PRESS RELEASE

Ipsen presents Phase III NAPOLI 3 trial of Onivyde® regimen demonstrating positive survival results in previously untreated metastatic pancreatic ductal adenocarcinoma at ASCO GI

- Investigational Onivyde® (irinotecan liposome injection) in the NALIRIFOX treatment regimen demonstrated statistically significant improvements in overall survival and progression-free survival compared to nab-paclitaxel plus gemcitabine with a manageable safety profile[1]
- Results represent a potential advance in an aggressive and difficult-to-treat cancer
- Ipsen plans to file a supplemental New Drug Application with the U.S. Food and Drug Administration

PARIS, FRANCE, January 20, 2023, Ipsen (Euronext: IPN; ADR: IPSEY) today presented positive results from the pivotal Phase III NAPOLI 3 trial evaluating an investigational regimen of Onivyde® (irinotecan liposome injection), a long-circulating, liposomal topoisomerase inhibitor, in previously untreated patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). In a late-breaking abstracts session presentation (LBA661) at the 2023 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, the data demonstrating investigational novel NALIRIFOX regimen (liposomal irinotecan 50 mg/m^2 + 5-FU 2400 mg/m^2 + leucovorin 400 mg/m^2 + oxaliplatin 60 mg/m^2) improved overall survival (OS) and progression-free survival (PFS) compared to nab-paclitaxel plus gemcitabine.[1] At the median follow-up of 16.1 months, the investigational Onivyde regimen met its primary endpoint demonstrating a statistically significant improvement in OS of 11.1 months compared to 9.2 months for patients treated with nab-paclitaxel and gemcitabine (HR 0.83 [95% CI 0.70–0.99]; p=0.04).[1†]

“For the first time, a clinical study in the first-line setting for metastatic pancreatic ductal adenocarcinoma demonstrated superior overall survival and progression-free survival for an investigational regimen when compared to standard of care treatment with nab-paclitaxel and gemcitabine,” said Zev Wainberg, M.D. Professor of Medicine at UCLA and co-director of the UCLA GI Oncology Program. “These findings are especially meaningful to people living with this aggressive and difficult-to-treat cancer, representing the potential to prolong life with a safety profile consistent with the safety profile of the treatment components."

“Very few clinical studies in metastatic pancreatic ductal adenocarcinoma have demonstrated efficacy in the past few decades. Progress has been slow with limited treatment options, hence the NAPOLI 3 results are a meaningful advance for people with previously untreated metastatic pancreatic ductal adenocarcinoma,” said Howard Mayer, Executive Vice President and Head of Research and Development for Ipsen. “In totality, the data demonstrate that the investigational Onivyde treatment regimen (NALIRIFOX) provides a survival benefit over nab-paclitaxel plus gemcitabine. We look forward to submitting the data to the FDA.”

NAPOLI 3 secondary outcome measures included PFS, objective response rate (ORR), incidence of treatment-emergent adverse events, serious adverse events, and laboratory abnormalities.

- Trial met its secondary endpoint showing patients treated with NALIRIFOX had a statistically significant improvement in median PFS of 7.4 months versus 5.6 months for nab-paclitaxel and gemcitabine (HR 0.69 [95% CI 0.58–0.83]; p=0.0001).[1†]

- ORR was 41.8 percent (36.8%-46.9%; 95% CI) for patients treated with the NALIRIFOX regimen versus 36.2 percent (31.4%-41.2%; 95% CI) for patients treated with nab-paclitaxel and gemcitabine.[1]
- The safety profile of NALIRIFOX was manageable and consistent with the profiles of the treatment components. The most common grade 3/4 treatment-emergent adverse events (TEAEs) with more than 10 percent frequency in patients receiving NALIRIFOX versus nab-paclitaxel and gemcitabine included diarrhea (20.3% vs 4.5%), nausea (11.9% vs 2.6%), hypokalemia (15.1% vs 4.0%), anemia (10.5% vs 17.4%) and neutropenia (14.1% vs 24.5%).[1]

About the NAPOLI 3 trial[1]
NAPOLI 3 is a randomized, open-label Phase III trial of Onivyde treatment regimen (NALIRIFOX) in patients who have not previously received chemotherapy for metastatic pancreatic ductal adenocarcinoma. NAPOLI 3 enrolled 770 patients across 205 trial site locations in 18 countries. Patients were randomized to receive Onivyde plus 5 fluorouracil/leucovorin and oxaliplatin (NALIRIFOX regimen; n=383) twice in a month (days 1 and 15 of 28-day cycle) compared to an injection of nab-paclitaxel and gemcitabine (n=387) administered three times a month (days 1, 8, 15 of a 28-day cycle).

