9 November 2017
EMA/795015/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Onzeald

International non-proprietary name: etirinotecan pegol

Procedure No. EMEA/H/C/003874/0000

Note

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

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Administrative information

Name of the medicinal product:	Onzeald
Applicant:	Nektar Therapeutics UK Limited Elizabeth House 13-19 Queen Street Leeds LS12TW UNITED KINGDOM
Active substance:	Etirinotecan pegol
International Non-proprietary Name:	Etirinotecan pegol
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agents (L01XX56)
Therapeutic indication:	Treatment of adult patients with advanced breast cancer that has metastasised to the brain, who also have extra-cranial metastases, and who have previously received systemic anthracycline, taxane, and capecitabine therapy, unless patients were not suitable for these treatments. Brain metastases must have been previously treated with prior local therapy (surgery and/or radiotherapy) (see section 5.1).
Pharmaceutical form:	Powder for concentration for solution for infusion
Strength:	100 mg
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

5-FU 5-Fluorouracil	EORTC European Organisation for Research and Treatment of Cancer
ABC ATP-binding cassette	EPR Enhanced permeation and retention
ACN Acetonitrile	ESMO European Society for Medical Oncology
ADME Absorption, distribution, metabolism, and excretion	EU European Union
ADR Adverse drug reactions	FAC Fluorouracil, doxorubicin, and cyclophosphamide
AE Adverse events	FDA Food and Drug Administration
ALTA Alta Analytical Laboratories	FI Flow injection
APC 7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecin	FMEA Failure Mode Effects Analysis
ATC Anatomical Therapeutic Chemical	FU 5-flurouracil
ATC anthracycline, taxane, or capecitabine	GC -FID Gas Chromatography-flame ionisation detector
AUC Area under the curve	GCP Good Clinical Practice
AUC[0,21d] AUC from time 0 to 21 days	GCSF Granulocyte colony-stimulating factor
AUC[0,EOT] AUC from time 0 to end of treatment	GI Gastrointestinal
AUClast AUC from time 0 (pre-dose) to time of last quantifiable concentration	GMP Good Manufacturing Practice
AV Atrioventricular	GPA Graded Prognostic Assessment
BA Bioavailability	HER2 Human epidermal growth factor receptor 2
BBB Blood-brain barrier	HGG High-grade glioma
BCBM Breast cancer with brain metastases	HPLC High-pressure liquid chromatography
BCNU 1-3-bis(2-chloroethyl)-1-nitrosourea	HR Hazard ratio
BCRP Breast cancer resistance protein	HRQL Health- Related Quality Of Life
BE Bioequivalence	HRQoL Health-related quality of life
BEACON BrEAst Cancer Outcomes with NKTR-102	IC50 Half maximal inhibitory concentration
BFI Brief Fatigue Inventory	ICH International Conference on Harmonisation
BLQ Below the limit of quantitation	IHC Immunohistochemistry
BSA Body surface area	IPC(s) In-process control(s)
BTB Blood-tumour barrier	IPFI Initial progression-free interval
BTIC Brain tumor investigational consortium	IRT Irinotecan
cAUC Cumulative AUC	IR Infrared
Cave Average plasma concentration	ISR Incurred Sample Reanalysis
CBR Clinical benefit rate	ISS Integrated Summary of Safety
CC Calibration Curve	ITT Intent-to-treat
CHMP Committee for Medicinal Products for Human Use	IV Intravenous
CI Confidence interval	KPS Karnofsky Performance Status
CL Clearance	KRAS Kirsten rat sarcoma viral oncogene homolog
Cmax Maximum plasma concentration	LC-MS/MS Liquid chromatography–tandem mass spectrometry
CNS Central nervous system	
CR Complete response	LLE Liquid Liquid Extraction
CPP(s) critical process parameter(s)	LLOQ Lower limit of quantification
CQA Critical quality attribute	MBC Metastatic breast cancer
CSR Clinical Study Report	MDCK Madin-Darby Canine Kidney
CTCAE Common Terminology Criteria for Adverse Events	MedDRA Medical Dictionary of Regulatory Activities
CYP Cytochrome P450	MGMT O6-methylguanine-DNA methyltransferase
DFS Disease-free survival	MID Minimal important difference
DLT Dose-limiting toxicity	
DMC Data monitoring committee	
DMSO Dimethyl sulfoxide	
DNA Deoxyribonucleic acid	
DoE Design of Experiments	
DoR Duration of response	
DS4 4ArmPEG20K-CM-Glycineirinotecan	
ECG Electrocardiogram	
ECOG Eastern Cooperative Oncology Group	
EDTA Ethylenediaminetetraacetic acid	
eCRF Electronic case report form	
eGFR Estimated glomerular filtration rate	
ELSD evaporative light scattering detection	

MMRM Mixed effect Model Repeat Measurement
MPA Medical Products Agency (Sweden)
MRI Magnetic resonance imaging
MTBE Methyl tert-butyl ether
MTD Maximum tolerated dose
NA or N/A Not applicable or Not Analysed
Na2EDTA Disodium ethylenediaminetetraacetic acid
NaF Sodium Fluoride
NCI-ODWG National Cancer Institute Organ Dysfunction Working Group
NDA New Drug Application (US FDA)
NF National formulary
NH4OAc Ammonium Acetate
NKTR-102 Company code for Onzeald (etirinotecan pegol)
($^{1}H/^{13}C$-) NMR Nuclear Magnetic Resonance
NOR(s) normal operating range(s)
NPC
7-ethly-10-[4-amino-1-piperidino]-carbonyloxycamptothecin
n.s. Not (statistically) significant
OAT Organic anion transporter
OCT Organic cation transporter
ORR Objective response rate
OS Overall survival
PAR(s) proven acceptable range(s)
P-gp Permeability glycoprotein
PD Progressive disease
PEG Polyethylene glycol
PFS Progression-free survival
Ph. Eur. European Pharmacopoeia
PK Pharmacokinetics
PMSF Phenylmethylsulfonyl fluoride
PPT Protein Precipitation
PR Partial response
PRO Patient-reported outcomes
PT Preferred term
q14d Once every 14 days
q21d Once every 21 days
q28d Once every 28 days
QLQ-C30 Quality of Life Questionnaire Core 30
QLQ-BR23 Quality of Life Questionnaire Breast Cancer Module
QoL Quality of life
QOS Quality Overall Summary
QRA Quality Risk Assessment
QT Measure of the time between the start of the Q wave and the end of the T wave
in the heart's electrical cycle
QTc Corrected QT
RANO Response Assessment in Neuro-Oncology
RECIST Response Evaluation Criteria in Solid Tumours
RH relative humidity
RMP Risk management plan
RMST Restricted Means Survival Time
RoW Rest of World
RPTD Recommended Phase 2 dose
RT Radiation therapy
SAE Serious adverse event
SAG Scientific Advisory Group
SAP Statistical Analysis Plan
SBC Schwartz's Bayesian criterion
SD Stable disease OR Standard deviation
SN38 7-ethyl-10-hydroxycamptothecin
SN38G Glucuronide conjugate of SN38
SOC System organ class
SRS Stereotactic radiation surgery
SUSAR Suspected unexpected serious adverse reaction
T1/2 Half-life
TA Thymine-adenine
TEAE Treatment-emergent adverse event
TESAE Treatment-emergent serious adverse event
Tmax Time to maximum plasma concentration
TNBC Triple-negative breast cancer
topo-I Topoisomerase 1
TPC Treatment of Physician's Choice
TTBM Time to brain metastasis
UDP Uridine diphosphate
UGT Uridine 5'-diphospho-glucuronosyl transferase
UGT1A1 Uridine diphosphate-glucuronosyl transferase 1A1
US United States
USP United States Pharmacopeia
UV ultraviolet
v/v Volume by volume
V1 Volume of the central compartment
V1c Central volume of distribution
Vd Volume of distribution
Vss Volume of distribution at steady state
WAM Wald's Approximation Method
WBRT Whole brain radiation therapy
WHO World Health Organisation
wx3q4wk Once a week for 3 weeks every 4 weeks

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Nektar Therapeutics UK Limited submitted on 9 June 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Onzeald, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 October 2013.

The applicant applied for the following indication:

- treatment of advanced breast cancer with brain metastases in adult patients who have received prior anthracycline, taxane, and capecitabine therapy unless patients were not suitable for these treatments.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application. The applicant indicated that etirinotecan pegol was considered to be a new 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(s) (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.

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14(7) of the above mentioned Regulation.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance etirinotecan pegol contained in the above medicinal product to be considered as a new active substance in comparison to irinotecan previously authorised in the

European Union as Campto or Camptosar, as the applicant claimed that etirinotecan pegol differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 20 October 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 9 June 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 26 May 2016.
- The procedure started on 14 July 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 3 October 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 3 October 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 14 October 2016.
- During the meeting on October 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant 28 October 2016.
- During the meeting on 10 November 2016, 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 11 November 2016. The CHMP also concluded that it was no longer appropriate to pursue accelerated assessment as a number of concerns including major objections were not compatible with an accelerated assessment timeframe. The timetable of this procedure was reverted from accelerated to standard assessment timelines.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 January 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 February 2017.
- During the CHMP meeting on 23 March 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 12 April 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 8 May 2017.
- During the CHMP meeting on 16 May 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 18 May 2017, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.

- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 19 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 6 July 2017.
- During a meeting of a SAG on 12 July 2017, experts were convened to address questions raised by the CHMP.
- During the meeting on 17-20 July 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Onzeald on 20 July 2017.

1.3. Steps taken for the re-examination procedure

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

Rapporteur: Paula Boudewina van Hennik (NL) Co-Rapporteur: Hrefna Guðmundsdóttir (IS)

- The applicant submitted written notice to the EMA on 26 July 2017 to request a re-examination of Onzeald CHMP opinion of 20 July 2017. A revised written notice was submitted to the Agency by the applicant on 4 August 2017.
- During its meeting on 14 September 2017, the CHMP appointed Paula Boudewina van Hennik as Rapporteur and Hrefna Guðmundsdóttir as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 18 September 2017 (Appendix 2 of Final Opinion). The re-examination procedure started on 19 September 2017.
- The rapporteur's re-examination assessment report was circulated to all CHMP members on 20 October 2017. The co-rapporteur's assessment report was circulated to all CHMP members on 24 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 1 November 2017.
- During the CHMP meeting on 7 November 2017, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 9 November 2017, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication sought is for the treatment of advanced breast cancer with brain metastases (BCBM) in adult patients who have received prior anthracycline, taxane, and capecitabine therapy unless patients were not suitable for these treatments.

2.1.2. Epidemiology

Breast cancer is the most common cancer in women in Europe with approximately 464,000 new cases diagnosed in 2012 and metastatic breast cancer is the leading cause of cancer-related death in women[1]. As approximately 15-30% of patients with metastatic breast cancer will have brain metastasis[2], it is estimated that between 14000 and 42000 patients in the EU will be diagnosed with brain metastases from breast cancer in any given year.

2.1.3. Biologic features, Aetiology and pathogenesis

The formation of brain metastasis as a multistep process is thus far poorly understood. Metastasizing single tumour cells must pass through the tight blood–brain barrier (BBB). Animal studies have shown that, after passing the BBB, the tumour cells require close contact with endothelial cells and interact closely with many different brain residential cells, therefore, cellular adaptation processes within the new microenvironment may also determine the ability of a tumour cell to metastasize[3].

CNS metastases occur with higher frequency in younger and premenopausal breast cancer patients and in ER negative and PR negative cancers. Some studies have found correlation with nodal status, tumour grade, tumour size and HER2 status while others have described association with high proliferation rate, aneuploidy and p53 positivity. Triple negative disease (TNBC) confers a higher risk[4],[5].

2.1.4. Clinical presentation, diagnosis and stage / prognosis

78% of BCBM patients have multiple brain metastases. The BCBM patient population is one with high unmet need. The prognosis is poor with approximately 80% mortality within 9 months of diagnosis. The great majority of patients also have extracranial disease.

2.1.5. Management

Local treatments include surgery and radiation therapy, including stereotactic radiotherapy, which are generally associated with important toxicity affecting quality of life, including focal neurological and cognitive side effects including memory loss. Although it is typically recommended that BCBM is treated with systemic chemotherapy before or after radiotherapy or surgery, there are no approved

[1] GLOBOCAN, 2012
[2] Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Goncalves A. Recent trends in epidemiology of brain metastases: an overview. Anticancer Res. 2012;32:4655–62.
[3] Morris VL, Koop S, MacDonald IC, Schmidt EE, Grattan M, Percy D, et al. Mammary carcinoma cell lines of high and low metastatic potential differ not in extravasation but in subsequent migration and growth. Clin Exp Metastasis. 1994;12:357–67.
[4] Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010;28:3271–7.
[5] Yau T, Swanton C, Chua S, Sue A, Walsh G, Rostom A, et al. Incidence, pattern and timing of brain metastases among patients with advanced breast cancer treated with trastuzumab. Acta Oncol. 2006;45:196–201.

chemotherapy regimens for the management of BCBM, nor are there consensus-based recommendations for the chemotherapeutic management of BCBM.

There are a number of agents approved for use in metastatic breast cancer. However, efficacy data for systemic chemotherapy in brain metastases is scarce, in part because such patients have been traditionally excluded from registration trials.

Patients with metastatic breast cancer progressing after treatment with anthracycline, taxane, or capecitabine (ATC) are treated with a variety of agents (as recommended by the ESMO Clinical Practice Guidelines and/or the USA NCCN guidelines), including but not limited to vinorelbine, gemcitabine, eribulin, ixabepilone or an alternate taxane or a different schedule of previous taxanes.

Current agents used for treating patients with MBC after ATC failure achieved objective response rates (ORRs) in the range of 5-20%. The only single-agent chemotherapy for which a survival benefit has been shown in a target population similar to the one studied in the present drug development program is eribulin[6].

About the product

Etirinotecan pegol is a covalent conjugate of irinotecan with polyethylene glycol (PEG). Irinotecan is a camptothecin derivative belonging to the topoisomerase inhibitor class of antineoplastic agents. The irinotecan component of etirinotecan pegol is structurally equivalent to non-pegylated irinotecan, but it is neither pharmacologically, clinically, nor dose equivalent to non-pegylated irinotecan due to conjugation with the PEG moiety. After administration, irinotecan is slowly released from etirinotecan pegol by hydrolysis and metabolised to the lipophilic, active cytotoxic agent, SN38.

SN38 interferes with mammalian DNA topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Current research suggests that the cytotoxicity of SN38 is due to double-strand DNA breaks produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and SN38. Mammalian cells cannot efficiently repair these double-strand breaks.

Due to the PEG-conjugate nature of etirinotecan pegol, peak SN38 plasma concentrations are lower and the SN38 circulation time is prolonged compared to irinotecan.

<u>The initially applied indication was:</u>

Onzeald is indicated for the treatment of advanced breast cancer with brain metastases in adult patients who have received prior anthracycline, taxane, and capecitabine therapy unless patients were not suitable for these treatments.

<u>Subsequently revised proposed indication:</u>

Onzeald monotherapy is indicated for the treatment of adult patients with breast cancer that has metastasised to the brain, who have received prior local treatment for brain metastases (surgery and/or radiotherapy), and systemic anthracycline, taxane, and capecitabine, unless patients were not suitable for these treatments.

The proposed posology was:

The recommended dose of Onzeald is 145 mg/m^2 administered intravenously over 90 minutes on Day 1 of a 21-day cycle. The amount of Onzeald in milligrams (mg) that is to be administered to a patient should be determined on the basis of the patient's body surface area (BSA) in square metres (m^2).

[6] Chang 2015; Fabi 2015; Matsuoka 2013

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the following considerations:

- Agreement that brain metastasis in breast cancer constitutes an unmet medical need in the respect that it is at present a non-curable and fatal condition with limited treatment options.
- The potential achievement of approximately 5 months increase of overall survival (OS) in breast cancer patients with a history of brain metastasis (BCBM), who have a short expected OS and no established treatment options, was considered a major therapeutic innovation of major interest to public health.

However, during the plenary meeting of 7-10 November 2016, the CHMP concluded that it was no longer appropriate to pursue accelerated assessment considering the concerns and major objections raised in the first phase of the assessment. The CHMP agreed to revert the timetable of this procedure from accelerated to standard assessment.

The applicant requested a conditional marketing authorisation based on the following reasons:

- The company claimed that the benefit-risk balance is positive as the clinical data from the Phase 3 BEACON study (11-PIR-11) and the supportive data from the Phase 2 studies provides evidence of a positive overall benefit risk assessment over treatment of physician's choice (TPC) arm. In particular, a benefit was shown for Onzeald in patients with BCBM, a predefined subgroup with high unmet need, limited therapeutic options, and no approved chemotherapies. The safety profile which commonly included gastrointestinal toxicities is considered manageable by the applicant.
- It is likely that the applicant will be able to provide comprehensive data:

  Study 15-102-14 (ATTAIN) is an open-label, randomised, parallel, two-arm, multicentre, international Phase 3 study of Onzeald versus TPC in adult patients with metastatic breast cancer and a history of brain metastases that are non-progressing. Patients must have had prior therapy with an anthracycline, a taxane, and capecitabine in the neoadjuvant, adjuvant, and/or metastatic setting. It is planned to enrol 350 patients. ATTAIN has thus far initiated at 30 sites in the US with an additional 134 sites world-wide projected to initiate throughout 2017. The first patient was randomised and dosed in March 2017. The current estimated timeline is for primary analysis (top line data available) is Q1 2020 and final clinical study report Q2 2020.
- Unmet medical needs will be addressed:

  Breast cancer with a history of brain metastasis (BCBM) is a fatal condition with a critical need for new active treatments. According to the applicant, the observed improvement in median OS of 5.2 months (Onzeald: 10.0 months vs. TPC: 4.8 months, p = 0.010; HR = 0.51, 95% CI: 0.30-0.86) with fewer Grade ≥3 toxicities and less deterioration in HRQoL than the current standard of care (TPC) in patients with BCBM, who have a very poor prognosis and no approved therapies, is an unprecedented clinical result in this population. In addition, Onzeald offers a predictable, manageable, different, and more favourable safety profile with fewer Grade ≥3 toxicities than the current standard of care, and less deterioration in HRQoL than the current standard of care.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

The observed clinical efficacy results in the BCBM subpopulation are considered of clinical importance and of a magnitude that fulfils major therapeutic advantage in this disease context.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a sterile powder for concentrate for solution for infusion containing 100 mg of etirinotecan pegol (referring to irinotecan moiety of etirinotecan pegol) as the active substance.

Other ingredients of medicinal product are lactic acid (E270), hydrochloric acid, concentrated (E507) (for pH adjustment) and sodium hydroxide (E524) (for pH adjustment).

The product is available in amber type I glass vial closed by a grey bromobutyl coated rubber stopper and aluminium crimps with flip-off caps.

2.2.2. Active Substance

General information

The chemical name of etirinotecan pegol is poly(oxy-1,2-ethanediyl), α-hydro-ω-[2-[[2-[[(4*S*)-9-[([1,4'-bipiperidin]-1'-ylcarbonyl)oxy]-4,11-diethyl-3,4,12,14-tetrahydro-3,14-dioxo-1*H*pyrano [3',4':6,7]indolizino[1,2-*b*]quinolin-4-yl]oxy]-2-oxoethyl]amino]-2- oxoethoxy]-, ether with 2,2-bis(hydroxymethyl)-1,3-propanediol, hydrochloride, 2,2,2-trifluoroacetate (4:1:2:1.2). It corresponds to the molecular formula $C_{153}H_{176}N_{20}O_{36}[C_8H_{16}O_4]_n \cdot 2HCl \cdot 1.2(C_2HF_3O_2)$. It has a relative molecular mass 20,900–24,900 Da and has the structure shown in Figure 1.

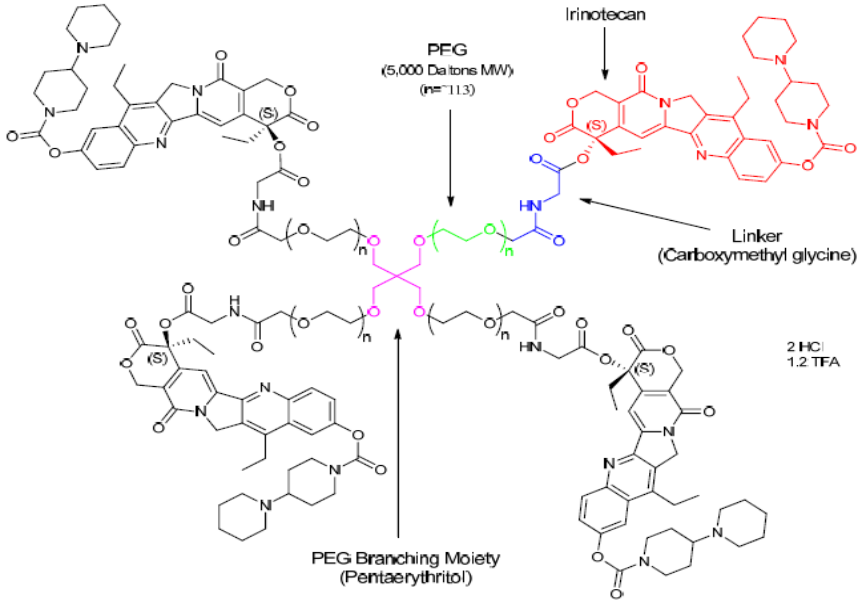


Figure 1 - Structure of etirinotecan pegol

Etirinotecan pegol is a partial mixed salt of hydrochloric and trifluoroacetic acids. The active substance, etirinotecan pegol, is defined as representing all PEGylated species that release irinotecan upon hydrolysis. Thus, etirinotecan pegol comprises a mixture of species, for which composition is controlled by the drug substance specification.

Etirinotecan pegol and key component PEGylated irinotecan species (DS4, DS3-Gly, DS3-OH, DS3-CM, DS3-Gly-Me, DS4-(Gly-Gly), DS4-(Gly-NBOC-Gly) and low and high molecular weight species have been analysed by spectroscopy (IR, UV, and 1D and 2D 1H-NMR and 13C-NMR), mass spectrometry, elemental analysis and x-ray powder crystallography. The proposed structures have been shown to be consistent with the analytical and spectroscopic data. Hydrolysis studies have established that irinotecan retains its S-configuration upon hydrolysis.

Etirinotecan pegol appears as a white, off-white to pale yellow modestly hygroscopic powder. It is freely soluble to very soluble in water, various aqueous buffers, 0.1M lactic acid, methanol, acetonitrile, dichloromethane and dimethylsulfoxide; slightly soluble in ethyl acetate; and practically insoluble in 1-octanol, methyl *tert*-butyl ether and 2-propanol. It exhibits two pKa values of 9.5–9.6 and 2.9–3.0, which correspond to the piperidine and quinoline moieties in irinotecan, respectively. The estimated partition coefficient is approximately $2.26x10^{-6}$.

Etirinotecan pegol contains S-irinotecan; studies have shown that irinotecan contained in etirinotecan pegol remains in the S-configuration; the R-enantiomer is not formed throughout manufacture and shelf-life.

When administered, the active substance etirinotecan pegol slowly releases irinotecan in vivo. The irinotecan is then metabolised to the cytotoxic agent, SN38. This is the same metabolic reaction that normally occurs following administration of non-pegylated irinotecan containing products.

Irinotecan is already authorised as an active substance in the EU. Based on the review of data on the quality properties of the active substance, etirinotecan pegol can not be qualified as a new active substance from a chemical point of view, however, the CHMP considers that etirinotecan pegol can be qualified as a new active substance as it differs significantly in properties with regard to safety and efficacy compared to the previously authorised active substance, irinotecan.

Manufacture, characterisation and process controls

The synthesis of etirinotecan pegol comprises three main stages commencing with the separate syntheses of two key intermediates; which are then combined in a further synthetic step to yield etirinotecan pegol.

There are four acceptable well characterised starting materials controlled by suitable specifications.

To identify critical process parameters (CPPs), a Quality Risk Assessment (QRA) was performed using a Failure Mode Effects Analysis (FMEA) model. Appropriate proven acceptable ranges (PARs) for process parameters were established through development studies. Risk management and scientific knowledge were used to understand process parameters and unit operations that impact the etirinotecan pegol CQAs, and the preferred conditions for the manufacture of etirinotecan pegol were selected following univariate experimentation. The proposed narrow normal operating ranges (NORs) are sufficiently supported and adequate in-process controls are applied during the synthesis.

The characterisation of the active substance and its impurities, including genotoxic 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. Observed or potential impurities present in the starting materials or formed during the manufacturing process were evaluated for their

potential to persist through the multiple purification steps of the etirinotecan pegol process. As a result of these studiesthe specification of the active substance has been established.

The bags used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

The etirinotecan pegol specification includes appropriate tests and limits for appearance (visual), appearance of solution (Ph. Eur.), identity (^{1}H-NMR, HPLC-UV), irinotecan content (UV), PEGylated irinotecan species (HPLC-UV), counterions (ion chromatography), bound small molecule impurities (HPLC-UV), non-conjugated species (HPLC-ELSD), small molecule impurities (HPLC-UV), residue on ignition (Ph. Eur.), water content (Karl Fischer), residual solvents (GC-FID), elemental impurities (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and microbiological quality (Ph. Eur.).

Etirinotecan pegol is a cytotoxic drug for the treatment of patients with advanced breast cancer, hence control of genotoxic impurities to a limit of 1.5 µg/day, as stipulated in the ICH M7 guideline, is not required. Omission of tests for genotoxic impurities has been justified since all potential mutagenic impurities identified in etirinotecan pegol have consistently been detected in validated batch analyses at levels below the qualification threshold described in ICH Q3A.

Satisfactory information has been presented regarding the control of chiral purity, molecular weight and polydispersity of the active substance.

The analytical methods used have been adequately described, validated and are suitable for the quality control of etirinotecan pegol active substance. Information regarding the reference standards used in the analytical testing is satisfactory.

Batch analysis data from commercial scale and six pilot scale batches of the active substance manufactured at the proposed manufacturing site were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on five commercial scale and 4 pilot scale batches of active substance stored in the intended commercial packaging for up to 48 months under long term conditions (-20°C and 5°C) and for up to 6 months under accelerated conditions (25 °C / 60 % RH) was provided according to the ICH guidelines.

The stability parameters studied are appearance, IRT content, PEGylated irinotecan (PEG-IRT) species, bound small molecules, non-conjugated PEGylated species, small molecule impurities, water content, bacterial endotoxins, and microbiological quality. The test methods were the same as for release and are stability indicating. A new analytical procedure for the determination of PEG-IRT species and small molecule impurities was implemented during the period of the stability study and replaced the PEG-IRT species Assay and Impurities by Ion Pair Chromatography. The updated method was implemented through a stability cross-over activity for the first three pilot batches put in stability. No significant changes or trends were observed in any of the monitored parameters through 48 months of storage at -20 °C and 5 °C compared to the initial values. Results also remained within specifications during the 6 months at accelerated conditions.

The temperature cycling stability study results demonstrated that the etirinotecan pegol is stable for at least four temperature cycles (i.e., 6 days at -20°C and 1 day at 25°C) as there were no changes in any test results as compared to results for initial and the -20°C control sample.

Photostability testing on one pilot scale following the ICH guideline Q1B was provided. The study results demonstrated that etirinotecan pegol is sensitive to light as compared to initial and the dark control sample. Therefore, it was concluded that etirinotecan pegol should be protected from light.

In conclusion, the stability results justify the proposed retest period of 48 months when packaged in the container stored at -20 ± 5°C. Short-term excursions up to 25°C are permitted.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Onzeald 100 mg powder for concentrate for solution for infusion comprises a sterile, white to yellow powder for reconstitution with 20 ml of either dextrose 5% injection or sodium chloride 0.9% injection. The reconstituted solution contains the equivalent of 100 mg/vial or 5 mg/ml of irinotecan (as 1100 mg/vial of etirinotecan pegol). Each vial of Onzeald contains approximately 1.1 g etirinotecan pegol and 94.5 mg of lactic acid.

Etirinotecan pegol is a polymer-based conjugate (PEGylated) prodrug of an established drug, IRT, designed to deliver IRT and the active metabolite, SN38. The PEGylation prolongs circulation half-life compared with conventional irinotecan, and achieves lower peak plasma concentrations of irinotecan by controlled release from the PEG scaffold, predicted to reduce toxicity.

The starting point for choosing appropriate excipients was to mimic the marketed product Camptosar (IRT hydrochloride). Etirinotecan pegol and excipient compatibility was demonstrated by the stability of Onzeald. The list of excipients is included in section 2.2.1 of this report.

The influence of pH, temperature, light sensitivity, solubility, hygroscopicity and oxygen exposure upon the stability of etirinotecan pegol has been investigated in the context of formulation design.

A Design of Experiments (DOE) study at laboratory scale was conducted as a formulation evaluation study to evaluate the effect of buffer and solution pH on the quality of Onzeald with regards to bulk compounding solution, lyophilised finished product, and reconstituted infusion solution. Buffer molarity and pH were selected based on the results of DoE.

Taking into account the physicochemical properties of the etirinotecan pegol the manufacturing process was developed in order to protect the active substance from degradation.

The choice of sterilisation by aseptic filtration over terminal sterilisation was supported by data. Therefore the choice of sterilisation by aseptic filtration is accepted as appropriate.

Validation studies were provided to support the suitability of filters and to demonstrate bacterial retention according to compendial recommendations; some modifications to the compendial recommendations to account for the acidic solution and the bactericidal nature of the drug substance are considered justified and appropriate. The retention capability of the filters was satisfactorily demonstrated. Data are also presented that support chemical compatibility and satisfactory levels of extractables from the filters.

The development and optimisation of the lyophilisation cycle was described in detail, to produce an appropriate physical characteristics (without melt-back or shrinkage) and low residual moisture content.

The recommended lyophilisation cycle was transferred from development to clinical manufacturing. During the manufacture of clinical batches, additional changes were made to the lyophilisation cycle based on further observations during runs, which have been sufficiently justified. Formal risk analysis was conducted to evaluate critical manufacturing process parameters for production of Onzeald. A Failure Mode and Effects Analysis (FMEA) model was used for risk analysis. The key process inputs used in the

FMEA risk analysis is included in the documentation. All process inputs determined to be critical have been mitigated through SOPs, calibration, batch records, change controls, and IPCs.

Onzeald has been shown to be compatible with the container closure system following an assessment of leachables from the primary container closure. In addition, compatibility with the primary container closure following reconstitution solvents showed no observable semi-volatile leachables. Data have confirmed the compatibility of the contact material with the lyophilised and reconstituted Onzeald. Acceptance criteria were based on those in place for the finished product at the time of testing. Studies were conducted to assess the stability of Onzeald in the primary container closure system after reconstitution with D5W and 0.9% Saline. Data showed that Onzeald, when reconstituted with either D5W or 0.9% Saline, was stable up to 24 hours refrigerated or at room temperature. Reconstituted Onzeald, therefore, is compatible with the borosilicate Type 1 amber glass vial and coated bromobutyl rubber stoppers.

To demonstrate that the reconstituted finished product is stable and compatible with IV administration sets studies were performed, in accordance with directions of use, with infusion bags and infusion sets from multiple suppliers at low and high etirinotecan pegol concentrations.
Additional studies conducted demonstrated that Onzeald is compatible with 0.2 µm in-line filters following storage in an IV bag at room temperature under ambient lighting for up to 6 hours.

The container closure system of Onzeald powder for concentrate for solution for infusion is a 25 mL single use vial of neutral borosilicate Type 1 amber glass with bromobutyl coated rubber stoppers and aluminium crimps with flip-off caps. The glass vials comply with the requirements of Ph. Eur. 3.2.1 and the rubber stoppers comply with the requirements of Ph. Eur. 3.2.9. The documentation contains specifications and certificates of analysis. 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 of Onzeald is divided into eight operations: compounding, sterile filtration, aseptic filling, lyophilisation, capping, external vial washing/printing/inspection, sampling for release and stability testing and secondary packaging. The product contact equipment and packaging components are sterilised prior to use.

The critical steps have been defined and appropriate in process controls are in place. No intermediates are defined and control parameters for process equipment are outlined and justified. Control limits for bioburden following first sterile filtration are in line with that recommended for sterilisation by aseptic filtration and are accepted. The manufacturing process is considered to be a non-standard in line with Annex II of the process validation guideline, given that complex processes (aseptic filtration and lyophilisation) are used. The process has been validated by three batches at the proposed commercial scale.

Satisfactory results for media fill studies were presented and batch analysis confirms compliance with the proposed finished product specification. Hold time data for the bulk solution was presented and support the physico-chemical stability of the product over this time period.

In conclusion, it is considered that the manufacturing process is sufficiently validated and robust to provide assurance that the finished product is of consistent quality whilst complying with the designated specification.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification (HPLC, UV), reconstitution time (visual), completeness of reconstituted solutions (Ph. Eur.), visible particulate matter of reconstituted solutions (Ph. Eur.), clarity and colour of reconstituted solutions (Ph. Eur.), pH of reconstituted solution (potentiometry), water content (Ph. Eur.), subvisible particulate matter after reconstitution (light obscuration), irinotecan content (UV), uniformity of dosage units (Ph. Eur.), PEGylated irinotecan species (HPLC-UV), small molecule impurities[b] (HPLC-UV), bound small molecule impurities[a] (HPLC-UV), Sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

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 has been presented.

Batch analysis results were provided for five commercial scale and eight smaller 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 five commercial scale and eight smaller batches of Onzeald stored under long term conditions for up to 60 months at 5 ± 3 °C and for up to six months under accelerated conditions at (25 ± 2 °C /60 ± 5% RH) according to the ICH guidelines were provided. Samples were stored in inverted and upright position. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for product appearance, reconstitution time and appearance of the reconstituted solution, pH, water content, sub-visible particulates, irinotecan content, PEGylated irinotecan species, small molecule impurities, bacterial endotoxins, together with molecular weight and polydispersity for earlier stability studies. The analytical procedures used are stability indicating. Some variability was observed in the results but no apparent trends and all parameters remain within the specification limits.

Photostability testing on a pilot batch as per the ICH guideline demonstrated similar test results as the control sample. The results for sub-visual particulate matter after reconstitution, molecular weight, HPLC purity, and IRT content differed slightly within the variation of the methods applied. It can be concluded that the proposed commercial packaging provides adequate light protection for Onzeald.

Thermal Cycling Study demonstrated that temperature effects between -20 °C and 40 °C/75% RH likely to occur during transportation, shipping and product storage do not have a significant impact on the physical, chemical and microbial stability.

Onzeald is intended to be administered after reconstitution and dilution into 0.9% Sodium Chloride Injection (0.9% Saline) or 5% Dextrose Injection (D5W) for an IV infusion. The microbiological stability of reconstituted Onzeald diluted with 250 mL of 0.9% Saline or D5W in infusion bags was evaluated. The study demonstrated that no microbial growth was detected following product reconstitution, dilution, handling, and storage of the Onzeald diluted solution in infusion bags as determined by the bioburden testing. Therefore, it is concluded that Onzeald after reconstitution and dilution into 0.9 % Saline or D5W did not show any microbial growth for 8 hours at room temperature.

Based on available stability data, the proposed shelf-life of 30 months and “store in a refrigerator (2 °C-8 °C)”, “store in the original package in order to protect from light are acceptable.

Adventitious agents

No materials of animal origin are used in the manufacture of Onzeald.

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 active substance has been satisfactorily characterised. The PEGylation prolongs circulation half-life compared with conventional irinotecan, and achieves lower peak plasma concentrations of irinotecan which is predicted to reduce toxicity. There is also evidence that, unlike conventional irinotecan, the PEGylated macromolecule crosses the blood-brain barrier and accumulates in brain tumour deposits.

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.

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 proposed conditions of use. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical data package included *in vitro* and *in vivo* pharmacology, pharmacokinetics (PK), and toxicity studies. The toxicity profile of etirinotecan pegol was characterized in rats and dogs in studies up to 14 weeks duration that were compliant with GLP. The ADME studies were not conducted in accordance with GLP.

2.3.2. Pharmacology

The effect of etirinotecan pegol was assessed in cell cultures, and in mouse models of human cancers, including breast cancer, and has been compared to the effect of irinotecan.

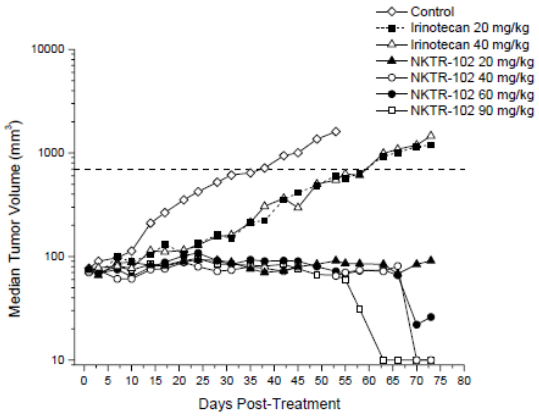
Primary Pharmacology

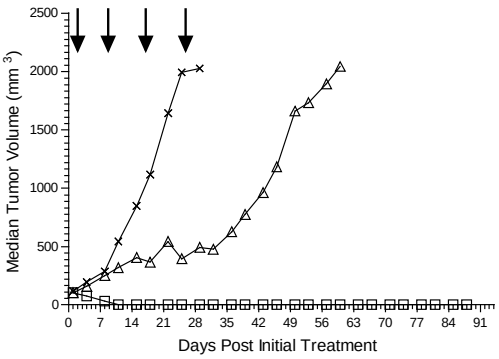
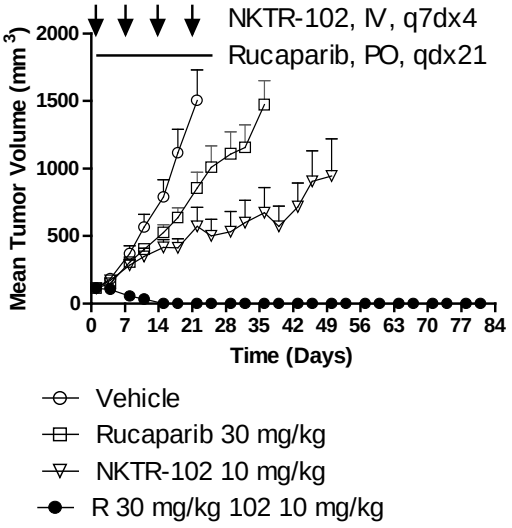
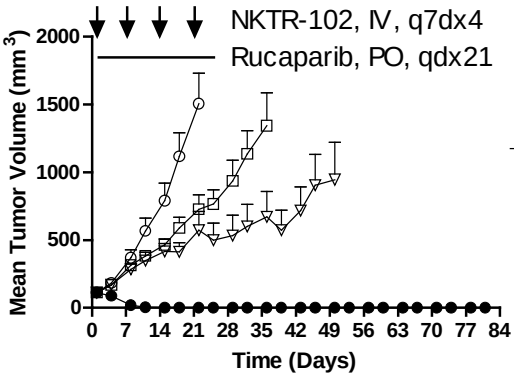
In vitro etirinotecan pegol was studied in the human HT29 colon carcinoma, NCI-H460 lung carcinoma, NCI-H522 lung carcinoma, MCF-7 mammary carcinoma, MX-1 mammary carcinoma cell lines and compared to irinotecan and its active metabolite SN38. Etirinotecan pegol, displayed slightly less potency (HT29, 88%; NCI-H460, 80%; NCI-H522, 74%; MCF-7, 40%; MX-1, 81%) compared to irinotecan in all tumour cell lines tested and both etirinotecan pegol and irinotecan were approximately 1-3 log units less potent relative to the active metabolite SN-38.

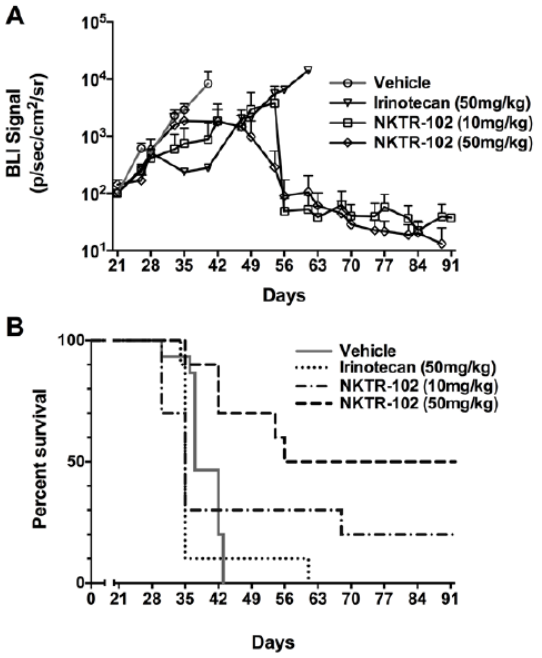
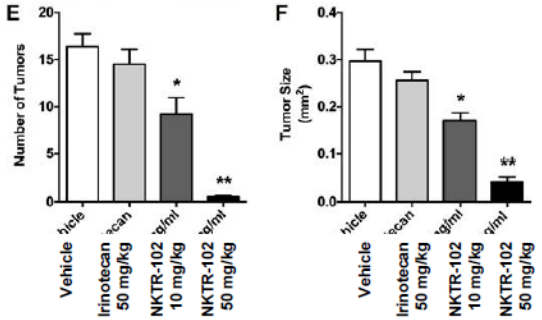
In vivo effects of etirinotecan pegol were studied in several different experimental models using cell lines of human origin to establish tumours by implanting tumour fragments from serial passages or

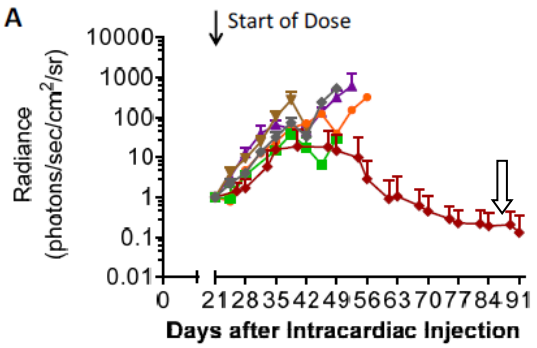
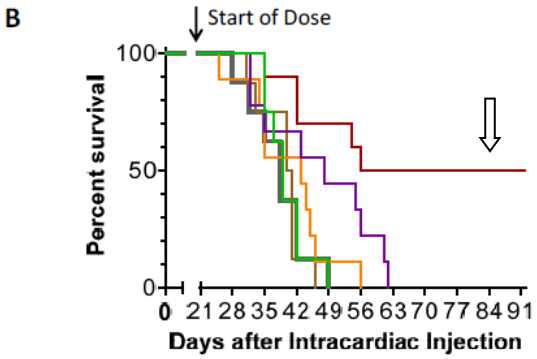
suspensions of tumour cells. Three different models were used to study the effects of etirinotecan pegol on breast cancer, the MCF-7 (expressing the oestrogen receptor) and the MX-1 breast cancer models, where cells or tumour fragments are implanted subcutaneously and a breast cancer brain metastases model using a brain seeking clone of the MDA-MB-231 cell-line expressing firefly luciferase (MDA-MB-231Br-Luc). Six additional mouse tumour models of human cancers other than breast cancer were also used to study the effects of etirinotecan pegol *in vivo*. Female athymic nude mice were used for MCF-7, MX-1, MDA-MB-231Br-Luc, HT29, NCI-H460, H69, and A2780 xenograft studies, male athymic nude mice for the DLD-1 studies and female SCID mice was used for NCI-N87. The median time to reach endpoints was determined and treatment outcomes was evaluated by tumour growth delay (TGD) and regression.

Table 1 - Summary of results obtained in the MCF-7, MX-1 and MDA-MB-231 breast cancer models

Type of Study / Study Number	**Test System**	**Doses and Method of Administration**	**Summary of results**
Effect of etirinotecan pegol in the MCF-7 breast cancer model LS-2010-004 2-PCP-003.21	Female athymic NU/NU mice injected subcutaneously with MCF-7 tumour cells (and implanted with a 17β-estradiol pellet) N=10/group	Etirinotecan pegol 20, 40, 60, or 90 mg/kg IV q4dx3 (Days 0, 4 and 8.) Irinotecan 20 and 40 mg/kg IV, q4dx3 Vehicle (0.9% w/v sterile saline)	**Tumour growth delay curves following treatment with etirinotecan pegol or irinotecan in MCF-7 human breast tumours**  All doses of etirinotecan pegol (NKTR-102) and irinotecan were well tolerated with a maximum 10% loss in body weight relative to the start of treatment (40 mg/kg MTD for irinotecan and 90 mg/kg MTD for etirinotecan pegol). *Etirinotecan pegol (TGD=tumour grpwth delay in days):* 90 mg/kg, 2 PR + 6 CR/9, 9/9 survivors, TGD>36 60 mg/kg, 3 CR/8, 8/8 survivors, TGD>36 40 mg/kg, 6 CR/9, 8/9 survivors, TGD>36 *Irinotecan* 40 mg/kg, 3 CR/10, 2/10 survivors, TGD=22 20 mg/kg, 1 CR/9, 3/9 survivors, TGD=22 **Conclusion**: Etirinotecan pegol showed superior effect over irinotecan based on tumour growth delay and regression response rates in the MCF-7 breast cancer model.
Effect of etirinotecan pegol alone or in combination with rucaparib in the MX-1 breast cancer model	Female athymic NU/NU mice implanted subcutaneously with MX-1 tumour fragments (1 mm^3).	Etirinotecan pegol (NKTR-102) 10 or 50 mg/kg, IV q7dx4 Rucaparib 30 or	**Tumour volumes over time following treatment with etirinotecan pegol (NKTR-102)**

Type of Study / Study Number	Test System	Doses and Method of Administration	Summary of results
LS-2013-015	Individual tumour volumes ranged from 63 to 196 mm^3 and group mean tumour volumes from 113 to 115 mm^3 at the start of experiment. N=10/group	150 mg/kg PO, qdx21	 X = vehicle, Δ = 10 mg/kg, □ = 50 mg/kg   **Conclusion**: All treatments were well-tolerated. Etirinotecan pegol monotherapies at 10 and 50 mg/kg gave doserelated effect with 50 mg/kg

Type of Study / Study Number	Test System	Doses and Method of Administration	Summary of results
			being curative. Rucaparib monotherapies at 30 and 150 mg/kg were modestly efficacious. An improved effect was seen with the combination therapies of 10 mg/kg etirinotecan pegol / 30 or 150 mg/kg rucaparib compared to their corresponding monotherapies.
Effect of etirinotecan pegol in an experimental model of MDA-MB-231 breast cancer brain metastases LS-2012-501	Female athymic NU/NU mice inoculated with MDA-MB-231Br-Luc, brain-seeking human metastatic breast cancer cells expressing firefly luciferase, in the left cardiac ventricle	Etirinotecan pegol IV, q7d Irinotecan IV, q7d	(A) Mean BLI signal versus time by treatment in mice exhibiting brain metastases. (B) Survival analysis of mice bearing brain metastases. Vehicle, irinotecan (50 mg/kg), etirinotecan pegol (10 or 20 mg/kg were injected IV every 7 days starting 21 days post intracardiac injection of human breast MDA-MB-213 tumour cells. (BLI = bioluminescence)  Each data point represents mean ± SEM (n=5-18 per time point) Number of detectable brain metastases by treatment (E). Average size of the CNS metastasis (µm2) (F). 

Type of Study / Study Number	Test System	Doses and Method of Administration	Summary of results
			All data are Mean + SEM (n=5-10). *, ** **Conclusion**: Significant differences ($p<0.05$ and $p<0.01$) were observed in the number of CNS metastases in animals treated with low dose (9.2 + 1.7) and high dose Etirinotecan pegol (0.54 + 0.2) compared to vehicle (16.4 + 1.4) and irinotecan (14.5 + 1.6) treated animals. Average size was smaller in animals treated with low dose (0.17 + 0.02) and high dose Etirinotecan pegol (0.04 + 0.01) compared to vehicle (0.29 + 0.3) and irinotecan (0.26 + 0.2) treated animals.
Experimental model of MDA-MB-231 breast cancer brain metastases Comparison of etirinotecan pegol with gemcitabine, eribulin, vinorelbine, and docetaxel LS-2015-011	Female athymic NU/NU mice inoculated with MDA-MB-231Br-Luc, brain-seeking human metastatic breast cancer cells expressing firefly luciferase, in the left cardiac ventricle	Vehicle control (normal saline, n=12), docetaxel (10 mg/kg, n=8), vinorelbine (10 mg/kg, n=9), eribulin (1.5 mg/kg, n=8), and gemcitabine (60 mg/kg, n=9), administered intravenously (IV) or intraperitoneally (IP) repeated once weekly (IV, vehicle control, docetaxel, vinorelbine) or once every four days (IP, eribulin, gemcitabine)	Selection of pharmacologically relevant doses of eribulin, vinorelbine, docetaxel, and gemcitabine in the present study was based on published literature describing the effect of these agents in mouse cancer models   *Open arrow = animals treated with 50 mg/kg etirinotecan pegol (Data taken from study LS-2012-501).* Tumour growth and survival curves of control treated animals in studies LS-2015-011 and LS-2012-501 were similar (not shown). In etirinotecan pegol-treated animals tumour burden determined by bioluminescence started to decrease two weeks after the start of treatment and was nearly completely eliminated in the animals still on treatment during the last two weeks of the study. Etirinotecan pegol significantly increased median survival by 37 days compared to vehicle control, with five of ten animals surviving to

Type of Study / Study Number	Test System	Doses and Method of Administration	Summary of results
			the end of the study with minimal residual disease. Based on quantitation of bioluminescence, central nervous system (CNS) tumour burden was similar to vehicle control for gemcitabine, eribulin, vinorelbine, and docetaxel. There was neither any significant difference in survival curves. **Conclusion**: Contrary to etirinotecan pegol, gemcitabine, eribulin, vinorelbine, and docetaxel showed no activity in this in vivo model.

A summary of results obtained with etirinotecan pegol in the 6 mouse tumour models of human cancers other than breast cancer used, is presented in Table 5.

Table 2 - Regressions and tumour growth delay for tumour-bearing mice after administration of etirinotecan pegol (NKTR-102), irinotecan, or topotecan

Test compound	Dose[a] (mg/kg)	Tumour regression[b]		Median TTE[d] (days)
		Partial	Complete	
[Q4dx3 (IV)]	Colorectal cancer, HT29 (Study LS-2010-004)[c]			
Control	0	0/20	0/20	16
Etirinotecan pegol	90	0/10	2/10	>60
Etirinotecan pegol	60	0/10	0/10	46
Etirinotecan pegol	40	0/10	0/10	36
Irinotecan	90	0/10	0/10	27.5
Irinotecan	60	0/10	0/10	30
Irinotecan	40	0/10	0/10	26.5
[Q4dx3 (IV)]	Non-small cell lung cancer NCI-H460 (Study LS-2010-004)[c]			
Control	0	0/20	0/20	12
Etirinotecan pegol	90	0/9	1/9	48
Etirinotecan pegol	60	0/10	1/10	42.5
Etirinotecan pegol	40	0/8	0/8	28.5
Irinotecan	90	0/10	0/10	24.5
Irinotecan	60	0/10	0/10	24
Irinotecan	40	0/10	0/10	23
[Q4dx3 or Qd5^{Topo} (IV)]	Small cell lung cancer, H69 (Study LS-2007-048) [c]			
Control	0	Not reported	0/8	30
Etirinotecan pegol	11.5		0/8	59
Etirinotecan pegol	5.75		0/8	52
Etirinotecan pegol	2.3		0/8	38
Topotecan	1.0		0/8	45

Test compound	Dose[a] (mg/kg)	Tumour regression[b]		Median TTE[d] (days)
		Partial	Complete	
Topotecan	0.5		0/8	40
Topotecan	0.13		0/8	33
[Q7dx7 (IV)] Colorectal, DLD-1 (Study LS-2007-046)[c]				
Control	0	Not reported	0/8	21
Etirinotecan pegol	69		0/8	83
Irinotecan	60*)/40 *) 2 first doses		0/8	28
[Q7dx3 (IV)] Gastric, NCI-N87 (Study LS-2009-003)[c]				
No Treatment	-	0/9	0/9	18
Etirinotecan pegol	150	1/9	8/9	84
Etirinotecan pegol	100	4/10	6/10	84
Etirinotecan pegol	60	2/10	1/10	84
Irinotecan	60	0/9	0/9	30
5-FU	100 ip	0/10	0/10	22
[Q7dx3 (IV)] Ovarian, A2780 (Study LS-2008-009)[c]				
No Treatment		0/10	0/10	14
Etirinotecan pegol	150	1/10	9/10	49
Etirinotecan pegol	100	2/10	8/10	46
Etirinotecan pegol	50	5/10	5/10	48
Irinotecan	150	1/10	0/10	30
Irinotecan	100	0/10	0/10	29
Irinotecan	50	0/10	0/10	26
[Qdx1 (IV)] Ovarian, A2780 (Study LS-2011-610)				
Control		0/10	0/10	12
Etirinotecan pegol	100	0/10	10/10	44
Etirinotecan pegol	150	0/10	10/10	50

a. Refers to irinotecan equivalents administered in each dose.
b. Tumour regression must be evident for 3 consecutive measurements to be so designated. Partial: ≤50% of volume on Day 1; Complete: not palpable.
c. Endpoints were as follows: NCI-H460: 1500 mm3 or day 61, HT29: 1000 mm3 or day 60, DLD-1:1500 mg or Day 84, H69: 2000 mg or Day 60, A2880: 2000 mm3 or Day 76, NCI-N87: 800 mm3 or Day 84.
d. Time to Endpoint (TTE); median number of days for tumours to reach endpoint. Studies were terminated on Days 60 (HT29), 85 (DLD-1), 61 (NCI-H460), 60 (H69), 60 (A2780, q7dx3), 76 (A2780, qdx1), and 84 (NCI-N87).

PK/PD

PK/PD relationships between tumour SN38 exposure and tumour growth delay were studied in HT29 colorectal and H460 non-small cell lung cancer models following administration of irinotecan and etirinotecan pegol. It was shown that SN38 concentrations in both plasma and tumour resulting from etirinotecan pegol administration declined at a much slower rate than those resulting from irinotecan administration. The increased SN38 half-life values contributed to a greater SN38 AUC values observed

after etirinotecan pegol administration as compared to SN38 resulting from irinotecan administration. Tumour SN38 concentration correlated with the inhibitory treatment effect on tumour growth and the inhibitory effects become apparent once a threshold concentration of SN38 was exceeded and maintained. In the HT29 colorectal tumour model, the threshold was approximately 200 ng/g and in the H460 colorectal tumour model 1000 ng/g, concentrations of SN38 that were not achieved with administration of irinotecan.

PK/PD relationship between SN38 exposure and neutropenia was also studied. An increasing incidence of neutropenia was observed in Beagle dogs with increasing SN38 Cmax with SN38 Cmax values < 5 ng/mL associated with low incidences of neutropenia (<10%) and neutropenia increasing to 67% at SN38 Cmax values between 5-<10 ng/mL, and reaching 100% for SN38 Cmax values between 10-<20 ng/mL. Cmax values after administration of etirinotecan pegol were lower (<10 ng/mL, with 74% of dogs exhibiting SN38 Cmax values of <5 ng/mL) than after administration of irinotecan which lead to SN38 Cmax values between 10-50 ng/mL at similar dose levels (mg irinotecan equivalents). In contrast to SN38 Cmax, there was no apparent relationship between SN38 AUC0-168h and the incidence of neutropenia.

Secondary pharmacodynamics

No secondary pharmacodynamic studies were submitted.

Safety pharmacology

No stand-alone safety pharmacology studies were submitted. Detailed clinical observations in repeat-dose GLP toxicology studies in rats and dogs were used to assess respiratory and central nervous system (CNS) safety. There were no reported effects of etirinotecan pegol treatment on CNS or respiratory-related clinical observations or on any electrocardiography parameter at doses up to MTD (see Toxicology section).Cardiovascular safety (ECG) was assessed as part of dog GLP toxicology studies.

Table 3 - Cardiovascular safety studies completed as part of the GLP repeat dose toxicity studies

Test System / Study number	Doses and Method of Administration	Summary of results
Beagle dog 5-7/sex LS-2005-036 /GLP	Etirinotecan Pegol IV q7dx4 1-hour Infusion 0 (control),6, 15, 40/25 Irinotecan IV q7dx4	Dose-related mean increases of 17-33% in heart rate at dose levels >15 mg/kg with a complete recovery; no effects on morphology
Beagle dog 3-4/sex LS-2005-038 /GLP	Etirinotecan Pegol IV q7dx4 1-hour Infusion 0 (control), 20, 25 Irinotecan IV q7dx4	No changes in any ECG parameter; no effects on morphology
Beagle dog 6/sex LS-2009-008 /GLP	Etirinotecan Pegol q14dx7 1-hour Infusion 0 (control),6, 15, 30	No changes in any ECG parameter; no effects on morphology

q7dx4= once every 7 days for a total of 4 doses; q14dx7=once every 14 days for a total of 7 doses
IV = 1-hour iv infusion

2.3.3. Pharmacokinetics

The pharmacokinetics and metabolism of etirinotecan pegol were studied in mice, rats and dogs. Tumour distribution studies in mice were also performed.

Absorption

Since etirinotecan pegol is administered as an IV infusion, there is no absorption process to consider.

