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SCIENCE MEDICINES HEALTH

21 March 2024
EMA/162308/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Onivyde pegylated liposomal

International non-proprietary name: Irinotecan hydrochloride trihydrate

Procedure No. EMEA/H/C/004125/II/0034

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-FU	5-Fluorouracil
ACS	American Cancer Society
ADR	Adverse Drug Reaction
AE	Adverse event
BOR	Best overall response
Cavg	Average concentration
CA 19-9	Carbohydrate Antigen 19-9
CI	Confidence interval
Cmax	Maximum concentration
CHMP	Committee for Medicinal Products for Human Use
CR	Complete response
CSR	Clinical study report
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPR	Enhanced permeability and retention
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration (USA)
FOLFIRI	Regimen: 5-fluorouracil/leucovorin, irinotecan (non-liposomal)
FOLFIRINOX	Regimen: 5-fluorouracil/leucovorin, irinotecan (non-liposomal) + oxaliplatin
FOLFOX	Regimen: 5-fluorouracil/leucovorin and oxaliplatin
GCP	Good Clinical Practice
Gem+NabP	Regimen: gemcitabine + nanoparticle albumin-bound paclitaxel
HR	Hazard ratio
ICH	International Council for Harmonization
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
i.v.	Intravenous

ABBREVIATION	Wording Definition
IWRS	Interactive web response system
KM	Kaplan-Meier method
LV	Leucovorin
MAH	Marketing authorization holder
Nab-paclitaxel	Nanoparticle albumin-bound paclitaxel
NALIRIFOX	Regimen: irinotecan liposome injection, oxaliplatin and 5-fluorouracil/leucovorin
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
PBRER	Periodic benefit risk evaluation report
PD	Progressive disease or disease progression
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PRAC	Pharmacovigilance risk assessment committee
PSUR	Periodic safety update report
PT	Preferred term
RECIST	Response evaluation criteria in solid tumours
RMP	Risk management plan
SAP	Statistical analysis plan
SD	Stable disease
SmPC	Summary of product characteristics
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TOP1	Topoisomerase-1
UGT	Uridine diphosphate glucuronosyl transferase
UGT1A1	Uridine diphosphate glucuronosyl transferase 1A1
UGT1A1*28	Uridine diphosphate glucuronosyl transferase 1A1 pharmacogenetic variant *28
US(A)	United States of America
USPI	United States package insert

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Les Laboratoires Servier submitted to the European Medicines Agency on 26 June 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas for Onivyde in combination with oxaliplatin, 5 fluorouracil (5 FU) and leucovorin (LV) based on final results from phase 3 study NAPOLI 3 (D-US-60010-001); this is an interventional study with a primary objective to evaluate the efficacy of the regimen of irinotecan liposome injection + oxaliplatin + 5-fluorouracil (5-FU)/leucovorin (LV) versus nab-paclitaxel + gemcitabine in improving overall survival (OS) in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas; As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. The updated RMP version 4.1 is also submitted.

Information relating to orphan designation

Onivyde pegylated liposomal, was designated as an orphan medicinal product EU/3/11/933 on 9 December 2011. Onivyde pegylated liposomal was designated as an orphan medicinal product in the following indication:

treatment of pancreatic cancer.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0241/2023 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC)

726/2004 - one year of market protection for a new indication.

Protocol assistance

The Sponsor of NAPOLI-3 study received Protocol Assistance from the CHMP on 28 June 2018 (EMA/CHMP/SAWP/415559/2018). The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	26 June 2023
Start of procedure:	15 July 2023
CHMP Rapporteur Assessment Report	11 September 2023
PRAC Rapporteur Assessment Report	15 September 2023
PRAC Outcome	28 September 2023
CHMP members comments	2 October 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	5 October 2023
Request for supplementary information (RSI)	12 October 2023
CHMP Rapporteur Assessment Report	20 February 2024
PRAC Rapporteur Assessment Report	22 February 2024
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	07 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur Assessment Report	14 March 2024
Opinion	21 March 2024
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Onivyde pegylated liposomal in comparison with existing therapies	21 March 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Globally, more than 495 000 new cases of pancreatic cancers and 466 000 new deaths were estimated to occur in 2020. Pancreatic cancer is the seventh leading cause of cancer-related mortality worldwide, and the fourth most common cause of neoplastic deaths in the European Union (EU). [Sung 2021, Carioli 2021].

Pancreatic ductal adenocarcinoma and its variants account for almost 90% of pancreatic malignancies. Owing to the lack of early symptoms and the aggressive nature of the disease, up to 80% of patients with pancreatic adenocarcinoma receive a diagnosis at an advanced stage, by which time the tumour is unresectable. [Martinez-Bosch 2018, Lambert 2019].

Compared with most other malignancies, it has a very unfavourable prognosis with a mortality to incidence ratio of 0.94, thus almost as many deaths as cases. Median OS of less than 1 year and a 5-year survival rate of 0 to 11%, depending upon the geographic location. However, for patients with metastatic disease who comprise the majority of patients with pancreatic adenocarcinoma at the time of diagnosis, the 5-year survival is only 3%.[ACS 2022, Rawla 2019, Lambert 2019].

State the claimed therapeutic indication

The presently claimed indication is 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).

Management

Gemcitabine monotherapy was the major first-line metastatic pancreatic cancer treatment proven to prolong OS over 5-FU [Burris 1997], leading to the approvals in European countries and by the Food and Drug Administration (FDA) in 1996. The median OS durations were 5.7 and 4.4 months for participants treated with gemcitabine and 5-FU, respectively (a statistically significant difference). The 12-month survival rate was 18% and 2% for participants treated with gemcitabine and 5-FU, respectively.

Erlotinib in combination with gemcitabine was approved by EMA in 2005 based on a RCT vs. gemcitabine monotherapy. Median OS of 6.4 vs. 6.0 months, HR 0.82 (95% CI 0.68, 0.97; p=0.028). In 2013 gemcitabine in combination with nab-paclitaxel was approved by EMA based on a RCT vs. gemcitabine monotherapy. Median OS of 8.5 vs. 6.7 months, HR 0.72 (95% CI 0.62, 0.83; p<0.001).

Both the FOLFIRINOX regimen (irinotecan (non-liposomal) + oxaliplatin + 5-FU/LV) and gemcitabine + nab-paclitaxel have been included in the National Comprehensive Cancer Network (NCCN) [NCCN 2022] and European Society for Medical Oncology (ESMO) practice guidelines as standards of

care for first-line treatment of patients with metastatic pancreatic ductal adenocarcinoma with good performance status.

Despite these treatments, further investigation of first-line treatment options for patients with metastatic adenocarcinoma of the pancreas remains important in view of the poor prognosis and the low median survival rates of less than one-year.

2.1.2. About the product

The active substance in ONIVYDE pegylated liposomal is irinotecan (topoisomerase I inhibitor) encapsulated in a lipid bilayer vesicle or liposome.

Irinotecan is a derivative of camptothecin. Camptothecins act as specific inhibitors of the enzyme DNA topoisomerase I. Irinotecan and its active metabolite SN 38 bind reversibly to the topoisomerase I DNA complex and induce single strand DNA lesions which block the DNA replication fork and are responsible for the cytotoxicity. Irinotecan is metabolised by carboxylesterase to SN 38. SN 38 is approximately 1,000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumour cell lines.

The presently approved therapeutic indication in EU is:

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.

The applied extension of indication is:

ONIVYDE pegylated liposomal is indicated in:

- First-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV).

- Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-FU and LV, in adult patients who have progressed following gemcitabine based therapy.

The approved indication is:

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.

ONIVYDE pegylated liposomal should not be administered as a single agent and should be continued until disease progression or no longer tolerated by the patient.

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:

ONIVYDE pegylated liposomal, oxaliplatin, LV and 5-FU should be administered sequentially. The recommended dose of ONIVYDE pegylated liposomal is 50 mg/m² intravenously over 90 minutes, followed by oxaliplatin 60 mg/m2 intravenously over 120 minutes, followed by LV 400 mg/m2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m2 intravenously over 46 hours. This regimen should be administered every 2 weeks.

Oxaliplatin may be discontinued if not well tolerated and treatment with ONIVYDE pegylated liposomal + 5-FU/LV can continue.

The recommended starting dose of ONIVYDE pegylated liposomal in patients known to be homozygous for UGT1A1*28 allele is unchanged and remains 50 mg/m2 administered intravenously over 90 minutes.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:

ONIVYDE pegylated liposomal, leucovorin and 5-fluorouracil should be administered sequentially. The recommended dose and regimen of ONIVYDE pegylated liposomal is 70 mg/m2 intravenously over 90 minutes, followed by LV 400 mg/m2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m2 intravenously over 46 hours, administered every 2 weeks.

A reduced starting dose of ONIVYDE pegylated liposomal of 50 mg/m2 should be considered for patients known to be homozygous for the UGT1A1*28 allele (see sections 4.8 and 5.1). A dose increase of ONIVYDE pegylated liposomal to 70 mg/m2 should be considered if tolerated in subsequent cycles.

*Table 1:**Recommended dose modifications for ONIVYDE pegylated liposomal + oxaliplatin/5-FU/LV***

Toxicity grade (value) by NCI CTCAE v5.0†	***ONIVYDE pegylated liposomal/Oxaliplatin/5-FU adjustments***	
Haematological toxicities		
Neutropenia	A new cycle of therapy should not begin until the absolute neutrophil count is ≥2,000/mm^3 (2x10^9/L)	
Grade 3 or Grade 4 (<1,000 cells/mm^3) or Neutropenic fever	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 80% of initial dose Reduce oxaliplatin and 5-FU dose by 20%
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 65% of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Third occurrence	Reduce ONIVYDE pegylated liposomal dose to 50% of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Fourth occurrence	Discontinue treatment
Thrombocytopenia Leukopenia	A new cycle of therapy should not begin until the platelet count is ≥100,000/mm^3 (100x10^9/L). Dose modifications for leukopenia and thrombocytopenia are based on NCI CTCAE toxicity grading and are the same as recommended for neutropenia above.	
Non-haematological toxicities‡		
Diarrhoea	A new cycle of therapy should not begin until diarrhoea resolves to ≤ Grade 1 (2-3 stools/day more than pre-treatment frequency).	
Grade 2	A new cycle of therapy should not begin until diarrhoea resolves to ≤ Grade 1 (2-3 stools/day more than pre-treatment frequency).	
Grade 3 or 4	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 80% of initial dose Reduce oxaliplatin and 5-FU dose by 20%

Toxicity grade (value) by NCI CTCAE v5.0†	***ONIVYDE pegylated liposomal/Oxaliplatin/5-FU adjustments***	
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 65% of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Third occurrence	Reduce ONIVYDE pegylated liposomal dose to 50% of initial dose Reduce oxaliplatin and 5-FU dose by an additional15%
	Fourth occurrence	Discontinue treatment
All other toxicities* *Grade 3 or 4*	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 80% of initial dose Reduce oxaliplatin and 5-FU dose by 20%
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to65% of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Third occurrence	Reduce ONIVYDE pegylated liposomal dose to 50% of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Fourth occurrence	Discontinue treatment
For Grade ≥ 3 nausea and vomiting	Reduce dose only if occurs despite optimal anti-emetic therapy	
Hand foot syndrome: Grade 3 or 4	***First occurrence***	Discontinue treatment
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	***First occurrence***	Discontinue treatment
Anaphylactic reaction	***First occurrence***	Discontinue treatment
Interstitial lung disease	***First occurrence***	Discontinue treatment

* Excludes asthenia and anorexia; † NCI CTCAE =National Cancer Institute Common Terminology Criteria for Adverse Events, current version

Patients homozygous for the UGT1A1*28 allele should initiate ONIVYDE pegylated liposomal at the same dose and the same dose reduction requirements should apply.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

EMA scientific advice (SA) was received by the Sponsor of the study on 28 June 2018. (EMEA/H/SA/2441/4/2018/PA/II)

The scope of the SA covered the pivotal trial for ONIVYDE first-line treatment of metastatic adenocarcinoma of the pancreas. The design was overall found acceptable.

2.1.4. General comments on compliance with GCP

The clinical trials were performed in accordance with GCP as claimed by the Applicant.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The extension of the indication applied by the MAH is expected to result in an increased consumption and hence an increased environmental entry, the environmental risks related to the clinical usage of Onivyde Pegylated Liposomal are therefore re-assessed.

PECSURFACE WATER has been re-calculated to include the increased environmental exposure as a consequence of the 1st line treatment of mPaC patients. In practice, the Fpen was refined using the 5-year prevalence of pancreatic cancer in Hungary, which has the highest prevalence of pancreatic cancer in Europe. The reference publication used for the data is considered to be published by a reliable and independent source (IARC) and is thus acceptable. Since the prevalence of all pancreatic cancer represents a worst-case scenario in terms of environmental exposure, it also represents all approved indications for onivyde including this type-II variation.

A Phase I ERA for the API irinotecan has been performed.

Since a log Kow value could not be determined experimentally, the log Dow at pHs 4, 7 and 9 were measured instead. The determined values were -2.03 (pH 4), 0.27 (pH 7) and -0.81 (pH 9) (Table 1). Moreover, an in silico prediction of the log Kow revealed values of 2.33 (neutral molecule) and 0.841 (protonated molecule). All determined values fall well below the threshold of 4.5 defined in the guideline and consequently, PBT testing is not required.

PECSURFACE WATER was calculated for the clinical use of Onivyde Pegylated Liposomal in treatment of mPaC patients. A refinement was performed, taking into account prevalence data published by the Global Cancer Observatory. These can be considered a worst-case scenario, i.e. use of Onivyde Pegylated Liposomal in the overall population of pancreatic cancer patients. As proposed in the guideline, data from the EU country with the highest prevalence for the indication, in this case, Hungary, was used. In addition, the value for PECSURFACE WATER was refined with regards to the dosing regimen. Using appropriate figures in the associated calculations, a PECSURFACE WATER of 0.00113 µg/L was estimated. This figure is below the action limit above which a Phase II ERA is needed. PECSURFACE WATER fell below the action limit of 0.01 µg/L defined in the guideline.

Table 2.Summary of main results

Onivyde pegylated liposomal			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log Kow	OECD 107	Log Dow (pH 4.0) = -2.03 ± 0.01 Log Dow (pH 7.0) = 0.27 ± 0.02 Log Dow (pH 9.0) = -0.81 ± 0.02	Not PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined	0.00113	µg/L	< 0.01 threshold
Other Concerns (e.g. chemical class)		N	N

2.2.2. Discussion and conclusion on non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of Onivyde pegylated liposomal.

Considering the above data, irinotecan is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- *Table 3-Tabular overview of clinical studies:*

Study Identifier	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Participants Enrolled**	**Healthy Participants or Diagnosis of Participants**	**Duration of the Trial**	**Study Status**
NAPOLI 3 D-US-60010-001 (Module 5.3.5.1, NP42379) Pivotal study	Evaluate the efficacy and safety of the regimen of irinotecan liposome injection + oxaliplatin + 5-FU/LV versus nab-paclitaxel+gemcitabine in participants who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas	An open label, randomised, multicentre phase III study with an active control group	NALIRIFOX regimen: Irinotecan liposome injection 50 mg/m^2 + oxaliplatin 60 mg/m^2 + 5-FU/LV 2400/400 mg/m^2, IV infusion q2w versus Gem+NabP regimen: nab-paclitaxel 125 mg/m^2 +gemcitabine 1000 mg/m^2, IV infusion Days 1,8,15 q4w.	770	Metastatic adenocarcinoma of the pancreas	First participant enrolled date: 11 February 2020 Data cut-off for final analysis: 23 July 2022	Ongoing

MM-398-07-02-03 (Module 5.3.5.2, NP42373) Supportive study	Examine the safety, tolerability, and preliminary efficacy of irinotecan liposome injection in combination with 5-FU/LV and oxaliplatin, in participants not previously treated for metastatic pancreatic adenocarcinoma	An open-label, non-randomised multicentre phase II study with no control group	NALIRIFOX regimen and three other regimens[a]: Irinotecan liposome injection 50 mg/m^2 + oxaliplatin 60 mg/m^2 + 5-FU/LV 2400/400 mg/m^2, IV infusion q2w	56 (of which 32 are discussed in this module, since they were treated with the same NALIRIFOX regimen)	Unresectable, locally advanced and metastatic adenocarcinoma of the pancreas	First participant enrolled date: 19 October 2015 Study completion date: 15 February 2021	Completed

5-FU=5-fluorouracil, IV=intravenous, LV=leucovorin, q2w=every 2 weeks, q4w=every 4 weeks a Other dose levels include

irinotecan liposome injection 70 mg/m^2 + oxaliplatin 60 mg/m^2 + 5-FU/LV 2400/400 mg/m^2 irinotecan liposome injection 50 mg/m^2 + oxaliplatin 85 mg/m^2 + 5-FU/LV 2400/400 mg/m^2 irinotecan liposome injection 55 mg/m^2 + oxaliplatin 70 mg/m^2 + 5-FU/LV 2400/400 mg/m^2

2.3.2. Pharmacokinetics

The basic pharmacokinetic properties of irinotecan and SN-38 (metabolite) have been described in detail in the initial MAA CHMP assessment report.

The current application concerns extension of indication to include first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas for Onivyde in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV) based on results from phase 3 study NAPOLI 3.

This was a Phase 3 interventional study with a primary objective to evaluate the efficacy of the regimen of irinotecan liposome injection (50 mg/m2 Q2W) + oxaliplatin + 5-fluorouracil (5-FU)/leucovorin (LV) versus nab-paclitaxel + gemcitabine in improving overall survival (OS) in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.

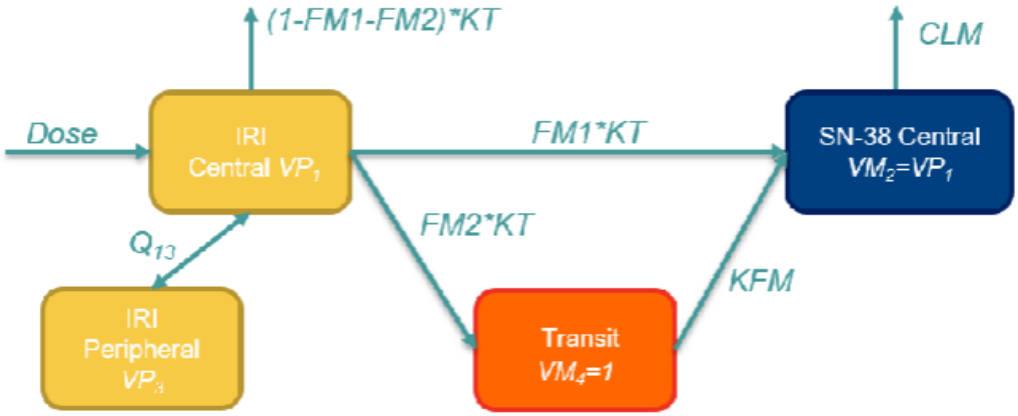
Pharmacokinetic sampling was conducted, and the data were analysed using a population PK approach, exposure-efficacy, and exposure-safety assessment. The purpose of the analysis is to describe the pharmacokinetics in the target population.

Population Pharmacokinetic analysis

The purpose of this analysis was to re-assess a previously developed PopPK model, Report title: *Final Population PK and PK/PD Analysis Update for Onivyde* (Phase 3 SCLC Study MM398-01-03-04 (RESILIENT); Date Issued: 6 SEP 2022). A previously developed model was used as a starting point in this analysis and consisted of two-compartments for irinotecan and one-compartment for SN-38 with first-order elimination for both compounds and two parallel metabolic pathways, one direct and one

delayed by an additional transit compartment, from irinotecan to SN-38. The volume of distribution for SN-38 was assumed to be the same estimated for irinotecan.

Figure 1. Structural PopPK Model for Irinotecan and SN-38



Abbreviations: CLP=irinotecan elimination clearance; FR1 = fraction of parent metabolized via 1st order process; FR2 = fraction of parent metabolized via transit; CLM=SN-38 elimination clearance; FM1=fraction of total rate of elimination accounting for direct transformation of irinotecan into SN-38; FM2=fraction of total rate of elimination accounting for delayed transformation of irinotecan into SN-38; KT=total rate of irinotecan elimination; KFM=rate of SN-38 formation out of transit compartment; Q13=irinotecan apparent inter-compartmental clearance to the peripheral compartment; VM_2=SN-38 central compartment volume; VM4=transit compartment volume; VP1=irinotecan central compartment volume; VP3=irinotecan peripheral compartment volume.

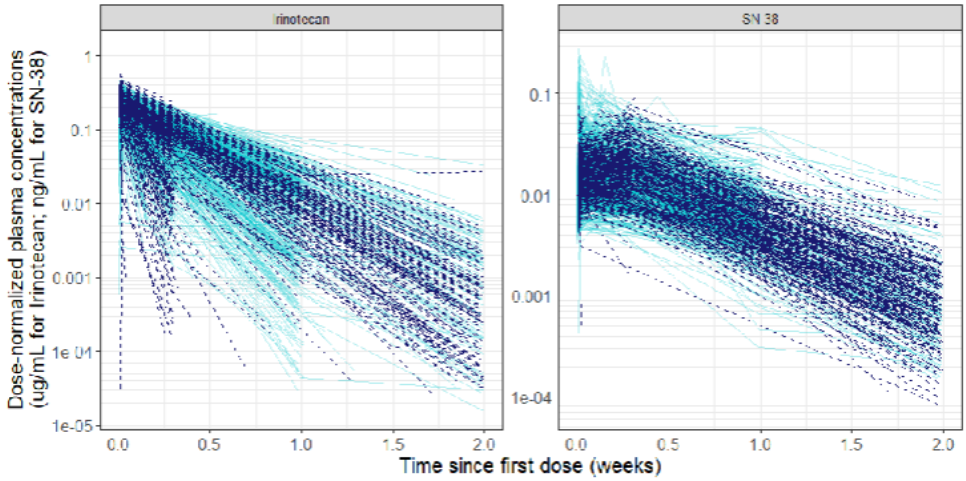
Note: FM1 = FR1 / (1+FR1+FR2), FM2 = FR2 / (1+FR1+FR2)

Irinotecan and SN-38 plasma concentration data from Phase 3 Study D-US-60010-001 (NAPOLI3) were pooled with those collected in former early phase clinical studies (MM398-01-03-04, MM398-07-02-03, PEP0201, PEP0203, PEP0206, PIST-CRC-01, MM398-01-01-02, and MM398-07-03-01).

In NAPOLI3 PK sample collection occurred as follows: Day 1 prior to irinotecan infusion, Day 1 at the end of irinotecan infusion, Day 1 at the end of oxaliplatin infusion, Day 3 within 2 hours prior to the completion of the 5-FU infusion, Days 4 to 14, and Day 15 prior to irinotecan infusion. Samples with irinotecan and/or SN-38 concentrations less than LLOQ were assigned a fictitious concentration of LLOQ/2 when building the PopPK dataset and were treated as missing throughout the PopPK analysis unless otherwise specified. Overall, there were 16.1% of values below the LLOQ (18.3% for irinotecan and 13.9% for SN-38).

Prior to performing the external prediction-corrected visual predictive check (pcVPC) on the new PK data from Study D-US-60010-001, the raw data was explored via R Version 4.1.1 (Figure 2). Exploratory graphical evaluations of the data were performed to detect outlier observations or individuals and to identify potential outstanding differences with data collected in the former clinical studies. Data analyses were performed using the NONMEM software (Version 7.4.3, ICON Development Solutions, Hanover, MD, USA) for nonlinear mixed effects models, on a grid of Intel Xeon servers running the CentOS 7 Linux with Open Grid Scheduler, GNU Fortran Compiler (Version 4.8.5), and Perl-speaks-NONMEM (PsN, Version 4.8.1). Graphical analysis was performed using R software package (Version 4.0.5 or higher).

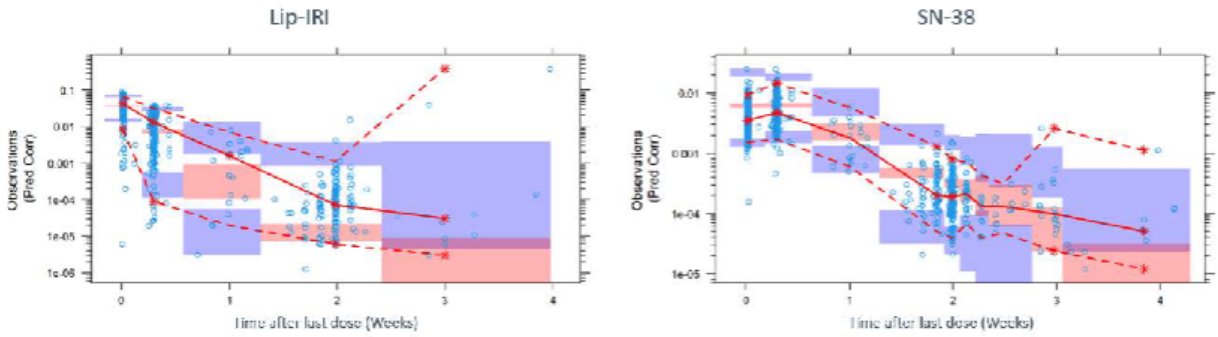
Figure 2. Comparison of Dose-Normalised Irinotecan and SN-38 Plasma Concentration-Time Profiles from Study D.US.60010-001 versus other studies



Note: Blue lines represent NAPOLI3 study, and turquoise represent all other studies.
Final_2022Nov21_IPSEN-EDA_AM_v5.html

As a starting point, the predictive performance of the previously final PopPK model for liposomal irinotecan and SN-38 was assessed on the available PK data collected from Study D-US-60010-001 as an external validation (no re-estimation of parameters, Figure 3)). The exposure was underestimated, and the model was therefore re-assessed (parameter estimates were estimated using the updated dataset). In pcVPCs, both the observations and the model predictions were normalized to population predictions in each bin of the independent variable (i.e., nominal time). Based on the PopPK parameter estimates of the final PopPK model, time profiles of analytes concentrations were simulated in 250 replicates. Within each bin, 90% prediction intervals (PIs) of the 5th, 50th, and 95th percentiles of simulated concentrations were computed across the 250 replicates and compared with the same percentiles of the external data from Study D-US-60010-001.

Figure 3. pcVPC (run223) for External Validation (Study D-US-60010-001 Only, i.e., NAPOLI3)

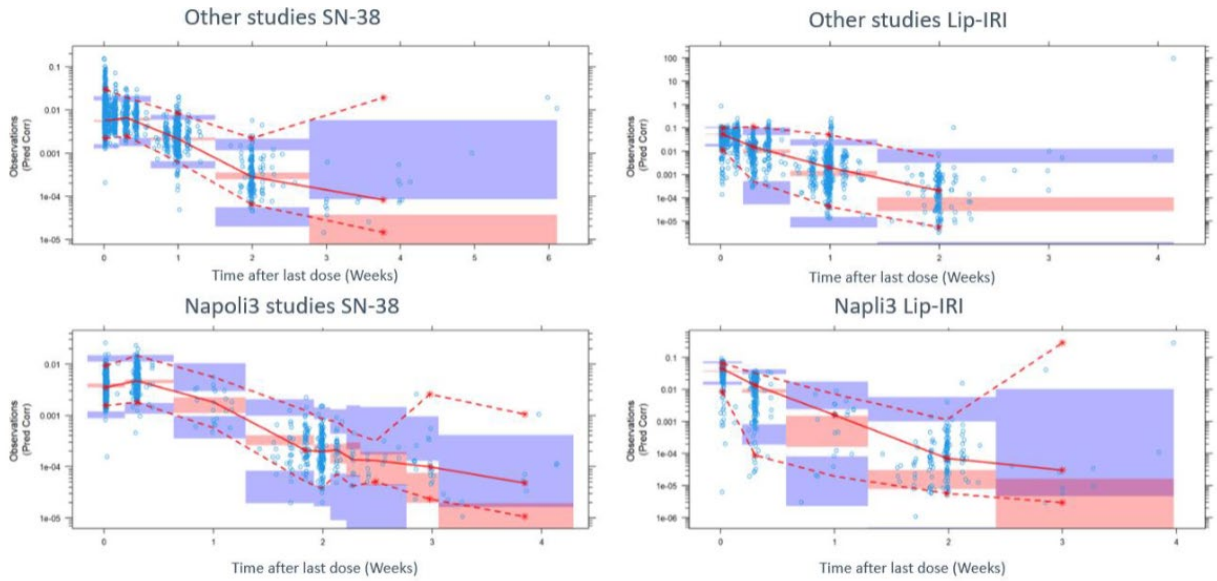


Abbreviations: CI=confidence interval; n=number of observations; Lip-IRI=liposomal irinotecan; pcVPC=prediction-corrected visual predictive check; Pred Corr=prediction corrected.
Notes: The median (solid line), 5th and 95th percentiles (dashed lines) of the observed data are compared to the 90% CIs (shaded areas) for the median (grey area), the 5th and 95th percentiles of the simulated (n=250) data (blue areas). Dotted lines represent predicted 5th and 95th percentiles, while central dashed line represents the predicted median.
Source: IPSEN-runEV001-AA-.html

The model was re-estimated on the full dataset, including available data from Study D-US-60010-001, with no change to either the structure of the model or covariate assumptions (RHO in error model was fixed to 1 due to very high relative standard error [RSE]). The re-estimated model was named F004

(Figure 4). A comparison between parameter estimates (with precision) from the new and the former model showed that the inclusion of data from the NAPOLI3 study (with no further modifications of the joint PK model) led to changes in most parameter estimates as well as in their precisions. However, the percent relative change in the estimated parameters was low across fixed and random effects (with the highest difference in intercompartmental clearance and peripheral compartment volume), with similar, if not better, precision.

