25 March 2024
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EMADOC-1700519818-1128306
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Onivyde pegylated liposomal (nanoliposomal irinotecan)
Treatment of pancreatic cancer
EU/3/11/933

Sponsor: Les Laboratoires Servier

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Product and administrative information

Product	
Designated active substance	Nanoliposomal irinotecan
Other name(s)	-
International Non-Proprietary Name	Nanoliposomal irinotecan
Tradename	Onivyde pegylated liposomal
Orphan condition	Treatment of pancreatic cancer
Sponsor's details:	Les Laboratoires Servier 50 Rue Carnot 92284 Suresnes Cedex France
Orphan medicinal product designation procedural history	
Sponsor/applicant	Merrimack Pharmaceuticals UK Limited
COMP opinion	7 October 2011
EC decision	9 December 2011
EC registration number	EU/3/11/933
Post-designation procedural history	
Transfer of sponsorship	Transfer from Merrimack Pharmaceuticals UK Limited, United Kingdom, to Baxter Innovations GmbH, Austria – EC decision of 3 December 2014
Sponsor's name change	Name change from Baxter Innovations GmbH to Baxalta Innovations GmbH – EC letter of 28 May 2015
COMP opinion on review of orphan designation at the time of marketing authorisation	8 September 2016
Transfer of sponsorship	Transfer from Baxalta Innovations GmbH, Austria, to Les Laboratoires Servier, France – EC decision of 6 December 2018
Type II variation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson / Armando Genazzani
Applicant	Les Laboratoires Servier
Application submission	26 June 2023
Procedure start	15 July 2023
Procedure number	EMA/H/C/004125/II/0034
Invented name	Onivyde pegylated liposomal

Therapeutic indication	Onivyde pegylated liposomal is indicated: • in combination with oxaliplatin, 5 fluorouracil (5 FU) and leucovorin (LV) for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, • in combination with 5-FU and LV for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine based therapy. Further information on Onivyde pegylated liposomal can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/onivyde pegylated liposomal
CHMP opinion	21 March 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Brigitte Schwarzer-Daum / Frauke Naumann-Winter
Sponsor's report submission	19 July 2023
COMP discussion	12-14 March 2024
COMP opinion (adoption via written procedure)	25 March 2024

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2011 was based on the following grounds:

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- pancreatic cancer (hereinafter referred to as "the condition") was estimated to be affecting approximately 1.4 in 10,000 persons in the European Union, at the time the application was made;
- condition is life threatening due to poor overall survival;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that nanoliposomal irinotecan may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on the characteristics of the new formulation of the product which could provide improved antitumor activity.

The COMP recommends the designation of this medicinal product, containing nanoliposomal irinotecan, as an orphan medicinal product for the orphan indication: treatment of pancreatic cancer.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2016 was based on the following grounds:

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of pancreatic cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression; and life-threatening with a median survival of about 6 months;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that nanoliposomal irinotecan may be of potential significant benefit to those affected by the orphan condition still holds. This is based on the results of a phase III clinical trial showing statistically significant improvement of overall survival in patients treated with the proposed product in combination with 5-fluorouracil and leucovorin, who have progressed following gemcitabine based therapy. No medicinal products are currently authorised for this patient population.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Onivyde, nanoliposomal irinotecan, irinotecan, EU/3/11/933 for treatment of pancreatic cancer is not removed from the Community Register of Orphan Medicinal Products.

3. Review of criteria for orphan designation at the time of type II variation

3.1. Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The commonly used term "pancreatic cancer" usually refers to a ductal adenocarcinoma of the pancreas (including all of its subtypes), which represents approximately up to 85 percent of all pancreatic neoplasms. With regards to aetiology and risk factors most ductal pancreatic cancers are considered sporadic but smoking, obesity and dietary factors such as high consumption of processed meat increase the risk. The signs and symptoms that eventually lead to the diagnosis depend on the

location, the size, and the tissue type of the tumour, and may include abdominal pain, lower back pain, and jaundice. The prognosis is still dismal.

Pancreatic cancer is a severe and challenging malignancy, ranking as the seventh leading cause of cancer-related deaths globally in industrialized countries and the third in the USA. According to GLOBOCAN 2018, it is the 11th most common cancer worldwide, with nearly 459,000 new cases and over 432,000 deaths in 2018. The incidence and mortality rates are higher in older populations and slightly more prevalent in men than in women. Despite advancements in understanding risk factors and early diagnosis tools, the incidence of pancreatic cancer is expected to rise, projecting around 124.278 new cases by 2040 (ECIS).

Diagnosis in early-stage disease is challenging due to the non-specific nature of available tests. Treatment options, including surgery, chemotherapy, and radiotherapy, aim to extend survival or alleviate symptoms, but there is no definitive cure for advanced-stage disease. This highlights the urgent need for continuous research, development of new therapies, and assessment of their outcomes to improve the epidemiology and mortality trends of pancreatic cancer.

The approved therapeutic indication "Onivyde pegylated liposomal is indicated in first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, in combination with oxaliplatin, 5fluorouracil (5FU) and leucovorin (LV)" falls within the scope of the designated orphan condition "Treatment of pancreatic cancer".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor discussed the life-threatening and chronically debilitating nature of the disease.