After IV administration, mean systemic clearance (CLp) of etirinotecan pegol was high in rats and measured in the range of 9.2 to 30.6 mL/(hr·kg). Clearance decreased with increasing doses. The mean volume of distribution of etirinotecan pegol was smaller than total body water (0.6 L/kg) and ranged from 53.6 to 113.8 mL/kg. Mean t1/2 ranged from 2.68 to 5.89 hours.

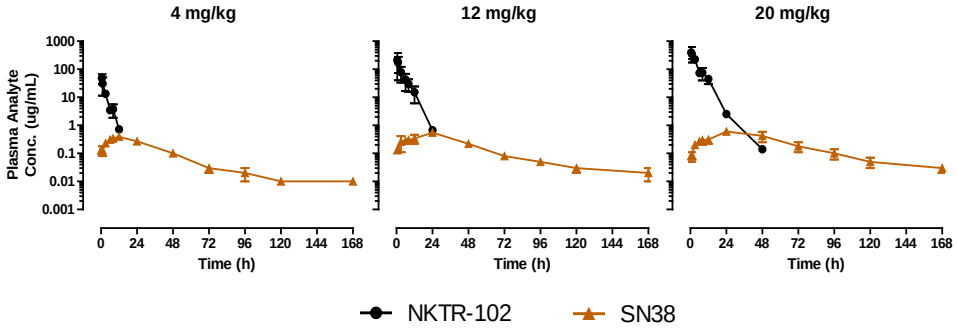
Pharmacokinetics parameters of etirinotecan pegol and SN38 in the rat are presented in the table below.

Table 4 - Mean plasma etirinotecan pegol, and SN38 pharmacokinetic parameter values following intravenous administration of etirinotecan pegol to male Sprague Dawley rats (PEGI-R-002)

Dose (mg/kg)	Analyte	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (µg*hr/mL)	$AUC_{0-\infty}$/Dose (µg*hr/mL/mg)	CL (mL/hr/kg)	V_d (mL/kg)	$t_{1/2}$ (hr)
4	Etirinotecan pegol	628	0.5	136	34.1	30.6	114	2.7
	SN38	0.4	11	14.9	3.7	NA	NA	51.4
12	Etirinotecan pegol	2780	0.7	920	76.7	13.4	53.6	2.8
	SN38	0.55	24	25.8	2.2	NA	NA	44
20	Etirinotecan pegol	5230	0.7	2190	110	9.2	78.3	5.9
	SN38	0.6	24	36.6	1.8	NA	NA	40

NA=not applicable.

SN38 concentrations released from etirinotecan pegol reached Cmax 10-24 hours post dose and remained detectable for the 168 hr study period, providing evidence for the slow but sustained release of the active metabolite (see Figure below).



Shown is mean ± SD for n=3 rats/dose group.

Figure 2 - Mean plasma etirinotecan pegol (NKTR-102) and SN38 concentration-time profiles following intravenous administration of 4, 12, and 20 mg/kg etirinotecan pegol (NKTR-102) to male Sprague Dawley rats (PEGI-R-002)

After administration of 20, 40, or 80 mg/kg etirinotecan pegol as 30-min intravenous infusion (tail vein) etirinotecan pegol C_{max} was observed immediately after the end of the infusion. Etirinotecan pegol CL

was independent of dose, and exposure increased in proportion to dose. Etirinotecan pegol V_{ss} ranged from approximately 60 to 150 mL/kg, about 2 to 5 times greater than that of plasma volume. Clearance of etirinotecan pegol was also low (average 6.54 mL/hr/kg) relative to hepatic plasma flow (1800 mL/hr/kg), which contributed to the long half-life of 8 to 25 days.

Among the etirinotecan pegol metabolites, C_{max} values decreased in the order irinotecan ~ SN38 > SN38G > APC. Irinotecan, SN38, and SN38G exposure increased with dose (irinotecan and SN38 more than dose proportionally, SN38G less than dose proportionally). Similar to etirinotecan pegol, SN38 and SN38G concentrations remained detectable over the course of the 21-day study; both metabolites had half-lives similar to those of etirinotecan pegol. Consistent with high esterase activity in rodents, irinotecan concentrations declined rapidly and the highest dose was required to achieve sustained irinotecan concentrations. APC concentrations were detected for only a short period of time post dose (PK parameters were not determined for this analyte) (see Table 8).

Table 5: Mean plasma pharmacokinetic parameters of etirinotecan pegol, irinotecan, SN38-glucoronide and SN38 after single intravenous infusion in male Sprague Dawley rats (LS-2010-502)

Dose (mg/kg)	Analyte	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (µg*hr/mL)	$AUC_{0-\infty}$ /Dose (µg*hr/mL/mg/kg)	CL (mL/hr/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (hr)
20	Etirinotecan pegol	701	0.5	2770	139	7.20	150	590
	Irinotecan	0.115	1	0.372	0.0186	NA	NA	5.1
	SN38	0.046	1	9.47	0.473	NA	NA	335
	SN38G	0.0834	24	6.67	0.333	NA	NA	243
40	Etirinotecan pegol	797	0.5	6140	154	6.54	95	190
	Irinotecan	0.552	1	ND	ND	NA	NA	ND
	SN38	0.996	24	ND	ND	NA	NA	ND
	SN38G	0.113	24	10.2	0.256	NA	NA	289
80	Etirinotecan pegol	1730	0.5	13700	172	5.82	63	371
	Irinotecan	1.01	0.5	14.8	0.185	NA	NA	322
	SN38	0.659	48	68.1	0.851	NA	NA	242
	SN38G	0.180	0.5	13.9	0.174	NA	NA	272

Means based on N=3 rats/observation time; 1 observation time/rat. NA = not applicable; ND=not determined.

The single dose pharmacokinetics of etirinotecan pegol was also evaluated as part of a radiolabelled study in rat using a 30 min intravenous infusion of etirinotecan pegol (20 mg/kg irinotecan equivalents, infusion rate of 24 mL/kg/hr) with a ^{14}C-label incorporated in the PEG moiety (^{14}C-20K-PEG-Gly-irinotecan) or in the irinotecan moiety (20K-Gly-^{14}C-irinotecan) as well as ^{14}C-irinotecan (20 mg/kg). The Cmax of total radioactivity from [^{14}C]-irinotecan was slightly higher in blood (8.54 µg eq./mL) than in plasma (7.83 µg eq./mL), both occurring at the end of the infusion, thereafter declining in a multi-exponential fashion with a terminal plasma half-life of 35 hr. The AUC_{0-t} was higher in blood (42.3 µg eq. hr/mL) than in plasma (22.3 µg eq.*hr/mL), suggesting that irinotecan-related products distributed into erythrocytes. Unlike conventional irinotecan, the two etirinotecan pegol radiolabelled forms had much higher and similar Cmax values (214 and approximately 340 µg equiv./mL for blood and plasma, respectively) occurring at the end of infusion, indicating that virtually all the radioactivity derives from intact etirinotecan pegol at 0.5 hr after dosing. The half-lives of both [^{14}C]-20K-PEG-Gly-irinotecan (blood, 312 hr; plasma 215 hr) and 20K

PEG Gly [^{14}C] irinotecan (blood, 903 hr; plasma, 983 hr) were longer than those of unconjugated irinotecan, although it was not possible to definitively compare the half-life between the two radiolabelled forms of etirinotecan pegol due to the sampling times being different, combined with the respective half-lives being so long that they were only measured over approximately one half-life. Despite the shorter sampling period (504 hr) when [^{14}C]-20K-PEG-Gly-irinotecan was administered compared to when 20K-PEG-Gly-[^{14}C]-irinotecan was dosed (1344 hr), the AUC0 t for both blood and plasma for the former radiolabelled form was higher.

Single dose pharmacokinetics of etirinotecan pegol in comparison to irinotecan have been evaluated in dog as part of a maximum tolerated dose toxicology study. Dogs (1/sex) received either 3.6, 26.4, 36.8 or 52 mg/kg etirinotecan pegol or 5.2, 16, 26 mg/kg irinotecan as a 30 min intravenous infusion.

Pharmacokinetic parameter values were similar for male and female dogs. CL, V_d and $t_{1/2}$ were independent of dose and AUC increased approximately in proportion to dose. For all but C_{max} and AUC, average PK parameter values are presented. Etirinotecan pegol volume of distribution averaged 188 mL/kg, which is higher than average plasma volume (51 mL/kg). Etirinotecan pegol clearance was low, contributing to the long half-life of 48 hr. SN38 released from etirinotecan pegol reached C_{max} on average 10 hr post dose. At the higher etirinotecan pegol doses, SN38 concentrations remained in circulation for the entire duration of the study (360 hr). After irinotecan administration, SN38 C_{max} was observed shortly after the end of infusion, and was reduced to concentrations below the LLOQ (BLQ) by 72 hours post dose. Etirinotecan pegol administration resulted in sustained plasma SN38 concentrations that yielded a 6-fold higher AUC (1.9 vs. 0.3 µg.hr/mL) while maintaining the same SN38 C_{max} (0.02 vs. 0.03 µg/mL) at the 26 mg/kg equivalent dose level.

Etirinotecan pegol showed low permeability in both Madin-Darby canine kidney (MDCK) and Caco-2 cell monolayers. Papp in MDCK-MDR1 were 0.25 nm/s (=0.025 10^{-6} cm/s) in both A>B and B>A direction and in Caco-2 cells 0.38 nm/s A>B and 0.35 nm/s B>A (A=apical, B=basolateral).

Distribution

Protein binding

The large molecular size prevented separation from plasma proteins using dialysis, ultrafiltration, ultracentrifugation, or size exclusion chromatography. Interaction with human serum albumin was therefore examined with an albumin affinity column. Nonlinear regression analysis of per cent plasma protein binding versus the retention times of control articles and etirinotecan pegol, suggest minimal (≤4%) binding of etirinotecan pegol to human serum albumin. Plasma protein binding of SN38 was 98.4% in human plasma, 85.6% in dog plasma and 95.9% in rat plasma, and was concentration-independent across species. No distribution of etirinotecan pegol to red blood cells was detected.

Tissue distribution

After administration of ^{14}C-20K-PEG-Gly-irinotecan and 20K-PEG-Gly-^{14}C-irinotecan tissue distribution was similar, but differed from that of ^{14}C-irinotecan. ^{14}C-etirinotecan pegol forms showed less extensive initial distribution out of plasma with tissue to blood ratios less than unity for the majority of tissues at the earlier times after dosing. The highest concentrations were observed in highly perfused tissues such as lung, adrenal gland, liver, spleen, and myocardium, as well as the lymph nodes, indicating uptake by the reticuloendothelial system.

Although the tissue to blood ratio for the two ^{14}C-etirinotecan pegol forms started at <1, over time they became >1 suggesting a slower equilibration into tissues than for irinotecan and a slower clearance from tissues than plasma. Lowest levels of radioactivity were observed in brain and spinal cord, indicating poor

distribution to the central nervous system. Only low levels of radioactivity were observed in the eye and pigmented skin of Long Evans rats, suggesting that melanin binding was not extensive.A reversible binding of ^{14}C-irinotecan-related products to melanin was indicated after administration of irinotecan. Unlike ^{14}C-irinotecan, for which radioactivity was relatively quickly eliminated from tissues, the radioactivity from the two radiolabelled forms of etirinotecan pegol declined much more slowly, with radioactivity persisting in most tissues, especially the liver, until the last sampling time (1344 hr). Etirinotecan pegol associated radioactivity was cleared faster from blood compared to tissue compartments, indicating that etirinotecan pegol in tissues served as reservoir for prolonged release of irinotecan.

Tissue distribution of total radioactivity in male albino, male-pigmented and time-mated female albino rats was also assessed following administration of the ^{14}C-labeled polymer core and linker of etirinotecan pegol (^{14}C-Gly-20K-PEG) and the distribution of radioactivity observed was similar to that observed with the two radiolabelled forms of etirinotecan pegol, suggesting that the PEG moiety is a major determinant of the distribution of etirinotecan pegol.

Distribution to brain tumours and brain metastases

Uptake of irinotecan and etirinotecan pegol in brain tumours and brain metastases were assessed in mice bearing intracranial tumours. Tumours were established by administrating the human breast cancer cell line (MDAMB-231Br-Luc) intracranial (“brain tumours”) or into the left cardiac ventricle (“brain metastases”). Brain tissue distant to tumour (BDT) was also assessed in mice with established brain metastases. Plasma and brain tumour samples were assayed for etirinotecan pegol, irinotecan, and SN38, SN38G, APC, and NPC using validated liquid chromatography–tandem mass spectrometry (LC/MS/MS) methods or brain sections mounted onto slides for quantitation of radioactivity in brain metastases and BDT using quantitative autoradiography (QAR).

After administration of etirinotecan pegol, concentrations of etirinotecan pegol and SN38 remained at measurable levels in plasma for 168 hours and concentrations of etirinotecan pegol continued to accumulate in brain tumours, and exceeded corresponding plasma concentrations by 170-fold at 168 hours post dose. Brain tumour etirinotecan pegol concentrations only declined by 4-fold from its corresponding Cmax value by 168 hours post dose.

After irinotecan administration, highest concentrations of both irinotecan and SN38 were observed at the first observation time point in both plasma and tumour. SN38 concentrations continued to accumulate in brain tumour, reaching a Cmax by 24 hours post dose and exceeded plasma concentrations by 30-fold at 168 hours. Administration of irinotecan only gave short exposures and tumour to plasma concentration ratios ranging between 0.5 to 4 for irinotecan and 0.8-2.8 for SN38.

Table 6: Plasma and brain tumour concentrations after IV bolus administration of 50 mg/kg etirinotecan pegol (NKTR-102) or irinotecan to NU/NU mice with established MDA-MB-231Br Brain Tumours (LS-2012-501).

Treatment	NKTR-102				Irinotecan			
Time (hr)	6	24	72	168	2	6	12	24
NKTR-102 Concentration ± SEM (ng/mL or ng/g)								
Plasma	72450 ± 48790	210 ± 126	14 ± 7.5	5.0 ± 0.09				
Tumor	3200 ± 3700	2572 ± 1323	1207 ± 904	833 ± 240				
Tumor/Plasma	0.4	12	80	170				
Irinotecan Concentration ± SEM (ng/mL or ng/g)								
Plasma	134 ± 31	11 ± 1.6	1.2 ± 0.18	0.55 ± 0.06	1100 ± 306	2.9 ± 1.4	0.7 ± 0.3	2.3 ± 1.8
Tumor	32 ± 18	138 ± 42	11 ± 5.7	2.8 ± 1.3	554 ± 667	7.7 ± 5.8	2.8 ± 1.2	7.4 ± 5.2
Tumor/Plasma	0.24	12	9.2	5.1	0.5	2.7	3	4
SN38 Concentration ± SEM (ng/mL or ng/g)								
Plasma	63 ± 50	34 ± 13	2.2 ± 1.4	0.65 ± 0.08	36 ± 12	2.4 ± 1.3	0.7 ± 0.1	0.4 ± 0.4
Tumor	13 ± 16	208 ± 126	60 ± 78	23 ± 28	29 ± 46	0.8 ± 0.4	0.6 ± 0.4	1.1 ± 1.1
Tumor/Plasma	0.2	6	27	31	0.8	0.3	0.9	2.8

N=4-5/timepoint

After administration of irinotecan, radioactivity in brain, as measured by quantitative autoradiography, varied widely between and within metastases (ranging between ~25 ng/g to ~350 ng/g) averaging 66 ng/mL, 4.7 times the average radioactivity of BDT (14 ng/g). Etirinotecan pegol, gave a higher radioactivity level in brain metastases (ranging from ~390 ng/g to ~1800 ng/g), compared to radioactivity after administration of irinotecan with an average brain metastatic radioactivity of 672 ng/g.

Metabolism

Irinotecan is extensively metabolised in the liver to various metabolites. It is cleaved enzymatically by carboxylesterases to form SN38 and this active metabolite of irinotecan has cytotoxic activity that is 100 to 1000 times greater that of the parent drug. SN38 is conjugated to an inactive glucuronide by UGT. The additional metabolites APC and NPC, result from metabolism of irinotecan by cytochrome P4503A.

Hydrolysis of etirinotecan pegol followed first order kinetics but was predominantly chemical and not enzymatic. However, etirinotecan pegol appeared to be metabolised by esterases in mouse, rat, dog, and human plasma. The loss of etirinotecan pegol was similar in human and dog plasma but occurred approximately 4 times faster in rodent plasma (t1/2 of 2 to 4 hr rodent plasma vs. t1/2 of 10 to 12 hr in non-rodent plasma). Metabolism in rodent plasma included formation of PEG-SN38, irinotecan and SN38, while in non-rodent plasma, irinotecan was the primary end product. The major human metabolites SN38, SN38G and APC were all present in non-clinical species. NPC concentrations were reported to be below the limit of quantitation in the clinical studies performed. In addition, PEG-SN38, was observed in rodents which suggests metabolism of irinotecan to SN38 while still attached to the PEG core in these species. PEG-SN38 concentrations were also observed in human and dog plasma, but these findings were

later shown to be due to an analytical artefact. No quantitative comparison between metabolites found in human plasma and plasma from non-clinical species after exposure to etirinotecan pegol was presented. This is considered to be acceptable and in line with the ICH S9 Guideline.

No direct data on the metabolism of etirinotecan pegol was provided. However, most of the radioactivity in plasma (98.2%) and urine (88.4%) was indicated to be associated with intact etirinotecan pegol.

Excretion

The majority of radioactivity from both forms of ^{14}C-labelled etirinotecan pegol (^{14}C-20K-PEG-Gly-irinotecan and 20K-PEG-Gly-^{14}C-irinotecan) was excreted via the kidneys (approximately 52%), while for ^{14}C-irinotecan, elimination was mainly via the faeces (approximately 71%). Low biliary excretion of the two forms of ^{14}C-labelled etirinotecan pegol was observed. The biliary excretion of radioactivity from 20K-PEG-Gly-^{14}C-irinotecan (9.35%) was higher than that of ^{14}C-20K-PEG-Gly-irinotecan (0.66%), suggested to reflect the release of ^{14}C-irinotecan from the former and its subsequent elimination via the bile.

Toxicology

The toxicology program included eight single- or repeat-dose toxicity studies up to 14 weeks, in addition to cardiac safety pharmacology and genotoxicity characterized in dog and rat respectively.

Table 7 - Summary of toxicity studies with etirinotecan pegol.

Study Type Duration	Species Strain	Administration	Study Report Number	Test Article(s) (Batch Number)	GLP[a] Compliant
Single-dose Toxicity					
Single-Dose	Rat (SD)	30 minute IV infusion	2-PCP-003.14	NKTR-102 (ZR-7E-140-18 and ZR-7E-140-19)	No
Single-Dose	Dog (Beagle)	30-70 minute IV infusion	LS-2005-003[b]	NKTR-102 (ZR-11E-140-65),	No
Repeat-dose Toxicity					
4 weeks (q7dx	Rat (SD)	30 minute IV infusion	LS-2005-005[c,e]	NKTR-102 (ZR-2F-140-89), Irinotecan	No
4 weeks (q7dx4)	Dog (Beagle)	60 minute IV infusion	LS-2005-004[e]	NKTR-102 (0145-18-01), Irinotecan, 4arm-PEG20K-glyci	No
4 weeks (q7dx4)	Rat (SD)	30 minute IV infusion	LS-2005-035[e, f]	NKTR-102 (2623.54)	Yes
4 weeks (q7dx4)	Dog (Beagl	60 minute IV infusion	LS-2005-036[d,e]	NKTR-102 (2623.54)	Yes
4 weeks (q7dx4)	Dog (Beagl	60 minute IV infusion	LS-2005-038[d,e]	NKTR-102 (0145-63),	Yes
14 weeks (q14dx7)	Dog (Beagl	60 minute IV infusion	LS-2009-008[d,g]	NKTR-102 (F08-06304)	Yes

Abbreviations: NKTR-102 = Company or Laboratory code for etirinotecan pegol; IV = intravenous; q7dx4=once every week for 4 weeks; q14dx7= once every 2 weeks for 7 cycles; SD = Sprague Dawley; TK = toxicokinetics.

a. GLP and non-GLP toxicology studies were conducted using the identical laboratory procedures and documentation practices; the only difference between GLP and non-GLP studies is a quality audit of all data is conducted for GLP studies.
b. This study included a non-GLP TK assessment that is summarised in a separate report (PEGI-R-008 that was associated with protocol PEGI-P-008) and presented in Table 2.6.5-6.
c. This study included a non-GLP TK assessment that is summarised in a separate report (PEGI-R-012, also referenced as RD00000897.00) and presented in Table 2.6.5-8.
d. This study included a cardiovascular safety pharmacology assessment that is summarised in Section 2.6.2.4.
e. Formulation = 5% Dextrose in Water; used for studies LS-2005-004, LS-2005-005, LS-2005-035, LS-2005-036, and LS-2005-038.
f. This study included an *in vivo* micronucleus assay in rat (Study LS-2005-035) for assessment of genotoxicity that is summarised in Section 2.6.6.1.3 (see also Table 2.6.7-11).
g. Formulation = 6.0 mg/mL lactic acid in 5% dextrose in water for injection USP at pH 4.5 ± 0.2; used only for pivotal Study LS-2009-008. This formulation is representative (in terms of excipients and impurity profile) of the final drug product intended for marketing.

Single-dose toxicity

In rats dosed with a single intravenous administration (30 minutes) of etirinotecan pegol, the highest non-lethal dose was 90 mg/kg. One female rat died at 120 mg/kg with anogenital staining, labored breathing, shaking body and thin appearance. In dogs, all (one male and one female) died after a 30-70 minute IV administration of 60 mg/kg. Changes in the dogs included cryptal necrosis, GALT atrophy, bone marrow hypocellularity and lymphoid atrophy and hypoplasia. Single dose toxicity studies identified MTD values of 90 and 36,8 mg/kg for rat and dog respectively.

Table 8 - Summary of single-dose toxicity studies performed with etirinotecan pegol

Study ID / GLP	Species / Sex / Number / Group	Dose (mg/kg) / Route	Approximate Lethal Dose / Observed max non-lethal dose	Noteworthy findings
2-PCP-003. 14 /non-GLP	SD rat 3/sex/group 90: 6/sex/group	0, 30, 60, 90, 120 /IV (30 minutes)	120 / 90	Mortality: 1♀ at 120 mg/kg. Anogenital staining, labored breathing, shaking body and thin appearances occurring sporadically in the groups.
LS-2005-003 /non-GLP	Beagle dog 1/sex/group	0, 6, 30, 40, 60 /IV (30-70 minutes)	52mg/kg (actual) /36,8 mg/kg (actual)	Mortality: 1♀, 1♂ at 60 mg/kg. Changes included cryptal necrosis, GALT atrophy, bone marrow (hypocellularity), mesenteric ymph node, spleen, and thymus (lymphoid atrophy and hypoplasia). ≥26,4 mg/kg: emesis, skin discoloration (reddened), soft stool, diarrhea, and/or drooling, ↑WBC. 6 mg/kg was well tolerated PK:

Repeat-dose toxicity

6 repeat-dose toxicity studies (2 in rats and 4 in dogs) were performed in Sprague-Dawley rats and Beagle dogs in studies up to 14 weeks duration. 4 of these were GLP-compliant, whereas one 4-week study in each species was a dose-range finding study.

In the 4-week GLP-studies (both species), dosing was performed IV once a week on days 1, 8, 15 and 22 followed by 14- or 28-day recovery. In the longer pivotal 3-month study in dog, dosing was performed biweekly, where the 1-hour dosing was followed by 2 weeks of observation. To assess the reversibility of any compound-related effects, an 8-week recovery period followed the 7th cycle on study day 85.

Table 9 - Summary of non-GLP repeat-dose toxicology studies performed with etirinotecan pegol

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg)/ Route	NOAEL/NOEL
LS-2005-005 /non- GLP/ Pilot 4 weeks	SD rats/ 5/sex/group 6/ sex /group for TK	etirinotecan pegol: 0, 10, 60, 90. Irinotecan: 60 (I60) /IV 30 minutes day 1, 8, 15 and 22	**NOAEL:** None
Mortality: None; Clinical signs: No clinical signs considered related to etirinotecan pegol administration; Body weight, food consumption: ≥10 and Irinotecan 60♂:↓bw dose-dependently. HD and I60 show similar effect; Hematology: ≥10 and I60:↓WBC (especially neutrophils). I60♀:↑RBC; I60♂♀↓ hemoglobin and reticulocytes. Clinical chemistry: ≥10♀ and I60♀: ↓Bilirubin; ≥60♂♀:↓globulins and total protein. ↑ALT ; 90: ↑urea and creatinine Organ weights: ≥60: ↓thymus (abs, rel), correlated microscopically with lymphoid atrophy. ≥10 and I60: ↑ liver Macroscopic findings: ≥60 and I60:small thymus, ♀↑discoloration on kidneys. Histopathology: ≥60 and I60: thymic lymphoid atrophy (minimal-moderate), dose-related foamy histiocytes in lung, kidneys, liver, lymph nodes, ovaries, small and large intestines, spleen, thymus, testis. Vacuolation of interstitial cells in testes and ovaries. Tubular vacuolation in kidneys.			
LS-2005-004 /non-GLP 4 weeks +14-day recovery	Beagle dog/ 1/sex/group 2/sex/group for 20, 30 and I20	etirinotecan pegol:0, vehicle, 6, 20, 30, 40, Irinotecan 20 (I20) /IV 60 minutes on day 1, 8, 15 and 22	**NOAEL: 6**
Mortality: 1♂30mg/kg was found dead day 12. Findings included dark focus/area/discoloration and/or mottling of the digestive tract, mesenteric lymph node, lungs, enlarged thyroid lobes and thymus. Small spleen and thymus were recorded. Microscopic findings included marked hypocellular marrow, severe lymphoid atrophy of the thymus and mild hypoplasia of the mesenteric lymph node. Additionally, moderate histiocytic infiltration of the thyroid lobes was found. Clinical signs: ≥60 and I20: changes in the consistency, color and amount of feces dose dependently. Body weight: ≥30, I20♀: ↓weight during treatment period. Food consumption: ≥30, I20:↓throughout treatment period, but most on day after dosing. No increase during recovery. Hematology: etirinotecan pegol and I20: ↓reticulocytes, neutrophils and monocytes dose dependently. Clinical chemistry: No effects; Urinalysis: No effects; Organ weights: 40:↑ liver weight Gross pathology: No findings in main animals. Recovery HD animals had mottled bronchial or mediastinal lymph nodes. Histopathology: ≥6: Thymic atrophy, frequent lesions in digestive system, diffuse apoptosis in pyloric mucosa, lymphoid hypoplasia of the Peyer's patch; ≥20: hypocellular marrow (minimal to severe); ≥30: lymphoid hypoplasia of spleen and mesenteric lymphnode.; I20: minimal to moderate hypocellular marrow, thymic atrophy and lymphoid hypoplasia of the spleen, lymphoid hypoplasia of the Peyer's patches in the small intestine, duodenal villous atrophy and/or crypt dilatation with cell debris, purulent pneumonia in and lymphoid hypoplasia of the mediastinal lymph node. Recovery: HD: Lymphoid hypoplasia of the mesenteric lymph node, characterized by germinal center hypoplasia. Mild lymphoid hypoplasia of the iliac Peyer's patches and minimal apoptosis of the pyloric epithelium. Purulent pneumonia extending into bronchioles associated with neutrophil infiltrate and lymphoid hyperplasia of the bronchial lymph nodes. Multifocal alveolar macrophages of the lungs and medullary histiocytosis of the mediastinal lymph node.			

Table 10. Summary of GLP-compliant repeat-dose toxicity studies performed with etirinotecan pegol.

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg)/ Route	NOAEL/NOEL
LS-2005-035 / GLP/ 4 weeks + 14-day or 28-day recovery	SD Rats/ 10/sex/group 6/sex/group for TK 5/sex/group for recovery.	0, 10, 30, 90 /IV on days 1, 8, 15 and 22	**NOAEL: 10**
Mortality: One control animal was found dead on day 4 of the study. One TK animal (10mg/kg) was found dead on day 22, likely related to TK sampling. Clinical signs: No clinical signs considered related to etirinotecan pegol administration. Body weight, food consumption: ≥30: ↓bw dose dependently; ♂≥30 and ♂♀90: marked reduction in food intake. Ophthalmoscopy: No effects observed. Hematology: ≥10:↓WBC dose dependently; ≥10:♀↓neutrophils;≥30:↓reticulocytes; Anisocytosis, microcytosis, polychromasia, hyperchromia and platelet clump were observed in some individuals of all groups.; ≥10: ↑activated partial thromboplastin time (APTT) dose dependently. Serum chemistry: ≥10:↓globulin dese dependently (slight); ≥30:↑urea and creatinine: ≥90:↑cholesterol (slight) and ↓triglycerides (moderate). These changes (indicative of effects on liver and renal function) correlate with microscopic findings. Urinalysis: No effects observed; Micronucleus assay: ↑dose-related incidence of micronucleated immature erythrocytes (moderate and statistically significant). It is therefore concluded that PEG20K-Irinotecan has shown evidence of genotoxic activity in this assessment of chromosome damage in rat bone marrow. Organ weights: ≥10:↓thymus weight (abs. and rel.) dose dependently; ≥10:↑liver weights dose dependently Macroscopic findings: ≥10: infusion site lesions (procedure related); ≥90: small thymus Histopathology: ≥10: macrophage activation and foamy histiocytes in adrenals, spleen, lymph node (mandibular, mesenteric), testes, epididymides, uterus, ovaries, pituitary, sternum, femur, pancreas. ***Liver:*** ≥10:Kupffer cell activation; ***Lungs:*** ≥10: alveolar macrophages; ***Kidneys:*** ≥10:vacuolation (minimal-mild) dose dependently;***Lymphoid tissue:*** 90: thymic atrophy (minimal- severe) Recovery: No recovery, except for findings in lungs. Thymus weights did not recover after 14 days, but after 28 days the weight was increased compared to control values.			
LS-2005-036 /GLP /4 weeks + 14-day or 28-day recovery	Beagle dog/ 3/sex/group 2/sex/group for 14-day recovery 2/sex/group in Ctrl and HD for 28-day recovery	0*, 6, 15, 40/25** /IV on days 1, 8, 15 and 22	**NOAEL:** 6
Mortality: Four animals dosed at 40 mg/kg died or were euthanized in deteriorating condition during the study. Dark area/discoloration, mottling and/or thickening of the gastrointestinal mucosa and mesenteric lymph node were observed in all four dogs found dead or preterminally sacrificed. Numerous histological observations were noted in these animals: • Severe hematopoietic hypocellularity of the sternal and femoral bone marrow • Minimal to severe cryptal necrosis of the small intestinal mucosa, with or without cryptal dilatation, villous atrophy, cryptal epithelial hyperplasia/hypertrophy and lymphoid atrophy (GALT) • Glandular necrosis and dilatation were observed in the large intestinal mucosa, with severity ranging from minimal to severe. • Mild to severe lymphoid atrophy was seen in the mesenteric and/or mandibular lymph nodes, spleen and thymus. These findings were generally consistent with the gross findings. The probable cause of death was severe bone marrow hypocellularity and/or minimal to severe enteric (duodenum, jejunum, ileum, cecum, colon, rectum) cryptal/glandular necrosis and lymphoid atrophy of gut-associated lymphoid tissue (GALT or Peyer's patches). Clinical signs: ≥6: swelling and reddening/red spots of predominantly the head and facial region. Resolved by 4 hours post-dose. Excessive salivation and partially closed eyes and observations of emesis; ≥15: emetic episodes, retching, salivation, vocalizing, decreased activity, excessive lacrimation and eyes partially closed. ≥40/25: ↑incidence of findings at lower doses plus ↑emetic episodes and fecal changes, material (mucoid/wet) on the cage tray and changes in the color and consistency of feces (loose, liquid, dark and pale in color). Body weight: ≥40/25:↓bw, not full recovery Food consumption: ≥40/25: ↓food consumption (supplemented with canned food). Most pronounced around dosing. Electrocardiography (ECG): No effects on the morphology of the P-QRS-T complexes after 4th dose or at the end of the 14-day recovery. ≥6: ↑heart rate (mild-moderate) dose dependently. Ophtalmoscopy: No effects observed; Hematology: ≥6: hematologic ,dose-dependent cyclic irregularities over the study period (monocytes, neutrophils, lymphocytes, basophils, large unstained cells). The neutrophil levels were closely correlated with toxicity in that the lowest values observed were in the dogs that died prematurely. ≥6:↑ APTT significantly ($p \leq 0.05$); Urinalysis: No effects observed; Clinical chemistry: 40/25: ↓alkaline phosphatase Organ weights: ≥6♀: ↓spleeen (abs. and rel.); ≥15:↓prostate, thymus (abs. and rel.); 40/25:↓ testes, prostate (abs. and rel.)		

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg)/ Route	NOAEL/NOEL

Macroscopic findings: ≥6: dark/pale area, discoloration or focus and mottling in GI mucosa and mesenteric lymph node.; 15: small prostate (1/3); ≥6:small thymus
Histopathology: ≥6: dose-related atrophy of lymphoid tissue in mesenteric lymphnode, spleen and thymus (minimal-severe); ≥15: hematopoietic hypocellularity of the sternal and femoral bone marrow (minimal-moderate and in all animals); 40/25: cryptal necrosis (minimal-mild), villous atrophy of the small intestinal mucosa, with or without cryptal dilatation (mild-severe), cryptal epithelial hyperplasia/hypertrophy (mild-severe), lymphoid atrophy (GALT)(mild-moderate), glandular necrosis and glandular dilatation in large intestinal mucosa (minimal-moderate).
Recovery: Following the 14-day recovery period, minimal to mild hematopoietic hypocellularity of the sternal and femoral bone marrow was observed in 2/4 Group 4 dogs. Minimal to mild atrophy of lymphoid tissue was seen in the spleen of 1/4 Group 3 and 2/4 Group 4 dogs. Mild to severe thymic atrophy was observed in one dog each from Groups 1, 2 and 4.
After a 28-day recovery period, no test-article related changes were observed, suggesting complete resolution of all target organ changes.
*Control = vehicle, which was 5% dextrose in water.
**The High Dose animals were treated at 40 mg/kg for the first two treatment (Days 1 and 8) and were then dosed at 25 mg/kg on Days 15 and 22 due to the severe adverse clinical signs and mortalities observed on Day 8. However, for the animals in Replicate A (4001A, male and 4501A, female), the dose level was decreased to 25 mg/kg only for Day 22, since they were dosed on Day 15 prior to the decision to change the dose level.

LS-2005-038 /GLP 4 weeks + 14-day recovery	Beagle dog 3/sex/group 1/sex in ctrl, HD and comparator for recovery	0*, 20, 25 20 and 25 of comparator irinotecan (I20 and I25) /IV 1 hour on days 1, 8, 15, 22	**NOAEL** None

Mortality: No mortality in the etirinotecan pegol group. Two female dogs treated with 25 mg/kg Irinotecan were found dead on Day 5 (4 days after the first dose), as well as a male dog from the same group on Day 21 (6 days after third dose). Two moribund females from both the 20 mg/kg Irinotecan group and the 25 mg/kg Irinotecan were prematurely euthanized on Days 6 (5 days following the first treatment) and 13 (5 days following the second dose), respectively. The probable cause of death of the two female dogs from the group treated with 25 mg/kg Irinotecan was considered severe bone marrow hypocellularity and enteric pathology (cryptal/glandular/mucosal necrosis, cryptal/glandular epithelial hyperplasia/hypertrophy, atrophy of GALT or Peyer's patches) in the duodenum, jejunum, ileum, colon, cecum and rectum with severity ranging from minimal to severe.
In the male dog the probable cause of death was severe enteric pathology in the cecum (hemorrhagic mucosal ulceration) and severe pulmonary edema/congestion accompanied by intraalveolar hemorrhage.
The main findings in the female dogs from the 20 mg/kg and 25 mg/kg Irinotecan groups euthanized prematurely were considered minimal to moderate bone marrow hypocellularity, minimal to mild enteric pathology in the ileum (severe villous atrophy), colon and cecum (cryptal/glandular necrosis, cryptal/glandular epithelial hyperplasia/hypertrophy) , minimal to moderate atrophy of GALT in the jejunum, ileum, and rectum as well as severe lymphoid atrophy of the thymus in the dog treated with 25 mg/kg Irinotecan.
Clinical signs: ≥20: swelling and reddening/red spots of predominantly the head and facial region but spreading out to the limbs and whole body (mild-moderate). Some animals received diphenhydramine to alleviate symtoms; excessive salivation, material (mucoid/wet) or undigested food on the cage tray and changes in the consistency of feces (loose, liquid/liquid with other feces) dose dependently; I20: emesis (i.e. froth white and/or yellow liquid) and excessive salivation, as well as activity decreased/increased and vocalization; ⩾I20: excessive salivation, undigested food and material (i.e. mucoid/wet, yellow/beige or froth, yellow/beige) on the cage tray, loose/liquid feces.
Body weight: ≥20,≥I20: ↓bw dose dependently (more severely in comparator groups) .
Food consumption: ≥20, ≥I20:↓food consumption (severe, more severely in comparator groups). Canned food supplementation when needed.
Ophthalmoscopy: No effects observed; Electrocardiography (ECG): No consistent effect.
Hematology: ≤I25: ↓white blood cells, neutrophils (significantly).Neutrophils closely correlated with toxicity in the dogs that died prematurely. ≤25: inconsistent hematology variations when compared to controls. No treatment-related changes in prothrombin time (PT) or activated partial thromboplastin values (APTT) in the Main and Recovery surviving animals.
Clinical chemistry: No changes at the end of main phase and recovery.
Urinalysis: No effects observed.
Organ weights: ≥20, ≥I20:↓ thymus (abs. and rel.), correlated with thymic atrophy. ↓ spleen (abs. and rel.); ≥I20:↓ liver, prostate and/or testes.↓adrenals in ♀.
Gross pathology: I20:Dark areas in cecum, colon and rectum (1/5); I25: Pale areas in stomach (1/4) and dark digestive contents in stomach, jejunum and ileum (1/4).Small spleen (1/4); ≥20, ≥I20: small thymus
Histopathology: ≥20: hematopoietic hypocellularity of femoral and/or sternal bone marrow (minimal, 2/6 (4/5 in 25)), GALT atrophy in jejunum and ileum (minimal, 5/6 (3/5 in 25)), thymus lymphoid atrophy (moderate, 6/6 for both doses).; ≥I20: hematopoietic hypocellularity of the femoral and sternal bone marrow (mild-severe, 4/5), atrophy of GALT in jejunum and ileum (minimal-severe, 3/5 (5/5 in I25)), thymus lymphoid atrophy (5/5).; I25: Atrophy of

Study ID /GLP/ Duration	Species/Sex/ Number/Group	Dose (mg/kg)/ Route	NOAEL/NOEL
seminiferous tubules accompanied by oligospermia/aspermia of the epididymis (severe, 1/5). Recovery: All findings exhibited recovery.			
LS-2009-008 / GLP 3 months + 8-week recovery	Beagle dogs 6/sex/group 2/sex/group for recovery TK included	0, 6, 15, 30 IV 1 hour on days 1, 15, 29, 43, 57, 71, 85	**NOAEL** 6
Mortality: None Clinical signs: ≥6: excessive salivation during dosing, diarrhea (slight); ≥15: swelling, reddening and/or the presence of red spots on predominantly the head, eyes, muzzle, neck and pinnae, occasionally spreading out to the limbs. Body weight: ≥6:↓ dose- dependently (slight-moderate). 30♀ showed negative weight gain. Food consumption: ≥15: ↓food consumption (slight) Ophthalmoscopy: No effects observed. ECG: No changes in any of the electrocardiographic parameters Hematology: ≥15: ↓Red blood cell counts, hemoglobin and hematocrit (marginal-slight); ≥15:↓lymphocytes, monocytes, basophils and large unstained cells (marginal-slight) Serum chemistry: ≥15:↓total protein and albumin (marginal). Urinalysis: No effects observed. Organ weights: Organ weights were unaffected by treatment. Gross pathology: There were no treatment-related macroscopic findings observed at doses up to 30 mg/kg/dose at the end of the treatment and recovery periods. Histopathology: There were no treatment-related microscopic findings observed at doses up to 30 mg/kg/dose at the end of the treatment and recovery periods.			

Mortalities

Preterminal mortalities and/or unscheduled sacrifice of animals occurred in all dog repeat-dose toxicity studies. In total, 10 dogs and 2 rats died or were euthanized in the studies. The deteriorations that caused the demise of the dogs were clearly treatment related, whereas the rats likely died of non-treatment related reasons.

4 dogs died in the 4-week study LS-2005-036. The probable cause of death was severe bone marrow hypocellularity and/or minimal to severe enteric cryptal/glandular necrosis and lymphoid atrophy of gut-associated lymphoid tissue. In the 4-weeks study with irinotecan comparator, there were two deaths in the irinotecan groups. The causes of death in the female animals (25mg/kg irinotecan) were likely severe bone marrow hypocellularity and enteric pathology with severity ranging from minimal to severe. Similar findings were made in two females (20 and 25mg/kg) euthanized prematurely. In a male dog (25mg/kg) the probable cause of death was severe enteric pathology in the cecum (haemorrhagic mucosal ulceration) and severe pulmonary oedema/congestion accompanied by intraalveolar haemorrhage.

Clinical signs

While not specifically mentioned in the individual studies, there are several publications demonstrating that irinotecan is an acetylcholine esterase inhibitor. Indeed, the clinical signs displayed by particularly the dogs (including swelling and reddening/red spots of predominantly the head and facial region but spreading out to the limbs and whole body) are most likely cholinergic-like effects. Other clinical signs noted were emesis, excessive lacrimation, decreased activity and vocalizing.

Haematology

Overall there were hematologic, dose-dependent cyclic irregularities over the study period in the dosed animals. WBCs are clear targets of irinotecan toxicity, particularly neutrophils in dogs. The neutrophil levels were also closely correlated with toxicity in that the lowest values observed were in the dogs that died prematurely. APTT was significantly increased in dogs in study LS-2005-036, but this finding was not consistent across studies.

Lymphoid organs

The lymphoid system is one of the major target organs of etirinotecan pegol. In general, there were findings of dose-related atrophy of lymphoid tissue in mesenteriv lymph node, spleen and thymus in both rat and dog. These findings were reversible after 28-days of recovery in the dog.

Gastrointestinal tract

Increases in the incidence and frequency of occurrence of diarrhoea (revealed by the presence of slight to moderate amounts of loose and/or liquid faeces in the cage tray) were reported in the studies, starting from approximately 2-3 days following each dose of etirinotecan pegol in dogs using every other week dosing regimens. This was also correlated with macroscopic findings (dark/pale areas, discoloration or focus and mottling in GI mucosa) and histopathological findings (villous atrophy of the small intestinal mucosa, GALT atrophy in jejunum and ileum). The increased incidence occurred sporadically throughout the treatment periods with seemingly full recovery after the recovery periods.

PEG

Repeated administration of PEGylated proteins was associated with some safety concerns such as tissue vacuolation within renal tubules and the choroid plexus. In the present studies, tissue vacuolization in the kidneys was observed in rats after four weekly doses of etirinotecan pegol predominately at the high dose of 90 mg/kg/week. There was little to no recovery observed after a 4-week recovery period, which is consistent with data reported with other large molecular weight PEGs. Vacuolization and foamy macrophages were not observed in any tissue in the dog.

Genotoxicity

A genotoxicity toxicity study was not provided (see discussion on non-clinical aspects).

An *in vivo* micronucleus assay of bone marrow smears was conducted as part of Study LS-2005-035, a repeat-dose study of etirinotecan pegol in rats. In that study, 10 male and 10 female rats received etirinotecan pegol at 10, 30 or 90 mg/kg via IV infusion once weekly on days 1, 8, 15, and 22. Bone marrow smears for micronucleus assay were prepared from all Main Study animals 3 days following the last dose. Micronucleus assay of bone marrow smears revealed moderate and statistically significant dose- related increases in the incidence of micronucleated immature erythrocytes, indicating evidence of genotoxic activity in this assessment of chromosome damage in rat bone marrow. Therefore, etirinotecan pegol was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

Carcinogenicity studies were not provided (see discussion on non-clinical aspects).

Reproduction Toxicity

Reproductive toxicity studies were not provided (see discussion on non-clinical aspects).

In the repeat dose toxicity studies, following IV administration of etirinotecan pegol once every 7 days for 4 cycles in the rat, foamy macrophages in testes, epidydimides, uterus and ovaries were observed in rats with no apparent recovery. This was not found in the dog. The foamy macrophages may be related to the PEG moiety. No other findings were reported in reproductive organs, except a single finding of atrophy of seminiferous tubules accompanied by oligospermia/aspermia of the epididymis in one irinotecan-exposed (25mg/kg) dog.

Toxicokinetic data

In *Sprague Dawley Rats (LS-2005-035),* SN38 released from etirinotecan pegol reached Cmax on average 12-72 hr post dose, indicating slow release, and plasma SN38 concentrations remained detectable throughout the dosing interval, with mean half-life values of 26-129 hr. SN38 AUC increased with dose, but in a less than dose proportional fashion. Etirinotecan pegol toxicokinetics were similar in male and female rats, while SN38 exposure was almost 2-fold greater in males compared to females. Etirinotecan pegol toxicokinetics was also similar after a single and four weekly administrations, while SN38 showed approximately 2-fold accumulation in AUC.

In Beagle dogs (LS-2005-038), SN38 released from etirinotecan pegol reached Cmax 1-8 hours post dose. There were no clear differences between male and female dogs. Plasma SN38 concentrations showed clear differences for irinotecan and etirinotecan pegol administration.

Local Tolerance

Local tolerance studies were not submitted (see discussion on non-clinical aspects). Local tolerance was assessed within the repeat dose toxicity studies.

Other toxicity studies

Phototoxicity

Etirinotecan exhibits two absorbances >290 nm (~358 nm and ~ 371 nm) with average molar extinction coefficients (MEC) at both wavelengths of ~100,000 Lmol-1 cm-1. Irinotecan exhibits essentially the same two absorbances at ~358 nm and ~ 371 nm with average molar extinction coefficients (MEC) at both wavelengths of ~30,000 Lmol-1 cm-1. Since the MEC for etirinotecan pegol and irinotecan are above the 1000 Lmol-1cm-1 phototoxic risk threshold, both compounds could have phototoxicity potential. However, data obtained from a standard tissue distribution (QWBA) study in the rat using either radiolabelled [14C] NKTR-102 or [14C] irinotecan showed that etirinotecan pegol had low binding to melanin. Irinotecan did have higher binding to melanin but this was reversible.

2.3.4. Ecotoxicity / environmental risk assessment

Table 11 - Summary of main study results

Substance (INN / Invented Name): Etirinotecan (SN38 metabolite)			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG107	Log Kow = 2.3 (±0.3)	Potential PBT No
PBT-assessment – not further pursued due to the Logkw value (see above)			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log Kow = 2.3 (±0.3)	Unlikely B
	BCF	NA	B/not B
Persistence	DT50 or ready biodegradability	NA	P/not P

Toxicity	NOEC or CMR	NA	T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	PEC_{sw} of 0.0002	µg/L	PEC_{SW} > 0.01 threshold
Other concerns (e.g. chemical class)			No

Etirinotecan pegol PEC surfacewater value is below the action limit of 0.01 µg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5.

2.3.5. Discussion on non-clinical aspects

Effects of etirinotecan pegol were studied both *in vitro* and *in vivo* in several different experimental models using cell lines of human origin.

In vivo tumours were established by implanting tumour fragments from serial passages or suspensions of tumour cells. Three breast cancer models were used, the MCF-7, the MX-1 breast cancer models and an experimental breast cancer brain metastases model using a brain seeking clone of the MDA-MB-231 cell-line expressing firefly luciferase (MDA-MB-231Br-Luc). Etirinotecan pegol showed superior effect over irinotecan based on tumour growth delay and regression response rates in all *in vivo* models used. In the breast cancer brain metastases model, where brain metastases were established by inoculating cells in the left cardiac ventricle, etirinotecan pegol decreased tumour burden and increased survival, while irinotecan, gemcitabine, eribulin, vinorelbine, and docetaxel showed no significant activity.

The kinetics of etirinotecan pegol, irinotecan and SN38 in tumour tissue as compared to plasma suggests an intracellular trapping of etirinotecan and prolonged formation of irinotecan and SN38 in tumour cells after administration of etirinotecan pegol. In all species examined, etirinotecan pegol had a longer half-life compared to irinotecan when administered intravenously. Etirinotecan pegol exposure increased in proportion to dose and was similar in male and female animals.

PK/PD analysis showed a correlation between tumour SN38 concentration and the inhibitory treatment effect on tumour growth and indicated that a threshold concentration of SN38 has to be exceeded and maintained in order for etirinotecan pegol to have an effect. The apparent threshold concentrations of SN38 were not reached after treatment with irinotecan, when only short exposure to SN38 was achieved.

No secondary pharmacodynamic studies were provided considering the well-known mechanism of action of irinotecan which is considered acceptable. No standalone safety pharmacology studies were conducted with etirinotecan pegol but detailed clinical observations were performed as part of the repeat-dose GLP toxicology studies in rats and dogs which is considered to be acceptable. These clinical observations in revealed no effects of etirinotecan pegol treatment on CNS or respiratory-related clinical observations or on any electrocardiography parameter at doses up to MTD. In addition, it should be noted that the clinical safety of irinotecan is well established and that no new safety pharmacology effects might be expected with etirinotecan pegol.

Tissue distribution differed from that of irinotecan and demonstrated less extensive initial distribution out of plasma with tissue to blood ratios less than unity for the majority of tissues at the earlier time points

after dosing. The highest concentrations were observed in highly perfused tissues such as lung, adrenal gland, liver, spleen, and myocardium, as well as the lymph nodes, indicating uptake by the reticuloendothelial system. Although the tissue to blood ratio started at <1, over time they became >1 suggesting a slower equilibration into tissues than for irinotecan and a slower clearance from tissues than plasma, indicating that etirinotecan pegol in tissues serves as reservoir for prolonged release of irinotecan. The lowest levels of radioactivity were observed in brain and spinal cord, indicating poor distribution to the central nervous system. The PEG moiety is suggested to be a major determinant of the distribution of etirinotecan pegol. There is no information specifically concerning the metabolism and excretion of the PEG moiety after the release of the irinotecan. However, data indicates that most of the radioactivity in plasma (98.2%) and urine (88.4%) is associated with intact etirinotecan pegol and it is concluded that data available for excretion of etirinotecan pegol is in line with published literature for both unconjugated PEG and approved medicinal products with a PEG moiety.

Etirinotecan pegol, gave a higher radioactivity level in brain metastases (ranging from ~390 ng/g to ~1800 ng/g, with an average of 672 ng/g), compared to radioactivity after administration of irinotecan (ranging between ~25 ng/g to ~350 ng/g, averaging 66 ng/mL). Etirinotecan gave a higher labelling of the “brain distant to tumour” tissue which is likely due to a higher staining of the vasculature. Although only twice as high as the average radioactivity in BDT, the applicant suggested that the high plasma etirinotecan pegol levels seen at the 6 hour time point (72 µg/mL) largely explain the radioactive concentrations in BDT as being confined to the vasculature.

The Applicant has not specifically studied possible mechanisms for the uptake, accumulation, and retention of etirinotecan pegol across different tumour types. However, based on available data showing low permeability in Caco-2 cells and low penetration across normal intact blood-brain barrier, cellular uptake by passive diffusion is less likely to occur.

The general predictivity of the preclinical models for clinical response is not considered established through external data (see clinical efficacy section and SAG responses).

The Applicant provided one publication of a non-clinical study in mice as external support showing a direct correlation between tumour size and doxorubicin leakage (Nakasone 2012). The applicant also referred to direct clinical evidence using positron emission tomography (PET) imaging from a series of 19 patients that PEGylated liposomal doxorubicin accumulates in CNS metastases (Lee et al 2017, Clinical Cancer Research March 2017, published online in advance). However, clinical correlates of efficacy are lacking. The applicant also provided a review of literature data to discuss the predictability of non-clinical data to clinical data (data not shown). However, no convincing evidence of clinical correlation was shown.

Regarding the metabolism, irinotecan is extensively metabolised in the liver to various metabolites. All major human metabolites SN38, SN38G and APC are all present in the non-clinical species used. No quantitative comparison between metabolites found in human plasma and plasma from non-clinical species after exposure to etirinotecan pegol was presented by the applicant which is considered to be acceptable and in line with the ICH S9 Guideline.

The data available for excretion of etirinotecan pegol appears to agree with published literature for both unconjugated PEG and approved medicinal products with a PEG moiety. Studies in pregnant rats were not performed with etirinotecan pegol, but studies using the ^{14}C-labelled polymer core and linker suggest that etirinotecan pegol distributes to the foetus.

The metabolism and excretion of the unconjugated PEG moiety after the release of the irinotecan was not specifically evaluated in the nonclinical studies. However, PEG-conjugated irinotecan (etirinotecan pegol), unconjugated irinotecan, and the active metabolite, SN38, were all assessed in the nonclinical pharmacokinetic (PK) and toxicokinetic (TK) studies.

The toxicity profile of etirinotecan pegol has been characterized in rats and dogs in studies up to 14 weeks duration that were compliant with GLP. The programme was in line with the scientific advice received from the CHMP. The doses chosen for the studies were appropriate to characterize the toxicity of etirinotecan pegol and to make proper hazard evaluations and risk assessments. Local tolerance was assessed within the repeat dose toxicity studies, which is acceptable.

Intravenous dosing has been used in all pivotal toxicity *in vivo* studies, as this is the clinical administration route. Both rats and dogs are well-established in the assessment of toxicity of irinotecan and other topoisomerase inhibitors such as topotecan. The rat has higher esterase activity than dog and thus metabolizes etirinotecan pegol more rapidly, which results in a PK profile that is perhaps less representative of humans than that of dogs.

Across all repeat-dose toxicology studies, etirinotecan pegol exposure was similar in male and female animals. No accumulation of etirinotecan pegol was observed with repeated administration. SN38 released from etirinotecan pegol, reached Cmax between 2-48 hours post dose and increased either in proportion to dose (dog) or slightly less than dose proportionally (rat). SN38 exposure was similar in male and female dogs, while male rats achieved 1.2-2-fold greater SN38 exposure. SN38 accumulation with weekly or every 14-day administration schedules was ≤ 3.4-times. The long exposure to etirinotecan pegol resulted in sustained and greater exposure to the active metabolite SN38 than dosing with irinotecan at equivalent doses. In dogs, this greater exposure was achieved without an increase in SN38 Cmax.

Overall, the toxicities seen in the studies were consistent with the known toxicity profile of irinotecan (e.g. diarrhoea and neutropenia) which are due to the effects on tissues with high cell turnover. No new toxicities were identified for etirinotecan pegol that have not previously been reported for irinotecan, suggesting that the toxicological profiles are comparable. The toxicity was in general more enhanced after irinotecan exposure than etirinotecan pegol exposure. This increased level of toxicity can to some extent be explained by the increased Cmax of SN38 (the biologically active metabolite) in the irinotecan exposed groups compared to the etirinotecan groups. However, SN38 exposure (AUC) was higher in etirinotecan exposed animals. Major target organs identified in the studies are the bone marrow, lymphoid organs, the gastrointestinal tract and the hematological system. Overall, the identified toxicities are considered serious and with small margins to human clinical exposure. However, the toxicities are for the most part reversible (or possible to monitor) and may therefore be acceptable for the targeted population of advanced breast cancer patients with brain metastases.

The composition of the PEGylated entities in the etirinotecan pegol used in the pivotal non-clinical efficacy and toxicity studies have been compared to the composition of the compound intended for therapeutic use and data presented provides reassurance that the differences in the composition of the batches used in the non-clinical and clinical studies will not meaningfully affect efficacy or safety.

Full genotoxicity, carcinogenicity, reproductive toxicity and local tolerance assessments have not been conducted with etirinotecan pegol, because the drug core moiety, irinotecan and its primary active metabolite SN38 have been previously been shown to be embryotoxic, fetotoxic, and teratogenic. Based on these data and the mechanism of action, etirinotecan pegol is thus suspected to have teratogenic effects in humans Irinotecan was teratogenic in rats and rabbits at doses below the human therapeutic dose. In rats, pups born to irinotecan treated animals with external abnormalities, showed a decrease in fertility. In lactating rats administered irinotecan (a metabolite of etirinotecan pegol), ^{14}C-irinotecan was detected in milk. Onzeald is therefore not recommended during pregnancy and in women of childbearing potential not using contraception.

The possible immuno-modulatory and/or immunotoxic effects due to etirinotecan pegol were not specifically evaluated in either the nonclinical or clinical development programmes. Anti-PEG antibody induction leading to a risk of reduced efficacy and an increased risk of hypersensitivity to etirinotecan pegol should be closely followed and this has been included as an important potential risk in the risk management (see RMP).

Although etirinotecan absorbs light in the visible spectrum distribution to the eye and pigmented skin is either low or not persistent and there are no data available that indicates that reactive species are generated upon exposure to light in the visible range. Consequently, available data indicate that etirinotecan pegol is not likely to present a concern for phototoxicity.