Figure 4. pcVPCs (runF004) by Analyte (All Studies)



Abbreviations: CI=confidence interval; n=number of observations; Lip-IRI=liposomal irinotecan; pcVPC=prediction-corrected visual predictive check; Pred Corr=prediction corrected.
Note: The median (solid line), 5th and 95th percentiles (dashed lines) of the observed data are compared to the 90% CIs (shaded areas) for the median (grey area), the 5th and 95th percentiles of the simulated (n=250) data (blue areas). Dotted lines represent predicted 5th and 95th percentiles, while central dashed line represents the predicted median.
Source: IPSEN-runF004-AM.html

Some trend for underestimation was still apparent in irinotecan simulation results. This indicates the inability of the previous model to describe the new irinotecan data from NAPOLI3 study. In addition, the model showed slight underprediction of the SN-38 data after 3 weeks after the last dose, but the number of data points is limited. As a next step, the model was updated to incorporate the effect of potential covariate(s), if any, explaining the model misfit.

Using the base PopPK model (runBasecov derived from runF004 by removing existing covariates) a stepwise covariate search (SCM) was performed. All continuous and categorical covariates listed in Table 4 were tested.

Table 4.Covariates Tested in PopPK Model

Covariate	Reason for Investigation	Parameters				
		CLP	CLM	VP1	FR1	FR2
Age	Standard covariate	√	√			
Asian vs non-Asian	Standard covariate	√	√		√	√
BSA	Standard covariate	√	√	√	√	√
Gender	Standard covariate	√	√	√	√	√
Concomitant therapy: oxaliplatin, 5-FU/LV	Potential DDI	√	√			
Manufacturing sites	Differences in drug product	√	√	√	√	√
Albumin at baseline	Standard covariate	√	√			
Bilirubin, ALT, and AST at baseline	Standard covariate for liver function	√	√			
Presence of liver metastasis at screening/baseline	Potential covariate for liver function	√	√		√	√
UGT1A1*28 polymorphism	Test differences in metabolism rate		√			
Creatinine clearance at baseline	Standard covariate for kidney function	√	√			
ECOG status	Patient functional status	√	√			
Patient effect	Potential effects among different patient groups	√	√	√	√	√

Abbreviations: 5-FU=5-fluorouracil; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSA=body surface area; CLP=clearance of parent; CLM=clearance of metabolite; DDI=drug-drug interaction; ECOG=Eastern Cooperative Oncology Group; FR1=fraction of direct transfer of irinotecan to SN-38; FR2= fraction of direct transfer of irinotecan to SN-38; LV=leucovorin; PopPK=population pharmacokinetic; UGT1A1=uridine diphosphate glucuronosyltransferase 1A1; VP1=peripheral volume of distribution.

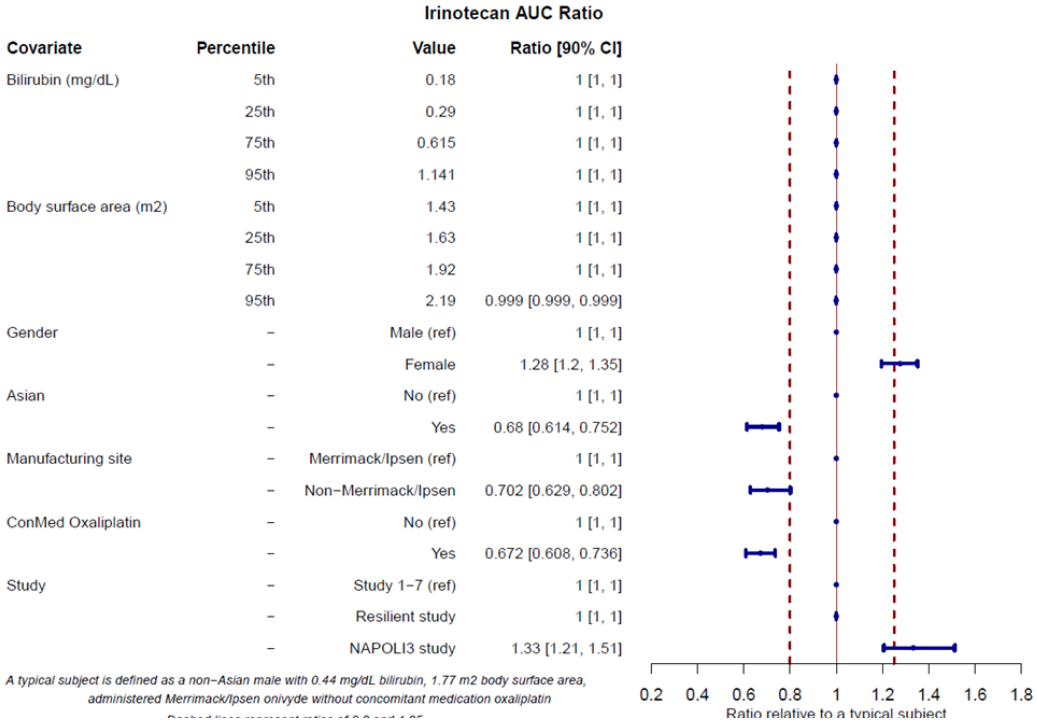
After the full SCM was done, the final model from backward search was used to perform sensitivity test on covariates with very small effect or high %RSE. The final PK parameters are presented in Table 5. A bootstrap with 250 samples has been run to ensure the stability of the final model. Post-hoc exposures were derived by dosing Q2W with last recorded dose for each subject in all the studies that are included in the analysis. The post-hoc exposures illustrating the effects of covariates on irinotecan and SN-38 parameters area under the curve (AUC) and Cmax, conditioned on a typical reference subject, based on the final PopPK model (run final_backward_scm2_2). Reference is a male, non-Asian, BSA 1.77 m², bilirubin 0.44 mg/dL, administered Merrimack/Ipsen site, and without concomitant medication oxaliplatin receiving 50 mg/m².

For irinotecan, Body surface area, female gender, manufacturing site, Asian effect and NAPOLI-3 study have a statistically significant effect on irinotecan Cmax whereas on irinotecan AUC gender, Asian effect, manufacturing site, concomitant Oxaliplatin use, and Resilient study have a statistically significant effect with clinically relevance on the PK (Figure 5). Irinotecan AUC increases are expected in female (28%) and in patient with SCLC indication corresponding to NAPOLI-3 study (33%). Irinotecan AUC decreases are expected in Asians (32%), in old manufacturing site (30%) and with oxaliplatin co-administration (33%).

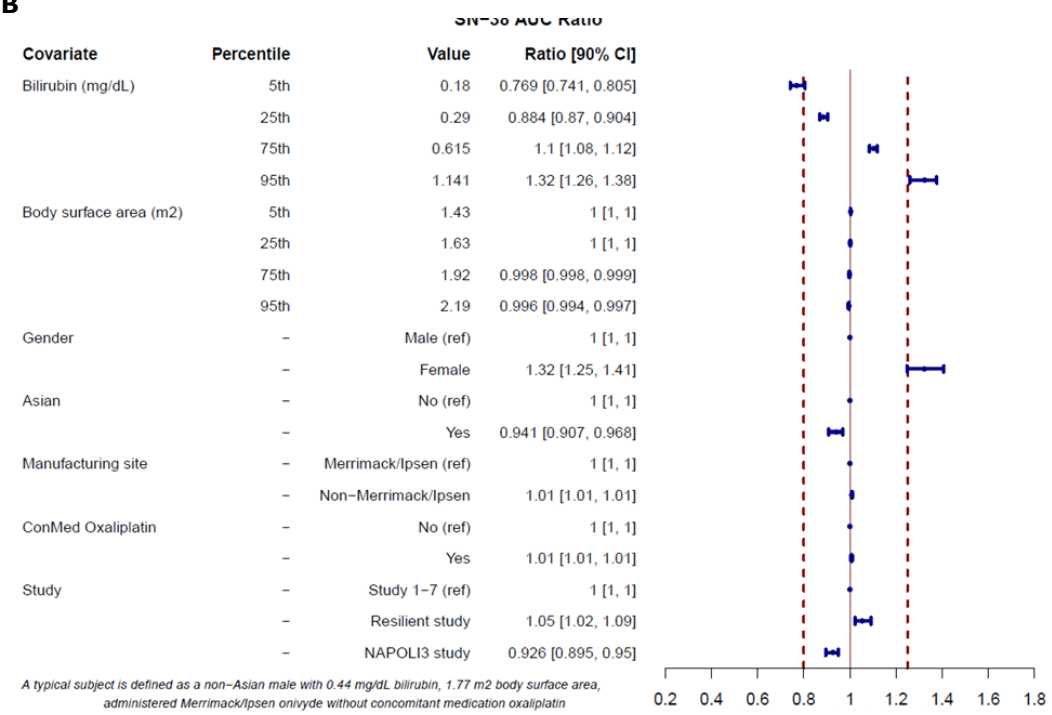
For SN-38, Bilirubin, female gender, manufacturing site, concomitant Oxaliplatin use, Asian effect, BSA, as well as Resilient and NAPOLI3 study have a statistically significant effect with clinical relevance on SN-38 Cmax. On SN-38 AUC, a statistically significant effect was observed with Asian race as well as Resilient and NAPOLI3 study (Figure 5). Furthermore, a statistically significant effect with clinical relevance with Bilirubin and female gender was detected SN-38 AUC. SN-38 AUC increase is expected in female (32%). Regarding bilirubin impact, AUC is decreasing by 23% for the 5th percentiles of bilirubin distribution (0.18 mg/dL) and is increasing by 32% for the 95th percentiles of bilirubin (in comparison with a bilirubin median value of 0.44 mg/dL).

Figure 5. Parametric Forest Plot to Assess the Effect of Relevant covariates on AUC of Plasma Irinotecan (A) and SN-38 (B)

A



B



Abbreviations: CI=confidence interval; AUC=area under the curve; NONMEM=nonlinear mixed-effects modeling.
Note: Closed dots and error bars, together with their specific values, represent the median of the predicted relative change from the reference subject and its associated 90% CIs; these values are calculated based on 500 sampled parameter vectors from the parameter uncertainty (standard error) obtained from NONMEM. The parameter values for a reference subject (for whom covariate characteristics are provided at the bottom of the plot) are shown by the solid vertical line; the dashed vertical lines indicate the 80% to 125% margins relative to the reference subject.

Table 5.Final PK Parameters (final_backward_scm2_2-v2)

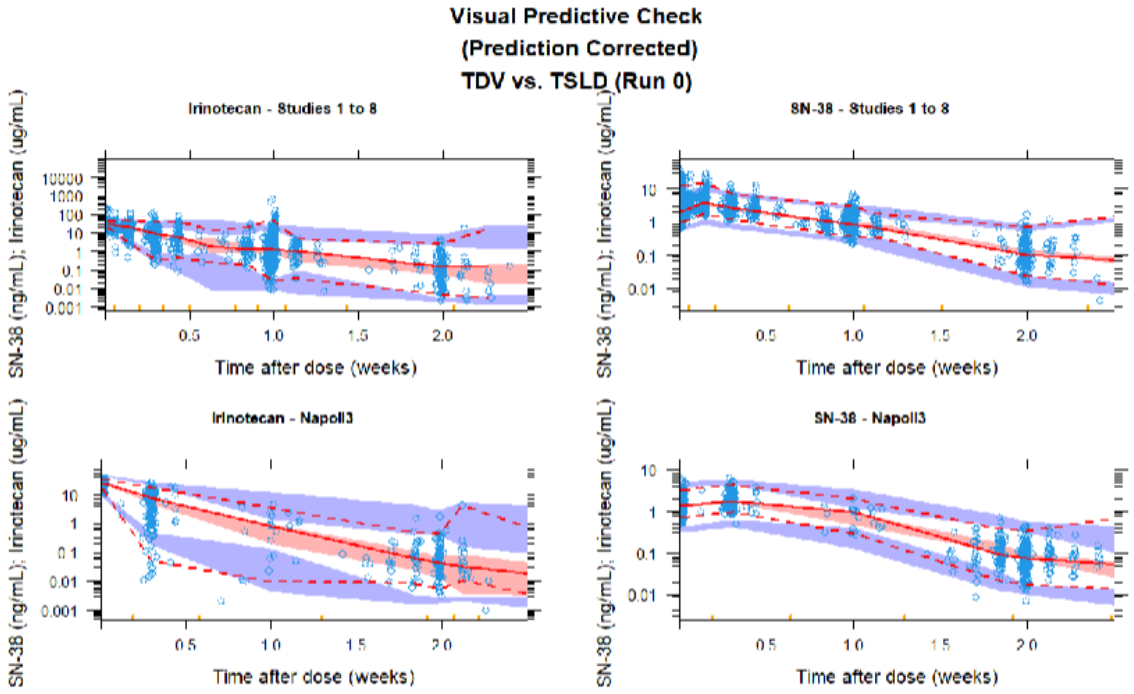
Parameters	Estimates	%RSE	Bootstrap results Median [5% - 95%]
Irinotecan CL (L/wk)	16.6	3.70	16.55 [15.47 – 17.83]
Irinotecan Vc (L)	4.17	1.43	4.17 [4.05 – 4.28]
Irinotecan Q (L/wk)	0.470	42.3	0.47 [0.07 – 0.87]
Irinotecan Vp (L)	0.168	31.0	0.17 [0.07 – 0.12]
f1 for direct transformation of irinotecan into SN-38	0.088	17.30	0.087 [0.061 – 0.12]
f2 for delayed transformation of irinotecan into SN-38	0.326	17.30	0.32 [0.23 – 0.43]
Rate of SN-38 formation out of transit compartment (1/wk)	2.1	1.57	2.11 [2.03 – 2.17]
SN-38 CL (L/wk)	12120	12.0	12069 [9428 – 14825]
Correlation between irinotecan and SN-38 errors	1 FIX	---	1 FIX
Bilirubin effect on SN-38 CL	-0.293	9.64	-0.29 [-0.35 – -0.23]
Gender (female) effect on SN-38 CL	-0.245	10.7	-0.24 [-0.29 – -0.18]
Asian effect on irinotecan CL	0.5	18.4	0.48 [0.33 – 0.66]
Manufacturing site effect on irinotecan CL	0.413	25.4	-0.25 [0.23 –0.65]
Patient effect (NAPOLI3) on irinotecan CL	-0.25	21.1	-0.25 [-0.33 – -0.12]
Gender (female) effect on irinotecan CL	-0.21	13.9	-0.21 [-0.26 – -0.15]
Co-administration with oxaliplatin effect irinotecan CL	0.50	17.6	0.50 [0.35 – 0.67]
Asian effect on f1	-0.312	18.6	-0.32 [-0.43 – -0.20]
Patient effect (NAPOLI3) on f1	-0.313	14.2	-0.30 [-0.39 – -0.21]
Patient effect (Resilient) on f1	0.25	30.9	0.27 [0.11 – 0.43]
BSA effect on irinotecan Vc	0.635	9.2	0.63 [0.52 – 0.74]
Manufacturing site effect on irinotecan Vc	-0.10	35.6	-0.10 [-0.18 – -0.02]

Table 6. Final PK Parameters (final_backward_scm2_2-v2) Cont.

Parameters	Estimates	%RSE	Bootstrap results Median [5% - 95%]
Gender (female) effect on Vc	-0.12	11.7	-0.13 [-0.16 – -0.10]
Patient effect (NAPOLI3) on irinotecan Vc	-0.12	11.4	-0.12 [-0.15 – -0.09]
Random effects			
BSV on SN-38 CL (%)	36.4	5.5	35.7 [31.9 – 39.7]
BSV on rate of SN-38 formation out of transit compartment (%)	25.5	6.73	24.4 [20.4 – 28.2]
BSV on f2 (%)	47.5	6.7	46.9 [40.8 –53.4]
BSV on irinotecan CL (%)	67.1	3.6	66.3 [62.0 –70.9]
BSV on f1 (%)	78.6	3.9	78.1 [72.1 – 84.2]
BSV on irinotecan Vc (%)	20.2	12.6	20.0 [14.9 – 24.2]
Cor (irinotecan CL, f1) (covariance)	-0.41	3.2	-0.41 [-0.47 – -0.35]
Cor (irinotecan CL, irinotecan Vc) (covariance)	0.09	1.2	0.09 [0.065 – 0.116]
Cor (f1, irinotecan Vc) (covariance)	-0.07	1.2	-0.07 [-0.10 – -0.051]
Residual error			
Irinotecan proportional residual variability (%)	26.7	3.7	26.7 [24.7 – 28.4]
SN-38 proportional residual variability (%)	28.5	3.0	28.3 [26.9– 30.1]

Abbreviations: ALT=alanine aminotransferase; BSA=body surface area; BSV=between-subject variability; BSV=between-subject variability; CL=central clearance; Cor=correlation; f1=fraction of total rate of elimination accounting for direct transformation of irinotecan into SN-38; f2=fraction of total rate of elimination accounting for delayed transformation of irinotecan into SN-38; Q=intercompartmental clearance; RSE=relative standard error; Vc=central volume of distribution; Vp=peripheral volume; wk=week.

Figure 6. pcVPCs (final_backward_scm2_2-vpc) for Irinotecan Napoli3 and all other studies



Abbreviations: CI=confidence interval; n=number of observations; Lip-IRI=liposomal irinotecan; pcVPC=prediction-corrected visual predictive check; Pred Corr=prediction corrected.
The median (solid line), 5th and 95th percentiles (dashed lines) of the observed data are compared to the 90% CIs (shaded areas) for the median (grey area), the 5th and 95th percentiles of the simulated (n=250) data (blue areas). Dotted lines represent predicted 5th and 95th percentiles, while central dashed line represents the predicted median.
Source: IPSEN-final_backward_scm2_2-AA-.html

2.3.1. Pharmacodynamics

2.3.2. PK/PD modelling

The updated PopPK model was used to derive individual estimates of Cmax and Cavg of irinotecan and SN-38 for each patient in NAPOLI3 study.

Exposure-safety analyses examining the association between total irinotecan or SN-38 exposures (C max or Cavg) and neutropenia of Grade 3 and above, and diarrhoea of Grade 3 and above were performed on data from the NAPOLI 3 study NALIRIFOX treatment arm after the data cut-off (23 July 2022). Exploratory and logistic regression (LR) analyses indicated that increase in irinotecan and SN-38 systemic exposure was significantly associated with the increased incidence of neutropenia of Grade 3 and above. According to the results from the LR analysis based on the Cavg at the dose prior to the event, increasing the exposure from the minimum (0.135 µg/mL) to the maximum estimated irinotecan Cavg (14.64 µg/mL) resulted in an increase of the probability of neutropenia of Grade 3 and above from 17% to 79% (with a 24% probability of neutropenia of Grade 3 and above for the median Cavg of 2.21 µg/mL). Exploratory and LR analyses indicated that increase in irinotecan and SN-38 systemic exposure was significantly associated with the increased incidence of diarrhoea of Grade 3 and above. According to the results from the LR analysis based on the Cavg at the dose prior to the event, increasing the exposure from the minimum (0.135 µg/mL) to the maximum estimated irinotecan Cavg (9.88 µg/mL) resulted in an increase of the probability of diarrhoea Grade 3 and above from 5% to 87% (with a 13% probability of diarrhoea Grade 3 and above for the median Cavg of 2.16 µg/mL).

Exposure-efficacy analysis examining the relationships between exposure (irinotecan and SN38 average concentration Cavg) and OS, ORR and PFS was performed on the NAPOLI 3 study after the data cut-off (23 July 2022). Participants with best overall response (BOR) of CR or PR were considered as responder for the ORR analysis, while participants with BOR of SD or progressive disease (PD) were not. No statistically significant relationships were found between irinotecan or SN-38 average concentration and OS, PFS or ORR efficacy endpoints.

2.3.3. Discussion on clinical pharmacology

The updated PK analysis dataset included 1058 subjects: 691 from the source dataset (studies PEP0201, PEP0203, PEP0206, PIST-CRC-01, MM398-01-01-02, MM398-07-03-01, MM398-07-02-03, and MM398-01-03-04), and 367 from study D-US-60010-001. Pharmacokinetic data was only available for 1040 patients for irinotecan and 1030 patients for SN-38. The total number of observations was 11763 (5906 for irinotecan and 5857 for SN-38), of which 3418 were from Study D-US-60010-001 (1714 for irinotecan and 1704 for SN-38). Overall, there were 16.1% of values below the LLOQ (18.3% for irinotecan and 13.9% for SN-38). Samples with irinotecan and/or SN-38 concentrations less than LLOQ were assigned a fictitious concentration of LLOQ/2 when building the PopPK dataset and were treated as missing throughout the PopPK analysis unless otherwise specified. When the number of samples below LLOQ is high, it may cause bias in estimates unless adequately handled. Usually a likelihood-based method is recommended as it has shown to reduce bias significantly. A potential problem with the handling of LLOQ-values in this model is that the remaining low observations misrepresent the true lower concentrations; the lower remaining observations are selectively too high. However, given the purpose of the model (Cmax and AUC are reported in section 5.2 of the SmPC and are also the exposure metrics used in the PKPD modelling) the impact of this possible bias is considered low and therefore acceptable.

The population PK analysis was developed mainly for descriptive purposes and the derived information was used to update several sections in the SmPC. The previously developed model that was used as a starting point is not the same as the model submitted in the initial MAA. The updated model was used as a starting point and consisted of two-compartments for irinotecan and one-compartment for SN-38 with first-order elimination for both compounds and two parallel metabolic pathways, one direct and one delayed by an additional transit compartment, from irinotecan to SN-38. The volume of distribution for SN-38 was assumed to be the same estimated for irinotecan.

The new additional data from NAPOLI3 and the supportive study MM-398-07-02-03 were pooled with previously collected data in other indications. First, pcVPCs were generated without re-estimating parameters as an external validation to investigate how well the model can describe the new data. As there was an underestimation of the irinotecan exposure, the parameters were re-estimated. As the model still showed underprediction in exposures from study NAPOLI3 after re-estimation, the covariates in this model were removed and a new covariate selection procedure was conducted using Stepwise Covariate Modelling methodology (SCM). Covariates with statistically significant effects on irinotecan and SN-38 exposures (AUC and Cmax) were evaluated for clinical relevance using Forest plots. According to the external validation plots, the covariates with largest impact on AUC of irinotecan are female gender, concomitant oxaliplatin medication and Asian ethnicity. In addition to concomitant oxaliplatin treatment (given in the study NAPOLI3) NAPOLI3 (study specific covariate) was also found to be a significant covariate in the covariate analysis. The covariates with largest impact on AUC of SN-38 are female gender and bilirubin concentrations. The influence of covariates on exposure is further visualised in forest plots.

The exposure appears to be higher in the NAPOLI3-population compared to other studies (evident through underestimation of exposure using the previously developed popPK model and the fact that

NAPOLI3 study specific covariate was included in the final model). With its response to the request for supplementary information, the MAH presented a comparison of dose-normalised irinotecan concentrations in NAPOLI3 and NAPOLI1 studies (non-first line treatment). It is evident that at early time points, the concentration is higher. The difference is less apparent at day 3, where the concentration intervals are largely overlapping between the studies. The final model included several study specific covariates (NAPOLI3 and concomitant use of oxaliplatin) on different irinotecan PK parameters (CL, f1, Vc). This result should be interpreted with caution since the patient effect cannot be separated from the effect of concomitant use of oxaliplatin (both unique for NAPOLI 3). The statement in section 4.4 of the SmPC on renal impairment was removed at the CHMP's request since there is no recommendation for the prescriber. Moreover, renal function is already mentioned in sections 4.2 and 5.2.

Additional 54 subjects in the dataset (from NAPOLI3 and the supportive study MM-398-07-02-03) were genotyped to be homozygous for UGT1A1*28. As in the market authorisation application, the UGT1A1*28 7/7 genotype was not found to have a clinically significant impact on the pharmacokinetic profile of irinotecan liposome injection. For this reason, the MAH does not propose a dose adjustment based on the UGT1A1*28 genotype for this indication. The applicant proposes that a possible explanation for this is that the liposomal encapsulation slows the release of irinotecan and therefore reduces the load of SN-38, such that the release of irinotecan is the rate-limiting step, and metabolism by UGT enzymes does not become saturated, even in patients with reduced UGT activities (e.g., UGT1A1*28 7/7 homozygous). However, this has not been established. Nevertheless, from a pharmacokinetic perspective it is agreed that a dose-adjustment may not be necessary.

In the population pharmacokinetic analysis, there was no significant association between UGT1A1*28 polymorphism (7/7 homozygous (8%) vs non 7/7 homozygous) and SN-38 clearance. The covariates tested in the population PK analysis are listed in Table 4, including UGT1A1. Furthermore, the statistically significant relationships are visualised in Figure 5 and reported in Table 5.

The model gave an overall acceptable description of the exposure for study NAPOLI3 and seems adequate for deriving individual post-hoc exposure for ER analyses. To ensure that the model can predict data from other studies (currently pooled into one pcVPC) the applicant was requested to provide pcVPCs stratified on study. Stratified pcVPCs were provided as part of the responses to the request for supplementary information. In general, both the irinotecan and the SN-38 models describe the data reasonably well, except for model irinotecan for study MM398-07-02-03 (figures not included). Given that study MM398-07-02-03 is supportive, further model refinement is not considered necessary. In section 5.2 of the SmPC, a table of the exposure in patients administered 50 mg/m2 or 70 mg/m2 has been added. The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received ONIVYDE pegylated liposomal as a single agent or as part of combination chemotherapy, at doses between 35 and 155 mg/m^2 in 1058 patients with cancer using population pharmacokinetic analysis. The pharmacokinetic parameters of total irinotecan and SN-38 analytes, following the administration of ONIVYDE pegylated liposomal 70 mg/m^2 as a single agent or as part of combination chemotherapy and 50 mg/m^2 in the NALIRIFOX regimen (ONIVYDE pegylated liposomal/oxaliplatin/5-FU/LV) are presented. The revised table presents exposure based on NAPOLI3 and NAPOLI1 dosing regimens, respectively, without dosing adjustments.

The ER analyses described included two safety endpoints (neutropenia and diarrhoea grade 3+ AEs) and three efficacy endpoints (ORR, OS, and PFS). Both types of analyses were conducted on data from Study D-US-60010-001, with the purpose of characterizing the probability of each endpoint as a function of irinotecan and SN-38 exposures (via the LR approach) but also explore the relationship with the time of endpoints occurrence/assessment. The results indicated that increase in irinotecan and SN-38 systemic exposure was significantly associated with the increased incidence of diarrhoea grade 3+

AEs and increased incidence of neutropenia grade 3+ AEs. The relationship between efficacy endpoints (ORR, OS, and PFS) and various metrics of systemic exposures (including Cavg and Cmax) for irinotecan and SN-38 was investigated in patients from NAPOLI3 study. No significant relationship was found. As all subjects received the same dosing regimen and combinations treatment, the conclusions that can be made are limited by this aspect. However, considering the rather low impact of the ER analyses within the current procedure, the provided analyses are considered acceptable (no concerns were raised).

2.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of irinotecan pegylated liposome in combination with oxaliplatin and 5-FU/LV in adult first-line patients with metastatic adenocarcinoma of the pancreas were described using model-based population PK analysis. The model is able to describe NAPOLI3 data adequately.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Study MM-398-07-02-03 was an open-label, phase II study to assess the safety, dose-limiting toxicities (DLTs; Part 1A only), followed by dose expansion (Part 1B) of the irinotecan liposome injection+oxaliplatin+5-FU/LV regimen in participants with unresectable, locally advanced and metastatic adenocarcinoma of the pancreas who had not previously received chemotherapy in the metastatic setting.