Despite some improvement in survival due to the availability of new therapeutic treatments, there has been no change in the life-threatening nature of the condition (Kolbeinsson 2023). While pancreatic cancer was reported to be the eighth leading cause of cancer related death in Europe in 2010, it is now predicted to be the fourth cause of cancer related deaths in EU-27, after lung, colorectum and prostate cancer for men and after breast, lung, and colorectum cancer for women with 44, 601 and 44,461 predicted deaths in 2023 respectively. Pancreatic cancer has remained an exception to the general trend of improvement in cancer-related mortality with rates being stable in men (8.2/100,000) and increasing by 3.4% in woman (5.9/100,000) in EU-27 between 2018 and 2023 (Malvezzi 2023). According to GLOBOCAN 2020, the estimated number of deaths in the EU-27 caused by pancreatic cancer is expected to increase by 15.5% from 2020 to 2030 to reach an estimated number of 104,107 deaths in 2030 (GLOBOCAN 2020).

Symptoms for pancreatic cancer are non-specific and tend to arise as a result of mass effect, with jaundice, abdominal pain, weight loss, steatorrhoea and new-onset diabetes being the common signs (Ducreux 2015). Due to the low disease prevalence, screening of asymptomatic adults is not feasible, and those who suffer from hereditary conditions linked to pancreatic cancers and would be eligible for screening only account for <10% of cases (Ducreux 2015, Pereira 2020). As such, most patients have already progressed to advanced or metastatic stage of the disease at the time of diagnosis, which contributes to the prognosis being the lowest of all cancers with a median OS of 9-11 months (Kolbeinsson 2023, Barros 2021). The 1-year and 3-year net survival rates are dismal. Around 25% of

patients with pancreatic cancer (all cases) will survive at 1 year but the rate decreases to below 10% at 3-year following diagnosis (Cabasag 2022).

Only about 20% of pancreatic cancer cases are diagnosed early enough to be eligible for surgery as patients with locally advanced and metastatic cancer, who represent most cases of the pancreatic cancers are not recommended for surgery. However, curative surgery still results in a median survival of 15-20 months and a poor 5-year survival of 8-15% due to a high frequency of local and distant relapses (Lambert 2019). Patients diagnosed with locally advanced or metastatic pancreatic cancer are considered non-curative and are managed with palliative treatment options only (Kolbeinsson 2023). In addition, patients with pancreatic cancers face particular challenges in view of the low curability and low survival rate and often have a lower quality of life than other patients with cancer (Cipora 2023).

The sponsor has presented an adequate level of description of the nature of the disease. The COMP concluded that the condition is chronically debilitating due to pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression and life-threatening with a markedly reduced life expectancy.

Number of people affected or at risk

At the time of maintenance of the orphan designation in 2016, the COMP concluded that the condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union (EU).

The sponsor selected the interactive web-based European Cancer Information System (ECIS) database and contemporary literature as the primary and most relevant sources for the estimation of the current incidence and prevalence of pancreatic cancer in the EU. According to the ECIS, 2020, 95,873 people were diagnosed with pancreatic cancer in the EU27 plus Iceland and Norway in 2020, and 90,169 died the same year. Therefore, the yearly incidence corresponds approximately to the yearly mortality. Table 1 shows the similarity in mortality and incidence, and any differences across the EU27 plus Iceland and Norway (Liechtenstein data was not available). The population of the EU27+ Iceland and Norway for 2020 was 453,060,630persons. (Eurostat, 2023). This corresponds to a crude incidence rate of 2.1 per 10,000.

As such, the sponsor proposes to estimate the prevalence using the yearly incidence instead of the point prevalence, in line with the guidance for diseases of short duration in the guidance document "points to consider in the calculation and reporting of the prevalence of a condition for Orphan Designation (EMA/COMP/436/01 Rev.1)".

Using the yearly incidence rate of pancreatic cancer of 2.1 per 10,000 in the EU27 plus Iceland and Norway, and a duration of the disease inferior to one year, the sponsor proposes a conservative prevalence estimate of 2.1 per 10,000.

Based on the review of the epidemiological data sources found and the assumptions made for the calculations as presented above, the sponsor considered that **2.1 per 10,000** people is the most contemporary, conservative estimate of the prevalence of pancreatic cancer in the EU. The sponsor concluded that the true prevalence for pancreatic cancer remain below the orphan designation threshold of 5 per 10,000 persons. The proposed estimate is in line with the prevalence figures accepted in recent designations and for the latest orphan maintenance procedures evaluated for pancreatic cancer. The prevalence estimate presented by the sponsor is based on comparable data sources, but with a focus on more recent data, to those used in the estimation accepted for the orphan maintenance of Onivyde pegylated liposomal at the time of the MA in 2016.

The COMP however noted that ECIS has been updated with more recent data from 2022 indicating that 101,374 people were diagnosed with pancreatic cancer in the EU27 plus Iceland and Norway in 2022, and 96,043 died the same year. This would slightly increase the prevalence to approximately 2.2 in 10,000. Therefore, for the sake of accuracy, the COMP concluded that pancreas currently affects **approximately 2.2 in 10,000** people in the European community.

