21 July 2016
EMA/CHMP/589179/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Onivyde

International non-proprietary name: irinotecan

Procedure No. EMEA/H/C/004125/0000

Note

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

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Importance
ALT	Alanine aminotransferase
APC	7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration time curve
BMI	Body Mass Index
BSA	Body Surface Area
CA 19-9	Carbohydrate antigen 19-9
CBR	Clinical Benefit Response
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CI	Confidence Interval
CL	Clearance
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
dL	Deciliter
DMSO	Dimethyl sulfoxide
DSC	Differential Scanning Calorimetry
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine
EC	Ethics Committee
eGFR	Estimated Glomerular Filtration Rate
ELSD	Evaporative Light Scattering Detector
EORTC	European Organization for Research and Treatment of Cancer

EP	Evaluable Population
5-FU	5-Fluorouracil
FDA	U.S. Food and Drug Administration
FID	Flame Ionisation Detection
FMEA	Failure mode effects analysis
FOLFIRI	5-FU+leucovorin+irinotecan
FOLFIRINOX	5-FU+leucovorin +irinotecan+oxaliplatin
FOLFOX	Oxaliplatin+5-FU+ leucovorin
GC	Gas Chromatography
GCP	Good Clinical Practice
GERCOR	Groupe Coopérateur Multidisciplinaire en Oncologie
GMP	Good Manufacturing Practice
HEPES	2-[4-(2 Hydroxyethyl)piperazin-1-yl] ethanesulfonic acid
HPLC	High performance liquid chromatography
HR	hazard ratio
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IPC	In-process Control
IQR	Inter-Quartile Range
IR	Infrared
ISS	Integrated Safety Summary
ITT	Intent-To-Treat
IV	Intravenous
IWRS	Interactive Web Response System
KF	Karl Fischer titration
KPS	Karnofsky Performance Score
L	Liter
LLOQ	Lower Limit of Quantification
LV	Leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram

ml	millilitre
mM	millimolar
Mono	Monotherapy
MPEG-2000-DSPE	N-(carbonyl-methoxypolyethlyeneglycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine
MTD	Maximum Tolerated Dose
NAPOLI	NAnoliPOsomal Irinotecan
NMR	Nuclear Magnetic Resonance
NPC	7-ethyl-10-(4-amino-1-piperidino) carbonyloxycamptothecin
OFF	Oxaliplatin+5-FU+Leucovorin
ORR	Objective Response Rate
OS	Overall Survival
PC	Process Control
PD	Progressive Disease
PEG	Polyethylene glycol
PFS	Progression Free Survival
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
pKa	acid dissociation constant
PP	Per Protocol
PPQ	Process Performance Qualification
PR	Partial Response
PT	Preferred Term
q2w	Every 2 weeks
q3w	Every 3 weeks
QbD	Quality by design
QOL	Quality Of Life
RECIST	Response Evaluation Criteria in Solid Tumours
RMSE	Root mean square error
SAE	Serious Adverse Event
SD	Stable Disease

SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Queries
SOC	System Organ Class
SOS	Sucrose Octasulphate
t1/2	Half life
TEAE	Treatment emergent adverse event
TEA-Pn	Triethylammonium polyphosphate
TEA-SOS	Triethylammonium Sucrose Octasulphate
TEM	Transmission Electron Microscopy
TGA	Thermo-Gravimetric Analysis
Tm	gel-liquid crystal transition temperature
TSE	Transmissible Spongiform Encephalopathy
TTF	Time to Treatment Failure
TTP	Time to Progression
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
UV	Ultraviolet
VAS	Visual Analog Scale
Vd	Volume of distribution
Vss	Volume of distribution at steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Baxalta Innovations GmbH submitted on 30 April 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Onivyde, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 November 2014.

Onivyde was designated as an orphan medicinal product EU/3/11/933 on 09 December 2011. Onivyde was designated as an orphan medicinal product in the following indication: Treatment of pancreatic cancer.

The applicant applied for the following indication:

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in patients who have been previously treated with gemcitabine. Onivyde is indicated in adults.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Onivyde as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that irinotecan was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class 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 applicant 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.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 6 December 2012. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 30 April 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 August 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 27 August 2015.
- During the meeting on 24 September 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 September 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 December 2015.
- With the responses to the CHMP consolidated List of Questions the applicant informed the Agency of the change of the applicant's company name from Baxter Innovations GmbH to Baxalta Innovations GmbH (effective as of 1st May 2015).
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 February 2016.
- During the PRAC meeting on 11 February 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 16 February 2016.
- During the CHMP meeting on 25 February 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 June 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 6 July 2016.
- The following GMP and GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

- GCP inspections at three clinical investigator sites in South Korea and Australia were conducted between September and October 2015. The outcome of the inspection carried out was issued on 18 December 2015.
- A GMP inspection at one finished product manufacturing site in USA conducted between 12-14 January 2016. The outcome of the inspection carried out was issued on 24th February 2016.

- During the meeting on 21 July 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Onivyde.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Pancreatic cancer is a malignant neoplasm of the pancreas (ICD-9, 2014). More than 80% of exocrine pancreatic cancers are infiltrating ductal adenocarcinomas, a majority of which exhibit KRAS mutations, predominantly G12V or G12D mutations (Seufferlein, et al, 2012), and the remaining types include adenosquamous carcinomas, squamous cell carcinomas, signet ring cell carcinomas, acinar cell carcinomas, undifferentiated carcinomas, undifferentiated carcinomas with giant cells, and solid pseudopapillary neoplasms of the pancreas. Exocrine pancreatic tumors are far more common than pancreatic neuroendocrine tumors, which make up about 3-5% of all pancreatic malignancies (Krampitz, 2013). Hereditary conditions account for ~5-10% of pancreatic cancer (Seufferlein et al., 2012).

2.1.2. Epidemiology

In Europe, cancer of the pancreas is the seventh most frequent cancer, accounting for some 2.9% of cancer in men and 3.2% in women) and the fifth leading cause of cancer-related death in Europe (GLOBOCAN 2012). The age-standardized mortality rates (ASR) per 100,000 are 8.0 for men and 5.5 for women (Malvezzi et al, 2013).

2.1.3. Clinical presentation, diagnosis and stage / prognosis

Mainly a disease of the elderly, pancreatic adenocarcinoma accounts for 85-95% of all pancreatic cancers. More than 50% of pancreatic cancers are identified in metastatic stage, with overall survival ranging from 7-11 months. In 30%-40% of patients the disease is localized, but not surgically resectable, with OS of 11-18 months. The overall 1-year survival rate ranges from 11% to 28.3% (Seufferlein T, Annals of Oncology 2012). Chemo- and radio-resistant, unresectable pancreatic adenocarcinoma has a dire prognosis, with a 5–year OS of 6 %, i.e. with an increase in OS of only 1% in the past three decades.

2.1.4. Management

Despite 5-fluorouracil/leucovorin with irinotecan and oxaliplatin (FOLFIRINOX) and gemcitabine/nab-paclitaxel significantly improving outcomes for metastatic cancer (response rates between 23% and 31%, PFS of 5.5–6.6 months, OS between 8.5 and 11 months), refractory disease still poses significant challenges.

Novel chemotherapeutics, stroma and immune-targeted agents are currently being developed (Drug Design, Development and Therapy 2015:9 3529–3545). However, there is no consensus on second-line treatment after failure on first-line therapy. The OFF regimen (oxaliplatin/5FU/LV) showed an OS advantage of 2.6 months in CONKO-003, a randomized study in patients with disease progression after first-line gemcitabine therapy.

About the product

Onivyde (also referred to as MM-398) is developed for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in patients who have been previously treated with gemcitabine.

The active substance in Onivyde 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 metabolized by carboxylesterase to SN-38. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumour cell lines.

The applicant applied for the following indication:

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in patients who have been previously treated with gemcitabine.

The recommended indication 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.

Onivyde must only be prescribed and administered to patients by healthcare professionals experienced in the use of anti cancer therapies.

Onivyde is not equivalent to non-liposomal irinotecan formulations and should not be interchanged.

Onivyde, leucovorin and 5 fluorouracil should be administered sequentially. The recommended dose and regimen Onivyde is 80 mg/m^2 intravenously over 90 minutes, followed by LV 400 mg/m^2 intravenously over 30 minutes, followed by 5 FU 2,400 mg/m^2 intravenously over 46 hours, administered every 2 weeks. Onivyde should not be administered as a single agent.

All dose modifications should be based on the worst preceding toxicity. LV dose does not require adjustment. For Grade 1 and 2 toxicities there are no dose modifications recommended. Dose adjustments, are recommended to manage Grade 3 or 4 toxicities related to Onivyde.

For patients who start treatment with 60 mg/m^2 Onivyde and do not dose escalate to 80 mg/m^2, the recommended first dose reduction is to 50 mg/m^2 and the second dose reduction is to 40 mg/m^2. Patients who require further dose reduction should discontinue treatment.

Table 1: Recommended dose modifications for ONIVYDE+5-FU/LV for Grade 3-4 toxicities for patients not homozygous for UGT1A1*28

Toxicity grade (value) by NCI CTCAE v 4.0[1]	**ONIVYDE/5-FU adjustment (for patients not homozygous for UGT1A1*28)**	
Haematological toxicities		
Neutropenia	A new cycle of therapy should not begin until the absolute neutrophil count is ≥ 1500/mm^3	
Grade 3 or Grade 4 (< 1000/mm^3)	***First occurrence***	Reduce ONIVYDE dose to 60 mg/m^2 Reduce 5-FU dose by 25% (1800 mg/m^2).

Toxicity grade (value) by NCI CTCAE v 4.0[1]	**ONIVYDE/5-FU adjustment (for patients not homozygous for UGT1A1*28)**	
or Neutropenic fever	***Second occurrence***	Reduce ONIVYDE dose to 50 mg/m^2 Reduce 5-FU dose by an additional 25% (1350 mg/m^2).
	Third occurrence	Discontinue treatment
Thrombocytopenia **Leukopenia**	A new cycle of therapy should not begin until the platelet count is ≥ 100,000/mm^3 Dose modifications for leukopenia and thrombocytopenia are based on NCI CTCAE toxicity grading and are the same as recommended for neutropenia above.	
Nonhaematological toxicities[2]		
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 dose to 60 mg/m^2 Reduce 5-FU dose by 25% (1800 mg/m^2)
	Second occurrence	Reduce ONIVYDE dose to 50 mg/m^2 Reduce 5-FU dose by an additional 25% (1350 mg/m^2)
	Third occurrence	Discontinue treatment
Nausea/vomiting	A new cycle of therapy should not begin until nausea/vomiting resolves to ≤ Grade 1 or baseline	
Grade 3 or 4 *(despite antiemetic therapy)*	***First occurrence***	Optimise antiemetic therapy Reduce ONIVYDE dose to 60 mg/m^2
	Second occurrence	Optimise antiemetic therapy Reduce ONIVYDE dose to 50 mg/m^2
	Third occurrence	Discontinue treatment
Hepatic, renal, respiratory or other[2] toxicities ***Grade 3 or 4***	A new cycle of therapy should not begin until the adverse reaction resolves to ≤ Grade 1	
	First occurrence	Reduce ONIVYDE dose to 60 mg/m^2 Reduce 5-FU dose by 25% (1800 mg/m^2)
	Second occurrence	Reduce ONIVYDE dose to 50 mg/m^2 Reduce 5-FU dose by an additional 25% (1350 mg/m^2)
	Third occurrence	Discontinue treatment
Anaphylactic reaction	***First occurrence***	Discontinue treatment

1 NCI CTCAE v 4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

2 Excludes asthenia and anorexia; Asthenia and Grade 3 anorexia do not require dose adjustment.

Type of Application and aspects on development

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 5 mg/ml of irinotecan hydrochloride trihydrate (as irinotecan sucrosofate salt) as active substance. The active substance is formulated in pegylated liposomes.

Other ingredients are:

Liposome forming lipids:

1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and N-(carbonyl-methoxypolyethylene glycol-2000)-1, 2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG 2000 DSPE).

Other excipients:

Sucrose octasulphate, 2-[4-(2 Hydroxyethyl)piperazin-1-yl] ethanesulfonic acid (HEPES buffer), sodium chloride, and water for injections.

The product is available in type I glass vial with a grey chlorobutyl stopper and an aluminium seal with a flip-off cap, containing 10 ml of concentrate, as described in section 6.5 of the SmPC. Each pack contains one vial.

2.2.2. Active Substance

General information

The chemical name of irinotecan hydrochloride trihydrate is (S)-[1,4'-bipiperidine]-1'-carboxylic acid 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester hydrochloride trihydrate corresponding to the molecular formula $C_{33}H_{38}N_4O_6$ • HCl • $3H_2O$. It has a relative molecular mass of 677.18 and has the following structure:

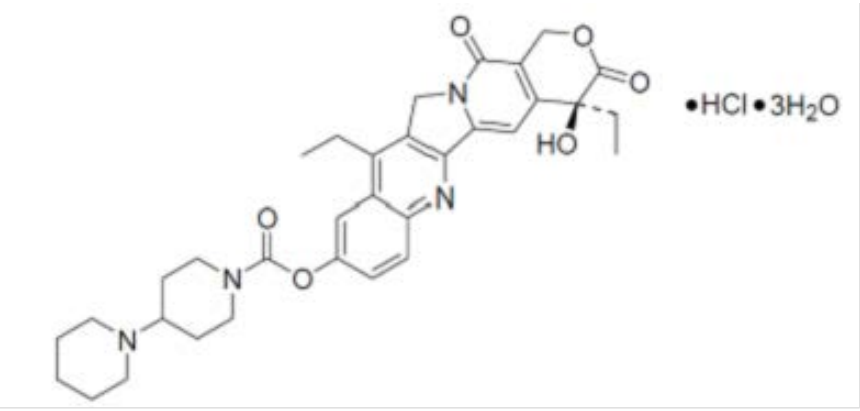


Figure 1. Structural formula of irinotecan hydrochloride trihydrate.

The molecular structure of irinotecan hydrochloride trihydrate has been confirmed by elemental analysis, IR spectroscopy, UV spectroscopy, mass spectrometry, ^{13}C and ^{1}H NMR spectroscopy, thermal analysis (TGA and DSC) and X-ray powder diffraction analysis.

The active substance is a pale yellow to yellow crystalline powder; it is hygroscopic and light sensitive; freely soluble in DMSO and anhydrous acetic acid, slightly soluble in ethanol, sparingly soluble in aqueous buffer at pH 4 and slightly soluble in aqueous buffer at pH 2.

Irinotecan exhibits stereoisomerism due to the presence of a chiral centre. The source of stereoisomerism is camptothecin starting material. Enantiomeric purity of the active substance is controlled routinely by chiral HPLC.

The active substance manufacturer has demonstrated that a single crystalline form of irinotecan hydrochloride trihydrate is consistently produced. Polymorphism has no relevance on the performance of the finished product, as the active substance is dissolved during the manufacturing process of the finished product.

Manufacture, characterisation and process controls

The active substance is currently sourced from a single manufacturer. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Irinotecan hydrochloride trihydrate is a semi-synthetic active substance. It is synthesized from well-defined starting materials. The originally proposed starting material was redefined during the assessment procedure, since the CHMP considered it necessary in support of a more exhaustive control strategy. The concerns raised were related to missing information on the source of the material, the supplier of the material, extraction process, control of the material, and the potential carry-over of impurities to the active substance. As a result of this redefinition, the route of synthesis of the active substance was expanded to include these additional steps under GMP and the requested information was provided. A revised process will be implemented once the necessary analyses and comparability studies have been finalised and a new active substance supplier is approved. This commitment is considered a legally binding post-authorisation measure, with the submission expected by 31 December 2016. As an additional measure until the new process is fully implemented, the CHMP required more information on the control strategy for aflatoxin, mycotoxin, pesticide, residual solvents, and elemental impurities, for the batches of intermediate initially defined as the starting material which was considered satisfactory.

The specifications and control methods for current starting materials and reagents have been presented and only those batches conforming to the specifications can be used in the manufacture of the active substance.

The CHMP considered that the information presented, the steps taken, and the commitments provided by the Applicant are sufficient to ensure that the quality of the product is warranted and raises no concerns that could impact the safety of the medicinal product.

The active substance is synthesized in four main steps, using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products have been presented.

Reprocessing procedure of the active substance is described in the dossier and the reprocessing activities were considered acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in two-layer polyethylene bag as the inner package, and the pharmaceutical aluminium tin as the outer package. Plastic materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, assay (HPLC), identity (IR, HPLC), chiral purity (UV, HPLC), chloride identification (Ph. Eur.), impurities (HPLC), residual solvents (Ph. Eur.), water content (KF), heavy metals (Ph. Eur.), pH (Ph. Eur.), solubility (Ph. Eur.), residue on ignition (Ph. Eur.), microbial limits (Ph. Eur.), and bacterial endotoxins (Ph. Eur.).

Due to its mechanism of action, irinotecan is potentially genotoxic and carcinogenic. Mutagenic and carcinogenic potential of the impurities of starting materials, intermediates generated during the synthesis or degradation products cannot be excluded. In line with ICH M7, exposure to a mutagenic impurity in these cases would not significantly add to the cancer risk of the active substance. Therefore, these impurities are controlled in the active substance at acceptable levels for non-mutagenic impurities, complying with the identification (0.10%) and qualification thresholds (0.15%) described in the ICH Q3A guideline.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay, identification, and impurities testing has been presented.

Batch analysis results for three consecutive commercial scale batches used for process validation and fifteen batches used in process performance qualification, stability, nonclinical, and clinical studies of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on nine commercial scale batches and three additional batches of pilot or lab scale of active substance from the proposed manufacturer stored in the intended commercial package for 48 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions including high temperature, high humidity, acidity, alkalinity, oxidation, reduction, and hydrolysis were also provided on one batch.

The following parameters were tested: appearance, assay, chiral purity, impurities, and pH. The analytical methods used were the same as for release and were stability indicating.

All tested parameters of the active substance stored under long term and accelerated conditions were within the specifications. No trends in the formation of impurities or water absorption were observed. The active substance was stable with respect to assay and impurity levels when tested under the stress conditions of high temperature, and high humidity. Water levels increased under both stress conditions demonstrating that the active substance is hygroscopic. Testing under acidic, alkaline, oxidative, reductive, and hydrolytic stress conditions showed the instability of the active substance, resulting in the increase in the level of impurities and

the decrease in assay. During the photostability testing the levels of impurities increased demonstrating that the active substance is sensitive to light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable when protected from light and moisture. The stability results justify the proposed retest period of 3 years when stored in the proposed container with no special storage conditions.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a white to slightly yellow opaque sterile concentrate for solution for infusion. It consists of an isotonic dispersion of liposomes containing irinotecan hydrochloride trihydrate.

The liposomes are small unilamellar lipid bilayer vesicles, approximately 110 nm in diameter, enclosing an aqueous compartment that contains irinotecan in a gelated or precipitated state, as sucrosofate salt. The lipid membrane is composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE). The liposomes are dispersed in an aqueous buffered solution.

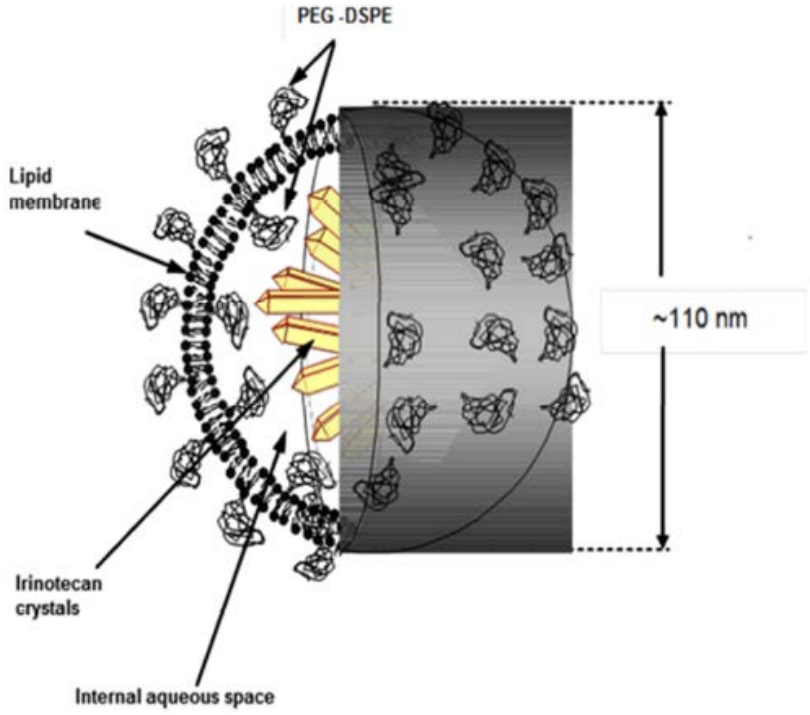


Figure 2. Schematic representation of the liposome.

As mentioned above, irinotecan hydrochloride trihydrate is present in the liposomes in the form of irinotecan sucrosofate salt. During pharmaceutical development, a number of formulations were screened where the anion of the drug entrapping solution was varied. Development identified sucrose octasulphate (SOS) as a superior anion of the drug entrapping solution. Sucrose octasulphate is added in the finished product manufacturing process as a triethylammonium salt, i.e. as triethylammonium sucrose octasulphate (TEA-SOS). It maintained

the encapsulation efficiency and had superior *in vitro* irinotecan retention in liposomes compared with the other formulation. Therefore this formulation was chosen for clinical and commercial use.

Sucrosofate potassium salt (K-SOS) is a novel excipient and it is listed in the composition of the finished product as a free base. It is used as the raw material for the preparation of sucrosofate triethylammonium salt (TEA-SOS) used in liposome formation. The excipient K-SOS is transformed into TEA-SOS by ion-exchange. TEA-SOS and the lipids form the liposomes by passive encapsulation following polycarbonate membrane extrusion. An electrochemical gradient is subsequently formed by removal of TEA-SOS from the exterior of the liposomes by diafiltration. Triethylamine is removed during the manufacturing process. Detailed information on the manufacture, characterization and controls, justification of the use and a summary of supporting toxicology data for sucrosofate potassium salt was requested by the CHMP during the assessment procedure and the provided data was considered satisfactory.

The lipid membrane is composed of 1, 2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and N-(carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE). The function of the liposomal excipients is to produce the liposomal bilayer membrane which forms small unilamellar vesicles encapsulating and retaining the active substance until it is passively delivered to the tumour site. The liposomal excipients were selected for their properties when combined to produce liposomes capable of actively loading and retaining the active substance, while maintaining low protein binding *in vivo* and consequently prolonging their circulation lifetime.

DSPC is the major lipid component in the liposome bilayer. It was selected based on its high purity. It is a synthetic lipid with a well-defined fatty acid composition. It has a relatively high phase transition (Tm of 55°C) and is present in the highly ordered structure termed the gel phase, which resists permeability to small molecule drugs at physiological temperature (37°C).

Cholesterol is another main component of the liposome bilayer. It is incorporated to stabilize liposomal phospholipid membranes from disruption by plasma proteins, to decrease binding of plasma opsonins responsible for rapid clearance of liposomes from the circulation, and to decrease permeability of solutes/drugs in combination with bilayer forming phospholipids.

MPEG-2000-DSPE is a minor component of the liposome bilayer. Its presence on the surface provides a minimal steric barrier preventing liposome aggregation. MPEG-2000-DSPE coated liposomes are shown to be stable with respect to size and drug-encapsulation. Mean molecular weight and polydispersity index is included in the specification. Stability of MPEG-2000-DSPE has been discussed and considered acceptable.

The liposomes are dispersed in an aqueous buffered solution consisting of HEPES buffer, sodium chloride, and water for injections.

HEPES is a novel excipient. Detailed information on the manufacture, characterization and controls, justification of its use and a summary of supporting toxicology data for HEPES was requested by the CHMP during the assessment procedure and the provided data was considered satisfactory.

The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

In the initial stages of the manufacturing process of the finished product, irinotecan hydrochloride trihydrate active substance is dissolved in a dextrose solution. It is subsequently mixed with formed liposomes and precipitated and encapsulated as irinotecan sucrose octasulphate (sucrosofate) salt within a liposome, using an active drug loading process. The hydrochloride counter ion is replaced with sucrosofate resulting in the formation of irinotecan sucrosofate salt within the liposome. Sucrosofate is encapsulated in the liposome with the active substance. A scientific discussion on physicochemical characterisation of liposomes was presented in

the dossier. It included entrapment volume, morphology using cryoTEM analysis, particle size, particle size distribution, percent encapsulated drug, drug to phospholipid ratio, lipid impurity, DSPC to cholesterol ratio, *in vitro* release, zeta potential, and pH.

The formulation used during phase 3 clinical studies is the same as that intended for marketing.

The results of the comparability study between the two formulations (used in phase 1 and phase 2 studies, and phase 3 studies and commercial manufacture, respectively) demonstrate that products manufactured by both processes meet release criteria with no significant differences in quality attributes. Additional physico-chemical characterization and purity analysis (including lipid analysis, *in vitro* drug release assay, liposome morphology and size analysis) found no significant differences between both processes except for improved lower levels of lysophosphatidylcholine impurity. Stability studies of the drug products were performed to help detect differences that are not readily detectable by the characterization studies. There were no significant differences in quality attributes between the initial process and the phase 3 process after four weeks of storage under stress stability conditions (30 ± 2°C). The provided comparability study between the initial process and the process used to manufacture phase 3 and commercial batches was found acceptable.

Pharmaceutical development of the finished product contains QbD elements.

The Quality Target Product Profile was to develop a medicinal product conforming to: an intravenous infusion of sterile liposomes, that is white to slightly yellow, opaque, packaged in a 10 mL single use glass vial. Irinotecan is encapsulated as irinotecan sucrose octasulphate salt, in a long circulating liposome composed of cholesterol, DSPC, and mPEG-2000-DSPE. Each 10 mL vial contains the equivalent of 50 mg irinotecan (reported on the hydrochloride trihydrate basis) at a concentration of 5 mg/mL irinotecan (4.3 mg/mL as reported on the anhydrous free base form). It is stable for 24-36 Months at 2-8°C.

The critical quality attributes (CQAs) identified were: visual appearance, irinotecan identity, lipid identity, cholesterol identity, irinotecan concentration, percent encapsulated drug, irinotecan impurities, lipid impurity, residual solvents, bacterial endotoxins, bioburden and sterility, drug to phospholipid ratio, DSPC to cholesterol ratio, extractable volume in container, *in vitro* release, osmolality, particle size, particle size distribution, particulate matter in injections, pH, and zeta potential.

The manufacturing process has been evaluated through the use of risk assessments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The critical process parameters have been adequately identified.

The *in vitro* release method was designed to detect defective, incorrectly formulated or degraded liposomes; which could potentially affect the release of the active substance from the encapsulating vesicle. Discriminating ability of the method has been demonstrated with a series of studies which included a generation of defective liposomes and use of the model independent approach using similarity and difference factors applied to compare the *in vitro* release results.

The product is manufactured using sterile filtration and aseptic filling. Due to the nature of the finished product which is a liposome formulation with a phase transition temperature of the lipid membrane of 55 °C, terminal sterilisation by moist heat in line with decision trees for sterilisation choices for aqueous products is not possible. The sterilisation method was therefore appropriately justified.

The primary packaging is type I glass vial with a grey chlorobutyl stopper. The container closure of the finished product is sealed by an aluminium seal with a flip-off cap. The material complies with Ph. Eur. and EC

requirements. Compatibility studies were performed and demonstrated the compatibility of the finished product diluted in 5% dextrose and 0.9% saline at concentrations ranging from 0.2 mg/mL to 2 mg/mL with standard intravenous bags and infusion sets. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: liposome formation (lipid dissolution, multi lamellar vesicle (MLV) formation and small unilamellar vesicle (SUV) formation and sizing), active drug loading (diafiltration, drug loading), bulk drug product formulation, filling finish including bioburden reduction and sterile filtration, and labelling and packaging. The process is considered to be a non-standard manufacturing process.

Process validation for the manufacture of the finished product has been performed on three commercial scale batches in two discrete steps (bulk product manufacturing process and filling finish manufacturing step) in line with the traditional approach to process validation. In addition three scale down validation runs with bacterial challenge were performed in support of the validation of filters used to sterilise the product prior to the filling process. Additional validation studies included aseptic process validation, steam sterilisation validation (for the container closure of the finished product, and the components and equipment parts required for filling of the vials), dry oven validation (used to depyrogenate non-heat liable materials used in the manufacturing process), and container closure validation.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (Ph. Eur.), irinotecan identity (HPLC, UV), DSPC identity (HPLC-ELSD), cholesterol identity (HPLC-ELSD), MPEG2000-DSPE identity (HPLC-ELSD), irinotecan concentration (assay) (HPLC-UV), percent encapsulated drug (HPLC-UV), irinotecan impurities (HPLC-UV), lipid impurity (HPLC-ELSD), residual solvents (GC), residual trimethylamine (GC-FID), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), drug to phospholipid ratio (calculation), DSPC to cholesterol ratio (calculation), extractable volume (Ph. Eur.), in vitro release (HPLC-UV), osmolality (Ph. Eur.), particle size (Ph. Eur.), particle size distribution (Ph. Eur.), particulate matter in injections (Ph. Eur.), pH (Ph. Eur), and zeta potential (in house).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing of the active substance and of the excipients has been presented.

Batch analysis results are provided for 11 commercial scale batches and additional 23 pilot or lab scale batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial scale batches and three additional pilot or lab scale batches of finished product stored under long term conditions for up to 30 months at 2 °C – 8 °C and for up to 6 months under accelerated conditions at 25 ± 2 °C / 60±5% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance (Ph. Eur.), irinotecan concentration (assay) (HPLC-UV), percent encapsulated drug (HPLC-UV), irinotecan impurities (HPLC-UV), lipid impurity (HPLC-ELSD), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), container closure integrity (in house), in vitro drug release (HPLC-UV), osmolality (Ph. Eur.), particle size (Ph. Eur.), particle size distribution (Ph. Eur.), particulate matter in injections (Ph. Eur.), and pH (Ph. Eur).

The analytical procedures used are stability indicating. No significant changes have been observed during long term and accelerated stability testing. Additional data from bulk finished product batches stored under accelerated conditions showed an increase in osmolality and irinotecan concentration, which was not observed in the vialled finished product. These results are consistent with a small loss of water from the bulk polycarbonate stability containers. For both bulk and vialled finished product, irinotecan impurities and lipid impurities increased slightly, but remained within the specification limit. These results confirm the expected irinotecan degradation and lipid hydrolysis seen at higher temperatures under temperature stress conditions.

In addition, three batches of both bulk and vialled finished product were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results from this study showed a decrease in pH (related to LysoPC impurity and associated stearic acid increase) and irinotecan concentration, and an increase in irinotecan and lipid impurities. No significant change was observed in percent encapsulated drug, in vitro release, osmolality or particle size distribution. These data demonstrate that the finished product is sensitive to light and should be protected from light exposure.

Additional results on three batches of the finished product used in stress studies were provided. These included freeze-thaw cycling (3 cycles of overnight exposure at -20°C followed by a minimum of 3 hours at ambient room temperature (~20°C)), demonstrating a decrease in percent encapsulated drug outside the specification limit. An increase in irinotecan impurities, lipid impurities and particle size was observed, but they remained within the specification limits. Particle size distribution showed variable results likely caused by freeze/thaw stress. No significant change was observed in irinotecan concentration, in vitro release, pH or osmolality. The data are consistent with expected loss of liposome integrity, potential liposome aggregation and leakage of the irinotecan from the liposome during freeze-thawing. The product is sensitive to freezing and thawing and therefore should be protected from freezing.

Finally, results from three batches of the finished product on thermal stress conditions (40 ± 2°C or 50 ± 2°C for 4 weeks) were provided. A decrease in percent encapsulated drug outside the specification limit, and an increase in irinotecan and lipid impurities within specification limits were observed, demonstrating that the finished product is heat sensitive.

Based on available stability data, the proposed shelf-life of 30 months for an unopened vial when stored in a refrigerator (2 °C – 8 °C) and in the outer carton in order to protect from light, as stated in the SmPC (section 6.3) are acceptable. The medicinal product must not be frozen.

Chemical and physical stability for the diluted solution for infusion has been demonstrated at 15-25°C for up to 6 hours or in the refrigerator (2ºC - 8ºC) for no more than 24 hours. The finished product was diluted in 5%

dextrose or 0.9% saline to 0.2, 0.48 (in dextrose only) and 2.0 mg/mL and held for 24 hours at 2-8 °C or 6 hours at room temperature prior to being infused for 90 minutes using an infusion pump. The samples were analyzed for visual appearance, pH, concentration, purity and identity of irinotecan, drug encapsulation ratio, particle size and for di(2-ethylhexyl)phthalate (DEHP) from the PVC infusion bags.

DEHP levels were below the detection limit in samples with lower irinotecan hydrochloride concentrations (0.2mg/mL and 0.48mg/mL), which corresponds to the commercial dose. The levels of DEHP detected in the high concentration samples correspond to a worst case exposure of 500 µg of DEHP per day, assuming an infusion volume of 500 mL. These levels were below (1% or less of) the parenteral tolerable intake level of 0.6 mg/kg/day (U.S. Food and Drug Administration, Center for Devices and Radiological Health. Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices, July 2002). Exposure of patients to DEHP at these doses is not expected to result in adverse effects.

The data demonstrate the compatibility of the drug product diluted in 5% dextrose or 0.9% saline at concentrations ranging from 0.2 mg/mL to 2 mg/mL with standard intravenous bags and infusion sets.

Adventitious agents

Cholesterol obtained from sheep wool is used in the product. Valid TSE CEP from the suppliers of the cholesterol used in the manufacture is provided. No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Onivyde is a concentrate for solution for infusion with irinotecan hydrochloride trihydrate, a semi synthetic active substance in a liposomal formulation.

These liposomes are unilamellar lipid bilayer vesicles, approximately 110 nm in diameter, which encapsulate irinotecan in a gelated or precipitated state, as sucrosofate salt. Sucrosofate salt is considered a novel excipient and it has been chosen as the optimal counter ion for precipitating, loading and retaining of the active substance within the liposome. The liposomes are dispersed in an aqueous buffered solution, containing HEPES which is a zwitterionic buffer and a novel excipient.

The liposomal formulation of irinotecan is designed to prolong circulation of the active substance in plasma and increase the delivery of the active substance in tumours to take advantage of the compromised vasculatures of tumours.

