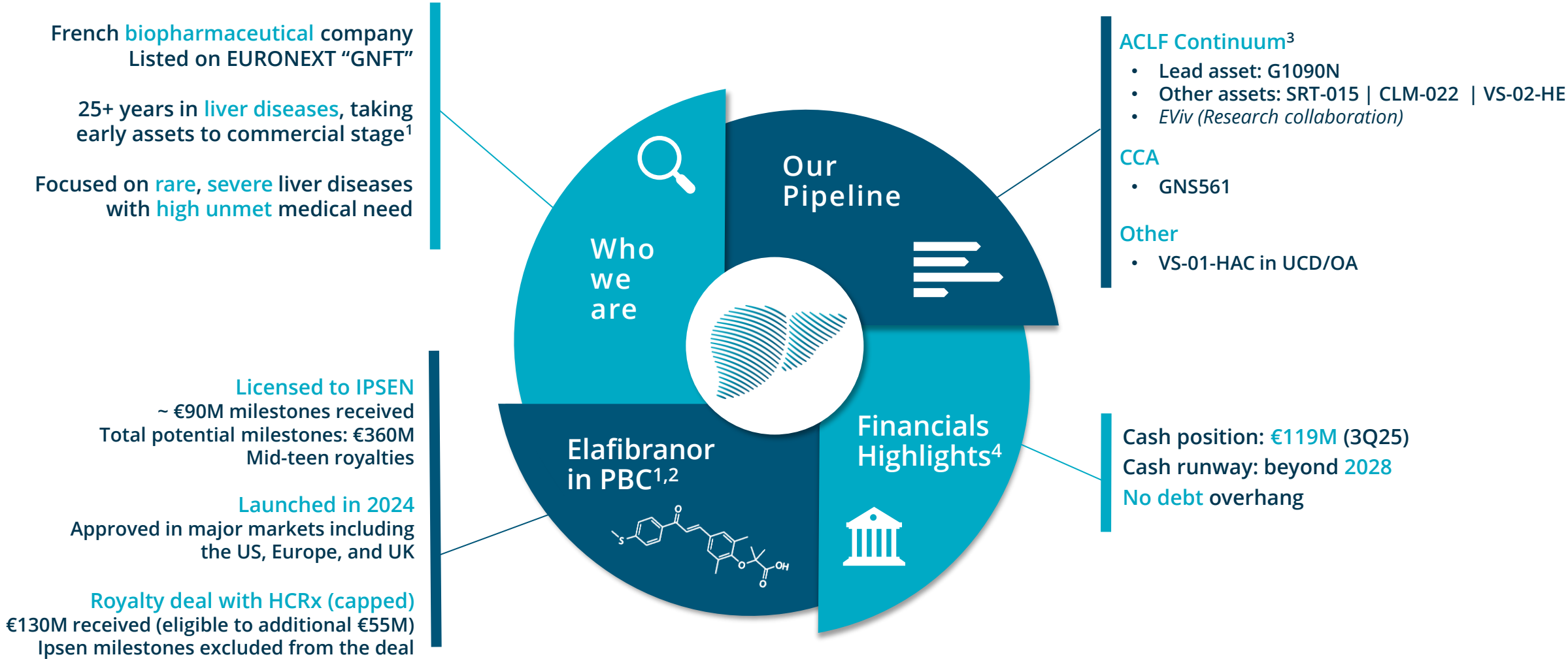
- Continuum ACLF: SRT-015, CLM-022, VS-02-HE, *EViv*<sup>2</sup>
- UCD/OA: VS-01-HAC

# 1. Who we are

2. *R&D focus*

3. *Iqirvo<sup>®</sup> in PBC*

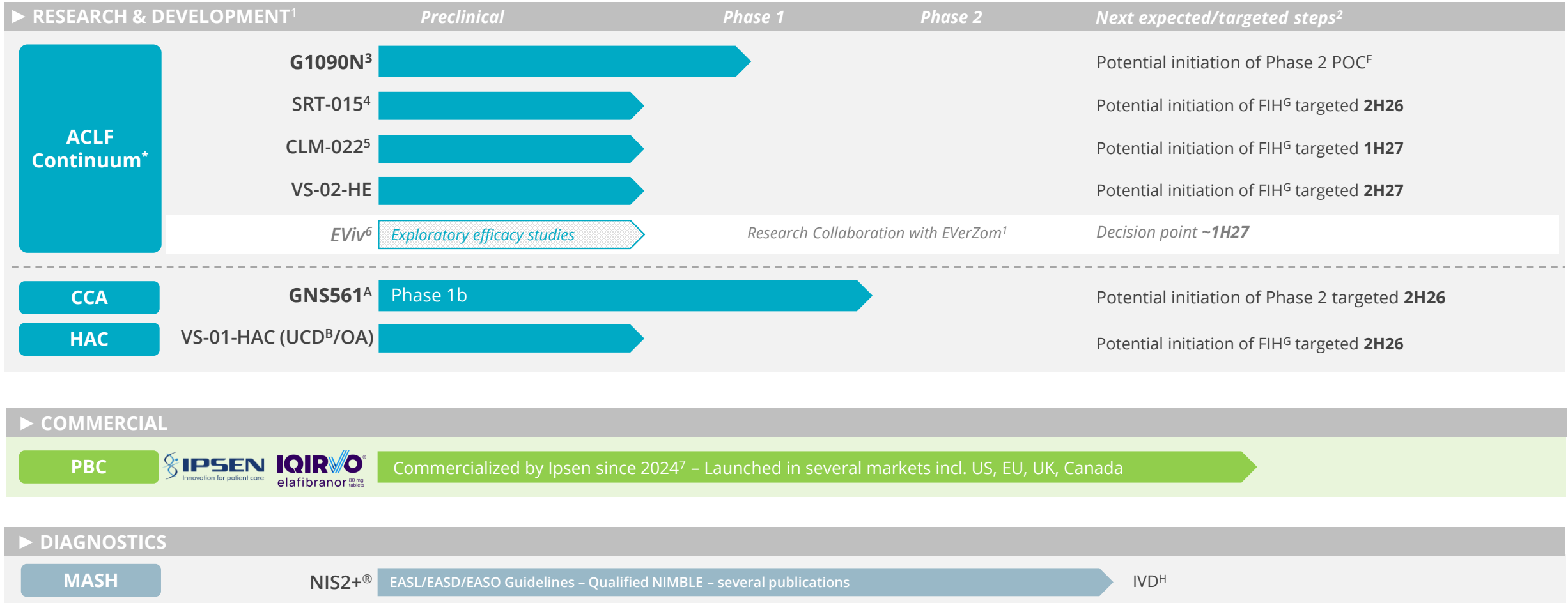
# Corporate Highlights



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  
 PR - GENFIT to receive a €26.5 million milestone payment following the approval of pricing and reimbursement of Ipsen's Igitovix in Italy  
 3. 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  
 4. PR - GENFIT Reports Third 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