The participants were treated with 28-day cycles of treatment, unless cycle duration was modified by toxicity. In Part 1A, safety and tolerability were evaluated in a 3+3 dose escalation design across cohorts of subjects treated with a range of irinotecan liposome injection and oxaliplatin dose permutations:

- Cohort 1: irinotecan liposome injection 70 mg/m2 + oxaliplatin 60 mg/m2 + 5-FU/LV 2400/400 mg/m2
- Cohort -1: irinotecan liposome injection 50 mg/m2 + oxaliplatin 60 mg/m2 + 5-FU/LV 2400/400 mg/m2
- Cohort -2B: irinotecan liposome injection 50 mg/m2 + oxaliplatin 85 mg/m2 + 5-FU/LV 2400/400 mg/m2
- Cohort -3: irinotecan liposome injection 55 mg/m2 + oxaliplatin 70 mg/m2 + 5-FU/LV 2400/400 mg/m2.

A planned part 2 covering a comparison of irinotecan liposome injection-containing regimens vs. gemcitabine + nab paclitaxel was removed in an amendment and never commenced.

In Part 1A, adverse events (AEs) were considered to be dose limiting toxicities (DLTs) if they occurred during the safety evaluation period (i.e. 28 days of Cycle 1 or 14 days after the second dose of study treatment if there was a treatment delay) and were deemed related to the study treatment regimen.

Safety evaluations were conducted regularly by the DLT committee to review all serious adverse events (SAEs), AEs and DLTs for each subject to determine the safety and tolerability in each cohort. The DLT committee was comprised of the investigators, the medical monitor, and the sponsor.

DLT definition:

The following adverse events was considered as dose limiting toxicities (DLTs) if they occurred during the first cycle of treatment and were deemed related to the study treatment regimen. Any toxicity that was related to disease progression will not be considered a DLT.

- Grade 4 neutropenia or thrombocytopenia that does not resolve within 7 days despite optimal therapy (withholding study drug and administering concomitant medication, e.g. G-CSF administration for neutropenia)
- Grade 4 neutropenia complicated by fever ≥ 38.5 °C (i.e. febrile neutropenia) and/or Grade 3 neutropenia with infection
- Inability to begin subsequent treatment course within 14 days of the scheduled date, due to drug-related toxicity
- Any grade 4 non-hematologic toxicity with the specific exclusion of:
    - Fatigue/asthenia < 2 weeks in duration
    - Increases in alkaline phosphatase levels
    - Nausea and vomiting ≤3 days duration (only considered dose limiting if they last > 72 hours after treatment with an optimal anti-emetic regimen)
    - Diarrhea ≤3 days duration (only considered dose limiting if diarrhea lasts > 72 hours after treatment with an optimal anti-diarrheal regimen)

In Part 1B, subjects were treated with the regimen chosen during the Part 1A dose exploration.

Planned enrollment was approximately 54 subjects. Subjects had to be at least 18 years of age and have pathologically confirmed adenocarcinoma of the pancreas that had not been previously treated in the metastatic setting: unresectable, locally advanced, or metastatic disease was allowed, diagnosed within 6 weeks prior to Screening.

Objectives

Primary Objective
• To evaluate the safety and tolerability of irinotecan liposome injection +5 fluorouracil/leucovorin (5 FU/LV) + oxaliplatin
• To characterise dose limiting toxicities (DLTs) associated with irinotecan liposome injection +5-FU/LV + oxaliplatin and determine the recommended dose of the triplet combination for future development.

Secondary Objectives
• To characterise the pharmacokinetics (PK) of irinotecan liposome injection in combination with 5-FU and oxaliplatin
• To evaluate efficacy signals with irinotecan liposome injection in combination with 5-FU/LV + oxaliplatin using overall response rate (ORR) (complete response (CR) + partial response (PR), per Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1), disease control rate (DCR) (CR + PR + stable disease (SD), per RECIST Version 1.1), duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

Exploratory Objectives
• To evaluate the relationship between plasma PK of irinotecan liposome injection (total irinotecan, SN-38), in combination with 5-FU and oxaliplatin, and safety and efficacy endpoints in first-line metastatic pancreatic cancer

• To evaluate blood samples and archived tumour tissue for potential biomarkers that may correlate with irinotecan liposome injection in combination with 5-FU/LV and oxaliplatin, PK, toxicity and/or response

Summary of Part 1A Dose Exploration

In Part 1A, safety and tolerability were evaluated across a range of irinotecan liposome injection and oxaliplatin dose permutations to select a recommended dose for the Part IB expansion phase.

- Dose level 1 (oxaliplatin 60 mg/m^2 + irinotecan liposome injection 70 mg/m^2, N=7) was considered not to be tolerable due to two subjects (28.6%) experiencing a DLT event: neutropenic infection in one subject and neutropenic sepsis in another subject.
- **Dose level -1 (oxaliplatin 60 mg/m^2 + irinotecan liposome injection 50 mg/m^2, N=7) was determined to be safe and tolerable since only one subject had a DLT of febrile neutropenia.**
- Dose level -2B (oxaliplatin 85 mg/m^2 + irinotecan liposome injection 50 mg/m^2, N=10) was not considered to be tolerable due to two subjects experiencing DLT events including: diarrhoea, vomiting, anal fissure, anal inflammation and proctalgia.
- Dose level -3 (oxaliplatin 70 mg/m^2 + irinotecan liposome injection 55 mg/m^2, N=7) No subjects experienced DLTs. The BOR was PR in one subject (14.3%) and SD in three subjects (42.9%). However, on review of the Grade 3 and Grade 4 TEAEs this dose level was considered not to be tolerable.

Part 1A: 31 subjects were enrolled and treated in the dose exploration.

Based on the DLTs and cumulative safety Dose level -1 (oxaliplatin 60 mg/m^2 + irinotecan liposome injection 50 mg/m^2) was considered tolerable, with promising antitumour activity and was selected for the Part 1B dose expansion phase.

Efficacy results

Overall, the analysis focused on the pooled population of 32 subjects, consisting of the seven subjects from Part 1A and the 25 subjects from Part 1B treated with irinotecan liposome injection 50 mg/m^2 + oxaliplatin 60 mg/m^2 + 5-FU/LV 2400/400 mg/m^2.

In the pooled population, all of the subjects (100%) discontinued study treatment, including 11 subjects (34.4%) for the primary reason of PD (RECIST Version 1.1 criteria), three subjects (9.4%) for radiologically determined PD (RECIST Version 1.1 criteria) and three subjects (9.4%) for symptomatic deterioration.

Of the 32 evaluable subjects in the pooled population an ORR of 34.4% (95% CI: 18.6 to 53.2) was observed with a median DOR estimate of 9.4 months. The median OS estimate for the pooled population was 12.6 months (95% CI: 8.74 to 19.12) with a 12-month OS rate of 56.3% (95% CI: 37.7 to 73.6); median PFS was 9.2 months (95% CI: 7.59 to 11.96).

Safety results

All 56 subjects (100%) included in the safety population presented with treatment emergent AEs (TEAEs). Of the 32 subjects treated at the selected dose level in the pooled population, all subjects had TEAEs that were evaluated (as per investigator assessment) as related to one or more of the four study drugs within the regimen: irinotecan liposome injection, oxaliplatin and 5 FU/LV. The most frequently reported TEAEs related to the study treatment (>40%) by preferred term (PT) in the pooled analysis were: nausea in 26 subjects (81.3%), diarrhoea in 25 subjects (78.1%), fatigue in 19

subjects (59.4%), vomiting in 15 subjects (46.9%), neutropenia in 13 subjects (40.6%) and decreased appetite in 13 subjects (40.6%).

For the pooled analysis, 29 subjects (90.6%) experienced TEAEs Grade 3 and above and three subjects (9.4%) had TEAEs that led to a fatal outcome (within 30 days following last treatment).

Of the 22 subjects (68.8%) in the pooled population who experienced TEAEs Grade 3 and above related to the study treatment, the most frequently reported were neutropenia in 10 subjects (31.3%); febrile neutropenia and hypokalaemia were both reported in four subjects (12.5%). Diarrhoea, nausea and neutrophil count decreased Grade 3 and above were all reported as treatment-related TEAEs in three subjects (9.4%) in the pooled population. When counting neutropenia and neutrophil count decreased together, a total of 13 subjects (40.6%) experienced these events.

SAEs were reported for 17 of the subjects in the pooled population (53.1%), including 10 subjects (31.3%) for whom the SAEs were assessed as related to treatment. The treatment-related SAEs with the highest incidences were nausea and febrile neutropenia, both experienced by three subjects (9.4%) and diarrhoea and vomiting both experienced by two subjects (6.3%). In the pooled population there were eight subjects (25.0%) with TEAEs leading to discontinuation of treatment and 26 subjects (81.3%) with at least one TEAE leading to dose adjustment. The only TEAE leading to discontinuation experienced by more than one subject in the pooled population was neuropathy peripheral (two subjects, 6.3%) and for which only oxaliplatin was discontinued. The most frequently reported TEAEs leading to dose adjustment in the pooled population were neutropenia/neutrophil count decreased, thrombocytopenia/platelet count decreased, febrile neutropenia, diarrhoea and nausea.

The treatment-related TEAEs experienced by the two subjects homozygous for UGT1A1*28 allele in the pooled population were: febrile neutropenia, diarrhoea, nausea, stomatitis and hypokalaemia.

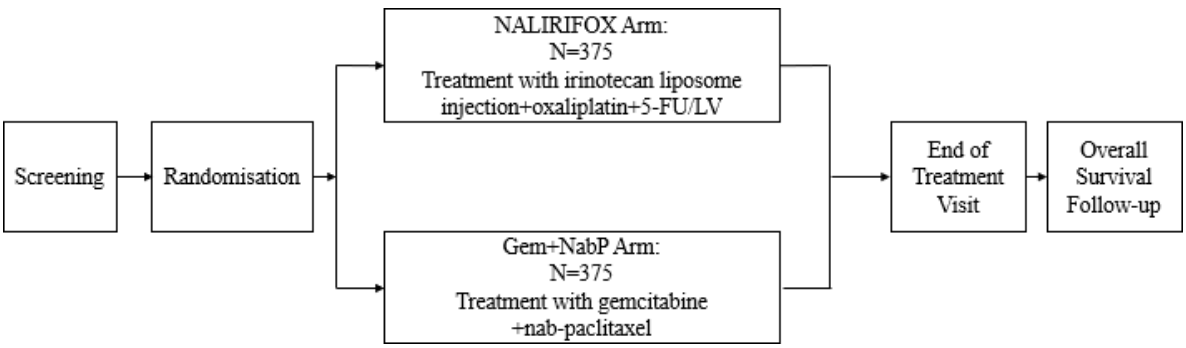
2.4.2. Main study(ies)

NAPOLI 3 (D-US-60010-001, NP42379)

The NAPOLI 3 study (D-US-60010-001, NP42379) is an open label, randomised, multicentre, international, phase III study. The study evaluated the efficacy and safety of NALIRIFOX versus Gem+NabP as first-line treatment for adults with metastatic adenocarcinoma of the pancreas.

Methods

Figure 7. NAPOLI 3 study design



Randomisation was stratified according to:

- Eastern Cooperative Oncology Group (ECOG) performance status (0/1)
- Region (North America/East Asia/Rest of the World (ROW))

- Liver metastases (Yes/No)

For each participant, this study consisted of a 28-day screening period followed by 28-day cycles of treatment until radiologically determined progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, unacceptable study medication related toxicity or withdrawal from study treatment.

Study participants

Main inclusion criteria

Participants were included with:

- Histopathologically or cytologically confirmed adenocarcinoma of the pancreas that had not been previously treated in the metastatic setting
- One or more metastatic lesions measurable by CT scan (or MRI, according to RECIST Version 1.1 criteria)
- Initial diagnosis of metastatic disease (as per American Joint Committee on Cancer 8th Edition [AJCC 2017]) must have occurred ≤6 weeks prior to screening.
- Adequate renal, hepatic and haematological parameters.
    - Subject has adequate biological parameters as demonstrated by the following blood counts:
        - Absolute neutrophil count (ANC) ≥2000/mm^3 without the use of hemopoietic growth factors within the last 7 days prior to randomization
        - Platelet count ≥100,000/mm^3
        - Haemoglobin (Hgb) ≥9 g/dL obtained ≤14 days prior to randomisation.
    - Adequate hepatic function as evidenced by:
        - Serum total bilirubin ≤1.5x upper limit of normal (ULN) (biliary drainage is allowed for biliary obstruction), and
        - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5x ULN (≤5x ULN is acceptable if liver metastases are present).
    - Adequate renal function with a creatinine clearance (CLCR) of >30 mL/min. Actual body weight should be used for calculating CLCR using the Cockcroft-Gault Equation: CLCR(mL/min) = ((140–Age [years]) * (Weight [kg]/(Serum Creatinine [mg/dL]*72). Multiply the result by 0.85 if the subject is female. For subjects with a body mass index (BMI) >30 kg/m^2, adjusted body weight should be used instead.
    - Electrocardiogram (ECG) without any clinically significant findings (QT interval corrected by Fridericia's formula (QTcF) ≤450 msec and no known arrhythmias) and per the investigator's assessment.

Main exclusion criteria

- Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy, however, palliative radiotherapy and placement of biliary stent/tube were permitted

- Prior treatment of pancreatic adenocarcinoma with chemotherapy in the adjuvant setting, except those where at least 12 months had elapsed since completion of the last dose and no persistent treatment-related toxicities were present
- Only localised advanced disease
- Known history of central nervous system (CNS) metastases (participants on a stable or decreasing dose of steroids deemed clinically stable as per the investigator's assessment were eligible)
- Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, diarrhoea > Grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease or partial bowel obstruction
- History of any second malignancy in the previous 2 years; participants with prior history of in situ cancer of basal or squamous cell skin cancer were eligible. Participants with a history of other malignancies were eligible if they had been continuously disease free for at least 2 years prior to screening. Participants who had a concurrent malignancy that was clinically stable and did not require tumour-directed treatment were eligible
- Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma.
- Subjects who have received a live vaccine within 4 weeks prior to randomisation.
- Known low or absent dihydropyrimidine dehydrogenase (DPD) activity. Where required by local regulations, testing for DPD deficiency must be performed using a validated method which is recommended by local health authorities.

Treatments

NALIRIFOX regimen:

Doses and administration of irinotecan liposome injection, oxaliplatin, 5-FU/LV on Days 1 and 15 of each 28-day cycle in the following order:

- Irinotecan liposome injection will be administered at 50 mg/m^2 i.v. over 90 minutes (±10 minutes)
- Oxaliplatin infusion, after completion of irinotecan liposome injection, will be administered at 60 mg/m^2 i.v. over 120 minutes (±10 minutes). Note that oxaliplatin may be omitted due to toxicity.
- LV (l+d racemic form-generic form) infusion will start 30 minutes (+10 minutes) after completion of oxaliplatin administration, at 400 mg/m^2, i.v. over 30 minutes (±5 minutes)
- 5-FU infusion will start within 60 minutes after completion of LV administration, at 2400 mg/m^2 i.v. over 46-hours (±120 minutes).
- As the infusion of 5-FU is administered over 46 hours the subject will go home with an administration pump. The subject will either need to return to the clinic at the end of infusion for removal of the pump or, alternatively, if possible, arrangements might be made for the pump to be removed at the subject's home (except on Cycle 1 Day 3)

Gem+NabP regimen:

Doses and administration of nab-paclitaxel+gemcitabine (established doses as per USPI nab-paclitaxel). On Days 1, 8 and 15 of each 28-day cycle:

- Nab-paclitaxel will be administered at 125 mg/m^2 i.v. over 35 minutes (±5 minutes)
- Gemcitabine will be administered at 1000 mg/m^2 i.v. over 30 minutes (±5 minutes)

Dose adjustment was permitted.

Treatment was continued until radiologically determined progressive disease (PD) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, unacceptable study medication related toxicity or withdrawal from study treatment. Participants could be permitted to receive study treatment beyond PD per RECIST 1.1 as assessed by investigator, if the participant was receiving clinical benefit from study treatment and had received written sponsor or sponsor's delegate approval.

Doses of the Gem+NabP regimen are according to standard dosing. For the NARIRIFOX regimen, LV and 5-FU are given in standard doses but the 5-FU bolus is omitted and oxaliplatin is reduced compared to the FOLFIRINOX regimen.

Objectives and Outcomes/endpoints

Tumour assessments

Tumour response was evaluated by investigators according to RECIST v.1.1, to establish disease progression by computed tomography (CT) or magnetic resonance imaging (MRI) at a scan schedule of every 8 weeks (± 7 days) after randomisation.

Tumour assessments were completed until it had been determined that the participant had PD (in accordance with RECIST v.1.1). For participants who did not have documented disease progression per RECIST 1.1 at the time of treatment termination, imaging studies continued to be performed into the follow-up period every 8 weeks until radiological disease progression was documented or until the start of subsequent anti-cancer treatment, whichever came first.

Objectives and Endpoints

Table 7. NAPOLI 3 Efficacy objectives and endpoints

Objective	Endpoint
Primary To evaluate the efficacy of NALIRIFOX vs Gem+NabP in improving OS in participants who had not previously received chemotherapy for metastatic adenocarcinoma of the pancreas	OS was defined as the time from the date of randomisation to the date of death (any cause)
Secondary • To evaluate PFS according to RECIST 1.1 per investigator assessment • To evaluate ORR according to RECIST 1.1 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 BOR characterised as either a CR or PR.
Exploratory • To evaluate time to deterioration or worsening of participants physical functioning, disease related symptoms and treatment-related symptoms of interest using PRO data collected using the EORTC QLQC30 (note this PRO objective was the only one analysed in the main CSR) • To compare TTF between treatment arms • To compare DOR between treatment arms • To compare TTR between treatment arms	• PRO exploratory endpoints were: ○ Time to deterioration or worsening ○ Rates for Stable, Improved and Worsened QoL Scores • TTF was defined as the time from randomisation to treatment discontinuation for any reason, including disease progression, treatment toxicity, participant preference, or death. • DOR was 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. • TTR was defined as the time from randomisation to the first objective tumour response using RECIST 1.1 per investigator assessment. TTR was computed only for subjects who achieved CR or PR.

BOR=best overall response, CR=complete response, DOR=duration of response, EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer quality-of-life-core questionnaire, ORR=objective response rate, OS=overall survival, PFS=progression-free survival, PRO=patient reported outcome, PR=partial response, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumours, TTF=time to treatment failure, TTR=time to response

Censoring rules for PFS and DoR:

- Subjects who receive non-protocol therapy before a PFS event (documented progression or death) will be right censored at the date of the last evaluable tumour assessment prior to the date of initiation of subsequent therapy/surgery.
- Subjects who have not experienced a PFS event (and are not otherwise censored) at the time of data cut-off will be right censored on the date of their last evaluable tumour assessment post randomisation that is on or prior to the data cut-off. If there is no such tumour

assessment post randomisation, the subject will be right censored on the date of randomisation.

- Subjects who miss two or more scheduled tumour assessments followed by a PFS event will be right censored on the date of their most-recent tumour assessment prior to the missing assessments.

Sample size

The planned sample size was approximately 750 subjects (1:1).

It was expected that 543 OS events were to provide at least 90% power to detect a true HR ≤0.75 (modified OS: 9 versus 12 months) using a stratified log rank test with overall 1-sided significance level of 0.025 (adjusted for the interim analysis).

Assuming enrolment over 16 months increasing to approximately 62 subjects per month and lost-to-follow-up rate of 5% across both treatment arms, the timing of the interim analysis was expected to be at 24 months after the first subject treated and the timing of the final analysis, estimated via simulation, was expected to be at 36.5 months after the first subject treated.

For operational purposes, the expected timing of the final analysis triggering event was to be periodically projected using blinded study data regardless of treatment arm.

Added with CSP amendment 2.0 (20 May 2020) was that the sample size could be increased if a review of accumulating OS events suggested that the timing of the final analysis was to be extended. If blinded projection of the accumulating OS events suggested that the number required for the final analysis was not to be reached (due to censoring) within 32 months of study initiation, the sample size could be increased up to 800 subjects or until prespecified events were met, whichever was earlier. The projection to inform the decision to potentially increase the number of subjects was to be carried out within 3 months prior to expected completion of planned enrolment of 750 subjects.

There were initially three planned analyses for OS: two interim analyses (IA) and a final analysis. Within CSP amendment 4.0 (19 August 2021) the first interim analysis for futility was omitted. The remaining IA was then planned when at least 272 OS events (i.e., 50% information time) had been observed in the Intention to treat (ITT) population. If at this IA, the study was not to be stopped for futility or efficacy the final analysis was planned when at least 543 OS events when 100% of the planned number of subjects had been enrolled.

The overall type I error was to be controlled at 1-sided significance level of 0.025. An alpha and beta spending function according to Hwang-Shi-Decani (HSD) γalpha =-4 and γbeta =-1 was used to control type I and type II errors for the OS comparison. In the computation of the type I error rate, futility analysis was considered non-binding. Since the futility and efficacy boundary was dependent on the number of OS events, the actual boundary used was to be re-calculated, incorporating the spending function, as defined, based on the number of actual OS events analysed at the time of analysis. The p-boundary was to be used as the criteria for the formal statistical inference.

Interim analysis specifications as per the original plan (CSP version 1.0, 3 October 2019) were submitted. In addition, the interim analysis specifications after the implementation of CSP amendment 2.0 (20 May 2020) was submitted.

In the table below the interim analysis specifications after the implementation of CSP amendment 4.0 (19 August 2021) is presented.

Table 8 Type I (α) and Type II (β) Error Spending for the Planned Analyses

(α = 0.025)

		Futility				Efficacy			
Analysis	**D**	**$Z_{boundary}$**	**$p_{boundary}$**	**CUM β spend**	**HR_{crit}**	**$Z_{boundary}$**	**$p_{boundary}$**	**CUM α spend**	**HR_{crit}**
Interim	272	-0.592	0.277	0.038	0.931	-2.750	0.003	0.003	0.716
Final	543	-1.981	0.024	0.100	0.844	-1.981	0.024	0.025	0.844

D = # of OS events at analysis. Z-boundary is the critical test statistic value at which futility (< Z) or efficacy (> Z) would be concluded. P-boundary is the critical one-sided p-value threshold for the comparison. Cum α-spend and cum β-spend are the amount of cumulative type I and type II error spent at each analysis, respectively. HR_{crit} is the observed hazard ratio threshold (> HR for futility, < HR for efficacy).

Randomisation

Patients were randomised using a block randomisation method in a 1:1 ratio with approximately 375 participants per arm. Participants were randomised to the treatment arms using an interactive web response system (IWRS) at a central location. Randomisation was stratified according to:

- Eastern Cooperative Oncology Group (ECOG) performance status (0/1)
- Region (North America/East Asia/Rest of the World).
- Liver metastases (Yes/No).

Blinding (masking)

NAPOLI 3 was not blinded.

Statistical methods

The submitted SAP is version 5.0, 20 September 2022. The first version of the SAP was finalized prior to the first subject randomised.

Analysis populations

Intent-to-Treat Population

This population was to include all randomised subjects. A subject was to be considered randomised if there was confirmation of successful allocation of a randomisation number through IWRS. Subjects were to be analysed according to the treatment and strata they had been assigned to during the randomisation procedure.

Protocol (PP) Population

This was to be a subset of the ITT population including subjects who had no major protocol deviations that could potentially affect the primary efficacy analysis (as described in the protocol deviations document).

PRO Population

All subjects of the randomised ITT population that provided baseline and at least one subsequent assessment on each PRO instrument.

Safety Population

The safety population was to be a subset of the ITT population including subjects who received at least one dose (including a partial dose) of any component of the study medication in the combination therapy). Subjects were to be analysed according to study treatment actually received.

Analysis of OS

Survival was defined as time from the date of randomisation to the date of death (any cause).

OS was to be calculated as follows:

OS (months) = (Death or Censoring Date – Date of Randomisation + 1)/30.4375

Subjects who did not have a date of death recorded at the time of the final analysis was to be censored at the last known time that the subject was alive. For each subject not known to have died as of the data-inclusion cut-off date for a particular analysis, OS was to be censored for that analysis at the date of the last known time that the subject was alive prior to the data cut-off date.

*Table 8-**OS defined per the use of the estimand framework (primary estimand)***

Statistical category	**Estimand:** **Treatment:** Randomized Arm 1 (irinotecan liposome injection+oxaliplatin+5-FU/LV) or Arm 2 (nab-paclitaxel+gemcitabine). **Population:** Subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas as specified in the inclusion and exclusion criteria (Protocol Section 4.1 and Section 4.2), respectively. **Endpoint (Variable)**: Overall survival, defined as the time from randomization date to the date of death. **Intercurrent events:** 1. Start of subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment 2. Permanently discontinuation from study treatment due to any reasons		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**
Primary	ITT	1. Treatment policy strategy: ICE 1 and 2 will not affect the assessment of OS.	Treatment comparison using a stratified log-rank test and HR estimated by stratified Cox regression model.

Stratified analyses, based on the randomisation stratification factors per IWRS, was to be used to compare treatment arms. Differences in the OS curves was to be tested using a stratified and unstratified log-rank test separately with the estimated treatment effect summarised by the HR (95% CI) from both a stratified and unstratified Cox regression analysis.

Overall survival for each treatment arm was to be summarised by median survival time and its 95% CIs from Kaplan-Meier (KM) estimation. KM based OS rates at 3, 6, 9, 12, and 18 months was to be estimated and associated two-sided 95% CIs provided.

Sensitivity Analyses

Besides an unstratified Cox analysis, the following additional sensitivity analyses could be carried out to evaluate the robustness of the primary analysis results:

- Log-rank comparisons of treatments on the PP population
- Log-rank test comparisons of treatments with OS censored at the date where any post study treatment anti-cancer therapy was first administered. This analysis was to be performed on the ITT population.

<u>Analysis of PFS and ORR</u>

Progression Free Survival

The PFS is the time from randomisation to the first documented objective disease progression using RECIST Version 1.1 or death due to any cause, whichever occurs first.

PFS will be calculated as follows:

PFS (months) = (Event or Censoring Date – Date of Randomisation + 1)/30.4375

Determination of PFS was per investigator assessment. Subjects were to be assessed for progression every 8 weeks. After end of treatment visit, subjects who discontinued the study for reasons other than radiologically confirmed disease progression only and had not started any further subsequent anti-cancer treatment was to have scan every 2 months, or 8 weeks.

Main analysis of PFS was planned to be performed on the ITT populations using the same approach as described for the primary analysis of OS.

*Table 9-**Date of Event or Censoring for PFS***

Situation	Date of progression or censoring	Outcome	Description in TLFs
No evaluable baseline tumour assessment	Date of randomisation	Censored	Censored on Day 1
No evaluable post-baseline tumour assessment			
Documented disease progression or death after missing ≥2 consecutive scheduled tumour assessments* of baseline or the last non-PD tumour assessment	Date of last evaluable tumour assessment prior to the first missed assessment or Date of randomisation	Censored	≥2 consecutive missing tumour assessments
Documented disease progression within 2 consecutive scheduled tumour assessments* of baseline or the last non-PD tumour assessment	The Earliest of: • date of tumour assessment showing new lesion (if progression based on new lesion) or • date of tumour assessment of target/non-target lesions in which progression is documented	Event	Progression disease
Death within 2 consecutive scheduled tumour assessments of last the non-PD tumour assessment	Date of death	Event	Death
Withdrawal of study consent and/or lost to follow-up without documented disease progression or death	Date of the last evaluable tumour assessment prior to withdrawal of study consent and/or lost to follow-up or Date of randomisation if no post-baseline tumor assessment	Censored	Withdrawal of study consent and/or lost to follow up
Subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery including subsequent antineoplastic treatment) started without disease progression or death	Date of the last evaluable tumour assessment prior to starting subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment or	Censored	Subsequent anti-cancer therapy
Situation	**Date of progression or censoring**	**Outcome**	**Description in TLFs**
	Date of randomisation if no post-baseline tumor assessment		
None of the following: • disease progression or death • 2 consecutive missing scheduled tumour assessments • Withdrawal of study consent and/or lost to follow-up • Subsequent anti-cancer therapy	Date of the last evaluable tumour assessment or Date of randomisation if no post-baseline tumor assessment	Censored	Censored on last tumour assessments

*Two consecutive post-baseline tumor assessments are based on protocol scheduled tumor assessments. The window of the tumor assessment is considered. Subjects are expected to have scans every 8 weeks, a subject who goes more than 18 weeks (16 weeks + 2 week) without a scan is considered missing 2 consecutive scheduled tumour assessments. If patients had subsequent anti-cancer therapy, missing 2 consecutive scheduled tumour assessments and withdrawal of study consent or lost to follow-up on same date, censored reason will be assigned in the order of 2 consecutive scheduled tumour assessments > anti-cancer therapy > withdrawal of study consent or lost to follow-up.