2.3.6. Conclusion on the non-clinical aspects

The non-clinical data package is considered acceptable. However, the predictivity of the models used for human drug distribution and clinical efficacy has not been substantiated.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Table 12 - Listing of Clinical Studies and population PK analysis

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage [b]; Regimen (all intravenous)	Number of Patients	Diagnosis of Patients	Study Status; Type of Report
Patient PK and Initial Tolerability	06-IN-IR001	MTD; Tolerability; PK; Efficacy	Dose-escalation, OL, UC	Onzeald (145, 170, 195, and 220 mg/m^2), q14d	N = 19	Adults (≥18 years of age) with metastatic or unresectable solid tumours for which standard curative or palliative therapies did not exist	Complete; Full
				Onzeald (145, 170, 195, 220, and 245 mg/m^2), q21d	N = 25		
				Onzeald (58, 115, 145, 173, and 230 mg/m^2), wx3q4wk	N = 32		
Intrinsic Factor PK	12-102-13	PK; Safety; Tolerability	OL, parallel group, MC	Onzeald (95, 120, or 145 mg/m^2), single dose	24 (planned) 22 (as of cut-off date 05 June	Advanced or metastatic solid tumours and reduced hepatic function	Ongoing; Interim

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage [b]; Regimen (all intravenous)	Number of Patients	Diagnosis of Patients	Study Status; Type of Report
					2015)		
Extrinsic Factor PK	07-PIR-02	MTD in combination with cetuximab; Safety; PK; Efficacy	Dose-escalation, OL, UC	Onzeald (100 or 125 mg/m^2) + cetuximab (starting dose of 400 mg/m2 on Day 1 and then weekly at 250 mg/m^2)	36 (planned) 18 (actual)	Adults (≥18 years of age) with refractory solid tumours	Complete; Full
Extrinsic Factor PK	09-PIR-07	MTD in combination with 5-fluorouracil and leucovorin; Efficacy; PK	Dose-escalation, OL, UC	Onzeald (25 or 50 q14d; 50, 75, 100, 125, or 145 mg/m^2 q14d x4 then q28d) + Leucovorin + 5-fluorouracil	N = 26	Adults (≥18 years of age) with refractory solid tumours	Complete; Full
Population PK	LS-2014-501	See Studies 06-IN-IR001, 07-PIR-02			N = 94	Adults (≥18 years of age) with refractory solid tumours	Complete; Clinical Development
Population PK	LS-2015-504	See Studies 06-IN-IR001, 12-102-13, 11-PIR-11			N = 192	Adults (≥18 years of age) with refractory solid tumours	Complete; Clinical Development
Population PK	LS-2015-508	See Study 11-PIR-11			N = 97	Adults (≥18 years of age) with locally recurrent or metastatic breast cancer previously treated with at least two and a maximum of five prior chemotherapy regimens including an anthracycline, a taxane, and capecitabine	Complete; Clinical Development
Efficacy	11-PIR-11 BEACON (pivotal study)	Efficacy; Safety; PK	AC, 2-arm, R, OL, MC	Onzeald: 145 mg/m^2, q21d	N = 429 (ITT), N = 425 (safety)	Adults (≥18 years of age) with locally recurrent or metastatic breast cancer previously treated with at least two and a maximum of five prior chemotherapy regimens including an anthracycline, a taxane, and capecitabine	Complete; Full
				TPC: Per approved standard of care	N = 423 (ITT), N = 406 (safety)		
Efficacy	Nagpal 2015	Efficacy	Single-arm, OL	Onzeald: 145 mg/m^2, q21d	20	High-grade glioblastoma that progressed after treatment with bevacizumab	Complete; Publication

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage [b]; Regimen (all intravenous)	Number of Patients	Diagnosis of Patients	Study Status; Type of Report
Efficacy	08-PIR-05	Efficacy; Safety; PK	2-arm, R, OL, MC	Onzeald: 145 mg/m^2, q14d	N = 35 (ITT), N = 35 (safety)	Adults (≥18 years of age) with metastatic breast cancer that failed prior taxane-based treatment	Complete; Full
				Onzeald: 145 mg/m^2, q21d	N = 35 (ITT), N = 35 (safety)		
Efficacy	08-PIR-04	Efficacy; Safety; PK	2-arm, R, OL, MC	Onzeald: 145 mg/m^2, q14d	N = 39 (ITT), N = 38 (safety)	Adults (≥18 years of age) with metastatic or unresectable platinum-resistant ovarian cancer	Complete; Full
				Onzeald: 145 mg/m^2, q21d	N = 139 (ITT), N = 139 (safety)		
Safety	11-PIR-09	Safety; Efficacy	MC, OL, extension	Onzeald: ≤145 mg/m^2, q21d	21 (as of 26 Oct 2015)	Patients with solid tumours who received Onzeald in a prior study	Ongoing; Interim synopsis
Safety: Analysis of Data from More Than One Study	Onzeald Integrated Safety	Pooled Safety	Pooled safety data analysis	Onzeald: any dose or regimen [c]	790	Patients with solid tumours who received Onzeald	Complete; Clinical Development
				Onzeald: 145 mg/m^2, q21d	644		
Other	08-PIR-03	Efficacy; Safety	2-arm, AC, R, OL, MC	Onzeald: 145 mg/m^2, q21d	N = 42 (ITT) N = 42 (safety)	Adults (≥18 years of age) with KRAS-mutant metastatic colorectal cancer, irinotecan naïve	Complete [d]; Full
				Irinotecan: 350 mg/m^2, q21d	N = 41 (ITT) N = 41 (safety)		

Abbreviations: AC = active-controlled; ITT = intent-to-treat; PK = pharmacokinetics; MC = multi-centre; MTD = maximum tolerated dose; N = number of patients; OL = open-label; q14d = once every 14 days; q21d = once every 21 days; q28d = once every 28 days; R = randomised; safety = safety population (patients that received at least one dose of study treatment); TPC = treatment of physician's choice (eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel); UC = uncontrolled; wx3q4wk = once a week for 3 weeks every 4 week.

a. In this document, 14 human pharmacokinetic, efficacy, and safety studies (Sections 5.3.3 and 5.3.5) supporting Onzeald in the treatment of breast cancer with brain metastases (BCBM) are tabulated. These 14 studies include the following: nine studies completed by the Applicant, one investigator-initiated study (Nagpal 2015), three population pharmacokinetic studies (studies with identifiers beginning with 'LS-'), and one integrated safety study. Biopharmaceutic studies (Section 5.3.1) and pharmacokinetics studies with human biomaterials (Section 5.3.2) are not tabulated. Human pharmacodynamics studies (Section 5.3.4) are not included in this submission.

b. All Onzeald doses were 90-minute (±15 minutes) intravenous infusions.

c. Dose/ regimens included <48.3 mg/m^2/week (median dose administered per infusion was 50 mg/m^2), 145 mg/m^2 q21d (48.3 mg/m^2/week), 145 mg/m^2 q14d (72.5 mg/m^2/week), or >72.5 mg/m^2/week (median dose administered per infusion was 169 mg/m^2).

d. At the time that Study 08-PIR-03 was initiated, single-agent irinotecan was considered an acceptable second-line option for patients with KRAS mutant mCRC. However, combination therapy combining irinotecan with 5-FU/leucovorin, ziv-aflibercept, and/or bevacizumab became the standard of

care before accrual for this study could be completed. Hence, recruitment to the study with single-agent camptothecin-based therapy was difficult (83 out of 174 planned patients actually enrolled) and the trial was discontinued prematurely 14 Nov 2014.

2.4.2. Pharmacokinetics

The clinical pharmacology program included data from 5 clinical studies, 2 population PK analyses and one exposure response analysis. In addition, an *in vitro* package containing 13 studies on e.g. the degradation, protein binding and interaction potential of etirinotecan pegol was submitted.

Comparison between etirinotecan pegol and other irinotecan formulations

Simulations were performed based on a published model of irinotecan PK (Xie et al, 2002) and compared with simulated metabolite exposure from the popPK model of etirinotecan pegol (LS-2015-504). The approved dose of irinotecan as monotherapy (350 mg/m2 Q3W) was compared with the proposed dose of etirinotecan pegol (145 mg/m2 irinotecan equivalents Q3W). Administrations of etirinotecan pegol results in substantially lower Cmax of both irinotecan and SN-38, a sustained exposure but with lower total AUC of irinotecan but a both prolonged exposure and higher total AUC for SN-38.

According to the popPK model, the terminal half-life of both etirinotecan pegol and all metabolites was around 38 days. After administration of free irinotecan, a half-life of both irinotecan and SN-38 of around 14 hours has been reported.

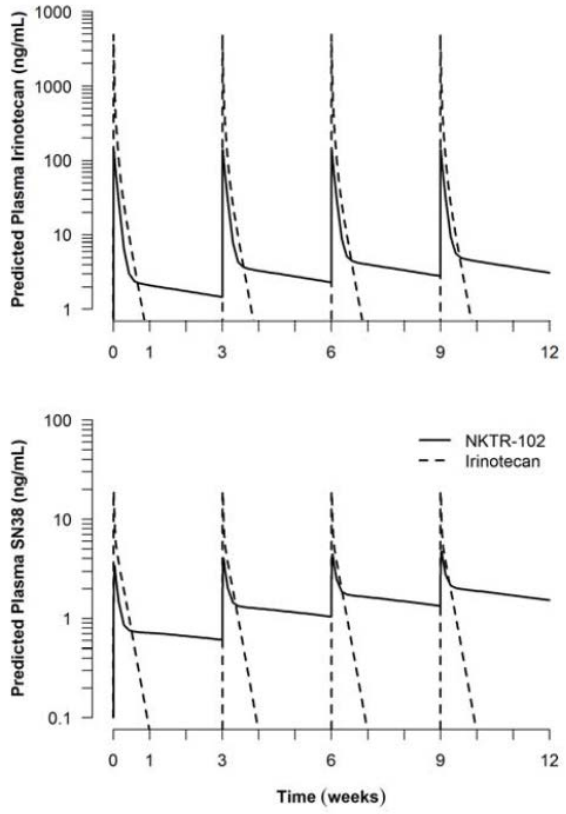


Figure 3 - Predicted Plasma irinotecan and SN38 concentration-time Profiles after administration of 145 mg/m2 etirinotecan pegol (NKTR-102) (solid line) or 350 mg/m2 irinotecan (dashed line)

Table 13 - Irinotecan and SN38 AUC and Cmax after administration of 145 mg/m2 Onzeald compared with 350 mg/m2 irinotecan

Analyte	# Cycles	Parameter	Irinotecan (350 mg/m^2)	Onzeald (145 mg/m^2)	Irinotecan/ Onzeald
Irinotecan	1	C_{max} (ng/mL)	4900	140	35
		AUC Cycle 1 (ng•h/mL)	20000	2900	7
	4	C_{max} (ng/mL)	4900	140	35
		AUC Cycles 1-4 (ng•h/mL)	82000	14000	6
SN38	1	C_{max} (ng/mL)	19	3.4	6
		AUC Cycle 1 (ng•h/mL)	315	380	0.8
	4	C_{max} (ng/mL)	19	4.7	4
		AUC Cycles 1-4 (ng•h/mL)	1300	2800	0.5

Abbreviations: AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration; SN38 = 7 ethyl 10 hydroxycamptothecin

Simulation of irinotecan and SN38 after irinotecan administration using parameter values from the literature (**Xie, 2002**).

Source: LS-2015-504, **Table 9**

Absorption

Etirinotecan pegol is administered by intravenous infusion and no absorption processes take place. Maximum plasma etirinotecan pegol concentration (Cmax) is reached shortly after the end of a 90 minute infusion, thereafter concentrations of etirinotecan pegol and its metabolites decline bi-exponentially. The relative times to Cmax (Tmax) for etirinotecan pegol metabolites correspond to the proposed metabolic progression (irinotecan <SN38 <SN38G <APC).

Distribution

Etirinotecan pegol and its metabolites are characterised by a distribution phase followed by a prolonged elimination phase. Etirinotecan pegol and metabolites, including SN38 have terminal half-lives (t½) of 38 days. Etirinotecan pegol has a small volume of distribution (5 L).

Etirinotecan pegol does not bind to human albumin. Plasma protein binding for the active metabolite SN38 (50-500 ng/mL) was 98% in human plasma. Plasma protein binding for irinotecan was approximately 65%.

Elimination

Irinotecan is slowly released from etirinotecan pegol *in vivo* via hydrolysis and metabolised further as described for irinotecan. However, in contrast to irinotecan, liver metabolism of etirinotecan pegol is less extensive. Irinotecan is metabolised predominantly by carboxylesterases (CES 2 and CES 1) and chemical hydrolysis to form SN38, which is then conjugated to a relatively inactive glucuronide (SN38G; 50-100-fold less active compared to SN38) by UGT1A1 and UGT1A9. In addition, APC (a carboxylate form) is produced, which is derived from the metabolism of irinotecan by cytochrome P450 3A4 (CYP 3A4). Numerous other minor metabolites, such as those formed by CYP3A5, have also been identified in the literature.Etirinotecan pegol has a low clearance (0.277 L/hr). No significant accumulation of etirinotecan pegol occurred when etirinotecan pegol was administered every 21 days (q21d), but the active metabolite SN38 accumulated approximately 3.5-fold, with 75% of accumulation

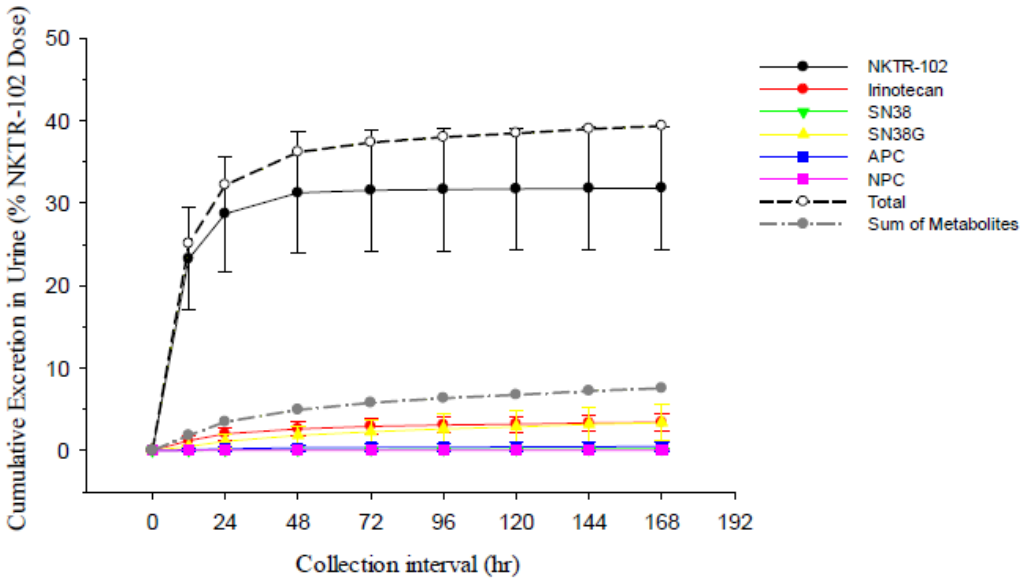
achieved by cycle 4. The pharmacokinetic (PK) properties of etirinotecan pegol and metabolites are not dose-dependent over the dose range of 57.5 to 230 mg/m2.

Etirinotecan pegol is eliminated by renal excretion (mean renal clearance [CLr] = 0.117 ± 0.0542 L/hr) and by hydrolysis to irinotecan. The primary mechanism for renal excretion of etirinotecan pegol appears to be glomerular filtration. In patients with normal renal and hepatic functions, 39% of the etirinotecan pegol dose was excreted in the urine within 168 hours (7 days). Unchanged etirinotecan pegol accounted for 32% of the dose, while etirinotecan pegol metabolites accounted for 7% of the dose.

The elimination pathways of irinotecan have been previously described to include renal elimination, hydrolysis to the active metabolite SN-38 (carboxylesterases, chemical hydrolysis) with downstream glucuronidation, and CYP3A4 catalysed oxidation to the inactive metabolites APC and NPC.

Excretion

In study 12-102-13, urine was collected for 7 days in all patients in a phase I hepatic impairment study. For the 12 patients with normal hepatic function, on average 32%±7.4 of the etirinotecan pegol dose was recovered as unchanged drug in urine, and renal clearance was estimated to 0.117 (± 0.0542) L/hr. 7.5% was recovered as known unpegylated entities in urine (3.4% irinotecan, 0.2% SN-38 and 3.4% SN-38G).



To facilitate comparison across analytes, the amounts, in mg, for each analyte were first converted to molar units before calculation of percentage of NKTR-102 dose excreted in urine.

Figure 4 - Mean cumulative percentage of etirinotecan pegol dose excreted in urine over 168 hours for each analyte in study 12-102-13.

In vitro at 100 ug/ml, etirinotecan was transported by OAT-1 but not by P-gp, BCRP, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP.

Metabolism

Several *in vitro* studies were performed to investigate the hydrolysis of etirinotecan pegol to irinotecan, and it was concluded that hydrolysis occurred mainly non-enzymatically (see non clinical aspects). Hydrolysis of p-nitrophenyl ester derivatives with different substitution was studied in plasma and buffer, and the Applicant concluded that the 4-armed PEG used in etirinotecan pegol would cause steric hindrance to plasma hydrolytic enzymes. Hydrolysis was pH dependent both in plasma and buffer. Three

enriched PEGylated irinotecan molecular variants were studied to assess their impact on the overall irinotecan release rates during plasma hydrolysis, and the variants released irinotecan with similar rates. No metabolism was observed after 30 minutes incubation with recombinant CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4.

The relative contribution of the different elimination pathways of irinotecan differed after administration of etirinotecan pegol and free irinotecan, as the AUC and Cmax ratio between SN-38 and irinotecan was substantially higher (12 and 8-fold, respectively) after administration of etirinotecan pegol (see Table below).

Table 14 - Molar AUC and Cmax Ratios for SN38, SN38G, and APC for Etirinotecan Pegol and Irinotecan

Molar Parameter Ratios[a]	Onzeald	Irinotecan[b]	Onzeald/Irinotecan
AUC ratios			
SN38/Irinotecan	0.39 ± 0.15	0.032 ± 0.015	12.2
SN38G/SN38	7.03 ± 5.12	7.60 ± 5.88	0.93
APC/Irinotecan	0.21 ± 0.15	0.21 ± 0.15	1
C_{max} ratios			
SN38/Irinotecan	0.053 ± 0.020	0.0064	8.3
SN38G/SN38	7.56 ± 5.65	6.60	1.14
APC/Irinotecan	0.056 ± 0.048	0.098	0.57

Abbreviations: AUC = area under the plasma concentration-time curve; APC = 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycampthothecin; C_{max} = maximum plasma concentration; SN38 = 7 ethyl 10 hydroxycamptothecin; SN38G = glucuronide of 7 ethyl 10 hydroxycamptothecin

a. Parameters reported as mean ± SD.

b. Irinotecan ratios from (**Mathijssen, 2003**) and (**Xie, 2002**)

Source: LS-2015-504, **Table 8**

Consequences of genetic polymorphisms

In the popPK analysis LS-2015-504, UGT1A1*28 was tested as a covariate, and genotyping was performed in almost all of the 181 patients included. 10% of the patients were homozygotes for the allele. UGT1A1*28 was found to be a significant covariate for SN38G volume of distribution in the popPK analysis, but it had very limited consequences for SN38 exposure.

Dose proportionality and time dependency

Study 06-IN-IR001 was a Phase 1 multicentre, open-label, dose-escalation study that tested three different schedules of etirinotecan pegol at dose levels between 58 and 245 mg/m2. Both etirinotecan, irinotecan, SN-38, SN-38G and the inactive metabolite APC were measured. Cmax and AUC appeared to increase approximately linear with dose for all analytes, albeit with substantial variability. There were no signs of time-dependency. No dose- or time dependency was included in the popPK modelling.

Intra- and inter individual variability (IIV)

In the popPK analysis, clearance and volume of distribution of etirinotecan pegol both had IIV below 30%. IIV was more than 50% for some of the other parameters. Intra-individual variability was not tested.

Pharmacokinetics in the target population

Pharmacokinetic data is available from three patients with the proposed indication (BC with brain metastases). These patients were part of the pivotal BEACON study (11-PIR-11) where plasma PK

sampling was performed in 95 of the 425 patients who received etirinotecan pegol. Rich PK sampling was performed in cycle 1 and 2, and predose samples were taken before subsequent cycles in 1 of the 3 patients who remained on therapy. Concentration-time data for the patients with brain metastases were consistent with the overall BC study population.

Two popPK analyses were submitted and the later, LS-2015-504, was used, e.g. for addressing the PK in special populations. Pooled concentration-time data for etirinotecan pegol and its major metabolites irinotecan, SN38, SN38G, and APC collected in three clinical trials were used. All analytes were described by two-compartment models. Covariates included in the model were BSA (on etirinotecan pegol Cl and V), baseline eGFR, gender and UGT1A1*28. The evaluation of covariate relevance using simulation-derived exposure parameters, including AUC and C_{max} of etirinotecan pegol and its metabolites, indicated minimal clinical impact of gender, renal impairment and UGT1A1 polymorphism.

Gender

The final population PK dataset included 45 (24.9%) male and 136 (75.1%) female patients. Median etirinotecan pegol C_{max} in males was approximately 80% that in females and the observed median SN38 C_{max} in male patients was 0.88 times compared to females.

Race

The population PK model included 152 (84%) Whites, 9 (5%) Blacks, 9 (5%) Asians, and 11 (6.1%) other ethnicity. Race was not identified as a significant covariate in the popPK analysis.

Weight

BSA was a significant covariate for etirinotecan pegol clearance and volume of distribution with lower clearance and lower volume of distribution with lower BSA.

Special population

Renal impairment

No dedicated study in patients with renal impairment was submitted. The popPK analysis included data from 89 patients with mild and 21 with moderate renal impairment, no patients with severe renal impairment have been studied. Renal function, represented by eGFR, was found to be a significant covariate of etirinotecan pegol clearance. Exposure simulations indicated that etirinotecan pegol AUC[0,126d] increases with decreasing eGFR, with median AUC[0,126d] values of 0.93-times, 1.03-times, 1.2-times, and 1.5-times that of the reference population (female with median BSA 1.79 m2 and eGFR 83.4 mL/min) for normal, mild, moderate, and severe renal impairment categories.

Hepatic impairment (HI)

Study 12-102-13 was a phase I study to investigate the influence of mild and moderate hepatic impairment on the pharmacokinetics of etirinotecan pegol and its metabolites. The study is ongoing, but an interim report is available. 12 patients have been included in the normal hepatic function group, 7 with mild HI and 3 with moderate HI. The patients were categorized using the NCI organ dysfunction working group (ODWG) criteria.

There was no apparent difference in exposure of parent compound, irinotecan or SN-38 between the patients with normal and mild hepatic impairment. In the three patients classified to have moderately impaired hepatic function, exposure to both irinotecan and SN-38 was significantly higher (point estimate 2 and 3-fold higher, respectively).

Age

The age of the patients in the population PK model ranged from 26 to 81 years, with a median of 56 years. Age was not a significant covariate in the etirinotecan pegol population PK model. No data is available in children.

Pharmacokinetic interaction studies

In vitro studies in hepatocytes were performed to investigate whether etirinotecan pegol or irinotecan was an inhibitor of major CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). Concentrations up to 200 ug/ml were tested, and no inhibition was observed. Literature *in vitro* data suggested some time-dependent inhibition of CYP3A4 by irinotecan. No TDI data on other enzymes was provided (see discussion on non-clinical aspects).

The inhibitory potential of etirinotecan pegol on P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP was also studied, at a single concentration of 100 ug/ml. Some inhibition was observed for several of the transporters, for OCT1 and OCT2 the IC50s could be determined to 1.7 and 57 ug/ml, respectively. For unpegylated irinotecan, published data on *in vitro* transporter inhibition has been provided. Ki-values around the cut-off concentration 50xCmax was observed for OCT1 and 2 as well as MATE-1, for all other transporters the Ki was well above the cut-off. *In vitro* inhibition data on BCRP was not provided (see discussion on non-clinical aspects).

In vitro induction potencies of irinotecan and etirinotecan pegol (1, 10, and 100 µg/mL) were investigated in 72 hrs incubations with fresh human hepatocytes. Enzyme activity was assessed with probe substrates, and normalised to viable cell number measured by analyzing the cellular conversion of a tetrazolium salt. A substantial decrease in enzyme activity at the highest concentration 100 ug/ml was observed in most experiments, indicating cell toxicity. This was not seen in the CYP1A2 experiments, where an increased enzyme activity at 100 ug/ml was observed in 2 out of 3 donors, and at 10 ug/ml in 1 out of 3 donors. In the CYP3A4 experiments, a 2-fold enzyme activity compared with control was observed at 1 ug/ml for both etirinotecan pegol and irinotecan. Although technical problems with cell toxicity were encountered in the *in vitro* experiments, signs of *in vitro* enzyme induction were seen for both CYP1A2 and CYP3A4.

As some signs of both TDI and induction of CYP3A4 was discerned in *in vitro* data, clinical data on the ratio between the CYP3A4 produced metabolite APC and irinotecan was summarised. A relatively constant ratio was observed over time, suggesting that irinotecan does not modulate CYP3A4 activity.

Regarding etirinotecan pegol as a victim for drug-drug interactions, no mechanistic drug-drug interaction studies were provided. Clinical data available for unpegylated irinotecan showed an interaction potential with CYP3A4 inhibitor and inducers (CYP3A4 is involved in irinotecan metabolism) and UGT1A1 inhibitors (SN-38 is eliminated through glucuronidation). Published *in vitro* as well as pharmacogenetic data suggested a role of OATP1B1 and potentially OATP1B3 in the hepatic uptake of irinotecan and SN-38. The interaction risk of inhibitors of CYP3A4, UGT1A1 as well as OATP1B1/3 for etirinotecan pegol was not studied clinically.

In the phase I study 09-PIR-07, etirinotecan pegol at different dose levels was studied in combination with 5-fluorouracil and leucovorin, to establish MTD in this combination. PK data was compared with data from single-agent etirinotecan pegol studies using the popPK model. For most dose levels, both etirinotecan pegol and its metabolites showed PK parameters in line with previous data from single agent studies. The PK of 5-FU in this study was also in line with published data from other studies. A higher than expected exposure to SN-38 was observed after a low (25 mg/m^2) etirinotecan dose when combined with 5-FU/leucovorin compared with data from other studies.

2.4.3. Pharmacodynamics

Mechanism of action

Etirinotecan pegol is a covalent conjugate of irinotecan with polyethylene glycol (PEG). Irinotecan is a camptothecin derivative belonging to the topoisomerase inhibitor class of antineoplastic agents. The irinotecan component of etirinotecan pegol is structurally equivalent to non-pegylated irinotecan, but it is neither pharmacologically, clinically, nor dose equivalent to non-pegylated irinotecan due to conjugation with the PEG moiety. After administration, irinotecan is slowly released from etirinotecan pegol by hydrolysis and metabolised to the lipophilic, active cytotoxic agent, SN38.

SN38 interferes with mammalian DNA topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Current research suggests that the cytotoxicity of SN38 is due to double-strand DNA breaks produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and SN38. Mammalian cells cannot efficiently repair these double-strand breaks.

Due to the PEG-conjugate nature of etirinotecan pegol, peak SN38 plasma concentrations are lower and the SN38 circulation time is prolonged compared to irinotecan.

2.4.4. Discussion on clinical pharmacology

There has been no direct comparison of the PK of irinotecan and etirinotecan pegol, but comparison with published data shows more prolonged exposure to the active metabolite SN-38 and lower peak levels of both irinotecan and SN-38 compared with administering irinotecan itself. No new *in vitro* and *in vivo* data on the metabolism and elimination of irinotecan itself were provided.

There is no human data on distribution to the brain or tumour/metastases. The applicant hypothesised that a preferential targeting to CNS metastases may occur through selective extravasation at highly angiogenic sites, and also put forward the lack of susceptibility to the principal brain efflux transporters allowing retention in the CNS as well as literature evidence for endocytic uptake of macromolecular drug conjugates.

No plasma protein binding or distribution to red blood cells *in vitro* was observed for etirinotecan pegol. At the only studied concentration, 100 ug/mL, etirinotecan pegol was not transported by Pgp or BCRP. No data or discussion regarding active transport of irinotecan or SN-38 was provided. No mass-balance study in man was performed.

The hydrolysis of etirinotecan pegol in plasma does not appear to be mediated by CYP450 enzymes. *In vitro* results indicated that etirinotecan pegol hydrolysis in human plasma is predominantly chemical rather than enzymatic presumably due to steric hindrance effects from the large PEG chain. *In vitro*, an effect of pH on hydrolysis rate is observed, but given that the physiological pH range is relatively narrow and that free irinotecan concentrations are relatively low, a clinical effect on irinotecan release of e.g. acidosis is not expected.

The relative contribution of the different metabolic routes of irinotecan seems to differ between administration of irinotecan and etirinotecan pegol. The relative importance of the CYP3A4 mediated pathway seems to be lower and a higher fraction of the dose is hydrolysed to SN-38. The reason for this, however, is not clear. The difference in relative contribution of the different pathways may affect the risk for drug-drug interactions, but as no clinical DDI studies have been performed with etirinotecan, the same warnings as for other irinotecan products would apply.

With regards to the PopPK analysis, the PK is descriptive as the exposure-response analysis only provides limited information. The applicant provided the requested GOF and VPCs, thus the model is considered adequate for descriptive purposes.

Nine patients in Study 06-IN-IR001 and two patients in Study 07-PIR-02 were excluded from population PK analysis due to the occurrence of unexpectedly high plasma irinotecan concentrations. The final model was run with and without all PK-samples from the 2 sites concerned and the results were minimally affected.

No dedicated renal impairment study has been conducted with Onzeald. Patients with mild and moderate renal impairment were studied in the clinical studies and according to simulations based on the popPK model, SN38 exposure was similar independently of renal impairment group. Therefore, it is agreed that no dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance [CLcr] ≥30 mL/min). Severe renal impairment may however also affect hepatically eliminated drugs, and simulations from the popPK model cannot be used to predict this potential effect. No data is available in patients with severe renal impairment. The Applicant has provided literature data from patients receiving irinotecan, suggesting higher unbound SN-38 concentrations in dialysis patients than patients with normal renal function. Based on this, Onzeald is not recommended for use in patients with severe renal impairment (CLcr <30 mL/min).

A dedicated hepatic impairment (HI) study is ongoing, and an interim report is available. The group mild hepatic impairment in general does not seem to be affected in bilirubin, albumin or prothrombin time, which are considered markers for affected metabolic function, but are mostly characterized by increased ALT only. No major difference in the exposure to parent compound or metabolites was observed in the mild HI group, which is expected. Only three patients were included in the moderate HI group up to now and drug exposure in these patients were in general higher than in the control group. Administration of Onzeald to patients with moderate (total bilirubin >1.5 to 3×ULN) or severe (total bilirubin >3.0×ULN) hepatic impairment is not recommended. No dose adjustment is recommended in patients with mild (total bilirubin >1.0 to 1.5× upper limit of normal [ULN], or aspartate transaminase [AST] >ULN) hepatic impairment. The final dosing recommendation in hepatic impairment will await completion of the hepatic impairment study. As plasma protein binding may be affected by hepatic function, and the unbound drug exposure is believed to be the most relevant for dose adjustments, unbound irinotecan as well as SN-38 exposure should be reported in addition to total plasma concentration (Category 3 study in the RMP).

SN-38 is metabolised by glucuronidation, and is a known substrate of e.g. UGT1A1. Genetic variants of this enzyme exist, and UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as UGT1A1*28 polymorphism. UGT1A1*28 was found to be a significant covariate for SN38G volume of distribution in the popPK analysis, but it this had very limited consequences for SN38 exposure. Since the modelling dataset only included 18 subjects homozygous for the UGT1A1*28 allele, it is difficult to draw conclusions. Further, other alleles than UGT1A1*28 can play a role. The limited data for UGT1A1*28, the absence of data for other alleles, and given the previously observed increased risk of toxicity in patients with reduced UGT1A1 activity for irinotecan, it cannot be excluded that the impact of UGT1A1 genotype may be similar to other irinotecan products. Given that UGT enzymes are expressed by a range of tissues including liver, whether SN-38 levels exceed a saturation threshold for a particular UGT1A1 genotype will therefore depend on SN-38 levels within tissues including liver after etirinotecan administration and this is currently unknown. Given that plasma PK appears to have limited potential to predict dose adjustment, a full analysis of adverse events in relation to UGT1A1 genotype need to be performed in the confirmatory study which is planned to include UGT1A1 genotyping (see discussion on clinicial safety and RMP). Even though it is accepted that the current data are not sufficient to propose a need for UGT-genotyping or define a different starting dose in

patients known to be homozygouts for UGT1A1*28 (7/7), the higher risk for drug-induced toxicity in certain genotypes should be described in the SmPC (see clinical safety).

For other irinotecan products not only the *28 allele but also the *6 allele would impact SN-38 metabolism and tolerability, and this allele may be more common in Asian populations. There is too little data for the Asian population to draw conclusions about impact on etirinotecan exposure from the popPK analysis.

As etirinotecan clearance is related to BSA, the relevance of BSA based dosing is agreed.

As etirinotecan pegol is a prodrug to irinotecan, in addition to the pegylated compound, the potential enzyme and transporter inhibiting or inducing properties of irinotecan also needs to be addressed. When etirinotecan pegol is considered as a victim for drug-drug interactions, the focus needs to be situations with a risk for changes in the levels of the active entities irinotecan and SN-38. When data from other irinotecan formulation is used to address this risk, the different PK profile and the differences in the relative contribution of the different elimination pathways of irinotecan need to be considered. The Applicant has both performed in house *in vitro* DDI studies and provided literature references.

The Applicant has performed a set of *in vitro* experiments addressing the potential of etirinotecan pegol being an enzyme or transporter inhibitor. The maximum concentration tested corresponds to around 1-2 x Cmaxu. It is acknowledged that testing concentrations as high as 50 x Cmaxu as described in the Guideline for Drug Drug interactions may not be feasible. This is acceptable for enzymes, which are located within the cell as low cellular distribution of the pegylated compound at the high initial plasma concentrations may be anticipated. For transporters, however, located on the cell surface, the risk for *in vivo* inhibition cannot be fully addressed.

Etirinotecan pegol was tested at a single concentration of 100 ug/ml and appeared to inhibit the renal transporters OCT1 and OCT2, which is now mentioned in the SmPC. Also for other transporters, however, at the highest concentration tested (approximately 1.6x Cmax,u) there appears to be some inhibition. The risk for *in vivo* transporter inhibition cannot therefore be fully assessed based on these data. The Applicant should address the risk for *in vivo* transporter inhibition by etirinotecan pegol. A literature review of *in vitro* and *in vivo* inhibition of transporters by other pegylated small molecules and/or PEG chains should be performed. If a risk for relevant transporter inhibition by pegylated small molecules cannot be excluded based on available literature data, additional *in vitro* transporter inhibition studies, with higher concentrations of etirinotecan pegol, should be performed. While there may be some issues with investigating concentrations at 50xCmax.u, the highest concentration possible should be used. If in the end, a risk for clinical transporter inhibition of any other transporters than OCT-1, OCT-2 and MATE-1 cannot be excluded, the SmPC should be updated to describe this risk.

Irinotecan was studied in the enzyme experiments, but the transporter inhibitory properties of irinotecan were not investigated in-house. The Applicant has however provided literature data, showing *in vitro* inhibitory effect of irinotecan on MATE-1, OCT-1 and OCT-2. Data on BCRP is still lacking and should be provided. Data on the *in vitro* potential of time-dependent CYP inhibition is also lacking for etirinotecan pegol as well as irinotecan and should be addressed. There are available literature data on irinotecan causing TDI of CYP3A4.

As administration of etirinotecan pegol gives rise to a continuous exposure to irinotecan, it is of importance to elucidate the potential of enzyme induction. Although *in vitro* experiments had problems with cell toxicity, signs of induction of both CYP1A2 and CYP3A4 were observed, but the *in vivo* relevance of this is not known. Based on available information, a risk for decreased plasma concentrations of medicinal products undergoing metabolism through CYP 1A2 (e.g., duloxetine, melatonin, theophylline,) or UGT enzymes (e.g., estradiol) cannot be excluded.

To evaluate whether the CYP3A4 induction and/or TDI observed *in vitro* may have clinical relevance, the Applicant has provided data on the ratio of irinotecan concentration and its CYP3A4 produced metabolite APC over time. The data shows a similar ratio from 24 hours and onwards, which suggests that autoinduction or time-dependent inhibition of CYP3A4 is not present. The mass balance study referred to by the Applicant suggests that APC is not metabolised further to any larger extent but is excreted in urine, bile and faeces. A conversion to NPC may be possible, but as the amount of NPC in excreta is low compared with APC amounts, this pathway appears to be minor. Thus, it does not seem likely that the elimination of APC would be influenced by a CYP3A4 inhibitor or inducer to any major extent. In addition, irinotecan conversion to APC is known to be sensitive to CYP3A4 modulation, as ketoconazole has been shown to decrease APC AUC by 87% (irinotecan SmPC). Thus, the APC/irinotecan ratio should be a reasonable sensitive measurement of CYP3A4 activity, and the conclusion made by the Applicant that irinotecan does not modulate CYP3A4 to a clinically relevant extent is supported.

Regarding etirinotecan pegol as a victim for drug-drug interactions, no mechanistic drug-drug interaction studies have been performed. The Applicant proposes that the hydrolysis of etirinotecan pegol is non-enzymatic, and therefore unlikely to be sensitive to clinically relevant drug-drug interactions, which is agreed.

The risk for drug –drug interactions with irinotecan and SN-38 as victims for drug-drug interactions after etirinotecan pegol administration is largely unknown, and therefore the SmPC recommendation needs to be based on what is known about interaction risks for other irinotecan products. Based on documented interaction risks with CYP3A4 inhibitors and inducers as well as UGT1A1 inhibitors for free irinotecan, warnings for these combinations are agreed to be included in the SmPC. Literature data also suggest a role of OATP1B1 and possibly OATP1B3 in the hepatic uptake of irinotecan and SN-38, which is also included in the SmPC.

An exposure-response analysis was provided (data not shown). The objectives evaluate the relationship between SN38 exposure parameter values and overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) as well as to evaluate the relationship between NKTR-102, irinotecan, and SN38 exposure parameter values with adverse effects of special interest. The value of the exposure-response analysis is limited since less than 50% of the patients received ≥3 cycles of NKTR-102 therapy. In addition, all patients started out on the same BSA based dose and schedule, and dose reductions were only allowed if toxicity occurred which further limits the analysis. With similar exposure in patients, it becomes difficult to find exposure-response correlations. No clear conclusions can be drawn from the exposure-response analysis.

Irinotecan is a well-known topoisomerase I-inhibitor used primarily for GI cancers but is not approved for use in breast cancer. The cytotoxic action comes mainly from the active metabolite, SN38, which induces double-strand DNA breaks during DNA synthesis. The PEGylation technology used for etirinotecan aims to alter the pharmacokinetic (PK) properties of irinotecan, resulting in increased circulation half-life, modified bio-distribution, and enhanced water solubility.

Plasma exposure to SN-38 was not correlated with overall survival or objective response rate (see clinical efficacy). As an inhibitor of DNA replication, the site of action of SN-38 is intracellular, within the nucleus.

The incidence of diarrhoea doubled in the highest SN38 exposure quartile, predicted to occur after 6 treatment cycles. Early treatment of diarrhoea is therefore recommended to facilitate continuation of etirinotecan therapy (see discussion on clinical safety).

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology data package is overall considered acceptable. However, some *in vitro* and *in vivo* data regarding the interaction risk of etirinotecan pegol as a perpetrator are still lacking.

2.5. Clinical efficacy

2.5.1. Dose response study

The Phase 1 study 06-IN-IR001 was performed to evaluate the dose-limiting toxicities and maximum tolerated dose of single agent etirinotecan. In addition, MTDs for combination therapy regimens were evaluated in studies 07-PIR-02 and 09-PIR-07.

Study 06-IN-IR001

This was a Phase 1, multicentre, open-label, dose-escalation study designed to evaluate the safety, tolerability, and PK of NKTR-102 in three different treatment schedules in patients with refractory solid tumours. Up to approximately 30 patients per treatment schedule were planned for enrolment.

The selection of etirinotecan starting doses and regimens for the dose-finding study was based on the results of preclinical studies in rats and dogs. Furthermore, as toxicology studies in both rats and dogs had shown that NKTR-102 exhibits a higher MTD than irinotecan itself, (FDA) approved dosing regimens of irinotecan were taken into account.

Primary Endpoints:

- Dose-limiting toxicities
- MTD of NKTR-102 on three different treatment schedules:
- treatment on Days 1, 8 and 15 every 4 weeks (wx3 q4wk),
- treatment on Day 1 every 3 weeks (q21d),
- treatment on Day 1 every 2 weeks (q14d).

Secondary Endpoints:

- Standard non-compartmental PK parameters of NKTR-102 and its metabolites
- Objective tumour response using RECIST 1.0 criteria

A standard 3 +3 dose escalation algorithm was used. Once the MTD was established for each treatment schedule, an additional 14 patients could be enrolled (for a total of up to 20 patients at that dose) to further characterize the safety and tolerability of the MTD for that treatment schedule.

DLTs

Cycle 1 dose-limiting toxicities (DLTs) were mainly gastro-intestinal of nature, as can be expected by the known safety profile of irinotecan. In accordance with the study protocol, toxicity in subsequent cycles was also considered in the identification of the maximum tolerated dose (MTD). DLTs in subsequent cycles included diarrhoea, vomiting, dehydration and electrolyte abnormalities, acute kidney injury, abdominal pain, ileus/ischemic colitis, fatigue, neutropenia, bone marrow hypoplasia, and fatal neutropenic sepsis.

Maximum tolerated dose:

The MTD is defined as the highest dose of NKTR-102 that was administered without causing any unacceptable side effects or AEs. The MTDs for the three treatment schedules of this study were:

- 115 mg/m2 for the wx3 q4wk treatment schedule,
- 145 mg/m2 for the q21d treatment schedule, and
- 145 mg/m2 for the q14d treatment schedule.

Diarrhoea was the predominant toxicity in each treatment schedule.

Safety

The most prevalent reasons for study termination across treatment schedules were Disease progression in 48.7% (37/76) of patients and AEs in 38.2% (29/76) of patients.

All patients experienced one or more treatment-emergent adverse events (TEAEs) during the course of the study. The most commonly encountered TEAEs across the three treatment schedules were diarrhoea (85.5%), nausea (81.6%), fatigue (64.5%), vomiting (57.9%), dehydration (42.1%), hypokalaemia (42.1%), and anorexia (40.8%.

Treatment-related SAEs occurred in 38 patients, with diarrhoea being the most prevalent.

On-study deaths occurred in 11 patients, two of which were probably related to study drug (neutropenic sepsis and diarrhoea)

Responses

Table 15 - Response to NKTR-102 Based on RECIST Guidelines by Schedule and by Dose (Study 06-IN-IR001)

Schedule	Dose	Anatomical Location of Primary Tumor	Response Duration (Days)
wx3 q4wk	58 mg/m^2	Lung - SCLC	109
wx3 q4wk	173 mg/m^2	Cervix	Unknown (60 days plus on-study)[1]
q21d	170 mg/m^2	Breast	87
q14d	145 mg/m^2	Bladder	68
q14d	170 mg/m^2	Head and Neck	273
q14d	195 mg/m^2	Pancreas/neuroendocrine	Unknown (84 days plus on-study)[1]
q14d	220 mg/m^2	Colorectal	97
q14d	220 mg/m^2	Lung - NSCLC	Unknown (84 days plus on-study)[1]

Only one of the eight responses was seen with the q21d (tri-weekly) regimen, proposed for authorisation, and then at a higher dose than proposed. Most responses occurred in the q14d (bi-weekly) regimen; one of five at the concluded MTD (145 mg/m), the others at higher doses.

Among the small number of breast cancer patients, the objective response rate (ORR) was 25% (1/4 patients), with indications of anti-tumour activity (reduction in plasma tumour marker CA27.29) in 50% (2/4). It is noted that 3 of the 4 patients had triple-negative disease, i.e. disease with generally poor-prognosis. The fourth had HER2-positive disease and did not receive anti-HER2 targeted therapy

during study, also affecting the prognosis. Breast cancer patients constituted a small minority of patients (4/76, 5%), all of whom had poor prognosis histologies.

Recommended Phase 2 dose (RP2D)

The dose145 mg/m2 on a q14d or q21d treatment schedule was concluded as RP2D. The tri-weekly schedule was subsequently chosen for phase 3 development based on the results of the Phase 2 studies 08-PIR-05 and 08-PIR-04, performed in patients with metastatic breast cancer and ovarian cancer comparing the safety and efficacy of Onzeald 145 mg/m2administered q14d vs q21d (see Supportive studies below).

2.5.2. Main study

11-PIR-11 - *(BEACON Study)*

Study title: *BEACON Study (BrEAst Cancer Outcomes with NKTR-102): A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 versus Treatment of Physician's Choice (TPC) in Patients with Locally Recurrent or Metastatic Breast Cancer Previously Treated with an Anthracycline, a Taxane, and Capecitabine*

Methods

This was an open-label, randomized, parallel, two-arm, multicentre, international Phase 3 study of NKTR-102 versus TPC in patients with locally recurrent or metastatic breast cancer previously treated with at least two prior and a maximum of five cytotoxic chemotherapy regimens including an anthracycline, taxane, and capecitabine (ATC).

Study Participants

Inclusion and exclusion criteria

Adult female patients ≥ 18 years of age with histologically or cytologically confirmed carcinoma of the breast. Patients could have had either measurable or non-measurable disease by RECIST, locally recurrent or metastatic disease.

Prior therapy (administered in the neoadjuvant, adjuvant, and/or metastatic setting) must include an anthracycline (unless not medically appropriate or contraindicated for the patient), a taxane, and capecitabine.

Patients must have received a minimum of two and a maximum of five prior cytotoxic chemotherapy regimens for the treatment of locally recurrent or metastatic breast cancer, with the last dose of cytotoxic chemotherapy administered within six months of the date of randomization into this trial. A "regimen" may be single-agent or combination therapy. Single-agent biological agent therapy (e.g., bevacizumab, trastuzumab, or pertuzumab) and single-agent hormonal therapy were not counted as "chemotherapy."

Patients with known HER2+ tumours should have been treated with trastuzumab. Patients with oestrogen receptor positive disease should have been treated with prior hormonal therapy.

Women of childbearing potential (WCBP) should have a negative serum pregnancy test and must agree to use highly effective methods of birth control. Protections against pregnancy must have been continued for at least eight months after the last dose of study drug.

Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with adequate organ function.

Patients with brain metastases were eligible, provided local therapy was completed and use of corticosteroids for this indication were discontinued for at least three weeks prior to randomization with stable brain metastases (by symptoms and imaging). Patients with leptomeningeal disease or meningeal carcinomatosis were excluded.

Concomitant use of biologic agents for the treatment of cancer including antibodies (e.g., bevacizumab, trastuzumab, or pertuzumab) or any investigational agent(s) was not allowed.

Prior treatment for cancer with a camptothecin derivative (e.g., irinotecan, topotecan, and investigational agents) was not allowed. Patients with chronic or acute GI disorders resulting in diarrhoea were excluded.

Other exclusion criteria included: pregnancy or lactation, pharmacotherapy for hepatitis B or C, tuberculosis, or human immunodeficiency virus (HIV), Child-Pugh Class A or higher liver disease, prior malignancy within last 5 years (except breast, non-melanoma skin cancer and carcinoma in situ of the cervix or bladder), and significant known cardiovascular impairment. Minimum intervals since most recent therapy, depending on treatment modality, were also stipulated.

Treatments

Etirinotecan pegol (a.k.a. NKTR-102) was administered at a dose level of etirinotecan 145 mg/m2 on a (q21d) schedule as a 90-minute (± 15 minutes) intravenous (IV) infusion on Day 1 of each treatment cycle. Body surface area was capped at 2.4 m2.

A dose modification schedule was provided with specific instructions for haematological and gastrointestinal adverse events (AEs), as well as for other drug-related non-hematologic toxicities (except fatigue/asthenia and alopecia).

Treatment of Physician's Choice (TPC) was administered per standard of care, in 21- or 28 day cycles. TPC was to be selected from the following list of seven single-agent intravenous therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. They were given according to local institutional guidelines or SmPC (eribulin).

Crossover from TPC to etirinotecan pegol was not permitted.

Concomitant medication

For treatment of late onset diarrhoea following NKTR-102 infusion, loperamide was dispensed to patients randomized to receive NKTR-102 so that it was available to the patient at home. Patients with diarrhoea were carefully monitored, and could be given fluid and electrolyte replacement if they became dehydrated and antibiotic support if they developed ileus, fever, or severe neutropenia.

In addition, standard supportive care and chemotherapy prophylaxis was allowed, including e.g. antiemetics, antihistamines, corticosteroids (for taxanes), bisphosphonates and denosumab, growth factor support, transfusions. Limited exposure/duration RT to treat pain was also permitted.

Objectives

Primary Objective: To compare the overall survival (OS) of patients who received NKTR-102 once every 21 days (q21d) to patients who received treatment of physician's choice (TPC) (per standard of care) selected from seven single-agent intravenous therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel.

Secondary Objectives:

• To compare the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (hereafter referred to as RECIST)

• To compare progression-free survival (PFS)

• To compare the clinical benefit rate (CBR; the proportion of patients having complete response [CR], partial response [PR], or stable disease [SD] for at least six months)

• To compare duration of response (DoR)

• To determine the safety profiles of NKTR-102 and TPC (including Grade 3 and higher toxicities, incidence of dose reductions and dose intensity)

• To compare health-related quality of life (HRQoL) using the Quality of Life-Core 30 (QLQ-C30) with the QLQ-breast cancer-specific module (QLQ-BR23) subscale

• To obtain pharmacokinetic (PK) data (in selected patients randomized to NKTR-102 only)

• To evaluate the pharmacoeconomic implications of NKTR-102 therapy using selected measures of health

Outcomes/endpoints

Primary endpoint

Overall survival defined as time from date of randomisation to death from any cause was selected as a single primary endpoint. Patients were followed until death, date of withdrawal of consent for survival follow-up, final database closure, or until the Sponsor terminated the study. OS for patients who received NKTR-102 q21d was compared with OS of patients who received TPC.

Secondary endpoints

- **Objective Response Rate**: The ORR was defined as the proportion of patients with a Complete Response (CR) or Partial response (PR) per RECIST based upon the best response as assessed by the Investigator. The ORR for the treatment group receiving NKTR-102 q21d was compared with the TPC treatment group for the Efficacy Evaluable population.

  The ORR was determined as the best overall response of both target and non-target lesions using the overall tumour burden at baseline as a basis for progression/ regression. Target lesions were selected on the basis of their size (lesions with the longest diameter) and ability to be repeatedly measured. When more than one measurable lesion was present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) were identified as target lesions. Non-target lesions were identified as all other lesions (or sites of disease) including pathological lymph nodes at baseline. The assessment of the change in tumour burden from baseline was conducted as per the revised 'RECIST (version 1.1) guidelines for the pivotal study and per the original RECIST (version 1.0) guidelines for the Phase II study.

- **Progression-free Survival (PFS):** PFS was defined as the time from the date of randomisation to the earliest evidence of documented PD or death from any cause. Disease progression was assessed by the Investigator according to RECIST. Scans were collected up to PD per RECIST or death. Progression was not assessed post-cessation of randomised therapy. The PFS for the treatment group receiving NKTR-102 q21d was compared with the TPC treatment group for the Intent-to-Treat (ITT) population.

- **Clinical Benefit Rate (CBR):** The CBR was defined as the proportion of patients having a CR, PR, or Stable Disease (SD) for at least six months (≥ 182 days). The CBR for the treatment group receiving NKTR-102 q21d was compared with the TPC treatment group for both the ITT and Efficacy Evaluable populations.
- **Duration of Response (DoR)**: The DoR was defined as the time from first documented CR or PR until the earliest evidence of disease progression or death from any cause. The DoR for the treatment group receiving NKTR-102 q21d was compared with the TPC treatment group calculated for the Efficacy Evaluable population.
- **EORTC QLQ-C30 (version 3.0)** supplemented by the breast cancer module **(QLQ-BR23)** was used to measure quality of life at baseline, prior to tumour measurements every 8 weeks and at end of treatment.

  The QLQ-C30 instrument was composed of five multi-item functional scales (physical, role, social, emotional and cognitive functioning), a global health status/quality of life (QoL) scale, three symptom scales (fatigue, nausea/vomiting, and pain), and six single items (financial impact, appetite loss, diarrhoea, constipation, sleep disturbance and dyspnoea). In conjunction with the C30 scale, the breast cancer module (QLQ-BR23) incorporated five multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning, and three single-items assess sexual enjoyment, hair loss and future perspective.

Tumour assessments

Documented tumor measurements were required using computed tomography (CT) scans, magnetic resonance imaging (MRI), physical examination (PE), and/or digital photography, as appropriate, and were performed at Screening, every eight weeks (± 7 days) from date of randomization until documented disease progression, withdrawal of consent for survival follow-up, or death. To ensure that both treatment arms of this study were assessed for progression in a similar manner, tumour assessment was obtained at this interval, regardless of delays in chemotherapy due to toxicity.

Response criteria

Evaluation of target lesions:

CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is considered progression.)
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Exploratory

To correlate specific biomarker data with response, PFS, survival, selected toxicities, and possibly PK parameters (in selected patients who consented).

Biomarker evaluation

Blood samples for biomarker analysis on circulating tumour cells were collected at Screening, Cycle 1 Day 1 (if not obtained at baseline), Cycle 2 Day 1(up to five days prior to dose), Cycle 4 Day 1 (up to five days prior to dose) and at the End-of-Treatment visit.

Blood samples were used to assess various biomarkers (e.g., topoisomerase 1 and 2 expression, DNA damage, proliferation and apoptosis) at baseline and determine change from baseline to End of Treatment.

Safety measurements

Safety endpoints for the study included the incidence and severity of treatment-emergent AEs (TEAEs), laboratory abnormalities, targeted symptoms (including diarrhea and neuropathy), incidence of dose reductions, and dose intensity.

Exploratory measurements

- Plasma concentrations of NKTR-102 and its metabolites were collected at intervals throughout the study
- UGT1A1 genotyping

Sample size

The study was powered to detect superiority of etirinotecan pegol versus TPC for the primary efficacy endpoint of OS. Patients were randomized in a 1:1 ratio to one of the two study treatment arms stratified by geographic region (North America/Western Europe versus Eastern Europe versus Asia), prior use of eribulin (Yes versus No), and receptor status (TNBC versus HER2+ versus Other).

The sample size calculations were event-driven. Approximately 840 patients (420 patients per treatment arm) were required in order that 615 deaths would have occurred within 36 months of randomizing the first patient.

The sample size calculations were based on the following assumptions:

- Overall two-sided Type I error rate: 0.05
- HR: 0.77 (median survival time of 10 months for the control versus 13 months for NKTR-102)
- Power of 90%
- One interim analysis was scheduled when 50% of the 615 deaths had occurred. At that point, the DMC may have recommended stopping the trial early for superiority or lack of efficacy on OS.
- An average accrual rate of 35 patients per month and an accrual period of 24 months

The type I error control at two-sided 0.05 is standard and acceptable.

Randomisation

Patients were randomised 1:1 between etirinotecan and Treatment of Physician's Choice (single drug, choice of seven pre-specified agents). Three stratification factors were used, with in total 3*2*3=18 strata, block size is 4 (within stratum). Subsequently two geographic strata were grouped together as one, resulting in a total of 2*2*3= 12 strata. The choice of TPC was made before randomisation.

Blinding (masking)

This was an open-label study.

Statistical methods

Primary Endpoint Analysis

Overall survival for the ITT population in the treatment groups was compared using a two-sided log-rank test stratified by geographic region, prior eribulin use, and receptor status (see Randomisation above). Median survival times and their 95% confidence intervals (CIs) were estimated using the Kaplan-Meier method. The hazard ratio for NKTR-102 and TPC and its 95% CI were estimated using a Cox regression model adjusting for geographic region, prior eribulin, and receptor status.

Sensitivity analysis comparing NKTR-102 with TPC was conducted using stratified Cox regression model. One formal interim analysis on OS was conducted using O'Brien-Fleming alpha spending function approach.

Additional post hoc analyses using Wilcoxon and Restricted Means Survival Time (RMST) were also performed. These methods are known to be more powerful to detect a true difference in treatment effect in the presence of certain patterns of non-proportionality.

Secondary Analyses

The secondary endpoint analyses of ORR and DoR were conducted using the Efficacy Evaluable population; other secondary efficacy analyses utilized the ITT population or both the Efficacy Evaluable and ITT populations. Key secondary endpoints including ORR and PFS were tested using the following fixed sequence strategy. If the comparison of OS demonstrated statistical superiority of NKTR-102 over TPC at the interim analysis (two-sided $p < 0.003$) or at the final analysis (two-sided $p < 0.049$), the key secondary endpoints (ORR and PFS) were planned to be tested hierarchically. The ORR was planned to be tested first. If the ORR was not statistically significant (two-sided $p < 0.05$), then PFS would not be formally tested.

Analysis for other secondary endpoints of CBR and DoR did not include any adjustment for multiplicity.

Statistical tests were two-sided with $p = 0.05$. The analysis of CBR was planned for the Efficacy Evaluable and ITT populations. The analysis of DoR was planned for patients who achieved a CR or PR in the Efficacy Evaluable population.