<sup>A</sup> Orphan Drug Designation (ODD) FDA

<sup>B</sup> Rare Pediatric Disease Designation FDA ; ODD FDA

<sup>C</sup> HV = Healthy Volunteers <sup>D</sup> HI = Hepatic Impairment Studies

<sup>E</sup> RI = Renal Impairment Studies <sup>F</sup> POC = Proof of Concept

<sup>G</sup> FIH = First-in-Human Study <sup>H</sup> 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](#) | [UE-EMA-approval](#) | [UK-MKRA-approval](#) | [Canada-approval](#); Potentially eligible for priority review voucher upon approval by the FDA

## ACLF

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

**Growing at Epidemic Rates**  
 +**26%** between 2006 and 2014<sup>1</sup>

**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. R&D focus**
3. *Iqirvo<sup>®</sup> in PBC*

## 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<sup>1</sup>**

## Cholangiocarcinoma (CCA)

GNS561

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

VS-01-HAC

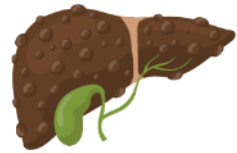
# ACLF: A High Unmet Need

## CHRONIC PHASE

Chronic Liver Disease

Cirrhosis

= UNDERLYING CONDITION

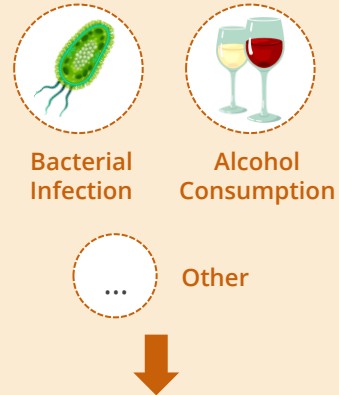


The liver is scarred but **still functioning** and people can live for **years** in this state **without noticeable symptoms**

## ACUTE PHASE

Acute  
Decompensation

= PRECIPITANT



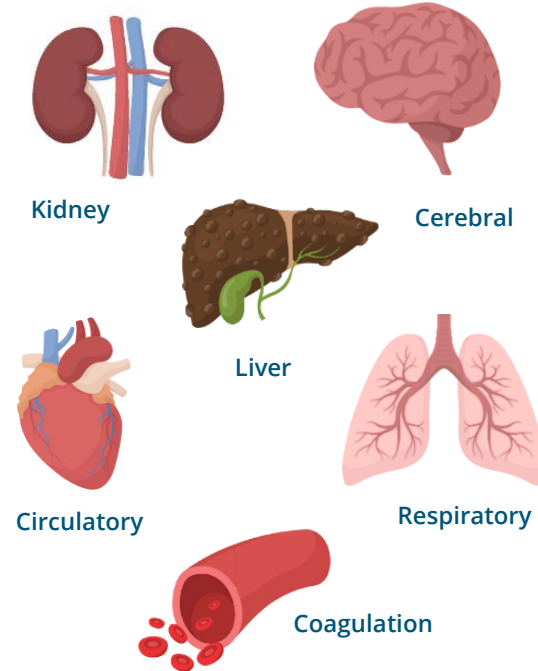
Liver function deteriorates and **serious complications** develop