About Onivyde® (irinotecan liposome injection)
Onivyde is a cancer medicine that blocks an enzyme called topoisomerase I, which is involved in copying cell DNA needed to make new cells. By blocking the enzyme, cancer cells are prevented from multiplying and eventually die. In Onivyde, irinotecan is enclosed in tiny fat particles called 'liposomes,' which accumulate in the tumor and release slowly over time.

Ipsen is planning to file a supplemental New Drug Application with the U.S. Food and Drug Administration for Onivyde in combination with oxaliplatin plus 5- fluorouracil/leucovorin for the treatment of patients with previously untreated mPDAC following the Fast Track Designation granted in 2020. Onivyde is currently approved in most major markets including the U.S., Europe and Asia in combination with fluorouracil (5-FU) and leucovorin (LV) for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. Onivyde is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

Ipsen has exclusive commercialization rights for the current and potential future indications for Onivyde in the U.S. Servier, an independent international pharmaceutical company with an international presence in 150 countries, is responsible for the commercialization of Onivyde outside of the U.S. and Taiwan. PharmaEngine is a commercial stage oncology company headquartered in Taipei and is responsible for the commercialization of Onivyde in Taiwan.

About Pancreatic Ductal Adenocarcinoma
PDAC is the most common type of cancer that forms in the pancreas with approximately 60,000 people diagnosed in the U.S. each year and nearly 500,000 people globally.[2,3] Since there are no specific symptoms in the early stages, PDAC is often detected late and after the disease has spread to other parts of the body (metastatic or stage IV).[4] Even in later stages, weight loss, abdominal pain and jaundice are the most common symptoms making PDAC difficult to detect.[5] Despite significant advances in cancer treatments since the 1970s, no treatment options for PDAC significantly extend life.[4] Currently, fewer than 20 percent of people diagnosed with PDAC survive longer than one year and overall, pancreatic cancer has the lowest five-year survival rate of all cancer types globally and in the U.S.[2,3]

U.S. IMPORTANT SAFETY INFORMATION

BOXED WARNINGS: SEVERE NEUTROPENIA and SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving Onivyde. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving Onivyde in combination with 5-FU and LV. Withhold Onivyde for absolute neutrophil count below 1500/mm3 or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving Onivyde in combination with 5-FU/LV. Do not administer Onivyde to patients with bowel obstruction. Withhold Onivyde for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

CONTRAINDICATION
Onivyde is contraindicated in patients who have experienced a severe hypersensitivity reaction to Onivyde or irinotecan hydrochloride.

Warnings and precautions
Severe neutropenia: **see boxed WARNING**. In patients receiving Onivyde/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients

Severe diarrhea: **see boxed WARNING**. Severe and life-threatening late-onset (onset >24 hours after chemotherapy [9%]) and early-onset diarrhea (onset ≤24 hours after chemotherapy [3%], sometimes with other symptoms of cholinergic reaction) were observed

Interstitial lung disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold Onivyde patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue Onivyde in patients with a confirmed diagnosis of ILD

Severe hypersensitivity reactions: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue Onivyde in patients who experience a severe hypersensitivity reaction

Embryo-fetal toxicity: Onivyde can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during and for 1 month after Onivyde treatment

Adverse reactions
- The most common adverse reactions (≥20%) were diarrhea (59%), fatigue/asthenia (56%), vomiting (52%), nausea (51%), decreased appetite (44%), stomatitis (32%), and pyrexia (23%)
- The most common Grade 3/4 adverse reactions (≥10%) were diarrhea (13%), fatigue/asthenia (21%), and vomiting (11%)
- Adverse reactions led to permanent discontinuation of Onivyde in 11% of patients receiving Onivyde/5- FU/LV; The most frequent adverse reactions resulting in discontinuation of Onivyde were diarrhea, vomiting, and sepsis
- Dose reductions of Onivyde for adverse reactions occurred in 33% of patients receiving Onivyde/5 FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia
- Onivyde was withheld or delayed for adverse reactions in 62% of patients receiving Onivyde/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia
- The most common laboratory abnormalities (≥20%) were anemia (97%), lymphopenia (81%), neutropenia (52%), increased ALT (51%), hypoalbuminemia (43%), thrombocytopenia (41%), hypomagnesemia (35%), hypokalemia (32%), hypocalcemia (32%), hypophosphatemia (29%), and hyponatremia (27%)

Drug Interactions
1. Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of Onivyde
2. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy

Special Populations

- Pregnancy and Reproductive Potential: See WARNINGS & PRECAUTIONS. Advise males with female partners of reproductive potential to use condoms during and for 4 months after Onivyde treatment
- Lactation: Advise nursing women not to breastfeed during and for 1 month after Onivyde treatment

Please see full U.S. **Prescribing Information** including Boxed WARNING for Onivyde.