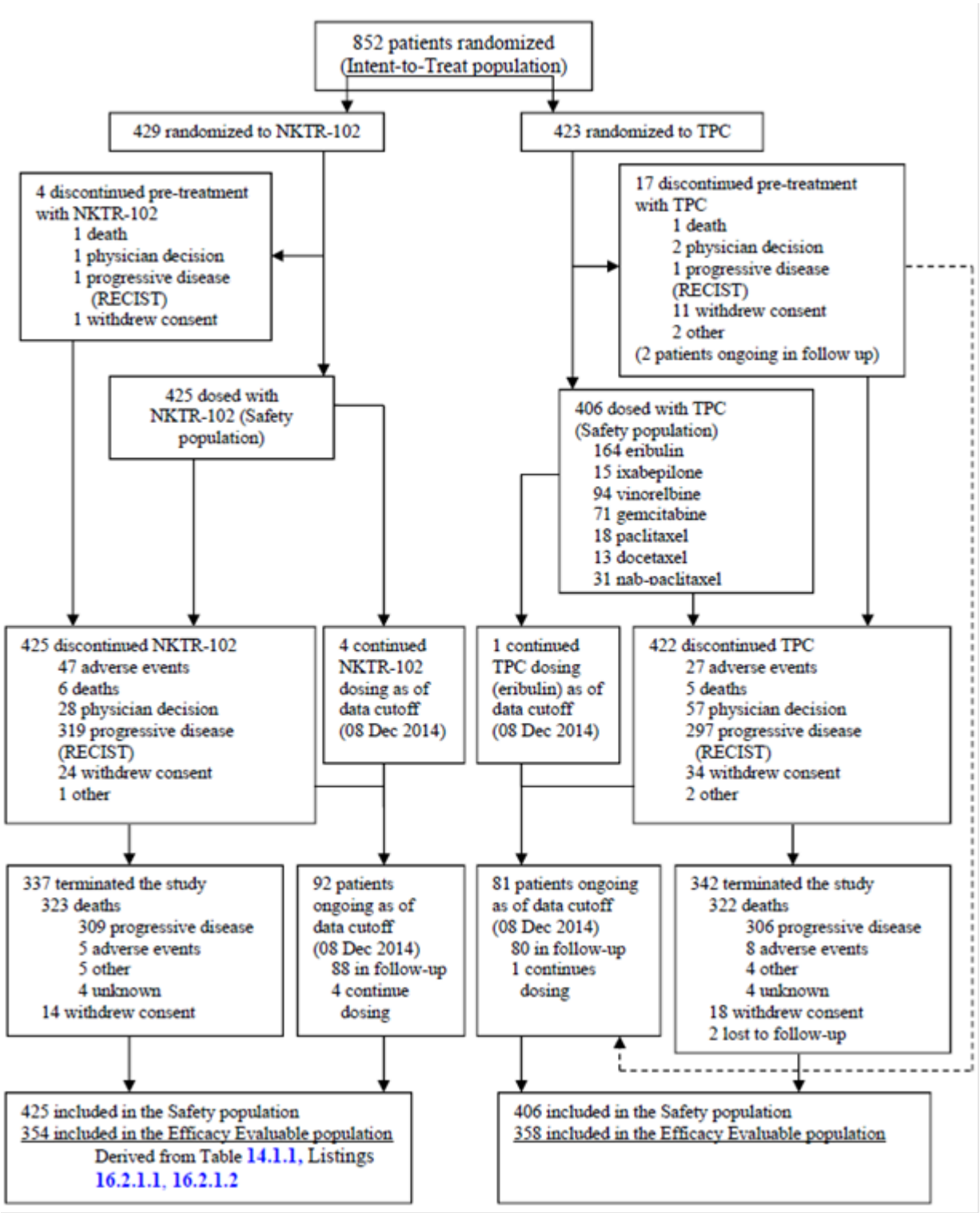
Subgroup analyses of OS were planned, without adjustment for multiplicity, to assess the degree of consistency among subgroups. Among other categories, these subgroups included demographics; baseline disease characteristics; and history of brain, liver, and lung metastases.

Results

Participant flow

An overview of patient allocation in each treatment group is shown in Figure 7 and in Table 19.

Figure 5 - Patient Disposition in Study 11-PIR-11 (All Randomized Patients)



Patients who discontinued from the study treatment due to clinical symptomatic progression without RECIST confirmation were reported under Physician Decision.

Table 16 - Patient Disposition in Study 11-PIR-11 (ITT Population)

	NXTR-102 (N=429)		TPC (N=423)		Total (N=852)	
Total Number of Patients						
Randomized (ITT Population)	429		423		852	
Received At Least One Dose of Study Drug (Safety Population)	425	(99.1%)	406	(96.0%)	831	(97.5%)
Had Measurable Disease at Baseline Per RECIST (Efficacy Evaluable)	354	(82.5%)	358	(84.6%)	712	(83.6%)
Discontinued From Study Drug	425	(99.1%)	422	(99.8%)	847	(99.4%)
Terminated From the Study	337	(78.6%)	342	(80.9%)	679	(79.7%)
Ongoing	92	(21.4%)	81	(19.1%)	173	(20.3%)
Primary Reason for Treatment Discontinuation						
Adverse Event	47	(11.0%)	27	(6.4%)	74	(8.7%)
Death	6	(1.4%)	5	(1.2%)	11	(1.3%)
Lost To Follow-Up	0	(0.0%)	0	(0.0%)	0	(0.0%)
Physician Decision	28	(6.5%)	57	(13.5%)	85	(10.0%)
Pregnancy	0	(0.0%)	0	(0.0%)	0	(0.0%)
Progression of Disease by RECIST	319	(74.4%)	297	(70.2%)	616	(72.3%)
Protocol Violation	0	(0.0%)	0	(0.0%)	0	(0.0%)
Study Termination By Sponsor	0	(0.0%)	0	(0.0%)	0	(0.0%)
Withdrawal By Subject	24	(5.6%)	34	(8.0%)	58	(6.8%)
Other	1	(0.2%)	2	(0.5%)	3	(0.4%)
Primary Reason for Study Termination						
Death	323	(75.3%)	322	(76.1%)	645	(75.7%)
Adverse Event	5	(1.2%)	8	(1.9%)	13	(1.5%)
Progressive Disease	309	(72.0%)	306	(72.3%)	615	(72.2%)
Other	5	(1.2%)	4	(0.9%)	9	(1.1%)
Unknown	4	(0.9%)	4	(0.9%)	8	(0.9%)
Lost To Follow-Up	0	(0.0%)	2	(0.5%)	2	(0.2%)
Study Termination By Sponsor	0	(0.0%)	0	(0.0%)	0	(0.0%)
Withdrawal By Subject	14	(3.3%)	18	(4.3%)	32	(3.8%)
Other	0	(0.0%)	0	(0.0%)	0	(0.0%)

Note: Percentages are based on the number of patients in the ITT population.

Recruitment

144 study sites participated in this study and screened patients at study sites worldwide, of which 139 study sites enrolled patients; five study sites screened patients but did not randomize any patients in the study. The study sites that screened patients were located in 11 countries including 83 in the United States; 42 in seven European countries (Belgium, France, Germany, Italy, Netherlands, Spain, and United Kingdom); eight in the Republic of Korea; six in Canada; and five in Russia.

Conduct of the study

Protocol amendments

Protocol Amendment 1.0 – Version 2.1 (Summary of Changes Document) (27 Oct 2011):	Administrative protocol amendment. With this amendment, randomization was stratified for receptor status (HER2+ breast cancer versus TNBC versus all others). References to the PK manual were replaced with Laboratory Manual. No data available to the Sponsor at the time of these changes.
Protocol Amendment 1.0 – Version 2.1 (clean) (27 Oct 2011):	Administrative protocol amendment to correct a grammatical/typographical error. No data available to the Sponsor at the time of this

	change.
Protocol Amendment 2.0 – Version 3.0 (France and UK only) (Summary of Changes Document) (24 May 2012):	No data available to the Sponsor at the time of these protocol amendments. • Clarification about seletion of a TPC drug n accordane with local CA approval • Added tissue acquisition protocol (TAP) sub-study to the main study • Updated eligibility criteria • Administrative changes • Dosing modification due to AEs • Amendments related to the procedures

The original BEACON Statistical Analysis Plan (SAP) version 1.0 (finalised on 12 October 2012) included assessment of whether patients had a history of brain metastases or not, but it was not a predefined subgroup analysis for efficacy at that time. On 16 November 2012, the Data Monitoring Committee (DMC) was made aware that the incidence of patients with history of brain metastases was 15 out of 168 enrolled patients (slightly less than 10%). This was higher than anticipated during the design phase of the study and supported that it could justify a separate subgroup analysis. The BCBM population was specifically defined for subgroup efficacy analyses in version 2.0 of the SAP, which was finalised on 22 October 2013, before the interim analysis data cut-off date of 03 December 2013. However, the SAP did not mention what was the purpose of this subgroup investigations, no alpha was spent for this subgroup analysis that was also not included in the confirmatory testing strategy. A total of 168 out of the final ITT Population of 852 (19.7%) patients were enrolled to the BEACON study under SAP version 1.0. Of these, 15 out of the final BCBM Population total of 67 (22.4%) patients' medical history included a history of brain metastases.

Table 17 - Study 11-PIR-11 (BEACON): Statistical Analysis Plan Revision History (BCBM Changes)

BEACON Start Date (First Patient Randomised): 19 December 2011, Data cut-off for interim analysis: 03 December 2013, Data cut-off for primary analysis: 23 February 2015.

SAP Version/ Date	Total Number of Patients Enrolled (% of Final ITT Population)	Total Number of BCBM Patients Enrolled (% of Final BCBM Population)	Summary of BCBM SAP Revision(s)	Primary Reasons for Key BCBM SAP Revision(s)
v. 1.0/ 12 Oct 2012	168 (19.7%) [a]	15 (22.4%) [a]	N/A	N/A
v. 2.0/ 22 Oct 2013	561 (65.8%) [b]	42 (62.7%) [b]	• Section 7.12.1 (Analysis of Primary Endpoint): Addition of history of brain metastases as a pre-defined subgroup analysis. • Section 10 (Subset Analysis): Addition Subset Analysis, which indicated that	• As of the 19 October 2012 data cut off (open session to DMC), there were more patients enrolled with BCBM than anticipated: 15/168 (8.9%) vs. < 5% based on initial discussions with Steering Committee. • As of the 18 April 2013 data cut-off (open session to DMC), more patients enrolled with BCBM than anticipated: 7.5%

			selected efficacy and safety analyses would be repeated for both patients with history of brain metastases. • Addition of reference to the unblinding plan that was created by Quintiles (CRO), which was finalised after the SAP v. 1.0.	(42/561) vs <5% based on initial discussions with Steering Committee. • As of Q3 2013, nonclinical pharmacology studies in mice showed that etirinotecan pegol exhibited preferential accumulation (170-fold) in brain tumours over the corresponding plasma concentrations and resulted in favourable survival and anti-tumour efficacy compared to irinotecan
v. 2.1/ 18 June 2014 No	852 (100.0%) [c]	64 (95.5%) [d]	N/A	N/A

Abbreviations: AE = adverse event; ATC = Anatomical, Therapeutic, or Chemical; BCBM = breast cancer with history of brain metastases; CRO = contract research organisation; DMC = data monitoring committee; ITT = intent to treat; N/A = not applicable; SAP = statistical analysis plan; v = version; WHO DDE = World Health Organization Drug Dictionary Enhanced.

a. Based on 19 October 2012 data cutoff for DMC open session report.
b. Based on 18 April 2013 data cutoff for DMC open session report.
c. Based on 11 April 2014 data cutoff for DMC open session report.
d. Based on 11 April 2014 data cutoff for DMC open session report. There were three missing data entries that were unknown at the time of report generation; the missing entries were later confirmed to be BCBM patients.

Protocol deviations

A total of 85/852 patients (10.0%) had at least one critical protocol deviation. Most deviations were related to not meeting eligibility/entry criteria (4.7% in etirinotecan arm and 6.4% in TPC arm) and stratification error (4.7% in etirinotecan arm and 3.3% in TPC arm); these stratification deviations do not include the 21 Russian patients who were incorrectly assigned to Western Europe. There were 295 (34.6%) patients with at least one major protocol deviation.

Protocol deviations were overall balanced across arms. The only larger imbalance concerned major deviations of Investigational product (IP) compliance (etirinotecan: 24%; TPC: 3%). When taking into account all severities of deviations, there were in total 28% IP compliance deviations (including 1 critical and 15 minor) in the etirinotecan arm compared with 5% (including 1 critical and 5 minor) in the TPC arm.

Baseline data

Table 18 - Summary of Demographic Characteristics in Full Study Population and BCBM subgroup (ITT Population) Study 11-PIR-11

Demographic Parameter	BEACON ITT Population		BCBM ITT Population	
	Onzeald [a] 145 mg/m² q21d	TPC per Standard of Care	Onzeald [a] 145 mg/m² q21d	TPC per Standard of Care
	N = 429	N = 423	N = 36	N = 31
Age (years)				
N	429	423	36	31
Mean (SD)	55.1 (10.3)	55.2 (10.1)	51.9 (10.3)	53.5 (9.4)
Median	55.0	55.0	54.5	54.0
Min., Max	28, 84	32, 80	28, 75	37, 76

Age Group (years)				
<65	340 (79.3%)	342 (80.9%)	33 (91.7%)	29 (93.5%)
≥ 65	89 (20.7%)	81 (19.1%)	3 (8.3%)	2 (6.5%)
Sex				
Female	429 (100%)	423 (100%)	36 (100%)	31 (100%)
Race				
White	305 (71.1%)	292 (69.0%)	28 (77.8%)	21 (67.7%)
Black or African American	35 (8.2%)	34 (8.0%)	2 (5.6%)	1 (3.2%)
Asian	50 (11.7%)	55 (13.0%)	5 (13.9%)	4 (12.9%)
American Indian or Alaska Native	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Native Hawaiian or Other Pacific Islander	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)
Multiple/ Other	3 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Not Reported	35 (8.2%)	42 (9.9%)	1 (2.8%)	5 (16.1%)
Ethnicity				
Hispanic or Latino	47 (11.0%)	45 (10.6%)	5 (13.9%)	8 (25.8%)
Not Hispanic or Latino	339 (79.0%)	332 (78.5%)	29 (80.6%)	18 (58.1%)
Not Reported	36 (8.4%)	33 (7.8%)	1 (2.8%)	5 (16.1%)
Unknown	7 (1.6%)	13 (3.1%)	1 (2.8%)	0 (0%)
ECOG Status at Baseline				
0	175 (40.8%)	134 (31.7%)	11 (30.6%)	5 (16.1%)
1	252 (58.7%)	285 (67.4%)	25 (69.4%)	25 (80.6%)
≥2	2 (0.5%)	4 (0.9%)	0 (0%)	1 (3.2%)
Fertility Status				
Child-bearing Potential	58 (13.5%)	61 (14.4%)	6 (16.7%)	5 (16.1%)
Surgically Sterile	83 (19.3%)	69 (16.3%)	10 (27.8%)	5 (16.1%)
Post-Menopausal	283 (66.0%)	289 (68.3%)	20 (55.6%)	20 (64.5%)
Not Child-bearing Potential, other	5 (1.2%)	4 (0.9%)	0 (%)	1 (3.2%)
Smoking History				
Smoker	35 (8.2%)	23 (5.4%)	4 (11.1%)	0 (0%)
Previous	103 (24.0%)	106 (25.1%)	13 (36.1%)	8 (25.8%)
Non-Smoker	289 (67.4%)	290 (68.6%)	19 (52.8%)	23 (74.2%)
Unknown/ missing	2 (0.5%)	4 (0.9%)	0 (0%)	0 (0%)

Abbreviations: BCBM = breast cancer with history of brain metastases; GPA = graded prognostic assessment (disease specific index); ECOG = Eastern Cooperative Oncology Group; HER2+ = positive for human epidermal growth factor receptor 2; ITT = intent to treat; TNBC = triple negative breast cancer; N/A = Not Applicable; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q21d = once every 21 days.

All Onzeald doses were by intravenous infusion over a 90 +/- 15 minute duration

Table 19 - Summary of Breast Cancer History (ITT and BCBM Population) Study 11-PIR-11

Parameter	BEACON ITT Population		BCBM ITT Population	
	Onzeald[a] 145 mg/m² q21d	TPC per Standard of Care	Onzeald[a] 145 mg/m² q21d	TPC per Standard of Care
	N = 429	N = 423	N = 36	N = 31
Time Since Initial Cancer Diagnosis (years)				
Mean (SD)	7.5 (5.5)	7.2 (5.3)	6.5 (5.4)	6.8 (4.5)
Median	5.8	5.4	4.4	5.2
Min., Max	0.6, 29.3	0.8, 31.9	1.1, 24.9	1.5, 18.9
0 to < 2 years	29 (6.8%)	35(8.3%)	3 (8.3%)	2 (6.5%)
2 to <10 years	288 (67.1%)	293 (69.3%)	26 (72.2%)	22 (71.0%)
≥ 10 years	112 (26.1%)	95 (22.5%)	7 (19.4%)	7 (22.6%)
Time Since Diagnosis of Locally Recurrent/Metastatic Disease (years)				
Mean (SD)	3.3 (2.8)	3.1 (2.5)	2.9 (2.3)	3.1 (2.2)
Median	2.5	2.5	2.6	2.4
Min., Max	0.3, 19.7	0.2, 22.9	0.6, 12.2	0.9, 10.6
0 to < 2 years	165 (38.5%)	167 (39.5%)	13 (36.1%)	12 (38.7%)
2 to <5 years	189 (44.1%)	191 (45.2%)	18 (50.0%)	14 (45.2%)
≥ 5 years	75 (17.5%)	65 (15.4%)	5 (13.9%)	5 (16.1%)
Visceral Disease at Enrolment				
Present	319 (74.4%)	324 (76.6%)	30 (83.3%)	27 (87.1%)
Absent	110 (25.6%)	99 (23.4%)	6 (16.7%)	4 (12.9%)
Cancer Stage at Initial Diagnosis				
I (includes IA-B)	52 (12.2%)	59 (13.9%)	4 (11.1%)	1 (3.2%)
II (includes IIA-B)	171 (39.9%)	155 (36.6%)	15 (41.7%)	14 (45.2%)
III (includes III A-C)	125 (29.1%)	119 (28.1%)	7 (19.4%)	11 (35.5%)
IV	70 (16.3%)	75 (17.7%)	9 (25.0%)	4 (12.9%)
Missing/ Unknown	11 (2.6%)	15(3.5%)	1 (2.8%)	1 (3.2%)
Current Cancer Stage				
IV (includes locally recurrent or metastatic)	429 (100%)	423 (100%)	36 (100%)	31 (100%)
Liver metastases present	229 (53.4%)	227 (53.7%)	26 (72.2%)	18 (58.1%)
Lung metastases present	155 (36.1%)	168 (39.7%)	15 (41.7%)	15 (48.4%)
Bone metastases present	246 (57.3%)	243 (57.4%)	27 (75.0%)	13 (41.9%)
Brain metastases present	19 (4.4%)	18 (4.3%)	19 (52.8%)	18 (58.1%)
Lymph node metastases present	184 (42.9%)	190 (44.9%)	16 (44.4%)	16 (51.6%)

Hormone Receptor Status				
Positive	295 (68.8%)	290 (68.6%)	25 (69.4%)	21 (67.7%)
Negative	133 (31.0%)	133 (31.4%)	11 (30.6%)	10 (32.3%)
Unknown	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Receptor Status				
TNBC	119 (27.7%)	117 (27.7%)	10 (27.8%)	8 (25.8%)
HER-2 Positive	30 (7.0%)	32 (7.6%)	4 (11.1%)	5 (16.1%)
Other	280 (65.3%)	274 (64.8%)	22 (61.1%)	18 (58.1%)
Prior Use of Eribulin				
Yes	71 (16.6%)	72 (17.0%)	7 (19.4%)	9 (29.0%)

Abbreviations: BCBM = breast cancer with history of brain metastases; HER2+ = positive for human epidermal growth factor receptor 2; ITT = intent to treat; TNBC = triple negative breast cancer TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer = eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q21d = once every 21 days.
a. All Onzeald doses were by intravenous infusion over a 90 ± 15 minute duration.

Table 20 - BCBM population- Summary of cancer history

Table 14.1.5.3
Summary of Cancer History for Patients with Brain Metastases
Intent-to-Treat Population

	NKTR-102 (N=36)	TPC (N=31)	Total (N=67)
Number of Sites of Disease			
0	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	2 (5.6%)	1 (3.2%)	3 (4.5%)
2	10 (27.8%)	6 (19.4%)	16 (23.9%)
3	5 (13.9%)	8 (25.8%)	13 (19.4%)
4	10 (27.8%)	7 (22.6%)	17 (25.4%)
5	6 (16.7%)	6 (19.4%)	12 (17.9%)
>=6	3 (8.3%)	3 (9.7%)	6 (9.0%)
Visceral Disease at Enrollment			
Present	30 (83.3%)	27 (87.1%)	57 (85.1%)
Absent	6 (16.7%)	4 (12.9%)	10 (14.9%)

Source Data: Listings 16.2.4.2 and 16.2.6.3.
Note: Percentages are based on the number of patients in the analysis subgroup of the Intent-to-Treat population.
[1] Initial disease-free interval is the duration between the initial diagnosis of breast cancer and the start date of first treatment in a locally recurrent or metastatic setting.
[2] Initial progression-free interval is the duration between the date of first dose and the date of progressive disease in the first systemic cancer treatment regimen for breast cancer in a locally recurrent or metastatic setting. If progression date is not reported, the earliest start date of the next regimen or the date of last scan prior to randomization is used.
[3] Visceral disease: tumor lesions (either target or non-target) located in the bladder, kidney, heart, spleen, adrenal gland, liver, lung, pancreas, esophagus, stomach, small intestine, colon, rectum, uterus, ovary, or thyroid.
[4] Receptor status data are based on the last pathology report.

Prior cancer therapies

Most patients had undergone multiple previous cancer treatments (median of 4 prior regimens) and were refractory to taxane and capecitabine (defined as disease progression while receiving therapy in the

metastatic setting within 8 weeks of last dose of the last regimen). Patients were typically not refractory to anthracyclines, as these were more commonly administered in the neoadjuvant/adjuvant setting.

Table 21 - Prior Cancer Therapies in ≥ 10% of Patients (Study 11-PIR-11: ITT Population)

Drug Class (ATC Level 2)/Preferred Term	BEACON ITT Population		BCBM ITT Population	
	Onzeald[a] 145 mg/m² q21d	TPC per Standard of Care	Onzeald[a] 145 mg/m² q21d	TPC per Standard of Care
	N = 429	N = 423	N = 36	N = 31
Number of Patients with at least one Prior Cancer Therapy	**429 (100.0%)**	**423 (100.0%)**	**36 (100.0%)**	**31 (100.0%)**
Antineoplastic agents	**429**	**423**	**36 (100.0%)**	**31 (100.0%)**
Capecitabine	429 (100.0%)	423 (100.0%)	36 (100.0%)	31 (100.0%)
Cyclophosphamide	383 (89.3%)	372 (87.9%)	29 (80.6%)	26 (83.9%)
Paclitaxel	326 (76.0%)	306 (72.3%)	25 (69.4%)	28 (90.3%)
Doxorubicin *	246 (57.3%)	263 (62.2%)	20 (55.6%)	23 (74.2%)
Docetaxel	247 (57.6%)	245 (57.9%)	19 (52.8%)	15 (48.4%)
Fluorouracil	164 (38.2%)	164 (38.8%)	12 (33.3%)	9 (29.0%)
Epirubicin *	146 (34.0%)	138 (32.6%)	12 (33.3%)	8 (25.8%)
Gemcitabine *	150 (35.0%)	116 (27.4%)	13 (36.1%)	11 (35.5%)
Vinorelbine *	107 (24.9%)	124 (29.3%)	11 (30.6%)	11 (35.5%)
Bevacizumab	92 (21.4%)	96 (22.7%)	7 (19.4%)	11 (35.5%)
Carboplatin	94 (21.9%)	80 (18.9%)	9 (25.0%)	6 (19.4%)
Eribulin *	71 (16.6%)	72 (17.0%)	7 (19.4%)	9 (29.0%)
Methotrexate *	49 (11.4%)	47 (11.1%)	4 (11.1%)	3 (9.7%)
Trastuzumab	45 (10.5%)	42 (9.9%)	6 (16.7%)	5 (16.1%)
Liposomal doxorubicin hydrochloride *	43 (10.0%)	36 (8.5%)	5 (13.9%)	2 (6.5%)
Endocrine therapy	**303 (70.6%)**	**305 (72.1%)**	**25 (69.4%)**	**19 (61.3%)**
Tamoxifen *	227 (52.9%)	232 (54.8%)	22 (61.1%)	13 (41.9%)
Letrozole	148 (34.5%)	152 (35.9%)	10 (27.8%)	7 (22.6%)
Exemestane	147 (34.3%)	133 (31.4%)	14 (38.9%)	8 (25.8%)
Anastrozole	139 (32.4%)	130 (30.7%)	10 (27.8%)	5 (16.1%)
Fulvestrant	118 (27.5%)	119 (28.1%)	6 (16.7%)	9 (29.0%)
Goserelin *	47 (11.0%)	42 (9.9%)	7 (19.4%)	4 (12.9%)

Abbreviations: BCBM = breast cancer with history of brain metastases; ITT = intent to treat; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer = eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q21d = once every 21 days.
*Drug names have been combined
a. All Onzeald doses were by intravenous infusion over a 90 ± 15 minute duration

Table 22 - Prior Local, CNS-directed Therapies in BCBM Patients with (i) History of Brain Metastases, (ii) with Radiographic Evidence of Brain Metastases at Screening, and (iii) without Radiographic Evidence of Brain Metastases at Screening Study 11-PIR-11 (BEACON)

Prior Therapies [a]	BCBM ITT Population		BCBM *with* Evidence of BM at Screening		BCBM *without* Evidence of BM at Screening	
	Onzeald	TPC	Onzeald	TPC	Onzeald	TPC
Total Number of Patients	N = 36	N = 31	N = 19	N = 18	N = 17	N = 13
Patients with Prior Resection of CNS Lesions	6 (16.7%)	5 (16.1%)	3 (15.8%)	0 (0.0%)	3 (17.6%)	5 (38.5%)
Patients with Prior radiotherapy to CNS Lesions	33 (91.7%)	26 (83.9%)	18 (94.7%)	15 (83.3%)	15 (88.2%)	11 (84.6%)

Abbreviations: BCBM = breast cancer with history of brain metastases; CNS -= central nervous system; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel).

a. Patients may have received multi-modality therapy, including surgery and/or radiotherapy.

Numbers analysed

Table 23 - Analysis Populations and Numbers Analysed (BEACON/11-PIR-11)

Analysis population	Description	Number of patients			
		Overall study N=852		BCBM subgroup N=67	
		Etirino-tecan	TPC	Etirino-tecan	TPC
Intent-to-Treat (ITT) population	All patients who were randomised into one of the two treatment arms. The primary endpoint of OS and secondary efficacy analyses (except ORR, CBR*, and DoR) utilised the ITT population. Patients were analysed by the treatment arm to which they were randomised.	429	423	36	31
Efficacy Evaluable (EE) population	The EE population included patients who were randomised in the study with measurable disease by RECIST at baseline (as determined by the Investigator) and was used to evaluate disease response. The secondary endpoint analyses of ORR, CBR*, and DoR were conducted using the Efficacy Evaluable Population. Patients were analysed by the treatment arm to which they were randomised.	354	358	32	27

Safety population	All patients who were randomised and received at least one dose (or partial dose) of study drug (Onzeald or TPC). Safety analyses were conducted using this population. Patients were analysed by the study drug (Onzeald or TPC) actually received, based on the first dose.	N=831		N=61	
		425	406	34	27

CBR= Clinical benefit rate: proportion of patients having a complete response, partial response or stable disease ≥ 6 months. DoR= duration of response, SD =stable disease. *CBR was planned to be analysed in both the EE and ITT populations.

Therapy received in TPC arm

Table 24 - Therapy Received in TPC arm in BCBM versus ITT Population

	TPC	
	BCBM (N=31)	ITT (N=423)
Therapy received in TPC		
Eribulin	8 (25.8%)	169 (40.0%)
Vinorelbine	7 (22.6%)	99 (23.4%)
Gemcitabine	9 (29.0%)	73 (17.3%)
nab-Paclitaxel	5 (16.1%)	34 (8.0%)
Paclitaxel	0	19 (4.5%)
Ixabepilone	1 (3.2%)	15 (3.5%)
Docetaxel	1 (3.2%)	14 (3.3%)

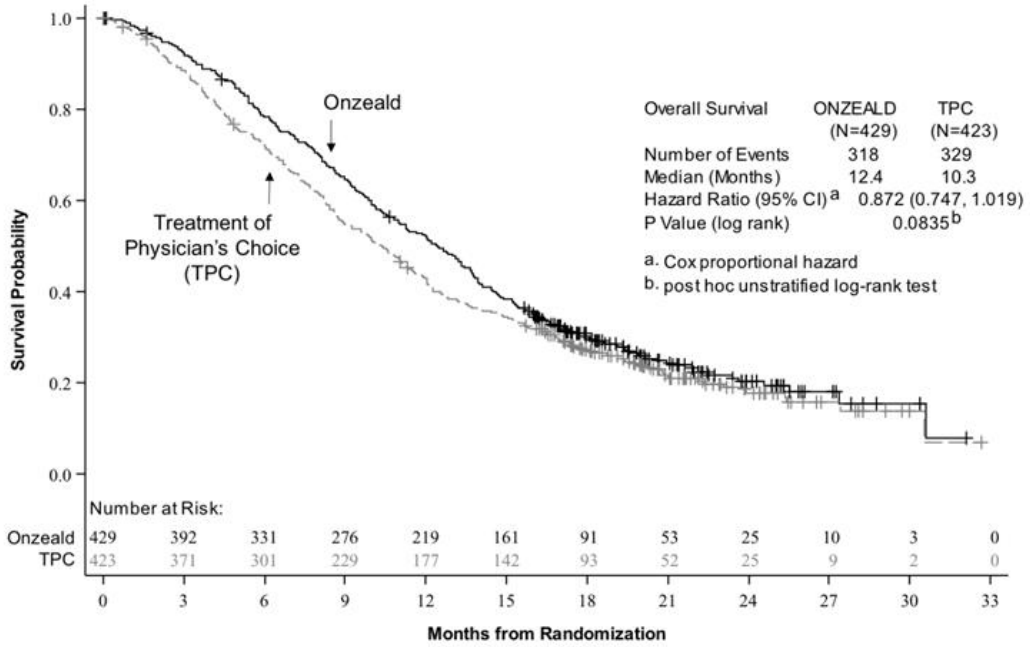
Source: Study 11-PIR-11 CSR Addendum, Table 14.4.10.2

Outcomes and estimation

As the subgroup of patients with history of brain metastases (denoted BCBM) is the study (sub)population of main interest for the sought indication, it is presented together with the ITT results. Other subgroup results are presented below.

Primary endpoint – Overall survival

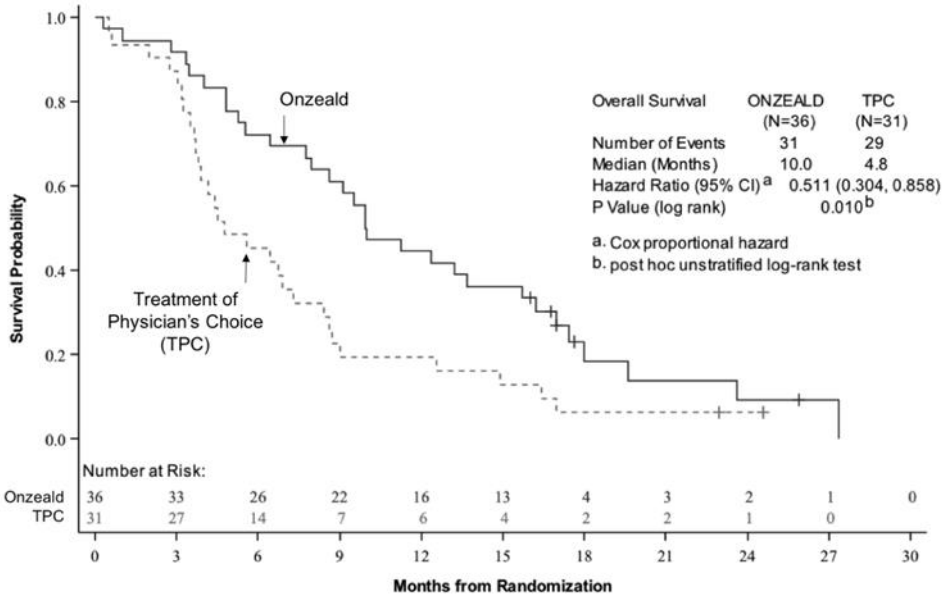
Figure 6 - Kaplan-Meier Plot of Overall Survival in the Full study population of Study 11-PIR-11



The median overall survival in the full study population was 2.1 months longer in the etirinotecan arm compared with the TPC arm (12.4 vs 10.3 months), with HR 0.87 (95% CI: 0.75-1.02), however not statistically significant (p=0.08).

History of Brain Metastases Subgroup (BCBM)

Figure 7 - Kaplan-Meier Plot of Overall Survival in the BCBM subgroup population of Study 11-PIR-11



In the BCBM subgroup, the median OS was 5.2 months longer in the etirinotecan arm compared with the TPC arm (10.0 vs 4.8 months), with HR 0.51 (95% CI: 0.30- 0.86), and statistically significant (p=0.01).

The separation of the OS curves comes early in both populations, at around 3 months.

BCBM “per protocol” analysis

A “per protocol” (PP) analysis in the BCBM subgroup was requested where only patients who received at least one dose of study drug were included, and where patients ineligible with regard to major inclusion criteria were excluded (n= 30 Onzeald, n=26 TPC). This showed a similar and nominally statistical significant OS HR as in the full BCBM subgroup. (PP HR 0.53, 95%CI: 0.30, 0.93; p = 0.028; overall BCBM population HR = 0.51, 95%CI: 0.30, 0.86; p = 0.010.)

Full study population (ITT)		
	Etirinotecan	**TPC**
Overall Survival (Months)		
N	429	423
Number of Deaths (%)	318 (74.1)	329 (77.8)
Number of Censored (%)	111 (25.9)	94 (22.2)
Median	12.4	10.3
95% CI of Median	11.0, 13.6	9.0, 11.3
Q1, Q3	6.8, 20.6	5.5, 19.4
Overall Survival Proportion at 6 months (%)	78.3	72.1
95% CI for Overall Survival Proportion at 6 months	74.0, 81.9	67.5, 76.1
Overall Survival Proportion at 12 months (%)	52.0	42.8
95% CI for Overall Survival Proportion at 12 months	47.1, 56.7	38.0, 47.5
P-value [1]	0.0835	
Hazard Ratio [2]	0.872	
95% CI for Hazard Ratio [2]	0.747, 1.019	
P-value [2]	0.0841	
History of brain metastases subpopulation (BCBM, ITT)		
Overall Survival (Months)		
N	36	31
Number of Deaths (%)	31 (86.1)	29 (93.5)
Number of Censored (%)	5 (13.9)	2 (6.5)
Median	10.0	4.8
95% CI of Median	7.8, 15.7	3.7, 7.3
Q1, Q3	5.4, 17.4	3.5, 8.7
Overall Survival Proportion at 6 months (%)	72.2	45.2
95% CI for Overall Survival Proportion at 6 months	54.5, 84.0	27.4, 61.4
Overall Survival Proportion at 12 months (%)	44.4	19.4
95% CI for Overall Survival Proportion at 12 months	28.0, 59.6	7.9, 34.6

P-value [1]	0.010
Hazard Ratio [2]	0.511
95% CI for Hazard Ratio [2]	0.304, 0.858
P-value [2]	0.011

Table 25 - Overall survival in the ITT and BCBM subpopulation (Study 11-PIR-11)

Overall survival was defined as the time from the date of randomization to death from any cause on or before the event cut-off date on 08 Dec 2014. Patients who were lost-to-follow-up or alive at the time of analysis were censored at the time they were last known alive, or the event cut-off date, whichever was earlier. Median, 95% CI of median, Q1, Q3, and survival proportion at 6 and 12 months are estimated using the Kaplan-Meier method.

[1] P-value was calculated based on a log-rank test stratified by geographic region, prior use of eribulin, and receptor status as randomized.

[2] Based on Cox proportional hazards model stratified by geographic region, prior use of eribulin, and receptor status as randomized.

Secondary endpoints

Table 26 - Summary of Secondary Efficacy Results in full Study Population and BCBM Subgroup (Study 11-PIR-11)

Secondary Endpoint	Full study population		BCBM subgroup	
	Onzeald N = 429	TPC N = 423	Onzeald N = 36	TPC N = 31
Progression-free Survival (ITT Population)			***Post-hoc analysis***	
Number of PD or Deaths (%)	369 (86.0)	350 (82.7)	32 (88.9%)	25 (80.6%)
Number of Censored (%)	60 (14.0)	73 (17.3)	4 (11.1%)	6 (19.4%)
Median (months)	2.4	2.8	3.1	2.7
95% CI of Median (months)	2.1, 3.5	2.1, 3.5	1.8, 4.0	1.8, 3.7
Q1, Q3	1.8, 5.7	1.8, 5.6	1.7, 7.2	1.5, 4.2
Progression-free Survival Proportion at 3 months (%)	48.5	48.3	50.1	50.0
95% CI for Progression-Free Proportion at 3 months (%)	43.6, 53.3	43.2, 53.2	32.5, 65.3	30.6, 66.6
Progression-Free Survival Proportion at 6 months (%)	23.4	21.8	28.6	19.5
95% CI for Progression-Free Proportion at 6 months (%)	19.3, 27.7	17.7, 26.3	14.5, 44.3	7.2, 36.1
Hazard ratio (95% CI) [a]	0.93 (0.80-1.08)		0.840 (0.492, 1.433)	
p-value [b]	0.302		0.523	
Response (Efficacy Evaluable Population)			***Post-hoc analysis***	
N	354	358	32	27
Objective Response Rate per RECIST (CR + PR)	58 (16.4%)	61 (17.0%)	5 (15.6%)	1 (3.7%)
Complete Response (CR)	2 (0.6%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Partial Response (PR)	56 (15.8%)	60 (16.8%)	5 (15.6%)	1 (3.7%)

Secondary Endpoint	Full study population		BCBM subgroup	
	Onzeald N = 429	TPC N = 423	Onzeald N = 36	TPC N = 31
95% CI for Objective Response Rate [c]	12.7%, 20.7%	13.3%,	5.3%, 32.8%	0.1%, 19.0%
Stable Disease (SD)	114 (32.2%)	107 (29.9%)	9 (28.1%)	9 (33.3%)
Progressive Disease (PD)	157 (44.4%)	144 (40.2%)	14 (43.8%)	9 (33.3%)
Not Evaluable (NE)	25 (7.1%)	46 (12.8%)	4 (12.5%)	8 (29.6%)
Duration of Response (Efficacy Evaluable Population)			***Post-hoc analysis***	
N	58	61	5	1
Number of PD or Deaths (%)	49 (84.5)	54 (88.5)	4 (80.0%)	1 (100.0%)
Number of Censored (%)	9 (15.5)	7 (11.5)	1 (20.0%)	0 (0.0%)
Median (months)	3.9	3.7	5.6	3.7
95% CI of Median (months)	3.5, 5.1	2.1, 3.9	1.9, 10.7	NE, NE
p-value [d]	0.272		0.247	
Clinical Benefit Rate (CR+PR+SD ≥6 months)				
Clinical Benefit Rate	88 (20.5%)	83 (19.6%)	NR	NR
95% CI [c]	16.8%, 24.6%	15.9%,	NR	NR
p-value [e]	0.727		NR	

Abbreviations: CR = complete response; ITT = intent to treat; NR = not reported; ORR = objective response rate, PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer = eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab paclitaxel).

a. Based on Cox proportional hazards model stratified by geographic region, prior use of eribulin, and receptor status as randomised.

b. Based on a log-rank test stratified by geographic region, prior use of eribulin, and receptor status as randomised.

c. Clopper-Pearson exact 2-sided 95% confidence limits were calculated for the proportion.

d. Based on an unstratified log-rank test.

e. P-value for CBR is calculated using a Cochran Mantel-Haenszel test stratified by the randomisation factors.

The PFS analysis was made at a mature stage with event rates over 80% in both arms in both populations (Full/ITT and BCBM).

In-brain activity

The ORR results presented above related to the overall result in all disease sites, while the intracranial ORR of etirinotecan on current brain metastases could not be evaluated.

Health-related Quality of Life (HRQoL) results

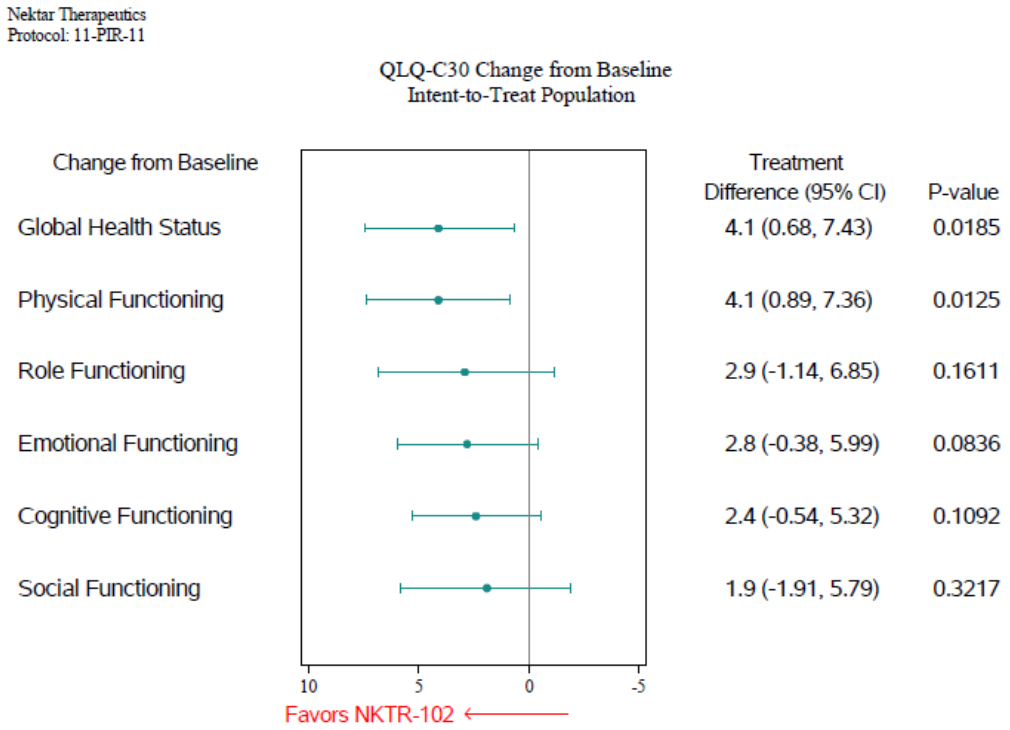
Patients were asked to complete a self-assessment HRQoL questionnaire at Screening, Cycle 1 (or baseline at the start of the study treatment), and prior to tumour measurements every eight weeks (± 7 days) during study drug treatment starting at Cycle 1, and at the End-of-Treatment visit. The EORTC QLQ-C30 (version 3.0) supplemented by the breast cancer module (QLQ-BR23) was used to measure the quality of life and assess the symptoms and side effects of treatment and their effects on everyday life.

The QLQ-C30 instrument was composed of five multi-item functional scales (physical, role, social, emotional, and cognitive functioning), a global health status/quality of life (QoL) scale, three symptom scales (fatigue, nausea/vomiting, and pain), and six single items (financial impact, appetite loss, diarrhoea, constipation, sleep disturbance, and dyspnoea).

The breast cancer module (QLQ-BR23) incorporated five multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image, and sexual functioning; and three single items to assess sexual enjoyment, hair loss, and future perspective.

The majority of the ITT population (NKTR-102/etirinotecan pegol: 88.1%, TPC: 83.9%) completed at least one post-baseline HRQoL questionnaire (either QLQ-C30 or QLQ-BR23). The compliance for completion of questionnaires at each visit during the treatment period was similar between treatment arms. Because the number of patients that completed the HRQoL questionnaires decreased to below 10% of the population beyond 32 weeks, meaningful HRQoL analyses were not reliable after Week 32.

Patient-reported outcomes in the global health status and the five functioning domains (physical, role, emotional, cognitive and social) of the QLQ-C30 deteriorated in both treatment arms over time. Up to Week 32, the deterioration was more profound in the TPC arm than in the etirinotecan arm.



Treatment differences were estimated using a mixed-effects model repeated measures (MMRM) in mean change from baseline over 32 weeks, with treatment group, visit, and treatment group-by-visit interaction, geographic region, prior use of eribulin, and receptor status as fixed effects, and baseline value as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. A positive difference represents an improvement of functioning or global health status, and worsening of symptoms. NKTR-102 = etirinotecan pegol.

Figure 8 - Health-related Quality of Life – EORTC QLQ-C30 (Study 11-PIR-11)

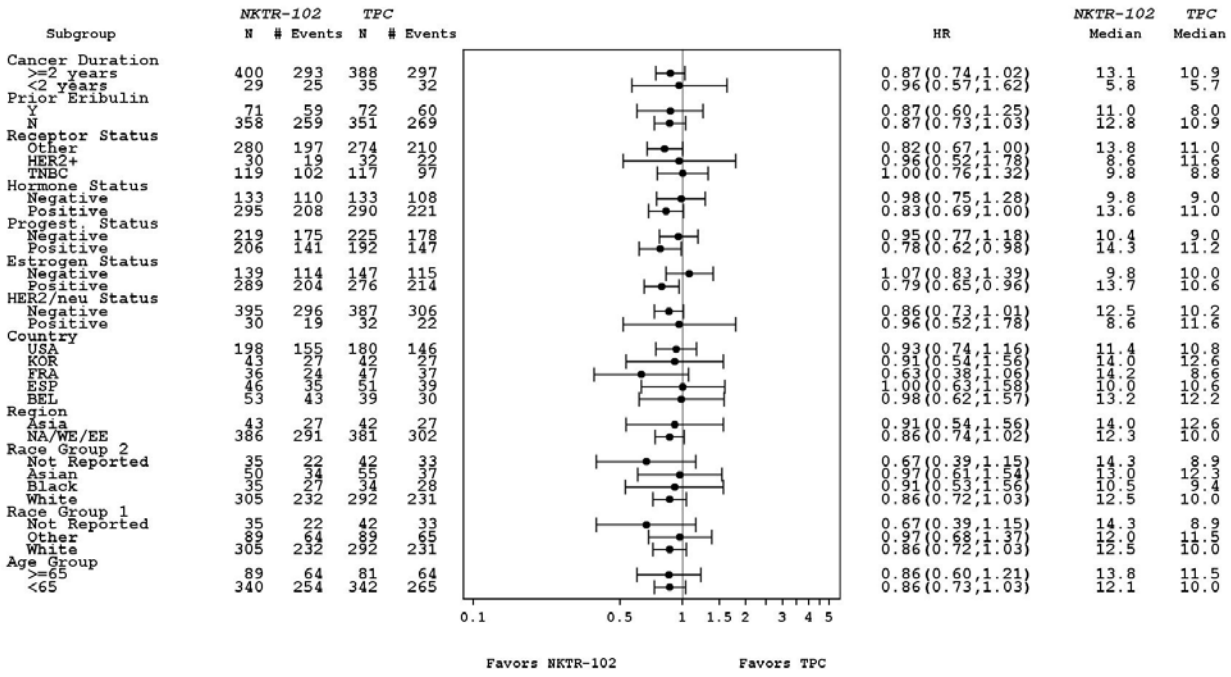
Symptom scales

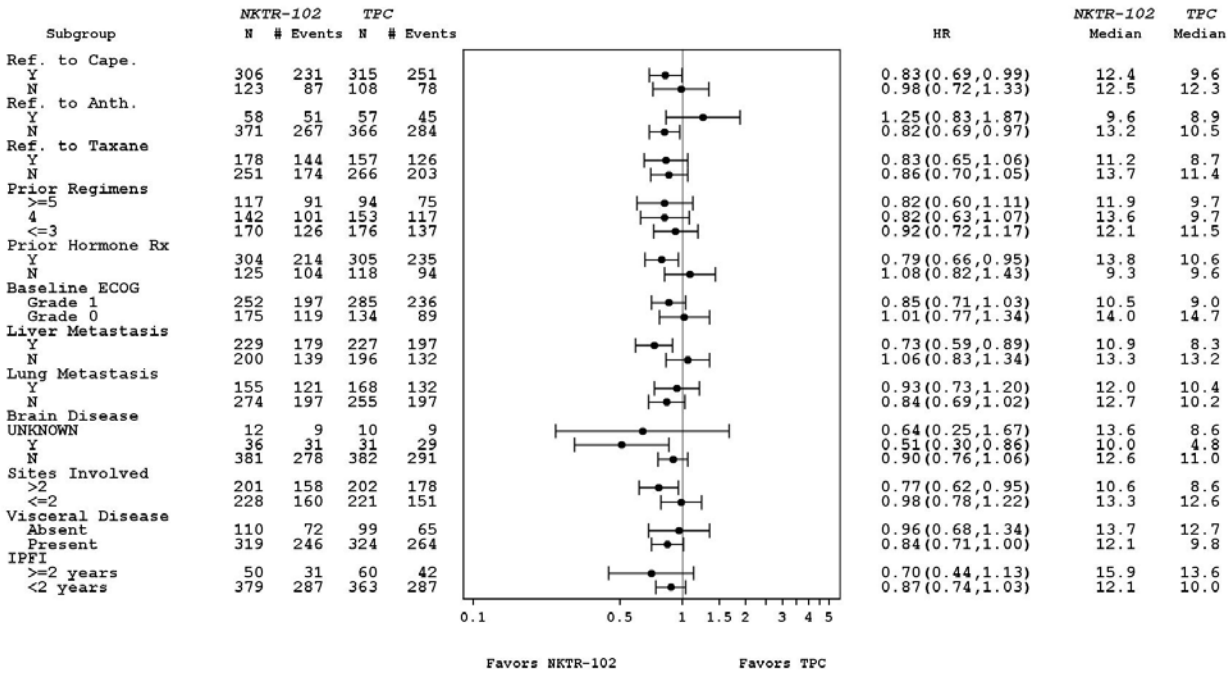
The minimal important difference (MID, ≥ 5 points) analysis of the 10 symptom scales that were collected (QLQ C-30: dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties; BR-23: arm, breast, hair loss, and systematic therapy) showed significant differences ($p < 0.05$) between the etirinotecan pegol and TPC arms on the following symptom domains: worse symptoms for etirinotecan pegol included diarrhoea (13.5% in etirinotecan pegol and 4.9% in TPC); nausea and vomiting symptoms (worsened: 18.3% in etirinotecan pegol and 8.5% in TPC); and appetite loss (worsened: 18.0% in etirinotecan pegol and 11.6% in TPC). The TPC treatment arm showed worse symptoms in dyspnoea, where a higher proportion of patients in the etirinotecan pegol arm had improved (13.5% in etirinotecan

pegol and 7.9% in TPC) and a higher proportion of patients in the TPC treatment arm had worsened (7.9% in etirinotecan pegol and 11.2% in TPC); and systemic therapy side effects (worsened: 13.9% in etirinotecan pegol and 23.1% in TPC).

In the statistical analysis plan, no hypothesis was specified and no attempt to control the type-1 error was made.

OS subgroup analyses





Abbreviations: ECOG = Eastern Cooperative Oncology Group (Performance Status); HER2 = human epidermal growth factor receptor 2; IPFI = initial progression-free interval; TNBC = triple negative breast cancer; TPC = treatment of physician's choice. Horizontal lines represent confidence intervals.

Figure 9 - Forest Plot of Hazard Ratios for Overall Survival Assessed by Subgroup Factors Date of Data-cut-off: 23 Feb 2015 (Study 11-PIR-11, ITT)

OS in patients with prior eribulin treatment

The OS HR point estimate was the same in the subgroups of patients with and without prior eribulin, respectively (HR 0.87, n.s., in both, and also the same as the ITT HR 0.87).

In the subgroup of patients who had received prior eribulin treatment (n=143), the median OS was 11.0 vs 8.0 months (n.s.) for etirinotecan vs. TPC; compared with 12.8 vs 10.9 months in patients without prior eribulin (n=709)

OS by receptor status in BCBM vs ITT population

Table 27 - Summary of Overall Survival by Receptor Status: BCBM versus ITT Population (Study 11-PIR-11)

Receptor Status	BCBM		ITT	
	Onzeald [a] 145 mg/m² q21d, N = 36	TPC per Standard of Care, N = 31	Onzeald [a] 145 mg/m² q21d, N = 429	TPC per Standard of Care, N = 423
TNBC				
N	10 (27.8%)	8 (25.8%)	119 (27.7%)	117 (27.7%)
Median OS (months)	6.7	3.8	9.4	8.7
HR (95% CI)	0.27 (0.09-0.81)		1.00 (0.76-1.32)	
HER2-positive				
N	4 (11.1%)	5 (16.1%)	30 (7.0%)	32 (7.6%)
Median OS (months)	16.1	8.6	8.6	11.2
HR (95% CI)	0.55 (0.10-3.03)		0.96 (0.52-1.78)	
Other				
N	22 (61.1%)	18 (58.1%)	280 (65.3%)	274 (64.8%)
Median OS (months)	12.2	5.2	13.7	10.6
HR (95% CI)	0.47 (0.24-0.93)		0.82 (0.67-1.00)	

Abbreviations: BCBM = breast cancer with history of brain metastases; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; ITT: intent-to-treat; OS = overall survival; TNBC: triple negative breast cancer; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer = eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q21d = once every 21 days.

a. All Onzeald doses were by intravenous infusion over a 90 ± 15 minute duration.
b. Cox regression with treatment effect (overall survival) and baseline disease parameter

OS subgroup analyses within the BCBM population

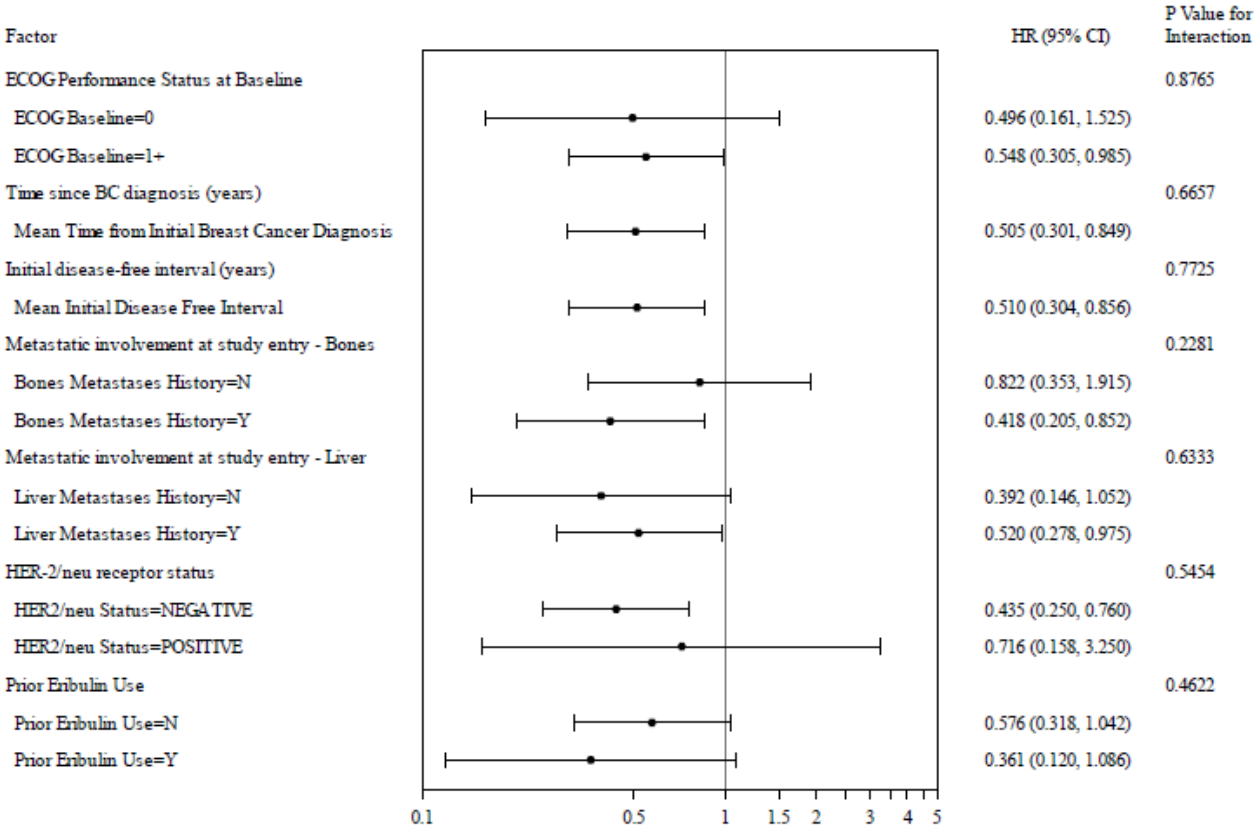
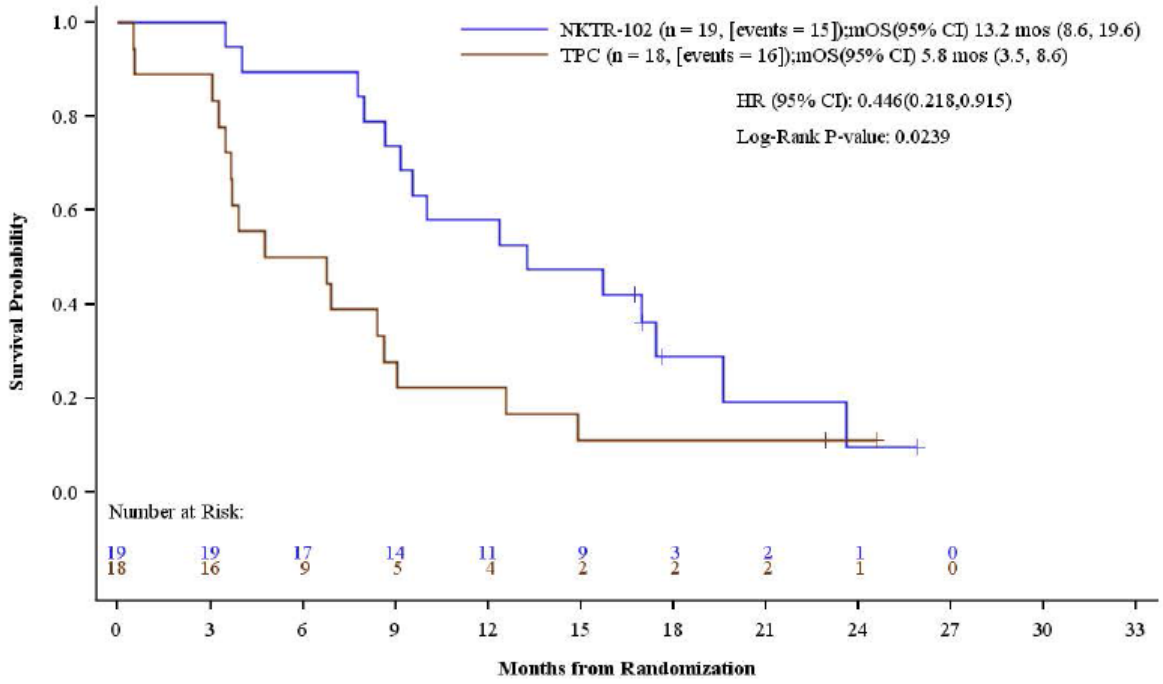


Figure 10 - Forest Plot of Hazard Ratios for Overal Survival subgroup in the BCBM population

Patients with detectable remaining brain lesion at study entry

In the subgroup with imaging detectable remaining brain metastasis (following prior local therapy) at study entry (n=37), the OS HR was 0.446 (95% CI: 0.218; 0.915), p = 0.024, with median OS 13.2 months (95% CI: 8.6; 19.6) vs. 5.8 months (95% CI: 3.5, 8.6) for etirinotecan pegol vs. TPC.