*Table 10-**PFS defined per the use of the estimand framework***

Statistical category	**Estimand:** **Treatment:** Randomized Arm 1 (irinotecan liposome injection+oxaliplatin+5-FU/LV) or Arm 2 (nab-paclitaxel+gemcitabine). **Population:** Subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas as specified in the inclusion and exclusion criteria (Protocol Section 4.1 and Section 4.2), respectively. **Endpoint (Variable)**: PFS, defined as the time from randomization date to the date of death or disease progression per RECIST v1.1. **Intercurrent events:** 1. Start of subsequent anti-cancer treatment(drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment 2. Withdrawal of study consent and/or lost to follow-up without documented disease progression or death 3. Two and more consecutively missing scheduled tumor assessments		
	Analysis set	**Intercurrent event handling strategy**	**Population-level summary (Analysis):**
Secondary	ITT	Hypothetical strategy: Patients with ICE 1, 2 and 3 will be censored at last evaluable tumour assessment prior to starting subsequent anti-cancer therapy (drug therapy, curative radiotherapy, curative surgery) including new antineoplastic treatment, withdrawal of study consent and/or lost to follow-up or the first missed tumour assessment, respectively	Treatment comparison using a stratified log-rank test and HR estimated by stratified Cox regression model.

As a sensitivity analysis, the primary (PFS) analysis was to be repeated based on the PP population. In addition, a sensitivity analysis was to be performed by applying a treatment policy on withdrawal of study consent and/or lost to follow-up without documented disease progression or death on ITT population.

KM curves were to be plotted by treatment arm on ITT and PP populations respectively.

Overall Response Rate

ORR was defined as the proportion of subjects with a best overall response (BOR) characterised as either a complete response or partial response per RECIST Version 1.1 as assessed by the investigator and analysed based on ITT.

Subjects with only non-measurable disease at baseline was to be part of the analysis and be included in the numerator only if a CR was observed. Tumour assessments performed before the start of any further subsequent anti-cancer therapy was to be considered in the assessment of BOR.

The ORR was to be summarized by treatment arm and associated 95% CI was to be estimated using the Clopper Pearson method using the ITT populations. The ORR of Arm 1 was to be compared to Arm 2 using a Cochran-Mantel-Haenszel test adjusting by randomisation stratification factors per IWRS, and odds ratio (and corresponding 95% CI) was to be estimated using Mantel-Haenszel method.

As a sensitivity analysis, the primary comparison was to be repeated for the PP population.

Multiple Comparisons/Multiplicity

The secondary efficacy endpoints, PFS and ORR, were only to be evaluated if OS/the primary efficacy endpoint demonstrated superiority for irinotecan liposome injection+oxaliplatin+5 FU/LV over nab paclitaxel + gemcitabine.

If the primary endpoint of OS was declared statistically significant at the interim, secondary endpoints were to be tested at the interim. Otherwise, the testing of secondary efficacy endpoints was to be performed at the final analysis of OS if found to be statistically significant at that analysis.

Hypothesis testing of secondary endpoints was to be conducted in a stagewise hierarchical manner incorporating alpha spending for each endpoint using HSD γalpha= -4, similar to that specified for the primary efficacy analysis. The nominal level for each comparison was to depend on whether the analysis was carried out at the interim or at the planned final analysis. The first endpoint in the hierarchy of secondary endpoints was PFS. If OS and PFS were both significant, then ORR would be tested.

All other endpoints were to be regarded as descriptive and exploratory.

Interim analysis

An IDMC was established to operate as an independent expert advisory group with the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals. The same IDMC was to also evaluate the efficacy data as well as the safety data at the time of the interim analysis and were responsible for making appropriate recommendations based on those results.

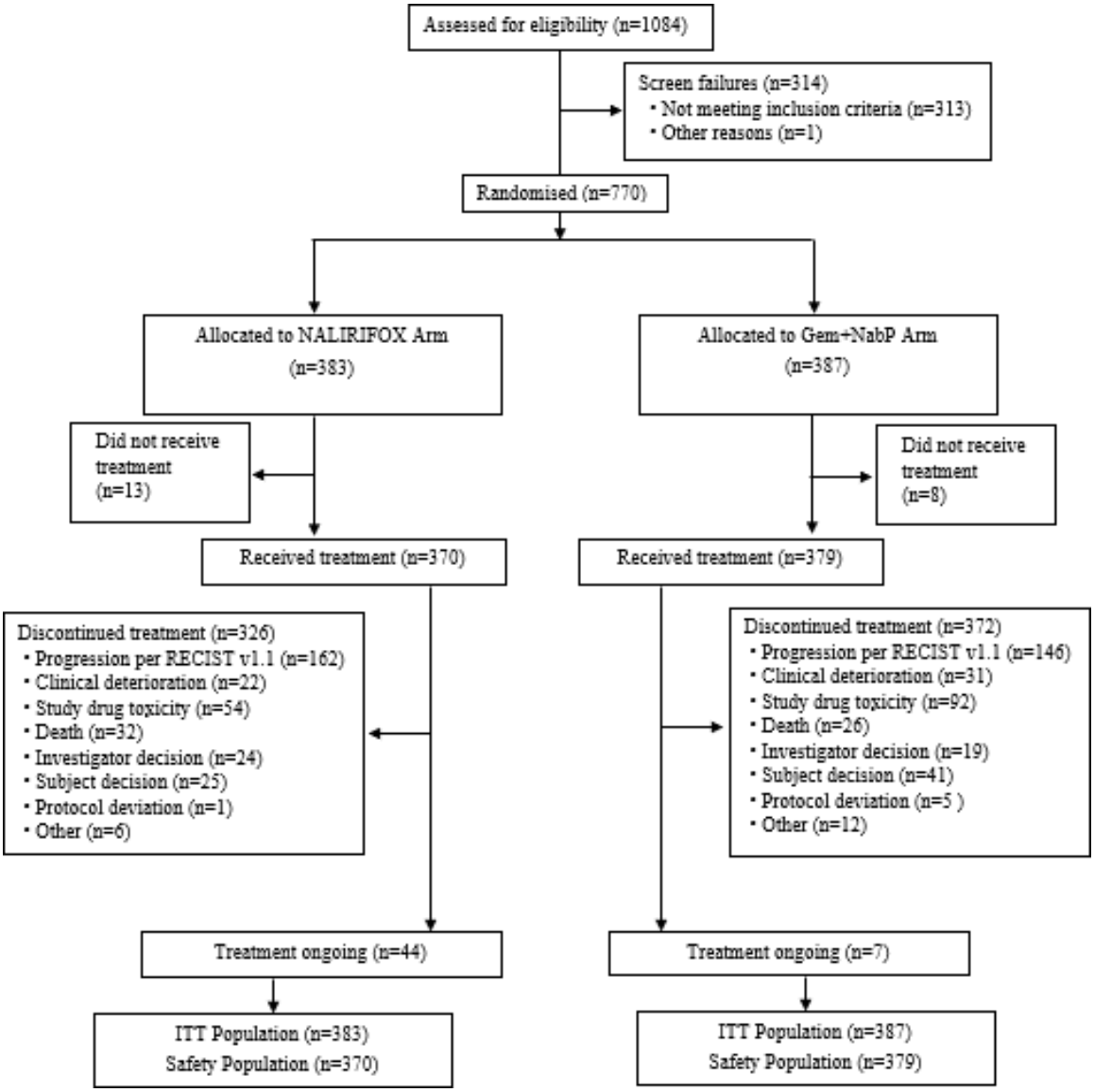
Details were documented in the separate IDMC charter.

To maintain the scientific integrity of this trial, access to by treatment arm study data was to be strictly controlled prior to the interim and final analyses. During this time, analyses using actual treatment codes were to be performed only at the interim analysis points and IDMC data review specified in the protocol/SAP. For those safety and efficacy analyses assigned to the IDMC, only the designed independent statistical team, was to perform the by treatment arm analyses.

Results

Participant flow

Figure 8. Participant disposition (all screened patients)



ITT= Intent-to-treat

The MAH submitted an updated DCO from 3 October 2023 during the evaluation procedure.

Table 11.Disposition of patients, based on October 3rd, 2023 snapshot

	NALIRIFOX (N=383) n (%)	Gem+NabP (N=387) n (%)	Total (N=770) n (%)
Screened Population			1084
Not Randomised			314
Primary Reason for Not Randomised			
Does Not Meet Entry Criteria			313
Other			1
Randomised	383 (100.0)	387 (100.0)	770 (100.0)
Never Treated	13 (3.4)	8 (2.1)	21 (2.7)
Treated as Randomised	370 (96.6)	379 (97.9)	749 (97.3)
Ongoing Study Treatment	11 (2.9)	0 (0.0)	11 (1.4)
Discontinued from Study Treatment	359 (93.7)	379 (97.9)	738 (95.8)
Entered Long-term Follow-up	265 (69.2)	269 (69.5)	534 (69.4)
Discontinued from Long-term Follow-up	235 (61.4)	238 (61.5)	473 (61.4)
Ongoing Long-term Follow-up	30 (7.8)	31 (8.0)	61 (7.9)
Discontinued from Study	338 (88.3)	356 (92.0)	694 (90.1)
Primary Reason for Treatment Discontinuation			
Progressive Disease	211 (55.1)	181 (46.8)	392 (50.9)
Progressive Disease Per RECIST	187 (48.8)	150 (38.8)	337 (43.8)
Progressive Disease Clinical	24 (6.3)	31 (8.0)	55 (7.1)
Adverse Event	54 (14.1)	94 (24.3)	148 (19.2)
Withdrawal by Subject	27 (7.0)	41 (10.6)	68 (8.8)
Death	32 (8.4)	26 (6.7)	58 (7.5)
Physician Decision	27 (7.0)	20 (5.2)	47 (6.1)
Other	7 (1.8)	12 (3.1)	19 (2.5)
Protocol Deviation	1 (0.3)	5 (1.3)	6 (0.8)
Treatment Discontinuation Due To COVID-19 Pandemic	0 (0.0)	1 (0.3)	1 (0.1)
Primary Reason for End of Study			
Death	321 (83.8)	337 (87.1)	658 (85.5)
Withdrawal by Subject	14 (3.7)	18 (4.7)	32 (4.2)
Lost To Follow-up	2 (0.5)	1 (0.3)	3 (0.4)
Does Not Meet Entry Criteria	1 (0.3)	0 (0.0)	1 (0.1)

Recruitment

Between 19 February 2020 to 17 August 2021, a total of 770 participants were randomised to receive the NALIRIFOX arm (N=383) or the Gem+NabP arm (N=387) in 187 sites across 18 countries worldwide. The number of patients enrolled and randomized per country summarized in descending order: United States (230), Spain (143), Italy (55), France (50), Germany (44), Brazil (40), Czech Republic (38), Australia (25), Russia (25), South Korea (22), Belgium (19), Hungary (18), Austria (17), United Kingdom (13), Canada (12), Portugal (10), Greece (4) and Israel (5).

Data presented are from the final analysis, DCO 23 July 2022 for final analysis planned to be conducted when at least 543 OS events were observed across the two treatment arms are presented.

Conduct of the study

Protocol amendments

The initial version of the protocol for NAPOLI 3 was dated 03 October 2019 and was amended four times.

Table 12. List of protocol amendments

Amendment	Release date	Amendment form
1	28 November 2019	Appendix 9
2	20 May 2020	Appendix 10
3	03 June 2020	Appendix 11
4	19 August 2021	Appendix 12

Major key changes are summarized below:

Amendment 2, 20 May 2020

The inclusion/exclusion criteria were modified, i.e. ANC was increased from ≥1500/mm^3 to ≥2000/mm^3 for the NALIRIFOX arm, QTcF decreased from ≤480 msec to ≤450 msec, patients receiving live vaccine within 4 weeks of randomisation was excluded, exclusion of patients with known low or absent dihydropyrimidine dehydrogenase (DPD) activity.

The option to increase sample size up to 800 patients if blinded projection of accumulating OS events suggests the number of events required for final analysis would not be reached within 32 months of study initiation due to censoring was added. The projection to inform this decision was to be carried out within 3 months of expected completion of planned enrolment of 750 patients.

An exploratory endpoint of gene mutations and genomic alterations added.

Amendment 4, 19 August 2021

The interim analysis plan was changed. Two planned interim analyses at 181 (futility) and 401 (futility and efficacy) OS events was replaced by one at 272 OS events.

The timing of final analysis was changed from 565 OS events to 543 events.

The definition of study duration was changed from "The study will be completed once all subjects have died, withdrawn consent or are lost to follow-up" to "The study will be completed once all subjects have discontinued the study treatment and at least 543 OS events have occurred in the randomised subjects".

An option and criteria to continue study treatment after progressive disease according to RECIST v1.1 was added.

It was added that no patient could be considered lost to follow-up before final study closure and that at follow-up contact should include information of subsequent treatment.

Protocol deviations

Major protocol deviations were reported for a total of 489 participants (63.5%) during the study: 256 participants (66.8%) in the NALIRIFOX arm and 233 participants (60.2%) in the Gem+NabP arm. The most common major protocol deviation for both arms was study treatment non-compliance for 353 participants (45.8%): 200 participants (52.2%) in the NALIRIFOX arm and 153 participants (39.5%) in the Gem+NabP arm.

Table 13. Summary of major protocol deviations (ITT)

	NALIRIFOX (N=383) n (%)	Gem+NabP (N=387) n (%)	Total (N=770) n (%)
Number of Patients with Major Protocol Deviations	256 (66.8)	233 (60.2)	489 (63.5)
Study Treatment Non-Compliance	200 (52.2)	153 (39.5)	353 (45.8)
Safety Reporting Non-Compliance	36 (9.4)	43 (11.1)	79 (10.3)
Eligibility Criteria Deviation	28 (7.3)	48 (12.4)	76 (9.9)
Informed Consent Non-Compliance	38 (9.9)	29 (7.5)	67 (8.7)
Rando/Treat Allocation Process Deviation	20 (5.2)	13 (3.4)	33 (4.3)
Procedures Deviation	18 (4.7)	13 (3.4)	31 (4.0)
GCP Non-Compliance	18 (4.7)	9 (2.3)	27 (3.5)
Prohibited Medication/Therapy/Surgery	14 (3.7)	9 (2.3)	23 (3.0)
Time Window Deviation	8 (2.1)	8 (2.1)	16 (2.1)
Withdrawal Criteria Deviation	3 (0.8)	7 (1.8)	10 (1.3)
Combination of Minor Deviations	0 (0.0)	6 (1.6)	6 (0.8)
Number of Patients with Major Protocol Deviations Due to COVID-19	5 (1.3)	8 (2.1)	13 (1.7)
Study Treatment Non-Compliance	3 (0.8)	5 (1.3)	8 (1.0)
Combination of Minor Deviations	0 (0.0)	2 (0.5)	2 (0.3)
Safety Reporting Non-Compliance	1 (0.3)	1 (0.3)	2 (0.3)
Procedures Deviation	1 (0.3)	0 (0.0)	1 (0.1)
Time Window Deviation	0 (0.0)	1 (0.3)	1 (0.1)

Source: Data listings 16.2.2.1a Analysis dataset: ADDV

The reported terms with >5% of patients were:

Study treatment non-compliance; Reported term	NALIRIFOX n (%)	Gem+NabP n (%)
Protocol guidance for dose delayed, modified or discontinued when required per protocol was not followed correctly	127 (33.2)	99 (25.6)
Duration of infusion and administration was not following protocol	73 (19.1)	36 (9.3)
ANC/Platelet count and diarrhoea values not assessed prior to each dose	24 (6.3)	38 (9.8)

The frequency of study treatment non-compliance is high.

Baseline data

Table 14. Demographics and Baseline Characteristics (ITT)

	NALIRIFOX (N=383) n (%)	**Gem+NabP (N=387) n (%)**	**Total (N=770) n (%)**
Age (years)			
n	383	387	770
Mean (SD)	62.8 (9.71)	64.0 (8.34)	63.4 (9.06)
Median (Min, Max)	64.0 (20, 85)	65.0 (36, 82)	65.0 (20, 85)
Age Category			
<65 Years	193 (50.4)	191 (49.4)	384 (49.9)
≥65 Years	190 (49.6)	196 (50.6)	386 (50.1)
65-75 Years	163 (42.6)	170 (43.9)	333 (43.2)
>75 Years	27 (7.0)	26 (6.7)	53 (6.9)
Sex			
Male	204 (53.3)	230 (59.4)	434 (56.4)
Female	179 (46.7)	157 (40.6)	336 (43.6)
Ethnicity			
Hispanic or Latino	49 (12.8)	30 (7.8)	79 (10.3)

Not Hispanic or Latino	305 (79.6)	328 (84.8)	633 (82.2)
Not Reported	29 (7.6)	29 (7.5)	58 (7.5)
Race			
White	315 (82.2)	324 (83.7)	639 (83.0)
Not Reported	26 (6.8)	29 (7.5)	55 (7.1)
Asian	20 (5.2)	18 (4.7)	38 (4.9)
Black or African American	12 (3.1)	7 (1.8)	19 (2.5)
Other	7 (1.8)	6 (1.6)	13 (1.7)
Multiple	3 (0.8)	0 (0.0)	3 (0.4)
American Indian or Alaska Native	0 (0.0)	2 (0.5)	2 (0.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.3)	1 (0.1)
Weight (kg)			
n	383	387	770
Mean (SD)	72.72 (17.559)	72.60 (15.940)	72.66 (16.754)
Median (Min, Max)	70.50 (30.0, 180.5)	71.60 (34.0, 122.0)	71.00 (30.0, 180.5)
Height (cm)			
n	383	387	770
Mean (SD)	168.2 (10.13)	168.9 (10.04)	168.6 (10.08)
Median (Min, Max)	169.0 (144, 195)	168.0 (144, 200)	168.0 (144, 200)
BMI (kg/m²)			
n	383	387	770
Mean (SD)	25.592 (5.2506)	25.319 (4.6034)	25.455 (4.9346)
Median (Min, Max)	24.623 (13.33, 55.86)	24.641 (14.72, 45.58)	24.632 (13.33, 55.86)
BSA (m²)			
n	383	387	770
Mean (SD)	1.819 (0.2352)	1.824 (0.2269)	1.821 (0.2309)
Median (Min, Max)	1.800 (1.15, 2.88)	1.810 (1.20, 2.42)	1.800 (1.15, 2.88)
Albumin(g/dL)			
n	383	387	770
Mean (SD)	38.04 (4.139)	38.07 (4.188)	38.06 (4.161)
Median (Min, Max)	38.00 (24.0, 49.0)	38.00 (26.0, 52.0)	38.00 (24.0, 52.0)
CA 19-9(U/mL)			
n	381	387	768
Median (Min, Max)	1856.00 (0.6, 8000.0)	1544.00 (0.6, 8000.0)	1632.00 (0.6, 8000.0)
CA 19-9			
<37 U/mL	60 (15.7)	71 (18.3)	131 (17.0)
≥37 U/mL	321 (83.8)	316 (81.7)	637 (82.7)
>=8000 U/mL	126 (32.9)	104 (26.9)	230 (29.9)
Missing	2 (0.5)	0 (0.0)	2 (0.3)
UGT1A1*28 Allele Status			
Homozygous	40 (10.4)	45 (11.6)	85 (11.0)
Non-Homozygous	339 (88.5)	338 (87.3)	677 (87.9)
Missing	4 (1.0)	4 (1.0)	8 (1.0)
ECOG			
0	160 (41.8)	168 (43.4)	328 (42.6)
1	222 (58.0)	219 (56.6)	441 (57.3)
2	1 (0.3)	0 (0.0)	1 (0.1)

Geographic Location			
North America	120 (31.3)	122 (31.5)	242 (31.4)
East Asia	11 (2.9)	11 (2.8)	22 (2.9)
ROW	252 (65.8)	254 (65.6)	506 (65.7)
Liver Metastases			
Yes	307 (80.2)	311 (80.4)	618 (80.3)
No	76 (19.8)	76 (19.6)	152 (19.7)

BMI = body mass index; BSA = body surface area, ECOG= Eastern Cooperation Oncology Group; eCRF=Electronic case report form PS = Performance Status; ROW = rest of the world, SD = standard deviation.

BSA is calculated based on Dubois equation. CA 19-9 upper detection limit is 8000 U/mL.

UGT1A1*28 Allele Status: homozygous is defined as TA7/7 and non-homozygous as other genotypes (heterozygote – TA6/7; negative =wild type TA6/6).

Baseline ECOG performance status, geographic location and liver metastases are from eCRF data.

Table 15. Baseline Disease Characteristics (ITT)

	NALIRIFOX (N=383) n (%)	**Gem+NabP (N=387) n (%)**	**Total (N=770) n (%)**
Time from Initial Diagnosis of Pancreatic Adenocarcinoma until Date of Randomisation (weeks)			
n	383	387	770
Mean (SD)	10.96 (43.808)	13.58 (41.683)	12.28 (42.746)
Median (Min, Max)	3.57 (0.6, 651.9)	3.86 (0.4, 323.4)	3.71 (0.4, 651.9)
Time from Diagnosis of Metastatic Disease (Stage IV) at Study Entry until Date of Randomisation (weeks)			
n	383	387	770
Mean (SD)	3.58 (1.839)	3.88 (1.858)	3.73 (1.854)
Median (Min, Max)	3.00 (0.6, 9.1)	3.57 (0.4, 10.9)	3.43 (0.4, 10.9)
Stage of Original Diagnosis			
Metastatic	344 (89.8)	342 (88.4)	686 (89.1)
Resectable	19 (5.0)	23 (5.9)	42 (5.5)
Locally Advanced	17 (4.4)	16 (4.1)	33 (4.3)
Borderline Resectable	3 (0.8)	6 (1.6)	9 (1.2)
Histological Grade			
Well Differentiated	28 (7.3)	29 (7.5)	57 (7.4)
Moderately Differentiated	111 (29.0)	105 (27.1)	216 (28.1)
Poorly Differentiated	62 (16.2)	85 (22.0)	147 (19.1)
Undifferentiated	4 (1.0)	8 (2.1)	12 (1.6)
Unknown	178 (46.5)	160 (41.3)	338 (43.9)
AJCC Prognostic Stage at Study Entry			
I-III	0 (0.0)	1 (0.3)	1 (0.1)
IV	383 (100.0)	386 (99.7)	769 (99.9)
Number of Metastatic Sites			
1	114 (29.8)	138 (35.7)	252 (32.7)
2	120 (31.3)	108 (27.9)	228 (29.6)
≥3	149 (38.9)	141 (36.4)	290 (37.7)

Selected Metastatic Site			
Liver	304 (79.4)	311 (80.4)	615 (79.9)
Lung	135 (35.2)	131 (33.9)	266 (34.5)
Main Pancreatic Cancer Tumour Location			
Head	147 (38.4)	156 (40.3)	303 (39.4)
Body	116 (30.3)	126 (32.6)	242 (31.4)
Tail	115 (30.0)	96 (24.8)	211 (27.4)
Unknown	5 (1.3)	9 (2.3)	14 (1.8)

AJCC=American Joint Committee on Cancer, eCRF=electronic case report form, SD = standard deviation. Liver and lung metastases are derived from anatomical metastatic sites recorded in eCRF.

Prior disease specific treatments

There were 49 participants (6.4%) in the ITT population who had prior anti-cancer therapy for pancreatic cancer: 22 participants (5.7%) in the NALIRIFOX arm and 27 participants (7.0%) in the Gem+NabP arm.

The number of participants with prior anti-cancer therapy was as follows overall and in the NALIRIFOX arm and Gem+NabP arm, respectively: 30 participants (3.9%) who had prior chemotherapy (14 participants (3.7%) and 16 participants (4.1%)),16 participants (2.1%) with prior radiotherapy (10 participants (2.6%) and six participants (1.6%)) and 43 participants (5.6%) who had undergone prior surgical procedures (18 participants (4.7%) and 25 participants 6.5%)), respectively.

Overall, 30 participants (3.9%) in the ITT had prior chemotherapy, hormonal or immunotherapy for pancreatic cancer: 14 participants (3.7%) in the NALIRIFOX arm and 16 participants (4.1%) in the Gem+NabP arm. The antineoplastic agents previously used most frequently overall (≥1%) were gemcitabine (2.1% and 1.8%), fluorouracil (0.8% and 2.1%), oxaliplatin (0.8% and 2.1%), and irinotecan (0.5% and 1.8%), in the NALIRIFOX arm and Gem+NabP arm, respectively.

Numbers analysed

Table 16. Participant Disposition, cut-off date = 23 July 2022

	NALIRIFOX (N=383) n (%)	**Gem+NabP (N=387) n (%)**	**Total (N=770) n (%)**
Randomised	383 (100.0)	387 (100.0)	770 (100.0)
Never Treated	13 (3.4)	8 (2.1)	21 (2.7)
Treated as Randomised	370 (96.6)	379 (97.9)	749 (97.3)
Ongoing Study Treatment	44 (11.5)	7 (1.8)	51 (6.6)
Discontinued from Study Treatment	326 (85.1)	372 (96.1)	698 (90.6)
Entered Long-term Follow-up	225 (58.7)	255 (65.9)	480 (62.3)
Discontinued from Long-term Follow-up	165 (43.1)	175 (45.2)	340 (44.2)
Ongoing Long-term Follow-up	60 (15.7)	80 (20.7)	140 (18.2)
Discontinued from Study	267 (69.7)	295 (76.2)	562 (73.0)
Primary Reason for Treatment Discontinuation			
Progressive Disease	184 (48.0)	177 (45.7)	361 (46.9)
Progressive Disease Per RECIST	162 (42.3)	146 (37.7)	308 (40.0)
Progressive Disease Clinical	22 (5.7)	31 (8.0)	53 (6.9)
Adverse Event	54 (14.1)	92 (23.8)	146 (19.0)
Withdrawal by Participant	25 (6.5)	41 (10.6)	66 (8.6)
Death	32 (8.4)	26 (6.7)	58 (7.5)
Physician Decision	24 (6.3)	19 (4.9)	43 (5.6)
Other	6 (1.6)	12 (3.1)	18 (2.3)

Protocol Deviation	1 (0.3)	5 (1.3)	6 (0.8)
Treatment Discontinuation Due To COVID-19 Pandemic	0 (0.0)	1 (0.3)	1 (0.1)
Primary Reason for End of Study			
Death	252 (65.8)	277 (71.6)	529 (68.7)
Withdrawal by Participant	13 (3.4)	17 (4.4)	30 (3.9)
Lost To Follow-up	1 (0.3)	1 (0.3)	2 (0.3)
Does Not Meet Entry Criteria	1 (0.3)	0 (0.0)	1 (0.1)
End Of Study Due To COVID-19 Pandemic	0 (0.0)	2 (0.5)	2 (0.3)
Survival Status at Data Cut-off			
Alive	123 (32.1)	101 (26.1)	224 (29.1)
Dead	259 (67.6)	285 (73.6)	544 (70.6)
Lost To Follow Up	1 (0.3)	1 (0.3)	2 (0.3)

RECIST=Response evaluation criteria in solid tumours All◦percentage◦denominators◦are◦based◦on◦the◦intent-to-treat◦population

Table 17. Summary of Data Sets Analysed (Intent-to-Treat Population)

	NALIRIFOX (N=383) n (%)	**Gem+NabP (N=387) n (%)**	**Total (N=770) n (%)**
Intent-to-Treat Population	383 (100.0)	387 (100.0)	770 (100.0)
Per-Protocol Population	363 (94.8)	372 (96.1)	735 (95.5)
Reason for Exclusion	20 (5.2)	15 (3.9)	35 (4.5)
Randomised but Not Dosed	11 (2.9)	8 (2.1)	19 (2.5)
Eligibility Violation	6 (1.6)	7 (1.8)	13 (1.7)
Eligibility Violation, Randomised but Not Dosed	2 (0.5)	0 (0.0)	2 (0.3)
Prohibited Concomitant Medication	1 (0.3)	0 (0.0)	1 (0.1)
Safety Population	370 (96.6)	379 (97.9)	749 (97.3)
Did not receive study treatment	13 (3.4)	8 (2.1)	21 (2.7)
Withdrawal by Participant	6 (1.6)	3 (0.8)	9 (1.2)
Other	1 (0.3)	3 (0.8)	4 (0.5)
Adverse Event	3 (0.8)	0 (0.0)	3 (0.4)
Protocol Deviation	2 (0.5)	0 (0.0)	2 (0.3)
Death	1 (0.3)	0 (0.0)	1 (0.1)
Physician Decision	0 (0.0)	1 (0.3)	1 (0.1)
Progressive Disease Clinical	0 (0.0)	1 (0.3)	1 (0.1)
PRO Population[a]	208 (54.3)	200 (51.7)	408 (53.0)
No Baseline or Post-Baseline Pro Assessment	175 (45.7)	187 (48.3)	362 (47.0)
Pharmacokinetic Population	367 (95.8)	NA	NA
Excluded from Pharmacokinetic Population	16 (4.2)	NA	NA
Not Treated	13 (3.4)	NA	NA
Participant Excluded As No Valid PK Result Available For Irinotecan (C1D1/C1D3/C1D15)	2 (0.5)	NA	NA
No Valid Numerical Irinotecan Concentration Available	1 (0.3)	NA	NA

C=Cycle, D=Day, ITT=intent-to-treat, PK=pharmacokinetics, PRO=patient reported outcome,

a PRO population: All participants of the randomised ITT population that have provided baseline and at least one subsequent assessment on each PRO instrument. PRO population might be used in future PRO sensitivity analyses only.