The pharmaceutical development was focused on 1) the selection of an optimal counter ion for active drug loading, 2) the selection of an optimal ratio of DSPC to cholesterol components of the lipid membrane which influence its physical properties and the capability of retaining the active substance in the liposome, 3) the selection of MPEG-2000-DSPE component of the liposome bilayer whose presence on the surface provides a steric barrier to avoid liposome aggregation, and 4) the selection of an appropriate buffer capable of retaining the optimal pH range for the concentrate for solution for infusion. At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The Applicant is

requested to resolve the requirement of GMP compliance for the entire route of synthesis of the active substance, as a legally binding measure:

To introduce the revised and agreed synthetic process for the manufacture of the active substance from the agreed starting materials by 31/12/2016.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Onivyde (also referred to as MM-398) is a liposome of ~100 nm average diameter that encapsulates the active pharmaceutical ingredient irinotecan hydrochloride (CPT-11). Irinotecan is a known active substance and its mechanism of action was previously established in primary pharmacology studies. No such studies have been performed with the new formulation Onivyde.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies
Three in vitro studies on murine and human cell lines, and tumour tissue lysates from patients or mouse models were provided, aiming at investigating MM-398 liposomal uptake/release at the cellular level and irinotecan (CPT-11) conversion into its active metabolite (SN-38). Furthermore, a recent publication profiling MM-398 PK/PD model in a colon cancer model was provided (Kalra et al., 2014).

Murine and human macrophage-like cell lines were shown to accumulate 10-40 times higher levels of liposomes as compared to tumour cell lines. Uptake of liposomes led to the release of irinotecan from macrophage cell lines. In experiments on tumour tissue lysates, including pancreatic, and human macrophage-like cells, enzymatic conversion of irinotecan to the active metabolite SN-38 (100-1000x more active than irinotecan) was demonstrated.

In vivo studies

In a series of *in vivo* pharmacology studies in xenograft tumour models of human breast, gastric, pancreatic, cervical, brain and colon cancer, the Applicant compared the efficacy of MM-398 relative to equivalent or higher

dosing levels of free irinotecan. Generally, increased efficacy (measured as significant inhibition of tumour growth) was achieved with MM-398. In view of the present indication, the pancreatic tumour studies are of special interest. The efficacy of MM-398 was evaluated in several orthotopic and ectopic xenograft models of pancreatic cancer. MM-398 showed more potent anti-tumour activity, including durable tumour regression, compared to the equivalent dose of free irinotecan, in an orthotopic L3.6pl-T tumour model. Best effect in this model was obtained when using EGFR-targeted MM-398. Treatment with MM-398 also caused reduced tumour growth and a lower metastatic burden in an orthotopic BxPC3 tumour model**,** and decreased tumour hypoxia preceding tumour regression in the high-hypoxia OCIP51 orthotopic model.

During the procedure, the Applicant submitted a new pharmacology study report (MM-398-NC-N-Ph-027), evaluating antitumor activity of MM-398 against ectopic patient-derived pancreatic cancer xenografts in SCID mice. The results have been summarized by the Applicant in the table below.

Table 2: Tumour growth inhibition after treatment with Onivyde or gemcitabine in PDX tumour-explant models of pancreatic cancer

PDX model	Passage	Treatment	Dose (mg/kg)[a]	TGI (%)	# doses; TGI day	2-way ANOVA[b]	Gemcitabine sensitive
12424	8	MM-398	5	28.6	4; d35	N	N
		MM-398	10	67.2		Y	
		Gemcitabine	100	-13.9		N	
12424	9	MM-398	10	76.4	4; d36	Y	N
14244	9	MM-398	5	69.7	4; d28	Y	Y
		MM-398	10	93.8		Y	
		Gemcitabine	100	78.4		Y	
14312	4	MM-398	20	96.2	4; d35	Y	N
		Gemcitabine	100	28.9		Y	
15010	4	MM-398	5	94.9	4; d35	Y	Y
		MM-398	10	97.8		Y	
		Gemcitabine	100	81.6		Y	
19015	7	MM-398	5	-13.4	4; d42	N	N
		MM-398	10	61.6		Y	
		Gemcitabine	100	-8.5		N	
		Gemcitabine	200	34.4		Y	
18254[c]	7	MM-398	10	70.8	4; d28	Y	Y
		MM-398	20	78.9		Y	
		MM-398	40	75.0		Y	
18254	8	MM-398	20	67.4	4; d28	Y	Y
18269	7	MM-398	20	39.4	4; d30	N	[d]
OCIP51	9	MM-398	20	71.6	3; d21	Y	NA

[a] Doses are given as bolus intravenously q7d

[b] Post-hoc test, simple effects within rows with Sidak's multiple comparisons test, Y indicates statistical significance ($p < 0.05$), N: no statistical significance; NA not available

[c] Evaluated in Es1[e] SCID mice without plasma CES activity

[d] Patient showed partial response to gemcitabine

Dosing schedules
In studies using a q4d schedule, body weight losses in the range of 10-20% were observed. This effect was diminished when a q7d schedule was applied, which more closely resembles the clinical treatment regimen. No study employing the clinical q14d schedule was conducted.

Combination studies
Combination studies with Onivyde and 5-fluorouracil (5-FU) or cisplatin, in xenograft models of colon and cervical cancer, respectively, demonstrated more potent effects than when the substances were administered as single agents. No combination studies were performed in pancreatic cancer models.

Mechanistic studies
Onivyde distribution and uptake were investigated in an orthotropic intracranial xenograft model of glioblastoma in rats. Intracranial delivery of MM-398 caused increased retention time (22 times higher t ½) in the brain as compared with free irinotecan. This correlated with increased survival. In contrast, iv administration of MM-398 in the same tumour model did not result in increased brain tissue retention, although the tissue exposure in terms of C_{max} and AUC was higher than that achieved with free irinotecan. Survival was increased in rats treated with MM-398.

Further investigation of the relationship between tissue pharmacokinetics and tumour treatment efficacy was conducted in a xenograft colon cancer model in mice, comparing Onivyde and free irinotecan (iv administration). Despite equal SN-38 exposure (plasma, tumour) the liposomal formulation resulted in 2-2.7 times better tumour growth control.

Tumour hypoxia is linked to aggressive disease progression and resistance to therapy. To investigate effects on hypoxia the Applicant conducted a non-invasive FAZA PET study in the HT-29 colon cancer model, monitoring changes in the tumour microenvironment after treatment with MM-398 or free irinotecan at similar SN-38 exposure in the tumour. Tumours in mice treated with MM-398 at 10 mg/kg bw showed significantly lower levels of hypoxia compared to those treated with CPT-11 at 50 mg/kg bw. Tumour growth was also significantly reduced in mice treated with MM-398 at 10 mg/kg bw, as compared with treatment with CPT-11 at 50 mg/kg bw.

In a final mechanistic study the Applicant performed flow cytometry analysis on cell suspensions from tumour tissue to investigate the distribution of fluorescently-tagged liposomes in various animal tumour models. The results showed that F4/80-positive mature macrophages accumulated a larger proportion of the overall cellular liposomal load relative to their population size compared to other myeloid or non-myeloid cell populations. Macrophage and myeloid populations accounted for 78-94% of the cellular liposomal uptake.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed.

Safety pharmacology programme

A study in conscious telemetered Beagle dogs was conducted to assess the effect of MM-398 on the cardiovascular and respiratory systems. Single iv infusion with MM-398 at doses up to 21 mg/kg (420 mg/m^2) had no effect on cardiovascular, hemodynamic, electrocardiographic, respiratory parameters, or body temperature. The maximum plasma concentrations of irinotecan and SN-38 at the end of infusion were 7.5x and 3.6x above therapeutic C_{max} respectively.

No CNS safety pharmacology study was conducted.

Pharmacodynamic drug interactions

No studies were performed with Onivyde to evaluate pharmacodynamic drug interactions.

2.3.3. Pharmacokinetics

The pharmacokinetics and toxicokinetics of irinotecan and the active metabolite SN-38 have been studied in relevant animal species, i.e. rats, dogs and tumour bearing mice, following IV administration of single and repeat doses of liposome encapsulated irinotecan (MM-398) and unencapsulated irinotecan (CPT-11). The TK analysis of the two pivotal toxicity studies in rats and dogs was not GLP compliant and is thus not considered valid to support the interpretation of these studies (see further under Toxicology).

In all studies, total irinotecan levels (i.e. liposome encapsulated irinotecan and free irinotecan) were measured and used for the evaluation of the pharmacokinetics of irinotecan. Determination of encapsulated irinotecan in dogs following an IV single bolus dose of 10 mg/kg Onivyde showed a stable degree of 75 to 86% encapsulation up to the last determination 36 hours post-dose which indicates that the concentrations of total irinotecan represent encapsulated irinotecan to a corresponding degree.

Absorption

Single doses of 90 min IV infusions of MM-398 to SD rats and Beagle dogs showed some deviations from dose proportional plasma exposure (in terms of AUC) for irinotecan at the dose levels studied (higher than dose proportional from the low [6 mg/kg] to the mid [20 mg/kg] dose in rats and from the mid [30 mg/kg] to the high [50 mg/kg] in dogs. For SN-38 the increase in AUC was overall approximately dose proportional in dogs but generally less than dose proportional in rats.

When compared at the same dose level (20 mg/kg in rats and 30 mg/kg in dogs) the AUC of irinotecan and SN-38 was higher for MM-398 than for unencapsulated irinotecan in rats (approximately 1700-fold and 90-fold, respectively) and dogs (approximately 40-fold and 3-fold, respectively). Terminal elimination half-life of irinotecan and SN-38 was longer for Onivyde (10 and 15h, respectively, in rats; 13h for both analytes in dogs) than following unencapsulated irinotecan (0.7 and 11h, respectively, in rats; 4.3 and 6.2h, respectively in dogs).

Repeated doses of 90 min IV infusions of MM-398 once every third week for 18 weeks to rats and dogs showed approximately dose proportional plasma exposure (in terms of AUC) for irinotecan at the dose levels studied in rats (30, 75 and 190 mg/kg) and dogs (9, 15 and 21 mg/kg). For SN-38 the increase in total AUC was overall approximately dose proportional in dogs but generally less than dose proportional in rats. The accumulation of irinotecan was about 2-fold in rats but there was no evidence for accumulation of SN-38 in rats or of irinotecan and SN-38 in dogs.

When compared at the same dose level (75 mg/kg in rats and 21 mg/kg in dogs) the AUC of irinotecan and SN-38 was higher for MM-398 than for unencapsulated irinotecan in rats (approximately 1000-fold and 50-fold, respectively) and dogs (approximately 150-fold and 3-fold, respectively). Terminal elimination half-life of irinotecan and SN-38 was longer for Onivyde (33 and 323h, respectively, in rats; 12 and 35h, respectively, in dogs) than following unencapsulated irinotecan (4.9 and 6.1h, respectively, in rats; 2.8 and 5.1h, respectively in dogs). MRT_{0-168} values for irinotecan and SN-38 were also longer for MM-398 (22.0 to 22.9h and 40.1 to 53.8h, respectively, in dogs) than for unencapsulated CPT-11 (3.4 to 4.1h and 4.8 to 6.0h, respectively, in

dogs). The very long half-life of SN-38 in rats is likely due to the presence in rodent species of a plasma carboxylesterase activity that contributes to the systemic levels of SN-38 after administration of MM-398.

Distribution

Quantitative whole-body autoradiography following a single 90 min IV infusion of 10 mg/kg ^{14}C-MM-398 and unencapsulated ^{14}C-CPT-11 in Long Evans rats showed a wide distribution to tissues for both formulations with the highest concentrations generally observed at the end of the infusion. For several of the tissues (e.g. including CNS, pigmented skin, liver [and bile], kidney, epididymis, testis, lung, trachea, heart, bone marrow, blood and spleen) the concentrations of radioactivity was higher for ^{14}C-MM-398 than for unencapsulated ^{14}C-CPT-11 with the highest levels for ^{14}C-MM-398 in plasma, bile and spleen. Tissue levels generally remained higher for a longer period following ^{14}C-MM-398. These results were supported by another study which showed increased levels and prolonged duration in plasma, spleen, and liver of total irinotecan and/or SN-38 for MM-398 as compared to unencapsulated CPT-11 following a single bolus IV infusion of 10 mg/kg.

The radioactive levels in the gastro-intestinal contents of rats were much higher for unencapsulated ^{14}C-CPT-11 than for^{14}C-MM-398 and the levels of irinotecan and SN-38 in intestines (with contents) in tumour bearing mice after a single IV bolus administration of 40 mg/kg were in general higher for unencapsulated CPT-11 than for MM-398. Together the results indicate a slower elimination of MM-398 than of unencapsulated CPT-11. This is a possible explanation for the increased and prolonged plasma and tissue levels observed for MM-398.

While the relative proportions of radioactivity in brain versus plasma were lower for ^{14}C-MM-398 than for unencapsulated drug, the absolute radioactive concentrations were 18x higher in the CNS of rats given ^{14}C-MM-398. This indicates that MM-398 may be able to pass the blood brain barrier Alternatively, the higher CNS concentrations could be due to a longer plasma half-life of MM-398. Retention of ^{14}C-MM-398-derived radioactivity in the uvea of the eye may indicate binding to ocular melanin. A lower distribution of radioactivity into the cellular fraction of blood following ^{14}C-MM-398 than following unencapsulated ^{14}C-CPT-11 was also indicated.

In tumour bearing mice, highest tissue exposure to irinotecan and SN-38 for MM-398 in terms of C_{max} and $AUC_{0-\infty}$ was obtained in the liver whereas tumours had the lowest C_{max} of irinotecan, and lowest C_{max} and $AUC_{0-\infty}$ of SN-38. The AUCs of irinotecan and SN-38 in plasma, organs and tumours were increased for MM-398 as compared to unencapsulated CPT-11. For irinotecan the largest increase was observed in tumours (28-fold) whereas for SN-38, the increase in tumours (6-fold) was lower than in the liver (16-fold) and the kidney (10-fold). Following MM-398, C_{max} of irinotecan was increased in tumours but to a slight extent also in the liver, 1.6-fold and 1.1-fold, respectively. For SN-38, C_{max} was increased in liver and kidney but decreased in tumours and in small and large intestine. The MRT and $t_{½}$ of irinotecan and SN-38 were increased for MM-398 as compared to unencapsulated CPT-11 and were longer in tumours than in the other tissues (at least approximately 3-fold for irinotecan and 2-fold for SN-38). According to the Applicant the increase in C_{max} of irinotecan in tumours together with a longer duration in tumours as compared to other tissues indicate favourable pharmacokinetic characteristics for MM-398 both with respect to efficacy and safety.

Metabolism

After release from the Onivyde liposomes, irinotecan is expected to follow the same metabolic fate as unencapsulated irinotecan. The active metabolite SN-38 is reported to be formed from irinotecan via carboxylesterase-mediated cleavage in the liver and intestines. Plasma carboxylesterase activity and possibly more efficient carboxylesterases in rodents suggest that exposure comparisons from dog studies may be more relevant for the estimation of margins to human exposure. The active SN-38 is further metabolised to the inactive SN-38 glucuronide (SN-38G) via uridine-5'-diphosphate-glucuronosyltransferase UGT1A isoforms in

the liver and subsequent deglucuronidation by intestinal β-glucuronidase. Irinotecan is also metabolised by CYP3A4 to various oxidative metabolites, including APC and NPC. While NPC can be converted to SN-38 by carboxylesterases, APC is not and does most likely not contribute directly to the activity and toxicity profile of irinotecan *in vivo*.

Excretion

A mass balance study of a single 90 min IV infusion of 5 mg/kg encapsulated ^{14}C-CPT-11 in intact and bile duct cannulated SD rats showed that faecal excretion was the major route for excretion in intact rats with 78.3 to 83.4% and 16.5 to 22.9% of the radioactive dose detected in faeces and urine, respectively, and that biliary excretion represented 77% of the faecal excretion.

2.3.4. Toxicology

The toxicity profile of Onivyde (MM-398) was characterized in mice, rats and dogs. The in life-phase of the pivotal toxicity studies in rats and dogs was GLP compliant; however, the TK/bioanalysis part was not (see below). The study package comprised single-dose and repeat-dose toxicity studies up to 18-weeks duration (dosing once every third weeks, in total 6 cycles), and an *in vitro* blood compatibility study. The genotoxic, carcinogenic, reproductive and developmental toxicity potential of the API irinotecan has been determined previously. Ninety (90)-minute intravenous (iv) dosing has been used in all *in vivo* studies, as this is the administration route that will be used clinically.

The general scientific integrity and validity of the pivotal toxicity studies was called into question, considering a number of GLP issues that needed to be addressed. The Applicant clarified that at the time of the initiation of the two pivotal studies, the test facility where the *in life phase* of both pivotal toxicity studies [6-cycle rat (PEP02-NC-G-Tx-010, 1005-3071) and dog (PEP02-NC-G-Tx-011, 1006-2162)] has been performed, was under OECD compliant GLP monitoring. Moreover, the full GLP compliance *status* of the i*n life phase* of the two studies has been confirmed by a dedicated GLP Study Audit (Study audit report 15842) performed at the CiToxLAB facility, in November 2015 as part of a biannual routine inspection program. However, the Monitoring Authority could not comment on the GLP status of the TK/bioanalytical phase of the studies performed at non-OECD subcontractor sites, therefore the audit does not cover the GLP status of the TK/bioanalytical analyses and this data cannot be used to support the interpretation of the study results.

Single dose toxicity

Single-dose studies were performed in ICR mice, Sprague Dawley rats and Beagle dogs. The approximate lethal dose in mice was 200 mg/kg for both MM-398 and CPT-11. Gastrointestinal (GI) toxicity was evident. Doses of MM-398 at ≥400mg/kg caused thymus atrophy, spleen atrophy and pale liver.

In rats, 960 mg/kg and 200 mg/kg were lethal doses in MM-398 and CPT-11 dosed animals, respectively. Main clinical signs were dose-dependent GI toxicity, hypoactivity and irregular respiration. Body weight reductions were evident in all dose groups. Rats dosed with MM-398 at ≥480 mg/kg showed reductions in leukocytes that partly recovered before termination of the study.

Dogs exposed to MM-398 and CPT-11 showed pronounced GI toxicity including emesis and diarrhoea. All treatment groups showed dose-dependent reductions in leukocytes. Preterminally euthanized animals had small spleens and thymuses. All exposed groups showed reductions in body weight and food consumption. The maximum tolerated dose (MTD) was 15 mg/kg bw (300 mg/m^2). The exposure margin from MTD to human therapeutic dose (80 mg/m^2) was 3.8x.

Table 3: Single dose toxicity studies with Onivyde

Study ID / GLP	Species / Sex / Number / Group	Dose / Route (i.v.) MM-398 mg/kg / empty liposome phospholipids concentration mM / Conventional CPT-11	Approx. lethal dose / observed max non-lethal dose (mg/kg)	Major findings
PEP02-NC-G-Tx-003 GLP	ICR Mouse/5/sex	LIIA06 200, 400, 800 LIIA06P 30.91mM CPT-11 200	Estimated LD50 237 (M), 336 (F)	Mortality M+F placebo 0/10, CPT-11: 2/10, MM-398 1/10, 10/10, and 10/10. Delayed onset of severe adverse clinical signs and death observed at 6 to 8 days post-dosing For CPT-11 rapid onset and death on the day of dosing
PEP02-NC-N-Tx-004 (PS00006) non GLP	SD male rats 3 /group	LIIA02 and LIIA03 200, 400 LIIA03P 32mM CPT-11 200	MM-398: 200 CPT 11: 200	CPT-11: 2 deaths on day 1; hypoactivity, exopthalmus, soft faeces, watery faeces, yellowish urine stain around the genital area, tremors and chromodacryrrhea MM-398 200 and 400 mg/kg: brown soft faeces on day 3 (2/3 and 3/3 rats. No clinical signs in controls groups. LIIA02 400 low bw gain
PEP02-NC-G-Tx-002 (No. 7082) GLP	SD male rats 5/sex/group	LIIA05, LIIA06 480, 720, 960 LIIA06P 30.91 mM CPT-11 320	About 960	Toxicity due to effects on GI tract responsible for the deaths of animals at 960 mg/kg. CPT-11 induce GI toxicity at 320 mg/kg
Study PEP 02-NC-N-TX001 (No. 6171) GLP	Beagle dogs	CPT-11 dose escalation 4 day wash out 30, 40 and 60.	MTD 30 (F), 40 (M)	Vomiting an severe GI alterations
PEP02-NC-G-Tx-005 (No. 6160)	Beagle dogs 3 /sex	LIIA05 dose escalation 4 day wash out 40, 50, 65 or 100 (infusion 90 min) Control 5 % dextrose in water	MTD 50	Severe, irreversible GI toxicity $\geq$ 65. Transient GI toxicity (loss of appetite, decrease in body weight, evidence of emesis and loose stool) 40 and 50
Protocol PEP02-NC-G-Tx-007 (6151) GLP	Beagle dogs 3 /sex	LIIA09; 15, 30, and 50 LIIA10P (41.56 mM) CPT-11 30	MTD 15 (300 mg/m^2) On this basis the dose for 4 weeks study was determined to be <30 mg/kg/day.	Emesis and GI toxicity. Neurologic events, such as tremors, along with the GI effects, were noted with CPT-11

Repeat dose toxicity

The potential toxicity and the TK profile of MM-398 was investigated in 4 studies:

-in Sprague-Dawley rats [PEP02-NC-G-Tx-006 (7083)] and Beagle dogs [PEP02-NC-G-Tx-009 (6152)] by i.v. infusion once each week during a 28-day period, followed by a 14-day recovery/observation period (4 weeks study),

- in Sprague-Dawley rats [PEP02-NC-G-Tx-010 (1005-3071)] and Beagle dogs [PEP02-NC-G-Tx-011 (1006-2162)] administered as 6 cycles (each cycle comprised of a single dose followed by a 3-week observation period (6 cycles study) via i.v. infusion, each over a period of 90 minutes.

Table 4: Repeat dose toxicity studies with Onivyde

Report	MM-398 batch (Drug/pho ratio mg/mmol)	Liposom concentr (mg/mL)	phospholipid content (mM)	Size (nm) (drug encapsulation %)	Placebo Batches Phosp. Concen (mM)	SOS amount dose/total (mg/kg)	TEA amount dose/total (mg/kg)
RATS							
PEP02-NC-G-Tx-006 (7083) 4 wks	LIIA07 (505)	17.36	29.8	87.9 (99.7%)	LIIA05-liposome (47.2)	57.9/231	51.7/207
	LIIA08 (501)	16.93	29.3	90.8 (99.7%)	LIIA08P placebo (23.8)	36.3/145.2	67.8/271.2
[a] Animals received ~ 357 - 447 mg/kg phospholipids. [b] animals received or ~ 282 - 353 mg/kg phospholipids. * used only when LIIA05-liposome had been exhausted							
No. PEP02-NCG-Tx-010 (1005-3071) 6 cyc	LIIAS3001 (510)	5	8.39	128 (98.75%)	LIIA12P (43.64)		
	LIIA12 (481)	18.7	33.4	104.7 (99%)	LIIA14P (45.26)		
	LIIA14 (514.6)	24.61	41.34	104.7 (99%)	LIIA14P-2 (40.22)		
DOGS							
PEP02-NC-G-Tx-009 (6152) 4 wks	LIIAS3001 (510)	5	8.39	128 (98.75%)	LIIA011 (19.33)	1.6/6.4	4.4/17.8
PEP02-NC-G-Tx-011, ITR 1006-2126 6 cyc	LIIPS5001 (517.5)	5	12.2	104.9 (99.68%)	LIIPS 5001 (12.2)		
	LIIAS4002 (498.3)	5	Not reported	116 (99.53%)			

Mortalities

Preterminal mortalities and unscheduled sacrifice of animals occurred in all repeat-dose toxicity studies with CPT-11 and MM-398. A clear species difference in sensitivity was observed. Despite high exposure to irinotecan and SN-38, only occasional rats treated with MM-398 or CPT-11 were found dead or preterminally sacrificed. In most cases, the cause of death was unrelated to the compound. In the 4-week study, one female rat died after treatment with MM-398 at a dose of 260mg/kg (1560 mg/m^2) on SD 13. No specific cause of death was determined. In the 18-week study, one male dosed with MM-398 at 190 mg/kg (1140 mg/m^2) was euthanized during the recovery period due to deteriorating condition. The margins between these mortalities and the human therapeutic dose are in the range of 14-19x.

In contrast, dogs showed severe GI toxicity at relatively low doses, causing preterminal sacrifice of two males treated at 16 mg/kg (320 mg/m^2) in the 4-week study. Both dogs had evidence of GI bleeding, and

histopathology revealed mucosal hemorrhage and atrophy, and crypt epithelial necrosis. The margin between the dose of irinotecan causing mortality in the 4-week dog study and the human therapeutic dose is 4x.

In the dog 6-cycle study, a total of 13 dogs were found dead and an additional 6 dogs were removed from the study early. Changes in the bone marrow, GI tract and lymphoid tissues accounted for the mortality in the majority of dogs (see below). At LOAEL for mortality (21 mg/kg bw = 420 mg/m^2) the margin to human therapeutic dose of irinotecan was 5x.

Gastrointestinal tract

The GI tract was a target of toxicity for MM-398 and CPT-11 in the repeat-dose toxicity testing. The effects were not as dramatic as in the single-dose studies, since the doses used were lower. In rats, the GI-effects were mainly limited to reductions in food consumption and body weight decrease. Body weights were dose-dependently decreased immediately following the 90-minute infusions but returned to control levels within 9 days in the 6 cycle study. Food consumption decreased in all dose-groups but returned to control levels in males during recovery. CPT-11 caused less pronounced effects on body weight and food consumption as compared to MM-398 at the same dose.

In dogs, the high dose group (16mg/kg) in the 4–week study showed reductions in food intake with accompanying reductions in body weight. Two preterminally sacrificed dogs showed GI haemorrhage, intestinal mucosal atrophy and crypt epithelial necrosis (see above). In the 6-cycle study, all dose groups showed transient reduction in food intake, but no significant reduction in body weight. Pre-terminally dead/euthanized dogs at ≥ 21 mg/kg showed intestinal crypt epithelium necrosis and dilatation, mucosal villous atrophy, and congestion/haemorrhage. MM-398 and CPT-11 caused similar GI toxicity in dogs when given at the same dose.

Bone marrow

Bone marrow hypocellularity, reflected by peripheral haematology effects, was consistently found in the repeat-dose toxicity studies. In the 4-week rat study, red blood cells (RBC), haemoglobin (HGB) and white blood cells (WBC) were dose-dependently decreased and platelets (in males) were dose-dependently increased at MM-398 doses from 65 to 260 mg/kg. Similar effects were seen with CPT-11 at the same dose (130 mg/kg). Bone marrow hypocellularity was observed in MM-398 high dose (260 mg/kg) rats in the 4-week study, and at 190 mg/kg in the 18-week study. Female dogs exposed to 8 mg/kg MM-398 in the 4-week study showed reversible neutropenia. In the 18-week study, bone marrow hypocellularity was observed in pre-terminally dead/euthanized dogs treated with MM-398 or CPT-11 at $\geq$ 21 mg/kg bw. Dogs treated with MM-398 at ≥15mg/kg and with CPT-11 at 21 mg/kg had decreased levels of RBC, HGB, haematocrit and WBC.

Lymphoid organs

Lower thymus weights (32-80%) were observed in rats exposed to MM-398 ≥65mg/kg once weekly for 4 weeks. These effects correlated with thymic atrophy that was dose-dependent in severity and frequency. Dogs exposed to 16mg/kg MM-398 or CPT-11 for 4 weeks showed slightly reduced thymus weights, but without microscopic correlation. In the 18-week study, pre-terminally dead/euthanized dogs treated with MM-398 or CPT-11 at $\geq$ 21 mg/kg showed lower thymus weights correlated with lymphoid atrophy/necrosis.

Lymphoid atrophy/necrosis was present in the spleen, lymph nodes and Peyer´s patches of dogs treated with MM-398 at $\geq$ 15 mg/kg, and with CPT-11 at 21 mg/kg, for 18 weeks. Atrophy of Peyer´s patches was also present in dogs treated at $\geq$ 8 mg/kg in the 4-week study.

Spleen

Extramedullary haematopoiesis (EMH) was present in rats treated with CPT-11 (130mg/kg) in the 4-week study. In the 18-week rat study, all MM-398 exposed groups showed EMH in the spleen. In the 4-week dog study, splenic EMH was noted in the high dose MM-398 and CPT-11 groups. In the 18-week dog study, EMH was observed both in the spleen and liver in dogs treated with MM-398 at $\geq$ 15 mg/kg and with CPT-11 at $\geq$ 21 mg/kg.

Liver

Liver weights were 6-24% lower in rats exposed to MM-398 ≥65mg/kg in the 4-weeks study. No microscopic correlation was found. Minimal to mild multifocal liver degeneration/necrosis (without effect on liver weight or serum chemistry parameters) was reported for all MM-398 exposure groups in the 6-cycle study in rats. No similar findings were present in dogs. The margin between LOAEL (30 mg/kg = 180 mg/m^2, incidence 1/40 rats) and human therapeutic dose of irinotecan is 2x.

Vehicle-associated effects

In the repeat-dose toxicity studies in rats, vacuolation and histiocytosis in multiple organs were observed in all MM-398 dose groups, as well as in the vehicle control groups. These findings are considered to be related to phagocytosis of the liposome. On the whole, similar findings were seen in MM-398 treated animals and controls. Histiocytosis in the heart was only observed in rats treated with MM-398 at $\geq$ 190 mg/kg (1140 mg/m^2). In dogs, minimal histiocytosis in the spleen was present in vehicle controls and all MM-398 treated groups in the 18-week study.

Other findings

Other findings related to administration of MM-398 included renal medullary tubular hypertrophy in rats at 260 mg/kg in the 4-week study, decreased activated partial thromboplastin (APTT) in male rats at $\geq$ 65 mg /kg in the 4-week study, lower platelets, PCT and reticulocytes in dogs treated at $\geq$ 15 mg/kg MM-398 or 21 mg/kg CPT-11 in the dog 18-week study, and dental effects treated with MM-398 or CPT-11 in the rat 18 week-study.

Reversibility

All major findings related to treatment with MM-398 or CPT-11, and the vehicle-associated histiocytosis, were fully or partly reversible upon cessation of treatment.

Genotoxicity

No genotoxicity studies have been conducted with Onivyde.

Carcinogenicity

No carcinogenicity studies have been conducted with Onivyde.

Reproduction Toxicity

No reproductive and developmental toxicity studies have been conducted with Onivyde.

In the 4 week rat study, moderately lower prostate weights were reported in males at ≥65mg/kg MM-398. Histopathology showed mild atrophy of both prostate and seminal vesicles. In the 18 week study, 1 male rat in the high dose group had necrosis and atrophy of the testis unilaterally and severe aspermia of epididymis.

Dogs exposed to 16mg/kg MM-398 or CPT-11 in the 4-week study showed slightly lower prostate and testis weights, but no histological correlation could be made. In dogs that were euthanized/removed early from the study in the 6-cycle study ($\geq$ 21 mg/kg MM-398 or CPT-11), prostate and testes weight reductions of 45-73%

were observed. Microscopically, the lower prostate and testes weights correlated with acinar atrophy and degeneration/necrosis of seminiferous epithelium, respectively.

Ovary weight reduction of 16-24% without any obvious histopathological correlation was reported in the rat 4-week study in females exposed to ≥65 mg/kg MM-398. In the 4-week dog study, lower uterus weight without any histopathological correlation was present at 16 mg/kg MM-398 or CPT-11. Decreased ovary and uterus weight, correlated with reduced number of follicles and atrophy, respectively, was observed in the 18-week dog study at ≥ 21 mg/kg MM-398 or CPT-11.

Toxicokinetic data

Toxicokinetic evaluations have been performed for both CPT-11 and MM-398 in single- and repeat-dose studies. These analyses were not GLP compliant and thus cannot be used to calculate margins to human therapeutic exposure. Some of the TK data suggests that the rat conversion of irinotecan to the active metabolite SN-38 is more efficient in the rat than in the dog. A possible explanation is that rodent species have a plasma carboxylesterase activity that contributes to the systemic levels of SN-38 after administration of irinotecan, while dogs and humans do not express plasma carboxylesterase enzymes.

Local Tolerance

Transitory skin reactions, including reddening and/or swelling and slow skin edema were seen in rats and/or dogs treated with MM-398 at ≥21 mg/kg. Similar findings were recorded also in animal receiving CPT-11 and empty liposomes, suggesting these effects were procedure-related.

Other toxicity studies

Haemolytic and flocculation potential

The haemolytic and flocculation potential of MM-398 was tested *in vitro* using human whole blood and plasma. No haemolytic effect of MM-398 was observed, and although some flocculation was seen in the samples spiked with liposome or MM-398, this is not considered an issue for further consideration.

Phototoxicity

No phototoxicity studies were performed with MM-398.

2.3.5. Ecotoxicity / environmental risk assessment

The Applicant has performed a Phase I assessment, as specified in the ERA guideline. Since irinotecan is an ionisable compound, Log Dow values were applied instead of Log Kow. These values were determined experimentally according to the OECD 107 guideline. All three values were below the PBT action limit of 4.5, as specified in the ERA guideline.
The original ERA document was updated in terms of recalculated PECsw based on refined Fpen value for the sought indication. The refined Fpen was calculated to 0.00001. Applying this value to the formula, the resultant PECsw is 0.00064 µg/l, which is below the threshold of 0.01 µg/l. Thus there is no need for a Phase II environmental fate and effect analysis, provided that the Log Dow values can be supported by experimental data.

Table 5. Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log D_{ow} (pH 4.0) = -2.03 ± 0.01 Log D_{ow} (pH 7.0) = 0.27 ± 0.02 Log D_{ow} (pH 9.0) = -0.81 ± 0.02	Not PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	$6.4 \cdot 10^{-04}$ µg/L	µg/L	<0.01 threshold
Other concerns (e.g. chemical class)		N	N

2.3.6. Discussion on non-clinical aspects

Anti-tumour efficacy and proof of principle have been demonstrated in various rodent tumour models, including pancreatic cancer. The results of these studies have provided the basis for dose setting and schedule in the clinic. Comparisons between liposome encapsulated irinotecan (MM-398) and non-liposomal irinotecan (CPT-11) suggest that the liposomal formulation exerts a more potent anti-tumour effect.

Questions were raised about the role of tumour-associated macrophages (TAMs) as drug deposits for MM-398 drug uptake/release, the distribution of Onivyde in tumours and the liposomal uptake capabilities by pancreatic cancer cells. The Applicant clarified that TAMs were not proposed to be the sole provider of tumour-based drug release. Fluorescent immunohistochemistry (IHC) analysis on several pancreatic cancer models showed liposome “hotspots” in perivascular areas of the tumour stroma, which is known to be enriched with TAMs in pancreatic cancer. Despite this, DNA damage was localized to tumour cells, proving drug release from the tumour stroma.