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About Ipsen

Ipsen is a global, mid-sized biopharmaceutical company focused on transformative medicines in Oncology, Rare Disease and Neuroscience. With Specialty Care sales of €2.6bn in FY 2021, Ipsen sells medicines in over 100 countries. Alongside its external-innovation strategy, the Company's research and development efforts are focused on its innovative and differentiated technological platforms located in the heart of leading biotechnological and life-science hubs: Paris-Saclay, France; Oxford, U.K.; Cambridge, U.S.; Shanghai, China. Ipsen, excluding its Consumer HealthCare business, has around 5,000 colleagues worldwide and is listed in Paris (Euronext: IPN) and in the U.S. through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information, visit ipsen.com

Ipsen's Forward-Looking Statements

The forward-looking statements, objectives and targets contained herein are based on Ipsen's management strategy, current views and assumptions. Such statements involve known and unknown risks and uncertainties that may cause actual results, performance or events to differ materially from those anticipated herein. All of the above risks could affect Ipsen's future ability to achieve its financial targets, which were set assuming reasonable macroeconomic conditions based on the information available today. Use of the words 'believes', 'anticipates' and 'expects' and similar expressions are intended to identify forward-looking statements, including Ipsen's expectations regarding future events, including regulatory filings and determinations. Moreover, the targets described in this document were prepared without taking into account external growth assumptions and potential future acquisitions, which may alter these parameters. These objectives are based on data and assumptions regarded as reasonable by Ipsen. These targets depend on conditions or facts likely to happen in the future, and not exclusively on historical data. Actual results may depart significantly from these targets given the occurrence of certain risks and uncertainties, notably the fact that a promising medicine in early development phase or clinical trial may end up never being launched on the market or reaching its commercial targets, notably for regulatory or competition reasons. Ipsen must face or might face competition from generic medicine that might translate into a loss of market share. Furthermore, the research and development process involves several stages each of which involves the substantial risk that Ipsen may fail to achieve its objectives and be forced to abandon its efforts with regards to a medicine in which it has invested significant sums. Therefore, Ipsen cannot be certain that favorable results obtained during preclinical trials will be confirmed subsequently during clinical trials, or that the results of clinical trials will be sufficient to demonstrate the safe and effective nature of the medicine concerned. There can be no guarantees a medicine will receive the necessary regulatory approvals or that the medicine will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements. Other risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and healthcare legislation; global trends toward healthcare cost containment; technological advances, new medicine and patents attained by competitors; challenges inherent in new-medicine development, including obtaining regulatory approval; Ipsen's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Ipsen's patents and other protections for innovative medicines; and the exposure to litigation, including patent litigation, and/or regulatory actions. Ipsen also depends on third parties to develop and market some of its medicines which could potentially generate substantial royalties; these partners could behave in such ways which could cause damage to Ipsen's activities and financial results. Ipsen cannot be certain that its partners will fulfil their obligations. It might be unable to obtain any benefit from those agreements. A default by any of Ipsen's partners could generate lower revenues than expected. Such situations could have a negative impact on Ipsen's business, financial position or

performance. Ipsen expressly disclaims any obligation or undertaking to update or revise any forward-looking statements, targets or estimates contained in this press release to reflect any change in events, conditions, assumptions or circumstances on which any such statements are based, unless so required by applicable law. Ipsen's business is subject to the risk factors outlined in its registration documents filed with the French Autorité des Marchés Financiers. The risks and uncertainties set out are not exhaustive and the reader is advised to refer to Ipsen's 2021 Universal Registration Document, available on ipsen.com

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† Survival results (OS, PFS) reflect data included in the ASCO GI presentation. These data describe the final analysis after acceptance of the abstract.

References

1. Wainberg, Z.A et al. NAPOLI-3: A Randomized, Open-label Phase 3 Study of Liposomal Irinotecan + 5-fluorouracil/leucovorin + Oxaliplatin (NALIRIFOX) versus Nab-paclitaxel + Gemcitabine in Treatment-naïve Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC). Presented at ASCO Gastrointestinal Cancers Symposium, 2023 January 19-21; San Francisco, California.
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