Source: SR 11-PIR-11, Figure 7.3. (Date of Data-cut-off: 23 Feb 2015)

Figure 11 - Kaplan-Meier Plot for Overall Survival, ITT Population with Brain Metastases History and Brain Tumour at Entry

Impact of baseline differences in the History of Brain Metastases Subgroup

Table 28 - Effect of Prognostic Factor Differences Between Treatment Arms on the Overall Survival Analysis (BCBM Population) Study 11-PIR-11

Baseline Disease Parameter	Onzeald [a] N = 36	TPC N = 31	OS HR (95% CI)	Interaction p-value [b]
ECOG Performance Status at Baseline				
0	11 (30.6%)	5 (16.1%)	0.50 (0.16-1.53)	0.877
≥ 1	25 (69.4%)	26 (83.8%)	0.55 (0.31-0.99)	
Median Time Since Initial Breast Cancer Diagnosis (years)	4.4	5.2	0.51 (0.30-0.85)	0.666
Median Initial Disease-free Interval (years)	2.3	3.1	0.51 (0.30-0.86)	0.7725
Metastatic Involvement at Study Entry: Bones				
No	9 (25.0%)	18 (58.1%)	0.82 (0.35-1.92)	0.228
Yes	27 (75.0%)	13 (41.9%)	0.42 (0.21-0.85)	
Metastatic Involvement at Study Entry: Liver				
No	10 (27.8%)	13 (41.9%)	0.39 (0.15-1.05)	0.633
Yes	26 (72.2%)	18 (58.1%)	0.52 (0.28-0.98)	
HER-2/neu Receptor Status				
Positive	4 (11.1%)	5 (16.1%)	0.72 (0.16-3.25)	0.545
Negative	32 (88.9%)	26 (83.9%)	0.44 (0.25-0.76)	
Prior Eribulin Use				
No	29 (80.6%)	22 (71.0%)	0.58 (0.32-1.04)	0.462
Yes	7 (19.4%)	9 (29.0%)	0.36 (0.12-1.09)	

Abbreviations: BCBM = breast cancer with history of brain metastases; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer = eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q21d = once every 21 days.

a. All Onzeald doses were by intravenous infusion over a 90 ± 15 minute duration.

b. Cox regression with treatment effect (overall survival) and baseline disease parameter

OS in relation to tumour burden (target lesion size)

Table 29 - Overall Survival Analyses by Target Lesion Diameters at Screening (ITT Population) Study 11-PIR-11 (BEACON)

Overall Survival (Months)	Target Lesion Diameters at Screening							
	≤33.5mm		>33.5 and ≤51.5mm		>51.5mm and ≤80.0mm		>80.0mm	
	Onzeald	TPC	Onzeald	TPC	Onzeald	TPC	Onzeald	TPC
N in ITT population	84	94	83	95	93	88	94	81

n in BCM population	7	7	6	7	7	5	12	8
Number of Death (%)	61	70	64	72	68	72	79	74
Number of Censored (%)	23	24	19	23	25	16	15	7 (8.6%)
Median	13.3	12.6	11.0	10.8	12.6	10.9	10.2	6.9
95% CI of Median	12.0,	10.0,	8.1, 13.8	8.4, 13.7	9.4, 14.7	8.2, 12.2	8.0, 12.4	5.0, 8.1
Q1, Q3	9.1,	7.4,	6.4, 19.4	5.1, 19.6	7.2, 19.6	4.7, 16.4	5.4, 16.5	3.4, 10.3
Overall Survival Proportion at 6 months (%) [a]	84.5%	82.6%	77.9%	71.6%	80.0%	70.5%	69.1%	56.3%
95% CI for Overall Survival Proportion at 6 months	74.8%, 90.7%	73.2%, 89.0%	67.3%, 85.5%	61.4%, 79.5%	70.2%, 86.9%	59.7%, 78.8%	58.7%, 77.4%	44.8%, 66.3%
Overall Survival Proportion at 12 months (%)	60.7%	53.3%	45.8%	47.3%	52.2%	43.1%	41.5%	20.0%
95% CI for Overall Survival Proportion at 12 months	49.4%, 70.2%	42.6%, 62.8%	34.7%, 56.2%	37.0%, 56.9%	41.4%, 61.9%	32.6%, 53.1%	31.5%, 51.2%	12.1%, 29.4%
P-value [b]	0.957		0.721		0.093		0.003	
Hazard Ratio [c]	0.99		1.06		0.75		0.62	
95% CI for Hazard Ratio [c]	0.70, 1.40		0.76, 1.49		0.54, 1.05		0.45, 0.85	
P-value [c]	0.957		0.720		0.095		0.003	

Abbreviations: TPC = Treatment of Physician's Choice; CI = Confidence Interval.

a. Overall survival is defined as the time from the date of randomisation to death from any cause on or before the event cut-off date on 08DEC2014. Patients who are lost-to-follow-up or alive at the time of analysis will be censored at the time they were last known alive or the event cut-off date, whichever is earlier.

b. P-value is calculated based on a log-rank test without stratification.

c. Based on a Cox proportional hazards model without stratification

OS in relation to P-glycoprotein 1 (Pgp) substrate status

Table 30 - Overall Survival Analyses by Pgp substrate status

	BEACON ITT Population		**BCBM Population**	
	Onzeald (N = 429)	**TPC [a] (N = 301)**	**Onzeald (N = 36)**	**TPC [a] (N = 16)**
Onzeald versus Eribulin, Vinorelbine, Paclitaxel and Docetaxel (Pgp substrates)				
Number of Deaths (%)	318 (74.1%)	226 (75.1%)	31 (86.1%)	16 (100.0%)
Number Censored (%)	111 (25.9%)	75 (24.9%)	5 (13.9%)	0 (0.0%)
Median Overall Survival (months)	12.4	11.1	10.0	4.3
Overall Survival Proportion at 6 months (%)	78.3%	74.8%	72.2%	37.5%
Overall Survival Proportion at 12 months (%)	52.0%	46.1%	44.4%	12.5%
P-value [b]	0.506		0.0004	
Hazard Ratio [c]	0.94		0.33	
95% CI for Hazard Ratio [b]	0.80, 1.12		0.17, 0.63	
P-value [b]	0.506		0.0008	
Onzeald versus Ixabepilone, Gemcitabine and Nab-paclitaxel (non-Pgp substrates)				

	BEACON ITT Population		BCBM Population	
	Onzeald (N = 429)	TPC [a] (N = 301)	Onzeald (N = 36)	TPC [a] (N = 16)
Number of Deaths (%)	318 (74.1%)	103 (84.4%)	31 (86.1%)	13 (86.7%)
Number Censored (%)	111 (25.9%)	19 (15.6%)	5 (13.9%)	2 (13.3%)
Median Overall Survival (months)	12.4	8.3	10.0	6.9
Overall Survival Proportion at 6 months (%)	78.3%	65.3%	72.2%	53.3%
Overall Survival Proportion at 12 months (%)	52.0%	34.7%	44.4%	26.7%
P-value [b]	0.001		0.268	
Hazard Ratio [c]	0.69		0.69	
95% CI for Hazard Ratio [b]	0.55, 0.86		0.36, 1.33	
P-value [b]	0.0009		0.2670	

Abbreviations: CI = confidence interval; ITT = intent to treat; TPC = Treatment of Physician's Choice.

a. Eribulin, vinorelbine, paclitaxel, and docetaxel.

b. P-value is calculated based on a log-rank test without stratification.

c. Based on a Cox proportional hazards model without stratification.

PD in brain by baseline imaging status

The BEACON study protocol required CT or MRI imaging of the head only if the patient has focal neurological signs.

Table 31 - PD in brain by baseline imaging status

	BEACON ITT Population	
	Onzeald[a] 145 mg/m² q21d	TPC per Standard of Care
	N = 429	N = 423
Total Number of Patients Who Had Baseline Brain Imaging	**27**	**23**
Positive for Brain Metastases	19/27 (70.4%)	18/23 (78.3%)
PD in brain as PD site*	0/19 (0.0%)	0/18 (0.0%)
Negative for Brain Metastases	8/27 (29.6%)	5/23 (21.7%)
PD in brain as PD site*	1/8 (12.5%)	0/5 (0.0%)
Time to Event (Days)	51	N/A
Total Number of Patients Who Did Not Have Baseline Brain Imaging	**402**	**400**
PD in brain as PD site*	19/402 (4.7%)	21/400 (5.3%)
Time to Event [days]	57 (range: 3 - 408)	63 (range: 1 – 287)

Abbreviations: BCBM = breast cancer with brain metastases; ITT = intent to treat; N/A = not applicable; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer = eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab paclitaxel).* PD in brain as PD site counted those patients with PD as regular PFS event, and also had PD at brain site on the same day.

Table 32 - OS comparisons in randomised pairs in the ITT and BCBM populations

TPC Drug	ITT				BCBM			
	Median OS (95%CI) [months]		Difference in Median OS [months]	OS Hazard Ratio (95%CI) p-value	Median OS (95%CI) [months]	Median OS Difference [months]	Difference in Median Overall Survival [months]	OS Hazard Ratio (95%CI) p-value
	Onzeald	TPC			Onzeald	TPC		
Overall TPC	12.4 (11.0, 13.6) N = 429; E = 318	10.3 (9.0, 11.3) N = 423; E = 329	2.1	0.87 (0.75, 1.02)	10.0 N= 36	4.8 N= 31	5.2	0.51 (0.30, 0.86) p = 0.0099
Eribulin	11.4 (10.1, 13.7) N = 162; E = 122	10.6 (9.0, 11.9) N = 169; E = 131	0.8	0.92 (0.72, 1.18)	10.0 N =13	6.0 N = 8	4.0	0.18 (0.05, 0.60) p = 0.016
Vinorelbine	13.7 (11.3, 16.1) N = 122; E = 84	12.2 (8.9, 15.4) N = 99; E = 70	1.5	0.89 (0.65, 1.22)	16.2 N = 11	3.2 N = 7	13.0	0.15 (0.04, 0.49) p = 0.002
Gemcitabine	10.4 (8.1, 12.1) N = 67; E = 53	8.4 (6.9, 11.1) N = 73; E = 58	2.0	0.87 (0.60, 1.26)	10.0 N = 7	8.6 N = 9	1.4	0.66 (0.21, 2.09) p = 0.48
Nab-Paclitaxel	10.0 (5.5, 13.8) N = 29; E = 22	8.7 (6.0, 11.2) N = 34; E = 30	1.3	0.73 (0.42, 1.28)				
Paclitaxel	15.0 (10.2, 22.5) N = 22; E = 16	12.1 (6.4, 18.7) N = 19; E = 15	2.9	0.64 (0.31, 1.32)				
Docetaxel	15.3 (2.9, 16.2) N = 10; E = 7	16.4 (3.2, 20.3) N = 14; E = 10	-1.1	1.41 (0.52, 3.79)				
Taxanes (paclitaxel, docetaxel, and nab-paclitaxel)	13.2 (9.9, 15.3) N = 61; E = 45	10.6 (7.4, 12.7) N = 67; E = 55	2.6	0.76 (0.51, 1.13)	3.4 N = 5	7.1 N = 6 (5 nab-paclitaxel, 1 docetaxel)	- 3.4	2.90 (0.76, 11.1) p = 0.121

CI = confidence interval, E= events, N= numbers, OS = overall survival.

Source: Applicant's response to Day 150 LoOI, Q 16 and 30, Tables 3.1-1, and 3.3-1.

Post-study cancer therapy in BCBM group

Table 33 - Post-study cancer therapy in BCBM subgroup (Study11-PIR-11)

	NKTR-102 (N=36)	TPC (N=31)	Total (N=67)
Post Cancer Therapy			
n	36	31	67
Mean (SD)	1.7 (1.56)	0.8 (1.01)	1.3 (1.40)
Median	1.0	0.0	1.0
Min, Max	0, 6	0, 3	0, 6
No post therapy	10 (27.8%)	16 (51.6%)	26 (38.8%)
1 Regimen	9 (25.0%)	8 (25.8%)	17 (25.4%)
2 Regimens	6 (16.7%)	4 (12.9%)	10 (14.9%)
3 Regimens	7 (19.4%)	3 (9.7%)	10 (14.9%)
4 Regimens	2 (5.6%)	0	2 (3.0%)
5+ Regimens	2 (5.6%)	0	2 (3.0%)
Number of Patients with at least one Follow-up Cancer Therapy	26 (72.2%)	15 (48.4%)	41 (61.2%)
ANTINEOPLASTIC AGENTS	25 (69.4%)	13 (41.9%)	38 (56.7%)
ERIBULIN *	15 (41.7%)	2 (6.5%)	17 (25.4%)
PACLITAXEL	8 (22.2%)	4 (12.9%)	12 (17.9%)
VINORELBINE *	9 (25.0%)	2 (6.5%)	11 (16.4%)
GEMCITABINE *	10 (27.8%)	0	10 (14.9%)
CYCLOPHOSPHAMIDE	5 (13.9%)	4 (12.9%)	9 (13.4%)
LIPOSOMAL DOXORUBICIN HYDROCHLORIDE *	4 (11.1%)	3 (9.7%)	7 (10.4%)
METHOTREXATE *	3 (8.3%)	3 (9.7%)	6 (9.0%)
EVEROLIMUS	1 (2.8%)	3 (9.7%)	4 (6.0%)
FLUOROURACIL	2 (5.6%)	2 (6.5%)	4 (6.0%)
CARBOPLATIN	3 (8.3%)	0	3 (4.5%)
CISPLATIN	3 (8.3%)	0	3 (4.5%)
IRINOTECAN	2 (5.6%)	0	2 (3.0%)
ENDOCRINE THERAPY	5 (13.9%)	6 (19.4%)	11 (16.4%)
EXEMESTANE	2 (5.6%)	3 (9.7%)	5 (7.5%)
FULVESTRANT	4 (11.1%)	1 (3.2%)	5 (7.5%)

Source: 11-PIR-11-table-figs, Table 14.4.1.10 and Table 14.4.1.8 (selected items; cut-off for anticancer agents at 5% frequency in any arm).

Table 34 -Eribulin use in BCBM subgroup

	Etirinotecan	TPC
Prior	19%	29%

On study	0%	26%
Post	42%	6%
Sum	**61%**	**60%**

Summary of main efficacy results

Table 35 - Summary of efficacy for trial 11-PIR-11 (BEACON)

Title: BEACON Study (BrEAst Cancer Outcomes with NKTR-102): A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 versus Treatment of Physician's Choice (TPC) in Patients with Locally Recurrent or Metastatic Breast Cancer Previously Treated with an Anthracycline, a Taxane, and Capecitabine		
Study identifier	Protocol Number: 11-PIR-11 EudraCT identifier: 2011-003832-30 ClinicalTrials.gov identifier: NCT01492101	
Design	Open-label, randomized (1:1), parallel, two-arm, multicenter, international Phase 3 study in patients with locally recurrent or metastatic breast cancer that was previously treated with at least two and a maximum of five cytotoxic chemotherapy regimens that included an anthracycline, a taxane, and capecitabine (all branded or generic). Patients continued to receive study treatment until progression of disease, unacceptable toxicity, patient withdrawal of consent, Investigator decision, lost to follow-up, death, or patient non-compliance.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Overall study duration: 39 months (to data cutoff date) not applicable not applicable
Hypothesis	Superiority	
Treatments groups	ONZEALD	Onzeald (NKTR-102, etirinotecan pegol) 145 mg/m^2 by intravenous injection every 21 days (q21d) until progression of disease, unacceptable toxicity, patient withdrawal of consent, Investigator decision, lost to follow-up, death, or patient non-compliance 429 patients randomised
	TPC	Treatment of Physician's choice (TPC; per standard of care) until progression of disease, unacceptable toxicity, patient withdrawal of consent, Investigator decision, lost to follow-up, death, or patient non-compliance. TPC was selected from one of the following single-agent intravenous therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. 423 patients randomised

Endpoints and definitions	Primary endpoint	OS	Overall Survival (OS) was defined as the time from the date of randomization to death from any cause. Patients were followed until death, date of withdrawal of consent for survival follow-up, final database closure, or until the Sponsor terminated the study. Randomization date and date of death were recorded in the electronic case report form (eCRF) and used to calculate OS. The OS of patients who received Onzeald was compared with patients who received TPC.	
	Secondary endpoint	ORR	The Objective Response Rate (ORR) was defined as the proportion of patients with a complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumours (RECIST) based upon the best response as assessed by the Investigator. The ORR of the for the treatment group that received Onzeald was compared with that for the treatment group that received TPC (Efficacy Evaluable population).	
	Secondary endpoint	PFS	Progression-free Survival (PFS) was defined as the time from the date of randomization to the earliest evidence of documented PD or death from any cause. Disease progression was assessed by the Investigator according to RECIST. Scans were collected up to PD per RECIST or death. Progression was not assessed post-cessation of randomized therapy. The PFS for the treatment group that received Onzeald was compared with that for the treatment group that received TPC (Intent-to-Treat (ITT) population).	
Database lock	23 February 2015			
Results and Analysis				
Analysis description	Primary Analysis (OS), pre-defined			
Analysis population and time point description	Intent to treat; defined as all patients who were randomized into one of the two treatment arms (Onzeald or TPC). Time point: Time from the date of randomization to death from any cause.			
Descriptive statistics and estimate variability	Treatment group		Onzeald	TPC
	Number of subject		429	423
	OS (median)		12.4 months	10.3 months
	95%CI on OS		11.0, 13.6 months	9.0, 11.3 months
Effect estimate per comparison	Primary endpoint: OS		Comparison groups	Onzeald vs. TPC
			Hazard ratio	0.87
			95% CI	0.747, 1.019
			P-value	0.084
Analysis description	Secondary Analysis (PFS), pre-defined			
Analysis population and time point description	Intent to treat; defined as all patients who were randomized into one of the two treatment arms (Onzeald or TPC). Time point: Time from the date of randomization to the earliest evidence of documented PD or death from any cause.			
Descriptive statistics and	Treatment group		Onzeald	TPC
	Number of subject		429	423

estimate variability	PFS (median)	2.4 months	2.8 months
	95%CI on PFS	2.1, 3.5 months	2.1, 3.5 months
Effect estimate per comparison	Secondary endpoint: PFS	Comparison groups	Onzeald vs. TPC
		Hazard ratio	0.93
		95% CI	0.798, 1.075
		P-value	0.302
Analysis description	Secondary Analysis (ORR), pre-defined		
Analysis population and time point description	Efficacy Evaluable; defined as all patients who were randomized into one of the two treatment arms (Onzeald or TPC) and who had measurable disease at baseline.		
Descriptive statistics and estimate variability	Treatment group	Onzeald	TPC
	Number of subject	429	423
	ORR (% of Efficacy Evaluable Population with CR or PR)	16.4%	17.0%
	95%CI on ORR	12.7, 20.7%	13.3, 21.3%
Analysis description	Primary Analysis (OS) on subgroup of patients with baseline history of brain metastases (BCBM Population), pre-defined		
Analysis population and time point description	Intent to treat for BCBM Population; defined as all patients with baseline history of brain metastases and who were randomized into one of the two treatment arms (Onzeald or TPC). Time point: Time from the date of randomization to death from any cause.		
Descriptive statistics and estimate variability	Treatment group	Onzeald	TPC
	Number of subjects	36	31
	OS (median)	10.0 months	4.8 months
	95%CI on OS		
Effect estimate per comparison	Primary endpoint	Comparison groups	Onzeald vs. TPC
		Hazard ratio	0.51
		95% CI	0.304, 0.858
		P-value	0.010
Analysis description	Secondary Analysis (PFS), *post hoc*		
Analysis population and time point description	Intent to treat for BCBM Population; defined as all patients with baseline history of brain metastases and who were randomized into one of the two treatment arms (Onzeald or TPC). Time point: Time from the date of randomization to the earliest evidence of documented PD or death from any cause.		
Descriptive statistics and estimate variability	Treatment group	Onzeald	TPC
	Number of subject	36	31
	PFS (median)	3.1 months	2.7 months

	95%CI on PFS	1.8, 4.0 months	1.8, 3.7 months
Effect estimate per comparison	Secondary endpoint: PFS	Comparison groups	Onzeald vs. TPC
		Hazard ratio	0.84
		95% CI	0.49, 1.43
		P-value	0.523
Analysis description	Secondary Analysis (ORR), *post hoc*		
Analysis population and time point description	Efficacy Evaluable for BCBM Population; defined as all patients with baseline history of brain metastases, who were randomized into one of the two treatment arms (Onzeald or TPC), and who had measurable disease at baseline.		
Descriptive statistics and estimate variability	Treatment group	Onzeald	TPC
	Number of subject	32	27
	ORR (% of Efficacy Evaluable Population with CR or PR)	15.6%	3.7%
	95%CI on ORR	5.3, 32.8%	0.1, 19.0%

Clinical studies in special populations

Elderly

Table 36 - Numbers of Older Patients in the Studies of Etirinotecan Pegol at Recommended Dose

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	82/467 (17.6%)	15/467 (3.2%)	0/467 (0%)
Study 08-PIR-03	9/42	3/42	0/42
Study 11-PIR-11	73/425	12/425	0/425
Non Controlled trials	39/177 (22.0%)	9/177 (5.1%)	0/177 (0%)
Study 08-PIR-04	33/139	7/139	0/139
Study 08-PIR-05	5/35	2/35	0/35
Study 06-IN-IR001	1/3	0/3	0/3
Overall	121/644 (18.8%)	24/644 (3.7%)	0/644 (0%)

Note: Older subjects number by studies. Safety population patients who received Onzeald at the recommended dose and schedule (145 mg/m^2 q21d)

Asian patients

Higher median OS were observed for both arms in Asian patients compared with the full study population, in combination with a smaller difference between arms (HR 0.97).

Supportive studies

08-PIR-05 - Supportive Study in Patients with Metastatic Breast Cancer

Title: *A Multicenter, Open-label, Phase 2 Study to Evaluate the Safety and Efficacy of NKTR-102 (etirinotecan pegol) When Given on a Q14 Day or a Q21 Day Schedule in Patients with Metastatic Breast Cancer Whose Disease has Failed Prior Taxane-Based Treatment*

Design and Methods: In this open-label, multi-centre, randomised Phase 2 study, patients with metastatic breast cancer whose disease had failed prior taxane-based treatment in the adjuvant or the metastatic setting were randomly assigned (1:1) to one of two treatment schedules for Onzeald (145 mg/m² as a 90-minute IV infusion): q21d or q14d.

Eligibility: Adult patients with an ECOG performance status of 0–1 were eligible and patients must have had measurable disease per RECIST in at least one lesion not previously irradiated. The primary endpoint was ORR. Secondary endpoints included PFS and OS.

Adverse events were graded according to severity was based on the NCI-CTCAE version 3.0.

Baseline Data: Between February 2009 and October 2011, 70 patients were randomised to either Onzeald 145 mg/m² q21d (N = 35) or Onzeald 145 mg/m² q14d (N = 35). The median age (range) of the patients was 54.5 (33 to 83) years. The majority of the patients were white (64/70; 91.4%) and non-Hispanic (67/70; 95.7%).

A total of 28 patients (40.0%) had an ECOG performance status score of 0 at enrolment (q21d: 13/35 (37.1%), q14d: 15/35 (42.9%)). A total of 42 patients (60.0%) had an ECOG performance status of 1 at enrolment (q21d: 22/35 (62.9%), q14d: 20/35 (57.1%)).

The median times since the initial diagnosis to the first dose of Onzeald and from the primary diagnosis to metastatic disease were slightly shorter in the q14d schedule (4.0 and 1.5 years, respectively, for the q14d schedule and 5.4 and 2.0 years, respectively, for the q21d treatment schedule). Of the five HER-2 positive patients, three were randomised to the q14d schedule and two were randomised to the q21d schedule. There was a lower percentage of patients in the q14d schedule who had visceral disease as compared to the q21d schedule (80.0% and 91.4%). No other noticeable differences were observed between the two dose schedules.

Exposure: A total of 70 patients received at least one dose of either Onzeald (N = 35) or TPC (N = 35). Patients in each treatment arm completed a median of 6.0 cycles and had comparable relative median dose intensities (q21d: 94.4% vs q14d: 97.7%).

Efficacy Results: Ten (29%) patients on each schedule achieved an objective response (q14d: 95% CI: 14.6-46.3, 8 PRs, 2 complete responses; q21d: 95% CI: 14.6–46.3; all PRs). Median PFS was 3.3 months (2.6-5.7) for patients on the 14-day schedule, and 5.6 months (1.8-6.2) for patients on the 21-day schedule. Median OS was 8.8 months (5.4-15.0) for q14d; and 13.1 months (9·2-19·2) for q21d. Six-month OS was 57.1% (95% CI: 39.3-71.5) for patients on the q14d schedule and 82.9% (65.8-91.9) for patients on the q21d schedule. Twelve-month OS was 42.9% (95% CI: 26.4-58.3) for patients on the q14d schedule and 51.4% (34.0-66.4) for patients on the q21d schedule.

While ORR was the same across arms, the PFS and OS appeared to numerically favour the q21d schedule. The safety and efficacy results of this study informed the Phase 3 programme dose and schedule of Onzeald (145 mg/m² q21d).(See safety data in Clinical Safety, Details of supportive studies)

Study 24833 (Stanford University) - Supportive study

This was an Investigator initiated study conducted at Stanford University (Palo Alto, CA, US) to demonstrate the anti-tumour activity of etirinotecan pegol against intra-cranial lesions and further

support the ability of etirinotecan pegol to cross the brain-tumour barrier (BTB) in the intracranial region to effect clinically meaningful outcomes (Nagpal 2015).

Design and Methods: This was a *Phase II*, open-label, prospective, single-arm pilot study *of Single-agent Etirinotecan Pegol (NKTR-102) in Bevacizumab-Resistant High Grade Glioma*. Patients age >18 with histologically proven anaplastic astrocytoma or glioblastoma who previously received standard chemo-radiation and recurred after treatment with bevacizumab were eligible. A predicted life expectancy >6 weeks and KPS ≥ 50 were required. The primary endpoint was PFS at 6 weeks. The secondary endpoint was OS from first Onzeald infusion. Response was assessed by Response Assessment in Neuro-Oncology (RANO) criteria. Single agent Onzeald was administered by IV infusion q21d at a dose of 145 mg/m2. Patients did not receive bevacizumab during treatment with Onzeald.

Baseline Data and Efficacy Results: A total of 20 patients were enrolled with a median age of 50 years and a median KPS of 70. Out of 20, 18 patients (90%) were diagnosed with glioblastoma multiform. The median time from diagnosis of HGG to trial enrolment was 12.5 months. The median progression free interval on bevacizumab was 4.8 months. All 20 participants had undergone maximally feasible resection, standard chemo-radiation or stereotactic radiosurgery concurrent with chemotherapy (temozolomide). Patients received a median of 3 doses of Onzeald (range 1-22).

Three of the 18 (17%) with glioblastoma multiform had a partial response by imaging, with two responses lasting for ≥ 19 months. 5 more patients had SD at their first and second MRI scans, bringing total clinical benefit rate (PR +SD) to 44%. Progression-free survival at 6 weeks was 55%. Median PFS was 2.2 months (95% CI: 1.4-3.4 months); six-month PFS was 11.2 % (95% CI: 1.9-28.9 %). Median OS from first Onzeald infusion was 4.5 months (95% CI: 2.4-5.9).

Study NCT02312622 (Stanford University) – Supportive study

Design and Methods: This is an ongoing phase 2 Investigator-initiated Study at Stanford University in Patients with Brain Metastases of Lung or Breast Cancer.

This study is enrolling three cohorts of patients (male and female) who have metastatic brain lesions with the following malignancies:

- Cohort A - patients with advanced non-small-cell lung cancer (NSCLC)
- Cohort B - patients with advanced small-cell lung cancer (SCLC)
- Cohort C - patients with locally recurrent or metastatic breast cancer (MBC)

The primary objective of the study is to determine the CNS disease control rate (number of patients with stable disease (SD) or partial response (PR) or complete response (CR)/ total number of treated patients) at 12 weeks following treatment with Onzeald in patients with refractory brain metastases of advanced NSCLC (Cohort A) or breast cancer (Cohort C). Secondary objectives for Cohorts A and C included response rates, OS, and progression-free survival (PFS). Patients with SCLC (Cohort B) composed an exploratory, observational group.

Patients in this study must have received at least one line of prior systemic chemotherapy or targeted treatment for metastatic disease or had received prior adjudvant systemic chemotherapy within the 6 months prior to enrolment.

Results:

Enrolment at this single centre study initiated in February 2015 and is completed for the NSCLC (N = 12) and SCLC (N = 3) cohorts; enrolment is ongoing for the breast cancer cohort (N = 9 out of the planned

12). All patients enrolled to this study had active brain metastases that were progressing at the time of enrolment.

For the NSCLC cohort (N = 12 out of the planned 12), baseline demographics represent a heavily pre-treated population with median ECOG performance status of 2 and a median of 2.5 prior lines of chemotherapy (range 1-7). Two patients were receiving steroids at study entry (2 mg/day and 8 mg/day, respectively); all other patients were not receiving steroids. On-study steroid use was reviewed; no escalation in the daily steroid dose occurred that could confound the interpretation of the observed changes in CNS lesions. The median graded prognostic assessment (GPA) score, which incorporates four parameters (performance status, age, number of CNS lesions, and extra-cranial metastases), was 0.75 (range: 0-1.5).

For the three patients with SCLC, median ECOG performance status was 1 and these patients had received a median of 1 prior line of chemotherapy (range 1-3).

For the NSCLC cohort, patients received a median of 4 cycles of therapy (range 1-10). For the three SCLC patients, patients received 2, 3 and 4 cycles, respectively.

For patients in the NSCLC cohort, the in-brain objective response rate (ORR) was 25% (3/12) and the median PFS was 2.6 months (95%CI: 1.2, 2.8 months). For patients in the SCLC cohort, the ORR was 67% (2/3). For patients in the NSCLC cohort, the estimated median OS (with 10 events) was 7.0 months (95%CI: 1.3, 17.2 months) and the one-year survival was 33%. Two patients were censored on the Kaplan-Meier curve, with survival at the time of database cut-off greater than 18 months.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical study

The dose and schedule chosen for the pivotal phase 3 study was based on one Phase 1 study (Study 06-IN-IR001) arriving at the dose 145 mg/m2 on a q14d or q21d treatment schedule as recommended Phase 2 dose (RP2D). Due to the small number of patients with breast cancer (4/76, 5%) the study is not informative with regard to clinical efficacy in breast cancer. The tri-weekly schedule was subsequently chosen for phase 3 development based on the efficacy and safety results of the Phase 2 study 08-PIR-05, performed in patients with metastatic breast cancer comparing the two RP2D schedules. Similar ORR but longer PFS and OS were observed for the q21d schedule.

The dose in the product information refers to the irinotecan moiety of etirinotecan pegol without consideration of the pegylation and is therefore based on the weight of the irinotecan component of etirinotecan pegol, which constitutes approximately 10% of the whole pegylated complex. The potency of this medicinal product should not be compared to that of another pegylated or non pegylated medicinal product of the same therapeutic class.

The overall design of the pivotal Study 11-PIR-11 (BEACON) is considered acceptable. The patients were randomised 1:1 between etirinotecan pegol and Treatment of physician's choice (TPC), consisting of a choice of 7 single agent chemotherapies given according to label or standard of care. The subgroup of patients with a history of brain metastasis (BCBM) was pre-defined in a protocol amendment based on preclinical findings suggesting intracranial activity, and the fact that the recruitment of patients in this subgroup, which has traditionally been excluded from pivotal trials, was larger than anticipated. No stratification according to history of brain metastases was performed.

Regarding baseline characteristics in the BCBM population, the relevance of the imbalance with regard to Hispanic ethnicity (80.6% and 58.1% not of Hispanic ethnicity in the Onzeald arm vs TPC) in terms of efficacy or safety is unknown, but not expected to importantly affect the results. The impact of the

imbalances between arms with regard to post-menopausal status (9% difference 55.6% vs 64.5% in the Onzeald arm vs TPC) is also difficult to predict. Current smoker status (11.1% vs 0%) might impact negatively on efficacy due to a PD interaction. There was a 15% difference in patients with ECOG performance status (PS) ≥1 (30.6% vs 16.1%). The effect of prognostic factor differences was analysed in a post hoc analysis (see under efficacy data and additional analyses).

The baseline disease factors were overall balanced in the ITT population. In the much smaller, non-stratified, subgroup of patients with a history of brain metastases (BCBM), there is larger variation across arms, as expected. While there was only a less than 4% difference in the presence of visceral disease overall (more in TPC arm), the difference with regard to liver metastases was 14% (more in etirinotecan arm). The etirinotecan arm also had more bone metastases, a 33% difference compared with TPC. Imbalances in post-study therapies received by patients were also observed. Some of these imbalances might potentially affect the BCBM results and were explored further by the Applicant (see under efficacy data and additional analyses).

With regard to laboratory baseline characteristics (not shown) it was noted that although liver and bone metastasis was more frequent in the etirinotecan compared with the TPC arm of the BCBM subgroup, ALT, AST and ALP levels were similar.

In light of potential genetic differences of interest for etirinotecan metabolism/function (e.g. UGT1A1-phenotype), it is noted that the Asian subgroup is small (12.3%, n=105, in the total ITT population and 13.4% in the BCBM subpopulation) (see discussion on clinical safety).

With regards to prior cancer therapies received in the BCBM subgroup, some imbalances were observed, but these were not consistently “favouring” one arm. The TPC arm had a somewhat higher mean number of prior therapies (4.3 vs 3.9), prior therapies for metastatic/recurrent disease (3.5 vs 3.2), including slightly more use in later lines, as well as prior eribulin use (29% versus 19%). The etirinotecan arm, on the other hand, had higher frequencies of patients refractory to important prior chemotherapies (anthracycline refractory 17 vs 10%; taxane refractory 50 vs 39%; capecitabine refractory 69 vs 61%, respectively). The use of prior hormonal therapies was similar across arms. HER2 agents were also largely similarly used. The potential impact of these imbalances is unclear.

While constituting the most commonly administrated TPC in both the ITT population and the BCBM subgroup, eribulin was less frequently used in the BCBM compared with the overall ITT population, probably as a result of more pre-study use in this subgroup (prior eribulin in TPC patients: 29 vs 17% in BCBM vs ITT). Consequently, other agents were given to a higher degree, but in the same order of frequency in both populations.

Protocol deviations were overall balanced across arms. The only larger imbalance concerned major deviations of Investigational product (IP) compliance (etirinotecan: 24%; TPC: 3%). Upon search of the CSR listings, a large part of the IP compliance deviations in the etirinotecan arm consisted of protocol-specified dose reductions due to neutropenia not being performed, dose interruption and/or reduction due to diarrhoea not being performed, the i.v. infusion being given during a shorter time period (often around 60 min) than the stipulated 90 minutes, and failure to dispense loperamide medication. Potentially, some of these deviations could result in higher dose intensity than what is aimed for. The Applicant explained that this was due to prescribers being used to other chemotherapy agents where dose adjustments are not made until grade 3 toxicity and improvement in adherence to the dose modification schedules occurred during the course of the study.

Efficacy data and additional analyses

The median overall survival in the full study population (ITT) was 2.1 months longer in the etirinotecan arm compared with the TPC arm (12.4 vs 10.3 months), with a HR of 0.87 (95% CI: 0.75-1.02), however not statistically significant (p=0.08). An OS benefit was therefore not shown. The ORR was similar in both arms (16% versus 17%).

The clinical data presented in this pivotal study did not establish statistically persuasive evidence of superiority over TPC in the ITT population. However, the application is based on finding in the BCBM subgroup. Of all the tested subgroups, the BCBM group has both the lowest point estimate and upper limit of CI compared to TPC.

The applicant seeks an indication based on the BCBM subgroup findings. The decision to focus on the BCBM subgroup was not pre-planned, but instead data driven (see further above). It is noted that only 34 of the 67 patients (51%) in the BCBM subgroup had current brain metastases at the time of enrolment. Thus, half of the patients had no macroscopic signs of remaining BM upon imaging. No patients had target lesions in the CNS, and the intracranial objective response rate could not be assessed.

In the BCBM subgroup, the median OS was 5.2 months longer in the etirinotecan arm compared with the TPC arm (10.0 vs 4.8 months), with a HR of 0.51 (95% CI: 0.30- 0.86), and statistically significant (p=0.01), however unadjusted for multiplicity. Notably, this subgroup is small (n=67) which make it liable to potential confounding by unbalances in unidentified prognostic factors. Furthermore, the results are not statistically compelling in the light of multiple statistical testing.

Post-hoc analyses were performed to investigate the robustness of the results given the imbalance of baseline factors due to not controlling for them in the randomization. The analyses do not indicate that the results are driven by imbalance in baseline factors. The study was not powered to detect significant interactions and due to the lack of stratification potential, imbalances in unknown prognostic factors cannot be excluded.

A requested “per protocol” (PP) analysis in the BCBM subgroup where only patients who received at least one dose of study drug were included, and where patients ineligible with regard to major inclusion criteria were excluded (n= 30 Onzeald, n=26 TPC), showed a similar and nominally statistical significant OS HR as in the full BCBM subgroup (PP HR 0.53, 95%CI: 0.30, 0.93; p = 0.028).

In the subgroup with imaging-detectable remaining brain metastasis (following prior local therapy) at study entry (n=37), the OS HR was 0.45 (95% CI: 0.22; 0.91), p = 0.02, with median OS 13.2 months (95% CI: 8.6; 19.6) vs. 5.8 months (95% CI: 3.5, 8.6) for etirinotecan pegol vs. TPC. These data are consistent with the results in the overall BCBM subgroup.

A number of imbalances in post-study therapy were observed in the BCBM subgroup. The mean number of post-study cancer therapies was twice as high in the etirinotecan arm compared with the TPC arm (1.7 vs 0.8). The frequency of patients with at least one post-study cancer therapy was 72% vs 48% (etirinotecan vs TPC), and 69% vs 42% received chemotherapy. A large imbalance is noted with regard to post-study eribulin: 42 vs 6%, which may reflect the baseline difference in the other direction with regard to prior eribulin use. In this context, it is also notable that 40% of patients in the BCBM subgroup that received etirinotecan would have been allocated to eribulin if they had been randomised to the TPC arm, compared to 30% of those actually allocated to TPC. The impact of these imbalances on outcomes cannot be ascertained.

In terms of secondary endpoints, the PFS analysis was made at a mature stage with event rates over 80% in both arms in both populations (Full ITT and BCBM). In the full study population, the secondary efficacy results were consistently very similar across arms. Median PFS was 2.4 and 2.8 months (Q3 estimate 5.7

and 5.6 months) for etirinotecan and TPC, respectively, with PFS HR 0.93 (n.s.). As stated above, ORR was 16.4 and 17.0%, median DoR 3.9 vs 3.7 months, and CBR 20.5 vs 19.6%, with very similar CIs across arms for all parameters except DoR.

In the BCBM, the corresponding post-hoc analyses were performed, with larger numerical differences across arms. Median PFS was 3.1 vs 2.7 months (Q3 estimate 7.2 vs 4.2 months), with HR 0.84 (n.s.). ORR was 16 vs 4 % (all were PRs and all events were measured extracranially), and DoR 5.6 vs 3.7 months. CBR was not reported for this subgroup. No firm conclusions can be drawn regarding the secondary endpoints in the BCBM subgroup due to the small number of patients and consequent imprecision of the results.

The ORR results presented above related to the overall result in all disease sites, while the ORR of etirinotecan on current brain metastases could not be evaluated due to the formal lack of RECIST-evaluable brain lesions due to the prior local therapy.

While the analysis may be questioned on methodological grounds due to the inherent informative censoring, “In-brain PFS” HR was 0.6, i.e. roughly in line with the OS HR in the BCBM.

The OS HR by TPC Pgp substrate status was compared in the ITT and BCBM. In the Pgp substrate group (eribulin, vinorelbin, paclitaxel, docetaxel) the OS HR was 0.94 in the ITT population and 0.33 in the in the BCBM group, while no difference was observed between the ITT and the BCBM group (OS HR 0.69) for compounds not considered substrates of Pgp (ixabepilone, gemcitabine and Nab-paclitaxel). These comparisons do not refer to randomised pairs, but a comparison between the full etirinotecan pegol populations (ITT and BCBM) and the two Pgp defined subgroups. While, these analyses could be taken to support the findings of improved relative efficacy of etirinotecan pegol in BCBM (possibly largely due to the very poor intracranial activity of some of the compounds in the TPC group), it is notable that there is limited and inconsistent human evidence for a role of PgP in drug disposition with relevance to brain metastases, in view also of potential contribution of other drug efflux transporters at the blood-brain barrier.

In an analysis of OS by overall tumour burden at baseline, based on the size of target lesions, OS HRs were lower in patients with higher overall tumour burden: In the first two quartiles the OS HR was close to 1, in the third quartile (i.e., target lesion diameter sum >51 and ≤80 mm) HR was 0.75 and in the fourth quartile (target lesion >80 mm) HR was 0.62. This is of interest considering that in patients with high tumour burden, individual lesions are likely to be larger and tumour vasculature more extensive, suggesting that leakage of macromolecules may be more profound on average compared with in patients with lower overall tumour burden.

A protective effect against brain metastases was not observed in an analysis by baseline brain imaging. In patients who did not have baseline brain imaging, PD in brain as site of PD was observed in very similar proportions across study arms, 19/402 and 21/400. Provided that leaky vessels related to size of the tumour, or to prior radiotherapy, would be the basis for a higher activity of etirinotecan relative to its comparators, a protective effect would not be expected.

In the BCBM subgroup as well as in the full BEACON population, better relative efficacy (lower HRs) is observed for OS than PFS; HR 0.51 versus 0.84 (n.s.) in the BCBM subgroup; 0.87 versus 0.93 in the full population. However, since over 50% of progression events occurred prior to the first evaluation at week 8, there would be a tendency towards unity for PFS, which may be taken to explain the discrepancy between PFS and OS.

The PRO instruments are validated and standard. The open-label design of the study challenges interpretability of the PRO results. However, the HRQoL/PRO results appear consistent with the safety

profile of etirinotecan pegol. Worsening of symptom scales for diarrhoea, nausea and vomiting and appetite loss were thus seen. Global health status nevertheless deteriorated less in the etirinotecan compared with the TPC arm. The difference in global health status was mostly driven by physical functioning, but all five functioning domains were numerically better (i.e. showed less deterioration) in the etirinotecan arm. In the statistical analysis plan, no hypothesis is specified and no attempt to control the type-1 error is made. The claims for the SmPC are therefore not accepted, in line with current guidelines.

OS subgroup analyses in the full study population give the overall impression of similar efficacy across study arms. Most HR estimates are below 1.0, however (i.e. favouring etirinotecan over TPC), although CIs mostly encompass 1.0. HR estimates ≥ 1.0 was observed for triple negative disease (TNBC, HR 1.0), geographic region Spain (1.0), performance status ECOG 0 (1.01), no liver metastases (1.06), oestrogen receptor negativity (1.07), no prior hormonal therapy (1.08), and refractoriness to anthracyclines (1.25).

HRs with CIs below 1.0 were observed for some of the complementary subgroups: liver metastases present (HR 0.73, 95% CI 0.59, 0.89), oestrogen receptor positivity (HR 0.79; CI 0.65, 0.96), prior hormonal therapy (HR 0.79, CI 0.66, 0.95), no refractoriness to anthracyclines (HR 0.82, CI 0.69, 0.97), and furthermore in the subgroups with ≥3 disease sites (HR 0.77, CI 0.62, 0.95) and a history of brain metastases (HR 0.51, CI 0.30, 0.86).

A post hoc analysis evaluated the effect of selected baseline prognostic factor differences between treatment arms on OS. The HR and corresponding 95% CI and p-values (via Cox regression) were calculated for each factor and for the interaction. The interaction p-values were in the range of 0.228-0.877 for all prognostic factors selected; hence, the differences between treatment arms were not considered to significantly affect the primary survival analysis in the BCBM Population.

OS was also assessed in patients with prior eribulin treatment. Halaven (eribulin mesilate) is an approved drug for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease and following prior treatment with an anthracycline and a taxane. In the third and later lines of treatment, an OS improvement was observed for eribulin vs. TPC. Investigation of etirinotecan efficacy in relation to prior eribulin treatment is therefore of importance, since prior eribulin was not required for inclusion in Study 11-PIR-11. The subgroup results indicate that whether or not the patient had received prior eribulin therapy did not impact on the relative efficacy of etirinotecan in the full study population.

In terms of supportive studies, the investigator-initiated Study 24833 conducted at Stanford University was included in the application in support of the anti tumour activity of etirinotecan pegol against intra-cranial lesions and its ability to cross the brain-tumour barrier (BTB) in the intracranial region to induce clinically meaningful outcomes (Nagpal 2015). The results support the potential for activity of etirinotecan in intracranial tumours. However, due to fundamental biological and clinical differences between diseases, no direct inference relevant to the BCBM scenario can be drawn.

The plausibility of the findings in the BCBM subgroup from a mechanistic/pharmacological perspective taking into account supportive evidence from other studies was extensively discussed, also considering the SAG view. Altogether, there are insufficient data to establish the biological plausibility for in-brain activity and thus the potential contribution of any proposed mechanism or claimed activity to any effect on OS is unknown.

The role of prior irradiation for the activity of etirinotecan pegol is presently unclear. Leaky vessels may be of importance to the efficacy of Onzeald in brain metastasis, since the normal blood-brain-barrier (BBB) would not be expected to be permeable to such large molecules. Brain metastasis in itself is normally perceived to give rise to a more permeable blood-tumour-barrier (BTB) due to the imperfect

angioneogenesis of tumours. In addition, radiation therapy further increases permeability by destruction of tight junctions in the endothelium. The clinical study experience in BCBM to date is restricted to patients who have received prior local cranial therapy. The effect of prior radiotherapy on Onzeald efficacy in brain metastasis and the time-frame in which such effect might pertain remains unknown.

Additional expert consultation

1. What is the view of the SAG on the totality of evidence to support:

a. accumulation and retention of Onzeald in cerebral metastases

b. in-brain anti-tumour activity of Onzeald

c. in-brain anti-tumour activity contributes to overall survival benefit for Onzeald over TPC in BCBM patients

Accumulation and retention of etirinotecan pegol in cerebral metastases: The claims of such effects are partly based on theoretical considerations, in vitro data on major efflux transporters, one mouse xenograft study, and clinical data about PEGylated liposomal doxorubucin. However, it is impossible to establish such claims due to the following:

- There are no data about accumulation or retention of etirinotecan pegol in patients or subgroups of patients;
- The finding that in vitro etirinotecan pegol is not a substrate for the major efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) expressed at the brain-tumour-barrier is not useful because the relevance of the model for understanding the effect of the transporter in vivo is known to be very poor;
- The relevance of available clinical data about accumulation of PEGylated liposomal doxorubucin is not clear for etirinotecan pegol and the clinical effects for the latter are not really demonstrated;
- The claimed enhanced permeability and retention (EPR) qualities of etirinotecan pegol do not justify a supposed differential accumulation in cerebral metastases compared to peripheral tumours that could explain different clinical effect in the different subgroups.

The data presented from the only mouse model (MDA-mb-231Br model) are not convincing due to:

- Markedly higher concentrations of 14C-etirinotecan were noticed in brain metastases in the animal model of the only tested cell line MDA-MB231-BR cell line compared with 14C-irinotecan, the former (and likely its metabolite) has also a longer half-life. However, the ratio vs. the normal brain was higher for irinotecan although this might be possibly explained by inadequate washout as part of the experiment and unreliable estimates of radioactivity (which however raise concerns about reliability of results).

- The experience that such models poorly predict effects in humans; in the absence of consistent evidence in a number of different animal models, the relevance of the available non-clinical findings for understanding antitumor activity cannot be confirmed.

In conclusion, there are no data to support the claims of accumulation and retention of etirinotecan pegol in brain metastases.

In-brain anti-tumour activity; overall survival (OS) effect in BCBM patients: There are insufficient data to establish the biological plausibility for in-brain activity and the potential contribution of any proposed mechanism or claimed activity to any effect on OS is therefore unknown.

The OS effect claimed in a subgroup of patients with brain metastases is far from convincing due to many very obvious flaws and shortcomings in the available clinical evidence such as:

- Overall no statistically significant difference in OS (p=0.08), PFS, ORR, despite the large trial (n=852);
- Small BCBM subgroup (n= 36 v. 31 patients) and associated variability in point estimates and lack of replication in another data set;
- Multiplicity (at least 57 such analyses have been pre-specified at some point);
- Lack of internal consistency in terms of other endpoints in the subgroup (e.g., PFS)
- At least 4/57 subgroups other than patients with brain metastases showing apparent effects (e.g., presence of liver metastasis, HR=.73; 95% CI:.59, .89; refractory to capecitabine; not refractory to anthracycline; ER+);
- Lack of response data for brain metastases based on suitable imaging (e.g., longitudinal studies with PET/MRI); the claimed difference in objective response in the brain metastasis subgroup is based on responses in peripheral target lesions (brain metastases were not considered target lesions);
- Lack of longitudinal data about progression inside v. outside the brain to assess the claimed differential effect;
- Possible confounders in the subgroup such as prognostic factors, the observed imbalance in post-progression treatments and the effect of prior or concomitant radiotherapy (the impact of radiation on the blood-brain barrier is unpredictable and heterogeneous and carry-over effects of radiotherapy cannot be excluded);
- Claimed indication not reflecting the subgroup (patients with brain metastases were excluded from the trial unless local therapy was completed and use of corticosteroids discontinued for at least 3 weeks and signs or symptoms of brain metastases were stable for at least 28 days; exclusion of leptomeningeal disease or meningeal carcinomatosis).

Data to show reproducibility of the exploratory subgroup results are lacking (indeed, a randomised trial is ongoing in patients with breast cancer and brain metastases). The relevance of small series of patients in NSCLC and GBM for any claimed effect for breast cancer is unknown due to fundamental biological and clinical differences.

Non-clinical evidence to support the exploratory findings is also lacking. Concerning the supportive non-clinical model, the results are not convincing due to conflicting results and the unknown relevance for humans (see above), and conflicting findings between OS in mice and response in tumour lesions.

In conclusion, there are no convincing data to support the claims of in-brain anti-tumour activity and OS effect in BCBM patients.

Whilst the SAG agreed on the fact that there is very little evidence to support any of the above claimed effects, the SAG disagreed on whether the uncertainty about the effect on OS in the target indication is acceptable or not.

According to the predominant view of the SAG, including patient views, the available evidence is far from sufficient to establish the efficacy of Onzeald in the proposed indication. At best, the exploratory results could be considered hypothesis generating although apart from the subgroup analysis (which is considered far from convincing, also in view that brain metastasis was not systematically investigated at study entry), and some theoretical considerations about possible differential distribution of pegylated compounds, supportive clinical and non-clinical pharmacokinetic and pharmacodynamic evidence is lacking to formulate a sound hypothesis. Given the available treatment options, including eribulin that has shown an effect in terms of OS, and despite the poor prognosis associated with brain metastases, in the absence of evidence of efficacy according to conventional scientific standards, Onzeald cannot be considered as a useful treatment option in the proposed indication. Potentially exposing the target population to chemotherapy with Onzeald in the absence of established benefits and potentially delaying effective therapies was a major concern. Concerning the ongoing phase III study, although the hypothesised hazard ratio seems quite optimistic, a carefully planned and timed interim analysis could result in early stopping for efficacy should a similar effect on OS be confirmed, without undue delay. The study should of course be run with proper collection of relevant tumour biopsy material for predefined marker studies and up-to date imaging studies.

According to a minority/single experts, whilst acknowledging all the weaknesses and uncertainties and that efficacy cannot be considered convincingly established, an effect in the BCBM subgroup cannot be excluded based on theoretical grounds and exploratory findings, which look somewhat promising. Given the poor prognosis and the relatively favourable toxicity profile compared to some of the other available options, the large uncertainty about efficacy could be discussed when considering Onzeald as a possible therapeutic option while awaiting the results of the ongoing confirmatory study.

2. What is the view of the SAG on available evidence for the activity of each of the drugs used in the control arm as "treatment of physicians' choice" in the population treated in the BEACON study?

The "treatment of physicians' choice" defined in the protocol included active agents like eribulin with an established effect on OS, but also some notable limitations, namely:

- Exclusion of certain options considered active in this setting (e.g., liposomal doxorubicin, platinum-based chemotherapy, specific treatment options for HER2+ patients)
- Inclusion of options with likely relatively low activity were also noted (re-challenge with taxanes; gemcitabine monotherapy; unapproved agents in EU such as ixabepilone).

Notwithstanding the above limitations, the activity of each of the drugs is considered heterogeneous and probably in the range of 5% to 20% ORR. In terms of efficacy, the effect on OS or PFS of many of these agents is unknown or likely to be very small, if any. It is difficult to speculate what could be the efficacy of such a control arm compared to a hypothetical placebo. Such control arm would be considered appropriate for a superiority trial with OS. However, based on the unknown efficacy, it would not be possible to establish a largest clinically acceptable difference in terms of any endpoint (OS, PFS, ORR) for a hypothetical non-inferiority trial or statement using this "treatment of physicians' choice" as control group.

Additional efficacy data needed in the context of a conditional MA

The current data package is not considered comprehensive. The applicant requested a conditional marketing authorisation. The proposed confirmatory study is an open-label, randomised, parallel, two-arm, multicentre, international Phase 3 study of Onzeald versus TPC in adult patients with metastatic breast cancer and a history of brain metastases that are non-progressing (Study 15-102-14 (ATTAIN)).

Patients must have had prior therapy with an anthracycline, a taxane, and capecitabine in the neoadjuvant, adjuvant, and/or metastatic setting. It is planned to enrol 350 patients. ATTAIN has thus far initiated at 30 sites in the US with an additional 134 sites world-wide projected to initiate throughout 2017. The first patient was randomised and dosed in March 2017. The current estimated timeline is for primary analysis (top line data available) in Q1 2020 and final clinical study report in Q2 2020. The study could provide relevant clinical efficacy data in support of the current application. In-brain accumulation and anti-tumour activity of Onzeald is expected to be assessed as part of this study.

2.5.4. Conclusions on the clinical efficacy

The main evidence of efficacy is based on a subgroup analysis including a limited number of patients from a study which did not establish statistically persuasive evidence of superiority over TPC in the ITT population in terms of Overall Survival. Consequently, the results of the subgroup analysis on which the applicant's claim is based are not statistically compelling. In addition, the secondary endpoints showed no differences in PFS, ORR and DOR in the ITT population and numbers are too small to draw conclusions in the BCBM subgroup.

Furthermore, there is insufficient evidence in support of these findings from a mechanistic and pharmacology perspective. Therefore the clinical benefit of Onzeald in the claimed indication "Onzeald monotherapy is indicated for the treatment of adult patients with breast cancer that has metastasised to the brain, who have received prior local treatment for brain metastases (surgery and/or radiotherapy), and systemic anthracycline, taxane, and capecitabine, unless patients were not suitable for these treatments" has not been sufficiently demonstrated.

