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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**

Lille (France), Cambridge (Massachusetts, United States), Zurich (Switzerland), December 10, 2025 - **GENFIT (Euronext: GNFT)**, a biopharmaceutical company dedicated to improving the lives of patients with rare and life-threatening liver diseases, today reports encouraging preliminary Phase 1b data from its CCA clinical trial evaluating GNS561 in combination.

Clinical trial context and objective

CCA is a rare and aggressive cancer of the bile ducts, often diagnosed at an advanced stage. The unmet medical need is characterized by strong limitations in current treatments and poor prognosis. GNS561 is an investigational small molecule that targets PPT1, leading to autophagy inhibition and lysosomal dysfunction, which disrupt cancer cell survival mechanisms. By blocking autophagy, GNS561 aims to promote cancer cell death and may enhance sensitivity to other treatments. Combining GNS561 with a MEKi aims to unlock synergistic potential by simultaneously targeting autophagy and MAPK signaling pathways. In the on-going Phase 1b study, patients with advanced KRAS mutated CCA who have previously failed one or two lines of prior standard of care therapies are enrolled to evaluate the safety and tolerability of GNS561 when given in combination with trametinib, a MEKi, and to identify the recommended doses of the combination to be administered in Phase 2.

Preliminary results

The analysis evaluated 9 patients with measurable disease at baseline, 4 of them reaching tumor assessment at week 6. At this point, the combination therapy demonstrated:

- Disease stabilization observed in all 4 evaluated patients, who had all shown disease progression during previous treatment;
- Tumor shrinkage in a subgroup of patients with the best response showing a 20% reduction approaching the partial response (PR) threshold.

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Achieving disease control and tumor reduction in such heavily pretreated patient population with advanced CCA is a significant signal of antitumor activity.

Clinical Impact

The results to date show a potential to address a critical unmet medical need in oncology. Patients with advanced solid tumors who have progressed on multiple prior therapies have limited treatment options and poor prognoses. The ability of the investigational drug GNS561 associated with a MEKi to achieve disease control in this challenging patient population would represent a significant advance. The consistent pattern of disease stabilization observed across all evaluated patients, combined with objective tumor shrinkage in a subgroup of heavily pretreated patients, suggests the combination has the potential to provide meaningful clinical benefit. Optimization of dosing and patient selection could lead to further improvement in response rates.

Dr. Mark Yarchoan, Associate Professor of Oncology at John Hopkins Medicine (Baltimore, MD, USA), principal investigator of the program, commented: *"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."*

Pascal Prigent, Chief Executive Officer of GENFIT, added: "*These early results suggest a potential breakthrough for patients with limited options, and we are committed to advancing this program rapidly to individuals impacted by cholangiocarcinoma. We will also explore GNS561 potential in combination with other agents and in other tumors where autophagy inhibition plays a central role."*

Next development steps

Phase 1b dose escalation will continue as planned to confirm the activity signal, with new data for the next patient cohorts expected in 1Q26. These results will be used to establish the recommended Phase 2 combination doses, with completion expected in 1H26. Phase 2 initiation is targeted for 2H26.

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ABOUT CCA

Biliary tract cancer (BTC) is the second most common primary liver malignancy diagnosed globally. Cholangiocarcinoma (CCA) is a type of BTC and represents approximately 15% of all primary liver tumors and 3% of gastrointestinal cancers. Based on its anatomical origin, CCA is best classified anatomically as intrahepatic (iCCA) or extrahepatic (eCCA), which is comprised of perihilar (pCCA) and distal (dCCA) CCA. Early diagnosis is a major challenge as most patients with early-stage disease do not have symptoms due to limited biliary obstruction. Rather, patients characteristically manifest symptoms related to their underlying cirrhosis, a condition present in some patients with CCA. Taken together, the majority of patients with CCA are diagnosed with advanced disease, often precluding potentially curative therapies.

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There are limited therapeutic options for this aggressive disease. The 5-year survival rates drop to 5-15% in the advanced and unresectable settings. The only potentially curative treatment remains surgical resection. Unfortunately, at time of first diagnosis, only about 25% of the patients are eligible for surgery. Moreover, even after curative intent surgery, the clinical outcomes are disappointing, with 5-year survival rates of 7% to 20%.

ABOUT GNS561

GNS561 is a first-in-class investigational lysosomotropic agent with a novel mechanism of action. When combined with MEK inhibitors, GNS561 targets complementary pathways critical for cancer cell survival and proliferation, resulting in potent antitumor activity. The combination is being developed as a potential breakthrough therapy for patients with advanced solid tumors. In December 2021, we licensed the exclusive rights from Genoscience Pharma to develop and commercialize the investigational treatment GNS561 in CCA in the United States, Canada and Europe, including the United Kingdom and Switzerland. In early 2025, GENFIT completed the acquisition of the full intellectual property rights for GNS561 from Genoscience Pharma, expanding upon the limited rights initially obtained through the 2021 license.

ABOUT THE GNS561-222-1 TRIAL

The GNS561-222-1 trial is an ongoing Phase I/II clinical study evaluating the safety, tolerability, and efficacy of GNS561 in combination with a MEK inhibitor in patients with advanced solid tumors. The trial uses RECIST 1.1 criteria to assess tumor response and includes comprehensive biomarker analyses to identify predictive markers of response.

ABOUT GENFIT

GENFIT is a biopharmaceutical company committed to improving the lives of patients with rare, life-threatening liver diseases whose medical needs remain largely unmet. GENFIT is a pioneer in liver disease research and development with a rich history and a solid scientific heritage spanning more than two decades. Today, GENFIT focuses on Acute on-chronic Liver Failure (ACLF) and associated conditions such as acute decompensation (AD) and hepatic encephalopathy (HE). It develops therapeutic assets which have complementary mechanisms of action, selected to address key pathophysiological pathways. GENFIT also targets other serious diseases, such as cholangiocarcinoma (CCA), urea cycle disorders (UCD) and organic acidemia (OA). Its R&D portfolio, covering several stages of development, ensures a constant news flow. GENFIT's expertise in developing high-potential molecules – from early to advanced pre-commercialization stages – culminated in 2024 with the accelerated approval of Iqirvo® (elafibranor) by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom for the treatment of Primary Biliary Cholangitis (PBC). Iqirvo® is now marketed in several countries.[1] Beyond therapies, GENFIT also

[1] Elafibranor is marketed and commercialized, notably in the U.S and Europe, by Ipsen under the trademark Iqirvo®

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has a diagnostic franchise including NIS2+® for the detection of Metabolic dysfunction-associated steatohepatitis (MASH, formerly known as NASH for non-alcoholic steatohepatitis). GENFIT is headquartered in Lille, France and has offices in Paris (France), Zurich (Switzerland) and Cambridge, MA (USA). The Company is listed on the Euronext regulated market in Paris, Compartment B (Euronext: GNFT). In 2021, Ipsen became one of GENFIT's largest shareholders, acquiring an 8% stake in the Company's capital. www.genfit.com

FORWARD LOOKING STATEMENTS

This press release contains certain forward-looking statements with respect to GENFIT, including, but not limited to, statements about the anticipated completion of Phase 1b and initiation of Phase 2 clinical trials; the potential of GNS561 in combination with MEK inhibitors to provide meaningful clinical benefit and represent a breakthrough therapy for patients with advanced solid tumors; the possibility of improving response rates through optimization of dosing and patient selection; plans to potentially further investigate GNS561 in combination with other agents and in additional tumor types; and GENFIT's commitment to advancing treatment options for CCA. 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

PRESS RELEASE

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.

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