Outcomes and estimation

The final analysis was planned when at least 543 OS events were observed across the two treatment arms. Participants who had not experienced an event by this date were censored by last known alive date. As of the data cut-off date (23 July 2022), out of 770 randomised participants a total of 544 participants had experienced an OS event (two OS events occurred on 23 July 2022).

At the data cut-off for the final analysis, there were 51 participants remaining on treatment: 44 participants in the NALIRIFOX arm and seven participants in the Gem+NabP arm.

Primary endpoint: Overall survival

At the final analysis median follow-up time was 16.0 (95% CI 15.0, 16.8) months for the NALIRIFOX arm and 16.3 (95% CI 15.0, 17.5) months for the Gem+NabP arm when patients were censored at death. There was a total of 544 (70.6%) OS events.

The NALIRIFOX arm demonstrated a statistically significant difference in OS compared with Gem+NabP based on the stratified log-rank test p-value 0.04.

The median OS was 11.1 months (95% 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 (strata based on baseline ECOG performance status, region with 3 modalities - "East Asia", "North America", and "Rest of the World" -, and liver metastases per IWRS) of 0.84 (95% CI: 0.71, 0.99).

Table 18. Overall Survival (ITT), cut-off date = 23 July 2022

Table 14.2.1.1b: Overall Survival (OS)
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) [1]	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)
Stratified HR (95% CI) [p value] [2]	0.8379 (0.7074, 0.9925) [0.0403]	
Unstratified HR (95% CI) [p value]	0.8362 (0.7066, 0.9895) [0.0370]	
Event free Probability, n, % (95% CI) [1]		
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) [3]	16.0 (15.0, 16.8)	16.3 (15.0, 17.5)

Data source: Data listings: 16.2.6.1a Analysis dataset: ADTTE

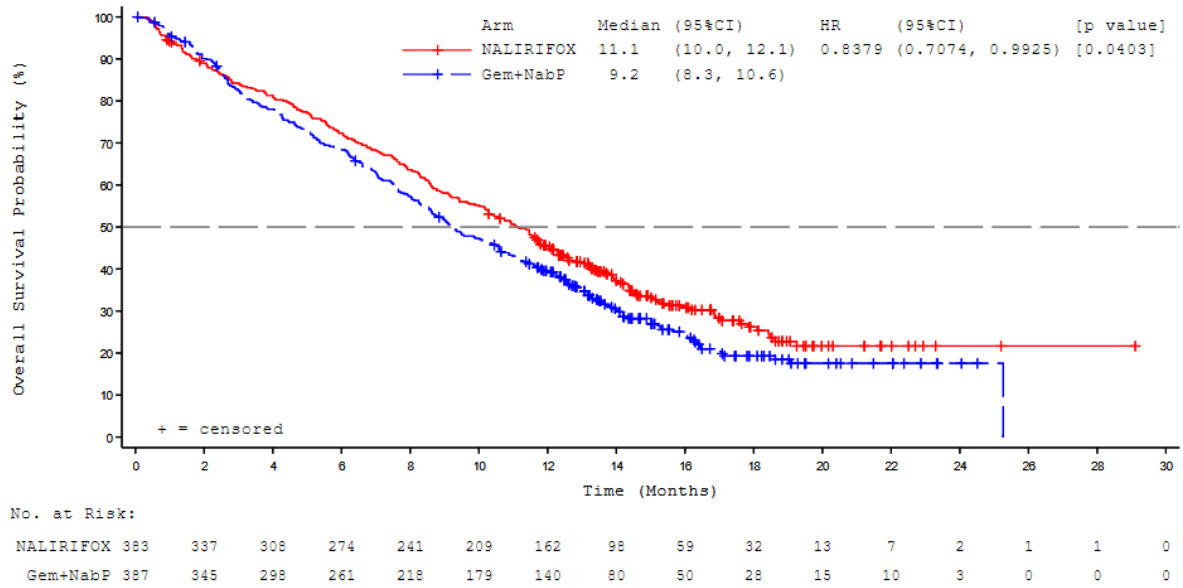
[1] Kaplan-Meier Estimate.
[2] The hazard ratio (HR) and 95% confidence interval (CI) are based on a stratified Cox proportional hazards regression model, stratified by baseline ECOG performance status, region and liver metastases per IWRS. Gem+NabP is reference.
[3] Median follow up is calculated by patients censored at death.
Data cutoff date:23JUL2022

Program: os_primary_b.sas; Date & time program was run: 03FEB2023 01:00; Date & time analysis dataset was run: 16JAN2023 13:07

Table 19: Reasons for censoring, cut-off date = 23 July 2022

	NALIRIFOX (N=383) n (%)	Gem+NabP (N=387) n (%)
Death	259 (67.6)	285 (73.6)
Censored	124 (32.4)	102 (26.4)
Alive	116 (30.3)	92 (23.8)
Withdrawal from Study - Lost to Follow-up	1 (0.3)	1 (0.3)
Withdrawal from Study - Withdrawal by Subject	7 (1.8)	9 (2.3)

Figure 9. Kaplan-Meier Curve of Overall Survival (Intent-to-Treat Population), cut-off date = 23 July 2022



CI=confidence interval, HR=hazard ratio Data Source: RSI 02 Jan Appendix 4, p. 2303.

Secondary endpoints

Progression Free Survival

There were a total of 508 PFS events. The NALIRIFOX arm demonstrated a statistically significant difference in PFS compared with Gem+NabP 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 (strata based on baseline ECOG performance status, region with 2 modalities - "North America" vs "Rest of the World" ("East Asia" being combined with "Rest of the World") , and liver metastases per IWRS) of 0.69 (95% CI: 0.58, 0.83).

Table 20. Progression-Free Survival According to Investigator Assessment (ITT)

	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, HR=hazard ratio, PFS=progression-free survival,

a Kaplan-Meier Estimate.

b The hazard ratio (HR) and 95% confidence interval (CI) are based on a stratified Cox proportional hazards regression model, stratified by baseline ECOG performance status, region ("North America"vs "Rest of the World") and liver metastases per IWRS. Gem+NabP is reference.

A high frequency of patients is censored on day one for the PFS analysis. This is due to lack of post baseline tumour assessments in 29(7.6%) and 18(4.7%) patients in NALIRIFOX and Gem+NabP arms respectively.

Figure 10. Kaplan-Meier Curve of Progression-Free Survival (ITT)

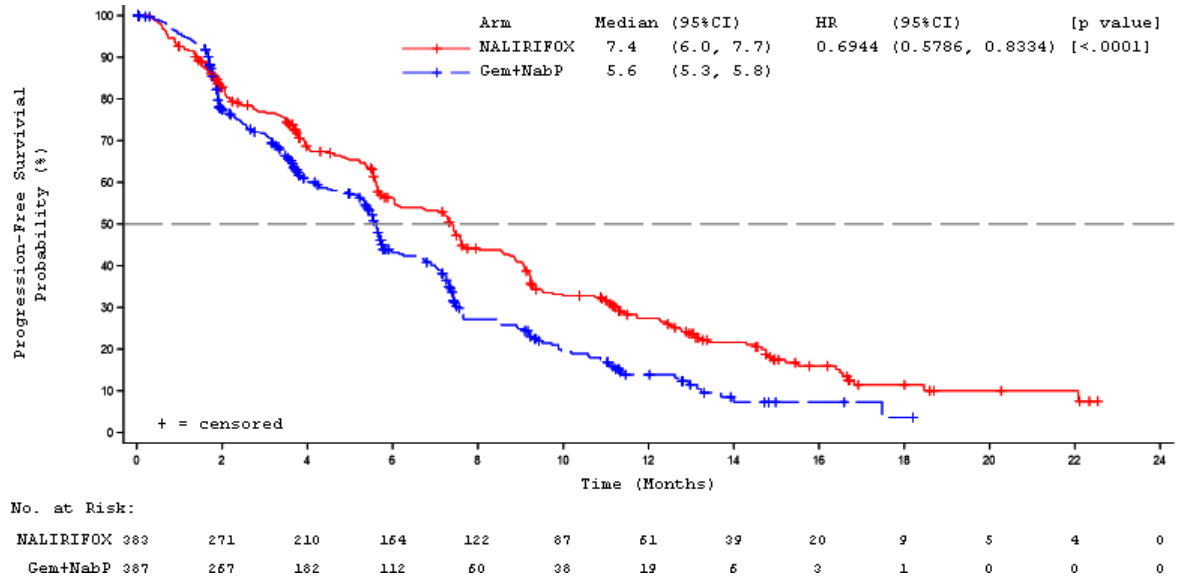
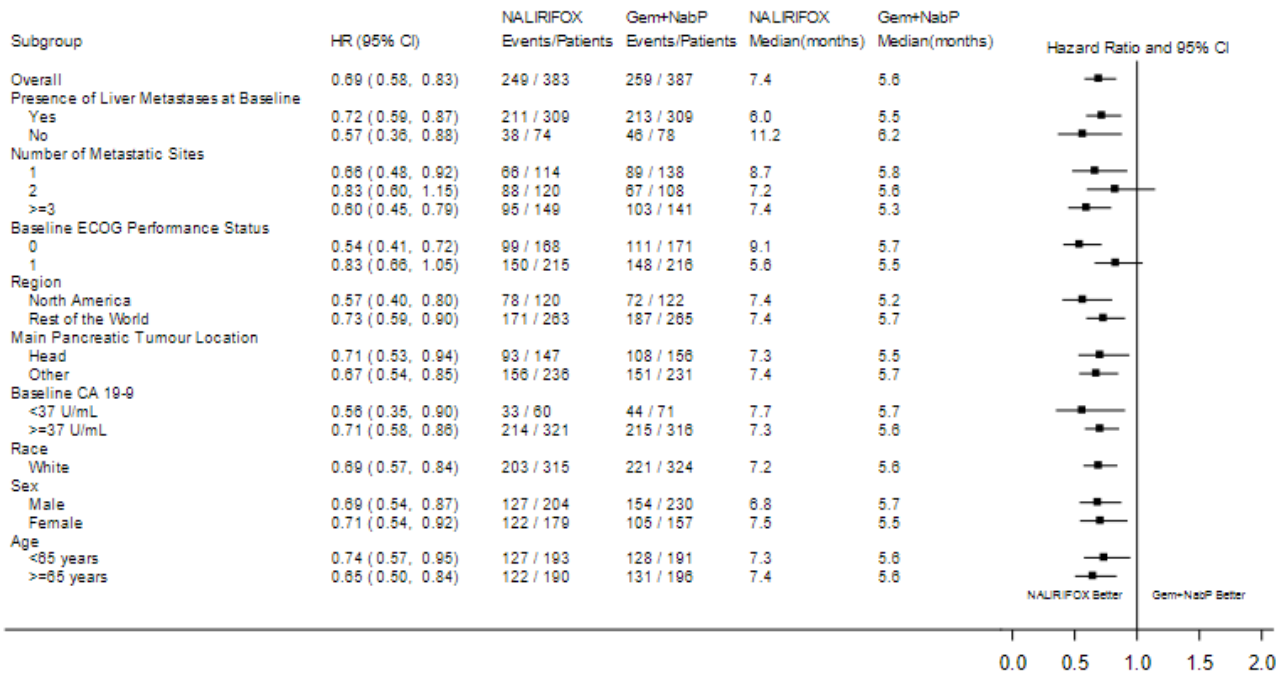


Figure 11. Forest Plot of Progression-Free Survival by Subgroup (Intent-to-Treat Population)



Data source: Data listings: 16.2.6.2 Analysis dataset: ADTTE, ADSL, ADBASE. The overall hazard ratio is based on stratified analysis and subgroup hazard ratios are based on unstratified analysis. Data cut-off date:23JUL2022.

Overall Response Rate

The BOR of CR was achieved for one participant (0.3%) in both arms. A PR for 159 participants (41.5%) was seen in the NALIRIFOX arm and for 139 participants (35.9%) in the Gem+NabP arm. ORR per RECIST 1.1 for the NALIRIFOX arm was 41.8% (95% CI: 36.8, 46.9) and in the Gem+NabP arm it was 36.2% (95% CI: 31.4, 41.2) giving an odds ratio of NALIRIFOX compared to Gem+NabP of 1.26 (95% CI: 0.95, 1.69).

Table 21. Best Overall Response and Overall Response Rate (Intent-to-Treat Population)

	NALIRIFOX (N=383) n (%)	**Gem+NabP (N=387) n (%)**
ORR (CR or PR)	160 (41.8)	140 (36.2)
95% CI [1]	(36.8, 46.9)	(31.4, 41.2)
Odds Ratio (95% CI) [2]	1.26 (0.95, 1.69)	
P-value [2]	0.11	
BOR		
Complete Response	1 (0.3)	1 (0.3)
Partial Response	159 (41.5)	139 (35.9)
Stable Disease	99 (25.8)	101 (26.1)
Progressive Disease	38 (9.9)	56 (14.5)
Not Evaluable	86 (22.5)	90 (23.3)

BOR=best overall response, CI=confidence interval, CR=complete response, ORR=objective response rate, PR=partial response.

[1] 95% confidence intervals (CIs) are using Clopper-Pearson method.

[2] Odds ratio, 95% confidence interval and p-value are obtained from the Cochran-Mantel-Haenszel test adjusting by baseline ECOG performance status, region and liver metastases per IWRS. Gem+NabP is reference.

Participants with Non-CR/Non-PD as BOR are categorised into SD.

Table 22. Summary of the reasons for Non-Evaluable Best overall response -Intent to treat population

	NALIRIFOX (N=383) n (%)	Gem+NabP (N=387) n (%)	Total (N=770) n (%)
Patients Belonging to Best Overall Response (BOR) as 'Not Evaluable (NE)'	86 (22.5)	90 (23.3)	176 (22.9)
No Evaluable Baseline Tumour Assessment	0 (0.0)	0 (0.0)	0 (0.0)
No Evaluable Post-baseline Tumour Assessment	70 (18.3)	67 (17.3)	137 (17.8)
Post-baseline Assessment Not Done or Missing	68 (17.8)	65 (16.8)	133 (17.3)

No Evaluable Scan/Assessment	2 (0.5)	2 (0.5)	4 (0.5)
No Evaluable Baseline and No Evaluable Post-baseline Tumour Assessment	0 (0.0)	1 (0.3)	1 (0.1)
Stable Disease (SD) Not Confirmed*	16 (4.2)	22 (5.7)	38 (4.9)

Percentages are calculated using N as the denominator.

*Not confirmed SD at 8 weeks

Source: Analysis dataset: ADSL, ADRS2

Data cutoff date: 23JUL2022

Update

The NAPOLI-3 study is ongoing. An update of the OS analysis was conducted based on October 3rd, 2023, a cut-off date of October 3rd, 2023.

Table 23. Disposition of patients, based on October 3rd, 2023 snapshot

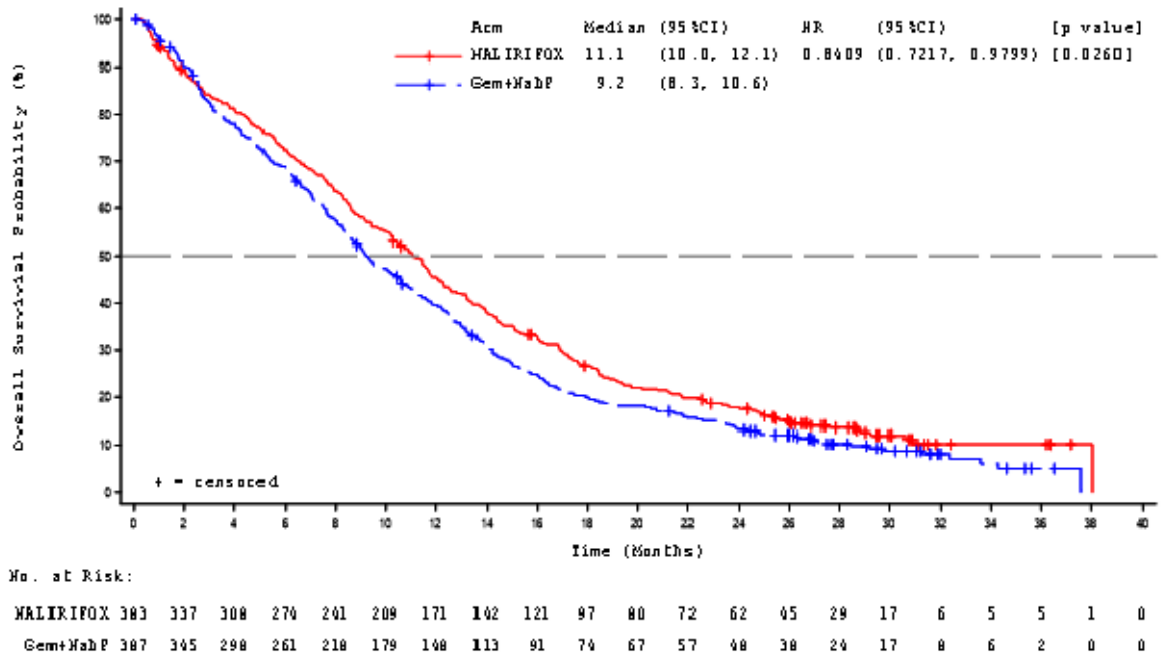
	NALIRIFOX (N=383) n (%)	Gem-NabP (N=387) n (%)	Total (N=770) n (%)
Screened Population			1084
Not Randomised			314
Primary Reason for Not Randomised			
Does Not Meet Entry Criteria			313
Other			1
Randomised	383 (100.0)	387 (100.0)	770 (100.0)
Never Treated	13 (3.4)	8 (2.1)	21 (2.7)
Treated as Randomised	370 (96.6)	379 (97.9)	749 (97.3)
Ongoing Study Treatment	11 (2.9)	0 (0.0)	11 (1.4)
Discontinued from Study Treatment	359 (93.7)	379 (97.9)	738 (95.8)
Entered Long-term Follow-up	265 (69.2)	269 (69.5)	534 (69.4)
Discontinued from Long-term Follow-up	235 (61.4)	238 (61.5)	473 (61.4)
Ongoing Long-term Follow-up	30 (7.8)	31 (8.0)	61 (7.9)
Discontinued from Study	338 (88.3)	356 (92.0)	694 (90.1)
Primary Reason for Treatment Discontinuation			
Progressive Disease	211 (55.1)	181 (46.8)	392 (50.9)
Progressive Disease Per RECIST	187 (48.8)	150 (38.8)	337 (43.8)
Progressive Disease Clinical	24 (6.3)	31 (8.0)	55 (7.1)
Adverse Event	54 (14.1)	94 (24.3)	148 (19.2)
Withdrawal by Subject	27 (7.0)	41 (10.6)	68 (8.8)
Death	32 (8.4)	26 (6.7)	58 (7.5)
Physician Decision	27 (7.0)	20 (5.2)	47 (6.1)
Other	7 (1.8)	12 (3.1)	19 (2.5)
Protocol Deviation	1 (0.3)	5 (1.3)	6 (0.8)
Treatment Discontinuation Due To COVID-19 Pandemic	0 (0.0)	1 (0.3)	1 (0.1)
Primary Reason for End of Study			
Death	321 (83.8)	337 (87.1)	658 (85.5)
Withdrawal by Subject	14 (3.7)	18 (4.7)	32 (4.2)
Lost To Follow-up	2 (0.5)	1 (0.3)	3 (0.4)
Does Not Meet Entry Criteria	1 (0.3)	0 (0.0)	1 (0.1)

Table 24. Overall Survival based on October 3rd, 2023 snapshot

	NALIRIFOX (N=383) n (%)	Gem+NabP (N=387) n (%)
Death	328 (85.6)	345 (89.1)
Censored	55 (14.4)	42 (10.9)
Alive	45 (11.7)	31 (8.0)
Withdrawal from Study - Lost to Follow-up	2 (0.5)	1 (0.3)
Withdrawal from Study - Withdrawal by Subject	8 (2.1)	10 (2.6)
Median (95% CI) (months) [1]	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)
Stratified HR (95% CI) [p value] [2]	0.8409 (0.7217, 0.9799) [0.0260]	
Unstratified HR (95% CI) [p value]	0.8447 (0.7260, 0.9829) [0.0290]	
Event free Probability, n, % (95% CI) [1]		
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	171, 45.6 (40.5, 50.5)	148, 39.6 (34.7, 44.5)
18 Months	97, 26.6 (22.2, 31.1)	74, 20.0 (16.1, 24.1)
Median (95% CI) Follow up (months) [3]	28.7 (27.3, 30.1)	29.7 (27.7, 31.6)

Source: Analysis dataset: ADSLOS, ADTTEOS
[1] Kaplan-Meier Estimate.
[2] The hazard ratio (HR) and 95% confidence interval (CI) are based on a stratified Cox proportional hazards regression
model, stratified by baseline ECOG performance status, region and liver metastases per IWRS. Gem+NabP is reference.
[3] Median follow up is calculated by patients censored at death.
SDTM data snapshot date: 03OCT2023
Program: T_FORM2_01_UNP41_OS_ITT.sas; Date & time program was run: 24OCT2023 06:45; Date & time analysis dataset was run: 24OCT2023 6:39

Figure 12. Kaplan-Meier of Overall Survival based on October 3rd, 2023 snapshot – Intent-to-Treat

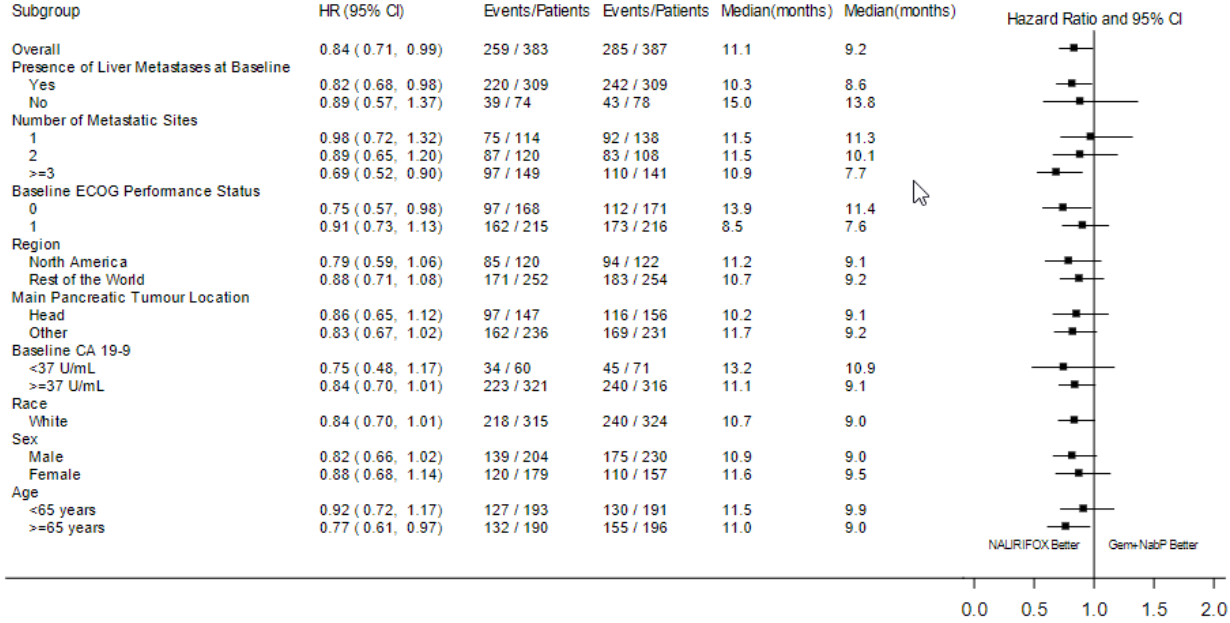


Ancillary analyses

Figure 13. Forest Plot of Overall Survival by Subgroup (Intent-to-Treat Population), cut-off date = 23 July 2022

Figure 14.2.1.8.1b: Forest Plot of Overall Survival (OS) by Subgroup
Intent-to-Treat Population

Subgroup	HR (95% CI)	NALIRIFOX Events/Patients	Gem+NabP Events/Patients	NALIRIFOX Median(months)	Gem+NabP Median(months)
Overall	0.84 (0.71, 0.99)	259 / 383	285 / 387	11.1	9.2
Presence of Liver Metastases at Baseline					
Yes	0.82 (0.68, 0.98)	220 / 309	242 / 309	10.3	8.6
No	0.89 (0.57, 1.37)	39 / 74	43 / 78	15.0	13.8
Number of Metastatic Sites					
1	0.98 (0.72, 1.32)	75 / 114	92 / 138	11.5	11.3
2	0.89 (0.65, 1.20)	87 / 120	83 / 108	11.5	10.1
>=3	0.69 (0.52, 0.90)	97 / 149	110 / 141	10.9	7.7
Baseline ECOG Performance Status					
0	0.75 (0.57, 0.98)	97 / 168	112 / 171	13.9	11.4
1	0.91 (0.73, 1.13)	162 / 215	173 / 216	8.5	7.6
Region					
North America	0.79 (0.59, 1.06)	85 / 120	94 / 122	11.2	9.1
Rest of the World	0.88 (0.71, 1.08)	171 / 252	183 / 254	10.7	9.2
Main Pancreatic Tumour Location					
Head	0.86 (0.65, 1.12)	97 / 147	116 / 156	10.2	9.1
Other	0.83 (0.67, 1.02)	162 / 236	169 / 231	11.7	9.2
Baseline CA 19-9					
<37 U/mL	0.75 (0.48, 1.17)	34 / 60	45 / 71	13.2	10.9
>=37 U/mL	0.84 (0.70, 1.01)	223 / 321	240 / 316	11.1	9.1
Race					
White	0.84 (0.70, 1.01)	218 / 315	240 / 324	10.7	9.0
Sex					
Male	0.82 (0.66, 1.02)	139 / 204	175 / 230	10.9	9.0
Female	0.88 (0.68, 1.14)	120 / 179	110 / 157	11.6	9.5
Age					
<65 years	0.92 (0.72, 1.17)	127 / 193	130 / 191	11.5	9.9
>=65 years	0.77 (0.61, 0.97)	132 / 190	155 / 196	11.0	9.0



Data source: Data listings: 16.2.6.1a Analysis dataset: ADTTE, ADSL, ADBASE
The overall hazard ratio is based on stratified analysis and subgroup hazard ratios are based on unstratified analysis.
Data cutoff date:23JUL2022

Program: forest tte b.sas; Date & time program was run: 06FEB2023 03:31; Date & time analysis dataset was run: 16JAN2023 13:07

Sensitivity analyses

Table 25. Overall Survival analysis results (ITT)

	Median OS (months) NALIRIFOX vs. Gem+NabP	HR (95% CI)	p-value
Primary Analysis [a]	11.1 vs. 9.2 (difference: 1.9)	0.83 (0.70, 0.99)	0.04
Sensitivity Analyses			
Per SAP [b]	11.1 vs. 9.2 (difference: 1.9)	0.84 (0.71, 0.99)	0.04
Unstratified	11.1 vs. 9.2 (difference: 1.9)	0.84 (0.71, 0.99)	0.04
Stratified (region omitted)[c]	11.1 vs. 9.2 (difference: 1.9)	0.84 (0.71, 0.99)	0.04
Censored at subsequent anti-cancer therapy [a]	15.1 vs. 9.2 (difference: 5.9)	0.71 (0.56, 0.90)	<0.01