The population of the EU27+ Iceland and Norway for 2023 was 454,630,565 persons (Eurostat, 2023).

Table 1. Estimated pancreatic cancer Incidence and Mortality by country (EU-27 plus Iceland and Norway) both sexes, all ages, 2020.

	Incidence			**Mortality**	
Country	**Number (new cases)**	**Crude Rate**	**ASR per 100,000**	**Number of deaths**	**ASR Mortality per 100,000**
Austria	2,011	22.9	22.1	1,940	21.4
Belgium	2,124	18.0	18.2	2,029	17.4
Bulgaria	1,353	19.4	17.9	1,239	16.5
Croatia	865	20.6	19.6	785	17.8
Cyprus	172	14.2	18.9	158	17.6
Czechia	2,466	23.2	23.3	2,207	21.0
Denmark	1,180	20.4	20.3	1,124	19.3
Estonia	295	23.0	21.8	270	19.9
Finland	1,407	25.0	23.0	1,367	22.3
France	14,461	21.4	20.7	13,793	19.6
Germany	21,541	26.7	21.9	20,683	21.0
Greece	2,302	21.5	18.9	2,097	17.2
Hungary	2,499	25.5	25.3	2,348	23.9
Ireland	676	14.7	19.1	618	17.8
Italy	14,155	22.8	19.4	12,917	17.7
Latvia	410	21.8	20.5	361	18.0
Lithuania	585	21.9	20.1	530	18.3
Luxembourg	111	17.5	21.8	89	17.7
Malta	98	22.4	21.7	89	19.7
Netherlands	3,331	19.4	19.2	3,137	18.1
Poland	5,934	15.5	16.5	5,768	16.1
Portugal	1,792	17.7	15.4	1,770	15.2
Romania	3,237	16.4	16.9	3,029	15.9
Slovakia	1,078	19.9	22.7	897	19.0
Slovenia	460	22.0	21.0	406	18.5
Spain	8,211	17.9	16.8	7,568	15.5
Sweden	2,143	21.1	20.6	2,037	19.5
EU-27	94,897	21.3	19.9	89,256	18.6
Iceland	52	15.2	18.9	45	13.2

	Incidence			Mortality	
Norway	924	16.7	19.0	868	17.9
EU-27 + Iceland+Norway	95,873	-	-	90,169	-

* Data exported as ECIS CSV file and presented for EU-27, Both sexes, All ages, 2020;
Source: https://ecis.jrc.ec.europa.eu/explorer.php
ASR: Age Standardised Rate

3.1. Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

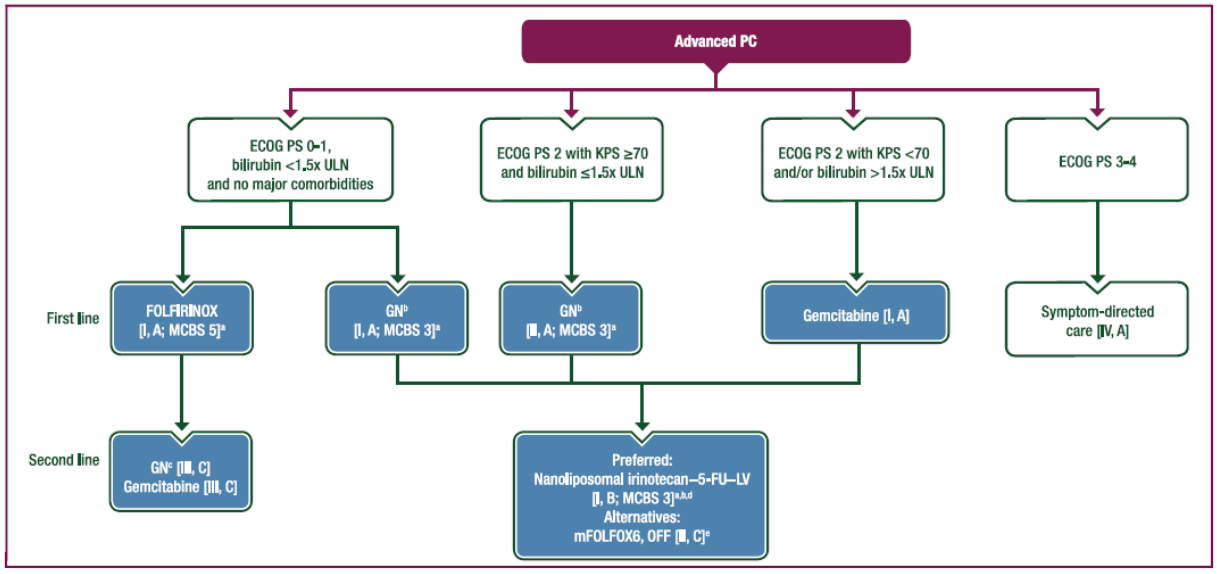
Existing methods

There are several medicinal products authorised in the European Community for treatment of pancreatic cancer in the first line setting both for the induction and the maintenance treatment. Central marketing authorisations (MAs) for the induction treatment include Erlotinib (TARCEVA various generics), Paclitaxel (albumin- bound nanoparticles) (ABRAXANE and PAZENIR), Larotrectinib (VITRAKVI), Entrectinib (ROZLYTREK). Central MAs for the maintenance treatment include Olaparib (LYNPARZA).