- Ascites
- Hepatic encephalopathy
- Gastrointestinal bleeding

Urgent Hospitalisation

ACLF

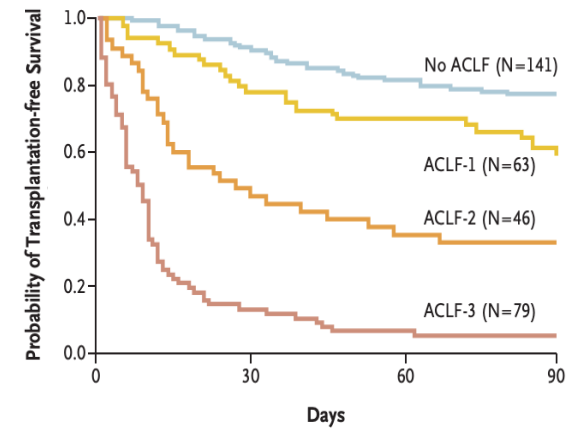
≥ 1 ORGAN DYSFUNCTIONS/FAILURES



Hospitalisation / Intensive Care Unit

23-74% mortality at 28 days

▶ NO APPROVED DRUGS



Death

# 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



**SRT-015**  
*Injectable*

**ASK1 inhibitor**

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

Potential initiation of First-in-human targeted 2H26

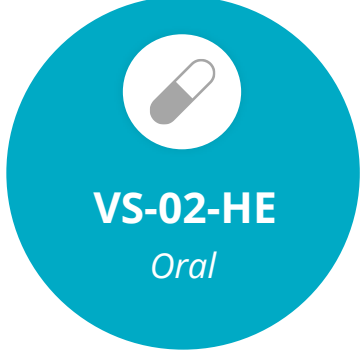


**CLM-022**

**NLRP3 inflammasome inhibitor**

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

Potential initiation of First-in-human targeted 1H27



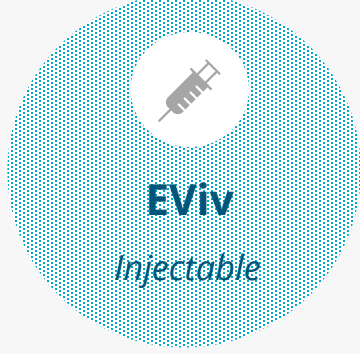
**VS-02-HE**  
*Oral*

**Urease inhibitor**

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

Potential initiation of First-in-human targeted 2H27

*Research Collaboration with EVerZom<sup>1</sup>*



**EViv**  
*Injectable*

**Exosome Technology**

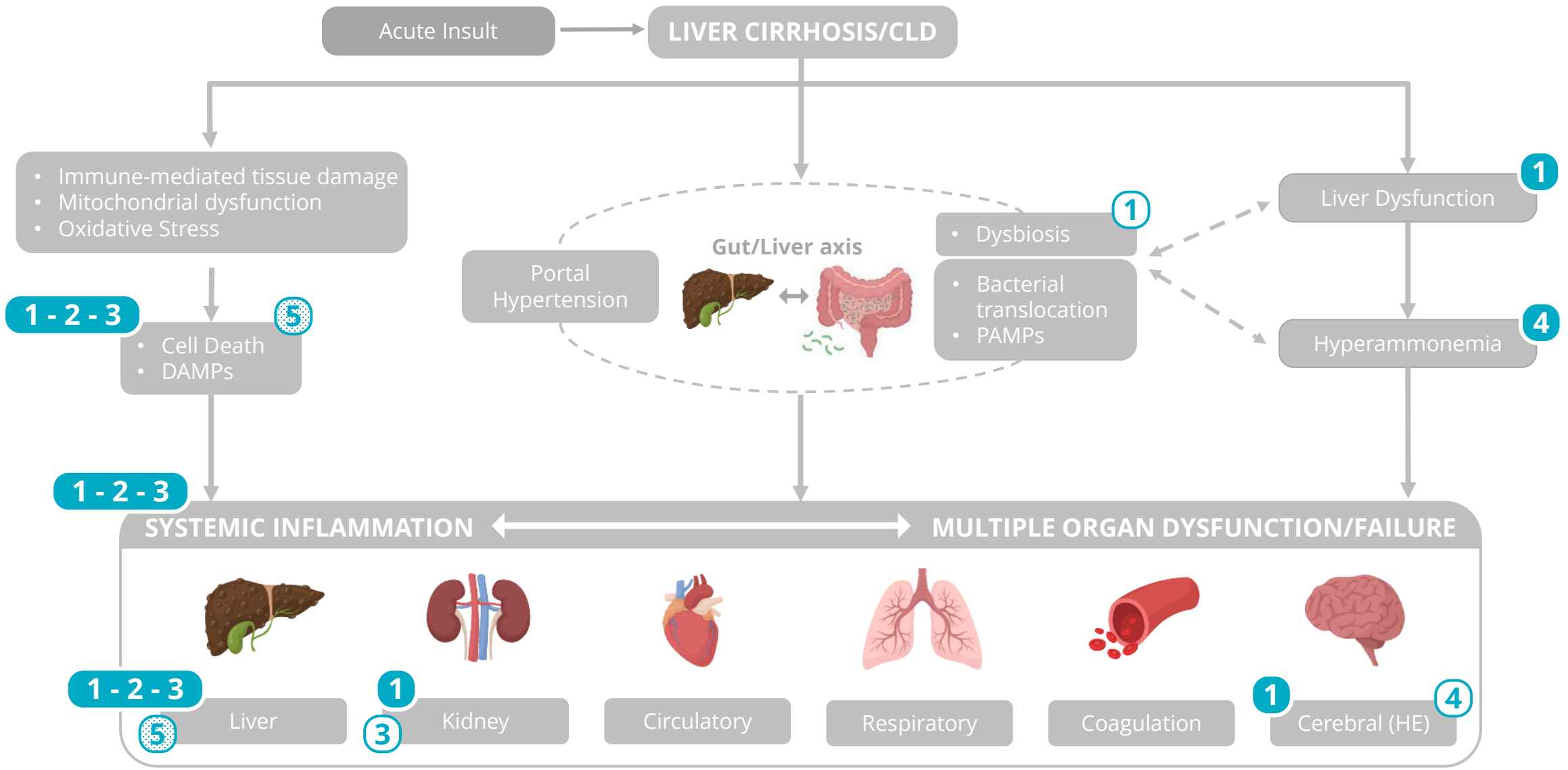
Novel approach to **regenerative therapies**

Decision point ~1H27

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

1. PR EVerZom

# Target Multiple Pathways



Demonstrated effect

Expected effect

1 1 G1090N

2 2 SRT-015

3 3 CLM-022

4 4 VS-02-HE

5 EViV (Research Collaboration with EverZom)

# A Strong Scientific Rationale for investigational drug G1090N, Our Lead Asset in ACLF

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)

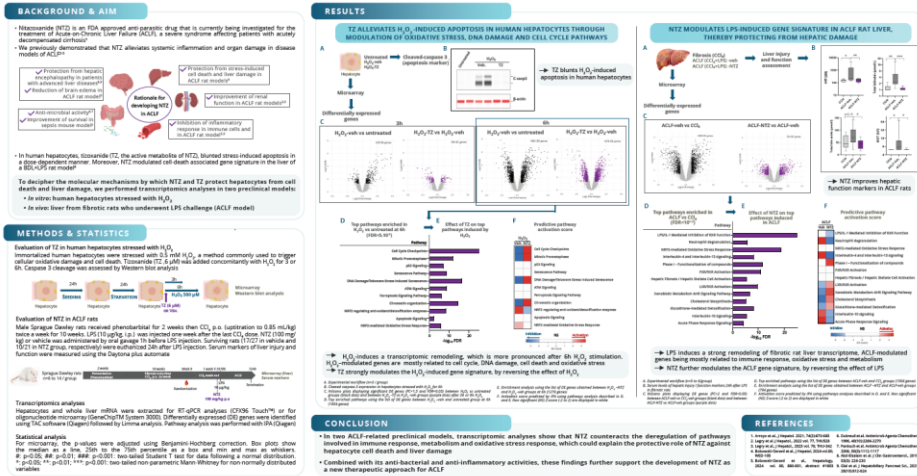
EASL 2025

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

Marie Bobowski-Gerard<sup>1</sup>, Nicolas Stramkovic Valentin<sup>1</sup>, Sylvie Delacourte<sup>1</sup>, Simon Debaecker<sup>1</sup>, Nina S'Ervenste<sup>1</sup>, Philippe Delattre<sup>1</sup>, Saïna Sayah Jeanne<sup>1</sup>, Dean Hum<sup>1</sup>, Vanessa Legry<sup>1</sup>, Jérôme Eeckhout<sup>1</sup>, Joan Claris<sup>1</sup>, Bart Staels<sup>1</sup>

<sup>1</sup>GENFIT SA, Louvain-la-Neuve, Belgium; <sup>2</sup>CHU Lille and Institut Pasteur de Lille, U1011 EDD, Lille, France; <sup>3</sup>Hospital 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