Lack of proof-of-concept of sufficient tumour SN-38 level achievement after TAM drug uptake/release was raised as a concern. The Applicant provided data showing that tumour SN-38 levels at 72 h were consistent with concentrations needed to elicit cell death as determined from in vitro experiments. The relationship between SN-38 concentration and cell death was measured in a panel of pancreatic cell lines and found IC50 levels of less than 10 nM for a large number of cell line models.

To address some uncertainties regarding the effect of Onivyde in animal models of pancreatic cancer, the Applicant submitted a new pharmacology study showing efficacy of Onivyde in three gemcitabine-resistant PDX models (#12424, #14312, #19015) as well as in two gemcitabine-sensitive PDX models (#14244, #15010). These results strengthen the non-clinical proof of concept for Onivyde. A comparison between MM-398 and unencapsulated irinotecan in a gemcitabine-sensitive PDX model showed significantly improved tumour growth inhibition (TGI) with Onivyde relative to unencapsulated irinotecan. Unfortunately, no comparison was made in a gemcitabine-resistant PDX model, which is the most relevant model for the sought indication. However, the Applicant submitted supportive data, showing consistently greater TGI upon treatment with Onivyde at lower

doses versus conventional irinotecan in cell-line derived pancreatic cancer models, including the gemcitabine-resistant AsPC-1 model. In summary, Onivyde at doses of 10-20 mg/kg bw (iv administration, q7d, 3-5 doses in total) showed efficacy in several different mouse models of pancreatic cancer. This corresponds to an efficacious dose of 30-60 mg/m2 in mice, which is somewhat lower than the recommended starting dose of 80 mg/m2 in patients.

In a xenograft colon cancer model in mice, comparing Onivyde and free irinotecan (iv administration) a much better tumour growth control despite equal SN-38 exposure (plasma, tumour) was observed with the liposomal formulation. The key factor behind this effect was proposed to be the longer duration of SN-38 exposure in the tumour obtained with Onivyde as compared with free irinotecan administration. This notion is somewhat contradictory to the results obtained in the rat glioblastoma model, suggesting differences between tumours and/or species.

Since irinotecan is a known active substance, the lack of secondary pharmacology studies is accepted. However, the Applicant's assertion that topoisomerase I is the exclusive target for irinotecan is not agreed with. There are several reports in the literature, describing the inhibition of acetylcholinesterase by irinotecan, at clinically relevant concentrations. This mechanism has been proposed as an explanation for the cholinergic syndrome observed in some patients treated with irinotecan, although other mechanisms have also been implicated. Cholinergic syndrome is listed as an adverse reaction in section 4.8 of the proposed SmPC.

In safety pharmacology studies in dogs, ONIVYDE had no effect on cardiovascular, hemodynamic, electrocardiographic, or respiratory parameters at doses up to 21 mg/kg (420 mg/m2). The lack of CNS safety pharmacology study can be accepted based on the already known safety pharmacology profile of irinotecan, and the fact that clinical CNS effects (cholinergic syndrome) have already been identified. Furthermore, in a limited evaluation of CNS effects in the 18-week repeat dose toxicity study in rats doses of MM-398 up to 190 mg/kg bw did not produce any CNS-related signs, in contrast to free irinotecan at 75 mg/kg bw, which caused uncoordinated gait and tremor (see section 5.3 of the SmPC). According to the Applicant, this difference may be explained by the prevention of entry into the brain due to the size of the liposome being too large to pass through the blood brain barrier. On the other hand, iv administration of Onivyde gave higher concentrations of irinotecan and SN-38 in the brain as compared with CPT-11 in the rat glioblastoma model.

The Applicant was asked to clarify the pharmacokinetics of Onivyde with regard to passage over the blood-barrier. It was suggested that the longer plasma half-life of Onivyde, causing extended systemically released irinotecan, was the most likely explanation for the higher concentrations of Onivyde in the brain versus non-liposomal irinotecan.

Since irinotecan has been co-administered with 5-FU/LV in clinical practice, non-clinical studies on pharmacodynamic drug interactions are not considered needed.

The Applicant was asked to clarify and discuss possible reasons for the large differences in half-life of SN-38 between MM-398 and CPT-11. The Applicant clarified that in both non-clinical and clinical studies the half-life of SN-38, as measured from the time of injection of both liposomal and unencapsulated irinotecan formulations, was increased by liposomal encapsulation. This was considered to be the key mechanism behind drug retention in tumours.

Single and repeat-dose non-GLP pharmacokinetic and toxicokinetic studies in rat and dogs showed that MM-398 results in higher plasma exposure (in terms of AUC) and a prolonged period in plasma of irinotecan and its active metabolite SN-38 as compared to non-liposomal irinotecan (CPT-11) when given at the same dose levels. This was related to slower CL, lower Vd, longer $t_{½}$ and longer MRT for the MM-398 formulation. A wide distribution to tissues was observed and for several tissues the levels were increased and remained higher for a longer period

following MM-398 as compared to CPT-11. In tumour bearing mice, the largest increase for MM-398 in tissue exposure in terms of AUC was observed in tumours for irinotecan, whereas for SN-38, the increase in tumours was lower than in the liver and the kidney. The MRT and $t_{½}$ of irinotecan and SN-38 were also increased and were at least 2 to 3-fold longer in tumours than in the other tissues. While C_{max} of irinotecan was increased in tumours, and to a slight extent also in the liver, C_{max} of SN-38 was decreased in tumours but increased in liver and kidney following MM-398.

Irinotecan is metabolised to SN-38 via carboxylesterase-mediated cleavage in the liver and intestines and CYP3A4 to APC and NPC, which can be converted to SN-38 by carboxylesterases. The active metabolite SN-38 is further metabolised to the inactive SN-38 glucuronide via UGT1A isoforms in the liver and subsequent deglucuronidation by intestinal β-glucuronidase. Faecal excretion, of which a major part is represented by biliary excretion, was shown to be the major route for excretion of MM-398-derived radioactivity in rats.

The doses chosen for the studies are appropriate to characterize the toxicity of Onivyde and to make proper hazard evaluations and risk assessments.

Single dose and repeat-dose toxicity studies with MM-398 in mice, rats and dogs have identified the GI system and bone marrow as main target organs for toxicity. The severity of effects was dose related and reversible. The no observed adverse effect level (NOAEL) in rats and dogs following 90 min intravenous infusion of ONIVYDE once every 3 weeks for 18 weeks was at least 180 mg/m2. GI toxicity is a well-known adverse effect of irinotecan. Diarrhoea has been included as an important identified risk in the RMP for Onyvide, and reflected in sections 4.4 and 4.8 of the proposed SmPC. Bone marrow adverse effects have also previously been reported for irinotecan. Leukopenia/neutropenia and anaemia are included as important identified risks in the RMP for Onyvide, and have been included under sections 4.4 and 4.8 of the proposed SmPC.

In addition, adverse effects have been observed in lymphoid organs, liver, and male and female reproductive organs. Some of the effects on lymphoid organs may be related to stress, while others appear to be secondary to bone marrow toxicity. The inclusion of Leukopenia as an important identified risk in the RMP for Onyvide is considered to cover the effects on lymphoid organs observed in the non-clinical repeat dose toxicity studies. The observed EMH in repeat dose toxicology studies is most likely a compensatory effect secondary to bone marrow toxicity and is not considered to be an adverse finding.

Histiocytosis in multiple organs of animals administered MM-398 as well as in animals given vehicle control (empty liposome) reflects phagocytosis of the liposome and, in the absence of other associated toxicity, is not considered an adverse finding. Nevertheless, the Applicant was asked to discuss findings of non-reversible accumulation of foamy histiocytes in the lungs of control dogs and presence of foamy histiocytes in the spleen of recovery animals. The Applicant clarified that foamy histiocytes in the lungs were observed also in dogs treated with unencapsulated irinotecan, and that interstitial pulmonary disease (IPD) has been reported in patients treated with non-liposomal irinotecan. For that reason, ILD is included as an important potential risk in the RMP for Onivyde. With regard to foamy histiocytes in the spleen, this was concluded to be of negligible clinical relevance.

All major toxicity findings, and the vehicle-associated histiocytosis, were fully or partially reversible upon cessation of treatment. Histiocytosis in the absence of signs of other toxicity (e.g. necrosis, inflammation) is not considered to be an adverse finding.

Unencapsulated irinotecan (CPT-11), included for comparison in these studies, showed a similar though less pronounced toxicity profile. The reason for the more prominent toxicity seen with MM-398 is most likely the considerably higher exposures achieved with this formulation.

Non liposomal irinotecan and SN 38 were genotoxic in vitro in the chromosomal aberration test on CHO cells as well as in the in vivo micronucleus test in mice. However, in other studies with irinotecan they have been shown to be devoid of any mutagenic potential in the Ames test. For non liposomal irinotecan, in rats treated once a week during 13 weeks at the maximum dose of 150 mg/m², no treatment related tumours were reported 91 weeks after the end of treatment. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Due to its mechanism of action, irinotecan is considered a potential carcinogen (see section 5.3 of the SmPC).

Non liposomal irinotecan was teratogenic in rats and rabbits at doses below the human therapeutic dose. In rats, pups born from treated animals and having external abnormalities showed a decrease in fertility. This was not seen in morphologically normal pups. In pregnant rats there was a decrease in placental weight and in the offspring a decrease in foetal viability and increase in behavioural abnormalities.

Non liposomal irinotecan caused atrophy of male reproductive organs both in rats and dogs after multiple daily doses of 20 mg/kg and 0.4 mg/kg, respectively. These effects were reversible upon cessation of treatment.

Adequate information has been reflected in sections 4.6 and 5.3 of the SmPC for Onivyde.

According to the distribution studies, MM-398 is distributed to the uvea. There is also UV absorbance at 360nm. The Applicant provided clinical data, emphasizing the lack of phototoxic events with unencapsulated irinotecan as well as the absence of such findings in the NAPOLI study. Based on this data it is concluded that there is no specific concern regarding a risk for photosensitivity reactions associated with treatment using MM-398.

2.3.7. Conclusion on the non-clinical aspects

No new toxicity issues have been identified with the liposomal formulation of irinotecan. Non-clinical GI and bone marrow toxicity of irinotecan are known to translate to the clinic. Both are included as important identified risks in the RMP for Onivyde.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects +	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Bioanalytical Methods	Bioanalytical methods for human studies across multiple studies	5.3.1.4	To validate measurements of concentration of analytes including total irinotecan, encapsulated irinotecan, SN-38, SN-38G, 5-FU, and the interference among the measurements	NA	NA	NA	NA	NA	Complete; Bioanalytical Methods Reports
PK	Human Plasma Protein Binding to Nanoliposomal Irinotecan (Nal-IRI; MM-398, PEP02)	5.3.2.1	To determine the levels of protein binding and identify the major binding proteins associated with the MM-398 liposomes	NA	NA	NA	NA	NA	Complete; Protein Binding Report
Safety and PK	PEP0201	5.3.3.2	Safety, MTD, PK and preliminary efficacy	Phase 1, open label, multi center, dose escalation study; non-comparative	MM-398 (PEP02); 60, 120, 180 mg/m^2 q3w; IV	11	Solid tumors	Maximum of 6 cycles	Complete; Legacy Study Report
Safety and PK	PEP0202	5.3.3.2	Phase 1: To define the recommended phase II dose of MM-398 (PEP02) in combination with cisplatin, safety, PK and pharmacogenetics Phase 2: To determine response rates of MM-398 single-agent and in combination with cisplatin, duration of tumor response, disease control rate, progression-free survival, the overall survival, tumor marker response, safety, PK, pharmacogenetics and QoI	Phase 1/2 study; Phase 1: dose escalation study Phase 2: MM-398 vs. MM-398 plus cisplatin	Phase 1: MM-398 in combination with cisplatin; MM-398: 60 and 80 mg/m^{2}q3w IV Cisplatin: 60 mg/m^{2}q3w IV Phase 2: not performed	6	Metastatic cervical cancer	Maximum of 6 cycles	Complete; Legacy Study Report
Safety and PK	PEP0203	5.3.3.2	To determine the recommended phase 2 dose of MM-398 (PEP02) in combination with 5-FU/LV, safety, PK, preliminary efficacy and pharmacogenetics	Phase 1, open label, multi center, dose escalation study of MM-398 in combination with 5-FU/LV; non-comparative	MM-398: 60, 80, 100, 120 mg/m^2 q3w IV 5-FU: 2000 mg/m^2 on Day 1 and 8 q3w IV Leucovorin: 200 mg/m^2 on Day 1 and 8 q3w IV	16	Solid tumors	Maximum of 6 cycles	Complete; Legacy Study Report
Safety and PK	PIST-CRC	5.3.3.2	To determine the MTD of MM-398, safety, PK, tumor response and pharmacogenetics	Phase 1, open label, dose escalation study; non-comparative	MM-398: 80, 90 and 100 mg/m^2 q2w IV	18	Colorectal cancer	Until disease progression	Complete; Legacy Study Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects +	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	Population Pharmacokinetics and Exposure-Response Analysis of MM-398	5.3.3.5	•To develop population pharmacokinetic models to describe the PK profiles for MM 398 (total irinotecan and SN-38) in patients with advanced solid cancer; • To evaluate the impact of intrinsic (body size, demographics, lab measurements of hepatic and renal functions, and UGT1A1*28 homozygosity) and extrinsic factors (co-administration with 5-FU, and manufacturing site) on the PK of MM 398; • To evaluate the relationship between exposure and safety endpoints of interest of diarrhea, neutropenia, and anemia; and • To evaluate the relationship between exposure and efficacy endpoints	Cross-study analysis	MM-398: multiple doses IV	355	Cancer patients	NA	Population Pharmacokinetics and Exposure-Response Analysis Report
Feasibility and safety	MM-398-01-01-02 (CITS)	5.3.4.2	Pilot phase: Evaluate the feasibility of Fe-MRI to identify tumor associated macrophages; measure tumor levels of irinotecan and SN-38; estimate the correlation between PD markers and administration of MM-398 Expansion phase: Further investigate the feasibility of ferumoxytol (FMX) quantitation in tumor lesions; characterize the relationship between FMX tumor uptake & tumor response to MM-398 All phases: Safety; tumor response and PK	Open label Phase 1 study; non-comparative	Ferumoxytol: single dose of 5 mg/kg (not to exceed 510 mg total) IV MM-398: 80 mg/m²q2w IV	13	Solid tumors	Until disease progression	Ongoing; Interim Synopsis Report
Efficacy and Safety	MM-398-07-03-01 (Napoli 1)	5.3.5.1	OS, PFS, TTF, ORR, tumor marker response, QoL, safety and PK	Open label, randomized, Phase 3 study of MM-398, with or without 5-FU/LV, vs. 5-FU/LV alone; active control (5-FU/LV)	Arm A: MM-398 120 mg/m² q3w Arm C: MM-398 80 mg/m² + 5-FU 2400 mg/m² + LV 400 mg/m² q2w IV	417	Metastatic pancreatic cancer	Until progression	Complete; eCTD Study Report
Efficacy and Safety	PEP0206	5.3.5.1	Tumor response, PFS, duration of response, time to progression, TTF, disease control rate, 1 year OS, OS, safety, dose intensity, PK, pharmacogenetics	Open label, randomized, Phase 2 study; non comparative	Arm 1: MM-398 120 mg/m² q3w IV Arm 2: Irinotecan 300 mg/m² q3w IV Arm 3: Docetaxel 75 mg/m² q3w IV	132	Gastric & GEJ cancer	Until progression	Complete; Legacy Study Report
Efficacy and Safety	PEP0208	5.3.5.2	3 month survival rate, objective tumor response, PFS, duration of response, OS, tumor marker response, clinical benefit response, safety and pharmacogenetics	Open label, single arm, Phase 2 multicenter study; non comparative	MM-398 120 mg/m² q3w IV	40	Metastatic pancreatic cancer	Until progression	Complete; Legacy Study Report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects +	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	PEPCOL	5.4	Objective response rate, safety, PFS, OS, QoL and pharmacogenetics	Open label, randomized, multicenter Phase 2 study comparing a combination of MM-398, 5-FU/LV & bevacizumab vs. 5-FU/LV, irinotecan and bevacizumab	Arm 1 Bevacizumab 5 mg/kg, irinotecan 180 mg/m^2, LV 400 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU continuous infusion 2400 mg/m^2, q2w IV OR Day 1: Bevacizumab 5 mg/kg, irinotecan 90 mg/m^2, LV 400 mg/m^2, 5-FU continuous infusion 2400 mg/m^2 Day 3: irinotecan 90 mg/m^2 Q2w IV	55	Colorectal cancer	Until disease progression	Ongoing; Published Literature

+ Number of patients enrolled in MM-398 studies as of October 24, 2014

2.4.2. Pharmacokinetics

The plasma pharmacokinetics of total irinotecan and total SN 38 were evaluated in patients with cancer who received Onivyde, as a single agent or as part of combination chemotherapy, at doses between 60 and 180 mg/m^2.

Bioanalysis

LC/MS/MS methods for determination of total irinotecan (encapsulated+un-encapsulated), the active metabolite SN-38 and the SN-38-glucuronide have been developed and pre-validated. A validated method for determination of liposome-encapsulated irinotecan and separation of un-encapsulated irinotecan is also reported.

Absorption

N/A

Distribution

Plasma exposure of total (encapsulated+un-encapsulated) irinotecan consists almost only of encapsulated irinotecan (the encapsulated form was 95.4% of the total and the un-encapsulated irinotecan, while not measured directly, was estimated to be <5%).

The volume of distribution (Vd) estimates in patients administered with MM-398 were approximately 2 L/m^2 (see table below).

The pharmacokinetic parameters of total irinotecan and SN 38 analytes, following the administration of Onivyde 80 mg/m^2 are presented in the table below.

Table 6: Summary of mean (±standard deviation) total irinotecan and total SN 38

Analyte	PK parameters	Unit	ONIVYDE geomean (95% CI)[a] 80 mg/m²(n=353)[b]	Non-liposomal irinotecan mean (SD) 125 mg/m² (n=99)[c]
Total irinotecan	AUC	h ng/ml	919228 (845653-999204)	10529 (3786)
	C_{max}	ng/ml	28353 (27761-28958)	1492 (452)
	Clearance (CL)	l/h/m2	0.087 (0.080-0.094)	13.0 (5.6)
	Volume (V)	l/m2	2.6 (2.6-2.7)	138 (60.9)
	$t_{1/2\ effective}$	h	20.8 (19.4-22.3)	6.07 (1.19)
Total SN-38	AUC	h ng/ml	341 (326-358)	267 (115)
	C_{max}	ng/ml	3.0 (2.9-3.1)	27.8 (11.6)
	$t_{1/2\ effective}$	h	40.9 (39.8-42.0)	11.7 (4.29)

SD= standard deviation
AUC= area under the plasma concentration curve (extrapolated to infinity for ONIVYDE and AUC_{24h} for non-liposomal irinotecan)
C_{max}= maximum plasma concentration
$t_{1/2\ effective}$= effective half-lives
[a]Values are estimated from population PK analysis
[b]N=353 refers to all the subjects included in the population PK analysis
[c]Values are obtained from published data [Schaaf LJ et al. *Clin Cancer Res*. 2006 Jun 15;12:3782-91]

The plasma protein binding of Onivyde is negligible (< 0.44% of total irinotecan in Onivyde). The plasma protein binding of non-liposomal irinotecan is moderate (30% to 68%), and SN 38 is highly bound to human plasma proteins (approximately 95%).

Table 7: In vitro plasma protein binding of MM-398

Method	Sample number	N	Mean (95%CI) Protein Bound (µg/µmol Phospholipid)	Mean (95%CI) Protein Bound (µg/mg CPT-11)
size-exclusion chromatography	1780	15	0.76 (-0.69, 2.21)	1.23 (-1.20, 3.66)
affinity capture on the magnetic carrier coated with anti-poly (ethylene glycol) antibody	1780	9	-1.79 (-4.66, 1.09)	-4.48 (-11.68, 2.73)
	1781	9	-1.32 (-4.44, 1.81)	-3.17 (-10.70, 4.36)
	1782	9	-3.33 (-6.18, -0.48)	-8.90 (-16.51, -1.29)
	Positive control	9	166.16 (132.8, 199.5)	NA

Source: MM-398 Protein Binding Report, Table 6, Table 11

Elimination

The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes. *In vitro* studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC) do not inhibit cytochrome P-450 isozymes. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite.

The systemic exposure of the active metabolite SN-38, following single iv infusions of 60-120 mg/m2 was <0.1% of the exposure of total irinotecan.

Preliminary data on systemic and local concentration in the tumour 72h post a single iv infusion of 80 mg/m2 Onivyde, show that the local concentration in the tumour of SN-38 is about 4-fold higher compared to the plasma level of SN-38 (Study MM-398-01-01-02). The plasma level of total irinotecan is about double as high as the level in the tumour.

SN-38 reached its C_{max} after about 21h following treatment with Onivyde, its $t_{1/2}$ varied between *ca* 60-75h.

UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Genotype frequency of genetic polymorphism of the UGT1A1 family has been performed for UGT1A1*28, *93 (UGT1A1 G3156A), *6, *27, *7 (UGT1A1T-3279G), *29, UGT1A9*22 (*1b) and DPYD*2A. No correlation between the different genes studied and PK of irinotecan/SN-38 were reported.

In the population pharmacokinetic analysis in patients with ONIVYDE using the results of a subset with UGT1A1*28 genotypic testing, in which the analysis adjusted for the lower dose administered to patients homozygous for the UGT1A1*28 allele, patients homozygous (N=14) and non-homozygous (N=244) for this allele had total SN-38 average steady-state concentrations of 1.06 and 0.95 ng/ml, respectively.

Both irinotecan and SN-38 are known to exist in an active lactone form and an inactive carboxylate form.

The half-life ($t_{1/2}$) of total irinotecan following infusion of Onivyde varies between 12–55 h. In study PEP0206, the $t_{1/2}$ was calculated to 21 and 8 h following infusion with Onivyde and the commercial available irinotecan, respectively

The urinary excretion of non-liposomal irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2) (see section 5.2 of the SmPC).

Unchanged drug was the major excretion product in both urine and faeces (Table xxx).

Table 8: **Overview of excretion pattern (percentage of radioactive dose) in urine and faeces following an iv dose of 125 mg/m^2 of 14C-irinotecan to patients diagnosed with solid tumours**

Excretion Matrix	Drug or Metabolite Name				
	SN-38G (M3)	NPC (M9)	APC (M11)	CPT-11	SN-38 (M17)
All patients (n = 7)					
Urine	3.02 ± 0.77	0.14 ± 0.08	2.23 ± 1.53	22.40 ± 5.50	0.43 ± 0.12
Feces	0.27 ± 0.17	1.36 ± 0.94	8.29 ± 2.95	32.31 ± 4.47	8.24 ± 2.51
Total	3.29	1.50	10.5	54.7	8.67

Dose proportionality and time dependencies

Dose-proportionality

In the literature, the exposure of irinotecan is reported to increase in a dose-proportional manner following iv infusion of a sterile solution (Mathijssen *et al*, 2001).

Following single doses of Onivyde 60-180 mg/m^2, a dose proportional increase in exposure of total irinotecan was observed. C_{max} of SN-38 increased dose-proportionally, but AUC increased less than dose-proportional.

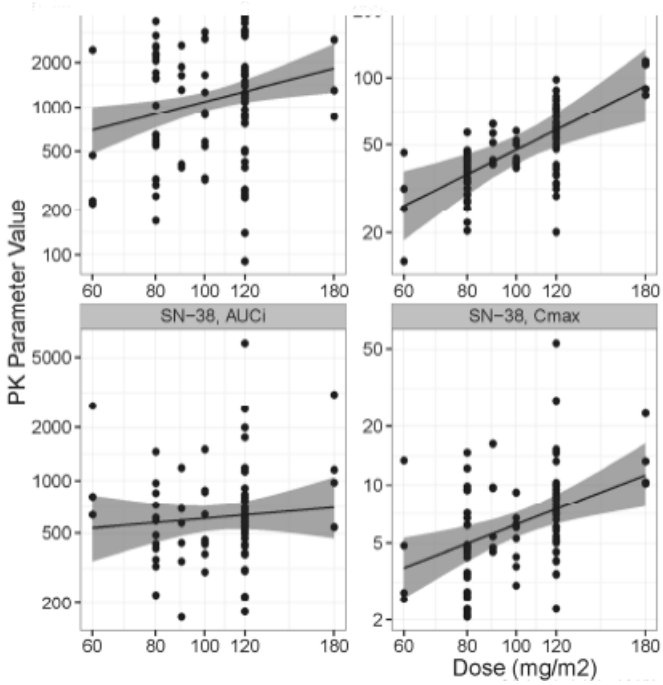


Figure 3: Exposure of total irinotecan and SN-38 across studies treated with Onivyde 60-180 mg/m²

Time-dependency

No PK following repeated dosing with Onivyde has been studied.

Special populations

Impaired renal function

No dedicated pharmacokinetic study has been conducted in patients with renal impairment. In a population pharmacokinetic analysis, mild-to-moderate renal impairment had no effect on the exposure of total SN-38 after adjusting for BSA. The analysis included 68 patients with moderate (CLcr 30 - 59 mL/min), 147 patients with mild (CLcr 60 - 89 ml/min) renal impairment, and 135 patients with normal renal function (CLcr > 90 ml/min). There was insufficient data in patients with severe renal impairment (CLcr < 30 ml/min) to assess its effect on pharmacokinetics (see sections 4.2, 4.4 and 5.2 of the SmPC).

Impaired hepatic function

No dedicated pharmacokinetic study has been conducted in patients with hepatic impairment. In a population pharmacokinetic analysis, patients with baseline total bilirubin concentrations of 1-2 mg/dl (n=19) had average steady state concentrations for total SN-38 that were increased by 37% (0.98 [95%CI: 0.94 - 1.02] and 1.29 [95%CI: 1.11 - 1.5] ng/ml, respectively) compared to patients with baseline bilirubin concentrations of < 1 mg/dl (n=329); however, there was no effect of elevated ALT/AST concentrations on total SN-38 concentrations. No data are available in patients with total bilirubin more than 2 times the ULN (see sections 4.2, 4.4 and 5.2 of the SmPC).

Race

The population pharmacokinetic analysis suggest that Asians have 56 % lower total irinotecan average steady state concentration (3.93 [95 %CI: 3.68- 4.2] and 1.74 [95 %CI: 1.58-1.93] mg/l, respectively) and 8 % higher

total SN-38 average steady state concentration (0.97 [95 %CI: 0.92-1.03] and 1.05 [95 %CI: 0.98-1.11] ng/ml, respectively) than Caucasians.

Gender

Gender was found as a covariate impacting the SN-38 exposure. Higher SN-38 concentrations were observed in females than in males: SN-38 Converted Cavg were 0.8 ng/mL in females and 0.7 ng/mL. The Applicant claimed this observation is likely confounded by the interaction between sex and BSA, as females had lower BSA compared to males (mean BSA of 1.8 m2 in males and 1.6 m2 in females).

The effect of gender was not reported for un-encapsulated irinotecan.

Weight

In the PPK analysis, there was no association between BSA and race-adjusted concentrations for irinotecan. For SN 38, increased BSA was associated with lower SN-38 exposure (despite higher doses administered in patients with higher BSA).

In the clinical studies, Onivyde was administered using BSA-based dosing. The proposed BSA-based dosing was further supported through simulations. Comparison of the simulated pharmacokinetic parameters for irinotecan and SN-38 was evaluated by simulating C_{avg} and C_{max} if patients had been dosed with either a BSA-based dose of 80mg/m^2 or an equivalent fixed dose of 135.73 mg (i.e., the nominal dose for a subject with median BSA). The analysis showed reduced variability in SN-38 C_{max} with BSA-based dosing (in line with the results from the covariate analysis). The interquartile range for SN-38 C_{max} was 74% with flat dose and 57% with BSA-based dose.

Elderly

The PopPK suggests that the effect of the covariate “age” had no clinically meaningful effect on the exposure of irinotecan and SN-38. No effect of age has been reported for un-encapsulated irinotecan.

Intra- and inter-individual variability

Variability of pharmacokinetic parameters was assessed in the popPK analysis. Total irinotecan was modelled as a two-compartmental model with central clearance inter-individual variability (IIV) of 88% and central volume IIV of 49%. SN-38 was modelled as a one-compartmental model with central clearance IIV of 55%.

The standard deviation of residual error was 0.30 and 0.16, for irinotecan and SN-38, respectively.

High inter-individual variability, up to 75%, was seen in total exposure following 90-min iv infusions of Onivyde.

PK in target population

The PK following treatment with Onivyde has been studied in patients with solid tumours including patients with the proposed indication metastatic pancreatic cancer. The exposure of total irinotecan, both Cmax and AUC, were much higher following an iv infusion of 120 mg/m^2 Onivyde compared to an infusion of 300 mg/m^2 with the un-encapsulated irinotecan. The C_{max} of SN-38 was about 5-fold higher after infusion with the commercial formulation compared to with Onivyde although the dose was just 2.5-fold higher. The total exposure of SN-38 after treatment with the un-encapsulated irinotecan was about half compared to with Onivyde.

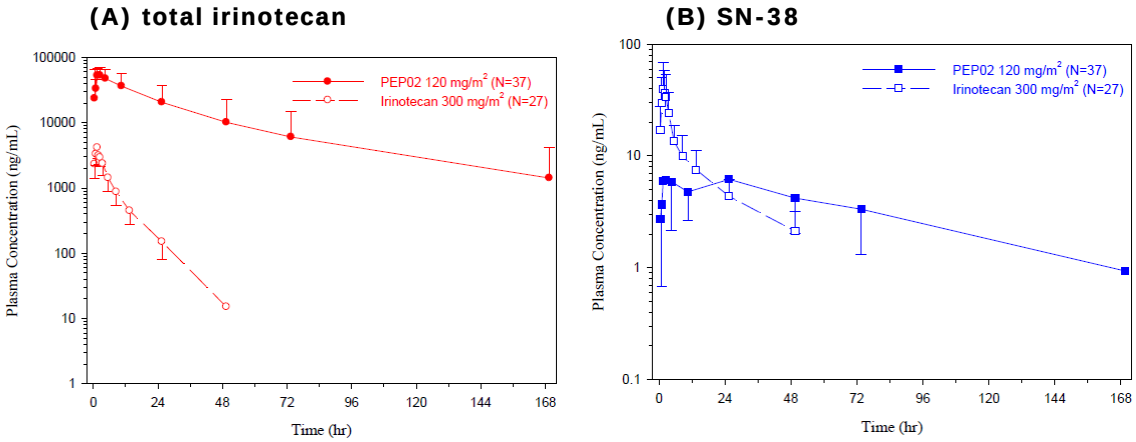


Figure 4: Mean plasma concentrations of total irionotectan (A) and SN-38 (B) versus time following iv infusions of 120 and 300 mg/m2 of Onivyde and commercial irinotecan, respectively, to patients

Table 9: PK of total irinotecan and SN-38 following 90- and 60-min iv infusion of Onivyde (120 mg/m²) and commercial irinotecan (300 mg/m²), respectively, in patients

	Onivyde 120 mg/m²	Irinotecan 300 mg/m²
$C_{max,\ irinotecan}$ (µg/ml)	61	4.3
$C_{max,\ SN-38}$ (µg/ml)	0.009	0.044
$AUC_{0-\infty,\ irinotecan}$ (µg/ml.h)	1812	26
$AUC_{0-\infty,\ SN-38}$ (ng/ml.h)	0.9	0.4
$t_{1/2,\ irinotecan}$ (h)	21	8
$t_{1/2,\ SN-38}$ (h)	89	23

Population pharmacokinetics analysis

PPK analysis was conducted with the objectives of describing the PK profiles of total irinotecan (CPT11) and the active metabolite SN-38, and to evaluate the impact of intrinsic and extrinsic factors.

Data from six studies were used to build the model, and included 1800 factors samples (355 subjects) and 1773 SN-38 samples (353 subjects).

Methods

Parameter estimations were performed using NONMEM version 7.3, with default setting FOCEI with Laplacian method. Measured concentrations below the limit of quantification were modelled as mixed continuous and categorical method (M3 method; Bergstrand & Karlsson, 2009). The M3 method was implemented using log-transformed values of concentration and the Laplacian estimation method.

The covariates investigated for influence on the pharmacokinetic parameters of irinotecan included BSA and CL on central volume and on clearance, respectively. Other covariates explored were:

- BSA: body surface area;
- Measurements of hepatic function: AST, ALT, albumin, liver metastasis status, bilirubin, UGT1A1*28);

- Renal function: creatinine clearance;
- Demographics: sex, age, race;
- External functions: co-administration with 5-FU and manufacturing site.

The covariate model was similar for SN-38, with the exception that the estimated clearance and volume of distribution of irinotecan, and manufacturing site were added as to the SN-38 input flux.

Covariate relationships were investigated using a full-covariate method (Gastonguay 2011). Highly correlated covariates were evaluated, but only the most significant was retained and considered for further evaluation.

Results

The final model for irinotecan was a two-compartment model. The final model for SN-38 pharmacokinetic was a one-compartmental model with two input fluxes: 1) initial amount administered with Onivyde as an impurity within liposomes, and 2) in vivo conversion of irinotecan released from Onivyde. Final estimated parameters of irinotecan and SN-38 are shown in Table and Table .