Onivyde pegylated liposomal was granted a MA in the EU (Product No. EMEA/H/C/004125) on 14-Oct-2016 and is authorised for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy. This indication extension of Onivyde pegylated liposomal is intended to include first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV).

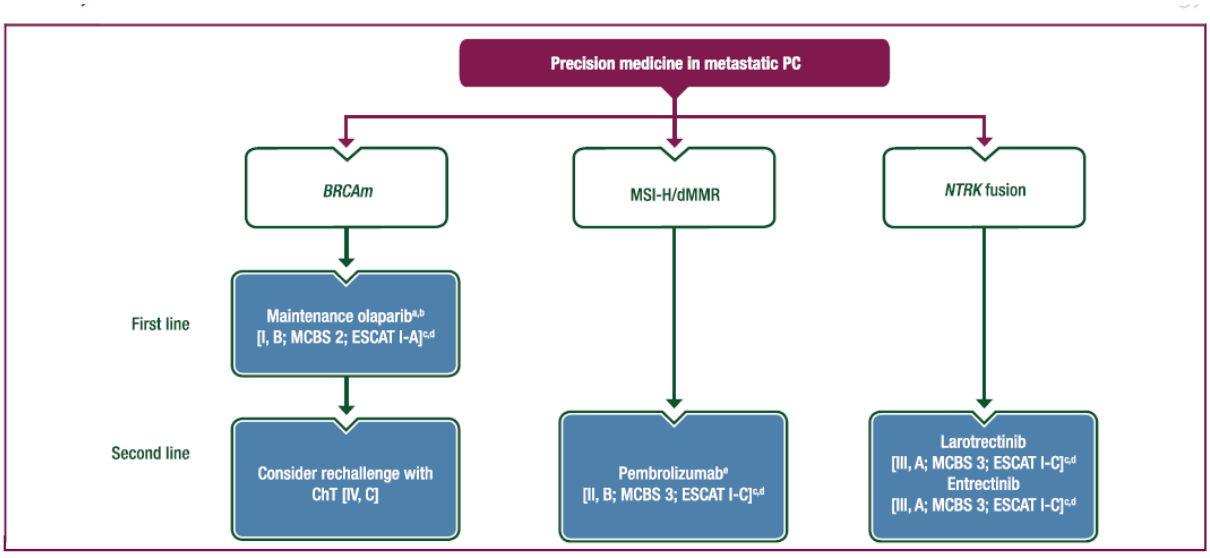
The European Society for Medical Oncology (ESMO) guidance for treatment of Pancreatic cancer, published in 2015 and further updated in 2017 and 2019, focuses firstly on staging the disease through an initial CT scan, endoscopic ultrasound and biopsies. Once staging has been determined, the choice of treatments options depends on the type of tumour (resectable, borderline resectable, locally advanced or metastatic). The treament algorithm in advanced pancreatic cancer is provided in Figures 1, and 2.

Figure 1. Systemic treatment of advanced PC.



Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management. 5-FU, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; FOLFIRINOX, leucovorin–5-fluorouracil–irinotecan–oxaliplatin; GN, gemcitabine–nab-paclitaxel; KPS, Karnofsky performance status; MCBS, ESMO-Magnitude of Clinical Benefit Scale; LV, leucovorin; mFOLFOX6, modified leucovorin–5-fluorouracil–oxaliplatin; OFF, oxaliplatin–fluorouracil–leucovorin; PC, pancreatic cancer; PS, performance status; ULN, upper limit of normal.
Source: ESMO guidelines

Figure 2. Precision medicine in metastatic PC



Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management. ChT, chemotherapy; dMMR, mismatch repair deficient; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; g, germline; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability-high; m, mutated; PC, pancreatic cancer.
Source: ESMO guidelines

Out of the currently approved therapies, Gem+NabP, erlotinib+Gem, 5-FU and Gem monotherapy are considered relevant for a discussion on the significant benefit of NALIRIFOX (Nanoliposomal irinotecan, oxaliplatin, LV and 5-FU) in first-line treatment of metastatic pancreatic cancers compared to other satisfactory method.

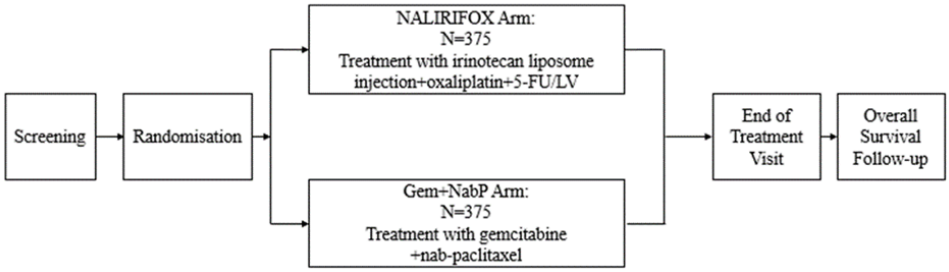
The other treatment options have not gone through regulatory assessment and are not authorised in the EU for the proposed indication. Therefore, these products cannot be considered as satisfactory methods and taken into account for the demonstration of the significant benefit of Onivyde pegylated liposomal in the proposed regimen referred to as NALIRIFOX (Onivyde pegylated liposomal, oxaliplatin, 5-fluorouracil, leucovorin).