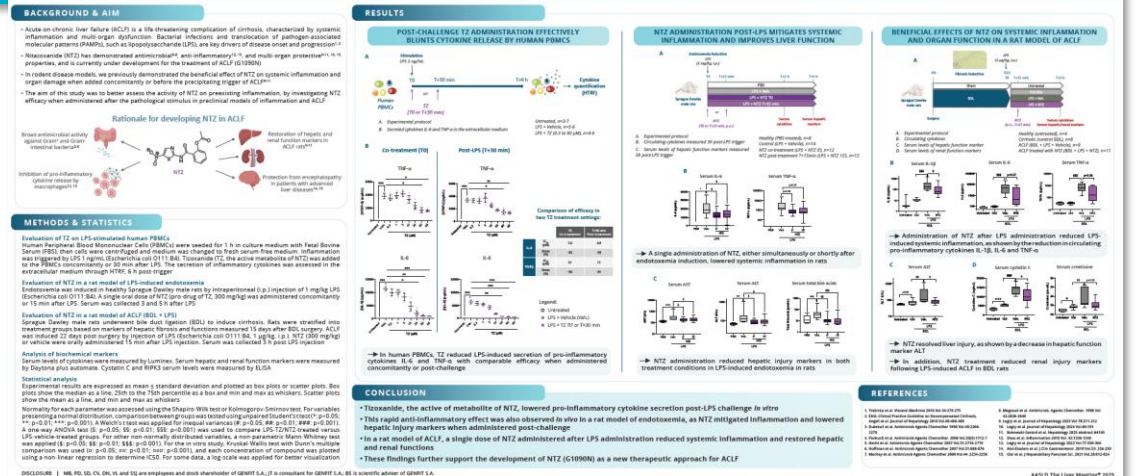
AASLD 2025

**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-Gerard<sup>1</sup>, Philippe Delattre<sup>1</sup>, Simon Debaecker<sup>1</sup>, Camille Vanbèsien<sup>1</sup>, Dean Hum<sup>1</sup>, Vanessa Legry<sup>1</sup>, Bart Staels<sup>1</sup>, Joël Trebicka<sup>1</sup>, Saïna Sayah Jeanne<sup>1</sup>

<sup>1</sup>GENFIT SA, Louvain-la-Neuve, Belgium; <sup>2</sup>CHU Lille and Institut Pasteur de Lille, U1011 EDD, Lille, France; <sup>3</sup>Hospital of the Geneva University, University Hospital, Geneva, Switzerland

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**  
Anti-inflammatory



Oral

### Key inclusion criteria

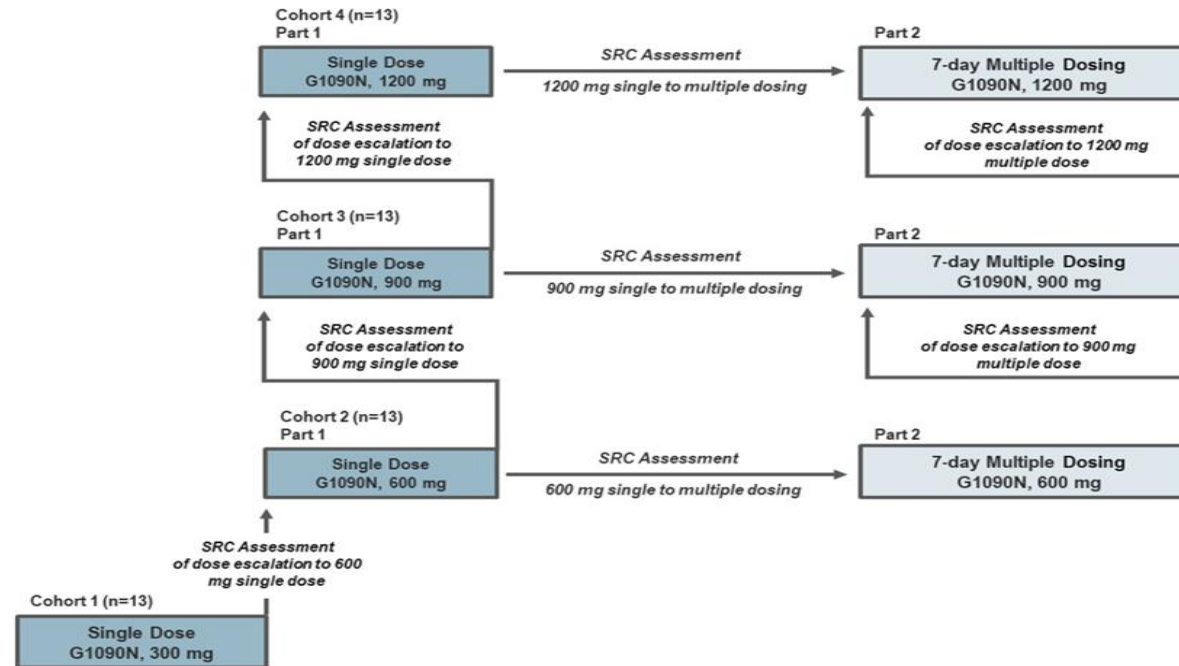
- **Healthy** Volunteers
- Normal liver and renal function

### 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**

# SRT-015

**SRT-015**  
**ASK1**  
**inhibitor**



*Injectable*

## 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**

**GENFIT**  
TOWARDS BETTER MEDICINE

### 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

Vanessa Legry<sup>1</sup>, Manon Clarisse<sup>1</sup>, Simon Debaccker<sup>1</sup>, Nicolas Stancovski<sup>2</sup>, Philippe Poulin<sup>1</sup>, Dean Hum<sup>1</sup>, Bart Staels<sup>1</sup>, Joan Clariá<sup>1</sup>, Sakina Sayah Jeanne<sup>1</sup>

<sup>1</sup>GENFIT SA, Les Fontaines, Sures-Lès-Lille, FRANCE; <sup>2</sup>INSERM, CNRS, Institut Pasteur de Lille, U1157, Lille, France; <sup>3</sup>Hospitaux Civils de Bordeaux, Université de Bordeaux, European Association for the Study of Liver, UMR 1018, Bordeaux, Spain

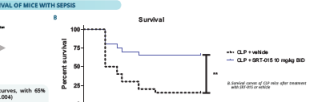
**THU-187**

**BACKGROUND & AIM**

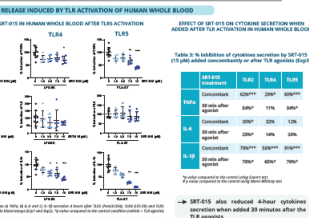
- Patients with liver cirrhosis have an increased risk of infection and are at high risk of death from sepsis. To reverse immune dysfunction, impaired liver function and altered gut microbiota and permeability.
- In these patients, immune dysfunction also results in a hyperinflammatory condition in the presence of PAMPS, as shown by elevation of circulating pro-inflammatory cytokines such as TNF $\alpha$ , IL-6, IL-1 $\beta$ , IL-8, IL-10, IL-17, IL-22, IL-23, IL-27, IL-33, 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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IL-885, IL-886, IL-887, IL-888, IL-889, IL-890, IL-891, IL-892, IL-893, IL-894, IL-895, IL-896, IL-897, IL-898, IL-899, IL-900, IL-901, IL-902, IL-903, IL-904, IL-905, IL-906, IL-907, IL-908, IL-909, IL-910, IL-911, IL-912, IL-913, IL-914, IL-915, IL-916, IL-917, IL-918, IL-919, IL-920, IL-921, IL-922, IL-923, IL-924, IL-925, IL-926, IL-927, IL-928, IL-929, IL-930, IL-931, IL-932, IL-933, IL-934, IL-935, IL-936, IL-937, IL-938, IL-939, IL-940, IL-941, IL-942, IL-943, IL-944, IL-945, IL-946, IL-947, IL-948, IL-949, IL-950, IL-951, IL-952, IL-953, IL-954, IL-955, IL-956, IL-957, IL-958, IL-959, IL-960, IL-961, IL-962, IL-963, IL-964, IL-965, IL-966, IL-967, IL-968, IL-969, IL-970, IL-971, IL-972, IL-973, IL-974, IL-975, IL-976, IL-977, IL-978, IL-979, IL-980, IL-981, IL-982, IL-983, IL-984, IL-985, IL-986, IL-987, IL-988, IL-989, IL-990, IL-991, IL-992, IL-993, IL-994, IL-995, IL-996, IL-997, IL-998, IL-999, IL-1000.