2.6. Clinical safety

The safety assessment is based on the studies and study populations presented in the following tables.

Table 37 - Summary of the Safety Populations in Support of Onzeald in the Treatment of Breast Cancer Having Brain Metastases

Safety Population	Subpopulation | Total Number of Patients who Received at Least one Dose			Clinical Studies
Overall	Onzeald (all doses)		790	Study 11-PIR-11 (BEACON), Phase 3, Breast cancer (N = 425) Study 08-PIR-05, Phase 2, Breast cancer (N = 70) Study 08-PIR-04, Phase 2, Ovarian cancer (N = 177) Study 08-PIR-03, Phase 2, Colorectal cancer (N = 42) Study 06-IN-IR001, Phase 1 dose-escalation, Solid, Refractory tumours (N = 76)
		Onzeald 145 mg/m^2 q21d[a]	644	Study 11-PIR-11 (BEACON), Phase 3, Breast cancer (N = 425) Study 08-PIR-05, Phase 2, Breast cancer (N = 35) Study 08-PIR-04, Phase 2, Ovarian cancer (N = 139) Study 08-PIR-03, Phase 2, Colorectal cancer (N = 42) Study 06-IN-IR001, Phase 1 dose-escalation, Solid, Refractory tumours (N = 3)
BEACON	Total		831	1. Study 11-PIR-11 (BEACON), Phase 3, Breast cancer
	Onzeald 145 mg/m^2 q21d[a]		425	
	TPC		406	

Safety Population	Subpopulation | Total Number of Patients who Received at Least one Dose		Clinical Studies
BCBM	Total	61	2. Study 11-PIR-11 (BEACON), Phase 3, Breast cancer
	Onzeald 145 mg/m^2 q21d[a]	34	
	TPC	27	

Abbreviations: BCBM = breast cancer with brain metastases; BEACON = the 'BrEAst Cancer Outcomes with NKTR-102' Study (Study 11-PIR-11); TPC = Treatment of Physician's Choice (standard of care treatment in advanced breast cancer; selected from the following list of seven single-agent intravenous therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel)
Dose and schedule intended for commercialisation.

In total 644 patients with a variety of solid tumours have received Onzeald (etirinotecan pegol) at the dose intended for approval, i.e. 145 mg/m^2 etirinotecan at 21 days' interval. Of these, 425 came from the pivotal BEACON study (11-PIR-11) performed in locally recurrent or metastatic breast cancer. Thirty-four etirinotecan-treated patients in the BEACON study had a history of brain metastases (BCBM) and represent the target indication for the present application (Table 41).

Table 38 - Summary of Clinical Studies Providing Safety Data (Data Cut-off Date: 23 February 2015)

Study[a] Identifier Location(s) Start- End	Study Group/ Treatments[c]	Total Enrolment	Study Design	Study Objec-tive(s)	Diagnosis or Tumour Type	Primary Endpoint	Key Secondary Endpoints and Study Status
Phase 3 Study							
11-PIR-11 (BEACON) MC/ international Dec 2011 - Feb 2015[b]	Onzeald: 145 mg/m^2, q21d	N = 429 (ITT), N = 425 (safety)	AC, 2-arm, R, OL, MC	Efficacy and Safety	Adults (≥ 18 years of age) with locally recurrent or metastatic breast cancer previously treated with at least two and a maximum of five prior chemotherapy regimens including an anthracycline, a taxane, and capecitabine	OS, which was defined as the time from the date of randomisation to death from any cause	PFS, ORR, DoR, CBR, HRQoL Complete
	TPC: Per approved standard of care	N = 423 (ITT), N = 406 (safety)					
Phase 2 Studies							
08-PIR-05 MC/ international Feb 2009 - Oct 2011	Onzeald: 145 mg/m^2, q14d	N = 35 (ITT), N = 35 (safety)	2-arm, R, OL, MC	Efficacy and Safety	Adults (≥ 18 years of age) with metastatic breast cancer that failed prior taxane-based treatment	ORR, as determined by RECIST	PFS, OS Complete
	Onzeald: 145 mg/m^2, q21d	N = 35 (ITT), N = 35 (safety)					

08-PIR-04 MC/ international Dec 2008-Oct 2012	Onzeald: 145 mg/m^2, q14d	N = 39 (ITT), N = 38 (safety)	2-arm, R, OL, MC	Efficacy and Safety	Adults (≥ 18 years of age) with metastatic or unresectable platinum-resistant ovarian cancer	ORR	DoR, PFS, OS, CBR Complete
	Onzeald: 145 mg/m^2, q21d	N = 139 (ITT), N = 139 (safety)					
08-PIR-03 MC/ international Feb 2009-Nov 2014	Onzeald: 145 mg/m^2, q21d	N = 42 (ITT) N = 42 (safety)	2-arm, AC, R, OL, MC	Efficacy and Safety	Adults (≥ 18 years of age) with KRAS-mutant metastatic colorectal cancer, irinotecan naïve	PFS	OS, ORR, DoR Complete[d]
	Irinotecan: 350 mg/m^2, q21d	N = 41 (ITT) N = 41 (safety)					
Phase 1 Studies							
06-IN-IR001 MC/ US Dec 2006-May 2009	Onzeald (145, 170, 195, and 220 mg/m^2), q14d	N = 19 (safety)	Dose-escalation, OL	Tolerability	Adults (≥ 18 years of age) with metastatic or unresectable solid tumours for which standard curative or palliative therapies did not exist	DLTs, MTD	PK, anti-tumour efficacy Complete
	Onzeald (145, 170, 195, 220, and 245 mg/m^2), q21d	N = 25 (safety)					
	Onzeald (58, 115, 145, 173, and 230 mg/m^2), wx3q4wk	N = 32 (safety)					

Abbreviations: AC = active-controlled; BEACON = Breast Cancer Outcomes With NKTR-102; CBR = clinical benefit rate (CR+PR+SD≥ 6 months); CR = complete response; DLT = dose-limiting toxicity; DoR = Duration of response; HRQoL = health-related quality of life; IIS = Investigator-initiated Study; ITT = intent-to-treat; PK = pharmacokinetics; MC = multi-centre; MTD = maximum tolerated dose; OL = open-label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; q14d = once every 14 days; q21d = once every 21 days; R = randomised; safety = safety population (patients that received at least one dose of study treatment); SD = stable disease; TPC = treatment of physician's choice (eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel); US = United States.

a. All studies presented in this Table were included in the pooled safety analysis.
b. The data cut-off date for the primary analysis was 23 February 2015. At the date of the primary analysis, 173 patients were in follow-up and still alive at the date of primary analysis.
c. All Onzeald doses were 90-minute (±15 minutes) intravenous infusions.
d. At the time that Study 08-PIR-03 was initiated, single-agent irinotecan was considered an acceptable second-line option for patients with KRAS mutant mCRC. However, combination therapy combining irinotecan with 5-FU/leucovorin, ziv-aflibercept, and/or bevacizumab became the standard of care before accrual for this study could be completed. Hence, recruitment to the study with single-agent camptothecin-based therapy was difficult (83 out of 174 planned patients actually enrolled) and the trial was discontinued prematurely 14 Nov 2014.

Patient exposure

The median number of received cycles was 3 in all safety sub-/populations. The mean relative dose intensity for etirinotecan was 92-93% in the overall, BEACON and BCBM safety populations. Patient exposure is summarised in the table below.

Table 39 - Patient Exposure to Single-agent Onzeald or Treatment of Physician's Choice across All Safety Populations

Cut-off Date: 23 Feb 2015						
	Overall Safety Population[a]		**BEACON Safety Population**		**BCBM Safety Population**	
	Onzeald[b] All Doses[c]	**Onzeald[b] 145 mg/m² q21d[d]**	**Onzeald[b] 145 mg/m² q21d[d]**	**TPC per Standard of Care**	**Onzeald[b] 145 mg/m² q21d[d]**	**TPC per Standard of Care**
	N = 790	**N = 644**	**N = 425**	**N = 406**	**N = 34**	**N = 27**
Number of Cycles Completed (Total)	**N/A**	**N/A**	**2348**	**2015**	**190**	**100**
Number of cycles (% of total cycles) with dose delay or reduction due to adverse event	N/A	N/A	276 (11.8%)	397 (19.7%)	20 (10.5%)	31 (31.0%)
Number of Cycles Completed (per Patient)						
Mean (SD)	5.4 (5.04)	5.4 (4.86)	5.5 (5.22)	5 (4.18)	5.5 (5.33)	3.7 (2.95)
Median	3.0	3.0	3.0	3.0	3.0	3.0
Min, Max	1, 40	1, 35	1, 35	1, 26	1, 23	1, 13
1-2	231 (29.2%)	180 (28.0%)	110 (25.9%)	117 (28.8%)	9 (26.5%)	11 (40.7%)
3-4	235 (29.7%)	202 (31.4%)	148 (34.8%)	133 (32.8%)	11 (32.4%)	9 (33.3%)
5-6	121 (15.3%)	97 (15.1%)	57 (13.4%)	58 (14.3%)	6 (17.6%)	4 (14.8%)
>6	203 (25.7%)	165 (25.6%)	110 (25.9%)	98 (24.1%)	8 (23.5%)	3 (11.1%)
Relative Dose Intensity (%)[e]						
Mean (SD)	91.8 (11.62)	92.3 (10.85)	92.6 (10.7)	89.1 (16.2)	92.5 (12.37)	92.3 (20.92)
Median	97.9	97.9	98.3	92.8	99.8	98.8
Min, Max	33, 108	53, 108	55, 108	32, 168	65, 101	47, 136
Number of Patients Who Had Any Dose Reduction	**221 (28.0%)**	**178 (27.6%)**	**117 (27.5%)**	**115 (28.3%)**	**7 (20.6%)**	**7 (25.9%)**
Due to Adverse Event	190 (24.1%)	171 (26.6%)	117 (27.5%)	108 (26.6%)	7 (20.6%)	6 (22.2%)
Due to Other/	15 (11.5%)	13 (2.0%)	0 (0%)	9 (2.2%)	0 (0%)	1 (3.7%)
Number of Patients Who Had Any Dose Delay	**339 (42.9%)**	**299 (46.4%)**	**178 (41.9%)**	**190 (46.8%)**	**13 (38.2%)**	**14 (51.9%)**
Due to Adverse Event	271 (34.3%)	245 (38.0%)	151 (35.5%)	150 (36.9%)	13 (38.2%)	10 (37.0%)
Due to Logistics	69 (8.7%)	58 (9.0%)	34 (8.0%)	49 (12.1%)	1 (2.9%)	4 (14.8%)
Due to Other/	167 (21.1%)	81 (12.6%)	38 (8.9%)	39 (9.6%)	3 (8.8%)	1 (3.7%)
Number of Patients Who Had Any Dose Interruption	**42 (5.3%)**	**32 (5.0%)**	**18 (4.2%)**	**8 (2.0%)**	**1 (2.9%)**	**0 (0%)**
Due to Adverse Event	31 (3.9%)	27 (4.2%)	15 (3.5%)	7 (1.7%)	1 (2.9%)	0 (0%)
Due to Other	12 (1.5%)	6 (0.9%)	4 (0.9%)	1 (0.2%)	0 (0%)	0 (0%)

Abbreviations: BCBM = breast cancer with history of brain metastases; N/A = not analysed; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q14d = once every 14 days; q21d = once every 21 days.

a. Includes Phase 1-3 studies conducted by the Applicant and that were included in the integrated safety analysis in patients with advanced breast cancer (Phase 3 Study 11-PIR-11 and Phase 2 Study 08-PIR-05), ovarian cancer (Phase 2 Study 08-PIR-04), metastatic colorectal cancer (Phase 2 Study 08-PIR-03), and refractory solid tumours (Phase 1 Study 06-IN-IR001).
b. All Onzeald doses were by intravenous infusion over a 90 +/- 15 minute duration.
c. Pooled dose levels include < 48.3 mg/m^2/week, 48.3 mg/m^2/week (145 mg/m^2 q21d, the dose and regimen intended for marketing), 72.5 mg/m^2/week (145 mg/m^2 q14d), and >72.5 mg/m^2/week
d. Equivalent to 48.3 mg/m^2/week
e. Calculated as dose intensity divided by expected dose intensity. Expected dose intensity (mg/m^2 per week) = assigned dose (mg/m^2) divided by planned cycle length (days) times 7.
f. Patients from 06-IN-IR001 study are counted under Unknown since information was not collected.

Table 40 - Allocation of Treatment of Physician's Choice Agents to Patients – BEACON and BCBM Safety Populations

Cut-off Date: 23 Feb 2015				
Therapy Received in TPC	**BEACON Safety Population**		**BCBM Safety Population**	
	TPC per Standard of Care (N = 406)		**TPC per Standard of Care (N = 27)**	
	Number of Patients	**%**	**Number of Patients**	**%**
Eribulin	164	40.4%	8	29.6%
Vinorelbine	94	23.2%	5	18.5%
Gemcitabine	71	17.5%	9	33.3%
Nab-paclitaxel	31	7.6%	3	11.1%
Paclitaxel	18	4.4%	0	0%
Ixabepilone	15	3.7%	1	3.7%
Docetaxel	13	3.2%	1	3.7%
Total	406	100%	27	100%

Table 41 -Extent of Exposure- Safety Population with Brain metastases history

Table 14.4.1.9
Extent of Exposure
Safety Population with Brain Metastases History

	NKTR-102 (N=34)	TPC (N=27)
Overall		
Therapy Received in TPC		
DOCETAXEL		1 (3.7%)
ERIBULIN		8 (29.6%)
GEMCITABINE		9 (33.3%)
IXABEPILONE		1 (3.7%)
NAB-PACLITAXEL		3 (11.1%)
PACLITAXEL		0
VINORELBINE		5 (18.5%)
Exposure Duration (days)		
n	34	27
Mean (SD)	104.3 (121.62)	71.8 (79.85)
Median	47.5	44.0

Source data: Listing 16.2.5.1 and 16.2.5.2.
Note: Only the summary from the first 4 cycles are presented.
[1] Calculated as dose intensity divided by expected dose intensity. Expected dose intensity (mg/m2 per week) = assigned dose (mg/m2) divided by cycle p
(days) times 7.

Adverse events

The term and abbreviation AE is used synonymously with treatment-emergent adverse event (TEAE), which is the definition used in the studies. All adverse events (AEs) in the pivotal 11-PIR-11/BEACON trial were assessed according to the NCI-CTCAE Version 4.0 (v4.03: 14 Jun 2010).

Table 42 - Overall Summary of Treatment-Emergent Adverse Events across All Safety Populations

	Overall Safety Population[a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald[b] All Doses[c]	Onzeald[b] 145 mg/m^2 q21d[d]	Onzeald[b] 145 mg/m^2 q21d	TPC per Standard of Care	Onzeald[b] 145 mg/m^2 q21d	TPC per Standard of Care
	N = 790	N = 644	N = 425	N = 406	N = 34	N = 27
Number of Patients with at Least 1 TEAE	782 (99.0%)	636 (98.8%)	417 (98.1%)	405 (99.8%)	34 (100%)	27 (100%)
Number of Patients with at Least 1 Grade 3 or Higher TEAE	449 (56.8%)	342 (53.1%)	204 (48.0%)	256 (63.1%)	17 (50.0%)	19 (70.4%)
Number of Patients with at Least 1 TEAE Related to	749 (94.8%)	604 (93.8%)	394 (92.7%)	356 (87.7%)	31 (91.2%)	21 (77.8%)

Study Drug						
Number of Patients with Adverse Events Leading to Death[e]	N/A	N/A	5 (1.2%)	8 (2.0%)	0	1 (3.7%)
Number of Patients With at Least One TEAE with Fatal Outcome	63 (8.0%)	43 (6.7%)	16 (3.8%)	25 (6.2%)	0	2 (7.4%)
Number of Patients with at Least 1 TESAE	322 (40.8%)	241 (37.4%)	128 (30.1%)	129 (31.8%)	12 (35.3%)	11 (40.7%)
Number of Patients with at Least 1 TESAE Related to Study Drug	171 (21.6%)	118 (18.3%)	52 (12.2%)	24 (5.9%)	3 (8.8%)	3 (11.1%)
Number of Patients with at Least 1 TEAE Leading to Study Drug Discontinuation	133 (16.8%)	84 (13.0%)	47 (11.1%)	27 (6.7%)	7 (20.6%)	1 (3.7%)

Abbreviations: BCBM = breast cancer with history of brain metastases; N/A = not analysed; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q14d = once every 14 days; q21d = once every 21 days; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

a. Includes Phase 1-3 studies conducted by the Applicant and that were included in the integrated safety analysis in patients with advanced breast cancer (Phase 3 Study 11-PIR-11 and Phase 2 Study 08-PIR-05), ovarian cancer (Phase 2 Study 08-PIR-04), metastatic colorectal cancer (Phase 2 Study 08-PIR-03), and refractory solid tumours (Phase 1 Study 06-IN-IR001).
b. All Onzeald doses were by intravenous infusion over a 90 +/- 15 minute duration.
c. Pooled dose levels include < 48.3 mg/m^2/week, 48.3 mg/m^2/week (145 mg/m^2 q21d, the dose and regimen intended for marketing), 72.5 mg/m^2/week (145 mg/m^2 q14d), and > 72.5 mg/m^2/week.
d. Equivalent to 48.3 mg/m^2/week
e. Adverse event that is reported as the primary cause of death. Cause of death was collected only in the BEACON Study. Percentages are based on the number of patients in the Safety population of the BEACON study.

Common adverse events (> 5%)

Table 43 - Adverse Events by System Organ Class and Preferred Term in > 5% of the Population or Treatment Arm Across All Safety Populations

System Organ Class/ Preferred Term	Overall Safety Population [a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald [b] All Doses [c]	Onzeald [b] 145 mg/m² q21d [d]	Onzeald [b] 145 mg/m² q21d [d]	TPC per Standard of Care	Onzeald [b] 145 mg/m² q21d [d]	TPC per Standard of Care
	N = 790	N = 644	N = 425	N = 406	N = 34	N = 27
Gastrointestinal disorders	**732 (92.7%)**	**590 (91.6%)**	**382 (89.9%)**	**293 (72.2%)**	**32 (94.1%)**	**18 (66.7%)**
Diarrhoea	562 (71.1%)	440 (68.3%)	281 (66.1%)	80 (19.7%)	19 (55.9%)	5 (18.5%)
Nausea	528 (66.8%)	415 (64.4%)	255 (60.0%)	156 (38.4%)	22 (64.7%)	10 (37.0%)
Vomiting	370 (46.8%)	284 (44.1%)	173 (40.7%)	75 (18.5%)	19 (55.9%)	5 (18.5%)
Abdominal pain	244 (30.9%)	196 (30.4%)	91 (21.4%)	48 (11.8%)	6 (17.6%)	6 (22.2%)
Constipation	227 (28.7%)	184 (28.6%)	112 (26.4%)	126 (31.0%)	8 (23.5%)	7 (25.9%)
Abdominal pain upper	89 (11.3%)	81 (12.6%)	56 (13.2%)	38 (9.4%)	5 (14.7%)	3 (11.1%)
Dyspepsia	75 (9.5%)	56 (8.7%)	34 (8.0%)	32 (7.9%)	1 (2.9%)	3 (11.1%)
Flatulence	55 (7.0%)	39 (6.1%)	20 (4.7%)	5 (1.2%)	0	0
Abdominal distension	50 (6.3%)	38 (5.9%)	20 (4.7%)	17 (4.2%)	1 (2.9%)	0
Stomatitis	46 (5.8%)	35 (5.4%)	17 (4.0%)	34 (8.4%)	1 (2.9%)	0
General disorders and administration site conditions	**542 (68.6%)**	**427 (66.3%)**	**274 (64.5%)**	**296 (72.9%)**	**23 (67.6%)**	**20 (74.1%)**
Fatigue	349 (44.2%)	266 (41.3%)	146 (34.4%)	130 (32.0%)	9 (26.5%)	8 (29.6%)
Asthenia	123 (15.6%)	113 (17.5%)	92 (21.6%)	117 (28.8%)	5 (14.7%)	8 (29.6%)
Pyrexia	91 (11.5%)	66 (10.2%)	33 (7.8%)	65 (16.0%)	1 (2.9%)	4 (14.8%)
Oedema peripheral	59 (7.5%)	38 (5.9%)	19 (4.5%)	43 (10.6%)	3 (8.8%)	2 (7.4%)
Chest pain	29 (3.7%)	26 (4.0%)	14 (3.3%)	23 (5.7%)	0	1 (3.7%)
Mucosal inflammation	24 (3.0%)	18 (2.8%)	15 (3.5%)	23 (5.7%)	0	3 (11.1%)
Metabolism and nutrition disorders	**436 (55.2%)**	**334 (51.9%)**	**195 (45.9%)**	**146 (36.0%)**	**13 (38.2%)**	**7 (25.9%)**
Decreased appetite	296 (37.5%)	226 (35.1%)	131 (30.8%)	98 (24.1%)	8 (23.5%)	4 (14.8%)
Dehydration	141 (17.8%)	86 (13.4%)	41 (9.6%)	23 (5.7%)	5 (14.7%)	2 (7.4%)
Hypokalaemia	133 (16.8%)	80 (12.4%)	40 (9.4%)	37 (9.1%)	3 (8.8%)	1 (3.7%)
Hypomagnesaemia	52 (6.6%)	28 (4.3%)	18 (4.2%)	10 (2.5%)	2 (5.9%)	1 (3.7%)
Hyponatraemia	49 (6.2%)	33 (5.1%)	10 (2.4%)	16 (3.9%)	1 (2.9%)	2 (7.4%)
Nervous system disorders	**388 (49.1%)**	**314 (48.8%)**	**207 (48.7%)**	**211 (52.0%)**	**20 (58.8%)**	**16 (59.3%)**
Headache	149 (18.9%)	127 (19.7%)	95 (22.4%)	71 (17.5%)	7 (20.6%)	8 (29.6%)
Dizziness	118 (14.9%)	91 (14.1%)	56 (13.2%)	41 (10.1%)	7 (20.6%)	5 (18.5%)
Dysgeusia	74 (9.4%)	59 (9.2%)	33 (7.8%)	28 (6.9%)	2 (5.9%)	2 (7.4%)
Neuropathy peripheral	22 (2.8%)	15 (2.3%)	9 (2.1%)	50 (12.3%)	1 (2.9%)	1 (3.7%)
Peripheral sensory neuropathy	16 (2.0%)	15 (2.3%)	9 (2.1%)	26 (6.4%)	0	0

System Organ Class/ Preferred Term	Overall Safety Population [a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald [b] All Doses [c]	Onzeald [b] 145 mg/m² q21d [d]	Onzeald [b] 145 mg/m² q21d [d]	TPC per Standard of Care	Onzeald [b] 145 mg/m² q21d [d]	TPC per Standard of Care
	N = 790	N = 644	N = 425	N = 406	N = 34	N = 27
Musculoskeletal and connective tissue disorders	**310 (39.2%)**	**254 (39.4%)**	**165 (38.8%)**	**216 (53.2%)**	**15 (44.1%)**	**14 (51.9%)**
Back pain	73 (9.2%)	60 (9.3%)	39 (9.2%)	40 (9.9%)	4 (11.8%)	0
Pain in extremity	55 (7.0%)	44 (6.8%)	28 (6.6%)	36 (8.9%)	0	1 (3.7%)
Arthralgia	54 (6.8%)	40 (6.2%)	28 (6.6%)	42 (10.3%)	1 (2.9%)	0
Muscle spasms	52 (6.6%)	46 (7.1%)	29 (6.8%)	16 (3.9%)	3 (8.8%)	1 (3.7%)
Myalgia	46 (5.8%)	39 (6.1%)	26 (6.1%)	59 (14.5%)	1 (2.9%)	6 (22.2%)
Musculoskeletal pain	39 (4.9%)	31 (4.8%)	24 (5.6%)	26 (6.4%)	2 (5.9%)	0
Musculoskeletal chest pain	29 (3.7%)	20 (3.1%)	16 (3.8%)	27 (6.7%)	2 (5.9%)	2 (7.4%)
Muscular weakness	23 (2.9%)	17 (2.6%)	5 (1.2%)	25 (6.2%)	3 (8.8%)	2 (7.4%)
Bone pain	21 (2.7%)	21 (3.3%)	18 (4.2%)	36 (8.9%)	2 (5.9%)	0
Investigations	**296 (37.5%)**	**230 (35.7%)**	**128 (30.1%)**	**126 (31.0%)**	**11 (32.4%)**	**8 (29.6%)**
Weight decreased	157 (19.9%)	119 (18.5%)	57 (13.4%)	24 (5.9%)	6 (17.6%)	1 (3.7%)
Neutrophil count decreased	48 (6.1%)	37 (5.7%)	25 (5.9%)	51 (12.6%)	1 (2.9%)	5 (18.5%)
Aspartate aminotransferase increased	28 (3.5%)	25 (3.9%)	23 (5.4%)	29 (7.1%)	3 (8.8%)	1 (3.7%)
Alanine aminotransferase increased	26 (3.3%)	22 (3.4%)	18 (4.2%)	23 (5.7%)	3 (8.8%)	1 (3.7%)
Respiratory, thoracic and mediastinal disorders	**285 (36.1%)**	**227 (35.2%)**	**150 (35.3%)**	**170 (41.9%)**	**13 (38.2%)**	**9 (33.3%)**
Dyspnoea	116 (14.7%)	95 (14.8%)	60 (14.1%)	76 (18.7%)	5 (14.7%)	3 (11.1%)
Cough	93 (11.8%)	76 (11.8%)	59 (13.9%)	52 (12.8%)	6 (17.6%)	3 (11.1%)
Pleural effusion	32 (4.1%)	31 (4.8%)	25 (5.9%)	31 (7.6%)	2 (5.9%)	3 (11.1%)
Blood and lymphatic system disorders	**284 (35.9%)**	**232 (36.0%)**	**147 (34.6%)**	**186 (45.8%)**	**16 (47.1%)**	**9 (33.3%)**
Neutropenia	154 (19.5%)	132 (20.5%)	91 (21.4%)	126 (31.0%)	13 (38.2%)	4 (14.8%)
Anaemia	145 (18.4%)	115 (17.9%)	66 (15.5%)	82 (20.2%)	3 (8.8%)	4 (14.8%)
Leukopenia	45 (5.7%)	35 (5.4%)	16 (3.8%)	25 (6.2%)	2 (5.9%)	0
Thrombocytopenia	29 (3.7%)	24 (3.7%)	12 (2.8%)	22 (5.4%)	1 (2.9%)	0
Infections and infestations	**255 (32.3%)**	**200 (31.1%)**	**131 (30.8%)**	**162 (39.9%)**	**10 (29.4%)**	**12 (44.4%)**
Urinary tract infection	57 (7.2%)	43 (6.7%)	28 (6.6%)	29 (7.1%)	0	2 (7.4%)
Upper respiratory tract infection	32 (4.1%)	24 (3.7%)	15 (3.5%)	27 (6.7%)	2 (5.9%)	1 (3.7%)
Skin and subcutaneous tissue disorders	**250 (31.6%)**	**190 (29.5%)**	**107 (25.2%)**	**166 (40.9%)**	**8 (23.5%)**	**9 (33.3%)**
Alopecia	121 (15.3%)	84 (13.0%)	44 (10.4%)	95 (23.4%)	3 (8.8%)	3 (11.1%)
Rash	56 (7.1%)	43 (6.7%)	22 (5.2%)	24 (5.9%)	3 (8.8%)	2 (7.4%)
Pruritus	26 (3.3%)	21 (3.3%)	13 (3.1%)	28 (6.9%)	0	3 (11.1%)

System Organ Class / Preferred Term	Overall Safety Population [a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald [b] All Doses [c]	Onzeald [b] 145 mg/m² q21d [d]	Onzeald [b] 145 mg/m² q21d [d]	TPC per Standard of Care	Onzeald [b] 145 mg/m² q21d [d]	TPC per Standard of Care
	N = 790	N = 644	N = 425	N = 406	N = 34	N = 27
Eye disorders	**219 (27.7%)**	**174 (27.0%)**	**112 (26.4%)**	**61 (15.0%)**	**11 (32.4%)**	**5 (18.5%)**
Vision blurred	137 (17.3%)	105 (16.3%)	68 (16.0%)	12 (3.0%)	5 (14.7%)	0
Psychiatric disorders	**152 (19.2%)**	**115 (17.9%)**	**65 (15.3%)**	**79 (19.5%)**	**7 (20.6%)**	**5 (18.5%)**
Insomnia	64 (8.1%)	46 (7.1%)	28 (6.6%)	33 (8.1%)	5 (14.7%)	2 (7.4%)
Anxiety	49 (6.2%)	38 (5.9%)	20 (4.7%)	22 (5.4%)	1 (2.9%)	1 (3.7%)
Depression	34 (4.3%)	26 (4.0%)	9 (2.1%)	22 (5.4%)	0	0
Vascular disorders	**120 (15.2%)**	**89 (13.8%)**	**57 (13.4%)**	**44 (10.8%)**	**2 (5.9%)**	**1 (3.7%)**
Hypotension	45 (5.7%)	33 (5.1%)	24 (5.6%)	11 (2.7%)	0	0
Renal and urinary disorders	81 (10.3%)	60 (9.3%)	33 (7.8%)	39 (9.6%)	2 (5.9%)	4 (14.8%)
Cardiac disorders	**60 (7.6%)**	**47 (7.3%)**	**26 (6.1%)**	**38 (9.4%)**	**1 (2.9%)**	**3 (11.1%)**
Injury, poisoning and procedural complications	**53 (6.7%)**	**46 (7.1%)**	**31 (7.3%)**	**32 (7.9%)**	**2 (5.9%)**	**3 (11.1%)**
Reproductive system and breast disorders	**44 (5.6%)**	**37 (5.7%)**	**22 (5.2%)**	**23 (5.7%)**	**3 (8.8%)**	**0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**28 (3.5%)**	**20 (3.1%)**	**17 (4.0%)**	**25 (6.2%)**	**3 (8.8%)**	**3 (11.1%)**

Abbreviations: BCBM = breast cancer with history of brain metastases; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q14d = once every 14 days; q21d = once every 21 days.

a. Includes Phase 1-3 studies conducted by the Applicant and that were included in the integrated safety analysis in patients with advanced breast cancer (Phase 3 Study 11-PIR-11 and Phase 2 Study 08-PIR-05), ovarian cancer (Phase 2 Study 08-PIR-04), metastatic colorectal cancer (Phase 2 Study 08-PIR-03), and refractory solid tumours (Phase 1 Study 06-IN-IR001).

b. All Onzeald doses were by intravenous infusion over a 90 ± 15 minute duration.

c. Pooled dose levels include < 48.3 mg/m^2/week, 48.3 mg/m^2/week (145 mg/m^2 q21d, the dose and regimen intended for marketing), 72.5 mg/m^2/week (145 mg/m^2 q14d), and > 72.5 mg/m^2/week.

d. Equivalent to 48.3 mg/m^2/week.

Serious adverse event / deaths / other significant events

AEs of special interest

Diarrhoea

According to the NCI-CTCAE toxicity grading, grade 1 and 2 diarrhoea constitute different levels of increase in number of stools over baseline, while grade 3 indicates a clinically more significant condition defined as ≥ 7 stools per day more than normal, incontinence, hospitalization indicated, severe increase in ostomy output compared to baseline, and/or diarrhoea that limits self-care Activities of Daily Living (ADL; including bathing, dressing and undressing, feeding self, using the toilet, taking medications). Grade 4 is life-threatening and 5 death.

Table 44 - Summary of Diarrhoea events (Study 11-PIR-11/BEACON, Safety Population)

	Onzeald 145 mg/m² q21d[a] (N = 425)	TPC Per Standard of Care (N = 406)	Total (N = 831)
Number of Diarrhoea Events	1216	130	1346
Number of Patients with at Least One Diarrhoea[b]	281 (66.1%)	80 (19.7%)	361 (43.4%)
Grade 1	177 (41.6%)	52 (12.8%)	229 (27.6%)
Grade 2	63 (14.8%)	23 (5.7%)	86 (10.3%)
Grade 3	41 (9.6%)	5 (1.2%)	46 (5.5%)
Grade 4	0 (0%)	0 (0%)	0 (0%)
Grade 5	0 (0%)	0 (0%)	0 (0%)
Onset[c] of Diarrhoea with Any Grade (days)			
n	281	80	361
Mean (SD)	28.3 (41.79)	51.2 (70.22)	33.3 (50.31)
Median	11.0	27.5	12.0
Min, Max	1, 347	1, 385	1, 385
≤ 60 days	244 (57.4%)	58 (14.3%)	302 (36.3%)
> 60 - 90 days	14 (3.3%)	8 (2.0%)	22 (2.6%)
> 90 - 150 days	18 (4.2%)	10 (2.5%)	28 (3.4%)
> 150 days	5 (1.2%)	4 (1.0%)	9 (1.1%)
Onset[c] of Grade 2 or Higher Diarrhoea (days)			
n	104	28	132
Mean (SD)	66.7 (78.90)	79.8 (86.42)	69.5 (80.39)
Median	39.5	66.5	43.0
Min, Max	1, 471	1, 385	1, 471
≤ 60 days	72 (16.9%)	13 (3.2%)	85 (10.2%)
> 60 - 90 days	10 (2.4%)	8 (2.0%)	18 (2.2%)
> 90 - 150 days	11 (2.6%)	4 (1.0%)	15 (1.8%)
> 150 days	11 (2.6%)	3 (0.7%)	14 (1.7%)
Onset[c] of Grade 3 or Higher Diarrhoea (days)			
n	41	5	46
Mean (SD)	80.6 (94.90)	22.0 (32.39)	74.3 (91.86)
Median	43.0	7.0	40.5
Min, Max	3, 488	1, 79	1, 488
≤ 60 days	25 (5.9%)	4 (1.0%)	29 (3.5%)
> 60 - 90 days	5 (1.2%)	1 (0.2%)	6 (0.7%)
> 90 - 150 days	5 (1.2%)	0	5 (0.6%)
> 150 days	6 (1.4%)	0	6 (0.7%)
Median Duration[d] of Any Grade Diarrhoea (days)			
n	278	73	351
Mean (SD)	3.3 (5.68)	9.8 (19.91)	4.6 (10.68)
Median	1.5	3.0	2.0
Min, Max	1, 52	1, 123	1, 123

Median Duration[d] of Grade 2 or Higher Diarrhoea (days)			
n	101	26	127
Mean (SD)	6.5 (7.83)	10.1 (23.73)	7.2 (12.75)
Median	3.5	4.0	3.5
Min, Max	1, 42	1, 123	1, 123
Median Duration[d] of Grade 3 or Higher Diarrhoea (days)			
n	39	5	44
Mean (SD)	8.5 (7.51)	6.8 (8.07)	8.3 (7.50)
Median	6.0	4.0	5.5
Min, Max	1, 31	1, 21	1, 31
Number of Patients with Dose Reduction Due to Diarrhoea	47 (11.1%)	2 (0.5%)	49 (5.9%)
Number of Patients with Dose Delay Due to Diarrhoea	63 (14.8%)	3 (0.7%)	66 (7.9%)
Median Duration[d] of Dose Delay (days)[e]			
n	46	NE	NE
Mean (SD)	10.0 (5.88)		
Median	7.0		
Min, Max	4, 35		
> 30 - 60 days	1 (0.2%)		
> 15 - 30 days	4 (0.9%)		
≤ 15 days	41 (9.6%)		
Maximum Duration[d] of Dose Delay (days)[e]			
n	46	NE	NE
Mean (SD)	11.2 (6.29)		
Median	8.0		
Min, Max	4, 35		
> 30 - 60 days	1 (0.2%)		
> 15 - 30 days	6 (1.4%)		
≤ 15 days	39 (9.2%)		
Number of Patients Permanently Discontinued from Study Drug Due to Diarrhoea	18 (4.2%)	1 (0.2%)	19 (2.3%)
With Resolution	15 (3.5%)	1 (0.2%)	16 (1.9%)
Without Resolution	3 (0.7%)	0	3 (0.4%)
Time to Resolution (days)[f]			
n	15	1	16
Mean (SD)	32.1 (18.23)	6.0 ()	30.4 (18.78)
Median	28.0	6.0	26.0
Min, Max	12, 81	6, 6	6, 81
> 60 - 90 days	1 (0.2%)	0	1 (0.1%)
> 30 - 60 days	5 (1.2%)	0	5 (0.6%)
> 15 - 30 days	7 (1.6%)	0	7 (0.8%)
≤ 15 days	2 (0.5%)	1 (0.2%)	3 (0.4%)
Number of Patients With at Least One TESAE of Diarrhoea	17 (4.0%)	2 (0.5%)	19 (2.3%)

Concomitant use of antidiarrheals, intestinal anti-inflammatory / anti-infective agents[f]	60.4% (259/429)	12.1% (51/423)	N/A
Concomitant loperamide	46.9% (201/429)	3.5% (15/423)	N/A

Abbreviations: N/A: not available, SD = standard deviation; TESAE = treatment-emergent serious adverse event; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel).

a. The recommended dose and schedule on the proposed label.
b. Patients were counted once at the highest grade.
c. Onset was determined using the date of onset of adverse event relative to the first dose of study treatment.
d. The median or maximum duration was determined using the median or maximum duration at the patient level then provided as a summary for the treatment group.
e. Duration of dose delay = date of dose resumed - date of last dose induced diarrhoea -21 days for Onzeald-treated patients; If a patient had multiple dose delays, the median duration or maximum duration was determined at the patient level then provided as a summary for the treatment group.
g. Time to resolution was calculated for patients who permanently discontinued from the study drug due to diarrhoea. The time was the stop date of the event - the date of last dose + 1.
f. Calculated based on the intent-to-treat population.

A majority of etirinotecan-treated patients in BEACON who had diarrhoea AEs experienced grade 1 events (177/281, 63%). Only 41/281 (15%) experienced grade 3 diarrhoea. The median time to any grade diarrhoea was 11 days and 43 days to grade ≥3 diarrhoea. The median duration of any grade diarrhoea was 1.5 days, while grade ≥3 diarrhoea duration was 6 days.

Diarrhoea resulted in study treatment discontinuation in 3.1% of patients, dose reductions in 10.1% of patients and dose delays in 12.9% of patients treated with Onzeald in BEACON study.

Renal Failure

Renal failure is an important severe potential effect of diarrhoea.

Table 45 - Summary of Renal Failure-Related Events (Study 11-PIR-11 / BEACON, Safety Population)

	Onzeald (N = 425)	**TPC (N = 406)**
Number of Renal Failure-Related Events	12	25
Number of Patients With at Least One Renal Failure-Related TEAE	12 (2.8%)	16 (3.9%)
Grade 1	5 (1.2%)	6 (1.5%)
Grade 2	3 (0.7%)	7 (1.7%)
Grade 3	2 (0.5%)	3 (0.7%)
Grade 4	1 (0.2%)	0 (0.0%)
Grade 5	1 (0.2%)	0 (0.0%)
Blood creatinine increased	3 (0.7%)	10 (2.5%)
Blood urea increased	0 (0.0%)	1 (0.2%)
Creatinine renal clearance decreased	2 (0.5%)	0 (0.0%)
Renal failure (Grade ≥ 3 by definition)	3 (0.7%)	3 (0.7%)
Renal failure acute (Grade ≥ 3 by definition)	4 (0.9%)	2 (0.5%)

Abbreviations: SD = standard deviation; TEAE = treatment-emergent adverse event; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel).

Renal failure-related events include MedDRA preferred terms blood creatinine increased, creatinine clearance decreased, blood urea increased, renal failure, and renal failure acute.

Neutropenia

Table 46 - Summary of neutropenia-Related Events (Overall safety population, Study 11-PIR-11/BEACON and BCBM Safety Population)

	Overall Safety Population[a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald[b] All Doses[c]	Onzeald[b] 145 mg/m^2 q21d[d]	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care
	N = 790	N = 644	N = 425	N = 406	N = 34	N = 27
Number of Neutropenia-related Events	**436**	**357**	**213**	**383**	**22**	**31**
Number of Patients With at Least One Neutropenia-related TEAE[e]	**198 (25.1%)**	**164 (25.5%)**	**111 (26.1%)**	**175 (43.1%)**	**13 (38.2%)**	**9 (33.3%)**
Grade 1	19 (2.4%)	15 (2.3%)	10 (2.4%)	6 (1.5%)	1 (2.9%)	0
Grade 2	94	86	60	44 (10.8%)	7 (20.6%)	0
Grade 3	60 (7.6%)	46 (7.1%)	32 (7.5%)	79 (19.5%)	3 (8.8%)	6 (22.2%)
Grade 4	22 (2.8%)	15 (2.3%)	9 (2.1%)	45 (11.1%)	2 (5.9%)	3 (11.1%)
Grade 5	3 (0.4%)	2 (0.3%)	0	1 (0.2%)	0	0
Neutropenia (all grades)	154	132	91	126	13	4 (14.8%)
Febrile neutropenia (Grade ≥ 3 by definition)	13 (1.6%)	6 (0.9%)	3 (0.7%)	8 (2.0%)	0	0
Neutrophil count decreased (all grades)	48 (6.1%)	37 (5.7%)	25 (5.9%)	51 (12.6%)	1 (2.9%)	5 (18.5%)
Neutropenic sepsis (Grade ≥ 3 by definition)	4 (0.5%)	3 (0.5%)	0	1 (0.2%)	0	0
Onset of Neutropenia with Any Grade (days)						
n	193	160	111	175	13	9
Mean (SD)	87.3	88.8	92.1	28.2	87.2	13.1
Median	63.0	62.5	62.0	17.0	94.0	8.0
Min, Max	1, 614	4, 614	4, 614	1, 225	22, 211	7, 29
Onset of Grade 3 or Higher Neutropenia (days)						
n	85	63	41	125	5	9
Mean (SD)	108.7	114.5	123.7	34.3	132.8	13.1
Median	93.0	105.0	120.0	16.0	135.0	8.0
Min, Max	4, 482	4, 482	4, 482	1, 304	46, 211	7, 29
Median Duration of Any Grade Neutropenia (days)						
n	183	151	101	169	12	9
Mean (SD)	15.2	14.4	14.8	12.1	15.8	10.1
Median	10.0	10.0	10.0	8.0	13.5	8.0
Min, Max	1, 128	1, 67	2, 67	1, 166	7, 38	3, 15

	Overall Safety Population[a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald[b] All Doses[c]	Onzeald[b] 145 mg/m^2 q21d[d]	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care
	N = 790	N = 644	N = 425	N = 406	N = 34	N = 27
Median Duration of Grade 3 or Higher Neutropenia (days)						
n	78	57	35	120	3	9
Mean (SD)	14.9	15.2	18.2	10.9 (9.31)	12.3	10.1
Median	11.0	11.0	12.0	8.0	8.0	8.0
Min, Max	1, 159	2, 159	3, 159	1, 70	7, 22	3, 15
Number of Patients with Dose Reduction Due to Neutropenia	**70 (8.9%)**	**68 (10.6%)**	**61 (14.4%)**	**56 (13.8%)**	**6 (17.6%)**	**5 (18.5%)**
Number of Patients with Dose Delay Due to Neutropenia	**79 (10.0%)**	**70 (10.9%)**	**34 (8.0%)**	**81 (20.0%)**	**1 (2.9%)**	**3 (11.1%)**
Number of Patients Permanently Discontinued from Study Drug Due to Neutropenia	**26 (3.3%)**	**21 (3.3%)**	**14 (3.3%)**	**7 (1.7%)**	**4 (11.8%)**	**2 (7.4%)**
With Resolution	15 (1.9%)	12 (1.9%)	7 (1.6%)	6 (1.5%)	3 (8.8%)	2 (7.4%)
Without Resolution	11 (1.4%)	9 (1.4%)	7 (1.6%)	1 (0.2%)	1 (2.9%)	0
Time to Resolution (days)						
n	159	129	7	6	3	2
Mean (SD)	24.2	22.0	43.3	17.0 (8.94)	50.3	10.5
Median	15.0	15.0	35.0	12.0	35.0	10.5
Min, Max	1, 128	1, 125	12, 82	10, 29	34, 82	10, 11

Neutropenia-related TEAEs include the preferred terms of febrile neutropenia, neutropenia, neutropenic sepsis, and neutrophil count decreased.

Abbreviations: BCBM = breast cancer with history of brain metastases; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q14d = once every 14 days; q21d = once every 21 days.

a. Includes Phase 1-3 studies conducted by the Applicant and that were included in the integrated safety analysis in patients with advanced breast cancer (Phase 3 Study 11-PIR-11 and Phase 2 Study 08-PIR-05), ovarian cancer (Phase 2 Study 08 PIR-04), metastatic colorectal cancer (Phase 2 Study 08-PIR-03), and refractory solid tumours (Phase 1 Study 06-IN-IR001).
b. All Onzeald doses were by intravenous infusion over a 90 +/- 15 minute duration.
c. Pooled dose levels include < 48.3 mg/m^2/week, 48.3 mg/m^2/week (145 mg/m^2 q21d, the dose and regimen intended for marketing), 72.5 mg/m^2/week (145 mg/m^2 q14d), and > 72.5 mg/m^2/week.
d. Equivalent to 48.3 mg/m^2/week.
e. Patients were counted once at the highest Grade.

The incidence of neutropenia-related AEs was approximately 25% in the overall safety populations (all doses and at target dose) and in the full BEACON population. It was lower in the etirinotecan compared with the TPC arm (43%). In the BCBM subpopulation, the frequencies were more similar (38 and 33%), but numbers are low and BCBM not a stratified population. The frequency of grade ≥3 neutropenia-related events were <10% in the three large etirinotecan safety populations, and 16% in BCBM, compared with >30% for TPC. The frequency of dose reduction was the same across study arms, 14% in full BEACON and 18% in BCBM pop, while dose delay was more frequent in the TCP arm (8 vs 30%

full pop). Permanent discontinuation was higher in the etirinotecan arm (3.3% vs 1.7%) (3.3% consistently in the three large safety population).

Cholinergic-like Reactions

Cholinergic-like reactions are a known class effect of topo-I inhibitors. The frequency of patients with any cholinergic-like reaction was 23% in the Overall safety population, all doses (180/790), 22% in the Overall safety population at target dose (141/644) and 23% in the full BEACON population (98/425).

The following AEs (preferred terms) for cholinergic-like reactions were reported for etirinotecan in the Overall safety population, with frequencies for Overall safety population at target dose/full BEACON pop.: Vision blurred (13/13%), visual impairment (2/3%), blepharospasm (1/2%), lacrimation increased (1/1%); muscle spasms (5/5%), muscle twitching (2/1%); muscle contractions involuntary (0.5/0.2%), cholinergic syndrome (0.6/0.9%); rhinorrhoea (1/2%); hyperhidrosis (0.8/0.5%); salivary hypersecretion (0.5/0.5%).

Nearly all patients that experienced a cholinergic-like reaction experienced Grade 1 or 2 events (178 out of 180 affected patients in Overall safety population all doses, 99%). Only two patients in the entire safety database experienced a Grade 3 event (vision blurred and cholinergic syndrome, both at 145 mg/m^2 q21d). There were no Grade 4 or 5 events in the entire safety database.

The median duration of cholinergic-like reactions was 3.0 days in the three populations the Overall safety population, all doses and at target dose, as well as in the full BEACON population. (2.0 days in BCBM pop.)

In the overall safety population at target dose, 74% (104 of 141 affected patients, 16% of population) reported eye disorders, and most of these were vision blurred (58%, 82 of 141 affected patients or 13% of the population). Similar frequencies were observed in the full BEACON population: 73% (72/98) of the patients with cholinergic-like reactions (17% of population) reported eye disorders, 57% (56/98) was vision blurred.

Cholinergic syndrome was reported in 4 patients in BEACON (0.9% of BEACON, 0.6% of Overall safety pop). One was grade 1, two were grade 2 and one was grade 3.

AEs of potential importance to quality of life

Table 47 - Summary of Events Considered Potentially Affecting Quality of Life across All Safety Populations

System Organ Class/ Preferred Term	Overall Safety Population [a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald [b] All Doses[c]	Onzeald [b], 145 mg/m^2 q21d [d]	Onzeald [b] 145 mg/m^2 q21d	TPC per Standard of Care	Onzeald [b] 145 mg/m^2 q21d	TPC per Standard of Care
	N = 790	N = 644	N = 425	N = 406	N = 34	N = 27
Alopecia	121 (15.3%)	84 (13.0%)	44 (10.4%)	95 (23.4%)	3 (8.8%)	3 (11.1%)
Grade ≥ 3	1 (0.1%)	1 (0.2%)	0	0	0	0
Asthenia and/or Fatigue	439 (55.6%)	349 (54.2%)	219 (51.5%)	236 (58.1%)	14 (41.2%)	15 (55.6%)
Grade ≥ 3	87 (11.0%)	62 (9.6%)	27 (6.4%)	31 (7.6%)	0 (0.0%)	0 (0.0%)
Myalgia	46 (5.8%)	39 (6.1%)	26 (6.1%)	59 (14.5%)	1 (2.9%)	6 (22.2%)
Grade ≥ 3	0	0	0	1 (0.2%)	0	0

Oedema peripheral	59 (7.5%)	38 (5.9%)	19 (4.5%)	43 (10.6%)	3 (8.8%)	2 (7.4%)
Grade ≥ 3	1 (0.1%)	0	0	0	0	0
Neuropathy-related events [e]	42 (5.3%)	33 (5.1%)	33 (7.8%)	104 (25.6%)	4 (11.8%)	2 (7.4%)
Grade ≥ 3	4 (0.5%)	3 (0.5%)	2 (0.5%)	15 (3.7%)	0	0

Abbreviations: BCBM = breast cancer with history of brain metastases; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q14d = once every 14 days; q21d = once every 21 days.

a. Includes Phase 1-3 studies conducted by the Applicant and that were included in the integrated safety analysis in patients with advanced breast cancer (Phase 3 Study 11-PIR-11 and Phase 2 Study 08-PIR-05), ovarian cancer (Phase 2 Study 08 PIR-04), metastatic colorectal cancer (Phase 2 Study 08-PIR-03), and refractory solid tumours (Phase 1 Study 06-IN-IR001).
b. All Onzeald doses were by intravenous infusion over a 90 +/- 15 minute duration
c. Pooled dose levels include < 48.3 mg/m^2/week, 48.3 mg/m^2/week (145 mg/m^2 q21d, the dose and regimen intended for marketing), 72.5 mg/m^2/week (145 mg/m^2 q14d), and > 72.5 mg/m^2/week
d. Equivalent to 48.3 mg/m^2/week
e. Neuropathy-related TEAEs include the preferred terms neuropathy peripheral, peripheral sensory neuropathy, paraesthesia, neurotoxicity, neuralgia, peripheral motor neuropathy, and polyneuropathy.

Immunological events

Hypersensitivity-like reactions

Hypersensitivity-like reactions occurred in 10.7% of patients treated with Onzeald at the dose and schedule intended for marketing (145 mg/m2 q21d), and in 9.4% of the BEACON population (15.0% for TPC).

Hypersensitivity-like reactions included the following preferred terms: dyspnoea (3.7%), rash (1.7%), pruritus (0.6%), pruritus generalised (0.2%), rash erythematous (0.2%), flushing (1.7%), hot flush (0.8%), hypotension (0.5), hypersensitivity (1.1%), drug hypersensitivity (0.2%), swollen tongue (1.1%), and chills (0.2%; frequencies are given for the overall study population at target dose).

The median duration was 8.0 days. There was not a clear association of occurrence with dose level. Nearly all patients that experienced a hypersensitivity-like reaction experienced Grade 1 or 2 events (67 out of 69 affected patients, 97%). Only three patients in the entire safety database experienced a Grade 3 event (two patients with dyspnoea at 145 mg/m2 q21d and one patient with hypersensitivity at 145 mg/m2 q14d). There were no Grade 4 or 5 events in the entire safety database.

Relatively few patients at the dose and schedule intended for marketing experienced hypersensitivity-type reactions classified as immune system disorders (1.2%), gastrointestinal disorders (1.1%), or general disorders and administration site conditions (0.2%).

Infusion-related reactions

Approximately half of all Onzeald-treated patients experienced at least one infusion-related reaction (Overall: 57.8%, BEACON: 55.5%, BCBM: 50.0). Nearly all events were Grade 1 or 2 and there were no Grade 4 or 5 events in any population. Grade 3 events were experienced by 3.4% of the Overall Safety Population, 2.8% of Onzeald-treated patients in the BEACON Safety Population, and by none of the Onzeald-treated patients in the BEACON Safety Population.

The most common infusion-related TEAE in Onzeald-treated patients across all Safety Populations was nausea (Overall: 40.4%, BEACON: 37.9%, BCBM: 32.4%). Grade 3 nausea was experienced relatively rarely (≤ 2%) (Overall: 1.3%, BEACON: 1.2%, BCBM: 0%).

Serious adverse events and deaths

SAEs

Table 48 - Incidence of Serious Adverse Events in ≥ 1% of the Population or Treatment Arm Across All Safety Populations

System Organ Class / Preferred Term	Overall Safety Population[a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald[b] All Doses[c]	Onzeald[b] 145 mg/m^2 q21d[d]	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care
	N = 790	N = 644	N = 425	N = 406	N = 34	N = 27
Total Number of TESAEs	**637**	**466**	**225**	**206**	**28**	**17**
Number of Patients With at Least One TESAE	**322 (40.8%)**	**241 (37.4%)**	**128 (30.1%)**	**129 (31.8%)**	**12 (35.3%)**	**11 (40.7%)**
Gastrointestinal disorders	**161 (20.4%)**	**110 (17.1%)**	**39 (9.2%)**	**22 (5.4%)**	**5 (14.7%)**	**1 (3.7%)**
Diarrhoea	77 (9.7%)	46 (7.1%)	17 (4.0%)	2 (0.5%)	1 (2.9%)	0
Vomiting	28 (3.5%)	22 (3.4%)	10 (2.4%)	6 (1.5%)	2 (5.9%)	0
Abdominal pain	19 (2.4%)	11 (1.7%)	2 (0.5%)	1 (0.2%)	0	0
Nausea	16 (2.0%)	13 (2.0%)	4 (0.9%)	3 (0.7%)	1 (2.9%)	0
Small intestinal obstruction	15 (1.9%)	13 (2.0%)	0	0	0	0
Intestinal obstruction	11 (1.4%)	8 (1.2%)	0	1 (0.2%)	0	0
Ascites	7 (0.9%)	6 (0.9%)	4 (0.9%)	5 (1.2%)	1 (2.9%)	1 (3.7%)
Metabolism and nutrition disorders	**53 (6.7%)**	**39 (6.1%)**	**16 (3.8%)**	**12 (3.0%)**	**1 (2.9%)**	**1 (3.7%)**
Dehydration	40 (5.1%)	28 (4.3%)	8 (1.9%)	6 (1.5%)	0	0
Infections and infestations	**50 (6.3%)**	**36 (5.6%)**	**25 (5.9%)**	**29 (7.1%)**	**1 (2.9%)**	**5 (18.5%)**
Pneumonia	8 (1.0%)	4 (0.6%)	4 (0.9%)	4 (1.0%)	0	0
Urinary tract infection	8 (1.0%)	6 (0.9%)	4 (0.9%)	3 (0.7%)	0	1 (3.7%)
General disorders and administration site conditions	**49 (6.2%)**	**38 (5.9%)**	**13 (3.1%)**	**18 (4.4%)**	**1 (2.9%)**	**1 (3.7%)**
Disease progression	23 (2.9%)	16 (2.5%)	0	0	0	0
Pyrexia	9 (1.1%)	7 (1.1%)	3 (0.7%)	5 (1.2%)	0	1 (3.7%)

System Organ Class / Preferred Term	Overall Safety Population[a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald[b] All Doses[c]	Onzeald[b] 145 mg/m^2 q21d[d]	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care
Respiratory, thoracic and mediastinal disorders	**43 (5.4%)**	**34 (5.3%)**	**24 (5.6%)**	**29 (7.1%)**	**1 (2.9%)**	**0**
Pleural effusion	16 (2.0%)	16 (2.5%)	15 (3.5%)	18 (4.4%)	1 (2.9%)	0
Pulmonary embolism	14 (1.8%)	9 (1.4%)	4 (0.9%)	1 (0.2%)	0	0
Dyspnoea	4 (0.5%)	4 (0.6%)	2 (0.5%)	7 (1.7%)	0	0
Respiratory failure	1 (0.1%)	1 (0.2%)	1 (0.2%)	5 (1.2%)	0	0
Nervous system disorders	**27 (3.4%)**	**23 (3.6%)**	**15 (3.5%)**	**8 (2.0%)**	**2 (5.9%)**	**1 (3.7%)**
Blood and lymphatic system disorders	**23 (2.9%)**	**17 (2.6%)**	**6 (1.4%)**	**8 (2.0%)**	**0**	**0**
Febrile neutropenia	9 (1.1%)	5 (0.8%)	2 (0.5%)	6 (1.5%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**21 (2.7%)**	**15 (2.3%)**	**15 (3.5%)**	**18 (4.4%)**	**2 (5.9%)**	**2 (7.4%)**
Metastases to central nervous system	6 (0.8%)	6 (0.9%)	6 (1.4%)	10 (2.5%)	2 (5.9%)	1 (3.7%)
Metastases to meninges	2 (0.3%)	2 (0.3%)	2 (0.5%)	4 (1.0%)	0	1 (3.7%)
Hepatobiliary disorders	**14 (1.8%)**	**10 (1.6%)**	**8 (1.9%)**	**3 (0.7%)**	**2 (5.9%)**	**0**
Renal and urinary disorders	**14 (1.8%)**	**9 (1.4%)**	**5 (1.2%)**	**2 (0.5%)**	**0**	**0**
Cardiac disorders	**11 (1.4%)**	**7 (1.1%)**	**6 (1.4%)**	**6 (1.5%)**	**1 (2.9%)**	**0**
Musculoskeletal and connective tissue disorders	**11 (1.4%)**	**8 (1.2%)**	**5 (1.2%)**	**10 (2.5%)**	**0**	**2 (7.4%)**

Abbreviations: BCBM = breast cancer with history of brain metastases; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q14d = once every 14 days; q21d = once every 21 days.

a. Includes Phase 1-3 studies conducted by the Applicant and that were included in the integrated safety analysis in patients with advanced breast cancer (Phase 3 Study 11-PIR-11 and Phase 2 Study 08-PIR-05), ovarian cancer (Phase 2 Study 08-PIR-04), metastatic colorectal cancer (Phase 2 Study 08-PIR-03), and refractory solid tumours (Phase 1 Study 06-IN-IR001).
b. All Onzeald doses were by intravenous infusion over a 90 ± 15 minute duration.
c. Pooled dose levels include < 48.3 mg/m^2/week, 48.3 mg/m^2/week (145 mg/m^2 q21d, the dose and regimen intended for marketing), 72.5 mg/m^2/week (145 mg/m^2 q14d), and > 72.5 mg/m^2/week.
d. Equivalent to 48.3 mg/m^2/week.