CI=confidence interval, ECOG= Eastern Cooperative Oncology Group, HR=hazard rate, IWRS=interactive web response system, OS=overall survival, ROW=rest of the world
Gem+NabP is reference.
a Stratified by ECOG PS (0 vs. 1), region (North America vs. ROW), and liver metastases (yes vs. no) per IWRS
b Stratified by ECOG PS (0 vs. 1), region (North America vs. East Asia vs. ROW), and liver metastases (yes vs. no) per IWRS
c Stratified by ECOG PS (0 vs. 1) and liver metastases (yes vs. no) per IWRS.
Data Source Table 14.2.1.1a, Table 14.2.1.5a, Table 14.2.1.9a

Sensitivity analysis according to original analysis plan based on 565 events

Table 26. Disposition of patients: based on 565 OS events

	NALIRIFOX (N=383) n (%)	Gem+NabP (N=387) n (%)	Total (N=770) n (%)
Screened Population			1084
Not Randomized			314
Primary Reason for Not Randomized			
Does Not Meet Entry Criteria			313
Other			1
Randomized	383 (100.0)	387 (100.0)	770 (100.0)
Never Treated	13 (3.4)	8 (2.1)	21 (2.7)
Treated as Randomized	370 (96.6)	379 (97.9)	749 (97.3)
Ongoing Study Treatment	36 (9.4)	5 (1.3)	41 (5.3)
Discontinued from Study Treatment	334 (87.2)	374 (96.6)	708 (91.9)
Entered Long-term Follow-up	237 (61.9)	263 (68.0)	500 (64.9)
Discontinued from Long-term Follow-up	175 (45.7)	189 (48.8)	364 (47.3)
Ongoing Long-term Follow-up	62 (16.2)	74 (19.1)	136 (17.7)
Discontinued from Study	277 (72.3)	307 (79.3)	584 (75.8)
Primary Reason for Treatment Discontinuation			
Progressive Disease	191 (49.9)	178 (46.0)	369 (47.9)
Progressive Disease Per RECIST	167 (43.6)	147 (38.0)	314 (40.8)
Progressive Disease Clinical	24 (6.3)	31 (8.0)	55 (7.1)
Adverse Event	54 (14.1)	93 (24.0)	147 (19.1)
Withdrawal by Subject	25 (6.5)	41 (10.6)	66 (8.6)
Death	32 (8.4)	26 (6.7)	58 (7.5)
Physician Decision	24 (6.3)	19 (4.9)	43 (5.6)
Other	7 (1.8)	12 (3.1)	19 (2.5)
Protocol Deviation	1 (0.3)	5 (1.3)	6 (0.8)
Treatment Discontinuation Due To COVID-19 Pandemic	0 (0.0)	1 (0.3)	1 (0.1)
Primary Reason for End of Study			
Death	261 (68.1)	288 (74.4)	549 (71.3)
Withdrawal by Subject	13 (3.4)	18 (4.7)	31 (4.0)
Lost To Follow-up	2 (0.5)	1 (0.3)	3 (0.4)
End Of Study Due To COVID-19 Pandemic	0 (0.0)	2 (0.5)	2 (0.3)
Survival Status at Data Cut-off			
Alive	106 (27.7)	79 (20.4)	185 (24.0)
Dead	268 (70.0)	297 (76.7)	565 (73.4)
Lost To Follow Up	2 (0.5)	1 (0.3)	3 (0.4)
Withdrawal by Subject	7 (1.8)	10 (2.6)	17 (2.2)

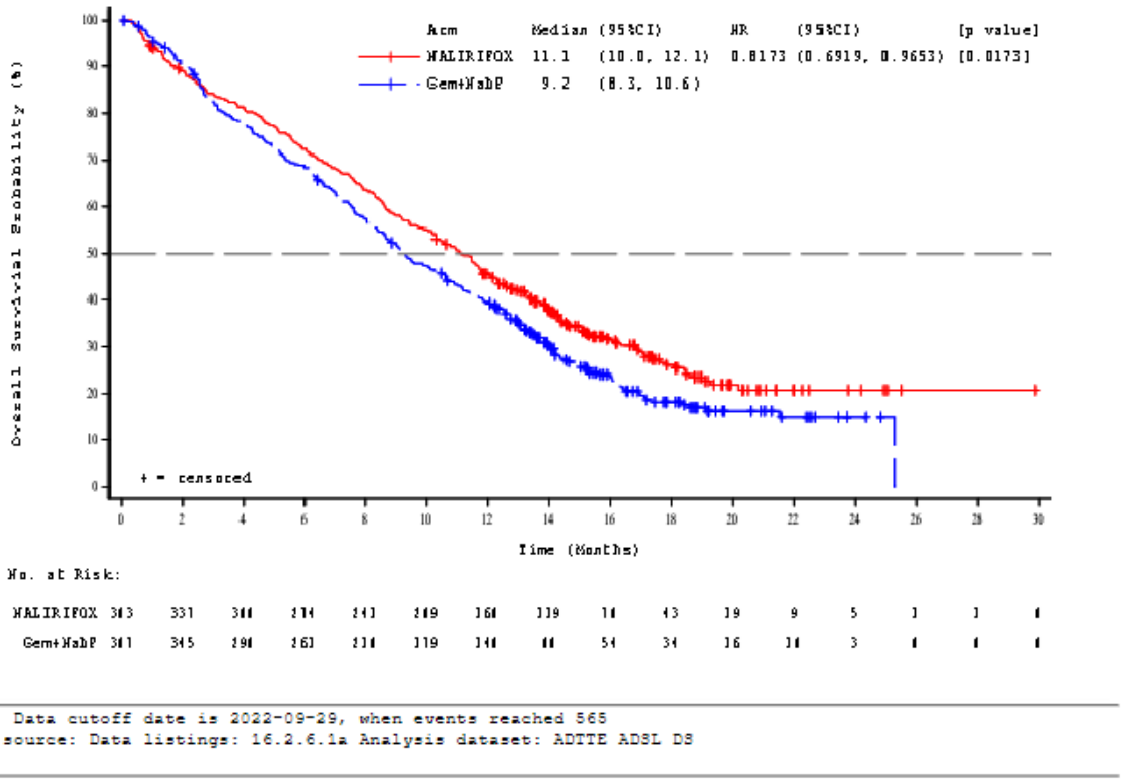
Source: Data listings 16.2.1.1a Analysis dataset: ADSL3
All percentage denominators are based on the intent-to-treat population.
Data cut-off date: 29SEP2022
Program: T_FORM1_01_UNP35_SCR.sas; Date & time program was run: 06OCT2023 11:08; Date & time analysis dataset wa run:05OCT2023 6:30

Table 27. Overall Survival based on 565 events - Intent to treat population (ITT)

	NALIRIFOX (N=383) n (%)	Gem+NabP (N=387) n (%)
Death	268 (70.0)	297 (76.7)
Censored	115 (30.0)	90 (23.3)
Alive	106 (27.7)	79 (20.4)
Withdrawal from Study - Lost to Follow-up	2 (0.5)	1 (0.3)
Withdrawal from Study - Withdrawal by subject	7 (1.8)	10 (2.6)
Median (95% CI) (months) [1]	11.1 (10.0, 12.1)	9.2 (8.3, 10.6)
Stratified HR (95% CI) [p value] [2]	0.8173 (0.6919, 0.9653) [0.0173]	
Unstratified HR (95% CI) [p value]	0.8164 (0.6920, 0.9632) [0.0161]	
Event free Probability, n, % (95% CI) [1]		
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	168, 45.6 (40.5, 50.5)	148, 39.6 (34.7, 44.5)
18 Months	43, 26.1 (21.2, 31.3)	34, 18.2 (14.0, 22.9)
Median (95% CI) Follow up (months) [3]	17.2 (15.9, 18.1)	17.8 (15.9, 18.7)

[1] Kaplan-Meier Estimate.
[2] The hazard ratio (HR) and 95% confidence interval (CI) are based on a stratified Cox proportional hazards regression
model, stratified by baseline ECOG performance status, region and liver metastases per IWRS. Gem+NabP is reference.
[3] Median follow up is calculated by patients censored at death.
Note: Data cutoff date is 2022-09-29, when event reached 565.
Program: em52-napolie3/ema/t7_1_os_km_b.sas 19SEP2023 5:51

Figure 14. Kaplan-Meier Curve of Overall Survival based on 565 events - Intent to treat population (ITT)



Source: RSI MO1a. Figure 1.

Tipping point analysis of OS

The tipping point methodology described by Lipkovich et al (2016), based on imputing the expected time to event in informatively censored patients for each treatment arm until the result of OS overturn from statistically significant to insignificant was used.

A tipping point parameter, noted δ, was only applied to OS among **informatively censored patients** who withdrew consent or lost to follow-up to stress-test the impact of the non-administrative censored values [Fink 2015] and quantify the excessive risk after withdrawal compared to a similar patient in the same treatment. Censoring at the time of the planned target OS events (543 OS events) due to administrative constraints (non-informative censoring) was considered unrelated to the study treatments.

A bootstrap-based semi-parametric multiple imputation approach was used to impute censored data and estimate the tipping point parameter δ, where series of assumptions were performed on the hazard function (equation (1)) with gradually increasing values of δ until the study conclusion was nullified [Jackson 2014]. The goal was to find the smallest δ such that the difference between NALIRIFOX and Gem+NabP arms was no longer significant.

$$h(t|C_i < t, Z_i) = h_0(t)\exp(\beta Z_i)\,\delta \text{ , equation (1)}$$

for subject i (i to 1 to $N_{informative\text{-}censor}$), where t is the time to event, Ci the censor time, Zi the treatment group, β the regression coefficient of the treatment group, and d the tipping point parameter

A range of increasing tipping point values $\delta_{Nalirifox}$ >1, unfavourable to the NALIRIFOX arm, were tested while maintaining the CAR assumption ($\delta_{Gem+NabP}$ =1) for the Gem+NabP arm.

It was assumed that OS informative censoring was associated with an increased risk of death, leading to the imposition of $\delta_{Nalirifox}$ >1 post withdrawal of consent or lost to follow-up for subjects in the NALIRIFOX arm.

For the Gem+NabP arm, it was assumed that subjects with OS informative censoring would have comparable death risk after censoring date to their counterparts who continued the study.

Based on 1000 multiple imputations, as $\delta_{Nalirifox}$ increased, the treatment effect shrank to 0 (HR toward 1) and eventually OS result became negative.

The smallest 'tipping point', where the OS result was no longer significant at the 5% level, occurred at $\delta_{Nalirifox}$ around 2.5 (*Table 28*) while $\delta_{Gem+NabP}$ was fixed to 1.

Table 28. Tipping point results based on $\delta_{Gem+NabP}$ =1 and $\delta_{Nalirifox}$ >1

$\delta_{Gem+NabP}$	$\delta_{Nalirifox}$	HR [1]	2-sided P-value [2]
1	2	0,843	0,0468
1	2,25	0,8443	0,0487
1	2,3	0,8445	0,049
1	2,35	0,8447	0,0493
1	2,4	0,8449	0,0496
1	2,45	0,8451	0,0499
1	**2,5**	**0,8454**	**0,0503**
1	3	0,8471	0,053

1] stratified hazard ratio (HR) by baseline ECOG performance status, region (US, RoW including Asia) and liver metastases per IWRS. Gem+NabP is the reference.
[2] P value estimation based on Rubin's rule methodology
Number of imputations=1000 based on cox model imputation method

Source: RSI MO1d. Table 4.

Exploratory endpoints

Duration of response

Table 29. Summary of Duration of Response (ITT)

	NALIRIFOX (N=383) n (%)	**Gem+NabP (N=387) n (%)**
Participants with CR or PR	160	140
Participants with DOR Events	102 (63.8)	75 (53.6)
Progressive Disease	93 (58.1)	61 (43.6)
Death	9 (5.6)	14 (10.0)

Participants Censored	58 (36.3)	65 (46.4)
Median (95% CI) (months) [1]	7.3 (5.8, 7.6)	5.0 (3.8, 5.6)
Stratified HR (95% CI) [p-value] [2]	0.67 (0.48, 0.93) [0.02]	

CI=confidence interval, CR=complete response, DOR=duration of response, ECOG= Eastern Cooperative Oncology Group, HR=hazard rate, , PR=partial response.

Percentage is calculated using the number of participants with CR or PR as the denominator.

[1] Kaplan-Meier Estimate.

[2] The HR and 95% CI are based on a stratified Cox proportional hazards regression model, stratified by baseline ECOG performance status, region ("North America", and "Rest of the World") and liver metastases per IWRS. Gem+NabP is reference.

Time to response

Table 30. Summary of Time to Response (ITT)

	NALIRIFOX (N=383)	**Gem+NabP (N=387)**
Time to Response (months)		
N	160	140
Median	3.58	3.43
Range	(1.5, 13.0)	(0.8, 9.5)

Patient reported outcomes

PRO was assessed using four different questionnaires, the European Organisation for Research and Treatment of Cancer quality-of-life-core questionnaire (EORTC QLQ-C30) and, specific pancreatic cancer module (QLQ-PAN26) questionnaire and patient reported outcomes Common Terminology Criteria of Adverse Events (PRO-CTCAE) and the EuroQol 5 dimension health status questionnaire (5 level) (EQ-5D-5L). Only data from the EORTC QLQ-C30 are presented here.

The EORTC QLQ-C30 (version 3) is a generic questionnaire that has been developed to assess the QoL of cancer patients. The minimally significant mean change is 5 to 10 points on a scale of 0 to 100. If at least half the components of a domain are present, then the domain score is calculated using the average of all items answered as the raw score; otherwise the score is set to missing. It was filled in on D1 of each treatment cycle before administration of treatment and other study assessments and at the EoT visit (30±14 days after last dose).

The compliance rate for EORTC QLQ-C30 was 77.3% at baseline for the NALIRIFOX arm and between 60.5% and 75.1% between week 4-52. For the Gem+NabP arm the compliance rate was 73.1% at baseline and between 57.1% and 79.2 % between week 4-52.

Based on EORTC QLQ-C30 global health status, there were 75 participants (19.6%) who deteriorated in the NALIRIFOX arm and 67 participants (17.3%) in the Gem+NabP arm. Median time to deterioration was 15.7 months in the NALIRIFOX arm and 12.2 months in the Gem+NabP arm. The stratified HR was 0.74 (95% CI: 0.53, 1.04, nominal p-value=0.08).

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for NAPOLI 3

Title: NAPOLI 3			
Study identifier	D-US-60010-001, NP42379		
Design	Open label, randomised, multicentre, international, phase III study of Onivyde containing NALIRIFOX vs. Gem+NabP		
	First patient randomised: Last patient randomised:		February 2020 August 2021
Hypothesis	Superiority		
Treatments groups	NALIRIFOX		Treatment: D1 and D15 in 28 days cycles with 50 mg/m^2 liposomal irinotecan, 60 mg/m^2 oxaliplatin, 4000 mg/m^2 LV and 2400 mg/m^2 5-FU until progression or toxicity. N=383
	Gem+NabP		Treatment: D1, D8 and D15 in 28 days cycles with 125 mg/m^2 nab-paclitaxel and 1000 mg/m^2 gemcitabine until progression or toxicity. N=387
Endpoints and definitions	Primary endpoint	OS	Time from date of randomisation to death due to any cause.
	Secondary endpoint	PFS-investigator assessed	Time from randomisation to radiological disease progression according to RECIST 1.1 or death due to any cause.

	Secondary endpoint	ORR-investigator assessed	Proportion of participants with a BOR of CR or PR according to RECIST 1.1

Database lock	05 October 2022 (DCO 23 July 2022)
Results and Analysis	
Analysis description	**Primary Analysis**
Analysis population and time point description	Intent to treat Final analysis DCO 23 July 2022

Descriptive statistics and estimate variability	Treatment group	NALIRIFOX	Gem+NabP	
	Number of subject	383	387	
	OS Median (months)	11.1	9.2	
	95% CI	10.0, 12.1	8.3, 10.6	
	PFS Median (months)	7.4	5.6	
	95% CI	6.0, 7.7	5.3, 5.8	
	ORR n (%)	160 (41.8)	140 (36.2)	
	95% CI (%)	36.8, 46.9	31.4, 41.2	

Effect estimate per comparison	Primary endpoint OS	Comparison groups	NALIRIFOX vs. Gem+NabP
		Stratified HR	0.84
		95% CI	0.71, 0.99
		P-value	0.04
	Secondary endpoint PFS (FDA censoring rules)	Comparison groups	NALIRIFOX vs. Gem+NabP
		Stratified HR	0.69
		95% CI	0.58, 0.83

		P-value	<0.0001
	Secondary endpoint	Comparison groups	NALIRIFOX vs. Gem+NabP
	ORR	Odds Ratio	1.26
		95% CI	0.95, 1.69
		P-value	0.11

	Age 65-74 (older subjects number / total number)	Age 75-84 (older subjects number / total number)	Age 85+ (older subjects number / total number)
NAPOLI3	322 / 770 (41.8%)	63 / 770 (8.2%)	1 / 770 (0.1%)

Source: Analysis datasets from NAPOLI3: ADSL

Data cutoff date: 23JUL2022.

Program: T_AGE_CLASSES_ITT.sas; Date & time program was run: 20MAR2024 09:48

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has applied to extend the marketing authorisation to first line metastatic adenocarcinoma of the pancreas from the current indication in later line. The proposed wording of the new 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,

The NAPOLI 3 study (D-US-60010-001, NP42379) is an open label, randomised, multicentre, international, phase III study. It evaluated the efficacy and safety of NALIRIFOX versus Gem+NabP as first-line treatment for adults with metastatic adenocarcinoma of the pancreas. Doses for NALIRIFOX were determined in Study MM-398-02-03.

Randomisation was stratified by ECOG performance status (0 vs. 1), region (North America/East Asia/Rest of the World) and liver metastases (y/n).

The test arm consisted of Onivyde pegylated liposomal in combination with oxaliplatin, 5-FU and LV, i.e. a variation of the standard FOLFIRINOX chemotherapy combination with omitted bolus 5-FU and reduced oxaliplatin.

The control arm consisted of the EU approved combination gemcitabine with nab-paclitaxel at standard doses. This is one of the current standard recommended options for patients with good performance status together with the FOLFIRINOX combination.

The primary endpoint of the NAPOLI 3 study was OS. A hierarchical testing procedure was specified including also investigator assessed PFS and ORR according to RECIST 1.1. The PFS analysis encompassed censoring if a patient missed two or more tumour assessments or started subsequent anti-cancer treatment prior to documented progression.

The protocol was amended four times:

Amendment 2 included modification of inclusion/exclusion criteria and an option to increase sample size if accrual of events for the primary analysis was not projected to be reached within 32 months due to censoring. This was done about three months after the first patient was randomised and is not considered to have had a major impact on the study results.

Amendment 4 was made less than one year before the final DCO date. Here the number of events required for the final analysis was reduced from 565 OS events to 543. In addition, one interim analysis for futility was removed, and the timing of the remaining interim analysis for futility and efficacy was adjusted.

With regards to the timing of amendment 4 and the previously planned first IA, the IDMC meeting preceding the 4th amendment was held in April 2021 and stated that the first IA was estimated to occur in September 2021, ie. after the addition of amendment 4 August 2021.

Changes performed in an open-label trial where a considerable amount of data have been collected and close to the final readout of results is inappropriate and concerning. However, a key sensitivity analysis according to the SAP where study integrity was considered to be retained was recreated and the results are consistent with the primary analysis. Furthermore, a tipping point analysis and updated OS results provided supports the robustness of the presented OS result.

Efficacy data and additional analyses

770 randomised participants were randomised. 383 patients were randomized to the NALIRIFOX arm and 387 to the Gem+NabP arm.

Efficacy data presented are from the final analysis with a DCO date of July 23, 2022. 51 patients were then remaining on treatment. 44 patients in the NALIRIFOX arm and 7 in the Gem+NabP arm.

At the final analysis median follow-up time was 16.0 (95% CI 15.0, 16.8) months for the NALIRIFOX arm and 16.3 (95% CI 15.0, 17.5) months for the Gem+NabP arm when patients were censored at death.

There was a total of 544 (70.6%) OS events. The NALIRIFOX arm demonstrated a statistically significant difference in OS compared with Gem+NabP based on the stratified log-rank test p-value 0.04.

The median OS was 11.1 months (95% 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 0.84 (95% CI: 0.71, 0.99).

Overall, the subgroup analyses of OS do not give rise to suspicion of detrimental effect in any presented subgroup.

Considering the late changes made to the primary endpoint in this open labelled study the type 1 error control is de facto lost. In addition, the p-value is quite high at 0.04 hence the robustness of the OS estimate needed to be further assessed.

Several sensitivity analyses have been provided for OS. The key sensitivity analysis according to the CSP version 3 based on 565 events was recreated. The outcome from this analysis, using a stratified analysis, was HR (95% CI): 0.82 (0.69, 0.97) with a 2-sided p-value of 0.017. In addition, a tipping point analysis was performed. The tipping point analysis demonstrated that all subjects in the NALIRIFOX arm censored due to lost to follow-up or withdrawal of consent, would need to have at least a 2.5-fold increase in the event hazard (death) compared to their counterparts who continued the

study to overturn the OS primary analysis result (two-sided p-value ≥ 0.05). These analyses are considered to support the robustness of the inferential OS analysis.

Furthermore, an updated analysis for OS based on a DCO October 3, 2023, have been provided. At the time, there were 11 subjects (all in the NALIRIFOX arm) still on-treatment. The median follow-up was 28.7 months (95% CI 27.3, 30.1) in the NALIRIFOX arm and 29.7 months (95% CI 27.7, 31.6) in the Gem+NabP arm. There were 673 OS events: 328 (85.6%) and 345 (89.1%) in the NALIRIFOX and Gem+NabP arms respectively. The outcome of this updated analysis was HR (95% CI): 0.84 (0.72, 0.98) with a 2-sided nominal p-value of 0.026. This is consistent with the primary OS analysis and reassuring.

There was a total of 508 PFS events. The NALIRIFOX arm demonstrated a statistically significant difference in PFS assessed by the investigator compared with Gem+NabP 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% CI: 0.58, 0.83), with a 2-sided nominal p-value of less than 0.0001.

Presented subgroup analyses are consistent with the ITT result. The high frequency of censoring on day one of the study in the PFS analysis is due to lack of post baseline tumour assessments in 29(7.6%) and 18(4.7%) patients in NALIRIFOX and Gem+NabP arms respectively.

Baseline demographics and patient characteristics were: median age of 65 years (range: 20-85); 50% age 65 or older ; 56% male; 83% White; 5% Asian; 3% Black or African American; ECOG performance status was 0 in 43% or 1 in 57% of patients; 87% liver metastases.

PFS assessment by an independent blinded review committee was not performed.

There were a considerable number of censoring events related to initiation of subsequent anti-cancer therapy with 22.5% of patients being censored for this reason in the Gem+NabP arm. An analysis using the EMA censoring recommendation seems not to be feasible as patients appears not to have been followed for progression if initiated on new anti-cancer therapy according to the protocol.

Considering that this is not the primary endpoint, the PFS gain is still considered statistically robust given the low p-value.

ORR per RECIST 1.1 for the NALIRIFOX arm was 41.8% (95% CI: 36.8, 46.9) and in the Gem+NabP arm it was 36.2% (95% CI: 31.4, 41.2) giving the odds ratio of NALIRIFOX compared to Gem+NabP 1.26 (95% CI: 0.95, 1.69), p=0.11. This was not statistically significant.

A high fraction of patients labelled as not evaluable for the analysis is noted, 86 (22.5%) for the NALIRIFOX arm and 90 (23.3%) for the Gem+NabP arm. Of these, 70 (18.3%) and 67 (17.3%) in the NALIRIFOX arm and Gem+NabP respectively is due to no evaluable post-baseline tumour assessments. The majority of these are due to lack of post-baseline assessment (not done or missing), 68 (17.8%) and 65 (16.8%) in the NALIRIFOX and GemNabP arm respectively. The other sizable category was SD not confirmed at 8 weeks, 16 (4.2%) and 22 (5.7%), in the NALIRIFOX arm and Gem+NabP respectively. The frequency is balanced between the treatment arms.

The DOR for the NALIRIFOX arm was 7.3 months (95% CI: 5.8, 7.6) versus 5.0 months (95% CI: 3.8, 5.6) for the Gem+NabP arm.

Considering the open label design and high degree of missing in the PRO data set the treatment effect on PRO and HRQoL cannot be reliably assessed.

2.4.4. Conclusions on the clinical efficacy

The statistical integrity of the NAPOLI 3 study was compromised by the late protocol amendment in this open label study. However, a key sensitivity analysis according to the SAP where study integrity was considered to be retained was recreated and the results are consistent with the primary analysis. Furthermore, a tipping point analysis and updated OS results provided supports the robustness of the presented OS result. In conclusion, efficacy in terms of OS and PFS is considered established for NALIRIFOX.

2.5. Clinical safety

Introduction

The MAH has submitted an integrated safety analysis encompassing data from the pivotal study D-US-60010-001 (NAPOLI 3) and study MM-398-07-02-03.