Table 10: Final estimated parameters of irinotecan pharmacokinetics (no units were provided in the PPK analysis report)

Parameter	Estimated Values (final model)	Estimated Values from Bootstrapping (N=497)		
		Median	2.5%	97.5%
Objective Function	-1196.3895	-1238.53	-2100.37	-506.661
Fixed effects				
Volume (V1)	4.498	4.498	4.1604	4.6668
Clearance (CL)	15.44	15.438	11.705	21.403
Q	0.05413	0.054	0.0254	0.6766
V2	0.06817	0.068	0.0524	43.9466
V1-BSA	0.3749	0.375	0.2004	0.534
CL-(race==Asian)	0.7172	0.715	0.5704	0.8842
CL-(treatment contains 5FU)	0.0331	0.029	-0.0982	0.1986
CL-(manufacturing site)	0.04327	0.037	-0.218	0.2572
CL-(liver metastasis)	-0.03806	-0.031	-0.228	0.1456
CL-(ALT)	-0.03428	-0.343	-0.6404	-0.0492
CL-(Albumin)	-1.731	-1.731	-3.5044	-0.5054
CL-(Bilirubin)	0.1716	0.172	-0.1128	0.5266
CL-(Creatinine Clearance)	0.002168	0.002	-0.001	0.004
Random effects				
Omega(V1)	0.2388	0.057	0.015	0.0966
Omega(CL)	0.7712	0.127	0.0474	0.2378
Omega(V1-CL)(off-diagonal)	0.6869	0.596	0.377	1.043
Residuals				
Standard deviation of residual error	0.3012	0.301	0.2008	0.3856

Table 11: Final estimated parameters of SN-38 pharmacokinetics (no units were provided in the PPK analysis report)

Parameter Name	Estimated Values (Final Model)	Estimated Values from Bootstrap (n=499)		
		Median	2.5%	97.5%
Objective Function	-2863.2540	-2897.94	-3191.04	-2560.65
Fixed effects				
Clearance (CL)	13.3	13.27	12.0126	14.0213
K13 conversion flux from CPT11	0.0683	0.07	0.064	0.077
Impurity (IMP)	0.0541	0.054	0.051	0.061
CL-(race==Asian)	-0.0733	-0.071	-0.1312	-0.00835
CL-(UGT1A1*28==homozygote)	-0.00259	-0.002	-0.003	-0.002
CL-(treatment contains 5FU)	0.00272	0.003	0.001	0.005
K13-(manufacturing site)	0.000557	0.001	0.001	0.001
CL-(liver metastasis)	-0.00551	-0.004	-0.008	-0.00045
CL-(ALT)	-0.000124	0	0	0
CL-(Albumin)	-0.0403	-0.023	-0.046	0.001
CL-(Bilirubin)	-0.571	-0.545	-0.95955	-0.22785
CL-(Creatinine Clearance)	-0.145	-0.11	-0.21	-0.00625
K13-CPT11clearance	1.97	1.966	1.7518	2.20155
K13-CPT11volume	-0.0552	-0.042	-0.083	0.011
K13-BSA	-1.24	-1.195	-1.733	-0.70485
Random effects				
Omega(CL)	0.2993	0.092	0.076	0.107
Omega(CL-K13) (off diagonal)	-0.1974	-0.013	-0.021	0.01555
Omega(K13)	0.4637	0.224	0.18145	0.275
Omega(CL-impurity) (off diagonal)	-0.0811	-0.007	-0.015	0
K13-impurity (off diagonal)	0.2512	0.091	0.0239	0.14955
Omega(Impurity)	0.795	0.61	0.462	0.67065
Residuals				
Standard deviation of residual error	0.156	0.157	0.139	0.17565

Pharmacokinetic interaction studies

No formal drug/drug interaction studies were performed. Information about drug interactions with Onivyde is referenced from the published scientific literature for nonliposomal irinotecan.

Strong CYP3A4 inducers

Patients receiving concomitant non-liposomal irinotecan and CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital or carbamazepine have substantially reduced exposure to irinotecan (AUC reduction by 12% with St John's wort, 57%-79% with phenytoin, phenobarbital, or carbamazepine) and SN-38 (AUC reduction by 42% with St John's wort, 36%-92% with phenytoin phenobarbital, or carbamazepine).

Strong CYP3A4 inhibitors and UGT1A1 inhibitors

Patients receiving concomitant non-liposomal irinotecan and ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased SN-38 exposure by 109 %. Therefore, co-administration of Onivyde with other inhibitors of CYP3A4 (e.g. grapefruit juice, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) may increase systemic exposure of Onivyde.

In study MM-398-07-03-01(NAPOLI 1) Onivyde was administered in combination with 5-Fluorouracil and Leucovorin. Co-administration of Onivyde with 5-fluorouracil/leucovorin does not alter the pharmacokinetics of Onivyde based on the population pharmacokinetic analysis.

2.4.3. Pharmacodynamics

Mechanism of action

The active substance of Onivyde is irinotecan which is encapsulated in long-circulating liposomes. The drug product liposome is a small unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state, as sucrosofate salt.

Onivyde has been shown to extend circulation of irinotecan and prolong the duration of active therapy at the site of tumour cells to inhibit tumour growth.

Irinotecan (irinotecan hydrochloride trihydrate) is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan is a semi-synthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata.* Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I - DNA complex and prevent religation of these single-strand breaks. Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38, which is formed from irinotecan primarily by liver carboxylesterase enzymes. The SN-38 metabolite is approximately 1000 times more potent than irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumour cell lines. The precise contribution of SN-38 to the activity of IRINOTECAN in humans has not been completely defined. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. An acidic pH promotes the formation of the lactone whereas a basic pH favours the hydroxy acid anion form.

Primary and Secondary pharmacology

No primary or secondary pharmacodynamics studies were performed. Topoisomerase I is the exclusive target for the API of MM-398, irinotecan.

PKPD relationship
The PK is considered descriptive in the current submission. However, the exposure-efficacy analysis indicates that increased exposure to irinotecan and SN-38 are associated with longer overall survival and progression-free survival.

Higher irinotecan exposures were associated to a higher probability of incidence and severity of diarrhoea and higher SN-38 exposures with higher probability and severity of neutropenia, and with higher probability of anaemia.

2.4.4. Discussion on clinical pharmacology

Onivyde is a liposomal formulation of irinotecan with different pharmacokinetic properties compared to non-liposomal irinotecan. The dose concentration and strength are different in comparison to non-liposomal irinotecans. Onivyde is not equivalent to other non-liposomal irinotecan formulations and should not be interchanged.

Once released from the liposome-based particles, irinotecan is hypothesized to follow the same excretion route as the un-encapsulated irinotecan. The Applicant has therefore not further characterised the elimination of irinotecan, drug-drug interactions and PK of irinotecan in special populations.

The PK following treatment with Onivyde has been studied in patients with solid tumours including patients with the proposed indication of metastatic pancreatic cancer. Analytes measured in clinical trials include total irinotecan (which includes encapsulated and un-encapsulated irinotecan), its active metabolite SN-38 and its inactive glucuronidated form SN-38G. In one study (PEP0201), encapsulated irinotecan and total irinotecan were directly measured.

Irinotecan released from liposome encapsulation follows a similar metabolic pathway reported with non-liposomal irinotecan. Liposome encapsulation of irinotecan extends circulation and limits distribution relative to those of the non-liposomal irinotecan. The small volume of distribution suggests that Onivyde is largely confined to vascular fluid (see section 5.2 of the SmPC).

The disposition of Onivyde and non-liposomal irinotecan has not been fully elucidated in humans.

Linear PK of irinotecan is reported following iv infusion with un-encapsulated irinotecan solutions as well as following single doses with Onivyde (60-180 mg/m^2)**.**

The systemic exposure of total irinotecan (C_{max} and AUC) was much higher following an iv infusion of 120 mg/m^2 Onivyde compared to an infusion of 300 mg/m^2 with the un-encapsulated irinotecan. A smaller Vss can be expected for a liposomal formulation. The C_{max} of SN-38 was about 5-fold higher with the commercial formulation compared to with Onivyde although the dose was just 2.5-fold higher. The total exposure of SN-38 after the commercial formulation was about half of exposure compared to after Onivyde.

Preliminary data on local concentration of irinotecan and SN-38 in tumours, following a single dose of 80 mg/m^2 Onivyde have been presented. Data on systemic and local concentration in the tumour 72h post a single iv infusion of 80 mg/m^2 Onivyde, show that the local concentration in the tumour of SN-38 is about 4-fold higher compared to the plasma level of SN-38 (the plasma level of total irinotecan is about double as high as the level in the tumour). However, the same comparison of tumour concentration and plasma levels following treatment with the un-encapsulated irinotecan is unknown.

No correlation between the different genes of the UGT1A1 family studied and PK of irinotecan/SN-38 were reported however, the data set was relatively limited and it is uncertain whether the study was too small to detect a difference in SN-38 exposure.

The PPK analysis appears to have been reasonably well performed.

No *in vivo* data following repeated dosing have been provided. But considering the long $t_{1/2}$ for SN-38 and the high inter-individual variability, patients might still be exposed at the time for next dose. Simulation of expected steady state exposure using single dose data will not predict any potential time-dependency in the PK. Patients have been repeatedly dosed and efficacy/safety data are available.

The systemic exposure of parent compound and/or metabolites are unknown in patients with different degrees of decreased renal function.

No data on influence of renal impairment on the PK of irinotecan have been presented however data from popPK analysis in patients with mild to moderate renal impairment indicated that no dose adjustment is recommended in those patients. Onivyde is not recommended for use in patients with severe renal impairment (CLcr < 30 ml/min) (see sections 4.2, 4.4 and 5.2 of the SmPC).

Neither has any dedicated study on PK of Onivyde in patients with different degrees of hepatic impairment been performed. Based on nonclinical data, an increased tissue distribution of 14C-irinotecan was seen in the rat, with higher levels in the liver, following administration with the liposomal compared to un-encapsulated solution for injection. The use of Onivyde should be avoided in patients with bilirubin > 2.0 mg/dl, or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 times upper limit of normal (ULN) or > 5 times ULN if liver metastasis is present (see sections 4.2, 4.4 and 5.2 of the SmPC).

The effect of hepatic impairment was explored. Higher baseline bilirubin was associated with higher SN-38 concentration following the administration of Onivyde. Albumin has a weak association to the exposure of total irinotecan. The Applicant claims no significant associations were observed between total irinotecan or SN-38 and ALT, AST, and liver metastasis status. However, a significant association between total irinotecan (Composite Cavg P=0.0001) and CPT 11 (Cavg P=0.0002) were found.

The association between UGT1A1*28 homozygosis to SN-38 exposure is evaluated stratified by race. While the effect of UGT1A1*28 homozygosis to SN-38 exposure was well-documented in Caucasians, the effect was less well-studied in Asians (Beutler1998), who have a relatively low incidence of UGT1A1*28 homozygosity. Data from Study MM-398-07-03-01 was consistent with the reduced incidence of UGT1A1*28 homozygosity in Asians compared to Caucasians: homozygosity was observed in 23/243 (9.5%) Caucasians, 2/129 (1.5%) Asians, and 2/26 (7.6%) other races. Because race was a strong covariate for CPT11, the evaluation of the association between the maximum concentration of SN-38 converted and UGT1A1*28 homozygous was performed separately for each race group. Caucasians UGT1A1*28 homozygous have higher level of SN-38 converted compared to non-homozygous Caucasians. However, this difference is not statistically significant.

Total and converted SN-38 Cavg is higher in Caucasian UGT1A1*28 homozygous due to reduced UGT1A1 enzymatic activity.

Co-administration of Onivyde with inducers of CYP3A4 may reduce systemic exposure of Onivyde. Onivyde should therefore not be administered with strong CYP3A4 enzyme inducers such as anticonvulsants (phenytoin, phenobarbital or carbamazepine), rifampin, rifabutin and St. John's wort unless there are no therapeutic alternatives. The appropriate starting dose for patients taking these anticonvulsants or other strong inducers has not been defined. Consideration should be given to substituting with non-enzyme inducing therapies at least 2 weeks prior to initiation of Onivyde therapy (see sections 4.4 and 4.5 of the SmPC).

Onivyde should not be administered with strong CYP3A4 enzyme inhibitors (e.g. grapefruit juice, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole). Strong CYP3A4 inhibitors should be discontinued at least one week prior to starting Onivyde therapy Onivyde should not be administered with strong UGT1A inhibitors (e.g. atazanavir, gemfibrozil, indinavir) unless there are no therapeutic alternatives (see sections 4.4 and 4.5 of the SmPC).

No interaction of Onivyde with other medicinal products is known.

The population pharmacokinetic analysis in patients aged 28 to 87 years, of whom 11% were ≥75 years suggests that age had no clinically meaningful effect on the exposure to irinotecan and SN 38 (see section 5.2 of the SmPC).

The population pharmacokinetic analysis in 196 male and 157 female patients suggests that gender had no clinically meaningful effect on the exposure to irinotecan and SN 38 after adjusting for body surface area (BSA).

2.4.5. Conclusions on clinical pharmacology

Irinotecan, the active substance of Onivyde, is a known active substance and overall the clinical pharmacology study package is considered sufficient. The PK of irinotecan/SN-38 following administration of Onivyde is considered descriptive.

2.5. Clinical efficacy

In support of the MAA, the applicant submitted one pivotal study (NAPOLI-1) and several supportive studies:

- PEP0208: phase II study of MM-398 in patients with metastatic pancreatic cancer previously treated with gemcitabine containing regimens (main supporting study)

- PEP0201: phase I, DLT and MTD in solid tumours

- PEP0202: phase I Dose Escalation Study Followed by Multi-National, Open-Label Randomized Phase II Study Evaluating the Efficacy and Tolerability of PEP02 with or without Cisplatin in Patients with Recurrent or Metastatic Squamous Carcinoma of the Uterine Cervix). Phase II not performed, study terminated.

- PEP0203: A multi-center, open-label phase I dose-escalation study of PEP02 in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in advanced solid tumours

- PIST-CRC: Phase I and Pharmacokinetic Study of Biweekly PEP02 (Liposome Irinotecan) in Patients with Metastatic Colorectal Cancer Refractory to First-line Oxaliplatin-based Chemotherapy

- PEP0206: A Randomized Phase II Study of PEP02, Irinotecan or Docetaxel as a Second Line Therapy in Patients with Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

- Interim results for ongoing studies **CITS** (MM-398-01-01-02; A Pilot Study in Patients Treated with MM-398 to Determine Tumour Drug Levels and to Evaluate the Feasibility of Ferumoxytol Magnetic Resonance Imaging to Measure Tumour Associated Macrophages and to Predict Patient Response to Treatment) and **PEPCOL**.

2.5.1. Dose response study(ies)

The single-agent MM-398 dose and schedule is based on results from a phase I dose escalating trial in advanced solid tumour patients (PEP0201). An accelerated titration design based on single-patient cohorts was used, starting from an initial MM-398 dose of 60 mg/m^2 (i.e 1/10 of the LD_{10} in mice) and escalated to 120 mg/m^2, 180 mg/m^2, 240 mg/m^2, 300 mg/m^2, and then subsequently escalated by 50 mg/m^2 with every 3 weeks infusions, until MTD was reached. Because the dose-toxicity correlation of irinotecan has been well established and documented, one to two patients cohorts were employed at the lower dose levels (up to 240 mg/m^2), followed by the three-patient cohort at the higher dose level (≥300 mg/m^2). A total of 11 patients were enrolled, including 1 patient at dose level 0 (60 mg/m2), 6 patients at dose level 1 (120 mg/m2) and 4 patients at dose level 2 (180 mg/m2). At this latter dose level, two out four patients had DLTs (i.e, grade 4 leucopenia and neutropenia lasting for longer than 3 days; grade 3 febrile neutropenia and grade 3 diarrhoea). The dose was then reduced (120 mg/m^2), and 1 patient among a total of 6 treated at this dose level experienced a DLT (Grade 3 infection). Therefore, based on these results 120 mg/m^2 was determined as MTD for MM-398 single agent (see further details in Section 2.1.3). Overall, 2 patients with advanced pancreatic cancer patients, both treated at 180 mg/m^2 dose level, were enrolled in study PEP0201, including 1 patient who achieved PR and 1 patient who reported PD.

This single-agent MM-398 regimen (120 mg/m^2 every 3 weeks) was then used in a phase II study, conducted in pancreatic cancer patients previously treated with gemcitabine (PEP0208), and based on its efficacy and safety results, the NAPOLI-1 study was originally designed and started enrolment.

The recommended dose of MM-398 in combination with 5-FU/LV when administered every 3 weeks was investigated in a dose-escalation study conducted in advanced solid tumours (PEP0203), with a MM-398 starting dose of 60 mg/m^2, subsequently escalated by increments of 20 mg/m^2 between dose levels. The 5-FU/LV was given on days 1 and 8 of each cycle at a fixed dose of 2,000 mg/m^2 and 200 mg/m^2, respectively. Overall, 16 patients were enrolled, including 3 patient at dose level 60 mg/m^2, 6 patients at dose level 80 mg/m^2, 5 patients at dose level 100 mg/m^2 and 2 patients at dose level 120 mg/m^2. Both patients treated with MM-398 120 mg/m^2 experienced DLTs (i.e, Grade III diarrhoea, Grade IV neutrophil count decreased, and Grade III infection in one patient and Grade III diarrhoea, Grade III leucopenia, and Grade III neutropenia in the other). Therefore, the dose level was decreased to 100 mg/m^2 and additional patients were included. Overall, two patients treated with MM-398 100 mg/m^2 experienced DLTs (i.e, fatigue, anaemia, white blood cell count decreased and neutrophil count decreased, all Grade III, in one patient; grade III anorexia, diarrhoea, abdominal pain, gastric ileus, febrile neutropenia and infection, and grade IV leucopenia, and neutropenia in the other patient). No DLTs were reported in the 6 patients treated at 80 mg/m^2 dose level that was considered the MTD of MM-398 in combination with 5-FU/LV given every 3 weeks. In total, 5 patients with advanced previously treated pancreatic cancer were enrolled in study PEP0203 across dose levels (1 at 60 mg/m^2, 3 at 80 mg/m^2, and 1 at 120 mg/m^2). Stable disease was reported in all patients, with the exception of 1 patient in which a PD was recorded after 2 cycles of MM-398 80 mg/m^2 treatment (see further details in Section 2.1.3). This schedule was not incorporated in the NAPOLI-1 study.

A combination arm of MM-398 + 5-FU/LV was only added when the NAPOLI-1 study had already started, based on the availability of acceptable safety data from an investigator initiated randomized phase II study, conducted by the GERCOR French cooperative group to compare MM-398 versus irinotecan in combination with 5-FU/LV as second line therapy in unresectable metastatic colorectal cancer patients (PEPCOL). In this study, the dose of MM-398 was 80 mg/m^2 administered every 2 weeks in combination with with 5-FU/LV at 2400/400 mg/ m^2.

2.5.2. Main study(ies)

NAPOLI -1: A randomized, open Label phase 3 study of MM-398, with or without 5-Fluorouracil and Leucovorin, versus 5-Fluorouracil and Leucovorin in patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy.

Methods

NAPOLI-1 is a 3-arm (initially 2-arm), open-label, randomized (1:1:1 ratio), active-controlled study.

Study Participants

Inclusion criteria

In order to be included in the study, patients were required to have:

1. Histologically or cytologically confirmed adenocarcinoma of exocrine pancreas

2. Documented metastatic disease; disease status was permitted to be measurable or non-measurable as defined by RECIST v. 1.1 guidelines

3. Documented disease progression after prior gemcitabine or gemcitabine-containing therapy, in locally advanced or metastatic setting. Examples of permitted therapies included, but were not limited to:

- Single agent gemcitabine
- Any one gemcitabine-based regimen, with or without maintenance gemcitabine
- Single agent gemcitabine to which a platinum agent, a fluoropyrimidine, or erlotinib was subsequently added
- Gemcitabine administered in the adjuvant setting, if disease recurrence occurred within 6 months of completing the adjuvant therapy

4. Karnofsky Performance Status (KPS) ≥ 70

5. Adequate bone marrow reserves as evidenced by:

- ANC > 1,500 cells/μL without the use of hematopoietic growth factors; and
- Platelet count > 100,000 cells/μL; and
- Haemoglobin > 9 g/dL (blood transfusions were permitted for patients with haemoglobin levels below 9 g/dL)

6. Adequate hepatic function as evidenced by:

- Serum total bilirubin within normal range for the institution (biliary drainage was allowed for biliary obstruction)
- Albumin levels ≥ 3.0 g/dL
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤ 5 x ULN was acceptable if liver metastases were present)

7. Adequate renal function as evidenced by a serum creatinine ≤ 1.5 x ULN

8. Normal ECG or ECG without any clinically significant findings

9. Recovered from the effects of any prior surgery, radiotherapy or other anti-neoplastic therapy

10. At least 18 years of age

11. Able to understand and sign an informed consent (or have a legal representative who is able to do so)

Exclusion criteria

Patients were required to meet all the inclusion criteria listed above and none of the following exclusion criteria:

1. Active CNS metastases (indicated by clinical symptoms, cerebral oedema, steroid requirement, or progressive disease); patient should have been off steroids for at least 28 days prior to starting study therapy

2. Clinically significant gastrointestinal disorder including hepatic disorders, bleeding, inflammation, occlusion, or diarrhoea > Grade 1

3. History of any second malignancy in the last 5 years; subjects with prior history of in-situ cancer or basal or squamous cell skin cancer were eligible. Subjects with other malignancies were eligible if they had been continuously disease free for at least 5 years.

4. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion.

5. NYHA Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure.

6. Active infection or an unexplained fever > 38.5°C during Screening visits or on the first scheduled day of dosing (at the discretion of the investigator, patients with tumour fever were permitted to be enrolled), which in the investigator's opinion might have compromised the patient's participation in the trial or affected the study outcome.

7. Known hypersensitivity to any of the components of Onivyde, other liposomal products, fluoropyrimidines, or leucovorin.

8. Investigational therapy administered within 4 weeks, or within a time interval less than at least 5 half-lives of the investigational agent, whichever was longer, prior to the first scheduled day of dosing in this study.

9. Any other medical or social condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results

10. Pregnant or breast feeding; females of child-bearing potential were required to test negative for pregnancy at the time of enrolment based on a urine or serum pregnancy test. Both male and female patients of reproductive potential were required to agree to use a reliable method of birth control, during the study and for 3 months following the last dose of study drug.

Treatments

MM-398, dose and mode of administration

- **Arm A** (MM-398):

Patients not homozygous for the UGT1A1*28 allele: 120 mg/m^2.

Patients homozygous for the UGT1A1*28 allele: initial dose of 80 mg/m^2 that could be increased in increments of 20 mg/m^2 (absent toxicity at the first administration) from cycle 2 onwards to a maximum dose of 120 mg/m^2.

MM-398 was administered every 3 weeks as IV infusion over 90 minutes.

- **Arm C** (MM-398 + 5-FU/LV):

Patients not homozygous for the UGT1A1*28 allele: 80 mg/m^2.

Patients homozygous for the UGT1A1*28 allele: initial dose of 60 mg/m^2 that could be increased (absent toxicity at the first administration) to a maximum dose of 80 mg/m^2.

MM-398 was administered every 2 weeks as an IV infusion over 90 minutes.

Reference therapy, dose and mode of administration

- **Arm B** (5-FU/LV): 5-FU 2,000 mg/m^2 by IV infusion over 24 hours (± 30 minutes) every week for 4 weeks (Study Days 1, 8, 15, and 22), followed by 2 weeks of rest in a 6-week cycle; LV 200 mg/m^2 of the *l* + *d* racemic form by IV infusion over 30 minutes every week for 4 weeks (Study Days 1, 8, 15, and 22) followed by 2 weeks of rest in a 6-week cycle.

Background 5FU/LV, dose and mode of administration

- Arm C (MM-398+5-FU/LV): 5-FU 2,400 mg/m^2 by IV infusion over 46 hours (± 60 minutes) every 2 weeks; LV 400 mg/m^2 of the *l* + *d* racemic form by IV infusion over 30 minutes every 2 weeks.

Anti-emetic premedication as per standard institutional practices was administered in all arms. Prophylactic atropine could be prescribed to patients treated with Onivyde who experienced acute cholinergic symptoms in the previous cycles.

In all arms, patients were to be treated until disease progression.

Objectives

Primary objective: To compare overall survival (OS) following treatment with MM-398, with or without 5-FU and leucovorin (5-FU/LV), versus 5-FU/LV, in patients with metastatic pancreatic cancer that had progressed on gemcitabine based therapy.

Secondary objective: To compare the following between the experimental and control arms: progression free survival (PFS), time to treatment failure (TTF), objective response rate (ORR), tumour marker response of CA19-9, clinical benefit response (CBR) rate, quality of life (QOL), safety and adverse event (AE) profiles, pharmacokinetic (PK) properties.

Outcomes/endpoints

Primary endpoint: OS defined as the time from the date of patient randomization to date of death or the date last known alive. For each patient who was not known to have died as of the cut-off date for a particular analysis, OS was censored for that analysis at the date of last contact prior to the data cut-off date.

Secondary endpoints:

- PFS defined as the time in months from the date of patient randomization to the date of death or disease progression, whichever occurred earlier.

- TTF defined by the occurrence of discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.

- ORR defined by the percentage of patients in the study population with a best overall response of Complete Response (CR) or Partial Response (PR) as assessed by the investigator. The best overall response was defined as the best response per RECIST (version 1.1) recorded from randomization until progression or end of study.

- Tumour marker response of CA19-9 defined as a decrease of ≥50% of CA19-9 in relation to the baseline level at least once during the treatment period. Only patients with elevated baseline CA19-9 value (> 30 U/mL), i.e. the TMRE population, were included in the calculation of tumour marker response rate.

- CBR is based on pain assessment and analgesic consumption. All patients were asked to complete a daily pain assessment and analgesic consumption diary throughout their participation in the study.

Sample size

For the sample size calculations, it was assumed that the median Overall Survival times were 4.5 months for the MM 398 monotherapy (Arm A), 3 months for the control arm (Arm B), and 6 months for the combination arm

(Arm C), corresponding to hazard ratios (HR) of 0.67 and 0.5 in favor of Arm A and Arm C relative to Arm B, respectively. Both Arm A and Arm C were compared to Arm B.

A total of 305 events provided at least 85% power to detect the hypothesized OS advantage for Arm A relative to Arm B. The planned study size also provided at least 99% power to detect the OS advantage for Arm C relative to Arm B. With a 14 month patient accrual and up to 3 months follow up time, it was expected that a total of approximately 405 patients would be randomized.

The sample size and power calculations also assumed that approximately 65 patients were randomized in protocol version 1 and that the remaining patients were randomized under the 3-arm versions of the protocol.

These power statements were based on the corresponding two pairwise unstratified logrank tests using a Bonferroni-Holm testing procedure which strongly controls the family wise error rate for the planned comparisons at the two-sided 0.05 level, i.e. one sided 0.025 level.

The primary analysis was to take place when at least 305 death events have occurred. The final number of patients enrolled and included in the analyses included all patients randomized under protocol version 1.1 (and later).

Randomisation

Patients have been randomized to treatment arms using an Interactive Web Response System (IWRS) at a central location, based on stratified factors such as baseline albumin levels (≥ 4.0 g/dL *vs* < 4.0 g/dL), KPS (70 and 80 *vs* ≥ 90), and ethnicity (Caucasian *vs* East Asian *vs* All Others).

In the original protocol, randomization in a 1:1 ratio to MM-398 monotherapy vs 5-FU/LV control arm was performed. Starting from protocol version 2, a third arm was added to investigate MM-398 in combination with 5-FU/LV, and patients were assigned to treatment arms via randomized blocks within a stratum (1:1:1 ratio).

Blinding (masking)

N/A

Statistical methods

Planned statistical analyses were conducted on the following 8 patient populations.

Table 12: Summary of the planned statistical analysis - study NAPOLI-1

Population	Definition	Analyses
Intent-to-Treat (ITT)	all patients randomized after confirmation of successful allocation of a randomization number through the IWRS	primary population for all efficacy parameters
Per-protocol population (PP)	patients who received treatment for at least 6 weeks and did not violate any inclusion/exclusion criteria nor significantly deviate from the protocol	Sensitivity analyses of OS, PFS, ORR, TTF
Evaluable Patient (EP) population for tumor response	all randomized and treated patients, who met all inclusion/exclusion criteria, had measurable disease at baseline and were evaluable for response°	PFS, ORR, TTF
Tumor marker	patients with elevated CA19.9 level	Tumor Marker (CA19.9)

response-evaluable (TMRE) population	(> 30 U/mL) at baseline	Response
CBR-evaluable (CBRE) population	patients with at least one of the following at baseline: • pain intensity ≥ 20 (out of 100) • morphine consumption ≥ 10 mg/day PO morphine equivalents • KPS of 70 to 90 points	Clinical Benefit Response
PRO population	all ITT patients with baseline and at least one subsequent EORTC-QLQ-C30 assessment	Quality of Life analyses
PK population	all treated patients with at least one PK assessment on treatment	pharmacokinetic analyses
Safety population	patients that received at least one dose (including a partial dose) of study medication	all safety analyses

° i.e. patients with at least one tumor evaluation while on treatment and those with early (≤ 12 weeks) disease progression, including symptomatic deterioration and death.

Primary Endpoint Analysis:

The primary analysis involved 2 pairwise comparisons of survival in the ITT population using un-stratified logrank test. The testing was carried out using a Bonferroni-Holm testing procedure to strongly control the family wise Type I error rate at the 2-sided 0.05 level. Kaplan-Meier analyses were performed on each treatment group to obtain nonparametric estimates of the survival function and the median survival time. Corresponding 95% confidence intervals were computed using the log-log method. Unstratified Cox proportional hazards regression were used to estimate hazard ratios and their corresponding 95% confidence intervals. The proportional hazards assumptions were examined by Cox regression models with treatment as a time-dependent covariate.

Secondary Endpoint Analysis:

PFS was compared pairwise (Arm A v. Arm B, Arm C v. Arm B) using un-stratified logrank tests. Kaplan-Meier analyses were performed on each treatment group to obtain nonparametric estimates of the PFS function and the median PFS time. Corresponding 95% confidence intervals were computed using the log-log method. Unstratified Cox proportional hazards regressions were used to estimate hazard ratios and their corresponding 95% confidence interval.

The number and percentage of patients in the ITT, PP, and EP populations experiencing objective response (confirmed CR + PR) at the time of analysis was presented and the 95% confidence interval for the proportion was calculated based on the normal approximation. Differences in objective response rates between treatment arms were compared pairwise using Fisher's exact tests. Analyses of ORR were based on unconfirmed tumour response assessments per investigator under RECIST version 1.1 criteria, as well as confirmed tumour responses.

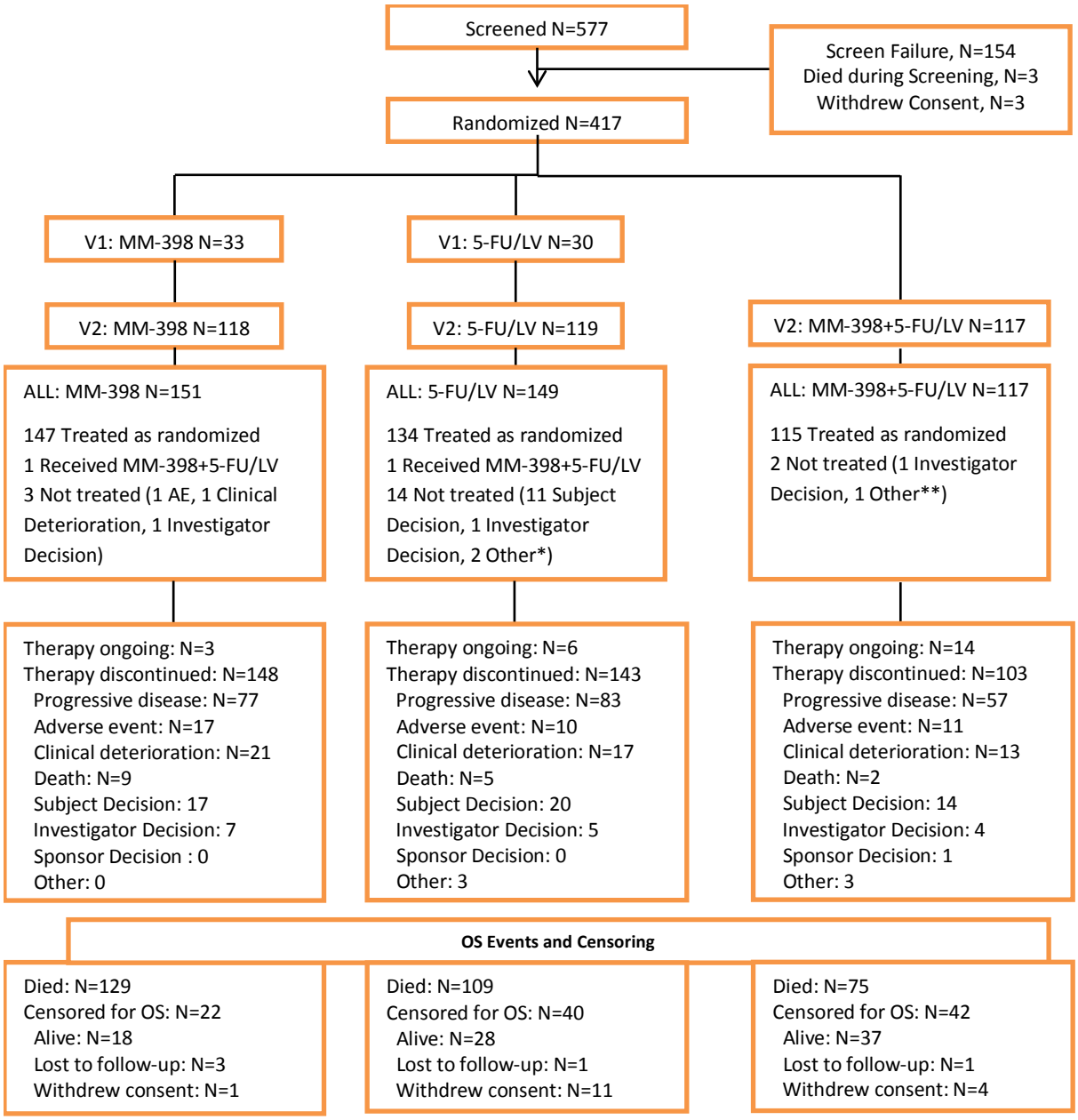
Clinical benefit response rates were compared pairwise on the CBRE population using Fisher's Exact Tests. Contingency tables for pain classification, KPS, and overall clinical benefit response, were also presented for each treatment group. Median time to clinical benefit response and median duration of clinical benefit response were computed using data from patients with clinical benefit response.

Regarding the Tumour Marker Response Analysis, CA 19-9 serum levels were measured within 7 days before the start of treatment (baseline), and subsequently every 6 weeks. Tumour marker response was evaluated by the change in CA19-9 serum levels and defined as a decrease of 50% of CA19-9 in relation to the baseline level at least once during the treatment period. Only patients with elevated baseline CA19-9 value (> 30 U/mL), i.e. the

TMRE population, were included in the calculation of tumour marker response rate. Tumour marker response rates from the treatment arms were compared pairwise using Fisher's exact tests.

Results

Participant flow



Recruitment

Of the 577 patients screened for inclusion, 417 patients were randomized and are included in the Intent-to-Treat (ITT) population. These patients were enrolled in 76 study sites in North America (20 sites), Europe (30 sites),

Asia (12 sites), South America (8 sites), and Oceania (6 sites). Out of the 417 patients included, 151 (36%) were enrolled in Europe, 125 patients (30%) in Asia, and 68 (16%) in North America, while the remaining part (18%) was from Australia and South America.

Conduct of the study

Overall, 2 protocol amendments were implemented to the original version of NAPOLI-1 study (dated 6 Oct 2011).