**RESULTS**

**SRT-015 IMPROVES SURVIVAL OF MICE WITH SEPSIS**



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



**CONCLUSION**

- Although further experiments are needed to fully understand how SRT-015 improves survival in septic mice, one potential mechanism may be by regulation of the innate immune response.
- These results further support the development of SRT-015 in advanced liver diseases and ACLF.

Abstract P940 presented at EASL International Liver Congress™ 2025 | 7 - 10 May, 2025 | Amsterdam, Netherlands

**AASLD 2025**

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

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**THU-188**

**BACKGROUND & AIM**

- Acute on Chronic Liver Failure (ACLF) is characterized by multiple organ failures and high systemic immune mortality. ACLF is closely associated with the presence of systemic inflammation 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. Practical 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<sup>1</sup>.
- 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<sup>2</sup>, as well as on human leukocyte functions *in vitro*.

**METHODS**

**Evaluation of SRT-015 in ACLF mice**

Male C57BL/6J mice were subjected to 14 days of CCl<sub>4</sub> treatment (100% v/v) for 10 weeks. A control group of mice receiving 10% saline (0.9% NaCl) was also included. Once mice received CCl<sub>4</sub> treatment, they were randomly divided into four groups: control group (10% saline), CCl<sub>4</sub> group, CCl<sub>4</sub> + SRT-015 group, and CCl<sub>4</sub> + SRT-015 + 10% saline group. SRT-015 (10 mg/kg) was administered daily for 7 days. Mice were sacrificed 24 hours after the last CCl<sub>4</sub> treatment. Liver and spleen were harvested and analyzed for cytokines and chemokines using multiplexed bead-based assays. Tissue and plasma were analyzed for oxidative stress markers using specific assays.

**Evaluation of SRT-015 effect on neutrophil phagocytosis**

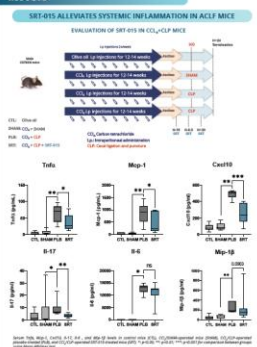
Human peripheral blood neutrophils were isolated from 10 healthy volunteers by dextran density gradient. The cells were resuspended in a concentration of 2 x 10<sup>6</sup> cells/ml and incubated with LPS (100 ng/ml) for 30 minutes. SRT-015 (100 nM) was added to the cells for the last 15 minutes of the incubation. Phagocytosis was measured by flow cytometry using FITC-labeled bacteria. The results were expressed as the percentage of phagocytosis.

**Evaluation of SRT-015 effect on neutrophil degradation**

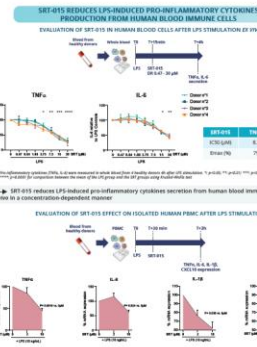
Neutrophils were isolated from 10 healthy volunteers by dextran density gradient. The cells were resuspended in a concentration of 2 x 10<sup>6</sup> cells/ml and incubated with LPS (100 ng/ml) for 30 minutes. SRT-015 (100 nM) was added to the cells for the last 15 minutes of the incubation. Neutrophil degradation was measured by flow cytometry using FITC-labeled bacteria. The results were expressed as the percentage of neutrophil degradation.

**RESULTS**

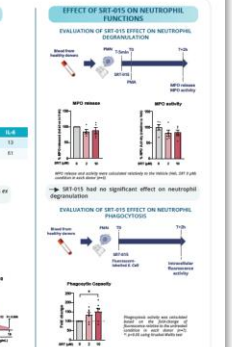
**SRT-015 ALLEVIATES SYSTEMIC INFLAMMATION IN ACLF MICE**



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



**EFFECT OF SRT-015 ON NEUTROPHIL FUNCTIONS**



**CONCLUSION**

- These data confirm the beneficial effect of SRT-015 on systemic inflammation in a preclinical model of ACLF and show its ability to improve the antibacterial function of neutrophils.
- These results support the development of the investigational drug SRT-015 for the treatment of patients with ACLF.

DECLARATION OF INTEREST: V.L., B.R., C.L., B.J.C., B.S.R., O.H., M.C., S.D., B.S., J.C., R.M., D.H., B.S., S.S.J., J.C. have nothing to disclose. V.L., B.R., C.L., B.J.C., B.S.R., O.H., M.C., S.D., B.S., J.C., R.M., D.H., B.S., S.S.J., J.C. have nothing to disclose.

- ▶ SRT-015 dose-dependently inhibits TNF- $\alpha$ , IL-6 and IL-1 $\beta$  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 $\beta$  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**

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**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 pathogen-associated molecular patterns (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 2019).
- Inflammation is characterized by activation of innate immune cells, production of pro-inflammatory cytokines, and generation of reactive oxygen and nitrogen species. Pyroptosis is regulated by inflammasomes which are composed of multiprotein complexes expressed in both parenchymal and non-parenchymal cells (Kumar 2019). NLRP3 inflammasome is composed of NLRP3, ASC, caspase-1, and IL-1 $\beta$  (Decker 2016).

**RESULTS**

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

Figure 1: CLM-022 inhibits NLRP3 priming in LPS-induced PBMCs. A: Schematic diagram of the experimental design. B: Bar graphs showing the effect of CLM-022 on NLRP3 priming markers (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ) in LPS-induced PBMCs. C: Western blot analysis of NLRP3 protein levels in LPS-induced PBMCs treated with CLM-022.

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

Figure 2: CLM-022 improves hepatic function and reduces NLRP3 protein expression in APAP-induced liver injury. A: Schematic diagram of the experimental design. B: Bar graphs showing the effect of CLM-022 on hepatic function markers (ALT, AST, ALP) and NLRP3 protein expression in APAP-induced liver injury. C: Western blot analysis of NLRP3 protein levels in APAP-induced liver injury treated with CLM-022.