Significant benefit

The sponsor received protocol assistance from EMA regarding the on the adequacy of the clinical and statistical design including the comparator arm and the primary efficacy endpoint intended to support a new indication. However, no feedback was sought on the justification of significant benefit with the proposed NALIRIFOX regimen.

The claim of significant benefit is based on the results from the study NAPOLI 3, an open label, randomised, multicentre, international, phase III study. The study evaluated the efficacy and safety of NALIRIFOX regimen (a combination regimen of irinotecan (also referred as irinotecan liposome injection) with oxaliplatin and 5-FU/LV) versus Gemcitabine (Gem) in combination with nanoparticle albumin-bound paclitaxel (NabP) as the first-line treatment for adults with metastatic adenocarcinoma of the pancreas. The study planned to randomise approximately 750 participants in a 1:1 ratio (approximately 375 participants per arm using a block randomisation method) to one of the treatment regimens NALIRIFOX arm (investigational arm) or Gem+NabP arm (control arm) (Figure 3).

Figure 3. NAPOLI 3 Study Design.



The primary objective of the study was to evaluate the efficacy of NALIRIFOX regimen versus Gem+NabP in improving OS as defined as the time from the date of randomisation to the date of death (any cause) in participants who had not previously received chemotherapy for metastatic adenocarcinoma of the pancreas. The secondary efficacy objectives were to evaluate progression-free survival (PFS) and objective response rate (ORR) according to RECIST 1.1 guidelines as per investigator assessment. PFS was defined as the time from randomisation to the first documented objective disease progression using RECIST 1.1 or death due to any cause, whichever occurred first. ORR was defined as the proportion of participants with a best overall response (BOR) characterised as either a complete response (CR) or partial response (PR). The safety of NALIRIFOX was also assessed as a secondary safety endpoint.

Exploratory objectives included Duration of Response (DOR) defined as the time of initial response (CR or PR) until documented tumour progression using RECIST 1.1 per investigator assessment or death due to any cause, Quality of Life (QoL) expressed as time to deterioration or worsening of participants physical functioning, disease related symptoms and treatment-related symptoms of interest using Patient-Reported Outcome (PRO) data collected using the EORTC Core Quality of Life Questionnaire (EORTC QLQ C30) and time to treatment failure (TTF) defined as the time from randomisation to

treatment discontinuation for any reason, including disease progression, treatment toxicity, participant preference, or death.

The sponsor pursued two different approaches to establish the significant benefit of NALIRIFOX over the satisfactory methods of treatment.

- Direct comparison as an efficacy analysis based on clinical data from the pivotal study NAPOLI 3: Comparative analysis of NALIRIFOX versus the regimen gemcitabine + nab-paclitaxel.
- Indirect comparison of efficacy outcomes across clinical studies, between participants treated with NALIRIFOX in study NAPOLI 3 and participants treated with erlotinib in combination with gemcitabine, 5-fluorouracil and gemcitabine monotherapies.

Direct comparison: Significant benefit of NALIRIFOX over the doublet regimen with gemcitabine + nab-paclitaxel

Overview of Efficacy Results

The pivotal study NAPOLI-3 met its primary endpoint of OS and the secondary endpoint of PFS. Efficacy results for the primary endpoint of OS and secondary endpoints of PFS and ORR for the study NAPOLI 3 are summarised in Table 2, Table 3, and Table 4. Secondary efficacy endpoints (PFS and ORR) were only to be evaluated if the primary efficacy endpoint demonstrated superiority for NALIRIFOX over Gem+NabP. According to the hierarchical testing procedure, PFS was first tested followed by ORR.

Overall Survival

Overall Survival is shown in Table 2 with the Kaplan-Meier curve presented in Figure 4. There was a total of 544 (70.6%) OS events. Fewer patients in the NALIRIFOX had died compared to the Gem+NabP arm (259 [67.6%] vs. 285 [73.6]). The NALIRIFOX arm demonstrated a statistically significant difference in OS compared with Gem+NabP based on the stratified log-rank test p-value of 0.04. The median OS was 11.1 months (95% confidence interval (CI): 10.0, 12.1) for the NALIRIFOX arm and 9.2 months (95% CI: 8.3, 10.6) for the Gem+NabP arm. The median OS difference was 1.9 months with a stratified HR of 0.83 (95% CI: 0.70, 0.99), which is clinically meaningful for a disease with a median OS of less than one year.