The main changes introduced by protocol amendments are reported in the following Table:

Amendment ≠	Protocol version (date)	Changes
01	2.1 (14 June 2012)	The study design was changed by the addition of the third treatment arm (MM-398 and 5-FU/LV combination). Based on statistical assumption for the 3-arm study, the total number of patients required to be enrolled was increased from 270 to 405; moreover, the primary analysis for overall survival was to take place after 305 death events instead of 220 initially planned. Requirement for a formal interim analysis, for safety and futility, was removed. Instead, a requirement for an intensive safety review of the first 15 subjects enrolled in each arm by the independent DSMB was added to ensure the safety of the new combination arm. The restriction excluding patients previously treated with irinotecan from participating in the study was removed to be consistent with the absence of restriction in case of previous treatment with 5-FU/LV. Inclusion of such patients was left to the investigator's discretion. Dose modification guideline for patients who were homozygous for UGT1A1*28 and had already had their dose increased was clarified. To keep the response assessment consistent with the RECIST 1.1. guidelines, confirmation of a PR or CR was no longer required. In case of study treatment discontinuation for reasons other than disease progression, tumour assessment every 6 weeks was continued during the follow-up period until documentation of objective disease progression. Since post-study therapy can affect the tumour response status, censoring for tumour response analysis was applied at the time of new anti-neoplastic therapy starts, and, not further tumour assessments was required from then onwards. In addition to Arm A, PK assessments were now required for patients on Arm B and C as well. The requirement of an optional PK sample was added to be collected in Cycle 1, any time between 8 and 72 hours following administration of MM-398, from patients in Arm A and C patients only.
02	2.2 (19 October 2012)	The dose for the *l* isomeric form of leucovorin was added, due to the ongoing global shortages for oncology drugs. Clarification that all efficacy comparisons between Arm A and Arm B would include all patients randomized to either arm, under all versions of the protocol. The efficacy comparisons between Arm B and Arm C would include only patients randomized under protocol version 2 or later. An additional sensitivity analysis was added to censor the overall survival at a date where any post-treatment anti-cancer therapy was first administered.

Baseline data

Demographic and baseline characteristics of the 417 patients enrolled in NAPOLI-1 study are summarized in the following tables:

Table 13: Demographics-ITT Population

Characteristic	MM-398 Mono N=151	5-FU/LV Mono Control N=149	MM-398+5-FU/LV Combo N=117	5-FU/LV Combo Control N=119*	*All ITT** N=417*
Gender, n (%)					
Female	64 (42.4)	68 (45.6)	48 (41.0)	52 (43.7)	*180 (43.2)*
Male	87 (57.6)	81 (54.4)	69 (59.0)	67 (56.3)	*237 (56.8)*
Race, n (%)					
American Indian Or Alaska Native	1 (0.7)	0	0	0	*1 (0.2)*
Asian	52 (34.4)	50 (33.6)	34 (29.1)	36 (30.3)	*136 (32.6)*
Black Or African American	3 (2.0)	3 (2.0)	4 (3.4)	3 (2.5)	*10 (2.4)*
White	89 (58.9)	92 (61.7)	72 (61.5)	76 (63.9)	*253 (60.7)*
Other	6 (4.0)	4 (2.7)	7 (6.0)	4 (3.4)	*17 (4.1)*
Age (yrs)					
Mean (SD)	63.6 (10.13)	61.8 (9.65)	63.2 (9.06)	61.0 (9.46)	*62.8 (9.68)*
Median	65.0	63.0	63.0	62.0	*63.0*
Min, Max	31, 87	34, 83	41, 81	34, 80	*31, 87*
Height (cm)					
Mean (SD)	166.6 (10.72)	166.2 (10.15)	167.5 (9.64)	166.7 (10.10)	*166.7 (10.21)*
Min, Max	144, 193	145, 193	142, 189	147, 193	*142, 193*
Weight (kg)					
Mean (SD)	64.7 (14.15)	65.6 (17.67)	65.9 (14.87)	66.1 (18.33)	*65.3 (15.66)*
Min, Max	38, 118	37, 151	40, 123	37, 151	*37, 151*
BMI (kg/m^2)					
Mean (SD)	23.09 (3.406)	23.57 (4.915)	23.33 (4.134)	23.57 (5.054)	*23.33 (4.193)*
Min, Max	15.1, 34.9	16.7, 42.9	16.0, 43.5	16.7, 42.9	*15.1, 43.5*

Baseline defined as last observation prior to study treatment
* This group is a subset of 5-FU/LV mono control group that was enrolled in the study after protocol Version 2 was activated.
** Rows do not add across because of the presentation of the control groups (mono controls are all patients treated with 5-FU/LV only; combo controls include a subset of these patients who were enrolled after protocol Version 2, which added the third treatment arm). Patients are counted only once in the All column.
5-FU= 5-fluorouracil; LV=leucovorin
Source: Table 14.1.3.1

Table 14: Baseline Characteristics-ITT Population

Characteristic	MM-398 Mono N=151	5-FU/LV Mono Control N=149	MM-398+5-FU/LV Combo N=117	5-FU/LV Combo Control N=119*	*All ITT** N=417*
Baseline KPS Level, n (%)					
50	0	0	1 (0.9)	0	*1 (0.2)*
60	0	0	2 (1.7)	0	*2 (0.5)*
70	15 (9.9)	11 (7.4)	7 (6.0)	10 (8.4)	*33 (7.9)*
80	50 (33.1)	61 (40.9)	38 (32.5)	51 (42.9)	*149 (35.7)*
90	64 (42.4)	54 (36.2)	51 (43.6)	40 (33.6)	*169 (40.5)*
100	22 (14.6)	22 (14.8)	18 (15.4)	17 (14.3)	*62 (14.9)*
Baseline Albumin (g/dL)					
Mean (SD)	3.97 (0.442)	3.96 (0.502)	3.97 (0.459)	3.98 (0.506)	*3.96 (0.468)*
Min, Max	2.9, 4.8	2.4, 5.1	2.6, 5.1	2.4, 5.0	*2.4, 5.1*
Measurable lesions at baseline	144 (95.4)	144 (96.6)	113 (96.6)	114 (95.8)	*401 (96.2)*
No measurable lesions at baseline	7 (4.6)	5 (3.4)	4 (3.4)	5 (4.2)	*16 (3.8)*
Measurable metastatic lesions at baseline	128 (84.8)	129 (86.6)	97 (82.9)	103 (86.6)	*354 (84.9)*
No measurable metastatic lesions at baseline	23 (15.2)	20 (13.4)	20 (17.1)	16 (13.4)	*63 (15.1)*
Number of subjects at baseline with:, n (%)					
1 measurable metastatic lesion	36 (23.8)	26 (17.4)	19 (16.2)	22 (18.5)	*81 (19.4)*
2 measurable metastatic lesion	63 (41.7)	72 (48.3)	49 (41.9)	58 (48.7)	*184 (44.1)*
3 measurable metastatic lesion	22 (14.6)	21 (14.1)	22 (18.8)	15 (12.6)	*65 (15.6)*
>3 measurable metastatic lesion	7 (4.6)	10 (6.7)	7 (6.0)	8 (6.7)	*24 (5.8)*
Anatomical location of lesions at baseline*, n (%)**					
Distant Lymph node	44 (29.1)	40 (26.8)	32 (27.4)	31 (26.1)	*116 (27.9)*
Liver	101 (66.9)	108 (72.5)	75 (64.1)	83 (69.7)	*284 (68.1)*
Lung	49 (32.5)	44 (29.5)	36 (30.8)	36 (30.3)	*129 (30.9)*
Pancreas	99 (65.6)	97 (65.1)	75 (64.1)	72 (60.5)	*271 (65.0)*
Peritoneal	48 (31.8)	39 (26.2)	28 (23.9)	32 (26.9)	*115 (27.6)*
Regional Lymph node	19 (2.6)	20 (13.4)	13 (11.1)	14 (11.8)	*52 (12.5)*
Other	38 (25.2)	48 (32.2)	27 (23.1)	39 (32.8)	*113 (27.1)*
Prior lines of treatment					
1st line advanced/metastatic	17 (11.3)	19 (12.8)	15 (12.8)	15 (12.8)	*51 (12.2)*
2nd line advanced/metastatic	86 (57.0)	86 (57.7)	62 (53.0)	67 (56.3)	*234 (56.1)*
3rd+ line advanced/metastatic	48 (31.8)	44 (29.5)	40 (34.2)	37 (31.1)	*132 (31.7)*

Baseline defined as last observation prior to study treatment
* This group is a subset of 5-FU/LV mono control group that was enrolled in the study after protocol Version 2 was activated.
** Rows do not add across because of the presentation of the control groups. Patients are counted only once in the All column.
*** Investigator reported.
5-FU= 5-fluorouracil; LV=leucovorin
Source: Table 14.1.3.1, Table 14.1.4.2.1

Further details and data on time since first cytological or histopathological diagnosis and first metastatic diagnosis are reported in the table below:

Table 15: Cancer Diagnosis-ITT Population

Characteristic Category/Statistic	MM-398 Mono (N=151)	5-FU/LV Mono Control (N=149)	MM-398+5-FU/LV Combo (N=117)	5-FU/LV Combo Control (N=119)	All ITT (N=417)
Location of Pancreatic Tumor of Diagnosis, n(%)					
Head only	92 (60.9)	77 (51.7)	70 (59.8)	65 (54.6)	239 (57.3)
Body only	16 (10.6)	26 (17.4)	12 (10.3)	19 (16.0)	54 (12.9)
Tail only	24 (15.9)	24 (16.1)	14 (12.0)	19 (16.0)	62 (14.9)
Multi-locations include head	7 (4.6)	4 (2.7)	6 (5.1)	4 (3.4)	17 (4.1)
Multi-locations not include head	7 (4.6)	14 (9.4)	9 (7.7)	10 (8.4)	30 (7.2)
Unknown	5 (3.3)	4 (2.7)	6 (5.1)	2 (1.7)	15 (3.6)
Disease Stage, n(%)					
IA	1 (0.7)	2 (1.3)	1 (0.9)	2 (1.7)	4 (1.0)
IB	4 (2.6)	3 (2.0)	1 (0.9)	3 (2.5)	8 (1.9)
IIA	19 (12.6)	11 (7.4)	6 (5.1)	9 (7.6)	36 (8.6)
IIB	26 (17.2)	25 (16.8)	26 (22.2)	22 (18.5)	77 (18.5)
III	30 (19.9)	24 (16.1)	21 (17.9)	19 (16.0)	75 (18.0)
IV	70 (46.4)	82 (55.0)	61 (52.1)	62 (52.1)	213 (51.1)
Missing	1 (0.7)	2 (1.3)	1 (0.9)	2 (1.7)	4 (1.0)
Time since first cytological or histo-pathological diagnosis (months)					
N	149	147	117	117	413
Mean (SD)	13.53(10.873)	12.17(10.097)	13.33(10.839)	12.81(10.316)	12.99(10.506)
Median	10.4	9.5	10.3	10.3	10.1
Q1, Q3	6.1, 17.2	5.7, 14.4	6.2, 17.1	6.2, 15.1	5.9, 16.1
Min, Max	0.4, 51.4	2.0, 57.7	0.5, 67.8	2.5, 57.7	0.4, 67.8
Time since first metastatic diagnosis (months)					
N	150	148	116	118	414
Mean (SD)	8.41(7.755)	7.78(7.364)	8.40(7.432)	7.74(7.120)	8.18(7.515)
Median	6.4	5.9	6.9	6.2	6.2
Q1, Q3	3.4, 11.3	2.8, 10.6	3.1, 10.9	2.5, 10.6	3.0, 10.9
Min, Max	0.3, 51.4	0.2, 48.1	0.3, 46.2	0.2, 48.1	0.2, 51.4

Note: Denominator for percentage corresponds to the N in each column.

Details on prior anticancer therapies and on response to previous treatments are shown below:

Table 16: Prior Anticancer Therapy-ITT Population

Characteristic Category/Statistic	MM-398 Mono (N=151)	5-FU/LV Mono Control (N=149)	MM-398+5-FU/LV Combo (N=117)	5-FU/LV Combo Control (N=119)	All ITT (N=417)
Prior lines of Treatment					
1st line advanced/metastatic	17 (11.3)	19 (12.8)	15 (12.8)	15 (12.6)	51 (12.2)
2nd line advanced/metastatic	86 (57.0)	86 (57.7)	62 (53.0)	67 (56.3)	234 (56.1)
3rd+ line advanced/metastatic	48 (31.8)	44 (29.5)	40 (34.2)	37 (31.1)	132 (31.7)
Anticancer therapy with special interest [1]					
Gemcitabine alone	67 (44.4)	66 (44.3)	53 (45.3)	55 (46.2)	186 (44.6)
Gemcitabine combination	84 (55.6)	83 (55.7)	64 (54.7)	64 (53.8)	231 (55.4)
5-FU based	70 (46.4)	63 (42.3)	50 (42.7)	52 (43.7)	183 (43.9)
Irinotecan based	17 (11.3)	17 (11.4)	12 (10.3)	17 (14.3)	46 (11.0)
Platinum based	54 (35.8)	45 (30.2)	38 (32.5)	41 (34.5)	137 (32.9)
Best Response to prior therapy					
Complete Response (CR)	1 (0.7)	5 (3.4)	2 (1.7)	4 (3.4)	8 (1.9)
Partial Response (PR)	21 (13.9)	17 (11.4)	9 (7.7)	17 (14.3)	47 (11.3)
Stable Disease (SD)	55 (36.4)	54 (36.2)	47 (40.2)	40 (33.6)	156 (37.4)
Progressive Disease (PD)	51 (33.8)	50 (33.6)	35 (29.9)	38 (31.9)	136 (32.6)
Not Evaluable (NE)	19 (12.6)	21 (14.1)	23 (19.7)	18 (15.1)	63 (15.1)
Unknown	4 (2.6)	2 (1.3)	1 (0.9)	2 (1.7)	7 (1.7)
Best Response - prior gemcitabine therapy					
Complete Response (CR)	1 (0.7)	5 (3.4)	0	4 (3.4)	6 (1.4)
Partial Response (PR)	15 (9.9)	13 (8.7)	6 (5.1)	13 (10.9)	34 (8.2)
Stable Disease (SD)	51 (33.8)	51 (34.2)	43 (36.8)	37 (31.1)	145 (34.8)
Progressive Disease (PD)	57 (37.7)	52 (34.9)	40 (34.2)	40 (33.6)	149 (35.7)
Not Evaluable (NE)	23 (15.2)	24 (16.1)	27 (23.1)	21 (17.6)	74 (17.7)
Unknown	4 (2.6)	4 (2.7)	1 (0.9)	4 (3.4)	9 (2.2)

Note: Denominator for percentage corresponds to the N in each column.
[1]: Subjects may receive more than one therapy and could appear in more than one category.

At study entry, the median time since the last any prior anticancer treatment was 1.3 months, with a median time of 1.4 months from the last prior gemcitabine therapy.

Numbers analysed

Analyses were conducted in 8 different patient populations (see also statistical analysis plan).

The number of patients included in each analysis population is reported in the table below:

Table 17: Analysis population

Population	MM-398 Mono N=151 (%)	5-FU/LV Mono Control N=149 (%)	MM-398+5-FU/LV Combo N=117 (%)	5-FU/LV Combo Control N=119* (%)	*All ITT N=417 (%)*
Intent-to-Treat (ITT)	151 (100)	149 (100)	117 (100)	119 (100)	*417 (100)*
Safety	147 (97.4)	134 (89.9)	117 (100)	105 (88.2)	*398 (95.4)*
Per-Protocol (PP)	116 (76.8)	95 (63.8)	66 (56.4)	71 (59.7)	*277 (66.4)*
Evaluable Patient (EP) for Tumor Response	133 (88.1)	120 (80.5)	104 (88.9)	92 (77.3)	*357 (85.6)*
Tumor Marker Response-evaluable (TMRE)	123 (81.5)	105 (70.5)	97 (82.9)	81 (68.1)	*325 (77.9)*
Clinical Benefit Response (CBR) Population	92 (60.9)	80 (53.7)	78 (66.7)	60 (50.4)	*250 (60.0)*
Patient Reported Outcome (PRO) Population	105 (69.5)	82 (55.0)	72 (61.5)	56 (47.1)	*259 (62.1)*
PK Population	144 (95.4)	85 (57.0)	116 (99.1)	85 (71.4)	*345 (82.7)*

* This group is a subset of 5-FU/LV mono control group that was enrolled in the study after protocol Version 2 was activated.
There were 2 subjects who received study drug not as randomized. The MM-398 and 5-FU/LV randomized groups each had 1 subject who received MM-398+5-FU/LV.
5-FU= 5-fluorouracil; LV=leucovorin; PP=Per Protocol
Source: Table 14.1.1.9

Outcomes and estimation

Primary efficacy endpoint: OS

Table 18: NAPOLI-1 CSR: Study Primary Efficacy Analysis (Overall Survival)

Primary Efficacy Analysis: Overall Survival	Monotherapy Comparison				Combination Therapy Comparison			
	MM-398	5-FU/LV	p-value [a]	Hazard Ratio [b]	MM-398 + 5-FU/LV	5-FU/LV	p-value [a]	Hazard Ratio [b]
ITT Population								
N	151	149			117	119		
Median OS, months (95% CI) [c]	4.9 (4.23, 5.62)	4.2 (3.58, 4.86)	0.9416	0.99	6.1 (4.76, 8.87)	4.2 (3.29, 5.32)	0.0122	0.67
Died, n (%)	129 (85.4)	109 (73.2)			75 (64.1)	80 (67.2)		
Reason for Censoring								
Alive, n (%)	18 (11.9)	28 (18.8)			37 (31.6)	27 (22.7)		
Lost to Follow-Up, n (%)	3 (2.0)	1 (0.7)			1 (0.9)	1 (0.8)		
Subject Withdrew Consent from Follow-Up, n (%)	1 (0.7)	11 (7.4)			4 (3.4)	11 (9.2)		

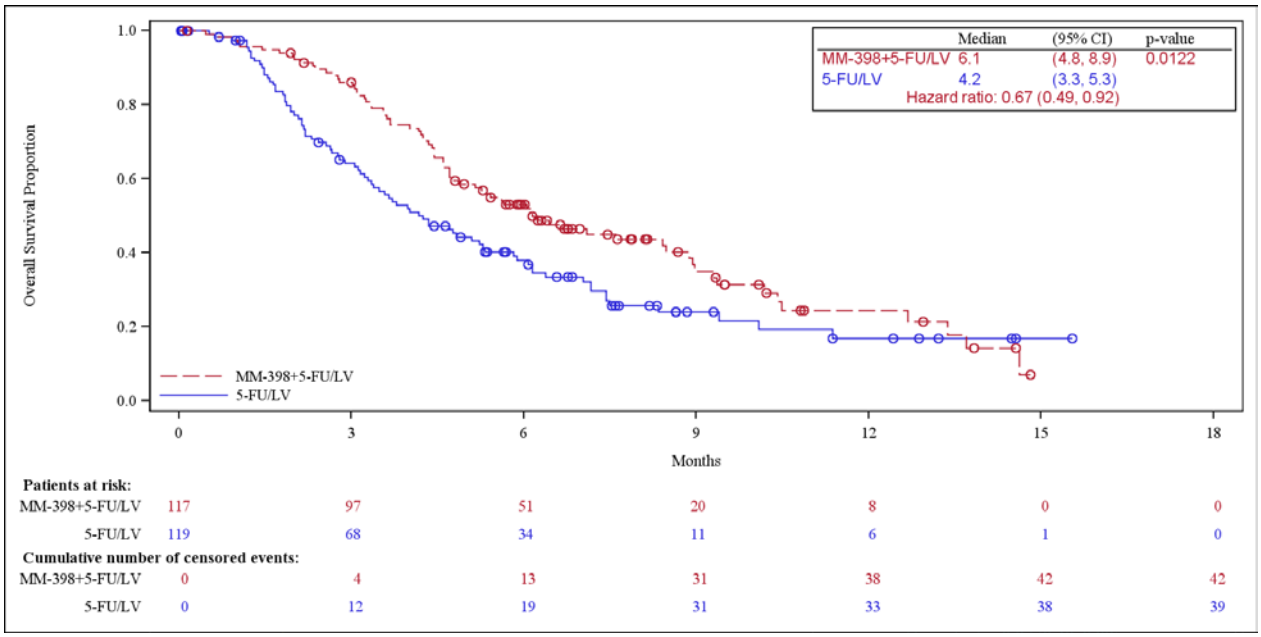


Figure 5: NAPOLI-1 CSR: Kaplan-Meier Plot for Overall Survival (Months) - MM-398+5-FU/LV versus 5-FU/LV Control (ITT Population)

Table 19: Sensitivity analyses of the primary efficacy endpoint (overall survival) – NAPOLI-1

Sensitivity Analyses of Overall Survival	Monotherapy Comparison				Combination Therapy Comparison			
	MM-398	5-FU/LV	p-value[1]	Hazard Ratio[2]	MM-398 + 5-FU/LV	5-FU/LV	p-value[1]	Hazard Ratio[2]
Stratified Analysis on ITT Population								
N	151	149			117	119		
Median OS, months (95% CI)[3,4]	4.9 (4.24, 5.62)	4.2 (3.58, 4.86)	0.5545	0.93	6.1 (4.76, 8.87)	4.2 (3.29, 5.32)	0.0009	0.57
Safety Population								
N	147	134			117	105		
Median OS, months (95% CI)[4]	4.9 (4.27, 5.62)	4.2 (3.58, 4.86)	0.8372	0.97	6.2 (4.86, 8.87)	4.2 (3.29, 5.29)	0.0108	0.66
Per Protocol Population								
N	116	95			66	71		
Median OS, months (95% CI)[4]	5.4 (4.80, 6.28)	4.8 (3.98, 5.88)	0.5174	1.11	8.9 (6.44, 10.5)	5.1 3.98, 7.16)	0.0106	0.57
ITT Population (Censoring at Change in Therapy)								
N	151	149			117	119		
Median OS, months (95% CI)[4]	4.8 (4.11, 5.39)	3.9 (3.12, 5.22)	0.7460	0.9506	6.1 (4.70, 12.68)	4.0 (3.06, 5.88)	0.0033	0.5665
ITT Population (Subjects Enrolled under Protocol Version 2)								
N	118	119						
Median OS, months (95% CI)[4]	4.8 (4.11, 5.62)	4.2 (3.29, 5.32)	0.6512	1.07				

1 Two-sided p-value from log-rank test.
2 Hazard ratios and the associated p-values are derived using Cox's proportional hazards model with treatment as the independent variable.
3 For the Stratified Analysis on the ITT population, p-value is derived from the two-sided stratified log rank test, incorporating randomization strata; Hazar ratios are derived using the stratified Cox's proportional hazards model with treatment as the independent variable.

Secondary efficacy endpoints

- Progression Free Survival (PFS)

Table 20: Study Secondary Efficacy Analysis (PFS) - NAPOLI-1

Secondary Efficacy Analysis: Progression Free Survival	Monotherapy Comparison				Combination Therapy Comparison			
	MM-398	5-FU/LV	p-value[a]	Hazard Ratio[b]	MM-398 + 5-FU/LV	5-FU/LV	p-value[a]	Hazard Ratio[b]
ITT Population								
N	151	149			117	119		
Median PFS Time, months (95% CI)[c]	2.7 (2.13, 2.89)	1.6 (1.41, 1.84)	0.1001	0.81	3.1 (2.69, 4.17)	1.5 (1.41, 1.84)	0.0001	0.56
Progressed, n (%)	89 (58.9)	89 (59.7)			65 (55.6)	69 (58.0)		
Died before progression, n (%)	38 (25.2)	31 (20.8)			18 (15.4)	23 (19.3)		
Reason for Censoring								
Clinical Deterioration, n (%)	4 (2.7)	3 (2.0)			3 (2.6)	2 (1.7)		
Last non-PD Assessment within 12 Weeks of Cutoff Date, n (%)	4 (2.7)	7 (4.7)			15 (12.8)	7 (5.9)		
Not Treated and No Post-Baseline Tumour Assessment, n (%)	1 (0.7)	10 (6.7)			1 (0.9)	10 (8.4)		
Other, n (%)	15 (9.9)	9 (6.0)			15 (12.8)	8 (6.7)		

[a]p-value is derived from the two-sided unstratified log rank test
[b]Hazard ratios are derived using unstratified Cox's proportional hazards model with treatment as the independent variable
[c]Median PFS time is the Kaplan-Meier estimate of the median survival time
Source: 5.3.5.1 NAPOLI-1 CSR, Section 7.4.1.2, Table 7-9

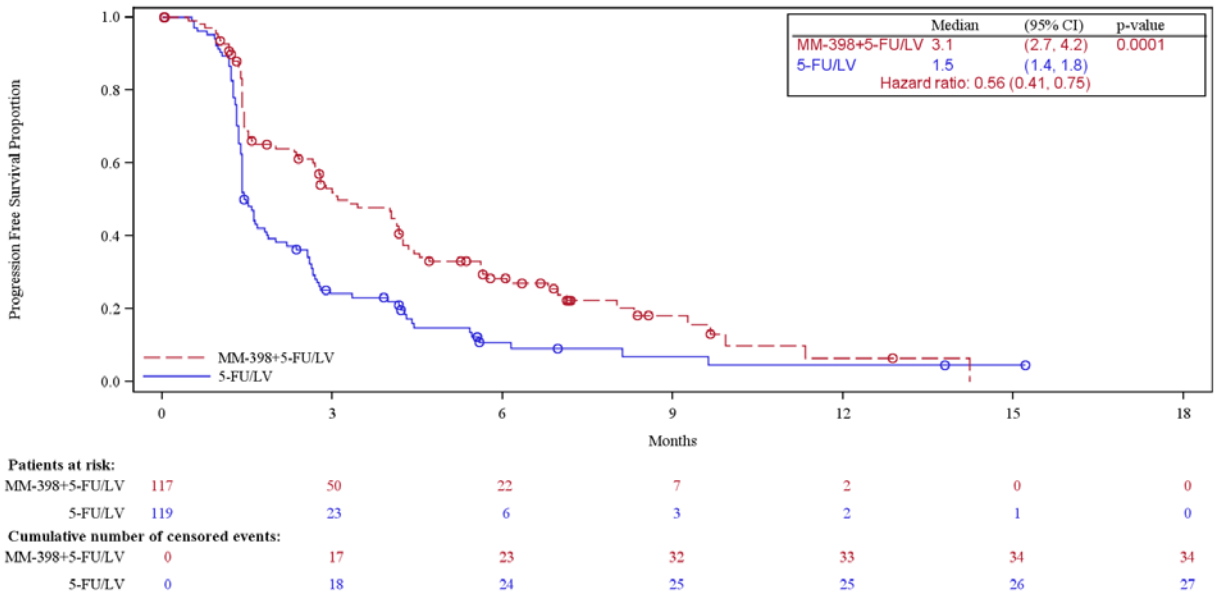


Figure 6: Kaplan-Meier Plot for PFS (Months) - MM-398+5-FU/LV versus 5-FU/LV Control (ITT Population) - NAPOLI-1

The combination of MM-398+5-FU/LV achieved a median PFS of twice that of the control arm of 5-FU/LV, 3.1 vs 1.5 months, HR 0.56, p=0.0001. However, the PFS was assessed by the investigator, not by IRC.

The HR for monotherapy comparison (MM-398 vs 5FU/LV) is 0.81, p-value=0.1, while the HR for the combination therapy comparison is 0.56, p-value=0.0001.

Table 21: Sensitivity analyses of PFS – NAPOLI-1

Sensitivity Analyses of Progression Free Survival	Monotherapy Comparison				Combination Therapy Comparison			
	MM-398	5-FU/LV	p-value[1]	Hazard Ratio[2]	MM-398 + 5-FU/LV	5-FU/LV	p-value[1]	Hazard Ratio[2]
Stratified Analysis on the ITT Population								
N	151	149			117	119		
Median PFS Time, months (95% CI)[3,4]	2.7 (2.14, 2.89)	1.6 (1.41, 1.84)	0.0346	0.75	3.1 (2.69, 4.17)	1.5 (1.41, 1.84)	<0.0001	0.51
Per Protocol Population								
N	116	95			66	71		
Median PFS Time, months (95% CI)[4]	2.8 (2.63, 3.71)	1.6 (1.41, 2.56)	0.1116	0.79	4.3 (3.06, 5.72)	1.6 (1.41, 2.60)	<0.0001	0.46
Evaluable Population								
N	133	120			104	92		
Median PFS Time, months (95% CI)[4]	2.8 (1.77, 2.92)	1.5 (1.41, 1.81)	0.0907	0.79	3.1 (2.66, 4.21)	1.4 (1.41, 1.81)	<0.0001	0.53
ITT Population (Early Discontinuation)								
N	151	149			117	119		
Median PFS Time, months (95% CI)[4]	2.6 (1.77, 2.79)	1.5 (1.41, 1.71)	0.1363	0.83	3.1 (2.66, 4.14)	1.4 (1.41, 1.68)	<0.0001	0.55
ITT Population (Missing Data)								
N	151	149			117	119		
Median PFS Time, months (95% CI)[4]	2.7 (2.14, 2.83)	1.6 (1.41, 1.84)	0.1021	0.81	3.1 (2.69, 4.17)	1.5 (1.41, 1.84)	0.0001	0.56
ITT Population (Progression Directly Derived from Lesion Data)								
N	151	149			117	119		
Median PFS Time, months (95% CI)[4]	2.8 (2.14, 2.92)	1.5 (1.41, 1.81)	0.0969	0.80	3.3 (2.66, 4.21)	1.4 (1.41, 1.84)	0.0001	0.56
ITT Population (Subjects Enrolled under Protocol Version 2)								
N	118	119						
Median PFS Time, months (95% CI)[4]	2.6 (1.68, 2.89)	1.5 (1.41, 1.84)	0.1724	0.82				

[1] Two-sided p-value from log-rank test.
[2] Hazard ratios and the associated p-values are derived using Cox's proportional hazards model with treatment as the independent variable.
[3] For the Stratified Analysis on the ITT population, p-value is derived from the two-sided stratified log rank test, incorporating randomization strata; Hazard ratios are derived using the stratified Cox's proportional hazards model with treatment as the independent variable.
[4] Median PFS time is the Kaplan-Meier estimate of the median survival time.
Abbreviations: 5-FU/LV=5-fluorouracil/leucovorin; CI=confidence interval; ITT=Intent-to-Treat; PFS=progression free survival

- Time to treatment failure (TTF)

Table 22: Time to Treatment Failure - NAPOLI-1

Secondary Efficacy Analysis: Time to Treatment Failure	Monotherapy Comparison				Combination Therapy Comparison			
	MM-398	5-FU/LV	p-value[a]	Hazard Ratio[b]	MM-398 + 5-FU/LV	5-FU/LV	p-value[a]	Hazard Ratio[b]
ITT Population								
N	151	149			117	119		
Median TTF, months (95% CI)[c]	1.7 (1.48, 2.66)	1.4 (1.31, 1.41)	0.1008	0.82	2.3 (1.58, 2.79)	1.4 (1.31, 1.41)	0.0002	0.60
Death, n (%)	9 (6.0)	5 (3.4)			1 (0.9)	5 (4.2)		
Progressive disease, n (%)	77 (51.0)	84 (56.4)			61 (52.1)	65 (54.6)		
Other Reason for Treatment Termination, n (%)	62 (41.1)	54 (36.2)			41 (35.0)	43 (36.1)		

Table 23: Time to treatment discontinuation: adverse event discontinuations

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	11 (9.4)	5.2	5.1	1.7 – 9.1
5-FU/LV (protocol V2)	7 (5.9)	7.1	6.3	3.3 – 15.9

Table 24: Time to treatment discontinuation: clinical deterioration discontinuations

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	13 (11.1)	11.3	10.1	1.3 – 32.4
5-FU/LV (protocol V2)	12 (10.1)	9.5	8.5	1.3 – 25.7

Table 25: Time to treatment discontinuation: investigator decision discontinuations

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	4 (3.4)	14.8	12.9	9.9 – 23.3
5-FU/LV (protocol V2)	4 (3.4)	3.4	3.2	1.1 – 6.1

Table 26: Time to treatment discontinuation: subject decision discontinuations

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	14 (12.0)	6.7	5.4	0.6 – 14.1
5-FU/LV (protocol V2)	19 (16.0)	6.4	0.3	0.1 – 66.1

Table 27: Time to treatment discontinuation: all non-PD discontinuations (i.e. discontinuations for RECIST 1.1 PD or death are excluded)

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	44 (37.6)	8.6	7.8	0.6 – 32.4
5-FU/LV (protocol V2)	44 (37.0)	7.0	3.5	0.1 – 66.1

Table 28: Time from treatment discontinuation to PD: all non-PD discontinuations (i.e. discontinuations for RECIST 1.1 PD or death are excluded)

Treatment Group	# progressed/# discontinued	Time from discontinuation to progression (weeks) Kaplan-Meier estimates		
		25th percentile	Median	75th percentile
MM-398+5-FU/LV	25/44	8.1	5.1	2.6
5-FU/LV (protocol V2)	23/44	5.1	3.0	1.3

- Confirmed objective response rate, ORR

Table 29: Objective Response (ITT Population) - NAPOLI-1

Factor	Monotherapy Comparison		Combination Therapy Comparison	
	MM-398 (N=151)	5-FU/LV (N=149)	MM-398 + 5-FU/LV (N=117)	5-FU/LV (N=119)
Confirmed (≥ 4 weeks After Investigator Assessment of PR or CR)				
Best Overall Response, n (%)				
• Partial Response	5 (3.3)	1 (0.7)	9 (7.7)	1 (0.8)
• Stable Disease	57 (37.7)	35 (23.5)	47 (40.2)	26 (21.8)

Factor	Monotherapy Comparison		Combination Therapy Comparison	
	MM-398 (N=151)	5-FU/LV (N=149)	MM-398 + 5-FU/LV (N=117)	5-FU/LV (N=119)
• Non-Complete Response/ Non-Progressive Disease[a]	3 (2.0)	2 (1.3)	3 (2.6)	2 (1.7)
• Progressive Disease	51 (33.8)	71 (47.7)	35 (29.9)	56 (47.1)
• Not Evaluable	35 (23.2)	40 (26.8)	23 (19.7)	34 (28.6)
Objective Response Rate				
N	5	1	9	1
Rate (%)	3.31	0.67	7.69	0.84
95% CI of Rate[b]	0.46, 6.17	(0.0, 1.98)	2.86, 12.52	0.0, 2.48
Rate Difference (95% CI)	2.64 (-0.50, 5.78)		6.85 (1.75, 11.95)	
p-value[c]	0.2141		0.0097	

[a]Applies only to those patients without measurable disease at Baseline who could only be classified as CR, non-CR/non-PD, or PD
[b]95% CI is of Overall Response Rate for individual treatment arms and for the rate difference (treatment vs control) were calculated based on the normal approximation
[c]Two-sided p-values from pairwise (MM-398 monotherapy vs. Control; MM-398 combination therapy vs. Control) Fisher's exact test
Source: 5.3.5.1 NAPOLI-1 CSR, Section 7.4.1.2, Table 7-13

The ORR sensitivity analyses (PP and evaluable population) were consistent with the results in the ITT population.