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

Figure 3: CLM-022 inhibits pyroptosis induced by inflammasome activation in WT but not in NLRP3-KO THP-1 cells. A: Schematic diagram of the experimental design. B: Bar graphs showing the effect of CLM-022 on pyroptosis markers (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ) in WT and NLRP3-KO THP-1 cells. C: Western blot analysis of NLRP3 protein levels in WT and NLRP3-KO THP-1 cells.

**CLM-022 INHIBITS SYSTEMIC INFLAMMATION AND IMPROVES HEPATIC PARAMETERS IN ENDOTOXEMIA INDUCED BY POLYMERIZATION OF LPS**

Figure 4: CLM-022 inhibits systemic inflammation and improves hepatic parameters in endotoxemia induced by polymerization of LPS. A: Schematic diagram of the experimental design. B: Bar graphs showing the effect of CLM-022 on systemic inflammation markers (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ) and hepatic parameters (ALT, AST, ALP) in endotoxemia induced by polymerization of LPS. C: Western blot analysis of NLRP3 protein levels in endotoxemia induced by polymerization of LPS treated with CLM-022.

**CONCLUSION**

CLM-022 inhibits NLRP3 inflammasome priming and activation steps, reduces NLRP3 protein expression, and improves hepatic function and parameters in APAP-induced liver injury and endotoxemia induced by polymerization of LPS. CLM-022 also inhibits pyroptosis induced by inflammasome activation in WT but not in NLRP3-KO THP-1 cells.

**REFERENCES**

1. Kumar D. Gut microbiota and liver disease. *World J Gastroenterol*. 2019;25(12):1381-1391. doi:10.3746/journal.wjg.v25.i12.1381

2. Decker MW. NLRP3 inflammasome: a molecular platform for activation of caspase-1 and IL-1 $\beta$  secretion. *Cell Mol Life Sci*. 2016;322(1):1-10. doi:10.1007/s00122-015-2600-0

3. Kumar D. Gut microbiota and liver disease. *World J Gastroenterol*. 2019;25(12):1381-1391. doi:10.3746/journal.wjg.v25.i12.1381

4. Kumar D. Gut microbiota and liver disease. *World J Gastroenterol*. 2019;25(12):1381-1391. doi:10.3746/journal.wjg.v25.i12.1381

AASLD  
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**EFFICACY OF CLM-022\*, AN INHIBITOR OF THE NLRP3 INFLAMMASOME, IN IN VIVO AND IN VITRO PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPs)-INDUCED DISEASE MODELS**

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**BACKGROUND & AIM**

- Patients with liver cirrhosis are characterized by impaired liver function, severe immune dysregulation, and increased gut permeability. These alterations drive the progression of gut-derived pathogen-associated molecular patterns (PAMPs) and immune dysregulation-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 dysregulation-associated molecular patterns (DAMPs), which stimulate immune responses via receptors (TLRs and NLRs). CLM-022, a novel inhibitor of inflammasome priming and activation, has demonstrated hepatoprotective and immunomodulatory effects in pre-clinical models of acute liver injury and endotoxemia, as presented in the 2025 EASL International Liver Congress\*.

**RESULTS**

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

Figure 1: CLM-022 improves survival in a mouse model of CLP-induced sepsis. A: Schematic diagram of the experimental design. B: Kaplan-Meier survival curves showing the effect of CLM-022 on survival in a mouse model of CLP-induced sepsis. C: Bar graphs showing the effect of CLM-022 on survival in a mouse model of CLP-induced sepsis.

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

Figure 2: CLM-022 reduces pro-inflammatory cytokine release in human whole blood assay. A: Schematic diagram of the experimental design. B: Bar graphs showing the effect of CLM-022 on pro-inflammatory cytokine release (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ) in human whole blood assay. C: Bar graphs showing the effect of CLM-022 on pro-inflammatory cytokine release (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ) in human whole blood assay.

**CONCLUSION**

CLM-022 improves survival in a mouse model of CLP-induced sepsis and 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.

**REFERENCES**

1. Kumar D. Gut microbiota and liver disease. *World J Gastroenterol*. 2019;25(12):1381-1391. doi:10.3746/journal.wjg.v25.i12.1381

2. Kumar D. Gut microbiota and liver disease. *World J Gastroenterol*. 2019;25(12):1381-1391. doi:10.3746/journal.wjg.v25.i12.1381

3. Kumar D. Gut microbiota and liver disease. *World J Gastroenterol*. 2019;25(12):1381-1391. doi:10.3746/journal.wjg.v25.i12.1381

4. Kumar D. Gut microbiota and liver disease. *World J Gastroenterol*. 2019;25(12):1381-1391. doi:10.3746/journal.wjg.v25.i12.1381

- ▶ CLM-022 inhibits NLRP3 inflammasome priming of LPS-induced human PBMCs
- ▶ Inhibition of IL-1 $\beta$  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**



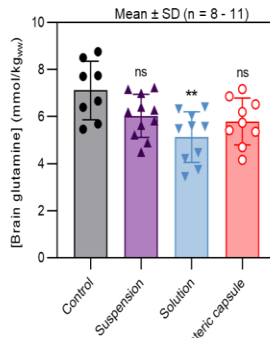
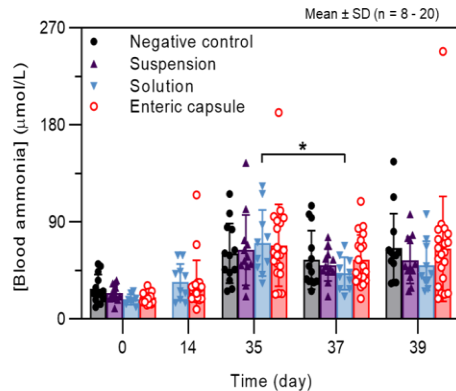
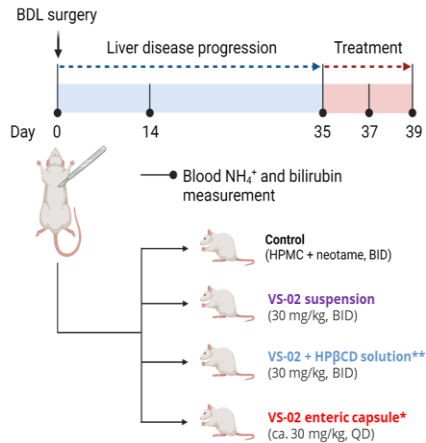
Oral

**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 HE<sup>1</sup>**
- 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**

Verónica Lagay<sup>1</sup>, Diana Esteban<sup>1</sup>, Valérie Dasi<sup>1</sup>, Philippe Delaillie<sup>1</sup>, Emanuele Wekstein<sup>1</sup>, Nicolas Demarez<sup>1</sup>, Dean Huai<sup>1</sup>, Bart Steels<sup>1</sup>, Sakina Sayan-Jeanne<sup>1</sup>

<sup>1</sup>GENFIT SA, Les Fontaines, 11800 Saint-Omer, France

**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, *α*-hydroxycarboxylic acid (AHA), *α*-ketoisobutyric acid (AKIA), *α*-ketoglutaric acid (AKG), and *α*-ketoglutaric acid (AKG) are the only ones that have been clinically tested in liver disease patients. However, in studies conducted between 1970 and 1975, these compounds showed limited efficacy, 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 urease production while minimizing systemic exposure.