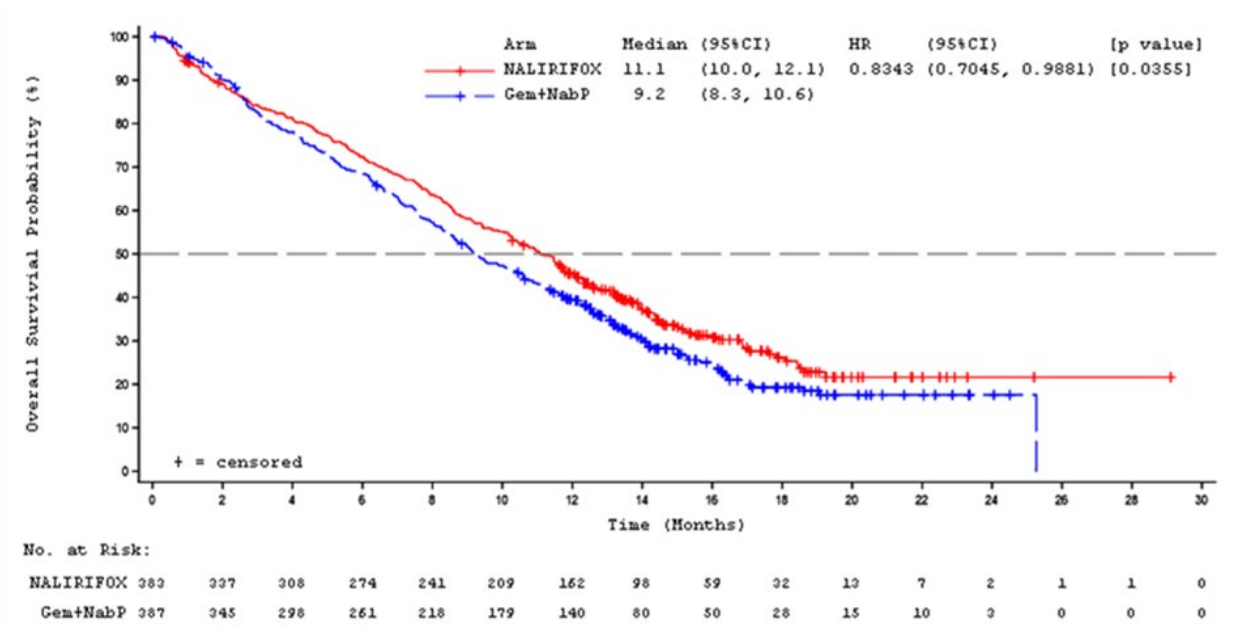
The survival rates at 12 and 18 months were 45.6% and 26.2%, respectively, in the NALIRIFOX arm and 39.5% and 19.3%, respectively, in the Gem+NabP arm.

Table 2. NAPOLI 3 Overall Survival (Intent-to-Treat) Population.

	NALIRIFOX (N=383) n (%)	**Gem+NabP (N=387) n (%)**
Death	259 (67.6)	285 (73.6)
Censored	124 (32.4)	102 (26.4)
Median (95% CI) (months) [a]	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)
Stratified HR (95% CI) [p-value] [b]	0.83 (0.70, 0.99) [0.04]	
Unstratified HR (95% CI) [p-value]	0.84 (0.71, 0.99) [0.04]	
Event free Probability, n, % (95% CI) [a]		
3 Months	319, 84.2 (80.2, 87.5)	315, 82.5 (78.3, 86.0)
6 Months	274, 72.4 (67.6, 76.6)	261, 68.4 (63.5, 72.8)
9 Months	220, 58.1 (53.0, 62.9)	196, 51.8 (46.7, 56.7)
12 Months	162, 45.6 (40.5, 50.5)	140, 39.5 (34.6, 44.4)
18 Months	32, 26.2 (20.9, 31.7)	28, 19.3 (14.8, 24.2)
Median (95% CI) Follow-up (months) [c]	16.0 (15.0, 16.8)	16.3 (15.0, 17.5)

CI=confidence interval, ECOG= Eastern Cooperative Oncology Group, HR=hazard ratio; IWRS=Interactive web response system
a Kaplan-Meier Estimate.
BThe HR and 95% CI are based on a stratified Cox proportional hazards regression model, stratified by baseline ECOG performance status (0 vs. 1), region (North America vs. ROW) and liver metastases (yes vs. no) per IWRS. Gem+NabP is reference.
C Median follow-up is calculated by participants censored at death.
Data Source: CSR NP42379

Figure 4. NAPOLI 3 Kaplan-Meier Curve of Overall Survival (Intent-to-treat Population)