- Tumour marker response (CA19-9)

A summary of tumour marker (CA19-9) response is presented below:

Table 30: Summary of Tumor Marker (CA19-9) Response (TMRE Population)

	Monotherapy Comparison		Combination Therapy Comparison	
	MM-398 (N=123)	5-FU/LV (N=105)	MM-398 + 5-FU/LV (N=97)	5-FU/LV (N=81)
Tumor Marker Response Eval, n (%)	29 (23.6)	12 (11.4)	28 (28.9)	7 (8.6)
p-value [1]	0.0238		0.0006	
Median Time to First Tumor Marker Response [2] (months), (95% CI)	4.4 (3.19, -)	3.91, -	4.3 (2.92, -)	3.91, -
Log-rank p-value [3]	0.1859		0.0392	
Wilcoxon p-value [3]	0.1550		0.0180	

[1] Two-sided p-values from pairwise comparisons of Tumor Marker Response rates using Fisher's exact test.
[2] Median time to First Tumor Response is Kaplan-Meier estimate of the median time to First Tumor Marker Response, in months.
[3] Two-sided p-values from pairwise comparisons of Time to First Tumor Marker Response.
Abbreviations: 5-FU/LV=5-fluorouracil/leucovorin; CI=confidence interval; TMRE=tumor marker response-evaluable
Source: Table 14.2.6

- Clinical Benefit Response (CBR):

Table 31: Clinical Benefit Response (pairwise comparison: combination therapy vs control) CBRE Population

	MM-398+5-FU/LV Combo (N= 78)			5-FU/LV Combo Control (N= 60)		
	Analgesic Consumption			Analgesic Consumption		
Pain Intensity, n(%)	Positive	Stable	Negative	Positive	Stable	Negative
Positive	6 (7.69)	3 (3.85)	3 (3.85)	0	3 (5.00)	2 (3.33)
Stable	2 (2.56)	31 (39.74)	10 (12.82)	2 (3.33)	21 (35.00)	8 (13.33)
Negative	0	5 (6.41)	18 (23.08)	0	7 (11.67)	17 (28.33)
	Performance Status			Performance Status		
Pain Classification, n(%)	Positive	Stable	Negative	Positive	Stable	Negative
Positive	1 (1.28)	9 (11.54)	1 (1.28)	0 (0.00)	4 (6.67)	1 (1.67)
Stable	0	27 (34.62)	4 (5.13)	0 (0.00)	16 (26.67)	5 (8.33)
Negative	0	24 (30.77)	12 (15.38)	0 (0.00)	15 (25.00)	19 (31.67)
	Primary Measure			Primary Measure		
Weight, n(%)	Response	Stable	Non-Response	Response	Stable	Non-Response
Positive	1 (1.28)	1 (1.28)	0	0	3 (5.00)	0
Non-Positive	9 (11.54)	26 (33.33)	41 (52.56)	4 (6.67)	13 (21.67)	40 (66.67)
Clinical Benefit Response [1], n (%)		11(14.10)		7(11.67)		
p-value [2]		0.8007				

Note: Refer to Protocol v2.2, Section 12.4.3.1 for the definition of Pain Classification, Primary Measures of the Classification and the Clinical Benefit Response based on the above sequential contingency tabulations. Treatment group comparisons are carried out separately for MM-398 Monotherapy vs Mono Control and MM-398+5-FU/LV Combination vs Combination control. The Combination comparisons include only randomized subjects under protocol version 2 or later. CBRE= Clinical Benefit Response Evaluable.
[1]:Rates are based on the CBR population.
[2]: Two-sided p-values from pairwise comparison of CBR rates using Fisher's exact test.

Program Source: t14-2-5-2-cbr-cbre-combo.sas
Run On: 17FEB15, 10:30

- Quality of life (QoL):

The status of QoL (improved, stable, or worsened) is registered through the EORTC QLQ-C30 questionnaire.

Baseline median Global Health Status, Functional Scale and Symptoms Scale scores were similar among treatment arms. For Physical Functioning, Emotional Functioning, and Cognitive Functioning median scores at baseline were ≥75, indicating a high/healthy level of functioning. At Week 6 and Week 12 no appreciable changes from baseline were registered for both domains.

Regarding symptom scales, median baseline scores were in the range 0-33, indicating low levels of symptomatology. No appreciable change from baseline in median scores were reported at Week 6 and Week 12 for pain, dyspnea, insomnia, appetite loss, and constipation. A post-baseline increase in median symptom scores from 0 (i.e., no symptomatology) to 16.7-33.3 was registered for nausea/vomiting and diarrhoea.

Ancillary analyses

Subgroup OS analyses:

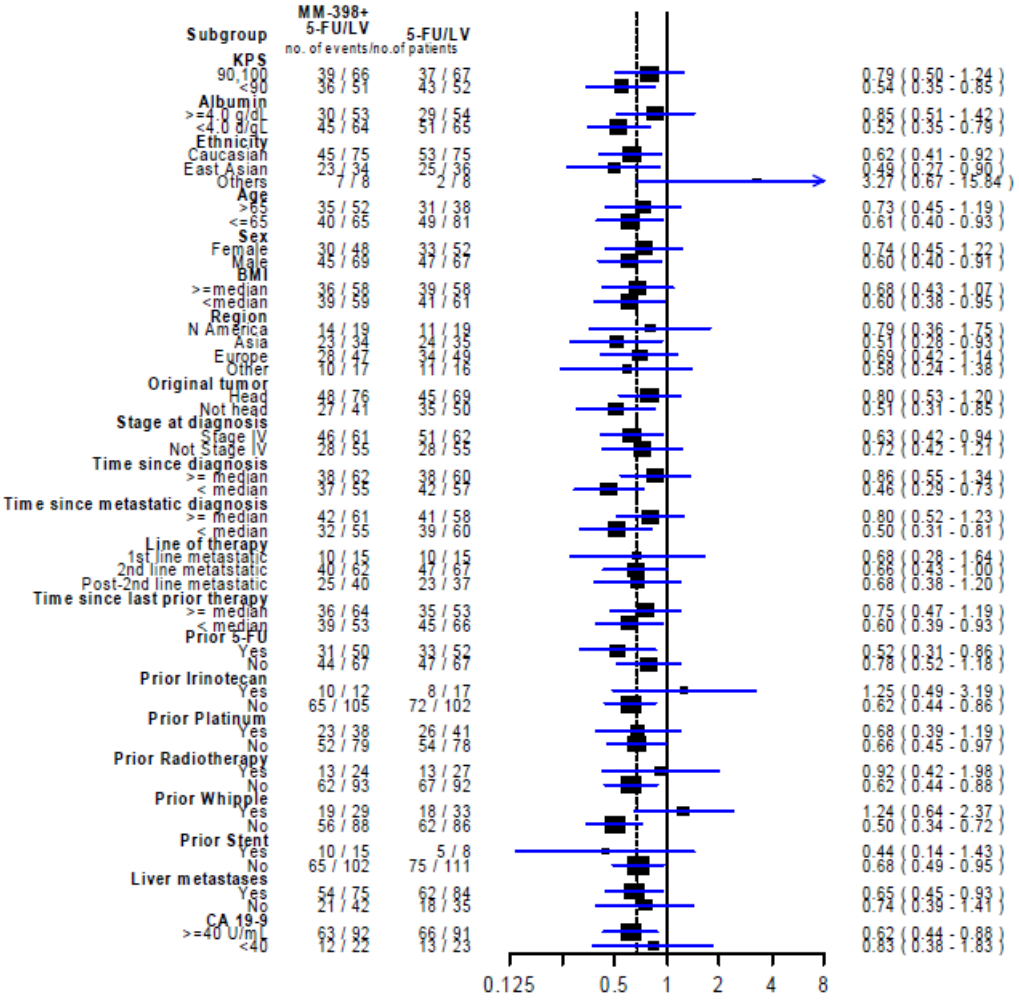


Figure 7: Pre-planned subgroup analysis of Overall Survival – NAPOLI-1

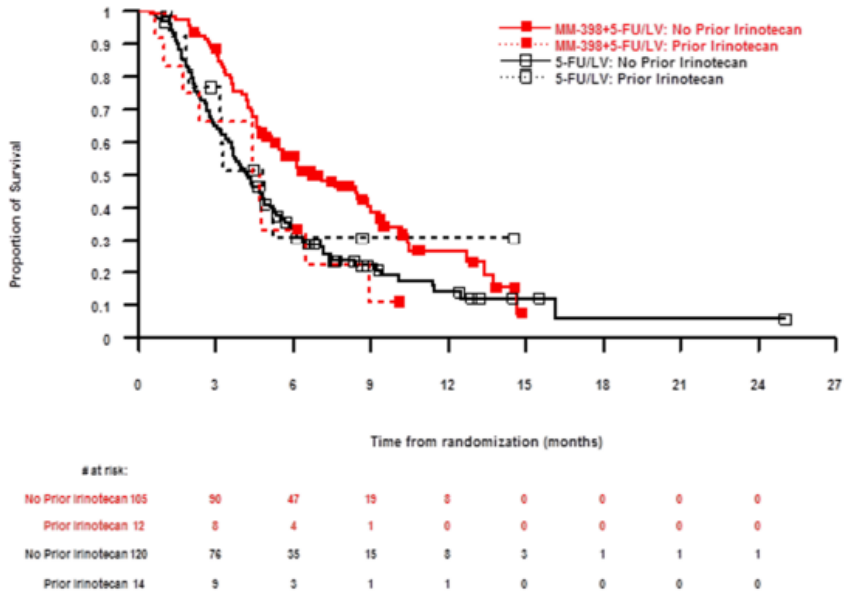


Figure 8: Analysis of OS in treated patients by prior irinotecan exposure (MM-398+5-FU/LV treatments)

Summary of main study

The following table summarises 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 32: Summary of Efficacy for trial MM-398-07-03-01 (NAPOLI-1)

Title: A Randomized, Open Label Phase 3 Study of MM-398, With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin in Patients With Metastatic Pancreatic Cancer Who Have Failed Prior Gemcitabine-Based Therapy			
Study identifier	MM-398-07-03-01 NAPOLI-1		
Design	Multicenter, multinational open label, randomized, three-arm study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Until disease progression not applicable not applicable
Hypothesis	Superiority		
Treatments groups	MM-398		120 mg/m^2 IV over 90 minutes, every 3 weeks. In case of homozygosity UGT1A1*28, dose was reduced at 80 mg/m^2 for the first cycle of therapy. If not drug related toxicity, from Cycle 2 onwards, the dose could be increased by 20 mg/m^2, up to a maximum of 120 mg/m^2. 151 randomized patients
	5-FU/LV		5-FU 2000 mg/m^2 IV over 24-hours, every week for 4, followed by 2 weeks of rest, in a 6 week cycle LV 200 mg/m^2 IV over 30 minutes, every week for 4 weeks, followed by 2 weeks of rest, in a 6 week cycle. 149 randomized patients
	MM-398+5-FU/LV		MM-398 80 mg/m^2 IV over 90 minutes, every 3 weeks. 5-FU 2400 mg/m^2 IV over 46-hours, every 2 weeks LV 400 mg/m^2 IV over 30 minutes, every 2 weeks In case of homozygosity UGT1A1*28, MM-398 dose was reduced at 60 mg/m^2 for the first cycle of therapy. If not drug related toxicity, from Cycle 2 onwards, the dose could be increased to 80 mg/m^2. 117 randomized patients
Endpoints and definitions	Primary endpoint	OS	time from the date of patient randomization to date of death or the date last known alive.
	Secondary endpoint	PFS	time in months from the date of patient randomization to the date of death or disease progression, whichever occurred earlier.
	Secondary endpoint	TTF	occurrence of discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.
	Secondary endpoint	ORR	percentage of patients in the study population with a best overall response of CR or PR as assessed by the investigator.

	Secondary endpoint	Tumor marker response (CA19-9)	decrease of 50% of CA19-9 in relation to the baseline level at least once during the treatment period.			
Data cutoff date	14 February 2014					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Intent to treat 14 February 2014					
Descriptive statistics and estimate variability	Treatment group	MM-398	5-FU/LV	MM-398+ 5-FU/LV*	5-FU/LV*	
	Number of subject	151	149	117	119	
	Primary endpoint					
	OS N. events (%)	129 (85.4)	109 (73.2)	75 (64.1)	80 (67.2)	
	Median OS months (95% CI)	4.9 (4.23, 5.62)	4.2 (3.58, 4.86)	**6.1** (4.76, 8.87)	**4.2** (3.29, 5.32)	
	Unstratified HR p-value (two-sided, un stratified Log-Rank Test)	0.99 (0.77,1.28) 0.94		**0.67** (0.49, 0.92) **0.01**		
	Secondary endpoints					
	PFS N. events (%)	127 (84.1)	120 (80.5)	83 (70.9)	92 (77.3)	
	Median PFS months (95% CI)	2.7 (2.13, 2.89)	1.6 (1.41, 1.84)	3.1 (2.69, 4.17)	1.5 (1.41, 1.84)	
	Unstratified HR p-value (two-sided, un stratified Log-Rank Test)	0.81 0.10		0.56 0.0001		
	TTF N. events n (%)	86 (56.9)	89 (59.7)	62 (52.9)	70 (58.8)	
	Median TTF months (95% CI)	1.7 (1.48, 2.66)	1.4 (1.31, 1.41)	2.3 (1.58, 2.79)	1.4 (1.31, 1.41)	
	Unstratified HR p-value (two-sided unstratified Log-Rank Test)	0.82 0.10		0.60 0.0002		
	ORR (CR+PR) n(%) (95% CI)	5 (3.3) (0.46, 6.17)	1 (0.6) (0.0, 1.98)	9 (7.6) (2.86, 12.5)	1 (0.84) (0.0, 2.48)	
	p-value (2-sided Fisher's exact test)	0.21		0.009		
	Tumor Marker Response (CA19.9) TMRE Population N	123	105	97	81	
	Tumor Marker response n(%)	29 (23.6)	12 (11.4)	28 (28.9)	7 (8.6)	
	p-value (2-sided Fisher's exact test)	0.023		0.0006		
Notes	*patients enrolled under Version 2 of the protocol TMRE= Tumor Marker Response Evaluable					

Analysis performed across trials (pooled analyses and meta-analysis)

Clinical studies in special populations

- Age

Table 33: Patients enrolled by study and age groups

	Age Group [1]		
Study	65 – 74 n (%)	75 – 84 n (%)	85 – n (%)
Controlled Trials			
Across All Controlled Trials	181 (33)	50 (9)	2 (<1)
MM-398-07-03-01	149 (36)	41 (10)	2 (<1)
MM-398+5-FU/LV	40 (34)	14 (12)	0
MM-398 monotherapy	58 (38)	18 (12)	2 (1)
5-FU/LV control	51 (34)	9 (6)	0
PEP0206	32 (24)	9 (7)	0
MM-398	11 (24)	3 (7)	0
IRINOTECAN	13 (29)	4 (9)	0
DOCETAXEL	8 (18)	2 (4)	0
Non-controlled Trials			
Across All Non-Controlled Trials	19 (18)	7 (7)	0
PEP0201	1 (9)	0	0
PEP0202	1 (17)	0	0
PEP0203	2 (13)	0	0
PEP0208	9 (23)	3 (8)	0
PIST-CRC-01	2 (11)	3 (17)	0
MM-398-01-01-02	4 (31)	1 (8)	0

[1]: Denominator for % is study total. Total is per randomization for controlled studies.

Intra-arm median OS comparison of patients ≤65 vs >65 years of age

-In MM-398+5FU/LV arm, the mOS was 8.87 and 5.42 months, respectively, with a HR 1.55.

-In the control arm, the HR was 0.97.

-For monotherapy with MM-398, the mOS were similar for patients under and over 65y (HR 0.90).

Despite poorer outcome in patients >65 y vs. ≤65 in the combination arm, the HR versus 5FU/LV was 0.73.

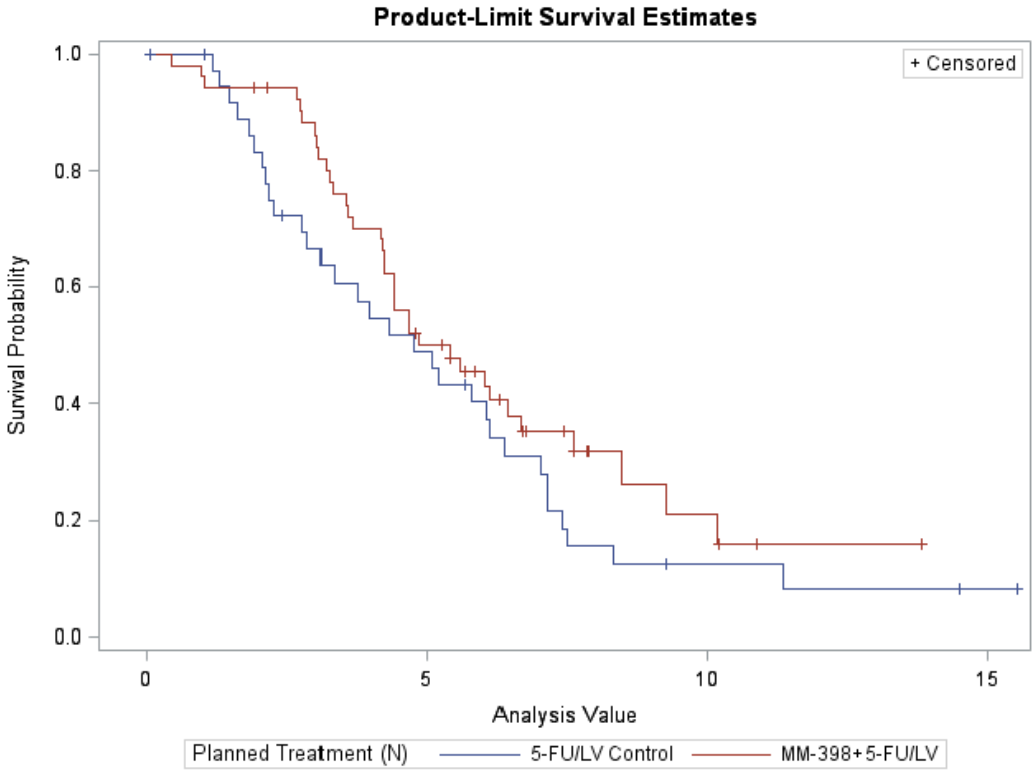


Figure 9: Kaplan Meier curves for patients age > 65 in NAPOLI-1 (MM-398 + 5-FU/LV vs its corresponding control)

Table 34: Survival estimates for patients age >65 in NAPOLI-1 (MM-398 + 5-FU/LV vs its corresponding control)

	MM-398+5-FU/LV (N=52)					5-FU/LV (N=38)			
	Survival					Survival			
Month	Estimate	Std Err	Number Failed	Number at risk		Estimate	Std Err	Number Failed	Number at risk
1	0.96	0.027	2	50		1	0	0	37
2	0.94	0.032	3	48		0.83	0.062	6	30
3	0.88	0.045	6	44		0.66	0.079	12	23
4	0.70	0.065	15	35		0.55	0.084	16	19
5	0.50	0.071	25	24		0.49	0.084	18	17
6	0.46	0.071	27	18		0.40	0.083	21	13
7	0.35	0.072	31	11		0.31	0.080	24	10
8	0.32	0.073	32	6		0.15	0.063	29	5
9	0.26	0.077	33	5		0.12	0.058	30	4
10	0.21	0.078	34	4		0.12	0.058	30	3
11	0.16	0.074	35	1		0.12	0.058	30	3
12	0.16	0.074	35	1		0.08	0.051	31	2

- Sex

The gender-related differences in OS are minimal.

- Ethnicity

No statistically significant difference in OS is observed between Caucasians and East-Asians, HR 0.62 and 0.49, respectively.

Supportive studies

- **PEP0208:** a phase II study of liposomal irinotecan (formerly PEP02) in patients with metastatic pancreatic cancer previously treated with gemcitabine containing regimens.

The results of PEP0208 led to the development of the phase 3 NAPOLI-1 study, which is the basis for this marketing authorization application. Forty (40) patients were enrolled to receive single-agent MM-398 120 mg/m^2 q3w until disease progression. Median OS was 5.2 months. Tumour response rate in the PP population was 7.5% and involved 3 patients with PR.

- **PEP02** (human plasma protein binding to liposomal irinotecan)
- **PEP0201** (phase I, DLT and MTD in solid tumours).

The MTD was determined as a dose of 120mg/m^2 while in PEP02 MM-398 was given as a 90-minute infusion on a q3w schedule, and chosen as recommended dose of MM398 single agent in future studies.

- **PEP0202:** a Phase I Dose Escalation Study Followed by Multi-National, Open-Label Randomized Phase II Study Evaluating the Efficacy and Tolerability of PEP02 with or without Cisplatin in Patients with Recurrent or Metastatic Squamous Carcinoma of the Uterine Cervix).

When the dose was escalated to the second level (MM-398 80 mg/m2 + cisplatin 60 mg/m2), two of the patients in this cohort developed SAEs which led to death. The study was terminated before the MTD of MM-398 in combination with cisplatin 60 mg/m2 given every 3 weeks could be determined.

- **PEP0203:** a multi-center, open-label phase I dose-escalation study of PEP02 in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in advanced solid tumours.

MTD of MM-398 was determined to be 80 mg/m2. All treatment-related AEs and grade III or above at the MTD dose level were 51.1% and 10.6%, respectively.
Among the 15 efficacy evaluable patients with advanced solid tumour refractory to standard systemic treatment, the best tumour response were confirmed as PR in 2, SD in 9 and PD in 5. The overall tumour response rate and disease control rate were 13.3% and 73.3%, respectively. The dose of 80 mg/m^2 of PEP02 in combination with D1 and D8 infusion of 5-FU/LV in q3w schedule was recommended for the future phase II studies.

- **PIST-CRC:** a phase I and Pharmacokinetic Study of Biweekly MM-398 in Patients with Metastatic Colorectal Cancer Refractory to First-line Oxaliplatin-based Chemotherapy)

Of the 18 treated patients, the overall response rate achieved 22.2%. There were 4 patients with partial response (PR) (2 in 80mg/ m^2, 1 in 90 mg/ m^2, 1 in 100 mg/ m^2), 9 patients with stable disease (SD), and 5 with progressive disease (PD). The disease control rate was 72.2%.

- **PEP0206** : a randomized phase II Study of MM-398, Irinotecan or Docetaxel as a Second Line Therapy in Patients with Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

The number of patients with confirmed partial or complete response (PR or CR) was 6 in the MM-398 arm (objective tumour response rate of 13.6%), 3 in the irinotecan arm (6.8%), and 7 in the docetaxel arm (15.9%). No differences were seen in the mPFS: MM-398, 81 days, irinotecan 79.5 days, docetaxel 82 days. The 3 treatments showed similar efficacy in terms of the survival parameters.

- **PEPCOL:** a randomized phase II study of MM-398 or irinotecan in combination with leucovorin and 5-fluorouracil as second-line therapy in patients with unresectable metastatic colorectal cancer

Fifty-five patients with unresectable mCRC who had failed one prior oxaliplatin-based first-line therapy were randomly assigned to FUPEP (MM-398 80 mg/m² d1, folinic acid (FA) 400 mg/m² d1, 5-FU 2,400 mg/m² d1-2) or FOLFIRI (FOLFIRI1: irinotecan 180 mg/m² d1, FA 400 mg/m² d1, 5-FU bolus 400 mg/m² d1, 5-FU infusion 2,400 mg/m² d1-2; or modified FOLFIRI3: irinotecan 90 mg/m² d1 and 3, FA 400 mg/m² d1, 5-FU infusion 2,400 mg/m² d1-2). Bevacizumab q2w (5 mg/kg) was allowed in both arms as of June 2012 (TML study report). The primary endpoint was the objective tumour response (OR). OR rate were 16.7% (n=4/24) and 11.5% (n=3/26) in the FUPEP and the FOLFIRI arms, respectively. Most common grade 3-4 adverse events reported in the respective FUPEP and the FOLFIRI arms were diarrhoea (21% vs 33%), neutropenia (11% vs 30%), mucositis (11% vs 11%), and alopecia (G2: 25% vs 26%).

Translational research

Translational samples have been collected from a subset of consenting patients: archival tumour material has been collected from 26% of the patients, while plasma and whole blood PAXgene material has been collected from 47% of the patients. Discussions with vendors to evaluate best approaches, prioritization of sample use and methodologies as well as method development are ongoing.

2.5.3. Discussion on clinical efficacy

The MAA is based on one pivotal trial, NAPOLI-1, and several supportive studies.

The dose-escalation trial PEP0203 established the irinotecan dose of 80 mg/m^2, in combination with day 1 and day 8 5FU (2000 mg/m^2) / LV (200 mg/m^2) infusion q3w as the recommended schedule for further studies.

The PEPCOL trial (a randomized phase II study of MM-398 or irinotecan in combination with leucovorin and 5-fluorouracil as second-line therapy in patients with unresectable metastatic colorectal cancer) was the basis for the introduction of the combination arm (MM-398+5FU/LV) in the pivotal NAPOLI-1 trial; in PEPCOL, a combination of MM-398 (given q2w at a dose of 80 mg/m^2 to patients with metastatic colorectal cancer previously treated with oxaliplatin) with 5-FU (2400 mg/m^2 day1-2) / LV (400 mg/m^2 day 1) was administered with encouraging tumour response and less AEs (namely diarrhoea and neutropenia) than in the FOLFIRI arm.

Design and conduct of clinical studies

The study was subject to CHMP advice when a third arm (MM-398 + 5FU/LV) was proposed to be added to the ongoing MM-398 vs. 5FU/LV study. In the advice it was recommended that the design should be simplified, comparing MM-398 vs. standard irinotecan both on top of 5FU/LV, meaning that a completely new study was recommended. For obvious reasons this design would have provided a more straight forward possibility to assess the benefit of MM-398 compared with standard irinotecan.

Irinotecan in regimens such as FOLFIRI, however, has not been demonstrated to be beneficial in pancreatic cancer after failure on gemcitabine. Whilst not considered to be the most informative, the design, including 5FU/LV alone as reference therapy, is accepted from a regulatory perspective.

The 5FU/LV regimens in the control arm B versus the experimental arm C are dissimilar enough to warrant further discussion:

In the experimental arm (MM-398+5-FU/LV, arm C), the nominal dose of 5-FU was 2,400 mg/m^2 IV over 46 hours every 2 weeks, per 6 weeks 7,200 mg/m^2. Over a mean of 15 weeks of exposure, this led to a 6-week average dose intensity of 5065 mg/m^2 and relative dose intensity for 5FU of 83.9%.

In the control arm (5-FU/LV, arm B), the nominal dose of 5-FU was 2,000 mg/m^2 IV over 24 hours, administered weekly for the first 4 weeks, followed by 2 weeks' rest, per 6 weeks 8,000 mg/m^2. Over a mean of 10 weeks of exposure; the 6-week average dose intensity was 6,710 mg/m^2. The relative dose intensity for 5FU is 95.7%.

The nominal 6-week dose of 5FU was thus slightly higher in the control arm (8,000 vs. 7,200), but the infusion time was shorter (24 vs. 46 h). To this may be added that LV dose also differed: 200 mg/m^2 (arm B) vs 400 mg/m^2 (arm C). Qualitatively, longer infusion time and higher LV dose would favour the experimental arm, whilst the higher dose would favour the control group. Quantitatively, however, the differences are considered minor and highly unlikely per se to result in a difference in PFS/OS between arms B and C.

The 6-week average dose intensity over the mean period of exposure is a function of variability in exposure time/completion of cycles and dose reductions; the main factor in both study arms being variable exposure time, most notable for the control arm, where the relative dose intensity was very high (96%). The high relative dose intensity in the control arm, however, shows that there was room for a more intensive 5FU/LV regimen.

The number of different 5FU/LV regimens still in clinical use is large, meaning that there is no "gold standard"; here illustrated by two second-line studies conducted in patients with pancreatic cancer who have received gemcitabine first-line. In the phase III PANCREOX trial mFOLFOX6 was compared with 5FU/LV. The selected control regimen was LV 400 mg/m^2 and 5FU 2400mg/m^2 over 46 hours q2w, i.e. the same as the background 5FU/LV regimen in arm C. This was a negative trial (OS HR 1.8, p=0.02).

In the phase III CONKO-003 trial, a combination of oxaliplatin with 5-FU/LV (OFF regimen) was compared with 5FU/LV. The control regimen was LV 200 mg/m^2 followed by a continuous IV infusion of fluorouracil 2,000 mg/m^2 over 24 hours on days 1, 8, 15, and 22. After a 3-week rest period from day 23 to 42, the second course was initiated on day 43 (i.e. day 1 of the second cycle). The 5FU/LV regimen was the same for the experimental and the control arm; the difference with the control arm in NAPOLI-1 lies in the more spaced administration of 5FU/LV in CONKO, i.e. a less intensive regimen. A survival benefit related to oxaliplatin add-on was shown, HR 0.68 p=0.01. Efficacy wise the two regimes, OFF and MM398+5FU/LV, are indeed similar. However, oxaliplatin causes long lasting neurotoxicity.

Table 35: Summary of various R-FU/LV regimens used

		NAPOLI-1		CONKO-003	PANCREOX
		Control	Combination regimen	Control	Control
LV	Dose (mg/m^2)	200	400	200	400
	Infusion time	30min	30min	30min	30min
5-FU	Dose (mg/m^2)	2000	2400	2000	2400
	Infusion time	24h	46h	24h	46h
Regimen		d1, 8, 15, 22	q2w	d1, 8, 15, 22	q2w
Rest period		**2w**		**3w**	

Although it would have facilitated the assessment of the add-on benefit of MM-398 if the same 5FU/LV regimen had been used as background and control, the control regimen in NAPOLI-1 cannot be viewed as too non-intensive.

In the monotherapy arm, MM-398 was administered at 120 mg/m^2 every 3 weeks and in the combination arm 80 mg/m^2 every 2 weeks, i.e. the same dose intensity over a 6-week period. It cannot be excluded that this difference influences the anti-tumour activity. Therefore the add-on benefit of 5FU/LV to MM-398 cannot be disentangled, but it is considered acceptable from a regulatory perspective.

The study population was heterogeneous, mainly in terms of prior lines of therapy and therefore also in terms of exposure to different cytotoxic agents. Apart from prior exposure to irinotecan (46 patients, 10%), this apparently did not influence to a major degree the relative activity of the combination regimen.

Efficacy data and additional analyses

The primary efficacy analysis of OS was performed when 305 deaths had occurred (data cut-off 14 February 2014).

The primary endpoint assessment showed a median OS gain of 1.9 months in favour of the experimental arm (6.1 vs 4.2 months, HR 0.67, p=0.0122). A median OS benefit of two months (i.e. an about 50% increase from 4 to 6 months) in this clinical setting is relevant from a regulatory perspective. However, the p-value is borderline significant, bearing in mind that the alpha was split at a significance level of 0.025.

The primary analysis was non-stratified although it is normally expected that the primary analysis is stratified according to the factors used for stratification (EMA/CHMP/295050/2013). KPS was the only notable imbalance in stratification factors and seemingly favoured the experimental arm. It should be noticed, however, that the HR in patients with KPS <90 is 0.54 vs. 0.79 in those with KPS ≥90.

As a sensitivity analysis, a stratified analysis is reported and shows a lower hazard ratio and a lower p-value: HR 0.57 vs 0.67, p-value 0.0009 vs 0.012. These results, in the CHMP preferred analysis, make the “borderline concern” less of an issue.

Fourteen (14) patients in the control group did not receive any study drug but were analysed as if they had received 5 FU/LV causing a possible OS bias. A more conservative analysis with the imputation of OS times for patients who did not have observed OS time due to early discontinuation from OS follow-up was provided. The outcome of the imputed dataset simulations both stratified and non-stratified, yielded similar values, therefore supporting the robustness of the primary OS analysis.

Among the pre-planned OS subgroup analyses, a treatment effect favouring the 5-FU/LV over the combination arm has been observed for ethnicity other than caucasian and east asian, prior Whipple and prior irinotecan. This observation is also confirmed by univariate and multivariate analyses conducted to identify possible prognostic factors for both OS and PFS, which consistently showed prior irinotecan together with age>65 to negatively impact on the prognosis of patients treated with the combination arm.

Despites the limitations of subgroup analyses, the observation in patients pre-treated with irinotecan raises concerns due to the increasing use of irinotecan-containing regimen as first line therapy. Based on the limited data provided in patients with prior exposure to irinotecan, moreover showing no advantage (if not a detrimental effect) over 5FU/LV, the benefit of Onivyde in patients previously treated with an irinotecan-based regimen has not been demonstrated (see sections 4.4 and 5.1 of the SmPC).

The PFS was assessed by the investigator, not by IRC. The combination of MM-398+5-FU/LV achieved a median PFS of twice that of the control arm of 5-FU/LV (3.1 vs 1.5 months, HR 0.56, p=0.0001).

The combination of MM-398+5-FU/LV achieved a median TTF of 2.3 months compared to 1.4 months for the control arm of 5-FU/LV, HR 0.60, p=0.0002. TTF results are thus consistent with PFS outcomes.

The confirmed ORR for MM-398+5-FU/LV was 7.7% (95% CI: 2.86, 12.52) compared to 0.8% for 5-FU/LV. The confirmed ORR for MM-398 monotherapy was 3.3%, vs 0.7% for 5-FU/LV. As expected, the unconfirmed ORRs were higher than the confirmed ORRs: 16.2% for MM-398+5-FU/LV vs 0.8% of 5-FU/LV control arm; 6.0% for MM-398 vs 0.7% for 5-FU/LV.

When comparing Onivyde monotherapy to 5FU/LV, the OS results are very similar with a HR 0.99. A trend towards better PFS results was observed, however the HR was 0.8, p=0.1. The unconfirmed ORR (RECIST 1.1) was 6% vs. 0.7% in the 5FU/LV arm. This trend towards higher activity of MM-398 is of some importance as it underlines that the survival benefit seen in the combination arm cannot be explained by the differences in the 5FU/LV regimens and is caused by the add-on effect of MM-398.

The decreases in the CA19-9 levels are consistent with the findings of other efficacy endpoints.

The main objective of CBR assessment was to show an improvement in pain intensity in the combination arm which was not observed.