Table 31-Summary of Clinical Studies Conducted with Irinotecan Liposome Injection in Metastatic Pancreatic Adenocarcinoma Included in the Integrated Summary of Safety (ISS)

Study	Study Population	Study Design, Administration and Dose [a]	Primary Objective(s)	Study Duration	Total Number of Participants Treated (Safety Population)
Pivotal Study					
NAPOLI 3 D-US-60010-001 (Module 5.3.5.1, NP42379) Pivotal study	Metastatic adenocarcinoma of the pancreas	An open label, randomised, multicentre phase III study with an active control group. NALIRIFOX regimen: Irinotecan liposome injection 50 mg/m^2 + oxaliplatin 60 mg/m^2 + 5-FU/LV 2400/400 mg/m^2, IV infusion q2w versus Gem+NabP regimen: nab-paclitaxel 125 mg/m^2 +gemcitabine 1000 mg/m^2, i.v. infusion Days 1,8,15 q4w.	Investigate the efficacy and safety of the regimen of irinotecan liposome injection + oxaliplatin + 5-fluorouracil (5-FU) /leucovorin (LV) in participants who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas	First participant first visit: 11 February 2020 Data cut-off for final analysis: 23 July 2022	NALIRIFOX: 370 Gem+NabP: 379
Supportive Study					
MM-398-07-02-03 (Module 5.3.5.2, NP42373)	Unresectable locally advanced and metastatic adenocarcinoma of the pancreas	An open-label, non-randomised multicentre phase II study with no control group. NALIRIFOX regimen and three other regimens[a]: Irinotecan liposome injection 50 mg/m^2 + oxaliplatin 60 mg/m^2 + 5-FU/LV 2400/400 mg/m^2, IV infusion q2w	Examine the safety, tolerability, and preliminary efficacy of irinotecan liposome injection in combination with 5-FU/LV and oxaliplatin, in participants not previously treated for metastatic pancreatic adenocarcinoma	First participant first visit: 19 October 2015. Study completion date: 15 February 2021	56 (of which 32 are included in the ISS since they were treated with the same NALIRIFOX regimen)

5-FU=5-fluorouracil, i.v.=intravenous, LV=leucovorin, q2w=every 2 weeks, q4w=every 4 weeks

a Other dose levels include

1. irinotecan liposome injection 70 mg/m^2 + oxaliplatin 60 mg/m^2 + 5-FU/LV 2400/400 mg/m^2
2. irinotecan liposome injection 50 mg/m^2 + oxaliplatin 85 mg/m^2 + 5-FU/LV 2400/400 mg/m^2
3. irinotecan liposome injection 55 mg/m^2 + oxaliplatin 70 mg/m^2 + 5-FU/LV 2400/400 mg/m^2

Patient exposure

Table 32-Study Exposure and Compliance by Treatment Arm (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)
Duration in weeks		
n	370	379
Median	24.29	17.57
Q1, Q3	(8.43, 42.14)	(8.14, 30.14)
Range	(0.4, 100.9)	(0.7, 81.7)
Number of Cycles Administered		
n	370	379
Mean	6.5	5.1
SD	5.11	3.68
Median	5.0	4.0
Q1, Q3	(2.0, 10.0)	(2.0, 7.0)
Range	(1, 24)	(1, 20)
Cycle 1	370 (100.0)	379 (100.0)
Cycle 2	304 (82.2)	314 (82.8)
Cycle 3	260 (70.3)	254 (67.0)
Cycle 4	231 (62.4)	220 (58.0)
Cycle 5	200 (54.1)	184 (48.5)
Cycle 6	180 (48.6)	162 (42.7)
Cycle 7	154 (41.6)	116 (30.6)
≥Cycle 8	133 (35.9)	86 (22.7)
Any Dose Reductions	220 (59.5)	204 (53.8)

Table 33-Study Exposure and Compliance by Treatment Arm (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)
Any Dose Delays	260 (70.3)	200 (52.8)
Any Infusion Interruptions	43 (11.6)	8 (2.1)
Any Drug Withdrawals/Discontinuation	92 (24.9)	77 (20.3)
Any Dose Omitted	50 (13.5)	163 (43.0)

Q=quartile, SD=standard deviation
Data based on study treatment exposure eCRF.
Data Source: Table 14.1.10.1a

Adverse events

Overall Summary of Adverse Events (Safety Population)

Table 34-NAPOLI 3: Overall Summary of Adverse Events (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)
TEAEs	369 (99.7)	376 (99.2)
Related to treatment regimen	352 (95.1)	352 (92.9)
Grade ≥3 TEAEs	322 (87.0)	326 (86.0)
Related to treatment regimen	262 (70.8)	258 (68.1)
Serious TEAE	201 (54.3)	195 (51.5)
Related to treatment regimen	98 (26.5)	72 (19.0)
TEAEs Leading to Treatment Discontinuation	118 (31.9)	112 (29.6)
Related to treatment regimen	94 (25.4)	88 (23.2)
TEAEs Leading to Discontinuation of Irinotecan Liposome Injection	63 (17.0)	-
Related to irinotecan liposome injection	35 (9.5)	-
TEAEs Leading to Reduction of Treatment Regimen	208 (56.2)	190 (50.1)
Related to treatment regimen	198 (53.5)	184 (48.5)
TEAEs Leading to Interruption of Treatment Regimen	16 (4.3)	4 (1.1)
Related to treatment regimen	12 (3.2)	3 (0.8)
TEAEs Leading to Death	22 (5.9)	23 (6.1)
Related to treatment regimen	6 (1.6)	8 (2.1)
Serious TEAE due to COVID-19	19 (5.1)	26 (6.9)

TEAE=treatment-emergent adverse event
Data source: Module 5.3.5.1 CSR NP42379, Table 14.3.1.1a
Note: A TEAE was related to treatment regimen if the TEAE was related to any component of the study medication

TEAEs by System Organ Class and Preferred Term

Table 35-NAPOLI 3: Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term with an Incidence of 10% or More Participants in Either Arm (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)
Any Treatment-emergent Adverse Events	369 (99.7)	376 (99.2)
Gastrointestinal disorders		
Diarrhoea	261 (70.5)	139 (36.7)
Nausea	220 (59.5)	162 (42.7)
Vomiting	147 (39.7)	100 (26.4)
Abdominal pain	98 (26.5)	77 (20.3)
Constipation	93 (25.1)	113 (29.8)
Stomatitis	50 (13.5)	45 (11.9)
General disorders and administration site conditions		
Fatigue	120 (32.4)	143 (37.7)
Asthenia	114 (30.8)	104 (27.4)
Oedema peripheral	52 (14.1)	108 (28.5)
Mucosal inflammation	51 (13.8)	16 (4.2)
Pyrexia	39 (10.5)	87 (23.0)
Nervous system disorders		
Neuropathy peripheral	66 (17.8)	66 (17.4)
Dysgeusia	63 (17.0)	58 (15.3)
Peripheral sensory neuropathy	56 (15.1)	51 (13.5)
Paraesthesia	44 (11.9)	33 (8.7)
Dizziness	24 (6.5)	40 (10.6)
Blood and lymphatic system disorders		
Neutropenia	109 (29.5)	121 (31.9)
Anaemia	97 (26.2)	153 (40.4)
Thrombocytopenia	50 (13.5)	86 (22.7)
Metabolism and nutrition disorders		
Decreased appetite	136 (36.8)	106 (28.0)
Hypokalaemia	117 (31.6)	49 (12.9)
Dehydration	41 (11.1)	32 (8.4)
Investigations		
Weight decreased	82 (22.2)	33 (8.7)
Neutrophil count decreased	76 (20.5)	71 (18.7)

Table 36-NAPOLI 3: Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term with an Incidence of 10% or More Participants in Either Arm (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)
Alanine aminotransferase increased	45 (12.2)	48 (12.7)
Gamma-glutamyl transferase increased	45 (12.2)	34 (9.0)
Aspartate aminotransferase increased	40 (10.8)	40 (10.6)
Platelet count decreased	39 (10.5)	68 (17.9)
Blood alkaline phosphatase increased	39 (10.5)	31 (8.2)
Skin and subcutaneous tissue disorders		
Alopecia	52 (14.1)	119 (31.4)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	25 (6.8)	47 (12.4)
Epistaxis	14 (3.8)	43 (11.3)

Data source: Module 5.3.5.1 CSR NP42379 Table 14.3.2.1.1a

TEAEs by NCI-CTCAE Grading 3 or 4

Table 37-NAPOLI 3: Summary of Treatment Emergent Adverse Events of NCI-CTCAE Grade 3 or 4 by System Organ Class and Preferred Term with 2% Difference or more between treatment Arms (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)
Any Treatment-emergent Adverse Events of NCI-CTCAE Grade 3 or 4	316 (85.4)	322 (85.0)
Gastrointestinal disorders		
Diarrhoea	75 (20.3)	17 (4.5)
Nausea	44 (11.9)	10 (2.6)
Vomiting	26 (7.0)	8 (2.1)
Blood and lymphatic system disorders		
Anaemia	39 (10.5)	66 (17.4)
Neutropenia	52 (14.1)	93 (24.5)
Neutrophil count decreased*	36 (9.7)	51 (13.5)
Febrile neutropenia[#]	9 (2.4)	9 (2.4)
Leukopenia	4 (1.1)	17 (4.5)
White blood cell count decreased*	6 (1.6)	18 (4.7)
Thrombocytopenia	3 (0.8)	14 (3.7)
Platelet count decreased*[^]	3 (0.8)	9 (2.4)
General disorders and administration site conditions		
Asthenia	33 (8.9)	19 (5.0)
Nervous system disorders		
Neuropathy peripheral	12 (3.2)	22 (5.8)
Metabolism and nutrition disorders		
Decreased appetite	32 (8.6)	10 (2.6)
Hypokalaemia	56 (15.1)	15 (4.0)
Dehydration	12 (3.2)	4 (1.1)
Investigations		
Weight decreased	11 (3.0)	1 (0.3)
Infections and infestations		
Pneumonia	5 (1.4)	13 (3.4)

* Investigations SOC
[#] Difference less than 2%, but included due to its relevance to neutropenia
[^] Difference less than 2%, but included due to its relevance to thrombocytopenia
Data source: Module 5.3.5.1 CSR NP42379 Table 14.3.2.1.2a

Serious adverse event/deaths/other significant events

Serious adverse events

Table 38-NAPOLI 3: Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term Occurring in 2% or More Participants in Either Treatment Group (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)	Total (N=749) n (%)
Any Serious Treatment-emergent Adverse Events	201 (54.3)	195 (51.5)	396 (52.9)
Gastrointestinal disorders			
Diarrhoea	23 (6.2)	9 (2.4)	32 (4.3)
Vomiting	22 (5.9)	6 (1.6)	28 (3.7)
Nausea	18 (4.9)	3 (0.8)	21 (2.8)
Abdominal pain	9 (2.4)	8 (2.1)	17 (2.3)
Infections and infestations			
COVID-19	18 (4.9)	14 (3.7)	32 (4.3)
Sepsis	6 (1.6)	16 (4.2)	22 (2.9)
Pneumonia	7 (1.9)	13 (3.4)	20 (2.7)
General disorders and administration site conditions			
Pyrexia	8 (2.2)	12 (3.2)	20 (2.7)
Metabolism and nutrition disorders			
Dehydration	10 (2.7)	4 (1.1)	14 (1.9)
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	10 (2.7)	7 (1.8)	17 (2.3)
Blood and lymphatic system disorders			
Anaemia	5 (1.4)	8 (2.1)	13 (1.7)
Vascular disorders			
Deep vein thrombosis	4 (1.1)	8 (2.1)	12 (1.6)
Renal and urinary disorders			
Acute kidney injury	3 (0.8)	9 (2.4)	12 (1.6)

Data source: Module 5.3.5.1 CSR NP42379 Table 14.3.2.4a

Table 39-NAPOLI 3: Summary of Serious Treatment-Related Treatment Emergent Adverse Events Related to Any Study Medication by System Organ Class and Preferred Term Occurring in 2% or More Participants in Either Arm

SOC Preferred Term	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)	Total (N=749) n (%)
Any Serious Treatment-emergent Adverse Events Related to Any Study Medication	98 (26.5)	72 (19.0)	170 (22.7)
Gastrointestinal disorders			
Diarrhoea	22 (5.9)	6 (1.6)	28 (3.7)
Vomiting	15 (4.1)	4 (1.1)	19 (2.5)
Nausea	15 (4.1)	3 (0.8)	18 (2.4)
Infections and infestations			
Sepsis	4 (1.1)	9 (2.4)	13 (1.7)
Metabolism and nutrition disorders			
Dehydration	8 (2.2)	3 (0.8)	11 (1.5)

Data source: Module 5.3.5.1 CSR NP42379 Table 14.3.2.5a

In NAPOLI- 3 study, pneumonitis was reported in 0.3% of patients receiving ONIVYDE pegylated liposomal in combination with oxaliplatin and 5-FU/LV.

Deaths

Table 40- NAPOLI 3: Summary of Treatment Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)	Total (N=749) n (%)
Any Treatment-emergent Adverse Events Leading to Death	22 (5.9)	23 (6.1)	45 (6.0)
Infections and infestations	4 (1.1)	13 (3.4)	17 (2.3)
Sepsis	2 (0.5)	8 (2.1)	10 (1.3)
Pneumonia	2 (0.5)	3 (0.8)	5 (0.7)
COVID-19	0 (0.0)	1 (0.3)	1 (0.1)
Pneumonia aspiration	0 (0.0)	1 (0.3)	1 (0.1)
General disorders and administration site conditions			
General physical health deterioration	1 (0.3)	1 (0.3)	2 (0.3)
Condition aggravated	0 (0.0)	1 (0.3)	1 (0.1)
Sudden cardiac death	1 (0.3)	0 (0.0)	1 (0.1)
Sudden death	1 (0.3)	0 (0.0)	1 (0.1)
Blood and lymphatic system disorders			
Febrile neutropenia	1 (0.3)	1 (0.3)	2 (0.3)
Disseminated intravascular coagulation	0 (0.0)	1 (0.3)	1 (0.1)
Pancytopenia	1 (0.3)	0 (0.0)	1 (0.1)
Nervous system disorders			
Cerebrovascular accident	2 (0.5)	0 (0.0)	2 (0.3)
Ischaemic stroke	2 (0.5)	0 (0.0)	2 (0.3)
Respiratory, thoracic and mediastinal disorders			
Aspiration	1 (0.3)	0 (0.0)	1 (0.1)
Pneumonitis	0 (0.0)	1 (0.3)	1 (0.1)
Pulmonary embolism	1 (0.3)	0 (0.0)	1 (0.1)
Vascular disorders			
Haemorrhage	0 (0.0)	2 (0.5)	2 (0.3)
Embolism	0 (0.0)	1 (0.3)	1 (0.1)
Cardiac disorders			
Cardiac arrest	1 (0.3)	1 (0.3)	2 (0.3)
Gastrointestinal disorders			
Ascites	1 (0.3)	0 (0.0)	1 (0.1)
Gastrointestinal haemorrhage	1 (0.3)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Peritumoural oedema	1 (0.3)	0 (0.0)	1 (0.1)
Tumour haemorrhage	1 (0.3)	0 (0.0)	1 (0.1)
Hepatobiliary disorders			
Cholangitis	0 (0.0)	1 (0.3)	1 (0.1)
Injury, poisoning and procedural complications			
Head injury	1 (0.3)	0 (0.0)	1 (0.1)
Renal and urinary disorders			
Renal failure	1 (0.3)	0 (0.0)	1 (0.1)

Data source: Module 5.3.5.1 CSR NP42379 Table 14.3.2.16a

Table 41-NAPOLI 3: Summary of Treatment Emergent Adverse Events Leading to Death Related to Any Study Medication by System Organ Class and Preferred Term (Safety Population)

SOC Preferred Term	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)	Total (N=749) n (%)
Any Treatment-emergent Adverse Events Leading to Death Related to Any Study Medication	6 (1.6)	8 (2.1)	14 (1.9)
Infections and infestations			
Sepsis	1 (0.3)	5 (1.3)	6 (0.8)
Blood and lymphatic system disorders			
Febrile neutropenia	1 (0.3)	1 (0.3)	2 (0.3)
Pancytopenia	1 (0.3)	0 (0.0)	1 (0.1)
General disorders and administration site conditions			
General physical health deterioration	1 (0.3)	1 (0.3)	2 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Peritumoural oedema	1 (0.3)	0 (0.0)	1 (0.1)
Nervous system disorders			
Ischaemic stroke	1 (0.3)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	0 (0.0)	1 (0.3)	1 (0.1)

Data source: Module 5.3.5.1 CSR NP42379 Table 14.3.2.17a

Treatment Emergent Adverse Events of Special Interest

Table 42-NAPOLI 3: Treatment Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term Safety Population Occurring in Two or More Participants in Either Arm (Safety Population)

	NALIRIFOX (N=370)		Gem+NabP (N=379)	
	Any Grade n (%) event	Grade 3-4 n (%) event	Any Grade n (%) event	Grade 3-4 n (%) event
Any Treatment-emergent Adverse Events of Special Interest	81 (21.9) 98	36 (9.7) 40	81 (21.4) 99	32 (8.4) 36
Vascular disorders				
Deep vein thrombosis	15 (4.1) 15	4 (1.1) 4	20 (5.3) 20	4 (1.1) 4
Embolism	11 (3.0) 11	4 (1.1) 4	12 (3.2) 12	3 (0.8) 3
Venous thrombosis limb	0	0	5 (1.3) 5	1 (0.3) 1
Superficial vein thrombosis	1 (0.3) 1	0	3 (0.8) 3	0
Thrombosis	0	0	4 (1.1) 4	0
Venous thrombosis	2 (0.5) 2	1 (0.3) 1	2 (0.5) 2	0
Vena cava thrombosis	2 (0.5) 2	0	1 (0.3) 1	0
Jugular vein thrombosis	2 (0.5) 2	1 (0.3) 1	0	0
Phlebitis	2 (0.5) 2	0	0	0
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism	29 (7.8) 30	21 (5.7) 21	27 (7.1) 28	16 (4.2) 16
Nervous system disorders				
Cerebrovascular accident	4 (1.1) 4	2 (0.5) 2	2 (0.5) 2	2 (0.5) 2
Ischaemic stroke	4 (1.1) 4	2 (0.5) 2	2 (0.5) 3	2 (0.5) 2
Cerebral ischaemia	2 (0.5) 2	1 (0.3) 1	0	0
Blood and lymphatic system disorders				
Splenic vein thrombosis	4 (1.1) 4	0	0	0
Gastrointestinal disorders				
Mesenteric vein thrombosis	3 (0.8) 3	0	3 (0.8) 3	0
Hepatobiliary disorders				
Portal vein thrombosis	1 (0.3) 1	0	4 (1.1) 4	2 (0.5) 2
General disorders and administration site conditions				
Device related thrombosis	4 (1.1) 4	0	0	0
Product issues				
Thrombosis in device	1 (0.3) 1	0	2 (0.5) 2	0

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0
Adverse Events are coded using MedDRA Version 25.0
Data Source: Table 14.3.2.19a

Adverse drug reactions

*Table 43-**Adverse reactions reported with Onivyde Pegylated Liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin in NAPOLI 3.***

LABELING TERM GROUPING SOC	FREQUENCY CATEGORY	PT	GROUPING TERM PROPOSITION (FREQUENCY)
Infections	Uncommon	Pneumonia, Atypical pneumonia	**Pneumonia** (uncommon)
	Common	Candida infection, Oral candidiasis	**Candida infection** (common)
	Common	Urinary tract infection	**Urinary tract infection** (common)
	Uncommon	Cystitis	
	Uncommon	Rhinitis	Grouped under **Cholinergic syndrome** (frequency common - SOC Nervous system disorders)
Nervous system disorders	Very common	Dysgeusia	**Dysgeusia** (very common)
	Uncommon	Taste disorder	
	Very common	Neuropathy peripheral, Peripheral sensory neuropathy	**Neuropathy peripheral** (very common)
	Common	Polyneuropathy	
	Uncommon	Peripheral motor neuropathy	
	Common	Dysaesthesia	**Dysaesthesia** (common)
	Uncommon	Cold dysaesthesia	
	Uncommon	Rhinitis (SOC Infection)	**Addition of term Cholinergic syndrome** (common)
	Uncommon	Rhinorrhoea (SOC Respiratory, thoracic and mediastinal disorders)	
	Uncommon	Lacrimation increased (SOC eye disorders)	
	Uncommon	Flushing, and Hot flush	
	Common	Salivary hypersecretion	
	Uncommon	Generalised tonic-clonic seizure, Seizure	**Seizure** (uncommon)
Eye disorders	Uncommon	Lacrimation increased	Grouped under **Cholinergic syndrome** (frequency common - SOC Nervous system disorders)
Cardiac disorders	Uncommon	Tachycardia	**Tachycardia** (common)
		Sinus tachycardia	
Vascular disorders	Uncommon	Deep vein thrombosis, Embolism, Superficial vein thrombosis	**Thromboembolic events** (common)
	Uncommon	Flushing, Hot flush	Grouped under **Cholinergic syndrome** (frequency common - SOC Nervous system disorders)
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough, Upper-airway cough syndrome	**Cough** (uncommon)
	Uncommon	Rhinorrhoea	Grouped under **Cholinergic syndrome** (frequency common - SOC Nervous system disorders)
Gastro-intestinal disorders	Very common	Nausea	**Nausea** (very common)
	Uncommon	Retching	

Adverse reactions reported with Onivyde Pegylated Liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin in NAPOLI 3, continued Table 43.

	Common	Abdominal pain, Abdominal pain upper,	**Abdominal pain/discomfort** (very common)
	Uncommon	Abdominal pain lower, Gastrointestinal pain, Abdominal discomfort, Epigastric discomfort	
	Common	Colitis,	**Colitis** (common)
	Uncommon	Terminal ileitis, Neutropenic colitis,	
	Common	Enterocolitis	**Enterocolitis** (common)
	Uncommon	Enteritis	
	Uncommon	Tongue coated, Tongue discomfort, Tongue disorder	**Tongue disorder** (uncommon)
	Uncommon	Dysphagia, Odynophagia	**Dysphagia** (common)
	Common	Salivary hypersecretion	Grouped under **Cholinergic syndrome** (frequency common - SOC Nervous system disorders)
Hepatobiliary disorders	Uncommon	Hypertransaminasaemia	Grouped under the term **Transaminase (ALT and AST) increased** (frequency common - SOC Investigation)
Skin and subcutaneous tissue disorders	Common	Rash	**Rash (common)**
	Uncommon	Rash maculo-papular, Rash erythematous	
Musculoskeletal and connective tissue disorders	Common	Muscle spasms	**Muscle spasms** (common)
	Uncommon	Trismus	
General disorders and administration site conditions	Very common	Asthenia, Fatigue	**Asthenia** (very common)
	Common	Oedema peripheral	**Oedema** (common)
	Uncommon	Oedema, Localised oedema	
	Common	Chills	**Chills** (common)
	Uncommon	Feeling cold	
Investigations	Very Common	Platelet count decreased	Grouped under term **Thrombocytopenia** (very common) - SOC Blood and lymphatic disorders
	Common	White blood cell count decreased,	Grouped under term **Leukopenia** (common) - SOC Blood and lymphatic disorders
	Common	Lymphocyte count decreased,	Grouped under term **Lymphopenia** (common) - SOC Blood and lymphatic disorders
	Uncommon	Haemoglobin decreased,	Grouped under term **Anaemia** (very common) in SOC Blood and lymphatic disorders
	Common	Blood bilirubin increased	Grouped under term **Hyperbilirubinaemia**

Adverse reactions reported with Onivyde Pegylated Liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin in NAPOLI 3, continued Table 43.

			(common) - SOC Hepatobiliary disorders
	Uncommon	Blood magnesium decreased	Merge under term **Hypomagnesaemia** (common) in SOC Metabolism and nutrition disorders
	Uncommon	Blood potassium decreased	Grouped under term **Hypokalaemia** (very common) in SOC Metabolism and nutrition disorders
	Common	Alanine aminotransferase Increased, Aspartate aminotransferase Increased	**Transaminase (ALT and AST) increased** (frequency common in SOC Investigation) + addition under this term of the PT Hypertransaminasaemia (see SOC Hepatobiliary disorders)
	Uncommon	Transaminases increased	
	Very Common	Neutrophil count decreased	Grouped under term **Neutropenia** (very common) in SOC Blood and lymphatic disorders

Laboratory findings

The laboratory parameters showing a 5% difference in incidence for Grade 1-4 toxicity or 2% difference in incidence or more for Grade 3 to 4 toxicity between treatment arms are presented in Table 44 below.

Table 44-NAPOLI 3: Selected Laboratory Parameters with≥5% Difference in Incidence for Grade 1-4 Toxicity or≥2% Difference in Incidence for Grade 3-4 Toxicity between Treatment Arms (Safety Population)

	NALIRIFOX (N=370)		Gem+NabP (N=379)	
	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Chemistry				
Albumin Decreased (g/L)	275 (74.3)	3 (0.8)	274 (72.3)	15 (4.0)
Alanine Aminotransferase Increased (IU/L)	141 (38.1)	9 (2.4)	205 (54.1)	17 (4.5)
Potassium Decreased (mmol/L)	217 (58.6)	77 (20.8)	107 (28.2)	28 (7.4)
Aspartate Aminotransferase Increased (IU/L)	133 (35.9)	7 (1.9)	182 (48.0)	9 (2.4)
Alkaline Phosphatase Increased (IU/L)	157 (42.4)	10 (2.7)	130 (34.3)	10 (2.6)
Potassium Increased (mmol/L)	27 (7.3)	2 (0.5)	78 (20.6)	11 (2.9)
Haematology				
Haemoglobin Decreased (g/L)	319 (86.2)	36 (9.7)	359 (94.7)	55 (14.5)
Leukocytes Decreased (10^9/L)	216 (58.4)	28 (7.6)	287 (75.7)	106 (28.0)
Lymphocytes Decreased (10^9/L)	219 (59.2)	37 (10.0)	275 (72.6)	69 (18.2)
Platelets Decreased (10^9/L)	194 (52.4)	6 (1.6)	281 (74.1)	26 (6.9)
Neutrophils Decreased (10^9/L)	195 (52.7)	93 (25.1)	243 (64.1)	139 (36.7)

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.
Data Source: Table 14.3.9.3a

Safety in special populations

UGT1A1*28 Genotype Status

*Table 45-Overall Summary of Adverse Events for Participants Homozygous for UGT1A1*28 (TA7) Allele (Safety Population)*

	NALIRIFOX (N=370) n (%) event	Gem+NabP (N=379) n (%) event
Participants homozygous for UGT1A1*28 (TA7) Allele	39	44
AEs	39 (100.0) 695	44 (100.0) 674
TEAEs	39 (100.0) 672	44 (100.0) 657
Related to Any Study Medication	39 (100.0) 446	41 (93.2) 385
Related to Irinotecan Liposome Injection	38 (97.4) 370	-
Grade 3/4/5 TEAEs	31 (79.5) 105	34 (77.3) 128
Related to Any Study Medication	27 (69.2) 70	30 (68.2) 76
Related to Irinotecan Liposome Injection	24 (61.5) 63	-
Serious TEAE	24 (61.5) 42	24 (54.5) 45
Related to Any Study Medication	15 (38.5) 25	9 (20.5) 17
Related to Irinotecan Liposome Injection	13 (33.3) 22	-
Serious TEAE due to COVID-19	0	3 (6.8) 3
TEAEs Leading to Treatment Discontinuation	15 (38.5) 18	10 (22.7) 11
Related to Any Study Medication	11 (28.2) 14	7 (15.9) 8
Related to Irinotecan Liposome Injection	4 (10.3) 6	-
TEAEs Leading to Discontinuation of Irinotecan Liposome Injection	7 (17.9) 7	-
Related to Any Study Medication	4 (10.3) 4	-
Related to Irinotecan Liposome Injection	3 (7.7) 3	-
TEAEs Leading to Reduction of Any IMP	23 (59.0) 60	14 (31.8) 22
Related to Any Study Medication	22 (56.4) 57	14 (31.8) 22
Related to Irinotecan Liposome Injection	21 (53.8) 55	-
TEAEs Leading to Reduction of Irinotecan Liposome Injection	23 (59.0) 58	-
Related to Any Study Medication	22 (56.4) 55	-
Related to Irinotecan Liposome Injection	21 (53.8) 54	-
TEAEs Leading to Interruption of Any IMP	1 (2.6) 1	1 (2.3) 2
Related to Any Study Medication	0	0
Related to Irinotecan Liposome Injection	0	-
TEAEs Leading to Interruption of Irinotecan Liposome Injection	0	-
Related to Any Study Medication	0	-
Related to Irinotecan Liposome Injection	0	-
TEAEs Leading to Death	2 (5.1) 2	4 (9.1) 4
Related to Any Study Medication	1 (2.6) 1	1 (2.3) 1
Related to Irinotecan Liposome Injection	1 (2.6) 1	-

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0
Adverse Events are coded using MedDRA Version 25.0
Data Source: Table 14.3.3.1a

Electrocardiogram Results

Table 46-ECG: Participants with Abnormal QTcF Postbaseline (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)	Total (N=749) n (%)
Absolute QTcF >450 msec	47 (12.7)	34 (9.0)	81 (10.8)
Absolute QTcF >480 msec	10 (2.7)	5 (1.3)	15 (2.0)
Absolute QTcF >500 msec	7 (1.9)	2 (0.5)	9 (1.2)
Change from Baseline QTcF Increased >30 msec	58 (15.7)	37 (9.8)	95 (12.7)
Change from Baseline QTcF Increased >60 msec	11 (3.0)	7 (1.8)	18 (2.4)

Baseline for a safety assessment is defined as the last measurement prior to the first dose of study treatment.
Data Source: Table 14.3.12.1a

Table 47-Summary of ECG Overall Interpretation by Visit (Safety Population)

	NALIRIFOX (N=370) n (%)	Gem+NabP (N=379) n (%)	Total (N=749) n (%)
Baseline – N'	367	378	745
Normal	216 (58.9)	202 (53.4)	418 (56.1)
Abnormal, Not Clinically Significant	150 (40.9)	176 (46.6)	326 (43.8)
Abnormal, Clinically Significant	1 (0.3)	0	1 (0.1)
Worst Post-Baseline – N'	322	299	621
Normal	112 (34.8)	111 (37.1)	223 (35.9)
Abnormal, Not Clinically Significant	199 (61.8)	182 (60.9)	381 (61.4)
Abnormal, Clinically Significant	11 (3.4)	6 (2.0)	17 (2.7)

Percentage is calculated using the number of participants in the safety population with post-baseline assessment (N') at the time point as the denominator. Baseline for a safety assessment is defined as the last measurement prior to the first dose of study treatment.
Data Source: Table 14.3.13.1a

Discontinuation due to adverse events

Table 48-Summary of Treatment Emergent Adverse Events Leading to Treatment Discontinuation of Any Study Medication by System Organ Class and Preferred Term Occurring in 1% or More Participants in Either Treatment Group (Safety Population)

	NALIRIFOX (N=370)		Gem+NabP (N=379)	
	Any Grade n (%) event	Grade 3-4 n (%) event	Any Grade n (%) event	Grade 3-4 n (%) event
Any Treatment-emergent Adverse Events Leading to Discontinuation of Any Study Medication	118 (31.9) 156	72 (19.5) 79	112 (29.6) 140	87 (23.0) 102
Nervous system disorders				
Neuropathy peripheral	16 (4.3) 17	8 (2.2) 8	18 (4.7) 20	15 (4.0) 16
Peripheral sensory neuropathy	16 (4.3) 17	9 (2.4) 10	10 (2.6) 10	7 (1.8) 7
Neurotoxicity	8 (2.2) 8	6 (1.6) 6	3 (0.8) 3	2 (0.5) 2
Polyneuropathy	6 (1.6) 6	4 (1.1) 4	3 (0.8) 3	2 (0.5) 2
Blood and lymphatic system disorders				
Neutropenia	9 (2.4) 15	6 (1.6) 6	12 (3.2) 12	12 (3.2) 12
Thrombocytopenia	2 (0.5) 2	1 (0.3) 1	5 (1.3) 5	1 (0.3) 1
Gastrointestinal disorders				
Diarrhoea	5 (1.4) 6	2 (0.5) 2	1 (0.3) 1	1 (0.3) 1
Nausea	5 (1.4) 5	4 (1.1) 4	0	0
Investigations				
Platelet count decreased	8 (2.2) 8	1 (0.3) 1	4 (1.1) 4	1 (0.3) 1
Neutrophil count decreased	3 (0.8) 3	1 (0.3) 1	6 (1.6) 6	6 (1.6) 6
General disorders and administration site conditions				
Asthenia	4 (1.1) 4	3 (0.8) 3	3 (0.8) 3	2 (0.5) 2
Infections and infestations				
Sepsis	0	0	5 (1.3) 5	2 (0.5) 2
Renal and urinary disorders				
Acute kidney injury	0	0	4 (1.1) 4	4 (1.1) 4