**The aim of this study was:**

- to evaluate the efficacy of VS-02 in reducing ammonia *in vivo*, in comparison to other hydroxamic acids (AKIA and AKG)
- 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 NaCl, pH 6.8. After low-speed centrifugation to remove debris, bacteria were incubated with 100 µM 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**



## 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**

1. *Who we are*
2. **R&D focus**
3. *Iqirvo<sup>®</sup> in PBC*

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 diagnosis<sup>1</sup>. KRAS mutation is not addressed by current treatments.

**GNS561**

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

VS-01-HAC

<sup>1</sup> Lamarca et al. 2021

# CCA with KRAS mutation: A High Unmet Need

## Rare and aggressive liver malignancy that develops in the bile ducts

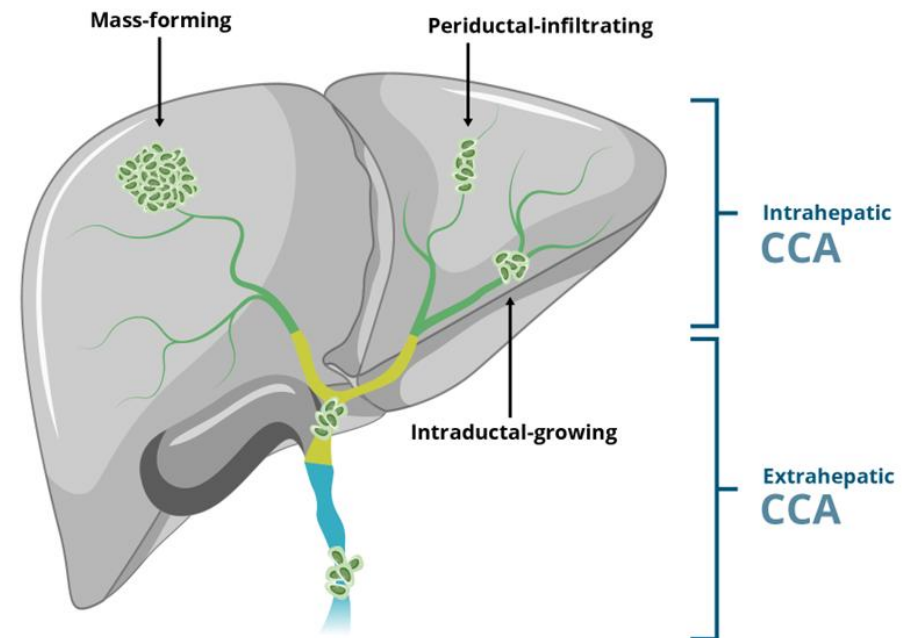
- As the cancer grows, it can **block the bile ducts** and lead to damage to the liver and other organs
- Without treatment **<20% of patients survive 5 years** from diagnosis<sup>1</sup>

## Unmet needs

- **Surgery** = primary treatment of CCA but **only 30%** of patients present with resectable tumors<sup>2</sup>
- First line and second line therapy = **survival is limited**<sup>2</sup>
- Rapid progression of the tumor until the **patient's death = 10–12 months** on current SoC<sup>3</sup>

## ~30% of patients with CCA harbor **KRAS mutations**<sup>4</sup>

- **one of the most common genes that might be mutated** or amplified resulting in the overactivation of some of these pathways<sup>5</sup>
- associate with **shorter survival**<sup>6</sup>
- 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



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## #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

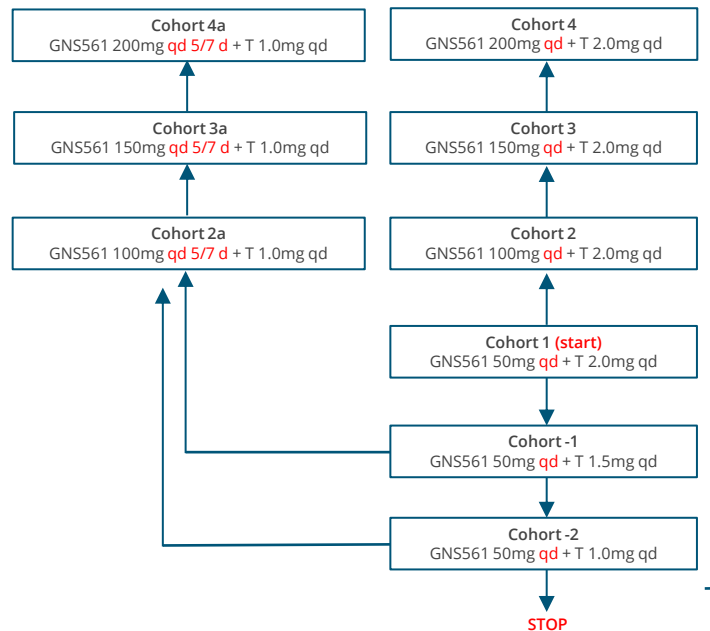
## ⊘ Key exclusion criteria

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

Ongoing recruitment

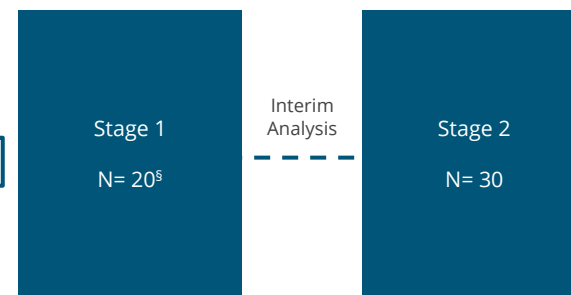
$N_{TOTAL}$   
=  
**74**  
**PTS**

### 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

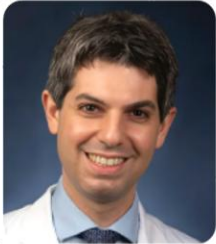
# Phase 1b: Highly Encouraging Early Data

## GNS561

PPT1 inhibitor in combination with a MEK inhibitor



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*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**

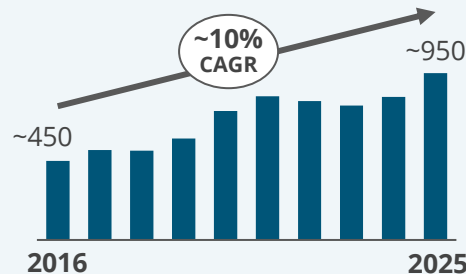
# Moving Forward



- **Phase 1b dose escalation** will continue as planned to confirm activity signal
- **1Q2026** - New data from next patient cohorts expected
- **1H2026** - Completion expected results will be used to establish recommended Phase 2 combination doses
- **2H2026** – 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<sup>1,2</sup>