Deaths

A TEAE leading to death is defined as an AE reported as the primary cause of death on the eCRF.

Table 49 - Summary of Deaths and TEAEs Leading to Death (Study 11-PIR-11/BEACON, Safety Population)

	BEACON Safety Population		BCBM Safety Population	
	Onzeald[a] 145 mg/m^2 q21d[b]	TPC per Standard of Care	Onzeald[a] 145 mg/m^2 q21d[b]	TPC per Standard of Care
	N = 425	N = 406	N = 34	N = 27
Number of Deaths Overall[c]	**327 (76.9%)**	**321 (79.1%)**	**30 (88.2%)**	**25 (92.6%)**
Progressive Disease Caused Death	312 (73.4%)	304 (74.9%)	30 (88.2%)	24 (88.9%)
AE Caused Death	5 (1.2%)	8 (2.0%)	0	1 (3.7%)
Other	5 (1.2%)	4 (1.0%)	0	0
Unknown	5 (1.2%)	5 (1.2%)	0	0
Number of Patients With at Least One TEAE Leading to Death	**5 (1.2%)**	**8 (2.0%)**	**0**	**1 (3.7%)**
Infections and infestations	**1 (0.2%)**	**3 (0.7%)**	**0**	**1 (3.7%)**
Septic shock	0	1 (0.2%)	0	1 (3.7%)
Lung infection	0	1 (0.2%)	0	0
Neutropenic sepsis	0	1 (0.2%)	0	0
Pneumonia	1 (0.2%)	0	0	0
Respiratory, thoracic and mediastinal disorders	**2 (0.5%)**	**3 (0.7%)**	**0**	**0**
Pleural effusion	1 (0.2%)	2 (0.5%)	0	0
Respiratory failure	1 (0.2%)	1 (0.2%)	0	0
Hepatobiliary disorders	**0**	**1 (0.2%)**	**0**	**0**
Hepatic failure	0	1 (0.2%)	0	0
Metabolism and nutrition disorders	**0**	**1 (0.2%)**	**0**	**0**
Fluid overload	0	1 (0.2%)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (0.2%)**	**0**	**0**	**0**
Myelodysplastic syndrome	1 (0.2%)	0	0	0
Renal and urinary disorders	**1 (0.2%)**	**0**	**0**	**0**
Renal failure acute	1 (0.2%)	0	0	0

Abbreviations: BCBM = breast cancer with history of brain metastases; N/A = not analysed; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab paclitaxel); q14d = once every 14 days; q21d = once every 21 days

a. All Onzeald doses were by intravenous infusion over a 90 ± 15 minute duration.
b. Equivalent to 48.3 mg/m^2/week
c. Causes are as reported on the electronic case report form.

AEs of interest with fatal outcome

In the etirinotecan arm of BEACON, there were no AEs with fatal outcome due to GI disorders (2 in TPC arm). There was 1 AE in the Infections SOC (pneumonia) with fatal outcome (3 in TPC arm). There was 1 acute renal failure, 2 hepatic encephalopathy, and 1 hepatic failure with fatal outcome (0, 0 and 2 in TPC arm).

Discontinuation due to adverse events

Table 50 - Adverse Events Leading to Study Drug Discontinuation in ≥ 1% (> 1 Patient in BCBM) of the Population or Treatment Arm Across All Safety Populations

System Organ Class/ Preferred Term	Overall Safety Population[a]		BEACON Safety Population		BCBM Safety Population	
	Onzeald[b] All Doses[c]	Onzeald[b] 145 mg/m^2 q21d[d]	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care	Onzeald[b] 145 mg/m^2 q21d[d]	TPC per Standard of Care
	N = 790	N = 644	N = 425	N = 406	N = 34	N = 27
Total Number of TEAEs Leading to Study Drug Discontinuation	**137**	**84**	**47**	**27**	**7**	**1**
Number of Patients With at Least One TEAE Leading to Study Drug discontinuation	**133 (16.8%)**	**84 (13.0%)**	**47 (11.1%)**	**27 (6.7%)**	**7 (20.6%)**	**1 (3.7%)**
Gastrointestinal disorders	**71 (9.0%)**	**39 (6.1%)**	**22 (5.2%)**	**1 (0.2%)**	**4 (11.8%)**	**0**
Diarrhoea	47 (5.9%)	25 (3.9%)	13 (3.1%)	0	2 (5.9%)	0
Blood and lymphatic system disorders	**18 (2.3%)**	**17 (2.6%)**	**12 (2.8%)**	**2 (0.5%)**	**2 (5.9%)**	**0**
Neutropenia	13 (1.6%)	12 (1.9%)	10 (2.4%)	1 (0.2%)	2 (5.9%)	0
General disorders and administration site conditions	**8 (1.0%)**	**4 (0.6%)**	**0**	**3 (0.7%)**	**0**	**0**
Metabolism and nutrition disorders	**8 (1.0%)**	**5 (0.8%)**	**3 (0.7%)**	**1 (0.2%)**	**0**	**0**
Nervous system disorders	**3 (0.4%)**	**3 (0.5%)**	**2 (0.5%)**	**9 (2.2%)**	**0**	**0**
Neuropathy peripheral	0	0	0	7 (1.7%)	0	0
Respiratory, thoracic and mediastinal disorders	**3 (0.4%)**	**2 (0.3%)**	**2 (0.5%)**	**5 (1.2%)**	0	0

Abbreviations: BCBM = breast cancer with history of brain metastases; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q14d = once every 14 days; q21d = once every 21 days.

a. Includes Phase 1-3 studies conducted by the Applicant and that were included in the integrated safety analysis in patients with advanced breast cancer (Phase 3 Study 11-PIR-11 and Phase 2 Study 08-PIR-05), ovarian cancer (Phase 2 Study 08-PIR-04), metastatic colorectal cancer (Phase 2 Study 08-PIR-03), and refractory solid tumours (Phase 1 Study 06-IN-IR001).

b. All Onzeald doses were by intravenous infusion over a 90 ± 15 minute duration.

c. Pooled dose levels include < 48.3 mg/m^2/week, 48.3 mg/m^2/week (145 mg/m^2 q21d, the dose and regimen intended for marketing), 72.5 mg/m^2/week (145 mg/m^2 q14d), and > 72.5 mg/m^2/week

d. Equivalent to 48.3 mg/m^2/week

Laboratory findings

Table 51 - Summary of Laboratory Abnormalities for Patients with Normal Laboratory Status at Baseline

Lab Tests	BEACON Safety Population				BCBM Safety Population			
	Onzeald [a], 145 mg/m^2 q21d [b] (N=425)		TPC per Standard of Care (N=406)		Onzeald [a], 145 mg/m^2 q21d [b] (N=34)		TPC per Standard of Care (N=27)	
	Normal at Baseline [c] N	Abnormal at Post Baseline N (%) [d]	Normal at Baseline [c] N	Abnormal at Post Baseline N (%) [d]	Normal at Baseline [c] N	Abnormal at Post Baseline N (%) [d]	Normal at Baseline [c] N	Abnormal at Post Baseline N (%) [d]
Neutrophils < LLN	382	149	351	128 (36.5%)	32	13	20	7 (35.0%)

		(39.0%)				(40.6%)		
RBC < LLN	212	130 (61.3%)	207	91 (44.0%)	18	12 (66.7%)	15	6 (40.0%)
Platelets < LLN	374	35 (9.4%)	355	27 (7.6%)	30	4 (13.3%)	25	1 (4.0%)
WBC < LLN	352	189 (53.7%)	336	145 (43.2%)	30	20 (66.7%)	21	9 (42.9%)
Potassium < LLN	413	40 (9.7%)	397	24 (6.0%)	33	5 (15.2%)	26	0
Urea > ULN	387	39 (10.1%)	370	54 (14.6%)	31	3 (9.7%)	24	4 (16.7%)
Creatinine > ULN	346	44 (12.7%)	339	40 (11.8%)	31	1 (3.2%)	23	2 (8.7%)
Alanine Aminotransferase > ULN	332	79 (23.8%)	307	103 (33.6%)	28	7 (25.0%)	24	7 (29.2%)
Aspartate Aminotransferase > ULN	263	66 (25.1%)	235	81 (34.5%)	20	5 (25.0%)	15	8 (53.3%)
Bilirubin > ULN	404	26 (6.4%)	391	16 (4.1%)	32	3 (9.4%)	27	2 (7.4%)
Haemoglobin < LLN	270	115 (42.6%)	252	119 (47.2%)	21	9 (42.9%)	13	6 (46.2%)
Albumin < LLN	393	54 (13.7%)	377	57 (15.1%)	28	5 (17.9%)	24	7 (29.2%)
Total protein < LLN	390	116 (29.7%)	379	92 (24.3%)	31	10 (32.3%)	22	6 (27.3%)
Alkaline phosphatase > ULN	251	81 (32.3%)	213	65 (30.5%)	19	6 (31.6%)	12	5 (41.7%)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; LLN = lower limit of normal; RBC = red blood cell; TPC = Treatment of Physician's Choice (selected from the following list of seven single-agent intravenous therapies that are the standard of care treatment in advanced breast cancer: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel or nab-paclitaxel); q21d = once every 21 days; ULN = upper limit of normal; WBC = white blood cell.

a. All Onzeald doses were by intravenous infusion over a 90 +/- 15-minute duration
b. Equivalent to 48.3 mg/m^2/week
c. Baseline is defined as the last test result prior to the first dose.
d. Percentages are based on the number of subjects in safety population with normal lab status at baseline.

Shifts x 3 ULN/LLN

With regard to both ALT and AST, approximately 26% of etirinotecan-treated patients had increases to above ULN and <2% had shifts to 3x ULN. Somewhat higher frequencies of increase were seen for TPC (> 30% and approx. 4%, respectively, for both ALT and AST). ALP shifts were similar across arms, approximately 30%, with slightly more shifts to > 3x ULN for TPC (2 vs 4%).

Creatinine shifts were also similar (15 vs 12%, etirinotecan vs TPC, no shifts x3 ULN); similarly urea shifts (12 vs 14%, no shifts x3).

Glucose shifts were more frequent in etirinotecan arm (6 vs 3.5%). LD shifts were less frequent (24 vs 42%). Phosphate shifts occurred in similar frequencies across arms, approximately 20%.

Safety in special populations

Table 52 - Safety in the Elderly population

MedDRA Terms	Age <65 N=499 number (percentage)	Age 65-74 N=121 number (percentage)	Age 75-84 N=24 number (percentage)	Age 85+ N=0 number (percentage)
Subjects with ≥1 Serious AE	257 (51.5%)	65 (53.7%)	9 (37.5%)	0 (0.0%)
Subjects with a fatal event	28 (5.6%)	10 (8.3%)	1 (3.6%)	0 (0.0%)
Subjects with hospitalization/prolonged events	215 (43.1%)	53 (43.8%)	6 (21.4%)	0 (0.0%)
Subjects with ≥1life-threatening event	20 (4.0%)	3 (2.5%)	2 (7.1%)	0 (0.0%)
Subjects with ≥1 disability event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subjects with ≥1 other medically significant events	10 (2.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)
AE leading to drop-out	52 (10.4%)	27 (22.3%)	5 (20.8%)	0 (0.0%)
Individual items of interest				
Psychiatric disorders	99 (19.8%)	14 (11.6%)	2 (8.3%)	0 (0.0%)
Nervous system disorders	240 (48.1%)	68 (56.2%)	6 (25.0%)	0 (0.0%)
Accidents and injuries	15 (3.0%)	4 (3.3%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	32 (6.4%)	11 (9.1%)	4 (16.7%)	0 (0.0%)
Vascular disorders	66 (13.2%)	20 (16.5%)	3 (12.5%)	0 (0.0%)
Cerebrovascular disorders	1 (0.2%)	2 (1.7%)	1 (4.2%)	0 (0.0%)
Infections and infestations	155 (31.1%)	40 (33.1%)	5 (20.8%)	0 (0.0%)
Diarrhoea	324 (64.9)	95 (78.5)	21 (87.5)	0 (0.0%)
Asthenia and/or Fatigue	256 (51.3)	80 (66.1)	13 (54.2)	0 (0.0%)
Anticholinergic syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cholinergic syndrome	6 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Quality of life decreased	406 (81.4%)	112 (92.6%)	24 (100.0%)	0 (0.0%)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	80 (16.0%)	24 (19.8%)	2 (8.3%)	0 (0.0%)
Other AE appearing more frequently in older patients				
Anaemia	79 (15.8%)	25 (20.7%)	11 (45.8%)	0 (0.0%)
Dehydration	53 (10.6%)	25 (20.7%)	8 (33.3%)	0 (0.0%)

Note: Subject numbers derived from the Safety population (N = 644) of patients who received Onzeald at the recommended dose and schedule (145 mg/m^2 q21d).

UGT1A1 Genotype

Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is involved in the metabolic deactivation of SN38, the active metabolite of etirinotecan pegol, to its inactive glucuronide, SN38G. The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. The SN38 metabolic capacity phenotypes are defined as poor (homozygous or 7/7), intermediate (heterozygous or 6/7), or normal (wild type or 6/6), depending on the number of thymine-adenine (TA) repeats found in each allele.

The Overall Safety Population provided data from 437 patients with known UGT1A1 phenotypes: 42 (9.6%) were poor (7/7) and 395 (90.4%) were either wild type or intermediate.

Table 53 - UGT1A1 Promoter Region TA Repeat Polymorphism and Diarrhoea, Dehydration and Neutropenia (Onzeald Safety Population)

AE /UGT1A1 Status	Overall Safety Population			
	Onzeald All Doses [a]		Onzeald 145 mg/m² q21d [b]	
	N = 437		N = 298	
UGT1A1 Phenotype: Poor	42		28	
UGT1A1 Phenotype: Intermediate/Normal	395		270	
	All grade	**Grade ≥ 3**	**All grade**	**Grade ≥ 3**
Diarrhoea				
Poor	33 (78.6%)	15/42 (35.7%)	21 (75.0%)	6/28 (21.4%)
Intermediate/Normal	292 (73.9%)	81/395 (20.5%)	186 (68.9%)	38/270 (14.1%)
Odds Ratio (95% CI)		2.15 (1.09 - 4.24)		1.67 (0.63 - 4.37)
Neutropenia				
Poor	14 (33.3%)	10/42 (23.8%)	8 (28.6%)	5/28 (17.9%)
Intermediate/Normal	90 (22.8%)	45/395 (11.4%)	64 (23.7%)	28/270 (10.4%)
Odds Ratio (95% CI)		2.43 (1.12 - 5.28)		1.88 (0.66 - 5.33)
Dehydration [c]				
Poor	14 (33.3%)	7/42 (16.7%)	4 (14.3%)	2/28 (7.1%)
Intermediate/Normal	54 (13.7%)	26/395 (6.6%)	20 (7.4%)	11/270 (4.1%)
Odds Ratio (95% CI)		2.84 (1.15 - 7.01)		1.81 (0.38 - 8.62)

The SN38 metabolic capacity (UGT1A1) phenotypes are defined as poor (7/7), intermediate (heterozygous or 6/7), or normal (wild type or 6/6), depending on the number of thymine-adenine (TA) repeats found in each allele. a) Dose levels include < 48.3 mg/m^2/week, 48.3 mg/m^2/week (145 mg/m^2 q21d, the dose and regimen intended for marketing), 72.5 mg/m^2/week (145 mg/m^2 q14d), and > 72.5 mg/m^2/week b) Equivalent to 48.3 mg/m^2/week, c) Only those events associated with diarrhoea

Patients homozygous for the UGT1A1*28 allelle ("7/7 genotype" or poor metaboliser) had higher frequencies of SN38-related AEs compared with patients with heterozygous or wildtype UGT1A1 status. This trend was most pronounced with regard to AEs of toxicity grade 3 or higher: diarrhoea (21 vs 14%, odds ratio 1.67, 95%CI 0.63 - 4.37), neutropenia (18 vs 10%, odds ratio 1.88, 95%CI 0.66 - 5.33), and diarrhoea-related dehydration events (7 vs 4%, odds ratio 1.81, 95%CI 0.38 - 8.62).

Safety related to drug-drug interactions and other interactions

Drug-drug interactions

The use of potent cytochrome P450 3A4 (CYP3A4) inducers or inhibitors did not exclude participation in the study, providing an opportunity to do so. Only 2.5% in the entire Onzeald Safety Population and 1.2% in the BEACON ITT Population used a strong CYP3A4 inducer or inhibitor concomitant with Onzeald.

Use of Tobacco

Cigarette smoking has been reported to reduce the exposure of both irinotecan and SN38, with consequent lower frequencies of haematologic toxicity from irinotecan therapy. No analysis of PK or safety in relation to smoking was submitted for Onzeald.

Supportive studies

Studies 08-PIR-05 and 08-PIR-04 – comparing RP2D regimens

These Phase 2 studies compared the two doses concluded as recommended for phase 2 (RP2D) in the preceding Phase 1 study 06-IN-IR001, i.e. 145 mg/m^2 every two weeks (q14d) and 145 mg/m^2 every three weeks (q21d). They were performed in patients with metastatic breast cancer who had failed on prior taxane treatment, and in patients with metastatic or unresectable locally advanced platinum-resistant ovarian cancer, respectively.

Table 54 - Summary of Exposure (Studies 08-PIR-05 and 08-PIR-04)

	08-PIR-05 - Breast cancer		08-PIR-04 - Ovarian cancer	
	Etirinotecan q14d (N=35)	Etirinotecan q21d (N=35)	Etirinotecan q14d (N=38)	Etirinotecan q21d (N=139)
Exposure Duration (days)				
Mean (SD)	118.3 (113.66)	127.7 (98.34)	118.7 (119.53)	117.1 (98.36)
Median	98.0	130.0	83.5	91
Number of Cycles/Infusions				
Mean (SD)	7.8 (7.53)	5.7 (4.54)	7.5 (6.68)	5.1 (4.17)
Median	6.0	6.0	5.5	4
Cumulative Dose (mg)				
Mean (SD)	1928.7 (1771.32)	1428.3	1830.0 (1481.90)	1246.9
Median	1430.0	1445.0	1441	958
Dose Intensity (mg/m^2/week)				
Mean (SD)	67.1 (8.45)	44.3 (5.39)	64.6 (11.00)	44.5 (5.84)
Median	70.9	45.6	69.8	46.6
Relative Dose Intensity (%)				
Mean (SD)	92.5 (11.65)	91.7 (11.14)	89.0 (15.17)	92.0 (12.10)
Median	97.7	94.4	96.2	96.4

The q14d schedule naturally results in a higher dose intensity (mg/m^2/week) and shorter exposure duration compared with the q21d schedule. The mean number of cycles (etirinotecan infusions) and the cumulative dose were also higher for the q14d compared with the q21d schedule in both studies. The relative dose intensity, potentially reflecting tolerability, was very similar across arms in both studies (around 92%).

Table 55 - Summary of Adverse Events (Studies 08-PIR-05 and 08-PIR-04)

	08-PIR-05 - Breast cancer		08-PIR-04 - Ovarian cancer	
Etirinotecan pegol schedule (n)	**q14d** (N = 35)	**q21d** (N = 35)	**q14d** (N = 38)	**q21d** (N = 139)
Number of Patients with any Adverse Event	35 (100.0%)	35 (100.0%)	38 (100%)	139 (100%)
Number of Patients with any Treatment-related Adverse Event	35 (100.0%)	35 (100.0%)	38 (100%)	134 (96.4%)
Number of Patients with Adverse Events Leading to Study Drug Discontinuation	8 (22.9%)	7 (20.0%)	10 (26.3%)	23 (16.5%)
Number of Patients with Adverse Events Leading to Dose Reduction	7 (20.0%)	13 (37.1%)	10 (26.3%)	25 (18.0%)
Number of Patients with Adverse Events Leading to Dose Delay	8 (42.1%)	13 (59.1%)	16 (42.1%)	53 (38.1%)
Number of Patients with Adverse Events Leading to Death[a]	8 (22.9%)	2 (5.7%)	1 (2.6%)	21 (15.1%)
Number of Patients with at Least 1 Serious Adverse Event	18 (51.4%)	15 (42.9%)	23 (60.5%)	78 (56.1%)
Number of Patients with at Least 1 Adverse Event of Grade 3 or Higher	24 (68.6%)	19 (54.3%)	26 (68.4%)	91 (65.5%)
Number of Patients with at Least 1 Treatment-related Adverse Event of Grade 3 or Higher*			25 (65.8%)	65 (46.8%)

a: 08-PIR-05: Of these 10 patients, the cause of death was listed as progressive disease in 6 patients. 08-PIR-04: Of these 22 patients, the cause of death was listed as progressive disease in 8 patients.

The proportion of patients with AEs that led to etirinotecan discontinuation was similar across arms at around 20% in the breast cancer study 08-PIR-05 (numerically higher in q14d arm), and higher in the q14d arm of the ovarian cancer study 08-PIR-04. Diarrhoea lead to permanent discontinuation of etirinotecan treatment more frequently in the q14d arm compared with the q21d arm of both studies (around 10% vs 6% in both).

Dose reductions and dose delays were more frequent in the q21d arm compared with the q14d arm of study 08-PIR-05. In study 08-PIR-04 dose reductions were more frequently seen for q14d and with similar frequencies of dose delays across arms (numerically higher in q14d).

SAEs were more frequent in the q14d arm of both studies. AEs of toxicity grade ≥3 were more frequent with the q14 day schedule in 08-PIR-05, while similar in 08-PIR-04, where however a relevant difference in study drug-related grade ≥3 AEs was seen in favour of q21d.

With regard to AEs leading to death, there was 1 death due to acute renal failure on the q14d schedule of both studies, considered definitely and possibly related to study drug by investigator, respectively. Sepsis, septic shock and neutropenic sepsis constituted the most common AE leading to death. The frequency of sepsis-related AEs leading to death appeared similar across arms (1/35 =3% in q14d of 08-PIR-05, 4/139=3% in q 21d of 08-PIR-04). In addition, there was a death due to pneumonia in q14d of 08-PIR-05. The other AEs with fatal outcome occurred in single patients.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The information derived from the pivotal study 11-PIR-11 (BEACON) is considered of main interest to the safety assessment, as this was performed at target dose and in a breast cancer population. Furthermore, in BEACON, strict toxicity management guidelines were used that were based on the prior Phase 2 study experience, resulting in an improved toxicity profile.

The target population is a subpopulation of the breast cancer population, i.e. patients with breast cancer that has metastasised to the brain. This subpopulation can be expected to differ with regard to safety to some degree from the overall breast cancer population due to patients being in a later disease stage (there were more patients with performance status ECOG 1) and thereby potentially more susceptible or less tolerant to some adverse drug reactions. It is noted that the Phase 2 and 3 studies that evaluated Onzeald in breast cancer patients excluded patients with Eastern Cooperative Oncology Group (ECOG) scores greater than one. The safety profile of Onzeald in patients with ECOG scores greater than one is not known. There are also no data available in patients who have not received local therapy (surgical resection, whole brain radiotherapy, and/or stereotactic radiosurgery) for their brain metastases.

The safety information derived from the overall etirinotecan-treated study population is expected to be generally informative with regard also to the BCBM subgroup, whereas the small numbers in the latter group may cause the observed frequencies to be less representative and predictive of the safety in a future clinical use in a BCBM population.

In comparisons against TPC, the full BEACON population is also considered generally more informative and reliable, since the similar efficacy observed in the full population resulted in a similar observation times across arms, while the large difference in PFS in the BCBM subpopulation resulted in different observation times for AEs, impacting on the observed frequencies. The AE frequencies of the full BEACON etirinotecan-treated population are thus considered more robust than those of the small BCBM subgroup, where events in single patients may have an unrepresentatively large impact on the frequencies, and further complicated by the different impact of the several different TPCs in this small group.

In terms of exposure, the similar and relatively high mean relative dose intensities indicate that the target dose is overall well tolerated. Dose delays of etirinotecan due to adverse events occurred at frequencies of 35-38% in the safety population at target dose, while dose interruptions occurred in 3-4%.

Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is an enzyme involved in the metabolic deactivation of SN38, the active metabolite of etirinotecan pegol, to its inactive glucuronide, SN38G. The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. One specific variation of the UGT1A1 gene includes a polymorphism in the promoter region known as the UGT1A1*28 variant. Patients who are homozygous for the UGT1A1*28 allele (known as the ‘7/7’ genotype) have reduced SN38 to SN38G metabolism and hence are at greater risk for SN38-induced severe diarrhoea or neutropenia. Increased toxicity in patients with UGT1A1 genetic polymorphism has been included in the RMP. There is not enough data available to propose a starting dose adjustment based on UGT1A1 genotype. Close monitoring should be performed in patients known to be homozygous for the UGT1A1*28 allele during treatment with etirinotecan pegol because they are at increased risk for toxicity that may require dose reduction. It is not necessary to determine the UGT1A1 genotype of patients prior to administration of etirinotecan pegol.

The use of potent cytochrome P450 3A4 (CYP3A4) inducers or inhibitors did not exclude participation in the study. However, the sample size is not sufficient to assess the effects of concomitant strong CYP3A4 inducers and inhibitors on the Onzeald safety profile or to demonstrate that the risk for CYP3A4 interactions is lower than for other irinotecan formulations. Concomitant administration of etirinotecan pegol with a strong inhibitor (e.g., ketoconazole) or strong inducer of CYP 3A4 should be avoided.

Compared with the TPC arm, the patients in the etirinotecan arm of the BEACON trial had lower frequencies (at least numerically) of grade 3 AEs, SAEs, AEs leading to death, and AEs with fatal outcome, but higher frequencies of study drug-related AEs, study drug-related SAEs, and AEs leading to study drug discontinuation. The differential reporting of drug-related AEs and action taken with regard to discontinuations by investigators for the less familiar experimental drug compared with the well-known comparator treatment of investigator's choice may have contributed to this pattern.

As expected from the known toxicity profiles of topo-I inhibitors, the most commonly reported AEs for etirinotecan were gastrointestinal, i.e. diarrhoea, nausea, vomiting, constipation, and abdominal pain. Diarrhoea was approximately three times as common in the etirinotecan arm compared with the TPC arm. Vomiting was twice as common and weight loss was also more frequent in the etirinotecan arm. Patients should be monitored for gastrointestinal toxicity during therapy and dose adjustments should be performed and supportive pharmacological treatment given, as recommended.

Furthermore, etirinotecan pegol should be contraindicated in patients with chronic or acute gastrointestinal disorders with active diarrhoea of any severity and in patients with diarrhoea of any Grade within 7 days prior, or use of anti-diarrhoeal treatment within 7 days prior to treatment.

Untreated diarrhoea may result in severe dehydration, renal failure, or fatalities. It is noted that a majority of etirinotecan-treated patients in BEACON who had diarrhoea AEs experienced grade 1 event. The duration of diarrhoea was overall mostly limited, even when severe in grade. The diarrhoea management guidelines used in the BEACON study, which were based on the prior Phase 2 study experience, resulted in reduced frequency of diarrhoea and dehydration, including Grade ≥ 3 events, compared with the overall safety population. In study BEACON, study treatment was not restarted until diarrhoea had resolved for at least 7 days without anti diarrhoeal supportive measures, and patients were discontinued after the third occurrence of Grade 2 diarrhoea. These guidelines have been considered in both the proposed Onzeald Risk Management Plan and the proposed Onzeald SmPC. Diarrhoea has been included in the RMP as important identified risk.

Overall, renal failure plus acute renal failure events (both Grade ≥ 3 by definition) appeared similar across arms (1.6% vs 1.2 %), while presence of potential overlapping in the reporting of the terms is not known. Renal failure is an important identified risk in the RMP.

Based on documented evidence that SN38 levels are higher after irinotecan administration to patients with severe renal impairment, administration of etirinotecan pegol to patients with severe (CLcr <30 mL/min) renal impairment is not recommended. Based on the toxicity profile of etirinotecan pegol and in particular the risk of dehydration and renal failure, the use in patients with severel renal impairement has been identified as missing information and included in the RMP.

The use in patients with moderate to severe hepatic impairment has also been identified as missing information and included in the RMP considering the lack of data in this patient population (see also PK aspects).

Fatigue and asthenia appeared overall similar in frequency across arms, although a certain assessment cannot be made since the extent of overlapping in the reporting of the two terms is not known. Pyrexia, peripheral oedema, and (peripheral sensory) neuropathy were less commonly observed in the

etirinotecan arm compared with the TPC arm, as can be expected since these are ADRs mainly associated with other chemotherapies. Similarly, alopecia was lower in the etirinotecan compared with the TPC arm (10% vs 23%). Mucosal inflammation was relatively low in both arms (4% vs 6% in full BEACON population).

Myelosuppression AEs (neutropenia, leukopenia, anaemia, and thrombocytopenia) appeared lower in the etirinotecan arm, with an overall frequency for the SOC at 35% vs 46% in the full BEACON population (etirinotecan vs TPC). The pattern was different in the BCBM population but this may be attributed to uncertainty and imprecision related to the small subgroup, as the effect of etirinotecan on the bone marrow is not expected to differ importantly depending on the brain metastasis status itself. AEs from the infections SOC were lower in the etirinotecan compared with the TPC arm in both the full BEACON (31% vs 40%) and BCBM populations (29% vs 44%), respectively. Severe infections are important clinical consequences of neutropenia. Therefore they are considered an important identified risk and have been included in the RMP.

Blurred vision is an expected AE due to cholinergic-like effects of irinotecan, this occurred at higher frequency in the etirinotecan compared with the TPC arm.

Etirinotecan pegol can result in hypersensitivity reactions, manifested by chills, tingling, pruritus, flushing, hot flush, angioedema, swollen tongue, dyspnoea/bronchospasm, rash/urticaria, and hypotension that occur most commonly during or after the second or subsequent infusions.

As with any pegylated medicinal product, etirinotecan pegol can result in antibody induction to the PEG component, which may result in increased risk of hypersensitivity reactions or reduced efficacy due to accelerated blood clearance. There are no data on anti-PEG antibody induction in response to etirinotecan pegol. This has been included in the RMP as important potential risk.

Severe hypersensitivity reactions following the first administration of etirinotecan pegol can occur, although these are uncommon, and may be due to pre-existing anti-PEG antibodies arising from the widespread existence of PEG in household and cosmetic products. Etirinotecan pegol is not recommended for use in immunocompromised patients.

The selected AEs considered of potential importance to quality of life occurred at lower frequencies in the etirinotecan arm compared with the TPC arm in the BEACON population. Thus, the benefit risk balance is not affected negatively in these instances. However, the impact of gastro-intestinal toxicity (not selected for potential impact) on HRQoL is noted.

The overall occurrence of SAEs was similar across treatment arms in the BEACON study. The SAE frequencies for etirinotecan-treated patients were also similar to, or (numerically) lower than, the TPC arm in BEACON for most SAE items, with the exception of GI disorders SOC (9.2 vs 5.4%), Hepatobiliary disorders SOC (1.9 vs 0.7%) and Renal and urinary disorders SOC (1.2 vs 0.5%).

The frequency of AEs reported as the primary cause of death was similar across treatment arms of BEACON (numerically lower in etirinotecan arm). No safety issues are raised based on the assessment of deaths.

In terms of discontinuation due to AEs, a larger difference was seen in the BCBM, but again, numbers were small, and the observation time was considerably longer in the etirinotecan arm.

It is interesting to note that while the overall and grade ≥3 frequencies of neutropenia were higher in the TCP arm, as was the frequency of SAEs of febrile neutropenia and Blood SOC overall, the frequency of discontinuation due to neutropenia and Blood SOC AEs overall was higher in the etirinotecan arm. It may

be an effect of investigators being more used to the TPC treatments and thereby more comfortable with continuing treatment despite neutropenia and related AEs.

It is unknown whether etirinotecan pegol or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of irinotecan and its metabolites in milk. A risk to newborns and infants cannot be excluded, therefore Onzeald should not be used during breast-feeding. Use of etirinotecan pegol during lactation has been included in the RMP as important potential risk.

There are no fertility data on the use of etirinotecan pegol in men or women. Fertility studies in animals have not been conducted with etirinotecan pegol. In animals, adverse effects of irinotecan on the fertility of offspring have been reported. Use of etirinotecan pegol during pregnancy (embryotoxicity/teratogenicity) has been included in the RMP as important potential risk.

2.6.2. Conclusions on the clinical safety

The overall safety profile of etirinotecan pegol was consistent across the four studied Safety populations. The toxicity profile is dominated by gastrointestinal reactions together with myelosuppression. The overall burden of toxicity did not appear higher for etirinotecan pegol compared with treatment of physician's choice, based e.g. on the frequencies of overall grade ≥3 AEs as well as QoL assessments (while acknowledging the potential for bias in QoL-reporting due to the open-label study design).

Overall, etirinotecan pegol is considered to have a manageable safety profile, comparable to other late line chemotherapy options in metastatic breast cancer.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Diarrhoea Severe infection Renal failure
Important potential risks	Increased toxicity in patients with UGT1A1 genetic polymorphism Embryotoxicity/Teratogenicity Use during pregnancy (embryotoxicity/teratogenicity) Use during lactation Anti-PEG antibody induction leading to a risk of reduced efficacy and an increased risk of hypersensitivity to etirinotecan pegol
Missing information	Use in patients with severe renal impairment Use in patients with moderate to severe hepatic impairment

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
15-102-14, A Phase 3 Open-Label, Randomized, Multi-Center Study of NKTR-102 Versus Treatment of Physician's Choice (TPC) in Women with HER-2 Negative Metastatic Breast Cancer Who Have Non-Progressing Brain Metastases and Have Been Previously Treated with an Anthracycline, a Taxane and Capecitabine, Category 2	To determine if Onzeald prolongs overall survival in metastatic breast cancer patients with brain metastases compared to TPC To characterize the safety profile of Onzeald in metastatic breast cancer patients with brain metastases	Assess the nature and frequency of diarrhoea, severe infection and renal failure. Assess the impact of UGT1A1 status on the safety profile of Onzeald.	Ongoing	Final report planned 2Q 2020
12-102-13, An Open-Label, Parallel-Group, Multicenter Phase 1 Study to Investigate the Pharmacokinetics of NKTR-102 for Injection (Etirinotecan Pegol) in Patients with Advanced or Metastatic Solid Tumors and Mild, Moderate or Severe Hepatic Impairment, Category 3	To characterize the safety profile of Onzeald in patients with hepatic impairment and update the SmPC as necessary. To characterize the pharmacokinetics of Onzeald in patients with hepatic impairment, including exposure to unbound irinotecan and SN-38.	Use in patients with hepatic impairment	Ongoing	Final report planned for March, 2018
Evaluate the *in vitro* potential of irinotecan to inhibit BCRP. Category 3	To characterize the potential of etirinotecan pegol as a perpetrator of drug-drug interactions	Assess the potential for drug-drug interactions.	Planned	TBD
Evaluate the *in vitro* potential of etirinotecan pegol and irinotecan to be mechanism-based inhibitors of CYP450	To characterize the potential of etirinotecan pegol as a perpetrator of drug-drug interactions	Assess the potential for drug-drug interactions.	Planned	TBD

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
enzymes. Category 3				
Evaluate the risk for *in vivo* transporter inhibition by etirinotecan pegol. Perform a literature review of *in vitro* and *in vivo* inhibition of transporters by other pegylated small molecules and/or PEG chains. If a risk for relevant transporter inhibition by pegylated small molecules cannot be excluded based on the available literature, perform in vitro transporter inhibition studies with higher concentrations of etirinotecan pegol. Category 3	To characterize the potential of etirinotecan pegol as a perpetrator of drug interactions; update the SmPC as necessary.	Assess the potential for drug interactions.	Planned	TBD

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Diarrhoea	SmPC Warning and Precaution, Dose Modification	Not applicable.
Severe infection	SmPC Warning and Precaution, Dose Modification	Not applicable
Renal failure	SmPC Warning and Precaution	Not applicable
Important Potential Risks		
Increased toxicity in patients with UGT1A1 genetic polymorphism	SmPC Warning and Precaution .	Not applicable
Use in pregnancy (embryotoxicity/teratogenicity) and during lactation	SmPC Warning and Precaution .	Not applicable
Use during lactation	SmPC Warning and Precaution .	Not applicable
Anti-PEG antibody induction leading to a risk of reduced efficacy and an increased risk of hypersensitivity to etirinotecan pegol	SmPC Warning and Precaution	Not applicable
Missing Information		
Use in patients with severe renal impairment	SmPC Dose Modification	Not applicable
Use in patients with moderate to severe hepatic impairment	SmPC Dose Modification	Not applicable

Conclusion

The CHMP and PRAC, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

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.

Periodic Safety Update Reports submission requirements

N/A

2.9. New Active Substance

The applicant declared that etirinotecan pegol is composed of pegylated irinotecan, previously authorised in the European Union, and that compared to irinotecan it differs significantly in properties with regard to safety and/or efficacy.

The CHMP considers, based on the available quality, non-clinical and clinical data, that etirinotecan pegol is considered to be a new active substance as it differs significantly in properties with regard to safety and efficacy from irinotecan contained in medicinal products Campto or Camptosar previously authorised within the European Union.

The non-clinical findings showed differences between irinotecan and etirinotecan pegol regarding pharmacodynamics, pharmacokinetics and toxicity. Furthermore, a different pharmacokinetic profile of both irinotecan and the active metabolite SN-38 was observed after administration of etirinotecan pegol compared to the administration of irinotecan. Efficacy results from a single phase 2 head-to-head comparative study of etirinotecan pegol versus irinotecan (Study 08-PIR-03) in patient with colorectal cancer support that etirinotecan pegol is clinically relevantly different from irinotecan (data not shown). In addition, the large differences in frequency of several adverse events, e.g. grade 3 Blood disorders (i.e. mainly neutropenia and related AEs) indicated a clinically relevant pharmacological difference between the substances that justifies a New Active Substance status.

However, in light of the negative recommendation, new active substance status is not applicable at this stage.

2.10. Product information

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

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.*

However, in light of the negative recommendation a satisfactory package leaflet cannot be agreed at this stage.

2.10.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant's proposed indication is the following:

Onzeald monotherapy is indicated for the treatment of adult patients with breast cancer that has metastasised to the brain, who have received prior local treatment for brain metastases (surgery and/or radiotherapy), and systemic anthracycline, taxane, and capecitabine, unless patients were not suitable for these treatments.

Breast cancer is the most common cancer in women in Europe with approximately 464,000 new cases diagnosed in 2012 and metastatic breast cancer is the leading cause of cancer-related death in women. As approximately 15-30% of patients with metastatic breast cancer will have brain metastasis, an estimated 14000 to 42000 patients in the EU will be diagnosed with brain metastases from breast cancer in any given year. Patients with brain metastasis generally also have disease localised to other sites. The prognosis is poor with approximately 80% mortality within 9 months of diagnosis.

The aim of Onzeald therapy is to prolong life while reducing symptoms of disease and/or the speed by which they occur. The treatment is not curative.

3.1.2. Available therapies and unmet medical need

There is no curative treatment for patients with breast cancer with brain metastasis (BCBM). All available treatments are palliative. Local treatments include surgery and radiotherapy, which are generally associated with important toxicity affecting quality of life, including focal neurological and cognitive side effects. Systemic therapy may also be given. The efficacy of systemic therapy for breast cancer with brain metastasis is not very well described, as patients with known brain metastasis have generally been excluded from pivotal clinical trials.

There are a number of agents approved for use in metastatic breast cancer, including those used as comparator in the pivotal study. Among the treatment in the comparator arm, ixabepilone is not approved in the EU, but is approved in the US. Gemcitabine is approved as single agent in the US, but only in combination with paclitaxel in the EU. In the advanced treatment setting of the present pivotal trials, there is little evidence of efficacy for the different treatment options that are in use, with the exception of eribulin, for which a survival improvement has been shown in a similar setting.

3.1.3. Main clinical studies

The pivotal trial is Study 11-PIR-11 (BEACON). This was an open-label, randomized, parallel, two-arm, multicentre, international Phase 3 study of etirinotecan pegol versus treatment of physician's choice (TPC) in patients with locally recurrent or metastatic breast cancer previously treated with at least two prior and a maximum of five cytotoxic chemotherapy regimens including an anthracycline, taxane, and capecitabine (ATC). The primary endpoint was overall survival (OS). The Intent-to-treat (ITT) (full study) population consisted of 852 patients and the predefined subgroup of patients with a history of brain metastasis (BCBM), upon which the application rests, consisted of 67 patients. The most common TPC agents given were eribulin, vinorelbine and gemcitabine, followed by taxanes as group.

3.2. Favourable effects

The median overall survival in the full study population was 2.1 months longer in the etirinotecan arm compared with the TPC arm (12.4 vs 10.3 months), with a hazard ratio (HR) of 0.87 (95% CI: 0.75-1.02); this was not statistically significant (p=0.08).

The BCBM subgroup was one of 57 predefined subgroups, for which no adjustment for multiple statistical testing was planned. In this group, consisting of 67 patients, the median OS was 5.2 months longer in the etirinotecan arm compared with the TPC arm (10.0 vs 4.8 months), with HR 0.51 (95% CI: 0.30- 0.86). The p value for this, unadjusted for multiplicity, was 0.01. .

In the full study population, the secondary efficacy results were consistently very similar across arms. Median progression-free survival (PFS) was 2.4 and 2.8 months (Q3 estimate 5.7 and 5.6 months) for etirinotecan and TPC, respectively, with PFS HR 0.93 (n.s.). Furthermore, objective response rate (ORR) was 16.4% and 17.0%.

Upon request, an analysis of OS was undertaken in relation to tumour burden at baseline, as estimated by target lesions. Quartiles were used to present the results in relation to the summary of target lesion diameters. In the first two quartiles the OS HR was close to 1, in the third quartile (i.e., target lesion diameter sum >51 and ≤80 mm) HR was 0.75 and in the fourth (target lesion >80 mm) 0.62. The BCBM patients were reasonably evenly distributed across the tumour size quartiles and the two arms (considering that a single patient represents a relatively large proportion in these small subgroup strata). Despite an OS HR close to 1 in the ITT population for patients with a tumour burden below the median, the OS HR in the BCBM was 0.56. The corresponding data in the group with a tumour burden above the median was 0.7 and 0.2 respectively.

The Health-related quality of life (HRQoL) and Patient-reported outcomes (PRO) results indicated less deterioration in Global health status in the etirinotecan compared with the TPC arm. However, the results should be cautiously interpreted as this was an open label study.

As eribulin is an approved drug in metastatic breast cancer, results in relation to prior eribulin exposure were explored even though this was not required for study participation. In the full study population, the OS HR point estimate was the same (0.87) in the subgroups of patients with and without prior eribulin. In the BCBM subpopulation, the HRs were 0.58 and 0.36 in patients without and with prior eribulin, respectively.

3.3. Uncertainties and limitations about favourable effects

The single pivotal trial failed to demonstrate superiority for etirinotecan pegol compared with treatment of physician's choice in the ITT population, where only eribulin has demonstrated an OS improvement in a reasonably similar population. Furthermore, ORR was similar in both arms. This creates an inherent uncertainty about the reliability of any subgroup analysis establishing the efficacy of etirinotecan pegol.

The BCBM population was one of 57 predefined subgroups where testing was not corrected for statistical multiplicity. Thus it is not statistically compelling. Furthermore, it consisted of only 67 patients. The smallness of the dataset increases the risk that the results are confounded by an imbalance in unidentified prognostic factors.

Patients were included in the BCBM subgroup provided local therapy was completed and use of corticosteroids for this indication was discontinued for at least three weeks prior to randomization with stable brain metastases (by symptoms and imaging). Thus, the studied population may not be fully representative of the indication claim.

Since brain scans were not part of the screening at inclusion, it is unknown how many patients in the control arm actually had brain metastasis. This creates uncertainty about the biological plausibility of the differential outcomes in the BCBM and the ITT population.

The data on OS related to tumor burden are derived from a post hoc analysis.

In the BCBM subgroup as well as in the full BEACON population, better relative efficacy (lower HRs) was observed for OS than PFS; HR 0.51 versus 0.84 in BCBM, and HR 0.87 versus 0.93 in ITT. Such tendencies have previously been observed in other applications in breast cancer, e.g. with eribulin. An explanation could be the large fraction of patients that had progressed on both arms at the first time-point when progression is assessed, which would make the PFS HR tends towards unity. There was also a difference between arms in PFS events due to death, with a larger fraction in the TPC arm compared with the Onzeald arm (PFS event of death: ITT: 6 vs 10%; BCBM: 6 vs 26%, for Onzeald vs TPC, respectively).

A larger fraction of patients in the Onzeald arm compared to the TPC arm received post-study therapy. In the BCBM, the mean number of post-study cancer therapies was twice as high in the etirinotecan arm compared with the TPC arm (1.7 vs 0.8). The frequency of patients with at least one post-study cancer therapy was 72 vs 48% (etirinotecan vs TPC), and 69 vs 42% received chemotherapy. The impact of this on the OS outcomes is unclear.

As there were no target lesions in the CNS per RECIST, due to prior local therapy, and the study was not designed to evaluate intracranial objective response rates in the CNS, a direct measure of intracranial activity is not available.

3.4. Unfavourable effects

The overall safety profile of etirinotecan pegol was consistent across the four studied safety populations (overall, N = 790; overall at target dose, N=644; BEACON, N = 425; and BCBM, N = 34).

Adverse event (AE) frequencies from the pivotal BEACON study are presented below as they are considered representative of the safety profile and they reflect the use of the detailed toxicity management guidelines that are also proposed to be included in the SmPC.

The most common adverse events associated with the use of etirinotecan pegol were gastrointestinal toxicities manifested as diarrhoea (66%), nausea (60%), vomiting (41%), decreased appetite (31%), constipation (26%), abdominal pain (21%), and decreased weight (13%); and bone marrow suppression manifested as neutropenia (21%), anaemia (16%), thrombocytopenia (3%), and febrile neutropenia (0.7%).

Potentially related to these common GI and myelosuppression AEs, other clinically important AEs were observed. Dehydration occurred in 10% of patients, with Grade ≥ 3 reactions at 2% (4% in the Overall safety population at target dose). A serious potential consequence of dehydration is renal failure.

Renal failure AEs were reported in similar frequencies in the two treatment arms, etirinotecan: 1.6% vs TPC: 1.2%; and clinical laboratory results showed similar frequencies of creatinine and urea increases across study arms, and no shifts to x3 of upper limit of normal (ULN). An AE of acute renal failure was listed as primary cause of death in one patient in the etirinotecan arm of BEACON (0 in TPC arm).

Infections and infestations SOC AEs (all grades) occurred in 31%of etirinotecan-treated patients and 40% of TPC; Infection SOC serious adverse events (SAEs) were reported in 5.9 vs 7.1% of patients. The number of patients with an infection as primary cause of death was low; 1 (0.2%) vs 3 (0.7%) in etirinotecan vs TPC arm, respectively.

Cholinergic-like reactions are known to be associated with irinotecan and these occurred frequently (23% as a group). Only 2 patients (0.5%) had grade 3 reactions (blurred vision and cholinergic syndrome) and none had a cholinergic-like AE of higher toxicity grade. A majority of these AEs were eye disorders (73%), the most common blurred vision (57%). Cholinergic syndrome occurred in less than 1% (in total 4 patients, one grade 3.)

The overall occurrence of SAEs was similar across treatment arms in the BEACON study, 30.1 vs 31.8% (etirinotecan vs TPC). The SAE frequencies for etirinotecan-treated patients were also similar to, or (numerically) lower than, the TPC arm in BEACON for most SAE items, with the exception of GI disorders SOC (9.2 vs 5.4%), Hepatobiliary disorders SOC (1.9 vs 0.7%) and Renal and urinary disorders SOC (1.2 vs 0.5%).

The frequency of AEs reported as the primary cause of death was similar across treatment arms of BEACON (numerically lower in etirinotecan arm).

The Health-related quality of life (HRQoL) and Patient-reported outcomes (PRO) showed worsening of symptom scales for diarrhoea, nausea and vomiting and appetite loss, consistent with the safety profile of etirinotecan pegol.

Compared with the TPC arm, the patients in the etirinotecan arm of the BEACON trial had lower frequencies (at least numerically) of grade 3 AEs (48 vs 63%), SAEs (30 vs 32%), AEs leading to death (i.e. primary cause; 1.2% vs 2.0%), and AEs with fatal outcome (3.8 vs 6.2%), but higher frequencies of study drug-related AEs (93 vs 88%), study drug-related SAEs (12 vs 6%), and AEs leading to study drug discontinuation (11 vs 7%).

When selected AEs considered to have potential impact on quality of life were compared across arms, lower frequencies were generally seen for etirinotecan than TPC: Alopecia (10 vs 23%), Asthenia (22 vs 29%; grade ≥3: 1.9 vs 3.7%), Myalgia (6.1 vs 14.5%), Peripheral oedema (4.5 vs 10.6%), Neuropathy-related events (7.8 vs 25.6%; grade ≥3: 0.5 vs 3.7%). A numerically higher frequency was only observed for Fatigue (34% vs 32%) among these selected items. However, the etirinotecan-induced AEs with the strongest impact on patients' QoL were the GI toxicities.

3.5. Uncertainties and limitations about unfavourable effects

The pattern of overall lower frequencies of grade≥ 3 AEs, SAEs and fatal AEs, but higher frequencies of drug-related AEs and discontinuation due to AEs (see above) create an uncertainty about the relative safety of etirinotecan pegol and the sum of the comparators.

3.6. Effects Table

Table 56 - Effects Table for Onzeald (etirinotecan pegol) in the treatment of patients with breast cancer with brain metastasis (Data cut-off date 08 December 2014)

Effect	Short Description	Unit	Experi-mental	Control	Difference between arms	HR (95% CI)	p-value	Strength of evidence uncertainties
Favourable Effects			**Etirino-tecan pegol**	**TPC**				Pivotal phase 3 study "BEACON"
BCBM subgroup (ITT) – sought indication		n	36	31				Pre-defined subgroup
OS	Median Event rate	m %	10.0 74	4.8 78	5.2	0.51 (0.30, 0.86)	0.010	Small sample size Results not statistically compelling No strong support from mechanistic/ pharmacology perspective Clinically relevant difference in OS; p-value unadjusted for multiplicity. OS HR < PFS HR
PFS	Median Event rate	m %	3.1 86	2.7 83	0.4	0.84 (0.49, 1.43)	0.5	Small sample size
ORR (RECIST 1.1 [a])		n	32	27				
	Proportion of patients	%	15.6	5.6	10.0			Relevant increase from low level Includes responses in all sites, not only BM Small sample size
DoR		m	5.6	3.7	1.9			Longer DoR. Small sample size
Full ITT population		n	429	423				
OS	Median Event rate	m %	12.4 86	10.3 93	2.1	0.87 (0.75, 1.02)	0.08	Not statistically significant

PFS	Median Event rate	m %	2.4 89	2.8 81	-0.4	0.93 (0.80, 1.075)	0.3	OS HR < PFS HR No difference in PFS, but trend in OS
ORR (RECIST 1.1 [a])		n	354	358				
	Proportion of patients	%	16.4	17.0	-0.6			No difference
DoR	Median	m	3.9	3.7	0.2			No difference

Unfavourable Effects		**BEACON safety pop**		**BCBM safety pop**		**Comment**	
		Etirino-tecan pegol	**TPC**	**Etirino-tecan pegol**	**TPC**		
Proportion of patients with:	n	425	406	34	27		
Grade 3 AE	%	48	63	50	70		
Study drug related AE	%	93	88	91	78		
AE leading to death [b]	%	1.2	2.0	0	3.7		
SAE	%	30	32	35	41		
Study drug related SAE	%	12	6	9	11		
AE leading to discontinuation	%	11	7	21	4		
Selected AEs							
Diarrhoea Grade 3	% %	66 10	20 1	56	19		
Renal failure (acute) [c]	%	1.6*	1.2	n.r.	n.r.	*1 fatal renal failure in EP arm	
Neutropenia -related AE [d] Grade ≥3	% %	26 10	43 31*	38 15	33 33	*1 fatal neutropenic sepsis in TPC arm	
Myalgia	%	6	15	2	22		
Neuropathy-related events [e] Grade ≥3	% %	8 0.5	26 3.7	12 0	7 0		

Abbreviations: TPC = Treatment of physician's choice, OS = Overall survival, PFS = Progression-free survival, ORR = Objective response rate, DoR = Duration of response, n = numbers, n.r. = not reported, m = months, HR= hazard ratio, AE = Adverse event, SAE = Serious adverse event

[a] : RECIST 1.1 criteria do not require confirmation of responses

[b] : AE noted as primary cause of death

[c] : Grade 3 by definition.

[d] : Neutropenia-related events include the preferred terms of febrile neutropenia, neutropenia, neutropenic sepsis, and neutrophil count decreased

[e] : Neuropathy-related events include the preferred terms neuropathy peripheral, peripheral sensory neuropathy, paraesthesia, neurotoxicity, neuralgia, peripheral motor neuropathy, and polyneuropathy.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The condition of brain metastasis is characterised by pain, physical and cognitive losses of function, loss of autonomy, and frequently also personality change. A prolongation of median overall survival by 5 months in breast cancer patients with previously treated brain metastases would constitue an important improvement in the treatment of this condition, provided that it could reliably be identified as a drug effect. In this way, etirinotecan pegol would address an unmet medical need, which is a requirement for the sought conditional marketing authorisation.

3.7.2. Balance of benefits and risks

This application is based on a subgroup analysis from a study that failed to convincingly show increased OS compared to a comparator of treatment of physician's choice. Increased PFS could not be demonstrated, and ORR was similar across arms.

As the results of the subgroup analysis on which the applicant's claim is based are not statistically compelling, the applicant proposed that further confidence in this outcome can be based on preclinical data indicating the enhanced permeability and retention (EPR) qualities of etirinotecan pegol, illustrated by evidence of accumulation in brain metastases and superior activity in preclinical BCBM models.

It is noted that experience in such animal models are thought to poorly predict effects in humans. In the absence of consistent evidence in a number of different animal models, the relevance of the available non-clinical findings cannot be confirmed. Furthermore, there are no human data to support claims of significantly enhanced accumulation and retention of etirinitecan in cerebral metastases or in larger tumours. Moreover, there is little relevant external support from other drugs thought to have EPR qualities, to support the applicant's claims.

There are no clinical data on intracranial objective responses to support the claimed indication. During the assessment procedure, the applicant provided intracranial response data from small series of patients with non-small cell lung cancer or glioma. The relevance for any claimed effect for breast cancer is unknown due to fundamental biological and clinical differences.

In summary, the available evidence for efficacy is not considered sufficient to demonstrate a positive B/R in the target population.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease and seriously debilitating disease. Advanced breast cancer with brain metastases (BCBM) is end of line where patients have received prior local cranial therapy (surgery and/or radiotherapy), anthracycline, capecitabine and taxane, unless unsuitable. The presence of brain metastases dramatically worsens quality of life, with personality change and cognitive issues featuring prominently. The prognosis is extremely poor with approximately 80% mortality at 9 months.

However, the CHMP considers that the product does not fulfil the requirements for a conditional marketing authorisation considering the benefit-risk balance is negative, as discussed.

3.8. Conclusions

The overall B/R of Onzeald in monotherapy for the treatment of adult patients with breast cancer that has metastasised to the brain, who have received prior local treatment for brain metastases (surgery and/or radiotherapy), and systemic anthracycline, taxane, and capecitabine, unless patients were not suitable for these treatments is negative.

Divergent position is appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Onzeald monotherapy for the treatment of adult patients with breast cancer that has metastasised to the brain, who have received prior local treatment for brain metastases (surgery and/or radiotherapy), and systemic anthracycline, taxane, and capecitabine, unless patients were not suitable for these treatments, the CHMP considers by majority decision that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the conditional marketing authorisation for the above mentioned medicinal product. The CHMP considers that:

Evidence of therapeutic efficacy is insufficiently substantiated in the claimed indication of patients with breast cancer that has metastasised to the brain, who have received prior local treatment for brain metastases (surgery and/or radiotherapy), and systemic anthracycline, taxane, and capecitabine, unless patients were not suitable for these treatments.