Due to a very high attrition rate (only 60% had at least one post-baseline assessment), a conclusion on the effect of the addition of MM-398 to 5-FU/LV on the quality of life cannot be drawn.

In the combination arm, the OS outcome is clearly worse in patients above 65 years of age, but put in relation to the control arm, there is still a likely benefit in this group of patients (OS HR 0.7).

Discussions with participating investigators, key opinion leaders and internal experts are ongoing to determine priorities for the optimal studies on the translational samples collected in the context of the available results of the main study, NAPOLI-1, and emerging research in pancreatic cancer. Clinically relevant results will be communicated appropriately when they become available. Complete results will be provided as soon as possible, but are likely to be available in 2017, at the earliest. The Applicant is recommended to submit the results of the translational research as soon as available.

2.5.4. Conclusions on the clinical efficacy

The efficacy results observed with Onivyde in terms of OS benefit and supportive evidence are considered clinically meaningful and statistically sufficiently robust to support approval in metastatic pancreatic cancer.

The place of Onivyde in the algorithm of treatment in metastatic pancreatic cancer should be carefully considered given the increased use of FOLFIRINOX as first line therapy and the limited number of patients in the pivotal NAPOLI-1 study previously treated with both gemcitabine and irinotecan.

The CHMP considers the following measures necessary to address issues related to efficacy:

The Applicant is recommended to conduct and submit the results of a translational research program in pancreatic cancer based on samples collected from completed and ongoing studies.

2.6. Clinical safety

The table below summarises the safety database used for the assessment of Onivyde.

Table 36: Clinical Studies with MM-398 for Assessment of Safety

Study Identifier	Study Design	Test Product(s); Dosage Regimen	N	Diagnosis of Patients	MM-398 Treated Patients
MM-398-07-03-01 (NAPOLI-1)[a]	Open label, randomized, phase 3	Arm A: MM-398 120 mg/m^2 q3w Arm B: 5-FU 2000 mg/m^2+LV 200 mg/m^2 qw Arm C: MM-398 80 mg/m^2 + 5-FU 2400 mg/m^2 + LV 400 mg/m^2 q2w	417	Metastatic pancreatic cancer	264
PEP0208[a]	Open label, single arm, phase 2	MM-398 120 mg/m^2 q3w	40	Metastatic pancreatic cancer	40
PEP0206[a]	Open label, randomized, phase 2 study	Arm 1: MM-398 120 mg/m^2 q3w Arm 2: irinotecan 300 mg/m^2 q3w Arm 3: docetaxel 75 mg/m^2 q3w	132	Gastric & GEJ cancer	44
PEP0201[a]	Phase 1	MM-398 60, 120, 180 mg/m^2 q3w	11	Solid tumours	11
PEP0202[a]	Phase 1/2 study	MM-398: 60 and 80 mg/m^2 q3w + cisplatin: 60 mg/m^{2}q3w	6	Metastatic cervical cancer	6
PEP0203[a]	Phase 1 of MM-398 in combination with 5-FU/LV	MM-398: 60, 80, 100, 120 mg/m^2 q3w 5-FU: 2000 mg/m^2 on Day 1 and 8 q3w Leucovorin: 200 mg/m^2 on Day 1 and 8 q3w	16	Solid tumours	16
PIST-CRC-01[a]	Phase 1	MM-398: 80, 90 and 100 mg/m^2 q2w	18	Colorectal cancer	18
MM-398-01-01-02 (CITS)[a] (ongoing)	Open-label	80 mg/m^2 every 2 weeks	13	Solid tumour	13
PEPCOL[b] (ongoing)	Open label, randomized, phase 2	Arm 1 FOLFIRI1 or modified FOLFIRI-3 +/- bevacizumab 5 mg/kg Arm 2 MM-398 80 mg/m^2 + 5-FU 2400 mg/m^2 + LV 400 mg/m^2 q2w IV +/- bevacizumab 5mg/kg	55	Colorectal cancer	28[c]

N=patients enrolled; FOLFIRI: folinic acid; 5-FU and irinotecan; 5-FU: 5-fluorouracil; LV: leucovorin; IV: intravenous; qw: every week; q2 week: every other week; q3w: every third week;
[a]Merrimack has access to clinical database and study reports
[b]Safety is summarized based on published report
[c]Among the 28 patients receiving MM-398 in combination with 5-FU/LV, 12 patients also received bevacizumab. In the irinotecan in combination with 5-FU/LV group, 13 out of 27 patients received bevacizumab.
Source: 2.7.4 Summary of Clinical Safety Table 3

Patient exposure

To assess the safety of Onivyde 80 mg/m^2 plus 5-FU 2400 mg/m^2 and leucovorin (LV) 400 mg/m^2 administered every 2 weeks (q2w) in the proposed indication for pancreatic cancer, the most relevant data source is the safety analysis of the Phase 3, randomized controlled NAPOLI-1 study, focusing on the MM-398+5- FU/LV combination arm. The monotherapy Onivyde (120mg/m^2) was also analysed in detail in order to identify undesirable effects associated with Onivyde that may not been uncovered from the Onivyde +5-FU/LV combination arm.

Other than NAPOLI-1, only two studies contain Onivyde safety data in combination with 5-FU and LV, albeit in different patient populations:

1. PEPCOL, an investigator sponsored study in colorectal cancer

2. PEP0203 Phase 1 study in solid tumours

PEPCOL employed the same dose and schedule as studied in NAPOLI-1, whereas the PEP0203 study employed an every-3-week (Q3W) MM-398 dosing schedule. MM-398 doses were escalated: 60, 80, 100 and 120 mg/m^2. The dose and schedule for PEP0203 5-FU/LV administration was 5-FU 2000 mg/m2 mixed with leucovorin 200 mg/m2 as a 24-hour continuous infusion on Days 1 and 8, every 21 days (3 weeks).

All other studies with Onivyde (including an experimental arm of Onivyde 120 mg/m2 IV Q3W in the NAPOLI-1 study) were conducted as a monotherapy or in combination with agents other than 5-FU and leucovorin (PEP0201, PIST-CRC, PEP0206, PEP0208, CITS) or in combination with cisplatin (PEP0202). For these reasons, no formal pooling of the safety data from the NAPOLI-1 study with other studies was conducted.

Overall, 440 patients have received Onivyde in the completed and ongoing studies as of 14 February 2014. The 440 patients treated with Onivyde in these clinical trials had a variety of advanced solid tumours with high unmet medical need. The largest patient exposure to Onivyde has been in patients with advanced metastatic pancreatic cancer (a total of 304 patients), primarily in the Phase 3 study, NAPOLI-1 (264 patients).

Table 37: Clinical Studies with MM-398 for Assessment of Safety

Study Identifier	Study Design	Test Product(s); Dosage Regimen	N	Diagnosis of Patients	MM-398 Treated Patients
MM-398-07-03-01 (NAPOLI-1)[a]	Open label, randomized, phase 3	Arm A: MM-398 120 mg/m^2 q3w Arm B: 5-FU 2000 mg/m^2+LV 200 mg/m^2 qw Arm C: MM-398 80 mg/m^2 + 5-FU 2400 mg/m^2 + LV 400 mg/m^2 q2w	41 7	Metastatic pancreatic cancer	264
PEP0208[a]	Open label, single arm, phase 2	MM-398 120 mg/m^2 q3w	40	Metastatic pancreatic cancer	40
PEP0206[a]	Open label, randomized, phase 2 study	Arm 1: MM-398 120 mg/m^2 q3w Arm 2: irinotecan 300 mg/m^2 q3w Arm 3: docetaxel 75 mg/m^2 q3w	13 2	Gastric & GEJ cancer	44
PEP0201[a]	Phase 1	MM-398 60, 120, 180 mg/m^2 q3w	11	Solid tumors	11
PEP0202[a]	Phase 1/2 study	MM-398: 60 and 80 mg/m^2 q3w + cisplatin: 60 mg/m^{2}q3w	6	Metastatic cervical cancer	6
PEP0203[a]	Phase 1 of MM-398 in combination with 5-FU/LV	MM-398: 60, 80, 100, 120 mg/m^2 q3w 5-FU: 2000 mg/m^2 on Day 1 and 8 q3w Leucovorin: 200 mg/m^2 on Day 1 and 8 q3w	16	Solid tumors	16
PIST-CRC-01[a]	Phase 1	MM-398: 80, 90 and 100 mg/m^2 q2w	18	Colorectal cancer	18
MM-398-01-01-02 (CITS)[a] (ongoing)	Open-label	80 mg/m^2 every 2 weeks	13	Solid tumor	13
PEPCOL[b] (ongoing)	Open label, randomized, phase 2	Arm 1 FOLFIRI1 or modified FOLFIRI-3 +/- bevacizumab 5 mg/kg Arm 2 MM-398 80 mg/m^2 + 5-FU 2400 mg/m^2 + LV 400 mg/m^2 q2w IV +/- bevacizumab 5mg/kg	55	Colorectal cancer	28[c]

N=patients enrolled
FOLFIRI: folinic acid
5-FU and irinotecan; 5-FU: 5-fluorouracil
LV: leucovorin
IV: intravenous
qw: every week
q2 week: every other week
q3w: every third week
[a]Merrimack has access to clinical database and study reports
[b]Safety is summarized based on published report
[c]Among the 28 patients receiving MM-398 in combination with 5-FU/LV, 12 patients also received bevacizumab. In the irinotecan in combination with 5-FU/LV group, 13 out of 27 patients received bevacizumab.

Due to the differences in dose/dose regimen among study arms, the patient exposure was presented and discussed in the clinical efficacy section.

Adverse events

The Safety Analysis Population from the pivotal study NAPOLI-1 includes **398** of the 417 patients randomized in this study, who received at least one dose of study drug.

Adverse events (AEs) are coded using MedDRA version 14.1 Treatment emergent adverse events (TEAEs) are defined as events that occurred or worsened on or after the day of first dose of the study drug and within 30 days after last administration of study drug.

Table 38: Summary of All Adverse Events (Safety Population) – NAPOLI-1

	MM-398 120 mg/m² (N=147) n (%)	MM-398 80mg/m2+5-FU/LV (N=117) n (%)	5-FU/LV (N=134) n (%)
Subjects with at least one AE	146 (99.3)	116 (99.1)	132 (98.5)
Subjects with at least one TEAE	145 (98.6)	116 (99.1)	132 (98.5)
Subjects with CTCAE grade 3 or higher TEAE	112 (76.2)	90 (76.9)	75 (56.0)
Subjects with TEAE related to study drug	128 (87.1)	107 (91.5)	93 (69.4)
Subjects with drug related AE of CTCAE grade 3 or higher	76 (51.7)	63 (53.8)	24 (17.9)
Subjects with Grade 3 as most severe toxicity [a]	54 (36.7)	53 (45.3)	21 (15.7)
Subjects with Grade 4 as most severe toxicity [b]	18 (12.2)	9 (7.7)	3 (2.2)
Subjects with Grade 5 as most severe toxicity [c]	4 (2.7)	1 (0.9)	0
Subjects with serious TEAE	90 (61.2)	56 (47.9)	60 (44.8)
Subjects with TEAE leading to any dose modification	81 (55.1)	83 (70.9)	48 (35.8)
Subjects with TEAEs resulting in dose delay	49 (33.3)	72 (61.5)	43 (32.1)
Subjects with TEAE leading to dose reduction	46 (31.3)	39 (33.3)	5 (3.7)
Subjects with TEAE leading to dose discontinuation	17 (11.6)	13 (11.1)	10 (7.5)

Source: 5.3.5.1 NAPOLI-1 CSR Table 8-5

TEAEs by SOC

Table 39: Summary of Most Common Treatment Emergent Adverse Events by System Organ Class – NAPOLI-1

System Organ Class- - MedDRA version 14.1	MM-398 (N=147) n (%)	MM-398+5-FU/LV (N=117) n (%)	5-FU/LV (N=134) n (%)
Number of Subjects With Any TEAE(s)	145 (98.6)	116 (99.1)	132 (98.5)
Gastrointestinal disorders	140 (95.2)	108 (92.3)	109 (81.3)
General disorders and administration site conditions	107 (72.8)	84 (71.8)	80 (59.7)
Metabolism and nutrition disorders	106 (72.1)	73 (62.4)	67 (50.0)
Blood and lymphatic system disorders	68 (46.3)	**67 (57.3)**	36 (26.9)
Investigations	69 (46.9)	56 (47.9)	35 (26.1)
Infections and infestations	54 (36.7)	45 (38.5)	35 (26.1)
Nervous system disorders	41 (27.9)	36 (30.8)	27 (20.1)
Skin and subcutaneous tissue disorders	49 (33.3)	33 (28.2)	39 (29.1)
Respiratory, thoracic and mediastinal disorders	42 (28.6)	27 (23.1)	30 (22.4)
Musculoskeletal and connective tissue disorders	24 (16.3)	26 (22.2)	36 (26.9)
Psychiatric disorders	21 (14.3)	17 (14.5)	20 (14.9)
Injury, poisoning and procedural complications	6 (4.1)	15 (12.8)	13 (9.7)
Vascular disorders	15 (10.2)	14 (12.0)	18 (13.4)
Hepatobiliary disorders	18 (12.2)	9 (7.7)	11 (8.2)
Renal and urinary disorders	19 (12.9)	7 (6.0)	10 (7.5)
Cardiac disorders	8 (5.4)	4 (3.4)	5 (3.7)
Eye disorders	3 (2.0)	4 (3.4)	5 (3.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (4.1)	4 (3.4)	6 (4.5)
Immune system disorders	1 (0.7)	3 (2.6)	1 (0.7)
Ear and labyrinth disorders	3 (2.0)	2 (1.7)	2 (1.5)
Reproductive system and breast disorders	3 (2.0)	2 (1.7)	0

For most SOCs, the AEs that occurred/worsened from the first day of drug administration till up to 30 days to the last dose were more frequent in the MM-398 monotherapy arm, followed closely by the combination arm.

The most striking difference between the experimental arms in the opposite sense is 'blood': 46.9% AEs in the monotherapy arm, compared to 57.3% in the combination arm.

TEAE causality

Table 40: Most Common Treatment Emergent Adverse Events Related to Study Drug (≥10% of Patients in any Group)

MedDRA Preferred Term	MM-398 (N=147) n (%)	MM-398+5-FU/LV (N=117) n (%)	5-FU/LV (N=134) n (%)
Number of Subjects With Any Related TEAE(s)	**128 (87.1)**	**107 (91.5)**	**93 (69.4)**
Diarrhoea	91 (61.9)	55 (47.0)	20 (14.9)
Nausea	69 (46.9)	53 (45.3)	35 (26.1)
Vomiting	63 (42.9)	50 (42.7)	22 (16.4)
Fatigue	40 (27.2)	36 (30.8)	22 (16.4)
Decreased appetite	44 (29.9)	32 (27.4)	16 (11.9)
Neutropenia	22 (15.0)	**25 (21.4)**	3 (2.2)
Anaemia	27 (18.4)	20 (17.1)	12 (9.0)
Asthenia	20 (13.6)	18 (15.4)	5 (3.7)
White blood cell count decreased	10 (6.8)	**17 (14.5)**	2 (1.5)
Neutrophil count decreased	15 (10.2)	**16 (13.7)**	1 (0.7)
Alopecia	30 (20.4)	14 (12.0)	6 (4.5)
Weight decreased	12 (8.2)	14 (12.0)	3 (2.2)
Stomatitis	4 (2.7)	14 (12.0)	6 (4.5)
Abdominal pain	17 (11.6)	7 (6.0)	5 (3.7)

The TEAE causality is in line with the known safety profile of standard irinotecan, i.e. gastrointestinal AEs and hematotoxicity.

AEs' incidence and severity was proportional with dose intensity in the MM-398 containing arms, with the exception of the PTs 'neutropenia', 'WBC decreased', 'neutrophil count decreased'. 'Fatigue' and 'asthenia' were also more frequently observed in the combination arm. With regards to common TEAEs ≥ gr 3 (see also AESI), diarrhoea and vomiting were the leading AEs in MM-398 containing arms, and the incidence was proportional with the exposure to drug.

Adverse drug reactions

In order to determine the adverse drug reactions of MM-398 and to derive the frequencies of these adverse drug reactions for labelling, the following analyses of NAPOLI-1 study were performed.

Any grade treatment emergent adverse events that occurred 3% higher frequency and/or Grade 3 or higher TEAES that occurred 2% higher frequency in either the MM-398 monotherapy or MM-398+5-FU/LV combination arms compared to the 5-FU-LV control arms were tabulated using MedDRA Preferred Terms.

A similar analysis was performed using clustering of certain single MedDRA PT into medically relevant groups in order to avoid underreporting of adverse reactions frequencies due to the similarities between some single MedDRA Preferred Terms. In addition to the cumulative frequencies of treatment emergent adverse events, an exposure adjusted adverse event rate was also calculated per person-years as n/T, where n=number of subjects with specified event and T=total person-years. Person-years were calculated as the time from the first dose date to:

- the onset date of first event for subjects with event (patients with the event)

- the minimum of (date of last dose + 30 days, date of death, February 14, 2014) (patients without the event)

The following table of ADRs has been established on the basis of the criteria described above.

Table 41: Adverse Reactions Reported with Onivyde therapy in NAPOLI-1

MedDRA* System Organ Class	Adverse reaction	Frequency (%)
Infections and infestations	Septic shock	2.3
	Sepsis	3.0
	Pneumonia	3.4

MedDRA* System Organ Class	Adverse reaction	Frequency (%)
	Febrile neutropenia	3.8
	Gastroenteritis	3.0
	Oral candidiasis	3.8
	Biliary sepsis	0.8
Blood and lymphatic system disorders	Neutropenia	18.6
	Leukopenia	10.3
	Anaemia	34.8
	Thrombocytopenia	4.3
	Lymphopenia	1.9
Immune system disorders	Hypersensitivity	0.8
Metabolism and nutrition disorders	Hypokalaemia	17.4
	Hypomagnesaemia	10.2
	Dehydration	10.2
	Decreased appetite	47.0
	Hypoglycaemia	3.4
	Hyponatraemia	5.7
	Hypophosphataemia	3.4
Psychiatric disorders	Insomnia	8.0
Nervous system disorders	Dizziness	12.1
	Cholinergic syndrome	0.7
	Dysgeusia	3.8
Cardiac disorders	Hypotension	4.9
Vascular disorders	Pulmonary embolism	3.4
	Embolism	1.4
	Deep vein thrombosis	1.9
	Thrombosis	0.8
Respiratory, thoracic and mediastinal disorders	Dyspnoea	7.6
	Dysphonia	2.7
	Hypoxia	0.8
Gastrointestinal disorders	Diarrhoea	65.2
	Vomiting	53.4
	Nausea	56.4
	Abdominal pain	29.2
	Stomatitis	13.7
	Colitis	1.1
	Haemorrhoids	3.4
	Oesophagitis	0.8
	Proctitis	0.8
Hepatobiliary disorders	Hypoalbuminaemia	12.9
Skin and subcutaneous tissue disorders	Alopecia	18.2
	Rash maculo-papular	0.8
	Nail discolouration	0.8
Renal and urinary disorders	Acute renal failure	2.3
General disorders and administration site conditions	Pyrexia	21.2
	Peripheral oedema	15.5
	Mucosal inflammation	10.3
	Fatigue	38.3

MedDRA* System Organ Class	Adverse reaction	Frequency (%)
	Asthenia	22.3
	Infusion related reaction	2.3
	Oedema	1.9
Investigations	Weight decrease	18.6
	Increased bilirubin	3.8
	Increased alanine aminotransferase	4.9
	Increased aspartate aminotransferase	4.2
	Increased international normalized ratio	1.5

Serious adverse event/deaths/other significant events

SAEs

The incidence of SAEs in MM-398 containing arms was generally proportional with the exposure to liposomal irinotecan, with exception of 'infections and infestations'.

AESI: the AESIs were defined based on the known safety profile of Onivyde and on Camptosar label.

Longitudinal data for AESI were requested and provided by the Applicant, as well as the prevalence/incidence of AESI overall and by grade ≥3, however not per treatment cycle. Information on any repeated gr3 or 4 AESI were provided.

Most AESIs are early or very early events, according to the data; they wane / disappear after an average of six administrations. In the context of NAPOLI-1, six doses make up for 3 months (MM-398 administered q2w) of combination therapy and 4.5 moths for MM-398 monotherapy.

A brief look at the line listings reveals that the patients still in treatment after 6 doses are about a third from the total. So it is these patients who begin to benefit from a milder AESI profile of the treatment.

Table 42: Frequency of Treatment Emergent Adverse Events of Special Importance, NAPOLI-1 Study

AESI	MM-398 (N=147) n (%)		MM-398+5-FU/LV (N=117) n (%)		5-FU/LV (N=134) n (%)	
	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
Any AESI	140 (95.2)	91 (61.9)	113 (96.6)	71 (60.7)	115 (85.8)	46 (34.3)
Neutropenia	37 (25.2)	22 (15.0)	46 (39.3)	32 (27.4)	7 (5.2)	2 (1.5)
Leukopenia	41 (27.9)	24 (16.3)	53 (45.3)	34 (29.1)	10 (7.5)	2 (1.5)
Anaemia	49 (33.3)	16 (10.9)	45 (38.5)	12 (10.3)	31 (23.1)	9 (6.7)
Thrombocytopenia	8 (5.4)	1 (0.7)	15 (12.8)	3 (2.6)	9 (6.7)	-
Neutropenic fever/sepsis	7 (4.8)	6 (4.1)	4 (3.4)	3 (2.6)	1 (0.7)	-
diarrhoea	105 (71.4)	34 (23.1)	69 (59.0)	17 (14.5)	35 (26.1)	6 (4.5)
Nausea	89 (60.5)	8 (5.4)	60 (51.3)	9 (7.7)	46 (34.3)	4 (3.0)
Vomiting	80 (54.4)	20 (13.6)	61 (52.1)	13 (11.1)	35 (26.1)	4 (3.0)
Stomatitis	17 (11.6)	-	37 (31.6)	5 (4.3)	16 (11.9)	1 (0.7)
Gastrointestinal nonspecific inflammation	73 (49.7)	18 (12.2)	50 (42.7)	12 (10.3)	65 (48.5)	12 (9.0)
Colitis	5 (3.4)	1 (0.7)	1 (0.9)	-	-	-
Ileus	6 (4.1)	3 (2.0)	2 (1.7)	0	5 (3.7)	4 (3.0)
Cholinergic events	8 (5.4)	-	4 (3.4)	0	11 (8.2)	1 (0.7)
Acute pancreatitis	1 (0.7)	-	2 (1.7)	2 (1.7)	2 (1.5)	2 (1.5)
Hand-foot syndrome	3 (2.0)	-	3 (2.6)	0	5 (3.7)	0
Acute renal failure	10 (6.8)	4 (2.7)	6 (5.1)	-	6 (4.5)	1 (0.7)
Pulmonary toxicity (interstitial lung disease)	2 (1.4)	1 (0.7)	-	-	-	-
Thrombotic events[1]	21 (14.3)	10 (6.8)	7 (6.0)	4 (3.4)	12 (9.0)	9 (6.7)
Thrombotic events[2]	19 (12.9)	10 (6.8)	6 (5.1)	3 (2.6)	11 (8.2)	8 (6.0)
Infusion associated reactions	15 (10.2)	-	14 (12.0)	-	18 (13.4)	-
Infusion associated reactions, acute	3 (2.0)	-	8 (6.8)	-	8 (6.0)	-
Sepsis/bacteraemia	11 (7.5)	9 (6.1)	9 (7.7)	7 (6.0)	8 (6.0)	6 (4.5)

Diarrhoea

Severe diarrhoea occurred in 13% of patients in the combination arm. Diarrhoea starts early, after the first dose, but new onset diarrhoea is observed up to 4 doses. Early diarrhoea (onset day1, consistent with cholinergic hyperstimulation) occurred twice as frequently in the combination arm (29.9%) than in the other two arms. Late events (after day1) were more frequent in the monotherapy arm (66.7%) and in the combination arm (42.7%) than in the control arm. One third of the patients in the combination arm experience diarrhoea (mostly gr1-2) throughout the treatment, the prevalence of diarrhoea remains constant over time in MM-398 containing arms, however treatment discontinuation due to diarrhoea was very low. Diarrhoea is more frequent and more severe in Caucasians. However, diarrhoea was manageable with atropine/loperamide and supportive therapy.

Leukopenia/neutropenia

Neutropenia had the highest frequency reported after the initial two doses in the MM-398+5-FU/LV arm (any grade 13.7% and 16.3% respectively; ≥grade 3 neutropenia was 9.4% after the first and second dose). Neutropenia was generally present throughout MM-398 treatment with the highest any grade and ≥grade 3 prevalence after the second dose in the MM-398+5-FU/LV combination arm. In the MM-398+5-FU/LV arm the prevalence of any grade neutropenia ranged between 0-26.2 % while the prevalence of ≥grade 3 neutropenia was between 0-11.4%.

Neutropenic fever/sepsis: The incidence and prevalence frequencies by dose are similar for these acute events

which tended to occur early in the treatment. In the MM-398+5-FU/LV arm, 2 patients (1.9%) had an event after the second dose, 1 patient (1.3%) after the 3rd dose and 1 patient after the 9th dose. In the MM-398 monotherapy arm, 5 patients (3.4%) experienced and event after the first dose, 1 (0.8%) after the second dose and 1 patients (1.5%) after the 3rd dose. Almost all events of neutropenic fever/sepsis were grade 3 or higher severity.

Severe infections:

The incidence and prevalence of these acute events are similar regardless of the dose. All events were noted within the initial 5 doses of Onivyde administered in either Onivyde arms with one exception (1 patient was reported to have experienced septic shock after the 12th dose of Onivyde+5-FU/LV administration). The majority of the sepsis/bacteraemia events had a severity of grade 3 or higher.

Overall, severe neutropenia occurred in 20% of patients in the combination arm; severe neutropenic fever/sepsis in 3%; and fatal neutropenic sepsis in 0.8%. The cases of simultaneous occurrence of diarrhoea and neutropenia are especially complicated.

Patients with baseline serum bilirubin levels ≥1.0 mg/dL, or with deficient glucuronidation of bilirubin e.g. Gilbert's syndrome, may be at greater risk for leukopenia/neutropenia.

Patients with obstructing pancreatic head lesions and indwelling biliary stents experienced infectious complications such as ascending cholangitis and biliary sepsis that could be potentially life threatening in the setting of profound myelosuppression.

There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea; the clinician should be aware of the risk and complete blood cell counts should be performed in these patients.

Acute infusion reactions:

Acute infusion reactions (consisting of rash, urticaria, periorbital oedema or pruritus) were reported in 8 of 117 patients (6.8%) in the Onivyde+5-FU/LV arm, 3 of 147 patients (2.0%) in the Onivyde monotherapy arm, and 8 of 134 patients (6.0%) in the 5-FU/LV arm. New events (all grade 1 or grade 2) occurred generally early during Onivyde treatment, with only 2 out of 10 patients noted with events after the fifth dose.

Thromboembolic events

In NAPOLI-1, thromboembolic events were reported in up to 6% of the patients in the combination arm and up to 14.3% of patients treated Onivyde monotherapy. In clinical studies with Onivyde, deep vein thrombosis, pulmonary embolism, and embolism were considered common AEs.

Deaths attributed to treatment including Onivyde

The PFS event distribution is shown below:

	Monotherapy comparison		Combination therapy comparison	
	MM-398	5FU/LV	MM-398+5FU/LV	5FU/LV
Progressed	89 (58.9)	89 (59.7)	65 (55.6)	69 (58.0)
Died before progression	38 (25.2)	31 (20.8)	18 (15.4)	23 (19.3)

A trend towards fewer deaths before disease progression can be observed for the Onivyde+5FU/LV combination therapy.

In NAPOLI-1, most “treatment-related deaths” were observed in the Onivyde monotherapy arm, 4/147 (GI toxicity, DIC, septic shock and infectious colitis); in the combination arm, there was one drug-related death/117, namely septic shock.

Laboratory findings

Haematology

In NAPOLI-1, any grade decreased haemoglobin and decreased platelets were observed across arms, predominantly in the monotherapy and the combination arm; one case of gr4 thrombocytopenia was observed in the MM-398 arm. Any grade neutropenia was more frequent in the combination arm (51.8%), followed by monotherapy (35.6%), with control at 6%. Gr3 neutropenia had the same disposition: 15.8 vs 8.9 vs 2.3%. Gr4 neutropenia was at 7.5% in the MM-398 group, 4.4% in the combination arm, with no cases registered in the control arm.

Chemistry

In NAPOLI-1, changes in liver function tests and electrolytes were observed across arms: increased alkaline phosphatase, ALT, AST and decreased albumin; decreased K, Mg and Na. Gr3 (11 patients) and 4 (1 patient) hypopotassaemia were observed in MM-398 monotherapy arm; in the combination arm there was one gr 4 hypoK. As for hypoNa, in the monotherapy arm 14 patients experienced gr3 events and one a gr4 event.

The supportive studies seem to exhibit a similar pattern of laboratory findings.

Safety in special populations

Age

TEAEs by age group in all patients receiving Onivyde are summarised in the table below.

Table 43: Summary of Treatment-Emergent Adverse Events by Age Group - All patients receiving any MM-398: NAPOLI-1,PEP0201,PEP0202,PEP0203,PEP0206,PEP0208,PIST-CRC,398-01-01-02

Event type category	<65 N=242 n (%)	65-74 N=127 n (%)	75-84 N=41 n (%)	85+ N=2 n (%)
Any AE	240 (99.2)	125 (98.4)	41 (100.0)	2 (100.0)
Any Serious AE	121 (50.0)	60 (47.2)	26 (63.4)	1 (50.0)
Fatal	14 (5.8)	10 (7.9)	6 (14.6)	0
Hospitalization	112 (46.3)	57 (44.9)	26 (63.4)	1 (50.0)
Life-threatening	8 (3.3)	4 (3.1)	3 (7.3)	0
Disability	1 (0.4)	2 (1.6)	1 (2.4)	0
Other Med Signif.	9 (3.7)	6 (4.7)	2 (4.9)	0
AE leading to dropout	23 (9.5)	25 (19.7)	5 (12.2)	0
Psychiatric disorders	46 (19.0)	19 (15.0)	5 (12.2)	0
Nervous system disorders	75 (31.0)	42 (33.1)	12 (29.3)	1 (50.0)
Accidents and injuries	7 (2.9)	3 (2.4)	3 (7.3)	0
Cardiac disorders	15 (6.2)	6 (4.7)	3 (7.3)	0
Vascular disorders	27 (11.2)	14 (11.0)	4 (9.8)	0
Cerebrovascular disorders	1 (0.4)	5 (3.9)	0	0
Infections and infestations	93 (38.4)	47 (37.0)	17 (41.5)	0
Anticholinergic syndrome	93 (38.4)	46 (36.2)	13 (31.7)	1 (50.0)

Event type category	<65 N=242 n (%)	65-74 N=127 n (%)	75-84 N=41 n (%)	85+ N=2 n (%)
Sum of items[1]	37 (15.3)	21 (16.5)	7 (17.1)	1 (50.0)

Adverse events coded using MedDRA version 14.1.
[1]: Preferred terms: ORTHOSTATIC HYPOTENSION, FALL, LOSS OF CONSCIOUSNESS, DIZZINESS, SYNCOPE, AT AXIA, and any FRACTURE.
[2]: Preferred terms where (incidence in patients 65 and older)-(incidence in patients younger than 65) > 5.

Decrease in Quality of life by age group related to Onivyde treatment is reflected in the table below.

Table 44: Summary of Quality of Life Worsened by Age Group MM-398+5-FU/LV treated patients in NAPOLI-1, PRO Population

Event type category	<65 N=41 n (%)	65-74 N=24 n (%)	75-84 N=7 n (%)	85+ N=0 n (%)
Global Health Status Worsened	16 (39.0)	14 (58.3)	2 (28.6)	0

Based on changes in EORCTC-QLQ-C30 Global Health Status during the treatment period.
Global Health Status Worsened: Patient did not meet improvement criteria, defined as achievment of a 10 percentag e point increase
from baseline with improvement from baseline lasting at least 6 weeks,and either died OR had scores that decreased by percentage
points at a post baseline time point.

Overall, no major clinical differences in safety or efficacy were reported between patients ≥65 years and patients <65 years, although a higher frequency of discontinuation (14.8% vs. 7.9%) was noted in the former group treated with Onivyde+5-FU/LV in the NAPOLI-1 study and in some cases the adverse reactions did not resolve. Grade 3 or higher and serious treatment emergent adverse reactions were more frequent in patients < 65 years (84.1% and 50.8%) compared to patients ≥ 65 years (68.5 % and 44.4%). Conversely, patients > 75 years (n=12) experienced more frequent serious adverse reactions, dose delay, dose reduction and discontinuation compared to patients ≤ 75 years (n=105) when treated with Onivyde+5-FU/LV in the pancreatic adenocarcinoma study (see section 4.8 of the SmPC).

Table 45: Treatment emergent adverse events leading to treatment discontinuation

Group	Pt ID	Adverse Event Leading to Discontinuation	Age	Drug-related	Onset Date(Day)/ Resolution Date	Grade	Recovered
MM-398+5-FU/LV	114-0549	Gangrene and Pelvic Fracture	75	No	2013-09-07(18)	2	No
	136-0195	RENAL AND URINARY DISORDERS/ Acute Prerenal Failure	72	No	2013-03-27(57)/ 2013-04-03(64)	2	Yes
	421-0303	Vomiting, Diarrhea, Leukopenia, etc., considered as related to study	72	Yes	2013-04-25(16)	2	No
	617-0100	GASTROINTESTINAL DISORDERS/ Vomiting	67	Yes	2012-09-25(2)/ 2012-10-05(12)	3	Yes
	617-0185	Cerebrovascular Accident	70	Yes	2013-02-03(14)	3	No
	823-0197	Sepsis	66	Yes	2013-04-09(61)	3	Yes
	886-0285	Septic Shock/Neutropenia	80	Yes	2013-04-06(11)/ 2013-04-08(13)	5	No
5-FU/ LV	103-0068	ASTHENIA/weakness	75	No	2012-12-06(116	3	Yes
	111-0374	INVESTIGATIONS/NEUTROPHIL COUNT DECREASED	50	No	2013-05-23(15)/2013-06-12(35)	3	Yes
	121-0078	GASTROINTESTINAL DISORDERS	83	No	2012-11-16(73)/2012-11-30(87)	3	Yes

Hepatic Impairment

No dedicated hepatic impairment study has been conducted with Onivyde. In clinical studies of non-liposomal irinotecan administered on a weekly dosage schedule, patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dl) had a significantly greater likelihood of experiencing first cycle Grade 3 or Grade 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dl. No data are available for patients with total bilirubin > 2.0 mg/dl.