### 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)<sup>1</sup>

## 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 model<sup>3</sup>*

1. *Who we are*

2. **R&D focus**

3. *Iqirvo<sup>®</sup> in PBC*

Acute-On-Chronic Liver Failure (ACLF)

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

Cholangiocarcinoma (CCA)

GNS561

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

Ultra-rare disease: 1,900 HAC<sup>2,3,4</sup> per year in children in US+EU4+UK. High mortality (75% at 5 years<sup>2</sup>). 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**

# VS-01-HAC in UCD/OA

## VS-01-HAC

Potential bridging therapy or first-line treatment



Peritoneal

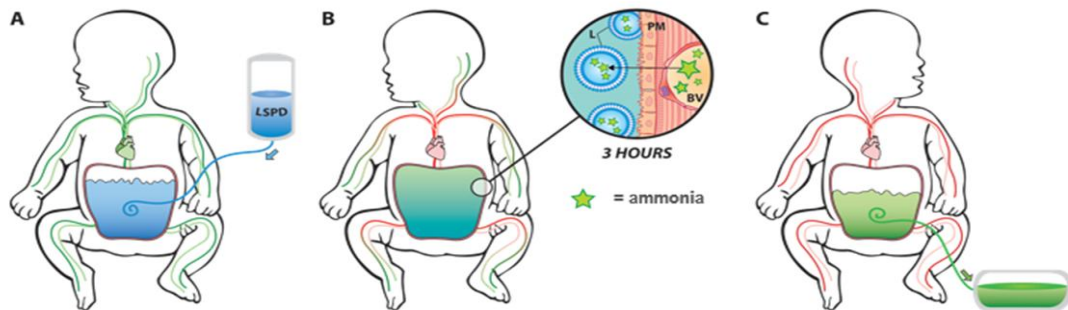
### Findings to date:

#### ✓ Preclinical proof of concept:

- VS-01 achieved robust ammonia clearance, ranging from  $6.0 \pm 2.8$  mL/min on Day 1 to  $9.5 \pm 3.8$  mL/min on Day 10<sup>1,2,3,4</sup> 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) modalities<sup>5</sup>



### 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<sup>6</sup>

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

1. *Who we are*

2. *R&D focus*

**3. Iqirvo<sup>®</sup> in PBC**

# Solid Commercial Performance from Ipsen in PBC

## 1. Rapid regulatory approvals<sup>1</sup>



2024



FDA



EMA



MHRA

2025

3 major EU countries

Reimbursement

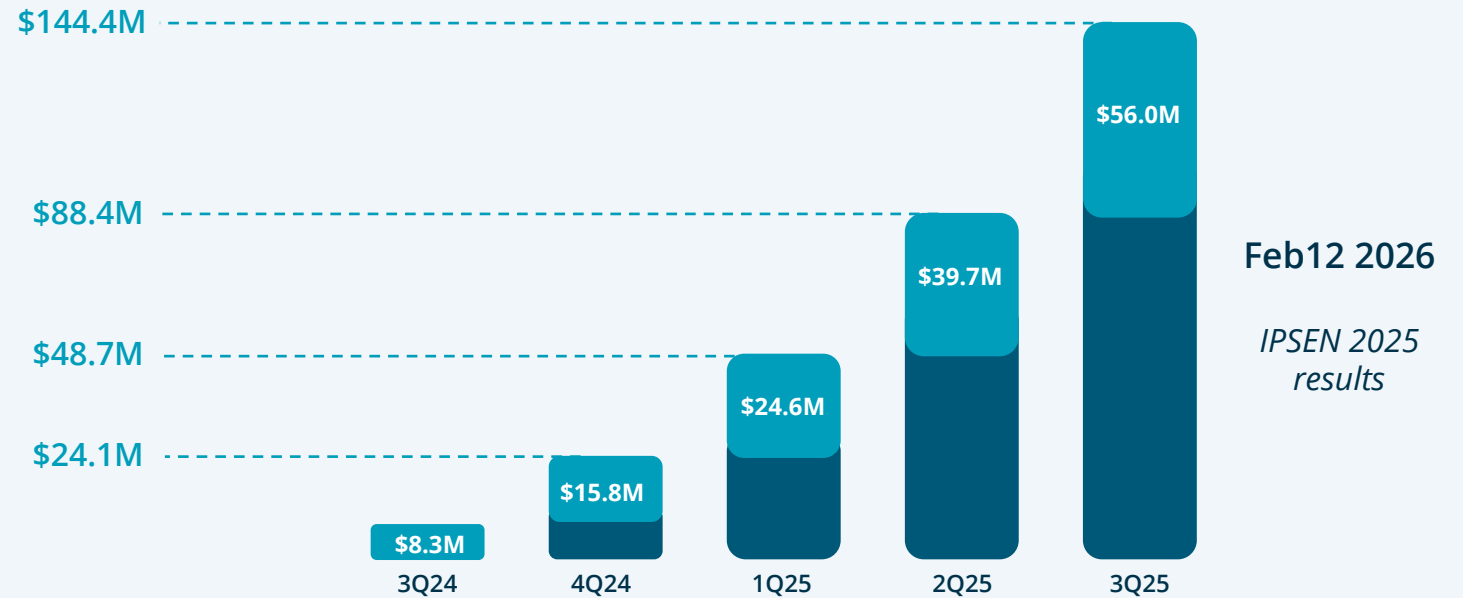


Cumul. milestones payments received<sup>3</sup>

€88.5M

## 2. Successful commercial launch

Iqirvo<sup>®</sup> sales (global, quarterly) since commercial launch<sup>2</sup>



Cumul. royalties received<sup>4</sup>

€15.3M

Sep'25: Intercept Announces Voluntary Withdrawal of OCALIVA<sup>®</sup> for Primary Biliary Cholangitis (PBC) from the US Market<sup>5</sup>

1. Ipsen's Iqirvo<sup>®</sup> receives U.S. FDA accelerated approval  
Ipsen's Iqirvo<sup>®</sup> (elafibranor) approved in the European Union

2. Ipsen delivers strong sales in the first quarter 2025  
Ipsen publishes its URD2024  
Ipsen sales 3Q25

3. FDA New Drug Application and EMA Marketing Authorization Application accepted | First commercial sale of Iqirvo<sup>®</sup> in the US | Reimbursement in a 3rd European country - Italy

4. 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

5. Intercept Announces Voluntary Withdrawal of OCALIVA<sup>®</sup> for Primary Biliary Cholangitis (PBC) from the US Market