Progression Free Survival

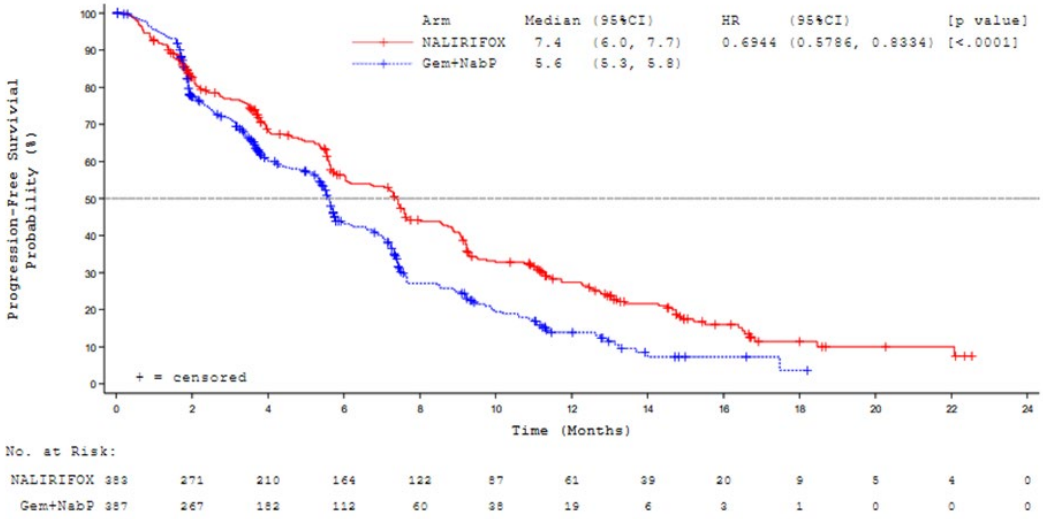
A summary of PFS is presented in Table 3 and Figure 5. There were 508 PFS events. The NALIRIFOX arm demonstrated a statistically significant difference in PFS compared with the Gem+NabP arm based on the stratified log-rank test p-value <0.0001. The median PFS was 7.4 months (95% CI: 6.0, 7.7) for the NALIRIFOX arm and 5.6 months (95% CI: 5.3, 5.8) for the Gem+NabP arm. The median PFS difference was 1.8 months with a stratified HR of 0.69 (95%: 0.58, 0.83).

Table 3. NAPOLI 3 Progression-free Survival According to Investigator Assessment (ITT Population)

	NALIRIFOX (N=383) n (%)	**Gem+NabP (N=387) n (%)**
Participants with PFS Event	249 (65.0)	259 (66.9)
Progressive Disease	183 (47.8)	176 (45.5)
Death	66 (17.2)	83 (21.4)
Participants Censored	134 (35.0)	128 (33.1)
Censored on Day 1	29 (7.6)	19 (4.9)
≥2 consecutive missing tumour assessments	5 (1.3)	2 (0.5)
Subsequent anti-cancer therapy	56 (14.6)	87 (22.5)
Withdrawal of study consent and lost to follow-up	0 (0.0)	8 (2.1)
Censored on last tumour assessments	44 (11.5)	12 (3.1)
Median (95% CI) (months) [a]	7.4 (6.0, 7.7)	5.6 (5.3, 5.8)
Stratified HR (95% CI) [p-value] [b]	0.69 (0.58, 0.83) [<0.0001]	
Unstratified HR (95% CI) [p-value]	0.69 (0.58, 0.83) [<0.0001]	
Event free Probability, n, % (95% CI) [a]		
3 Months	248, 76.9 (72.1, 81.1)	240, 71.5 (66.5, 75.9)
6 Months	164, 56.4 (50.7, 61.6)	112, 43.2 (37.6, 48.6)
9 Months	113, 40.9 (35.3, 46.4)	55, 24.9 (19.8, 30.2)
12 Months	61, 27.4 (22.3, 32.7)	19, 13.9 (9.7, 18.9)
18 Months	9, 11.4 (7.1, 16.9)	1, 3.6 (0.5, 12.3)

CI=confidence interval, ECOG= Eastern Cooperative Oncology Group; HR=hazard ratio, ITT=Intent-to-treat; IWRS=interactive web response system; PFS=progression-free survival
aKaplan-Meier Estimate.
bThe hazard ratio (HR) and 95% confidence interval (CI) are based on a stratified Cox proportional hazards regression model, stratified by baseline ECOG performance status (0 vs. 1), region (North America vs. ROW) and liver metastases (yes vs. no) per IWRS. Gem+NabP is reference.
Data Source: CSR NP42379

Figure 5. NAPOLI 3 Kaplan-Meier Curve of Progression-Free Survival (ITT Population)



Significant benefit of NALIRIFOX over erlotinib in combination with gemcitabine, 5-fluorouracil and gemcitabine monotherapy

Comparison with 5-FU/Fluorouracil and Gemcitabine monotherapies

Monotherapy with 5-FU was replaced with gemcitabine monotherapy as a standard of care following the results of a randomised phase III trial in patients with advanced pancreas cancer (Burris 1997). Gemcitabine showed improved median OS (5.65 months vs 4.41 months), 12-month survival (18% vs 2%) and median time to progressive disease (9 weeks vs 4 weeks) compared to 5-FU. Overall, both treatments were well tolerated, with gemcitabine having a low incidence of nausea, vomiting and alopecia, and some grade 3 or 4 myelosuppression events occurring in the gemcitabine arm. Gemcitabine monotherapy is approved for the same indication as NALIRIFOX, however Nab-paclitaxel in combination with gemcitabine demonstrated better efficacy over gemcitabine with an improved OS of 1.8 months (HR 0.72; 95%CI 0.62-0.83) and an increase of 1.8 months in mPFS (HR 0.69; 95%CI 0.58-0.82). The ESMO guidelines recommend gemcitabine use only for patients with PS of 2 and/or bilirubin level higher than 1.5× ULN, which differs from the population targeted with the NALIRIFOX regimen (patients with ECOG PS0-1). In addition, the mOS for NALIRIFOX regimen obtained in NAPOLI-3 (11.1 months) is nearly doubled to the one observed for gemcitabine monotherapies (5.65-6.7 months) (Table 4).