Renal Impairment

There are no safety data in patients with moderate to severe renal impairment.

Body Weight/BMI

Onivyde is dosed based on body surface area that is calculated using body weight. No further dose adjustment is recommended based on body weight or BMI. In NAPOLI-1 study, 5 of 8 underweight patients experienced a grade 3 or 4 adverse reaction, mostly myelosuppression, while 7 of the 8 patients required dose modification such as dose delay, dose reduction or dose discontinuation (see sections 4.4 and 4.8 of the SmPC).

Race

Compared to Caucasians, Asian patients were observed with a lower incidence of diarrhoea [14 (19.2%) out of 73 Caucasians had a ≥ Grade 3 diarrhoea, and 1 out of 33 (3.3%) Asians had a ≥ Grade 3 diarrhoea], but a higher incidence and higher severity of neutropenia. In patients receiving Onivyde+5-FU/LV, the incidence of ≥ Grade 3 neutropenia was higher among Asian patients [18 of 33 (55%)] compared to White patients [13 of 73 (18%)]. Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients compared to 1% of White patients (see section 4.8 of the SmPC).

Table 46: Observed incidence of grade ≥3 diarrhoea and neutropenia by race and by treatment in NAPOLI-1

Adverse Events	Treatment	Asians	Caucasians	Source
Diarrhea grade≥3, single MedDRA PT term	MM-398+5-FU/LV	3.0% (1/33)	19.2% (14/73)	NAPOLI -1 Clinical Study Report Table 14.3.2.8.2.3.1 and Table 14.3.2.8.2.3.2
	MM-398 alone	15.4% (8/52)	23.5% (20/85)	
Neutropenia grade≥3 (defined by product specific grouping for labeling)	MM-398+5-FU/LV	54.5% (18/33)	17.8% (13/73)	2.7.4. Summary Clinical Safety Section 2.7.4.2.1.6
	MM-398 alone	32.7% (17/52)	5.9% (5/85)	

Table 47: Predicted incidence of grade ≥3 diarrhoea and neutropenia by race based on population PK and exposure response analysis

Race	N	PK Param	Predicted Concentration with 80 mg/m^2 q2w			Predicted Incidence Rate of TEAEs Grade ≥ 3[a]		
			GLS mean	95%CI		Neu[b]	Neu[c]	Diarrhea
Caucasian	182	Total Irinotecan Cmax	29.76	29.29	30.24	NA	NA	14.7%
Asian	150		27.03	26.3	27.78	NA	NA	12.7%
Caucasian	182	SN-38 Converted Cmax	1.78	1.70	1.87	14.6%	25.8%	NA
Asian	150		2.76	2.62	2.90	21.4%	32.1%	NA

[a] Prediction of incidence rates of TEAEs were computed based on the estimates of univariate logistic regression obtained from exposure-safety relationship combined with the estimates of the predicted concentration of each subgroup from covariate analysis. The exposure used for neutropenia and anemia TEAEs was SN-38 Converted C_{max}, and the exposure for diarrhea TEAEs was CPT-11 C_{max}.

[b] Predicted incidence of grade ≥ 3 neutropenia based on logistic regression model estimated from all dataset (combined MM-398 monotherapy and MM-398+5FU/LV arm)

[c] Predicted incidence of grade ≥ 3 neutropenia based on logistic regression model estimated from MM-398+5FU/LV arm of Study MM-398-07-03-01

Additional notable clinically relevant differences in the frequency of other AEs include a higher rate of nausea, vomiting, decreased appetite and alopecia were reported for Asians compared to Caucasians in Onivyde containing arms. Fatigue was reported with higher frequency in the Caucasians compared to Asians.

Patients with prior Whipple procedure

In the clinical study evaluating Onivyde+5 FU/LV, patients with a prior Whipple procedure had a higher risk of serious infections following treatment with Onivyde+5 FU/LV [9 of 29 (30%) compared] to 11 of 88 (12.5%) patients with no prior Whipple procedure (see section 4.8 of the SmPC).

Patients with UGT1A1 allele

Individuals who are 7/7 homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from non-liposomal irinotecan. In the clinical study evaluating Onivyde+5-FU/LV, the frequency of ≥ Grade 3 neutropenia in these patients [2 of 7 (28.6%)] was similar to the frequency in patients not homozygous for the UGT1A1*28 allele who received a starting dose of Onivyde of 80 mg/m^2 [30 of 110 (27.3%)] (see sections 4.8 and 5.1 of the SmPC).

The Applicant provided data from NAPOLI-1 regarding the incidence /severity grade of leukopenia/neutropenia in UGT1A1*28 homozygous vs heterozygous patients during the first therapy cycle.

Table 48: Incidence and grade of neutropenia and diarrhoea AESI, NAPOLI-1 study, safety population, cycle 1, MM-398 + 5-FU/LV arm

Event	UGT1A1*28 6/6 (non-UGT1A1*28) N=63 n (%)		UGT1A1*28 6/7 or 6/8 (heterozygous UGT1A1*28) (N=47) n (%)		UGT1A1*28 7/7 (homozygous for UGTA1*28) (N=7) n (%)	
	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
Neutropenia	11 (17.5)	9 (14.3)	4 (8.5)	1 (2.1)	1 (14.3)	1 (14.3)
Diarrhea	23 (36.5)	4 (6.3)	14 (29.8)	3 (6.4)	1 (14.3)	0

Refer to Table 3.15.14.7, Table 3.15.14.5, Table 3.15.14.8, Table 3.15.14.1, Table 3.15.14.3 (in attachment)

Table 49: Incidence and grade of neutropenia and diarrhoea AESI, NAPOLI-1 study, safety population, cycle 1, MM-398 monotherapy arm

Event	UGT1A1*28 6/6 (non-UGT1A1*28) N=84 n (%)		UGT1A1*28 6/7 or 6/8 (heterozygous UGT1A1*28) (N=47) n (%)		UGT1A1*28 7/7 (homozygous for UGTA1*28) (N=7) n (%)	
	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
Neutropenia	15 (17.9)	10 (11.9)	10 (18.5)	4 (7.4)	1 (14.3)	0
Diarrhea	47 (56.0)	8 (9.5)	30 (55.6)	9 (16.7)	4 (57.1)	2 (28.6)

Refer to Table 3.15.14.7, Table 3.15.14.5, Table 3.15.14.8, Table 3.15.14.1, Table 3.15.14.3

The patients with UGT1A1*28 6/6 have been treated with higher doses than those with UGT1A1*28 7/7 (homozygous), leading to higher rates of neutropenia and diarrhoea in the former group.

Long-term safety data

Based on the limited number of patients who received MM-398 for more than 1 year (8 patients), and considering the across different characteristics (race, age, sex, dose exposure, TEAEs, grades, seriousness, dose modification), no specific patterns in frequency or types of AEs emerged in this long term safety population compared to the overall safety analysis population.

Safety related to drug-drug interactions and other interactions

No formal drug/drug interaction studies were performed. Interaction with other medicinal products has previously been described in the EU SmPC of irinotecan. In study MM-398-07-03-01(NAPOLI 1) Onivyde was administered in combination with 5-Fluorouracil and Leucovorin.

Compared to monotherapy administration, co-administration with 5-FU/LV in the Study MM-398-07-03-01 resulted in a reduced total irinotecan and SN-38 exposure.

Dose delays, dose reductions and discontinuations due to AEs

Table 50: Summary of dose reductions and treatment duration – NAPOLI-1

	MM-398 Mono (N=147)	5-FU/LV Mono Control (N=134)	MM-398+ 5-FU/LV Combo (N=117)	5-FU/LV Combo Control (N=105)
Subjects who had ≥1 dose reduction, n (%)	51 (34.7)	5 (3.7)	50 (42.7)	3 (2.9)
Subjects who had ≥2 dose reduction, n (%)	15 (10.2)	1 (0.7)	11 (9.4)	1 (1.0)
Subjects who had ≥3 dose reduction, n (%)	0	0	3 (2.6)	0
Treatment Duration ≥6 weeks, n (%)	118 (80.3)	100 (74.6)	84 (71.8)	76 (72.4)
Treatment Duration ≥12 weeks, n (%)	58 (39.5)	39 (29.1)	48 (41.0)	30 (28.6)
Treatment Duration ≥18 weeks, n (%)	33 (22.4)	21 (15.7)	41 (35.0)	16 (15.2)

The patients in MM-398+5FU/LV combination arm had more 1-dose and 3-dose reductions than the monotherapy arm, but also a treatment duration over 18 weeks in 35% of the patients (compared with 22.4 % in the monotherapy arm).

Dose delays

MM-398 monotherapy: 49 patients (33.3%) experienced TEAEs that required dose delay, mostly due to GI disorders (12.2%), followed by blood disorders (6.8%). The dose delay ranged from 14-33% during the first 10 doses administered, with delay of 7 days.

MM-398+5-FU/LV: dose delays were required in almost two thirds of the patients (61.5%). Neutropenia (14.5 %), WBC (12.0%), neutrophil count decreased (9.4%), diarrhoea (7.7%), fatigue (6.8%), vomiting (6.0%), and platelet decrease (5.1%) were the most common events requiring a dose delay; all other events were reported in less than 5% of patients. In the MM-398+5-FU/LV arm, 27% of patients required a dose delay in the beginning of the treatment with a subsequent gradual decrease in the frequency of patients who needed dose delay (range 8-17% during the first 10 doses administered). The median dose delay for most doses administered was 14 days, i.e. the investigators most often delayed treatment until the next scheduled treatment date.

5-FU/LV: 43 patients (32.1%) required dose delay due to TEAEs; mostly due to GI disorders (10.4%), and 'General Disorders and Administration Site Conditions (8.2%).

Dose reductions

MM-398 monotherapy: 46 patients (31.3%) experienced TEAEs that required dose reductions (34.7% subjects with more than one dose reduction). Diarrhoea was reported in 17 patients (11.6%) and vomiting in 9 patients (6.1%); all other events in this treatment group that required dose reductions were reported in less than 5% of patients.

MM-398+5-FU/LV: 39 patients (33.3%) experienced TEAEs that required dose reductions (42.7% subjects with more than one dose reduction in table 8.3). Neutropenia (10 patients, 8.5%), neutrophil count decreased (8 patients, 6.8%), diarrhoea (7 patients, 6.0%), and white blood cell count decreased (6 patients, 5.1%) were the most common events requiring a dose reduction; all other events were reported in less than 5% of patients. Dose reductions occurred in the first 6 cycles in the combination arm.

5-FU/LV: 5 patients (3.7%) required dose reductions due to TEAEs.

Discontinuations

Overall, 17 patients (11.6%) treated with MM-398 monotherapy experienced TEAEs leading to dose discontinuation, while with MM-398+5-FU/LV combination therapy, 13 patients (11.1%) required dose discontinuation; 7.5% of patients treated with 5-FU/LV required dose discontinuation.

Table 51: Adverse event discontinuations

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	11 (9.4)	5.2	5.1	1.7 – 9.1
5-FU/LV (combination control)	7 (5.9)	7.1	6.3	3.3 – 15.9
MM-398 monotherapy	17 (11.3)	9.5	5.0	1.7 – 29.7
5-FU/LV (monotherapy control)	10 (6.7)	8.3	6.5	3.0 – 17.0

Table 52: Clinical deterioration discontinuations

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	13 (11.1)	11.3	10.1	1.3 – 32.4
5-FU/LV (combination control)	12 (10.1)	9.5	8.5	1.3 – 25.7
MM-398 monotherapy	21 (13.9)	11.9	12.1	1.0 – 39.6
5-FU/LV (monotherapy control)	17 (11.4)	10.9	8.9	1.3 – 39.0

Table 53: Investigator decision

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	4 (3.4)	14.8	12.9	9.9 – 23.3
5-FU/LV (combination control)	4 (3.4)	3.4	3.2	1.1 – 6.1
MM-398 monotherapy	7 (4.6)	8.7	6.3	0.3 – 21.3
5-FU/LV (monotherapy control)	5 (3.4)	3.6	3.4	1.1 – 6.1

Table 54: Subject decision

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	14 (12.0)	6.7	5.4	0.6 – 14.1
5-FU/LV (combination control)	19 (16.0)	6.4	0.3	0.1 – 66.1
MM-398 monotherapy	17 (11.3)	9.1	7.0	2.1 – 20.3
5-FU/LV (monotherapy control)	20 (13.4)	6.2	0.5	0.1 – 66.1

Table 55: All reasons not related to PD (i.e. Discontinuations for progressive disease or death excluded)

Treatment Group	n (% of ITT)	Time to discontinuation (weeks)		
		Mean	Median	Min - Max
MM-398+5-FU/LV	44 (37.6)	8.6	7.8	0.6 – 32.4
5-FU/LV (combination control)	44 (37.0)	7.0	3.5	0.1 – 66.1
MM-398 monotherapy	62 (41.1)	10.1	6.8	0.3 – 39.6
5-FU/LV (monotherapy control)	55 (36.9)	7.7	4.0	0.1 – 66.1

2.6.1. Discussion on clinical safety

The safety database consists of 440 patients from 9 clinical studies. As the safety profile of the active substance is known, the size of the safety database is considered sufficient to assess the risks associated with MM-398/5FU/LV combination in the proposed indication. The pivotal study NAPOLI-1 was used to derive the Safety Analysis Population including 264 patients.

The most common AEs in the Onivyde-containing arms are similar to the known safety profile of standard irinotecan in cancer patients.

Diarrhoea is a very common adverse reaction leading to colitis, ileus, gastroenteritis, fatigue, dehydration, weight loss, renal toxicities, hyponatraemia, and hypokalaemia. Renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhoea. In the pivotal clinical study, Grade 3 or 4 diarrhoea occurred in 15 out of 117 patients (12.8%) receiving Onivyde +5-FU/LV. For patients experiencing late diarrhoea (> 24 hours), the median time to late diarrhoea onset was 8 days from the previous dose of Onivyde. Early onset diarrhoea, typically appearing ≤24 hours after dose administration, can occur and is usually transient. Early onset diarrhoea may also be accompanied by cholinergic symptoms that can include rhinitis, increased salivation, flushing, diaphoresis, bradycardia, miosis and hyperperistalsis that can induce abdominal cramping. In the pivotal clinical study, early diarrhoea onset occurred in 35 patients (29.9%) and cholinergic events occurred in 4 patients (3.4%) receiving Onivyde +5-FU/LV. In patients experiencing early diarrhoea, therapeutic and prophylactic atropine should be considered unless contraindicated. Patients should be made aware of the risk of delayed diarrhoea which can be debilitating and, on rare occasions, life threatening since persistent loose or watery stools can result in dehydration, electrolyte imbalance, colitis, gastrointestinal (GI) ulceration, infection or sepsis. As soon as the first liquid stool

occurs, the patient should start drinking large volumes of beverages containing electrolytes. Patients should have loperamide (or equivalent) readily available to begin treatment for late diarrhoea. Loperamide should be initiated at first occurrence of poorly formed or loose stools or at the earliest onset of bowel movements more frequent than normal. Loperamide should be given until patient is without diarrhoea for at least 12 hours. If diarrhoea persists while patient is on loperamide for more than 24 hours, adding oral antibiotic support (e.g. fluoroquinolone for 7 days) should be considered. Loperamide should not be used for more than 48 consecutive hours due to risk of paralytic ileus. If diarrhoea persists for more than 48 hours, stop loperamide, monitor and replace fluid electrolytes and continue antibiotic support until resolution for accompanying symptoms. Onivyde treatment should be delayed until diarrhoea resolves to ≤ Grade 1 (2 3 stools/day more than pre-treatment frequency). Onivyde must not be administered to patients with bowel obstruction and chronic inflammatory bowel disease, until it is resolved. Following Grade 3 or 4 diarrhoea, the subsequent dose of Onivyde should be reduced (see sections 4.2, 4.4 and 4.8 of the SmPC).

Myelosuppression, especially neutropenia, was more frequent and severe in the Onivyde-containing arms compared to the control arm, and were most frequent in the combination arm. Dose delay, dose reduction, and colony stimulating factors were used to manage myelosuppression. Complete blood cell count monitoring is recommended during Onivyde treatment. Patients should be aware of the risk of neutropenia and the significance of fever. The median time to nadir for ≥ Grade 3 neutropenia is 23 (range 8 - 104) days post first dose of treatment with Onivyde. Febrile neutropenia (body temperature > 38°C and neutrophil count ≤1,000 cells/mm^3) should be urgently treated in the hospital with broad spectrum intravenous antibiotics. Onivyde should be withheld if neutropenic fever occurs or the absolute neutrophil count drops below 1500/mm3. Sepsis with neutropenic fever and consequent septic shock with fatal outcome has been observed in patients with metastatic pancreatic adenocarcinoma treated with Onivyde. In patients who experienced severe haematological events, a dose reduction or treatment discontinuation is recommended (see sections 4.2 and 4.4). Patients with severe bone marrow failure should not be treated with Onivyde.

History of prior abdominal radiation increases the risk of severe neutropenia and febrile neutropenia following Onivyde treatment. Close monitoring of blood counts is recommended, and the use of myeloid growth factors should be considered for patients with a history of abdominal radiation. Caution should be exercised in patients receiving concurrent administration of Onivyde with irradiation.

Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with Onivyde.

Thrombocytopenia was infrequent, as has been documented with non-liposomal irinotecan.

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicinal products including Onivyde may result in serious or fatal infections; therefore vaccination with a live vaccine should be avoided. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished (see section 4.4 of the SmPC).

In patients treated with Onyvide, higher total irinotecan C_{max} is associated with higher probability of diarrhoea (gastrointestinal toxicity), and higher SN-38 C_{max} is associated with higher probability of developing neutropenia (bone marrow suppression).

As reported in the PK results, race was a strong covariate in the Onivyde treatment. In NAPOLI-I, Asians showed higher frequency of Grade ≥3 drug related TEAEs in the Onivyde combination arm compared to Caucasians **(72.7% vs 45.2%).** This is mainly due to an increased frequency of Grade 3 or higher neutropenia and febrile neutropenia in Asians compared to Caucasians. Diarrhoea was less frequent and less severe in Asians compared

to Caucasians in the MM-398 combination arm. This observation could be related to the high prevalence of UGT1A1*6 variant in Asian patients, and unfortunately this was not tested in the study.

The Applicant provided data from NAPOLI-1 regarding the incidence /severity grade of leukopenia/neutropenia in UGT1A1*28 homozygous vs heterozygous patients during the first therapy cycle.

A reduced starting dose of Onivyde (liposomal irinotecan) of 60 mg/ m2 should be considered for patients known to be homozygous for the UGT1A1*28 allele. Patients without drug related toxicities during the first cycle of therapy may have the dose of Onivyde increased to a total dose of 80 mg/m2 in subsequent cycles based on individual patient tolerance (see sections 4.2, 4.8 and 5.1 of the SmPC). In these patients, a new cycle of therapy should not begin until adverse event resolves to ≤ Grade 1. At a first occurrence of a Grade 3 or 4 adverse reaction (ADR), the Onivyde dose should be reduced to 50 mg/m^2. At a second occurrence of a Grade 3 or 4 ADR, the Onivyde dose should be reduced to 40 mg/$m^{2.}$ At a third occure, treatment should be discontinued.

Overall, the safety profiles of Onivyde monotherapy and Onivyde+5-FU/LV combination therapy were consistent with the safety profile of standard irinotecan and 5-FU.

In comparison with the reference product, certain known AEs of irinotecan have so far not been observed with Onivyde: anaphylaxis and anaphylactoid reactions; interstitial lung disease; acute pancreatitis, either because liposomal irinotecan does not exhibit these AEs or due to the limited safety database available.

The Onyvide+5-FU/LV combination was generally better tolerated than the Onyvide monotherapy (mostly due to less frequent and less severe GI adverse reactions), with the exception of higher incidence of neutropenia.

In the Onyvide+5-FU/LV arm, 27% of patients required a dose delay in the beginning of the treatment with a subsequent gradual decrease in the frequency of patients who needed dose delay (range 8-17% during the first 10 doses administered). The median dose delay for most doses administered was 14 days, i.e. the investigators most often delayed treatment until the next scheduled treatment date. For the Onyvide monotherapy arm the dose delay ranged from 14-33% during the first 10 doses administered, with delay of 7 days. Dose reductions occurred in the first 6 cycles in the combination arm. Regarding discontinuations, with the exception of a shorter mean time to discontinuation due to AEs in the combination arm, swift investigator decision in the control arm and subject's decision not to participate in the control arm (all expected), the results were overall balanced.

Hypersensitivity reactions, including acute infusion reaction may occur and Onivyde should be discontinued in case of severe hypersensitivity reactions.

In clinical studies of non-liposomal irinotecan administered on a weekly dosage schedule, patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dl) had a significantly greater likelihood of experiencing first cycle Grade 3 or Grade 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dl. Regular monitoring of complete blood counts should be conducted in patients with total bilirubin of 1.0 2.0 mg/dl due to possible increase of the concentration of SN 38 and thus increased risk of neutropenia in this population. The use of Onivyde should be avoided in patients with bilirubin > 2.0 mg/dl, or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 times upper limit of normal (ULN) or > 5 times ULN if liver metastasis is present. In addition, caution is required when Onivyde is given in combination with other hepatotoxic medicinal products, especially in patients with pre-existing hepatic impairment (see sections 4.2, 4.4 and 5.2 of the SmPC).

Patients with a history of a Whipple procedure have a higher risk of serious infections following Onivyde treatment. Patients should be monitored for signs of infections (see sections 4.4 and 4.8 of the SmPC).

Interstitial Lung Disease (ILD)-like events leading to fatalities have occurred in patients receiving non-liposomal irinotecan. No cases of ILD-like events have been reported with Onivyde therapy in clinical studies. Risk factors include pre-existing lung disease, use of pneumotoxic medicinal products, colony stimulating factors or having previously received radiation therapy. Patients with risk factors should be closely monitored for respiratory symptoms before and during Onivyde therapy. A reticulo-nodular pattern on chest X-ray was observed in a small percentage of patients enrolled in a clinical study with irinotecan. New or progressive dyspnoea, cough, and fever should prompt interruption of Onivyde treatment, pending diagnostic evaluation. Onivyde should be discontinued in patients with a confirmed diagnosis of ILD.

Because of the increased risk of ADRs (including Grade 3/4), caution should be exercised when using Onivyde in patients with body mass index <18.5 kg/m^2.

Forty one percent (41%) of patients treated with Onivyde across the clinical program were ≥ 65 years. No dose adjustment is recommended.

It is recommended that patients receive premedication with standard doses of dexamethasone (or an equivalent corticosteroid) together with a 5-HT3 antagonist (or other antiemetic) at least 30 minutes prior to Onivyde infusion (see section 4.2 of the SmPC).

Women of childbearing potential should use effective contraception during Onivyde treatment and 1 month thereafter. Males should use condoms during Onivyde treatment and 4 months thereafter.

There are no adequate data on the use of Onivyde in pregnant women. Onivyde can cause harm to the foetus when administered to the pregnant woman, as the main ingredient irinotecan has been shown to be embryotoxic and teratogenic in animals. Therefore, based on results from animal studies and the mechanism of action of irinotecan, Onivyde should not be used during pregnancy unless clearly necessary. If Onivyde is used during pregnancy or if the patient becomes pregnant while receiving therapy, the patient should be informed about the potential hazard to the foetus.

It is unknown whether Onivyde or its metabolites are excreted into human milk. Because of the potential for serious adverse reactions of Onivyde in breast-feeding infants, Onivyde is contraindicated during breast-feeding (see sections 4.3 and 4.6 of the SmPC). Patients should not breast-feed until one month after the last dose.

There are no data on the impact of Onivyde on human fertility. Non-liposomal irinotecan was shown to cause atrophy of male and female reproductive organs after multiple daily irinotecan doses in animals (see sections 4.6 and 5.3 of the SmPC).

In clinical trials, Onivyde was administered at doses up to 240 mg/m^2 to patients with various cancers. The adverse reactions in these patients were similar to those reported with the recommended dosage and regimen. There have been reports of overdose with non-liposomal irinotecan at doses up to approximately twice the recommended therapeutic dose of irinotecan, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhoea. There is no known antidote for overdose of Onivyde. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications (see section 4.9 of the SmPC).

Onivyde has moderate influence on the ability to drive and use machines. During treatment patients should observe caution when driving or using machines (see section 4.7 of the SmPC).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

Irinotecan hydrochloride trihydrate, contained in Onivyde, is a known active substance, whose safety profile is well established. In NAPOLI-1, most TEAEs of Onivyde in combination with 5FU/LV were manageable with supportive therapy, dose delays or both. No unexpected safety findings have so far emerged from the liposomal irinotecan development program to challenge what is previously known from standard irinotecan.

2.7. Risk Management Plan

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

The PRAC considered that the RMP version 1.0 (dated 21 April 2015) could be acceptable if the Applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report dated 10 September 2015.

The CHMP endorsed this advice.

The Applicant implemented all changes to the RMP as requested by the PRAC and the CHMP.

The CHMP endorsed the RMP version 1.0 (dated 27 April 2016) with the following content:

Table 56 - Summary of Safety Concerns

Important identified risks	Diarrhoea Leukopenia/Neutropenia Anaemia Acute infusion reactions Thromboembolic events
Important potential risks	Embryotoxicity/teratogenicity Hypersensitivity reactions Medication error related to drug/dose confusion with non-liposomal irinotecan Interstitial lung disease
Missing information	Use in patients with hepatic impairment Use in patients with renal impairment

Pharmacovigilance plan

Not applicable

Table 57 – Summary Table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Diarrhoea	Wording in SmPC section 4.2, 4.4 and 4.8.	None
Leukopenia/Neutropenia	Wording in SmPC section 4.2, 4.3, 4.4, 4.8.	None
Anaemia	Wording in SmPC section 4.8.	None
Acute infusion reactions	Wording in SmPC section 4.4, 4.8.	None
Thromboembolic events	Wording in SmPC section 4.8.	None
Important potential risks		
Embryotoxicity/teratogenicity	Wording in SmPC section 4.6, 5.3.	None
Hypersensitivity reactions	Wording in SmPC section 4.3, 4.4, 4.8.	None
Medication error related to drug/dose confusion with non-liposomal irinotecan	Wording in SmPC section 4.2.	None
Interstitial lung disease	Wording in SmPC section 4.4.	None
Missing information		
Use in patients with hepatic impairment	Wording in SmPC section 4.2, 4.4, 5.2.	None
Use in patients with renal impairment	Wording in SmPC section 4.2, 4.4, 5.2.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 (dated 27 April 2016) is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I

of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The CHMP, based on the available data, considers that irinotecan hydrochloride trihydrate is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional expert consultation

During the evaluation procedure for Onivyde, a Healthcare Professional consultation was launched to check whether there could be a potential risk of medication errors between the liposomal and non-liposomal formulation of irinotecan on the basis of the proposed product information and what measures could be implemented in the packaging or SmPC to minimise such risk.

The comments received in this consultation prompted the PRAC and CHMP to request further changes to the labelling (mainly to clearly differentiate both formulations and indicating that they are not equivalent). The MAH adequately addressed these concerns by amending the labelling and SmPC.

3. Benefit-Risk Balance

3.1. Favourable effects

In the pivotal trial, conducted in a heterogeneous population with respect to prior therapy, the primary endpoint of OS, resulted in a median 1.9 month survival benefit in favour of the experimental arm (6.1 vs 4.2 months, HR 0.67, p=0.0122, cut-off 0.025). As a sensitivity analysis, a stratified analysis by baseline stratification factors is reported and shows more convincing results with an HR of 0.57 (p-value = 0.0009). As this stratified analysis would be the CHMP preferred analysis, the concerns related to the statistically borderline character of the primary analysis are alleviated.

An improved survival of median 2 months, or a 50% prolongation of median survival, is considered clinically and regulatory meaningful in patients with relapsed/refractory pancreatic cancer.

The combination of Onivyde+5-FU/LV achieved a median investigator-assessed PFS of 3.1 vs 1.5 months for the control arm, HR 0.56, p=0.0001. Delayed tumour progression in pancreatic cancer is expected to delay symptom progression in this condition characterised by severe symptoms: mainly pain, weight loss and fatigue.

The confirmed ORR for Onivyde+5-FU/LV was 7.7% (95% CI: 2.86, 12.52) compared to 0.8% for 5-FU/LV.

3.2. Uncertainties and limitations about favourable effects

The 5FU/LV regimens in the control arm and the experimental arm were dissimilar enough to warrant further discussion. It would have facilitated the assessment of the add-on benefit of Onivyde if the same 5FU/LV regimen had been used as background and control, but the differences are considered too small to be of relevance in terms of survival.

With reference to the CONKO-003 trial, the control 5FU/LV regimen in NAPOLI-1 cannot be viewed as too non-intensive.

A trend towards improved PFS (HR 0.8, p=0.1) was shown in the comparison of Onivyde vs. 5FU/LV, at very similar OS (HR 0.99). In this context it is acknowledged that it is unknown whether 5FU/LV provides a survival benefit in this population.

In the monotherapy arm, Onivyde was administered at 120 mg/m^2 every 3 weeks and in the combination arm 80 mg/m^2 every 2 weeks, i.e. the same dose intensity over a 6-week period. The importance of this difference from a benefit/risk perspective is unknown. Therefore the add-on benefit of 5FU/LV to Onivyde cannot be disentangled, however this is not a regulatory concern.

Due to a too high early attrition rate, informative HRQoL data are not available.

Among the pre-planned OS subgroup analyses, a treatment effect favouring the 5-FU/LV over the combination arm has been observed for prior irinotecan use. This observation is also confirmed by univariate and multivariate analyses conducted to identify possible prognostic factors for both OS and PFS, which consistently showed that prior irinotecan, together with age>65, negatively impacted on the prognosis of patients treated with the combination arm.

The lack of benefit (if not a detrimental effect) in patients pre-treated with irinotecan raises concerns due to the increasing use of irinotecan-containing regimen as first line therapy. Due to the limited number of patients with prior exposure to non-liposomal irinotecan, the benefit of Onivyde has not been established in this population. This information has been reflected in section 4.4 of the SmPC.

3.3. Unfavourable effects

The TEAE causality seems in line with the known safety profile of irinotecan, i.e. gastrointestinal AEs and hematotoxicity. Whilst the dose intensity per 6 weeks was the same (120 mg/m^2 x 2 vs 80 mg/m^2 x 3), the 80 mg/m^2 regimen in combination with 5FU/LV resulted in more myelosuppression, but gastrointestinal adverse reactions were more commonly observed in the 120 mg/m^2 arm. 'Fatigue' and 'asthenia' were also more frequently observed in the combination arm.

In comparison with the 5-FU/LV control arm almost all adverse reactions were more commonly observed in the combination arm. These differences resulted in more dose reductions (33% vs. 4%) and discontinuations (11% vs. 8%).

Early diarrhoea (onset day1, consistent with cholinergic hyper-stimulation) occurred twice as frequently in the combination arm (29.9%) than in the other two arms. Late events (after day1) were more frequent in the combination arm (42.7%) than in the control arm. However, diarrhoea was manageable with supportive therapy.

Patients with baseline serum bilirubin levels ≥1.0 mg/dL, or with deficient glucuronidation of bilirubin e.g. Gilbert's syndrome, may be at greater risk for neutropenia. Patients who are homozygous for UGT1A1*28 have a greater risk of haematological toxicity with irinotecan.

In patients treated with Onyvide, diarrhoea (gastrointestinal toxicity) is associated with total irinotecan C_{max}, and neutropenia (bone marrow suppression) is associated with unencapsulated SN-38 C_{max}. The observed incidence of grade≥3 diarrhoea and neutropenia by race are also consistent with the difference in the pharmacokinetics.

There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. Close clinical monitoring is advised.

3.4. Uncertainties and limitations about unfavourable effects

In comparison with standard irinotecan, certain known AEs of irinotecan have so far not been observed with Onivyde, such as interstitial lung disease and acute pancreatitis; either because liposomal irinotecan does not exhibit these AEs or due to the limited safety database available. These events will be monitored through routine pharmacovigilance.

3.5. Effects Table

Table 58: Effects Table for Onivyde in adenocarcinoma of the pancreas (data cut-off: 14 February 2014)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects					
OS	Overall survival (median)	months	6.1	4.2	Modest increase in OS

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence
PFS	Progression free survival (median)	months	3.1	1.5	Supportive of OS (Investigator-assessed)
TTF	Time to treatment failure (median)	months	2.3	1.4	Supportive of OS
ORR	Overall response rate (confirmed RECIST 1.1)	%	7.69	0.84	Supportive of OS, PFS
DOR	Duration of response	weeks	10	6	In order to contextualise: OS benefit, 1.9 months Rates of discontinuation: 11% more PD in the control arm Open-label
Unfavourable Effects					
Total AE, excl. PD	Discontinuation Dose reduction	%	9.4 33.3	6.7 3.7	
Related AE	According to investigator	%	91.5	69.4	
SAE	GI disorders Infections Blood	%	22.2 17.1 6.0	15.7 11.2 2.2	
Diarrhoea	Grade all Grade 3/4	%	59 14.5	26.1 4.5	In order to contextualise: More, yet manageable, AEs in the Onivyde combination arm, and consistent with the safety profile of standard irinotecan/FOLFIRI.
Neutropenia	Grade all Grade 3/4	%	39.3 27.4	5.2 1.5	

Abbreviations: AE: Adverse event; GI: Gastro-intestinal; PD: progressive disease

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The newer approaches to the first-line treatment of metastatic pancreatic adenocarcinoma – e.g. 5-FU/LV with irinotecan and oxaliplatin (FOLFIRINOX) or gemcitabine/nab-paclitaxel have improved the outcomes in this patient group, with response rates between 23% and 31%, PFS of 5.5–6.6 months, and OS between 8.5 and 11 months. Due to good tolerability, however, gemcitabine monotherapy remains a viable treatment option.

In the next-line setting the prognosis is very poor and tolerability becomes an even more important issue. No patient reported outcome data are available to inform the assessment with regard to the perceived side effects of therapy. Therefore conventional adverse event reporting has to be used in the assessment of tolerability.

With respect to efficacy, survival is the best overall measure of treatment benefit, but delayed progression is likely to be related to delayed symptomatic progression.

3.6.2. Balance of benefits and risks

In view of the survival benefit of Onivyde in combination with 5-FU/LV and the identified risks of irinotecan, the benefit/risk balance of Onivyde in patients with adenocarcinoma of the pancreas previously treated with a gemcitabine based therapy is considered favourable.

3.7. Conclusions

The overall B/R of Onivyde is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Onivyde is favourable in the following indication:

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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable

New Active Substance Status

The CHMP, based on the available data, considers that irinotecan hydrochloride trihydrate is not a new active substance, as it is a constituent of a medicinal product previously authorised within the European Union.