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0
Adverse Events are coded using MedDRA Version 25.0
Data Source: Table 14.3.2.7a

Adverse Events Leading to Dose Modification

Dose Reduction

Table 49-Summary of Treatment Emergent Adverse Events Leading to Dose Reduction of Any Study Medication by System Organ Class and Preferred Term Occurring in 1% or More of Participants in Either Arm (Safety Population)

	NALIRIFOX (N=370)		Gem+NabP (N=379)	
	Any Grade n (%) event	Grade 3-4 n (%) event	Any Grade n (%) event	Grade 3-4 n (%) event
Any Treatment-emergent Adverse Events Leading to Dose Reduction of Any Study Medication	208 (56.2) 396	163 (44.1) 262	190 (50.1) 307	134 (35.4) 178
Blood and lymphatic system disorders				
Neutropenia	33 (8.9) 40	25 (6.8) 28	65 (17.2) 75	59 (15.6) 65
Thrombocytopenia	6 (1.6) 6	0	35 (9.2) 40	5 (1.3) 5
Anaemia	7 (1.9) 9	7 (1.9) 9	7 (1.8) 8	3 (0.8) 4
Febrile neutropenia	6 (1.6) 7	6 (1.6) 7	6 (1.6) 6	6 (1.6) 6
Leukopenia	1 (0.3) 1	0	4 (1.1) 4	3 (0.8) 3
Gastrointestinal disorders				
Diarrhoea	73 (19.7) 90	56 (15.1) 64	5 (1.3) 5	4 (1.1) 4
Nausea	35 (9.5) 43	26 (7.0) 33	3 (0.8) 3	3 (0.8) 3
Vomiting	15 (4.1) 15	9 (2.4) 9	2 (0.5) 2	1 (0.3) 1
Investigations				
Neutrophil count decreased	33 (8.9) 41	25 (6.8) 31	34 (9.0) 44	32 (8.4) 40
Platelet count decreased	4 (1.1) 5	1 (0.3) 1	23 (6.1) 27	1 (0.3) 1
White blood cell count decreased	1 (0.3) 2	1 (0.3) 2	7 (1.8) 8	6 (1.6) 7
Alanine aminotransferase increased	4 (1.1) 4	3 (0.8) 3	3 (0.8) 3	2 (0.5) 2
Weight decreased	5 (1.4) 6	1 (0.3) 1	0	0
Nervous system disorders				
Neuropathy peripheral	12 (3.2) 12	5 (1.4) 5	8 (2.1) 8	4 (1.1) 4
Peripheral sensory neuropathy	6 (1.6) 6	2 (0.5) 2	9 (2.4) 10	4 (1.1) 5
Neurotoxicity	3 (0.8)3	1 (0.3) 1	4 (1.1) 4	2 (0.5) 2
Paraesthesia	5 (1.4) 5	0	2 (0.5) 2	1 (0.3) 1
General disorders and administration site conditions				
Fatigue	10 (2.7) 10	3 (0.8) 3	10 (2.6) 10	2 (0.5) 2
Asthenia	12 (3.2) 12	8 (2.2) 8	4 (1.1) 4	2 (0.5) 2
Mucosal inflammation	5 (1.4) 5	3 (0.8) 3	1 (0.3) 1	1 (0.3) 1
Oedema peripheral	0	0	6 (1.6) 6	0

	NALIRIFOX (N=370)		Gem+NabP (N=379)	
	Any Grade n (%) event	Grade 3-4 n (%) event	Any Grade n (%) event	Grade 3-4 n (%) event
Metabolism and nutrition disorders				
Decreased appetite	11 (3.0) 11	7 (1.9) 7	0	0
Hypokalaemia	9 (2.4) 10	8 (2.2) 9	0	0

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0
Adverse Events are coded using MedDRA Version 25.0
Data Source: Table 14.3.2.12a

Post marketing experience

No post-marketing data for the 1st line treatment of patients with metastatic pancreatic adenocarcinoma is available for irinotecan liposome injection.

2.5.1. Discussion on clinical safety

An integrated safety analysis has been submitted, encompassing data from the pivotal study D-US-60010-001 (NAPOLI 3) and study MM-398-07-02-03. The focus of the safety assessment has been on the pivotal study (370 patients treated with NALIRIFOX vs. 379 treated with the Gem+NabP regimen) since the contribution in terms of number of patients from the supportive study MM-398-07-02-03 is considered limited with a mere 32 patients that received the same NALIRIFOX regimen as in NAPOLI 3.

The size of the safety data which is the basis of this assessment, is considered acceptable.

The relationship of an AE has been assessed for each drug of the regimen for each arm and has been classified according to the following: Related: reports including good reasons and sufficient information to assume a causal relationship with each drug of the regimen in the sense that it is plausible, conceivable or likely. Not related: reports including good reasons and sufficient information to rule out a causal relationship with each drug of the regimen.

Exposure: Patient exposure for the NALIRIFOX regimen was about 24 weeks (range 0.4 to 100.9 weeks) and about 18 weeks (range: 0.7 to 81.7 weeks) for the 379 patients exposed to the Gem+NabP regimen. Median number of cycles administered were 5 and 4 in the NALIRIFOX and control arm, respectively.

TEAEs: Almost all patients experienced at least one TEAE, similar between arms (99.7% treated in the NALIRIFOX arm and 99.2%treated in the control arm).

The most frequently reported TEAEs (≥20% participants) in the NALIRIFOX arm were GI related (diarrhoea [70.5%], nausea [59.5%], vomiting [39.7%], constipation [25.1%]). Others were decreased appetite (36.8%), fatigue (32.4%), hypokalaemia (31.6%), asthenia (30.8%), neutropenia (29.5%), with neutrophil count decreased (20.5) (as well as febrile neutropenia (2.4%)), abdominal pain (26.5%), anaemia (26.2%), and weight decreased (22.2%). These are all already established ADRs of ONIVYDE.

In regard to TEAEs by age group (<65 vs.≥65 years of age), the overall rates of reported TEAEs are similar between the two age cohorts, including by severity and according to SOCs and by PTs.

TEAEs by Grade 3 and 4: Any Treatment-emergent Adverse Event of NCI-CTCAE Grade 3 or 4 were reported in a similar proportion between the two arms (85%).

The most frequently reported TEAEs (≥10%) Grade 3 or 4 in the test arm were diarrhoea (20.3%), neutropenia (14.1%), with neutrophil count decreased and febrile neutropenia reported in 9.4% and 2.4%, respectively. Furthermore, hypokalaemia was reported in 15.1% of the patients, nausea in 11.9% and anaemia in 10.5%.

Severe and life-threatening diarrhoea have been reported. ONIVYDE pegylated liposomal must not be administered to patients with bowel obstruction, and chronic inflammatory bowel disease.

To help avoid severe diarrhoea, all lactose-containing products should be stopped, hydration should be maintained, and a low-fat diet implemented.

SAEs: The proportion of patients experiencing SAEs was similar between the arms with 54.3% in the NALIRIFOX arm and 51.5% in the control arm. Amongst the most frequently reported (≥2%) in the

test arm were diarrhoea (6.2%), vomiting (5.9%), nausea (4.9%), COVID-19 (4.9%), dehydration (2.7%), pulmonary embolism (2.7%), abdominal pain (2.4%) and pyrexia (2.2%). In NAPOLI- 3 study, pneumonitis was reported in 0.3% of patients receiving ONIVYDE pegylated liposomal in combination with oxaliplatin and 5-FU/LV.

Serious related TEAEs: More frequently reported for the NALIRIFOX arm compared to the control arm (26.5% and 19%, respectively).

Deaths: A total of 45 patients (6.0%) experienced TEAEs leading to death with similar proportions between the two arms; 5.9% in the test arm and 6.1% in the control arm.

The main TEAEs (i.e. in more than one patient) leading to death in the NALIRIFOX arm were sepsis, pneumonia, cerebrovascular accident and ischaemic stroke, occurring in two patients (0.5%) each.

Discontinuations due to AEs: A total of 31.9% experienced TEAEs leading to discontinuation of any component of the treatment regimen in the NALIRIFOX arm however a similar proportion was reported for the control arm (29.6%).

Oxaliplatin may be discontinued if not well tolerated and treatment with ONIVYDE pegylated liposomal + 5-FU/LV can continue.

Dose modifications due to TEAEs: A total 56.2% had at least one TEAE leading to dose reduction of any study medication in the NALIRIFOX arm and 50.1% in the Gem+NabP arm.

Dose modifications proposed in the SmPC are considered acceptable. For patients who start treatment with 50 mg/m2 ONIVYDE pegylated liposomal and do not dose escalate to 70 mg/m2, the recommended first dose reduction is to 43 mg/m2 and the second dose reduction is to 35 mg/m2. Patients who require further dose reduction should discontinue treatment.

Patients who are known to be homozygous for UGT1A1*28 and without drug related toxicities during the first cycle of therapy (reduced dose of 50 mg/m2) may have the dose of ONIVYDE pegylated liposomal increased to a total dose of 70 mg/m2 in subsequent cycles based on individual patient tolerance.

Diarrhoea (19.7%) led to the highest percentage of patients with dose reduction of any study medication in the NALIRIFOX arm. The proportion of patients with at least one TEAE leading to interruption of any study medication was low in both arms.

UGT1A1*28 Genotype Status: There were a total of 83 patients with homozygous UGT1A1*28 allele status enrolled in the NAPOLI 3 study: 39 patients in the NALIRIFOX arm and 44 in the Gem+NabP arm. All patients with homozygous UGT1A1*28 allele status reported at least one TEAE (100%). More serious TEAEs, TEAEs leading to treatment discontinuation and TEAEs leading to reduction of any IMP were reported in the NALIRIFOX-arm (61.5%, 38.5% and 59.0%, respectively) as compared with the control arm (54.5%, 22.7% and 31.8%, respectively).

The most frequently reported TEAEs (≥20%) by PT for patients homozygous for UGT1A1*28 allele treated in the NALIRIFOX arm were diarrhoea (59.0%), nausea (56.4%), vomiting (46.2%), anaemia (41.0%), hypokalaemia (38.5%), asthenia (35.9%), neutropenia (35.9%) with neutrophil count decreased (20.5%), weight decreased (33.3%), fatigue (28.2%), decreased appetite (25.6%), neuropathy peripheral (25.6%), oedema peripheral (23.1%) and abdominal pain (20.5%).

As requested, the MAH has provided a summary of TEAEs according to homozygosity for UGT1A1*28 allele versus non-homozygosity as well as a presentation by SOC and PT. The limited number of patients with homozygous UGT1A1*28 (N=39 in the NALIRIFOX arm and N=44 in the control arm) as

opposed to those without (N=331 and 335, respectively), is noted. It is agreed that there are no major differences in regard to safety between the two groups identified.

ECG abnormalities: There were 3.4% patients in the NALIRIFOX arm as compared to 2.0% in the Gem+NabP arm with clinically significant ECG abnormalities. Absolute QTcF abnormalities of >500 msec occurred in seven patients (1.9%) in the NALIRIFOX arm and two (0.5%) in the Gem+NabP arm and 3.0% and 1.8% with change from baseline QTcF more than 60 msec in the respective arms.

As it is noted that `Electrocardiogram QT prolonged´ is included as an ADR for Onivyde under the SOC `Investigations´ in section 4.8, Table 5, a review was performed by the MAH, on any possible clinical implication. This review revealed no identified cases reported from the literature or post-marketing experiences. There were three non-serious TEAEs of "ECG QT prolonged" in the NALIRIFOX arm in the study NAPOLI-3, however none of them considered related to ONIVYDE. There are no indications of a risk for QT-prolongation from pre-clinical studies.

Cardiotoxicity including the risk of QT-prolongation related to oxaliplatin and 5-FU are known and adequately addressed in the SmPC of the respective products.

Study MM-398-07-02-03 (supportive): Observations based on the 32 patients that received the same NALIRIFOX regimen as in NAPOLI 3, are consistent with the findings in the pivotal study NAPOLI 3.

The following adverse reactions, related to the administration of ONIVYDE pegylated liposomal, were reported in 370 patients treated in combination with oxaliplatin/5-FU/LV, who had not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.

The most common adverse reactions (incidence ≥20%) were diarrhoea, nausea, vomiting, decreased appetite, fatigue, hypokalaemia, asthenia, neutropenia, abdominal pain, anaemia, constipation, weight decreased and neutrophil count decreased. The most common, severe adverse reactions (≥5% Grade 3 or 4) were diarrhoea, hypokalaemia, neutropenia, nausea, anaemia, neutrophil count decreased, asthenia, decreased appetite, vomiting and fatigue, asthenia, neutropenia, neutrophil count decreased, anaemia and hypokalaemia. The most common serious adverse reactions (≥2%) were diarrhoea, vomiting, nausea, COVID-19, dehydration, pulmonary embolism, abdominal pain and pyrexia.

Adverse reactions seen with ONIVYDE pegylated liposomal which led to its permanent discontinuation occurred in 9.5 % of patients; the most frequent adverse reaction resulting in discontinuation was neutropenia.

Dose reductions of ONIVYDE pegylated liposomal due to adverse events (regardless of causality assessment), occurred in 52.4% of patients; the most frequent adverse events requiring dose reduction (≥5%) were diarrhoea, nausea, neutropenia and neutrophil count decreased.

ONIVYDE pegylated liposomal was withheld due to adverse events (regardless of causality assessment), in 1.9% of patients; the most frequent adverse events requiring interruption were hypersensitivity and infusion related reactions that occurred in 0.5% of patients.

Of note, the proposed dose to be recommended of ONIVYDE in combination with oxaliplatin/5-FU/leucovorin is 50 mg/m² as opposed to the recommended dose that is currently approved for ONIVYDE in combination with 5-FU/leucovorin (70 mg/m2). This is due to the use of oxaliplatin as combination partner, which decreases the tolerability of irinotecan.

2.5.2. Conclusions on clinical safety

The overall high report rates of TEAEs, TEAEs Grade ≥3, serious TEAEs, serious related TEAEs and TEAEs leading to treatment discontinuation/ reduction in the NALIRIFOX arm are recognised. However,

this is similar to that of the control arm. It is concluded that the safety profile remains in line with what has previously been characterized for Onivyde. No new safety concerns have been evoked based on the safety data from NAPOLI 3.

Provided that efficacy is established, the safety profile is considered acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH was requested to submit an updated RMP version 5.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The main RMP changes were the following:

- Update to include an additional indication and dosage regimen:
  - irinotecan liposome injection for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, in combination with oxaliplatin, 5-fluorouracil and leucovorin
- Update of epidemiology data relevant to the indication
- Update of exposure data with data from new clinical trials and post-authorisation use.

PRAC endorsed the RMP AR and its conclusions, without further additions.

The PRAC considered that the risk management plan version 5.0 is acceptable.

Safety concerns

Table 50-Table SVIII.1. Summary of Safety Concerns

Important identified risks	Thromboembolic events
Important potential risks	None
Missing information	None

Pharmacovigilance plan

There are no additional pharmacovigilance activities. Routine pharmacovigilance activities include adverse reactions reporting and signal detection.

No new safety concerns are identified in the current application, and no amendments to the PhV plan are suggested.

Risk minimisation measures

Table 51-Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Risk minimisation activities	Pharmacovigilance activities
Routine risk minimisation measures: SmPC Section 4.2 – Tables 1, 2 and 3 Recommended dose modifications for ONIVYDE. SmPC Section 4.4: Patients should be informed about the signs and symptoms of thromboembolism and advised to contact their physician or nurse immediately if any such signs or symptoms should occur. SmPC Section 4.8 PL Section 4 – Patients should notify their doctor immediately if they have any blood clots. **Additional risk minimisation measures:** No risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** No additional pharmacovigilance activities.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated.

The Package Leaflet (PL) is updated accordingly.

Please see Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes introduced by this variation do not substantially impact the readability of the package leaflet, and that ONIVYDE pegylated liposomal must only be prescribed and administered to patients by healthcare professionals (intravenous infusion).

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH has applied to extend the marketing authorisation to first line metastatic adenocarcinoma of the pancreas from the current indication in later line. The new indication is:

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.

3.1.1. Disease or condition

Globally, more than 495 000 new cases of pancreatic cancers and 466 000 new deaths were estimated to occur in 2020. Pancreatic cancer is the seventh leading cause of cancer-related mortality worldwide, and the fourth most common cause of neoplastic deaths in the EU. [Sung 2021, Carioli 2021].

Pancreatic ductal adenocarcinoma and its variants account for almost 90% of pancreatic malignancies. Owing to the lack of early symptoms and the aggressive nature of the disease, up to 80% of patients with pancreatic adenocarcinoma receive a diagnosis at an advanced stage, by which time the tumour is unresectable.

3.1.2. Available therapies and unmet medical need

Gemcitabine monotherapy was the major first-line metastatic pancreatic cancer treatment proven to prolong OS over 5-FU [Burris 1997], leading to the approvals in European countries and by the Food and Drug Administration (FDA) in 1996. The median OS durations were 5.7 and 4.4 months for participants treated with gemcitabine and 5-FU, respectively (statistically significant difference). Gemcitabine monotherapy is recommended to patients with PS of 2 and bilirubin higher than 1.5 ULN.

For patients with PS 0-1 FOLFIRINOX ((Irinotecan, oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV)) or gemcitabine + nab-paclitaxel (Gem+NabP) is recommended (ESMO guidelines). Gem+NabP is approved in EU since 2013 based on a RCT vs. gemcitabine monotherapy. Median OS were 8.5 vs. 6.7 months, HR 0.72 (95% CI 0.62, 0.83; p<0.001) (Abraxane | European Medicines Agency (europa.eu)).

For patients with metastatic disease, who comprise the majority of patients with pancreatic adenocarcinoma at the time of diagnosis, the 5-year survival is only 3%. [Burris 1997],

3.1.3. Main clinical studies

The pivotal study for this application is NAPOLI 3 (D-US-60010-001, NP42379), an open label, randomised, multicentre, international, phase III study.

The study evaluated the efficacy and safety of NALIRIFOX (Irinotecan liposome (Onivyde), oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV)) versus Gem+NabP as first-line treatment for adults with metastatic adenocarcinoma of the pancreas.

The primary endpoint was OS. PFS and ORR endpoint assessed by investigator were included in a hierarchical testing structure.

770 randomised participants were randomised. 383 patients were randomized to the NALIRIFOX arm and 387 to the Gem+NabP arm.

Efficacy data presented are from the final analysis with a DCO date of July 2022 at a total of 544 (70.6%) OS events.

3.2. Favourable effects

Median follow-up time was 16.0 (95% CI 15.0, 16.8) months for the NALIRIFOX arm and 16.3 (95% CI 15.0, 17.5) months for the Gem+NabP arm when patients were censored at death.

The NALIRIFOX arm demonstrated a statistically significant difference in OS compared with Gem+NabP based on the stratified log-rank test p-value 0.04.

The median OS was 11.1 months (95% 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 0.84 (95% CI: 0.71, 0.99).

The NALIRIFOX arm demonstrated a statistically significant difference in PFS assessed by the investigator compared with Gem+NabP 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% CI: 0.58, 0.83).

ORR was 41.8% (95% CI: 36.8, 46.9) in the NALIRIFOX arm and 36.2% (95% CI: 31.4, 41.2) in the Gem+NabP arm, p=0.11.

3.3. Uncertainties and limitations about favourable effects

For the PFS analysis censoring was carried out according to the FDA preferred guideline, which is generally acceptable. The number of censored patients was high in the PFS analysis for patients that initiated subsequent anti-cancer therapy before progression. In the NALIRIFOX arm 56 (14.6%) was censored for this reason and 87 (22.5%) in the Gem+NabP arm. Moreover, PFS assessment by an independent blinded review committee was not performed.

A high fraction of patients labelled as not evaluable for the ORR analysis is noted, 86 (22.5%) for the NALIRIFOX arm and 90 (23.3%) for the Gem+NabP arm questioning the reliability of the presented estimate.

3.4. Unfavourable effects

An integrated safety analysis has been submitted, encompassing data from the pivotal study D-US-60010-001 (NAPOLI 3) and study MM-398-07-02-03.

In NAPOLI 3, 370 patients were treated with NALIRIFOX vs. 379 treated with the Gem+NabP regimen.

The size of the safety data base upon which this assessment rests, is considered acceptable.

Exposure: Patient exposure for the NALIRIFOX regimen was about 24 weeks (range 0.4 to 100.9 weeks) and about 18 weeks (range: 0.7 to 81.7 weeks) for the Gem+NabP regimen. Median number of cycles administered were 5 and 4, respectively.

TEAEs: Almost all patients experienced at least one TEAE, similar between arms (99.7% treated in the NALIRIFOX arm and 99.2% treated in the control arm).

The most frequently reported TEAEs (≥20% participants) in the NALIRIFOX arm were GI related (diarrhoea [70.5%], nausea [59.5%], vomiting [39.7%], constipation [25.1%]). Others were fatigue (32.4%), hypokalaemia (31.6%), asthenia (30.8%), neutropenia (29.5%; febrile neutropenia 2.4%) and anaemia (26.2%). These are all already established ADRs for ONIVYDE.

TEAEs by Grade 3 and 4: Any Treatment-emergent Adverse Event of NCI-CTCAE Grade 3 or 4 were reported in a similar proportion between the two arms (85%).

The most frequently reported TEAEs (≥10%) Grade 3 or 4 in the NALIRIFOX arm were diarrhoea (20.3%), hypokalaemia (15.1%) and neutropenia (14.1%) with febrile neutropenia reported in 2.4%.

SAEs: The proportion of patients experiencing SAEs was similar between the arms with 54.3% in the NALIRIFOX arm and 51.5% in the control arm.

Amongst the most frequently reported (≥2% in the test arm were diarrhoea (6.2%), vomiting (5.9%), nausea (4.9%), COVID-19 (4.9%), and pulmonary embolism (2.7%).

Serious related TEAEs: More frequently reported for the NALIRIFOX arm compared to the control arm (26% and 19%, respectively).

Deaths: A total of 45 patients (6.0%) experienced TEAEs leading to death with similar proportions between the two arms; 5.9% in the test arm and (6.1%) in the control arm.

The main TEAEs (i.e. in more than one patient) leading to death in the NALIRIFOX arm were sepsis, pneumonia, cerebrovascular accident and ischaemic stroke, occurring in two patients (0.5%) each.

Discontinuations due to AEs: A total of 32% experienced TEAEs leading to discontinuation of any component of the treatment regimen in the NALIRIFOX arm. A similar proportion was reported for the control arm (30%).

Dose modifications due to TEAEs: A total 56.2% had at least one TEAE leading to dose reduction of any study medication in the NALIRIFOX arm and 50.1% in the Gem+NabP arm.

Diarrhoea (19.7%) led to the highest percentage of patients with dose reduction of any study medication in the NALIRIFOX arm. The proportion of patients with at least one TEAE leading to interruption of any study medication was low in both arms.

UGT1A1*28 Genotype Status: There were a total of 83 patients with homozygous UGT1A1*28 allele status enrolled in the NAPOLI 3 study: 39 patients in the NALIRIFOX arm and 44 in the Gem+NabP arm. Reported TEAEs for patients homozygous for UGT1A1*28 allele treated in the NALIRIFOX arm were in line with TEAEs in the overall population and there were no major differences in regard to the safety profile when comparing patients with homozygosity for UGT1A1*28 allele versus those without.

ECG abnormalities: There were 3.4% patients in the NALIRIFOX arm as compared to 2.0% in the Gem+NabP arm with clinically significant ECG abnormalities.

Absolute QTcF abnormalities of >500 msec occurred in seven patients (1.9%) in the NALIRIFOX arm and two (0.5%) in the Gem+NabP arm and 3.0% and 1.8% with change from baseline QTcF more than 60 msec in the respective arms.

Study MM-398-07-02-03 (supportive): Observations based on the 32 patients that received the same NALIRIFOX regimen as in NAPOLI 3, are consistent with the findings in the pivotal study NAPOLI 3.

3.5. Uncertainties and limitations about unfavourable effects

None remaining.

3.6. Effects Table

*Table 52-**Effects Table** for ONIVYDE pegylated liposomal for first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV) (final analysis, DCO July 2022).*

Effect	Short description	Unit	NALIRIFOX N=370	Gem+NabP N=379	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Median	Months	11.1	9.2	P=0.04. Sensitivity	

Effect	Short description	Unit	NALIRIFOX N=370	Gem+NabP N=379	Uncertainties / Strength of evidence	References
					analyses support the conclusion of robustness of the OS estimate.	
		HR (95% CI)	0.84 (0.71, 0.99)			
PFS	Median, INV, RECIST 1.1	Months	7.4	5.6	Censoring according to FDA-rules with a high fraction censored for initiation of new anti-cancer treatment before progression.	
		HR (95% CI)	0.69 (0.58, 0.83)			
ORR	CR+PR INV, RECIST 1.1	N (%)	160 (41.8%)	140 (36.2%)	High fraction of not evaluable patients.	
		Odds ratio (95% CI)	1.26 (0.95, 1.69)			
Unfavourable Effects						
TEAE ≥10% of pts	Any Diarrhoea Nausea Vomiting Fatigue Hypokalemia Neutropenia Febrile neutropenia	%	99.7 70.5 59.5 39.7 32.4 31.6 29.5 2.4	99.2 36.7 42.7 26.4 37.7 12.9 31.9 2.6		
Grade 3 or 4 ≥2% Diff btw arms	Any Diarrhoea Hypokalemia Neutropenia Nausea Anaemia Febrile neutropenia	%	85.4 20.3 15.1 14.1 11.9 10.5 2.4	85.0 4.5 4.0 24.5 2.6 17.4 2.4		
SAE ≥2% of pts	Any Diarrhoea Vomiting Nausea Covid-19 Pulm embol	%	54.3 6.2 5.9 4.9 4.9 2.7	51.5 2.4 1.6 0.8 3.7 1.8		
TEAE leading to discont	Any Peripheral neuropathy Neutropenia Diarrhoea	%	31.9 4.3 2.4 1.4	29.6 4.7 3.2 0.3		
Deaths related to TEAEs	l	%	5.9	6.1		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The final analysis from NAPOLI 3 demonstrated a statistically significant prolongation of OS according to the latest SAP for patients with metastatic adenocarcinoma of the pancreas treated in the first line with NALIRIFOX containing Onivyde pegylated liposomal compared to Gem+NabP.

The median OS difference presented between the treatment arms is limited to 1.9 months and the p-value is 0.4 with an upper 95% CI of 0.99.

A key sensitivity analysis according to the SAP where study integrity was considered to be retained was recreated and the results are consistent with the primary analysis. Furthermore, a tipping point analysis and updated OS results provided supports the robustness of the OS result.

In terms of unfavourable effects as observed in the NAPOLI 3 study, the overall high report rates of TEAEs, TEAEs Grade ≥3, serious TEAEs, serious related TEAEs and TEAEs leading to treatment discontinuation/ reduction in the NALIRIFOX arm are recognised. The safety profile remains in line with what has previously been characterized for ONIVYDE. No new safety concerns have been evoked based on the submitted safety data. The safety profile is acceptable for the proposed use.

3.7.2. Balance of benefits and risks

An OS gain has been demonstrated and the safety profile is acceptable in the therapeutic context. The B/R of Onivyde pegylated liposomal is positive.

3.8. Conclusions

The overall B/R of Onivyde pegylated liposomal is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas for Onivyde in combination with oxaliplatin, 5 fluorouracil (5 FU) and leucovorin (LV) based on final results from phase 3 study NAPOLI 3 (D-US-60010-001); this is an interventional study with a primary objective to evaluate the efficacy of the regimen of irinotecan liposome injection + oxaliplatin + 5-fluorouracil (5-FU)/leucovorin (LV) versus nab-paclitaxel + gemcitabine in improving overall survival (OS) in subjects who have not previously received chemotherapy for metastatic

adenocarcinoma of the pancreas; As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. The updated RMP version 5.0 is also submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.