Comparison with erlotinib/gemcitabine

The combination of erlotinib and gemcitabine showed an overall survival gain of 0.8 months (HR 0.80, 95% CI 0.66-0.98, p= 0.029) in the subset with metastatic cancer compared to gemcitabine. An advantage in terms of mOS and 1-year survival (43% for Grade 2/3 rash vs. 16% for no rash) was observed in the subgroup of patients who developed skin rash. Due to the lack of clinical relevance of improvement to OS (12 days) compared to gemcitabine, erlotinib is not widely used to treat pancreatic cancer (Ducreux 2015) (Table 4). In addition, the mOS for NALIRIFOX regimen obtained in NAPOLI-3 (11.1 months) is also superior to the one observed for erlotinib/gemcitabine (6.4 months).

Table 4. Comparison of efficacy and safety of irinotecan and authorised First-Line Treatment of Metastatic Adenocarcinoma of the Pancreas.

Treatment		**Gemcitabine vs 5-Fluorouracil**	**Erlotinib + Gemcitabine vs Gemcitabine**	**Nab-Paclitaxel + Gemcitabine vs Gemcitabine**	**NALIRIFOX vs Nab-paclitaxel+Gemcitabine**
Key study name		[Burris 1997]	NCIC CTG PA.3 [Moore 2007]	MPACT [Von Hoff 2014]	NAPOLI 3 (Zev A Wainberg 2023)
Dosing regimen		gemcitabine 1000 mg/m^2 on days 1, 8, 15, 22, 29, 36 and 43, then 1week rest and on day 1, 8, 15 for 3 weeks out of 4 weeks vs 5-FU 600mg/m^2 once weekly	erlotinib 100 mg daily + gemcitabine (see gemcitabine monotherapy)	nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 on days 1, 8, and 15, Q4W	50 mg/ m^2 Irinotecan liposome injection, 60 mg/m^2 oxaliplatin, 400 mg/m^2 LV, 2400 mg/ m^2 5FU on days 1 and 15 of each 28-day cycle and 125 mg/ m^2 nab-paclitaxel and 1000 mg/ m^2 gemcitabine on days 1, 8 and 15 of each 28-day cycle
Primary Efficacy End-point*	**mOS months**	5.65 vs 4.41	6.4 vs 5.9 (5.9 vs 5.1 in the sub-population of metastatic pancreatic cancer)	8.5 *vs* 6.7	11.1 vs 9.2
	OS Hazard Ratio (95% CI)	p=0.0025	0.81 (0.69 to 0.99); p=0.038	0.72 (0.62 to 0.83); p<0.0001	0.83 (0.70, 0.99); p=0.04
Secon-dary Efficacy End-point	**mPFS months**	2.3 vs 0.92 (Time to progressive disease)	3.8 *vs* 3.5	5.5 *vs* 3.7	7.4 vs 5.6
	PFS Hazard Ratio (95% CI)	p=0.0002	0.76 (0.64 to 0.92); p=0.006	0.69 (0.58 to 0.82); p<0.0001	0.69 (0.58, 0.83); p=<0.0001

The efficacy data from NAPOLI-3 combined with the presented results of the unadjusted indirect comparison provide adequate evidence to support the claim for significant benefit of NALIRIFOX based on better efficacy in terms of improvement in OS and PFS to treatment compared to the regimen with gemcitabine + nab-paclitaxel.

Conclusion

In conclusion, the claim of significant benefit based on a clinically relevant advantage for NALIRIFOX over the authorised regimens Gem+NabP, erlotinib+Gem, 5-FU and Gem monotherapy can be considered established based on the data provided. The COMP concluded that the data presented are considered sufficient to support maintenance of the orphan designation of Onivyde pegylated liposomal for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV).

4. COMP position adopted on 25 March 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;

- the prevalence of pancreatic cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 2.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;

- the condition is chronically debilitating due to pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression and life-threatening with a markedly reduced life expectancy;

- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Onivyde pegylated liposomal, the claim that Onivyde pegylated liposomal is of significant benefit to those affected by the orphan condition is established. The sponsor has provided clinical study data which demonstrated an improvement in overall survival and progression free survival in patients treated with the combination regimen of Onivyde pegylated liposomal, oxaliplatin, leucovorin and 5-fluorouracil as compared to the authorised medicinal products gemcitabine, nab-paclitaxel, erlotinib, and 5-fluorouracil which are all components of the authorised standard of care treatment regimens for the first line adult patients with metastatic adenocarcinoma of the pancreas.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;

- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Onivyde pegylated liposomal, nanoliposomal irinotecan for treatment of pancreatic cancer (EU/3/11/933) is not removed from the Community Register of Orphan Medicinal Products.