The efficacy claims are based on subgroup analysis from a single pivotal trial which failed to convincingly demonstrate efficacy. Given multiple tests, the subgroup findings are not statistically convincing. Furthermore they are not supported by a convincing biological rationale and/or corroborating clinical evidence from supportive studies.

Since the efficacy has not been sufficiently demonstrated the benefit risk balance cannot be considered positive.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Divergent position to the majority recommendation is appended to this report.

5. Re-examination of the CHMP opinion of 9 November 2017

Following the CHMP conclusion that Onzeald was not approvable (see section 4), the applicant submitted detailed grounds for the reexamination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing and at an oral explanation the following grounds for re-examination:

Ground #1 – Overall Efficacy

Summary of the Applicant's position

The Applicant strongly believes the conclusions of the CHMP on the efficacy of Onzeald in the ITT Population are incorrect because they appear to be based on a scientifically flawed interpretation of the data and reached by a narrow interpretation of the p-value that is not consistent with the CHMP Guideline on clinical trials in small populations (CHMP/EWP/83561/2005). Reference is made to Section 2, therein, which states that, "Although p<0.05 is a common but arbitrary threshold for 'statistical significance', no such value is adequate to confirm that a treatment effect truly does exist. In almost all cases, confidence intervals of estimates of the treatment effect are much more informative than P-values".

According to the Applicant, Onzeald resulted in a large positive effect on OS relative to TPC, an active comparator group receiving standard of care, in the population of patients with advanced breast cancer that has metastasised to the brain (BCBM), with a 49% reduction in the risk of death and a 5.2 month increase in median survival which is unprecedented for any therapy for patients with BCBM and are particularly important given the high unmet medical need with no approved effective therapies.

The Applicant provided additional discussion as follows:

- Onzeald resulted in 13% lower risk of death with HR of 0.87 and upper bound 95% CI of 1.02

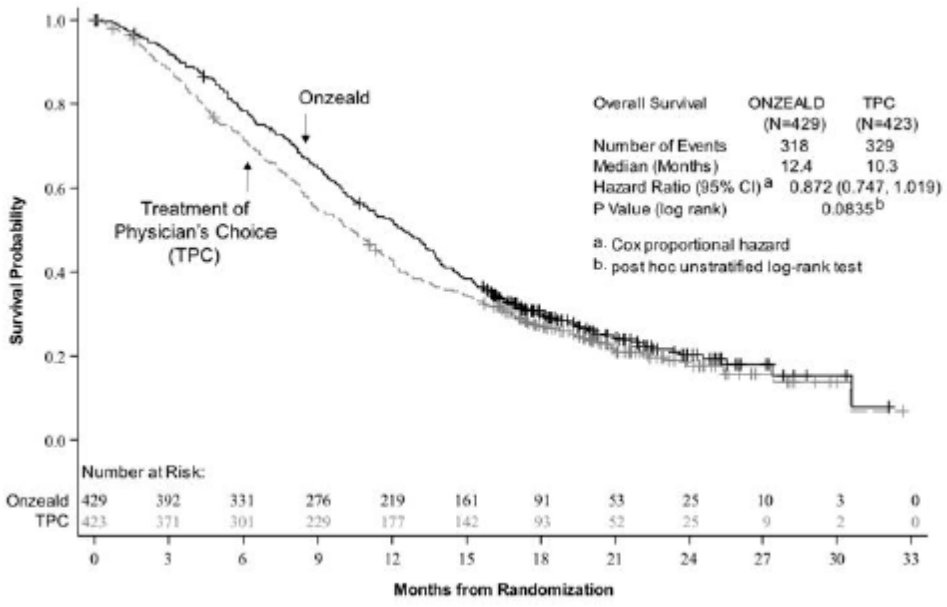
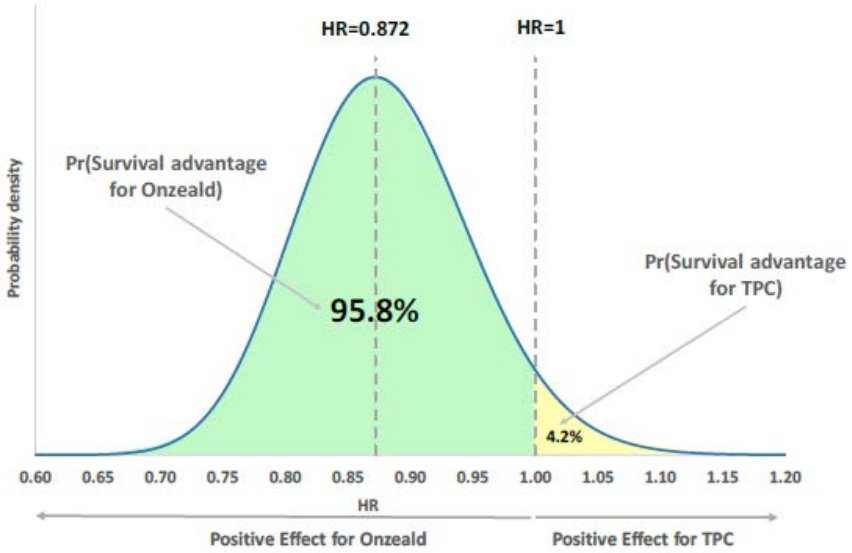


Figure 12: Study 11-PIR-11 (BEACON): Kaplan-Meier Curve of Overall Survival in the Full (ITT) Study Population

- Probability of survival benefit for onzeald was 95.8%
- Probability that TPC confers an OS advantage over onzeald is 4.2%.
- Probability of results being a false positive is very low (2%)



- The point estimate of HR = 0.87 represents an expected OS advantage of, at least, 6.5 weeks for onzeald over TPC and the lower CI of 0.75 represents, at best, an expected OS advantage of up to 14.5 weeks.
- The upper 95% CI of 1.02 would have met even the strictest definition of prospectively determined non-inferiority (NI) margins, thus reasonably supporting a conclusion that onzeald is at least non-inferior to TPC.
- Very narrow interpretation of the p-value which is not consistent with the CHMP's own guidance on clinical trials or FDA´s guidance.
- Support from international leaders in the field (both w/wo CoI) regarding the narrow interpretation of the p-value.
- Comparison to the initial approval of eribulin for advanced breast cancer based on study vs. capecitabine resulting in HR=0.88 and p=0.056.
- The difficulties inherent to studies in late line treatment of metastatic breast cancer likely due to heterogeneity of the disease.
- Factors identified as being likely to have contributed to p-value > 0.05 are i) reduced power due to non-proportionality and ii) extensive (approx. 40%) use of eribulin in the TPC group.
- Reference to the pivotal eribulin study in late line breast cancer patients resulting in similar OS figures for the TPC treatment arm with approx. 10month mOS in the 4th line of treatment.
- In the predefined subgroup (1 of 2 subgroups) of patients with advanced breast cancer patients that has metastasised to the brain (BCBM) there was a substantial and clinically meaningful benefit with a 50% reduction in the risk of death for patients treated with Onzeald (mOS 10 months with onzeald vs 4.8 months with TPC).

- Robustness of BCBM results maintained even after additional CHMP-requested statistical analyses including i) Per protocol HR=0.53, ii) Bivariate analysis vs individual TPC agent after adjusting for multiple prognostic factors HR= 0.37 – 0.54, iii) Prognostic factors not influencing result, iv) Conservative Bayesian shrinkage subgroup analysis in the BCBM patients resulting in HR=0.78; 95% CI: 0.40 – 0.96 and v) Statistical risk of a false positive findings of approximately 2%.
- The BCBM subgroup of the BEACOM study represent the largest and most robust dataset fro any of the standard of care chemotherapy options – including eribulin.

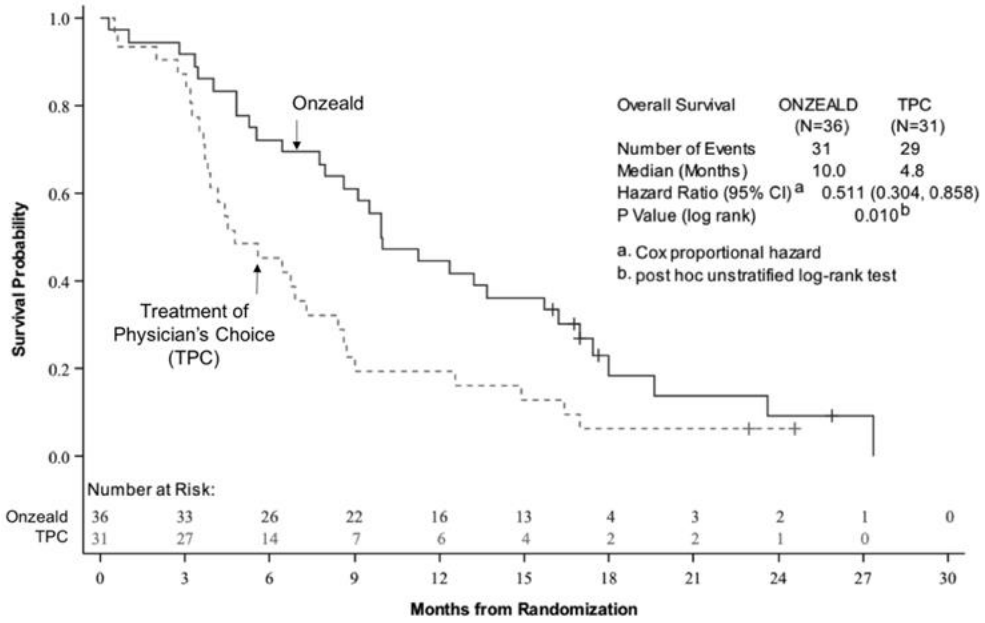


Figure 13: Study 11-PIR-11 (BEACON): Kaplan-Meier Curve of Overall Survival in the BCBM Study Population

- Expert opinions were expressed in support of the Statistical Interpretation of the BEACON Data.

CHMP assessment

Overall intent-to Treat (ITT) analysis

Pursuant to Article 4(1)(a) of Regulation (EC) No 507/2006, one of the requirements which must be culmatively fulfilled in order to obtain a conditional marketing authorisation is that the the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive. When one pivotal study is presented, particularly compelling results in terms of internal and external validity, data quality and statistical robustness are required. In the case of Onzeald, approval is requested essentially on the basis of the pivotal phase III randomized, open label BEACON study. Looking at the efficacy results in the ITT population, the study formally failed to meet the primary OS endpoint (p=0.0841, HR 0.872). As highlighted in Section 6.5 (Scenario 3) of the draft CHMP Guideline on the Investigation of Subgroups in Confirmatory Clinical Trials, from a statistical point of view, no confirmatory conclusions are possible in a clinical trial where the primary null hypothesis cannot be rejected (EMA/CHMP/539146/2013). A numerical (but not statistically significant) trend towards a prolonged median OS was observed with Onzeald (12.4 vs 10.3 months). However, this numerical trend in OS was not supported by any of the secondary endpoints analysed (i.e., PFS, ORR), reducing the credibility of the

claimed benefit. No statistically significant difference was observed in terms of PFS (HR 0.93, p=0.302), and looking at the medians, median PFS was even slightly numerically higher with TPC (2.8 months) compared with Onzeald (2.4 months). ORR was also very similar between the two treatment arms (Onzeald 16.4%, TPC 17%). Therefore, data presented do not support any superiority of efficacy of Onzeald vs TPC in the ITT population.

In the response document the Applicant clarifies that the non-inferiority exercise of Onzeald vs TPC was "not made to draw formal, regulatory conclusions on the benefit-risk of the ITT Population" but "to reinforce that Onzeald was in fact efficacious in the treatment of patients with advanced breast cancer and BEACON was not a failed trial". This is acknowledged. However, as already discussed during the original assessment, considering that the non-inferiority exercise is performed post-hoc and that, with the exception of eribulin, no treatment benefit (in terms of OS, PFS, etc) has been demonstrated in this setting with the TPC arm, any conclusion on this issue should be considered speculative.

Advanced breast cancer that has metastasised to the brain (BCBM)

In view of the formal failure of the primary analysis of the BEACON study, the Applicant decided to focus on the results obtained in the subgroups of patients enrolled in the study with a history of brain metastases (BCBM population). It should be noted that this subgroup analysis was added to the study protocol by the Applicant by a protocol amendment implemented before the results of the open label BEACON study were available. Looking at the inclusion/exclusion criteria as well as at the stratification factors it appears that when the study was designed no specific activity was expected with Onzeald in patients with brain localisation: indeed, only patients with pre-treated and stable brain metastases were enrolled and presence of brain metastases was not used as stratification criterion. Moreover, in the statistical analysis plan formally no correction of the Type I error at <5% for analysis of this subgroup was implemented. Therefore, a bias related to a data driven approach cannot be excluded.

Looking at the body of evidence presented, actually only 67 patients (Onzeald: n=36 and TPC: n=31) with history of brain metastases were enrolled. It should be noted that 34 of the 67 patients (51%) in the BCBM subgroup had no macroscopic evidence of brain metastases upon imaging at the time of enrolment. The efficacy claim is therefore based on a very small subgroup of patients enrolled.

In the BCBM subgroup, a statistically significant and clinically relevant improvement of OS with Onzeald was observed compared with TPC (median OS 6.7 vs 3.8 months, HR 0.511, p=0.010). However, a confounding effect of post-study therapies and in particular of eribulin on OS cannot be excluded as an imbalance is observed in the number of patients receiving eribulin as post-study therapy (42% in Onzeald arm vs 6% in the TPC arm), a drug that has been associated with OS benefit in this setting. Moreover, the OS results are not supported by PFS results (median PFS 3.1 vs 2.7 months, HR 0.84, p=0.523).

Regarding the evidence provided for plausibility of the effect in order to support credibility of the data:

1) No data are present from the pivotal study on intracranial activity (in terms of in brain PFS or ORR) as an element for the enrolment criteria and as a result brain lesions were not included as target lesions. If present, brain metastases were to be pre-treated and stable. According to the baseline characteristics, more than 50% of enrolled patients did not have macroscopic detectable brain disease at the time of enrolment.

2) Radiographic imaging of 3 Onzeald treated patients enrolled in the BEACON study indicating potential intracranial effect with potential reduction or stabilisation of brain disease localisations have been provided by the Applicant. This evidence is considered far from robust and compelling from a regulatory and a clinical point of view. In the literature, few series/case reports of intracranial activity of several cytotoxic drugs administerd as TPC in the BEACON study have been reported. In fact, there is no

confirmatory radiological evidence in the submitted dossier that in-brain pharmacodynamic activity of Onzeald is superior to TPC. Therefore, there is uncertainty on in-brain anti-tumour activity of Onzeald and how this might contribute to the superior OS seen in the BCBM subgroup.

3) Plausibility of the effect is also not sufficiently supported by pre-clinical or clinical evidence nor by a soundly demonstrated mechanistic effect (refer to Assessment of ground of refusal 3 and 4).

Consequently, the results of the BCBM subgroup are not considered sufficiently reliable to conclude on efficacy of Onzeald in this population.

Point not resolved.

Ground #2 – Subgroup analyses

Summary of the Applicant's position

The Applicant believes the CHMP incorrectly concluded that the group of patients with advanced breast cancer that has metastasised to the brain was 1 of 57 subgroups. This subgroup was only 1 of 2 pre-specified subsets of special interest for further analyses, as appropriately documented in the SAP, and being based on a sound a priori biological rationale for the possibility of a differential treatment effect.

The Applicant clarifies that in the BEACON study, 24 baseline factors were pre-specified for consistency analysis in the SAP (Section 8.5). Some of these factors resulted in two or more analyses and p-values (e.g., receptor status: TNBC versus HER2+ versus other), such that altogether, 57 p-values were computed. These types of consistency analyses are standard in large oncology trials where the goal is to qualitatively judge the consistency of the overall ITT result with the results in relevant subgroups, most often by the use of a visual display such as a Forest plot. The 24 factors demonstrated consistency of benefit across the ITT Population. This interpretation is also supported by the position paper of an independent statistician.

Rationale for a priori selection of the BCBM Population as One of Only Two Subsets of Special biological Interest

Importantly, of the 24 factors in the BEACON study, only 2 were identified in advance in a separate section of the SAP (Section 11.0) as subsets of special biological interest: patients whose race was Asian and patients with a history of brain metastases. Independent of the OS analyses based on the 24 baseline prognostic factors, these two separately identified populations were selected for further safety and efficacy analyses. The subset of patients with Asian race was predefined due to the high revalence of UGT1A1 polymorphisms that could potentially affect efficacy and patient safety. The BCBM subset was predefined based on the following:

• Nonclinical findings in mice generated before finalisation of the SAP. As of Q3 2013, nonclinical pharmacology studies in mice demonstrated that etirinotecan pegol preferentially accumulates (170-fold) in brain tumours over the corresponding plasma concentrations and resulted in prolonged survival and anti-tumour efficacy compared to irinotecan (later work in this model was repeated using representatives of the TPC drugs available in BEACON, including gemcitabine, eribulin, vinorelbine, and docetaxel).

• Interest in this subpopulation was also driven by higher than expected enrolment. Unlike other registration studies in advanced breast cancer, the BEACON study did not exclude patients with a history of brain metastases. As noted in the open session report for the Data Monitoring Committee's (DMC) meeting of 16 November 2012, there were more patients enrolled with brain metastases (15/168 (8.9%)) at the 19 October 2012 cut off than was initially anticipated based on initial discussions with the Steering

Committee. Consequently, the subpopulation of patients with a history of brain metastases was added to the BEACON SAP Section 11.0 for further analysis, a priori, on 22 October 2013, prior to any formal analysis of the trial data.

• Amendment of SAP 16 months prior to study unblinding: The Statistical Analysis Plan was amended on 22 October 2013 (Version 2.0) to include (among other revisions) a prospectively planned subgroup analysis of patients with "Brain Metastases". The date of the data cut-off for primary analysis of the BEACON study occurred 16-months later on 23 February 2015. The Applicant did not add the BCBM and Asian subgroups based on unblinded review of the data with aggregated treatment information. The BEACON database was held by Quintiles, a global contract research organisation (CRO), and strict rules regarding unblinding of the data were in place. Data flow and measures to manage the access to potentially unblinding data were described in the DMC Charter and the Biostatistics "Unblinding Plan".

Arguably, it would have been somewhat easier for the Applicant to focus on a larger, and hence seemingly more credible subgroup with $p < 0.05$ such as patients with liver metastases—a large subgroup with N = 446 patients and an HR of 0.73 (95% CI: 0.59, 0.89; $p < 0.0001$). However, this would have substantially lacked statistical credibility, being just one subgroup out of 24 factors that was not identified in advance as being of special interest in the SAP. Rather, despite the relatively small size of the BCBM subgroup, the Applicant remained consistent with their predefined analysis plan and focused on 1 of 2 subgroups of special interest (i.e., BCBM).

Applicability of the CHMP Guidance on Investigation of Subgroups in Confirmatory Clinical Trials

The Applicant's CMA Application for Onzeald for the treatment of patients with BCBM is based on clinically meaningful and statistically compelling OS results, in alignment with the provisions from the CHMP Guidance on Investigation of Subgroups in Confirmatory Clinical Trials, which states on p. 17 (Scenario 3) the following: "The clinical data presented fail to establish statistically persuasive evidence but there is interest in identifying a subgroup, where a relevant treatment effect and compelling evidence of a favourable risk-benefit profile can be assessed" (Guideline on the investigation of subgroups in confirmatory clinical trials; EMA/CHMP/539146/2013). As per CHMP guidance under Scenario 3, the minimum criteria that should be fulfilled are as follows: (1) "External evidence should exist that the subgroup of interest is a well-defined and clinically relevant entity." It is undisputed that the subset patients with BCBM are a well-defined and clinically relevant entity. (2) "A pharmacological rationale, or a mechanistically plausible explanation, should exist, why a certain drug or treatment could have different efficacy (or benefit/risk) in a sub-population and its complement (considering also the scale of assessment)." Multiple lines of evidence—with emphasis on clinical data— have been provided that together form a biological rationale sufficient to support a mechanistic plausibility that Onzeald would have a superior treatment effect compared to standard of care drugs. Furthermore, this plausibility is in alignment with the CHMP guidance on investigation of subgroups which defines biological plausibility, as "[…] a concept describing the extent to which a particular effect might be predicted or might be expected based on clinical, pharmacological and mechanistic considerations and considerations of other relevant external data sources", and is "[…] primarily a clinical and pharmacological judgement and is usually not a directly quantifiable or measurable concept" (EMA/CHMP/539146/2013). (3) "The estimated effect of treatment in the subgroup would usually be more pronounced in absolute terms (i.e. indicating a greater benefit) than in the all randomised population. The totality of statistical evidence, based on individual trials and pooled analyses, should meet the same standards of evidence as would usually be expected for the all-randomised population indicating that the size of the treatment effect in the subgroup is substantial as compared to the variability of the problem." The treatment effect in the BCBM Population is clearly more pronounced than in the overall population, with a 49% reduction in the risk of death and a 2.5-fold increase in the median survival advantage for Onzeald in the BCBM subgroup relative to the

overall ITT Population in the BEACON study. The positive effect for Onzeald was maintained even when conservative Bayesian subset analyses were applied. (4) “Replication of subgroup findings from other relevant trials (internal to the MAA or external trials that are relevant). A particular challenge exists in applications based on a single pivotal study since replication is a key component of credibility. In this instance, the biological plausibility and the clinical trial data from the subgroup would have to be exceptionally strong.” The OS results in the predefined BCBM subgroup are exceptionally strong, robust, and unlikely (2% probability) to be due to chance. All post hoc analyses, many of which were conducted at the request of the CHMP in the D120 LoQ and 1st D180 LOI, supported the robustness of the results in BCBM patients and gave reassurance that the result was not a false positive finding, nor attributable to any imbalance in important prognostic factors. The biological plausibility for a differential treatment effect of Onzeald over TPC is based on multiple lines of evidence—including in populations with either primary or metastatic CNS lesions and findings in complementary subgroups in the BEACON study (e.g., patients with metastases in highly perfused organs such as liver, or high tumour burden). The totality of the data supports the activity of Onzeald for the treatment of patients with BCBM. The EMA guidance for Scenario 3 (p. 18) also requires the following: “In addition, in such a situation, a clear rationale must exist as to why a properly planned trial has failed despite the drug being regarded as efficacious and why additional prospective studies to establish formal proof of efficacy are unfeasible or unwarranted.” Several factors very likely contributed to the BEACON study narrowly missing p <0.05, including non-proportional hazards and the extensive use of eribulin. A Phase 3 study (15-102-14; ATTAIN) to confirm the results of the BEACON BCBM OS analyses is ongoing. The Applicant believes that a CMA for Onzeald in advance of the completion of the ATTAIN study is warranted to provide urgently needed therapy for patients with BCBM.

Applicant’s Conclusion

Taken together, the correct interpretation of the BEACON SAP in terms of the two predefined subgroups of special interest and in particular, the BCBM subgroup, as well as the careful evaluation of the applicability of Scenario 3 of the CHMP guidance on the investigation of subgroups in confirmatory clinical trials, the Applicant strongly believes that the OS result in the subgroup of patients with BCBM is credible, not due to chance and clinically meaningful. Based on these data and the tremendously high unmet need and dire prognoses of patients with advanced breast cancer that has metastasised to the brain, the Applicant believes that a CMA for Onzeald is warranted, with subsequent provision of confirmatory data from the ongoing Phase 3 ATTAIN Study (15-102-14). The applicant provided an expert opinion letter to support the CMA.

CHMP Assessment

The Applicant clarified that the subgroup analysis in patients with BCBM was pre-specified, as added to the study protocol by a protocol amendment 16 months before the primary analysis of the results was performed. This is acknowledged. The Applicant clarified also that only 2 subgroup analyses were pre-planned in a separate section of the protocol and that the other OS subgroup analyses were included in the study protocol only to check for consistency of results. However, it is noted that formally no correction of the Type I error at <5% was implemented in the statistical analysis plan for analysis of the BCBM subgroup or of the other ones mentioned in the SAP and analysed. This seriously hampers interpretability of the results presented, as it is also outlined by the EMA guidelines cited by the Applicant (EMA/CHMP/539146/2013, Scenario 3: *The clinical data presented fail to establish statistically persuasive evidence but there is interest in identifying a subgroup, where a relevant treatment effect is evident and there is compelling evidence of a favourable risk-benefit. This relates to the use of a subgroup to rescue a trial that has formally failed, such that the primary analysis fails (usually classified as p>5%,*

two-sided). It is a well-known fact, from a formal statistical point of view, that no further confirmatory conclusions are possible in a clinical trial where the primary null hypothesis cannot be rejected. No formal proof of efficacy is possible under such circumstances and the potential for bias is such that data cannot be considered reliable. In this case there may be interest to try to rescue the trial in order to gain regulatory approval. However, it must be indicated that this type of exercise would be regarded as inadequate to support a licensing decision in most instances. One or more additional trials should usually be conducted."). Furthermore, as history of brain metastases was not used as stratification criterion, imbalances in (unknown) factors able to affect study results cannot be excluded, despite the various sensitivity analyses presented by the Applicant in order to address this issue. The very limited number of patients included in the BCBM subgroup, together with the lack of a sound biological rationale and/or supporting clinical evidence further hamper credibility of the data presented for a CMA. Replication of the results in a well designed and adequately powered clinical study is considered necessary in order to properly evaluate the efficacy of Onzeald in the proposed target population. The results of the ongoing ATTAIN study could allow a proper benefit-risk evaluation of the drug in the intended target population. According to the information provided by the Applicant, the projected interim analysis date is Q4 2018.

Point not resolved.

Ground #3 – Indication Statement

Summary of the Applicant's position

The CHMP's interpretation of the proposed indication for the treatment of advanced breast cancer patients with metastases to the brain as a "site-specific" indication (brain metastases only) and thereby setting a new regulatory precedent is considered incorrect by the Applicant. The indication for a systemic chemotherapy, such as Onzeald, cannot be considered as a 'site specific' only indication, but must be viewed as treating the patients' entire disease (intra-cranial and extra-cranial), such that the unit of treatment is the patient. Hence, the indication is a 'population-specific' indication based on Scenario 3 within the CHMP Guideline on the Investigation of Subgroups in Confirmatory Clinical Trials (EMA/CHMP/539146/2013).

The proposed indication statement for Onzeald, as it appears in the Onzeald Product Information, has evolved over the course of the assessment period based on numerous sources of feedback from CHMP/Rapporteurs. According to the Applicant, there are several critical problems with a "site-specific" (brain metastases only) interpretation of the indication statement and the subsequent request for evidence that Onzeald demonstrate superior efficacy versus TPC within brain versus outside the brain, including:

• It is biologically implausible for a systemically-administered chemotherapy, such as Onzeald, to only target intra-cranial disease; and

• The BCBM Population-specific indication is based on the CHMP guidance for the investigation of subgroups.

The Applicant has consistently maintained that the proposed indication is not intended to restrict the activity of Onzeald to brain lesions. Onzeald is intended to treat the whole breast cancer patient (including both extra- and intra-cranial metastases), whose disease is characterised by a history of brain metastases. It is well-documented and understood by practising oncologists that the death of patients with advanced breast cancer is typically the result of progression in both intra- and extra-cranial metastases (Eichler 2008). Hence, treatment of both intra- and extra-cranial metastases is crucial to improve both quality of life and OS in these patients. For Onzeald, a systemically administered

chemotherapy, which preferentially targets both intra- and extra-cranial tumours, the CHMP recommendation to show “increased relative activity in the CNS, compared to the relative activity of drugs in the whole body” was unreasonable and underscores a misunderstanding regarding the clinical chemotherapeutic management of patients with advanced breast cancer.

The proposed “population-specific” indication is based on Scenario 3 from the CHMP Guidance on Investigation of Subgroups in Confirmatory Clinical Trials: “The clinical data presented fail to establish statistically persuasive evidence but there is interest in identifying a subgroup, where a relevant treatment effect and compelling evidence of a favourable risk-benefit profile can be assessed” (Guideline on the investigation of subgroups in confirmatory clinical trials; EMA/CHMP/539146/2013). Additional details on the applicability and how the minimum requirements of the CHMP Guidance on Investigation of Subgroups in Confirmatory Clinical Trials are met are provided in Section 2.2, ‘Applicability of the CHMP Guidance on Investigation of Subgroups in Confirmatory Clinical Trials’.

In conclusion, the Applicant considers the CHMP misinterpreted the Applicant’s proposed indication statement as a ‘site-specific’ (brain metastases only) indication rather than a patient ‘population-specific’ indication based on Scenario 3 from the Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013). The proposed indication statement for Onzeald has been consistent with EMA’s principles for defining a therapeutic indication, which specifies that the indication should define “[…] the target disease and the population to benefit from the medicine” (SmPC Advisory Group Training Presentation – Section 4.1: Therapeutic indications). The expectation of a particular pharmacodynamic effect is not intrinsic to the principles guiding the definition of a therapeutic indication. The indication statement submitted in the final MAA before the negative CHMP Opinion was, “Onzeald monotherapy is indicated for the treatment of adult patients with breast cancer that has metastasised to the brain who have received prior local treatment for brain metastases (surgery and/or radiotherapy), and systemic anthracycline, taxane, and capecitabine, unless patients were not suitable for these treatments (see section 5.1).”.

An alternate indication statement for consideration is provided below, that clarifies the target population, is reflective of the BEACON BCBM Population, is clinically relevant, and implies that Onzeald treats the patients’ entire disease – i.e., patients with advanced breast cancer that has metastasised to the brain: “Onzeald monotherapy is indicated for the treatment of adult patients with advanced breast cancer that has metastasised to the brain, who also have extra-cranial metastases, and who have previously received systemic anthracycline, taxane, and capecitabine therapy, unless patients were not suitable for these treatments. Brain metastases must have been previously treated with prior local therapy (surgery and/or radiotherapy). (see section 5.1).” This alternate indication may better represent the intended target patient population, as:

• “Onzeald monotherapy…” – was the treatment studied in BEACON;

• “…advanced breast cancer that has metastasised to the brain, who also have extra-cranial metastases…” – locally recurrent or metastatic disease that is not resectable or amenable to curative treatment, that have either ‘current’ or ‘history of’ brain metastases, and, all of whom had at least one site of extra-cranial metastasis (per the BEACON study BCBM Population baseline disease characteristics);

• “…received systemic anthracycline, taxane, and capecitabine therapy…” – prior therapy (administered in the neoadjuvant, adjuvant, and/or metastatic setting) with an anthracycline (unless not medically appropriate or contraindicated for the patient), a taxane, and capecitabine (per the BEACON study inclusion criteria);

• "…prior local treatment for brain metastases (surgery and/or radiotherapy)" – patients for which local therapy (surgical resection, whole-brain radiation therapy or stereotactic radiation) for brain metastases must have been completed (per the BEACON study protocol inclusion criteria); and

• "(see section 5.1)" – refers prescriber to section 5.1 of SmPC, which describes the BEACON study population in regard to corticosteroid use, extent of systemic disease, ECOG status, and lack of data for patients who have not received local therapy for brain metastases. To further clarify the target Onzeald population with the highest benefit-risk balance, the Applicant proposes the following revisions (additions: underlined) to the description of baseline disease characteristics of the BEACON BCBM study population in the SmPC section 5.1: The BCBM population composed an important, predefined subgroup in the BEACON study (total: N = 67, Onzeald: N = 36, TPC: N = 31). All patients in the BCBM population received local therapy for their brain metastases (surgical resection: Onzeald: 17%, TPC: 16%; radiation therapy: Onzeald: 92%, TPC: 84%). There are no data available in patients who have not received local therapy for their brain metastases or who have actively progressing brain metastases. All patients (100%) received prior capecitabine and a taxane, 96% (Onzeald: 94%, TPC: 97%) received a prior anthracycline, and 24% (Onzeald: 19%, TPC: 29%) received prior eribulin. A total of 16% (Onzeald: 17%, TPC: 16%) of this population received prior HER2- directed therapy (including trastuzumab, lapatinib, pertuzumab, or trastuzumab emtansine). Use of corticosteroids for brain metastases had to be discontinued for at least 3 weeks prior to randomisation and signs or symptoms of brain metastases had to be stable, as determined by both symptoms and imaging, for at least 28 days prior to randomisation. Of these 67 patients with baseline history of brain metastases, 37 patients had radiographic evidence of brain metastases at study entry. All patients (100%) had at least one extra-cranial metastatic lesion and 66% had baseline liver metastases; there are no data available in patients who did not have at least one extracranial metastatic site.

CHMP Assessment

The Applicant sought to clarify that the scope of the proposed indication for the treatment of advanced breast cancer in adult patients with metastases to the brain was "population-specific" and not "site-specific" (brain metastases only) as it is biologically implausible for a systematically-administered chemotherapy to affect only intra-cranial disease. As a result, the Applicant suggested a revised wording of the indication as followed: "Onzeald monotherapy is indicated for the treatment of adult patients with advanced breast cancer that has metastasised to the brain, who also have extra-cranial metastases, and who have previously received systemic anthracycline, taxane, and capecitabine therapy, unless patients were not suitable for these treatments. Brain metastases must have been previously treated with prior local therapy (surgery and/or radiotherapy). (see section 5.1)."

The Applicant's effort to clarify the scope of the intended indication is acknowledged. It is also acknowledged that, in view of the cytotoxic nature and the claimed mechanism of action, it would be biologically implausible for Onzeald to affect only intracranial disease. However, it is underlined that it was the Applicant's decision to focus on the BCBM subpopulation. It is understood that this decision was motivated by 1) the lack of statistically significant superiority of the drug in the ITT population vs TPC, and 2) by the claimed biological rationale that the pegylated formulation of etirinotecan could allow brain penetration of the drug and consequently potential intracranial activity, therefore providing justification for activity (leading to prolonged OS) in this specific subgroup. Therefore, the initial and later revised versions of the Applicant's proposed indication is essentially based on the assumption of a claimed differential/improved activity of the drug in the BCBM subgroup (with intra-cranial and extra-cranial disease) in comparison with the overall metastatic breast cancer population enrolled in the trial and able to translate into prolonged survival. The specific questions raised during the initial assessment of the application and addressed to the Applicant and to the SAG-Oncology) were intended to understand the

level of evidence supporting plausibility of the proposed hypothesis. Indeed, due to the intrinsic design of the BEACON study, no data on intracranial activity of Onzeald (in comparison with TPC) could be collected. It is also noted that no new arguments have been provided by the Applicant within the course of the re-examination procedure in order to substantiate such hypothesis. As further discussed in the assessment of Ground #4, the evidence available is considered insufficient to establish the plausibility for intra-cranial activity of the drug and for any differential contribution to the claimed effect on OS in the BCBM population. The efficacy of the drug is therefore not considered demonstrated in the overall advanced/metastatic breast cancer population or in the subgroup of the population with extra-cranial and (history of) intra-cranial disease.

Point not resolved.

Ground #4 – Biological Plausibility

Summary of the Applicant's position

The Applicant believes that the clinical and pharmacological data provided in the submission of the application meet the criteria set out in the CHMP guidance on investigation of subgroups because it provides reasonable plausibility that patients with advanced breast cancer that has metastasised to the brain (BCBM) might be expected to derive significant benefit from treatment with Onzeald.

Nonclinical Data that Supports the Biological Plausibility of a Cytotoxic Effect of Onzeald

Onzeald (etirinotecan pegol) is a prodrug of irinotecan (Campto) and the active metabolite SN38. Irinotecan is a well-established and efficacious anti-cancer agent, which is licensed for the treatment of colorectal cancer in the EU. Nonclinical studies in tumour bearing mice demonstrated that Onzeald provides superior efficacy compared to irinotecan in subcutaneous mouse xenograft models (HT29 colorectal and H460 lung) and a brain metastatic breast cancer mouse model (MDA-MB-231Br). Prior to the finalisation of the BEACON SAP, nonclinical studies in an intra-cranial mouse tumour model were conducted comparing etirinotecan pegol versus unconjugated irinotecan and the results showed that etirinotecan pegol and its metabolite irinotecan preferentially accumulated in CNS lesions, much more so than unconjugated irinotecan and this led to greater in-brain exposure to SN38 derived from for Onzeald relative to unconjugated irinotecan. The high concentration and prolonged retention of intra-cranial SN38 translated into significantly greater tumour regression, as well as an OS benefit. After the completion of the BEACON study, additional nonclinical studies provided further supportive evidence for the superior intra-cranial effects of etirinotecan pegol compared to selected TPC agents. In the MDA-MB-231Br BCBM mouse model, etirinotecan pegol showed superior efficacy as measured by tumour regression and OS when compared to gemcitabine, eribulin, vinorelbine, and docetaxel. This body of data provides nonclinical evidence of the action of Onzeald in both extra-cranial and intra-cranial settings, which together support the biologic plausibility of a treatment effect of Onzeald in patients with advanced breast cancer and brain metastases.

Clinical Evidence of Intra-cranial Anti-tumour Activity Supports Biological Plausibility of Onzeald

Clinical evidence of intra-cranial responses after treatment with Onzeald at the recommended dose and schedule (145 mg/m2 q21d) demonstrate that Onzeald can cross the blood-tumour barrier and effectively reduce CNS lesions. These data serve to bridge the Onzeald nonclinical findings to the clinical setting, affirming the biological plausibility of Onzeald for the treatment of BCBM. Intra-cranial anti-tumour activity of Onzeald has been demonstrated in 3 separate clinical studies, for which data have been previously submitted:

– BEACON Study: Completed Phase 3 study in patients with advanced breast cancer. (Study NCT01492101). The BCBM subgroup of the BEACON study provided the pivotal efficacy data for this MAA;

– Study NCT01663012: Completed Phase 2 investigator-initiated study at Stanford University in patients with glioblastoma (Nagpal 2015);

– Study NCT02312622: Ongoing Phase 2 investigator-initiated study at Stanford University in patients with brain metastases of lung or breast cancer.

Completed Phase 3 BEACON Study in Patients with Advanced Breast Cancer that has Metastasised to the Brain:

Onzeald resulted in a large positive effect on OS relative to TPC in the population of patients with BCBM with a 49% reduction in the risk of death and a 5.2 month increase in median survival (10.0 vs 4.8 months; HR = 0.51 (95%CI: 0.30, 0.86); p = 0.010). These results are unprecedented for any therapy in the treatment of patients with BCBM and therefore are particularly important in light of these patients' high unmet medical need, especially poor prognosis and pronounced scarcity of effective chemotherapies (all patients were in a post-anthracycline, -capecitabine, and -taxane setting and many (24%) were also in a post-eribulin setting). In the BEACON study, only one overall category of tumour response was assessed using Response Evaluation Criteria in Solid Tumours (RECIST; v1.1). The BEACON study did not separately analyse response categories for intra-cranial and extra-cranial disease, nor did it incorporate the new RANO-BM criteria (which is being assessed in the ongoing ATTAIN Phase 3 Study (15-102-14). Patients in the BEACON study with a history of prior brain metastases were required to have had all CNS lesions treated previously (with either radiotherapy or surgery) and no evidence of radiographic progression or neurological symptoms prior to randomisation. As such, all brain lesions present at study entry should have been considered non-target lesions (NTLs) by RECIST, which states: "Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion." (Eisenhauer 2009). Three (3) Onzeald-treated patients in the BCBM Population had evidence of anti-tumour activity of brain lesion(s) during the BEACON study.

Completed Phase 2 Investigator-initiated Study at Stanford University in Patients with Glioblastoma (Study NCT01663012):

The brain penetration of Onzeald and its effects on brain tumour lesions is further supported by data from the Phase 2 investigator-initiated study at Stanford University in 18 patients with bevacizumab-refractory glioblastoma (having received a median of three prior therapies). Single-agent Onzeald treatment resulted in a 17% objective response rate (ORR). Three (3) patients had significant tumour reductions (86%, 72% and 59%) and two responses lasted for ≥ 19 months (Nagpal 2015). Objective responses in this population are very rare; in eight trials, with a total of 192 patients, using non-bevacizumab containing regimens after bevacizumab, there were only four partial responses (PR) (2%) per a Nagpal 2015 meta-analysis (Nagpal 2015).

Ongoing Phase 2 Investigator-initiated Study at Stanford University in Patients with Brain Metastases of Lung or Breast Cancer (Study NCT02312622):

This study is ongoing and a formal report is not yet available. Study NCT02312622, entitled "A phase II of etirinotecan pegol (NKTR-102) in subjects with advanced lung cancer or metastatic breast cancer with refractory brain metastases" is an ongoing investigator-initiated trial at Stanford University (Palo Alto, CA, United States (US)). This study is enrolling three (3) cohorts of patients (male and female) who have metastatic brain lesions with the following malignancies:

• Cohort A - patients with advanced non-small-cell lung cancer (NSCLC)

• Cohort B - patients with advanced small-cell lung cancer (SCLC)

• Cohort C - patients with locally recurrent or metastatic breast cancer

The primary objective of the study is to determine the CNS disease control rate (number of patients with stable disease (SD) or PR or complete response (CR)/ total number of treated patients) at 12 weeks following treatment with Onzeald in patients with refractory brain metastases of advanced NSCLC (Cohort A) or breast cancer (Cohort C). Secondary objectives for cohorts A and C included response rates, OS, and progression-free survival (PFS). Patients with SCLC (Cohort B) composed an exploratory, observational group. Patients in this study must have received at least one line of prior systemic chemotherapy or targeted treatment for metastatic disease OR had received prior adjuvant systemic chemotherapy within the 6 months prior to enrolment. Patients must also have received at least one CNS-directed treatment (e.g., surgery or radiation), or not have been eligible for CNS stereotactic radiosurgery. All patients were required to have measurable CNS lesions that were progressing at study entry. Enrolment at this single centre study initiated in February 2015 and is completed for the NSCLC (N = 12) and SCLC (N = 3) cohorts; enrolment is ongoing for the breast cancer cohort (N = 9 out of the planned 12). Complete study information is not yet available. Interim clinical data—including head imaging of responding patients and survival data in the lung cancer patients—are provided for the cohorts with completed enrolment (NSCLC and SCLC) to support the intra-cranial activity of Onzeald in BCBM. The NSCLC patient population was heavily pre-treated with median ECOG performance status of 2 and a median of 2.5 prior lines of chemotherapy (range 1-7). Two patients were receiving steroids at study entry (2 mg/day and 8 mg/day, respectively); no other patients were receiving steroids. On-study steroid use was reviewed; no escalation in the daily steroid dose occurred that could confound the interpretation of the observed changes in CNS lesions. The median GPA score, which incorporates four parameters (performance status, age, number of CNS lesions, and extra-cranial metastases), was 0.75 (range: 0-1.5). Based on GPA for newly diagnosed patients, the predicted median OS for the lung cancer cohorts was 3.0 months (Sperduto 2010). For the NSCLC cohort, patients received a median of four cycles of therapy (range 1-10). For the three SCLC patients, patients received 2, 3 and 4 cycles, respectively. For patients in the NSCLC cohort, the in-brain ORR was 25% (3/12) and the median PFS was 2.6 months (95%CI: 1.2, 2.8 months). The estimated median OS (with 10 events) was 7.0 months (95%CI: 1.3, 17.2 months) and the one-year survival was 33%. Two patients were censored on the Kaplan-Meier curve, with survival at the time of database cut-off greater than 18 months. For patients in the SCLC cohort, the ORR was 67% (2/3). The radiology scans for the five patients (NSCLC: 3, SCLC: 2) with objective responses are provided. All five patients had an in-brain PR. In addition, the head imaging for the one patient with metastatic breast cancer demonstrating intra-cranial activity of Onzeald is also provided.The significant number of intra-cranial responses in this heavily pre-treated patient population provides compelling evidence of the intra-cranial activity of Onzeald.

Clinical Extra-cranial Anti-tumour Activity that Supports Biological Plausibility of Onzeald

The Applicant strongly believes that the data supports that the survival benefit of Onzeald over TPC in the treatment of BCBM derives from anti-cancer activity against both intra- and extracranial metastases. It is well-documented that death of BCBM patients is typically a result of progression in both intra- and extra-cranial metastases (Eichler 2008). In a large study of BCBM patients conducted in Germany, nearly all patients had concomitant extra-cranial metastatic disease (< 5% of patients have brain-only MBC (Witzel 2016)). Of note, all 67 BCBM patients in the BEACON study had at least one extra-cranial site of disease at baseline, 66% (44/67) had liver metastases, and 63% (42/67) had ≥ 3 sites of metastatic disease. Hence, treatment of both intra and extra-cranial metastases is crucial to extend the survival of this BCBM patient population. In exploratory subgroup analyses to assess consistency, patients with metastases in highly perfused organs and relatively poor prognoses who were treated with Onzeald

consistently experienced improved survival outcomes relative to those treated with TPC. The subgroups that showed increased survival benefits included:

- Patients with a baseline history of brain metastases (n = 67; HR = 0.51; 95% CI: 0.30, 0.86);
- Patients with liver metastases at study entry (n = 456; HR = 0.73; 95% CI: 0.59, 0.81);
- Patients with ≥ 3 tumour sites of involvement at study entry (n = 403; HR = 0.77; 95% CI: 0.62, 0.95);
- Patients with visceral metastases at screening (n = 643; HR = 0.84; 95% CI = 0.71, 1.00), and
- Patients with high tumour burden at screening (sum of target lesions > the median) (n = 356; HR = 0.71, 95% CI: 0.56, 0.89; p = 0.003).

Applicant's conclusion

Multiple lines of evidence, including clinical data from 3 independent studies, have been provided to support a sound biological rationale, sufficiently convincing to support a mechanistic plausibility that Onzeald would have a superior treatment effect compared to standard of care drugs in advanced breast cancer patients with brain metastases. The efficacy data provided for primary brain tumours, such as glioblastoma, and brain metastases of lung cancer are considered supportive efficacy data in BCBM due to Onzeald's physical targeting of neoplastic tissue and mechanism of action. This is supported by an expert opinion letter. Furthermore, this plausibility is in alignment with the CHMP guidance on investigation of subgroups, which defines biological plausibility, as follows: "[…] a concept describing the extent to which a particular effect might be predicted or might be expected based on clinical, pharmacological and mechanistic considerations and considerations of other relevant external data sources", and is "[…] primarily a clinical and pharmacological judgement and is usually not a directly quantifiable or measurable concept" (EMA/CHMP/539146/2013). The totality of the nonclinical and clinical data for Onzeald clearly fulfils this CHMP guidance and therefore does meet the criteria for biological plausibility.

CHMP Assessment

In support of biological plausibility that patients with advanced breast cancer that has metastasised to the brain (BCBM) might be expected to derive significant benefit from treatment with Onzeald the Applicant has discussed 1) non-clinical data obtained in mouse models and 2) clinical data/imaging of patients enrolled in one study performed with glioblastoma and one study performed in patients with NSCLC or SCLC or breast cancer with brain metastases refractory to treatment, together with the imaging of the 3 patients enrolled in the BEACON study that could suggest some degree of intracranial activity of the drug. All these data were already available and duly assessed at the time of the initial MAA. Regarding the non-clinical data presented, the serious limitations of mouse models in predicting effects in humans are largely known, in particular regarding brain penetration of compounds. Moreover, some conflicting results are observed regarding tumour response and survival in the models presented.

From a mechanistic point of view, the claimed enhanced permeability and retention effects of Onzeald did not constitute per se a sufficient justification for plausibility for intracranial activity, due to 1) the lack of data in patients able to demonstrate the claimed phenomenon, and 2) the knowledge that other PEGylated compounds failed to show such qualities. Similarly, the claimed lack of affinity for P-gp and BCRP in vitro, is not considered sufficient to justify intracranial activity of Onzeald, due to the lack of the in vitro models to predict effects in humans.

Regarding the clinical evidence, small series of patients with pre-treated glioblastoma and NSCLC/SCLC and brain metastases treated with Onzeald is provided in support of potential intracranial activity of the drug. It is regrettable that no data were presented for the subgroup of patients with breast cancer and

brain metastases enrolled in the NCT02312622 study. In effect, due to biological and clinical differences, the relevance of the data presented for the breast cancer population is unknown, as different tumour types could present a different sensitivity to the drug. Intracranial activity of the drug could not be assessed in the BEACON study, as no patients in the study had target lesions in the brain and more than 50% did not present any radiologic evidence of brain localization at the time of enrolment. In the absence of comparative in-brain ORR and PFS data, there is no confirmatory radiological evidence that in-brain anti-tumour activity of Onzeald is superior to TPC. Therefore, there is uncertainty on how this might contribute to the superior OS seen in the BCBM subgroup.

Point not resolved.

Ground #5 – Conditional Marketing Authorisation (CMA)

Summary of the Applicant's position:

The Applicant maintains that Onzeald falls within the scope of Article 2(1) of Regulation (EC) No 507/2006 and the requirements for the grant of a conditional marketing authorisation, as laid down by Article 4(1) of the Regulation are fulfilled. The reasons for this are provided as followed:

Benefit-Risk Profile for Onzeald is positive

• The clinical relevance of the OS data from the BEACON study was not fully appreciated and the statistical rigour of the a priori analysis of the subgroup of patients with BCBM was not recognised;

• Benefit-risk balance was based on an incorrect interpretation of the proposed indication;

• The significant and unprecedented nature of the efficacy results in patients with BCBM—including CHMP requested post hoc analyses that showed robustness— were dismissed from the overall benefit-risk assessment; and

• Consideration of the following important attributes of Onzeald compared to current standard of care drugs were omitted from the overall benefit-risk assessment: favourable, manageable and differentiated safety profile, a more convenient dosing schedule (once every 3-weeks versus weekly), and less deterioration in HRQoL compared to TPC.

The background information for all justifications has been previously provided in this MAA. The benefit-risk assessment of Onzeald, and especially the uncertainty about the OS data in patients with BCBM, should be viewed in perspective of the following facts:

• Advanced breast cancer that has metastasised to the brain(BCBM)is a clinically distinct and fatal condition with no chemotherapies specifically approved to treat such patients; the level of evidence of efficacy in the treatment of BCBM provided by current standard of care chemotherapies to treat other advanced cancers is negligible (limited to case reports). Patients with BCBM are routinely excluded from pivotal trials of investigational chemotherapies. Robust efficacy data from the BEACON study showed that Onzeald doubled survival compared to TPC (10.0 vs 4.8 months); 67 patients with BCBM contributed randomised and controlled efficacy data. This is the largest BCBM dataset for any of the standard of care chemotherapies—including eribulin. Resampling analyses showed that the probability of obtaining a false positive for the survival results seen in BEACON under the null of no true treatment effect was only 2%.

• If Onzeald was used in preference to a TPC drug, there would be little or no risk of loss of chance or efficacy. In the ITT Population—in which 40% of TPC patients were treated with eribulin—this loss was at worst, 6 days compared to a10-month median OS on TPC. The upper limit of the OS confidence interval

for the BCBM result indicates no loss. Importantly, 50% of Onzeald-treated patients survived at least 5 months longer than TPC treated patients.

• It should also not be disregarded that the safety profile of Onzeald was manageable and compared to the TPC drugs, was differentiated and overall more favourable, with:

- fewer Grade ≥3 TEAEs than TPC in both the BEACON Safety Population of 831 patients (48.0 vs 63.1%, respectively; odds ratio: 0.54; 95% CI: 0.41-0.71) and the BCBM Safety Population of 61 patients (50.0 vs 70.4%); and

- fewer neutropenia-related TEAEs (26.1 vs 43.1%, respectively; odds ratio 0.47; 95% CI: 0.35-0.63), requirement for concomitant immunostimulant or granulocyte colony stimulating factor (G-CSF) (11.9 vs 26.0%, respectively), infections and infestations SOC (30.8 vs 39.9%), neuropathy (7.5 vs 25.4%, respectively) including Grade ≥ 3 neuropathy events (0.2 vs 3.7%), alopecia (10.4 vs 23.4%), and events with fatal outcomes (3.8 vs 6.2%).

• Onzeald has a more favourable dosing schedule of once every 3-weeks (vs weekly for current standard of care). The frequency of treatment schedules on the quality of the remaining life of patients in a late-line cancer setting should not be overlooked in the benefit-risk assessment.

Onzeald is a Major Therapeutic Advantage over Current Standard of Care

The Applicant fully agrees with the CHMP assessment that states, “A prolongation of median overall survival by 5 months in breast cancer patients with previously treated brain metastases would constitute an important improvement in the treatment of this condition, provided that it could reliably be identified as a drug effect. In this way, etirinotecan pegol would address an unmet medical need, which is a requirement for the sought conditional marketing authorisation.” (CHMP Assessment Report EMA/CHMP/163288/2017, p. 151); and: “The observed clinical efficacy results in the BCBM subpopulation are considered of clinical importance and of a magnitude that fulfils major therapeutic advantage in this disease context.” (CHMP Assessment Report EMA/CHMP/163288/2017, p. 13) However, as discussed below the CHMP did not recognise the following 3 additional significant attributes of Onzeald as contributing to a major therapeutic advantage over other standard of care chemotherapies: differentiated safety profile; less deterioration in health-related quality of life (HRQoL); and more convenient dosing schedule.

- *Differentiated Safety Profile*

The Applicant strongly asserts that the safety profile of Onzeald is sufficiently differentiated from other late-line chemotherapy options in patients with metastatic breast cancer in that different clinically important and/ or quality of life-altering toxicities occur in Onzeald treated and TPC-treated patients. In addition, Onzeald produces quantifiably fewer severe/life-threatening toxicities and it has a differentiated toxicity profile versus the standard of care TPC drugs. Because patients with advanced breast cancer receive multiple lines of chemotherapy, safety, tolerability, cumulative toxicities and effect on the quality of their remaining life are extremely important in assessing the benefit-risk profile. The distinct mechanism of action (topoisomerase-1 inhibitor) and molecular design of Onzeald (PEGylation that enhances pharmacodynamics profile) avoids overlapping toxicities, including neuropathy that can be both cumulative and irreversible with the heavy use of tubulin inhibitors in this population. Onzeald also does not cause cardiotoxicity and has a much lower risk for neutropenia compared to TPC agents. Onzeald results in more Grade ≥3 diarrhoea than TPC. However, the BEACON study also demonstrated that diarrhoea and its clinical sequelae (dehydration and renal failure) can be successfully managed using the guidelines provided in the proposed SmPC. Onzeald treatment was associated with notably fewer overall

Grade ≥3 events (48.0 vs 63.1%, neutropenia related events (9.6 vs 30.8%). Moreover, Onzeald resulted in a similar pattern of differentiation in toxicity profile when compared to each individual TPC agent.

Thus, in alignment with the CHMP guideline on CMAs (EMA/CHMP/509951/2006, Rev.1), Onzeald represents a major therapeutic advantage based on these meaningful safety improvements and differentiations versus the standard of care drugs. The safety profile is based on a large database (N = 790 total exposures, N = 644 at the recommended dose and schedule) with a predictable pattern of adverse events across all included populations. The applicant provided an expert opinion letter in support of the above.

- *Improved Health-related Quality of Life*

Health-related quality of life (HRQoL) was assessed in the BEACON study by European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire- Core 30 (QLQ-C30) (version 3.0) supplemented by the breast cancer-specific Quality of Life Questionnaire (QLQ-BR23). As summarised in the recently published, "Health-related quality of life in patients with locally recurrent or metastatic breast cancer treated with etirinotecan pegol versus treatment of physician's choice: Results from the randomised phase III BEACON trial" (Twelves 2017), differences were observed favouring Onzeald over TPC up to 32 weeks for global health status and physical functioning scales ($p < 0.02$); with numerical improvement reported in other functional scales. The findings from HRQoL symptom scales were consistent with adverse event profiles; Onzeald was associated with worsening gastrointestinal symptoms, whereas TPC was associated with worsened dyspnoea and other systemic adverse events. The authors concluded: "There was evidence of benefit associated with etirinotecan pegol compared with current standard of care agents in multiple HRQoL measurements, including global health status and physical functioning, despite worse gastrointestinal symptoms (e.g. diarrhoea)."; and "In the management of women with advanced breast cancer, where clinical outcomes with various treatment options may be similar and improvements modest, HRQoL provides crucial information beyond that of standard efficacy outcomes, especially where no single standard of care exists. There remains a need for new agents to treat advanced breast cancer that should preferably belong to a novel class, or have a novel mechanism of action, and impact survival while maintaining of improving QoL, being well-tolerated, and supported by a sound body of evidence." (Twelves 2017)

- *More Convenient Dosing Schedule and Other Quality of Life Effects*

Due to PEGylation, which results in a prolonged circulation half-life (38 days), Onzeald is administered only once every 21 days (q21d). In contrast, most standard of care chemotherapies are administered weekly. In fact, 86% of patients randomised to the TPC treatment arm of the Phase 3 BEACON study were assigned to an agent with a weekly treatment regimen. Patients with advanced breast cancer that has metastasised to the brain are in the late stages of life and having to go the hospital for their chemotherapy infusions frequently (i.e., weekly) is a significant quality of life issue.

Benefits of immediate availability outweigh risks inherent in the fact that additional data are still required

Comprehensive data packages have been provided for Onzeald quality, nonclinical, clinical safety, and pharmacokinetics. Less comprehensive data is available for clinical efficacy, which is in alignment with the CHMP guidance on CMA. Comprehensive data is either ongoing or planned, as described in the post-authorisation measures. Notably, comprehensive clinical data will be provided within a reasonable time period from the ongoing ATTAIN confirmatory Phase 3 Study (15-102-14). As shown in Annex 2, this study (the largest controlled trial in this population) has begun enrolling patients, with top-line results available in approximately Q2 2020. Thus, the Onzeald conditional MAA data package is sufficiently comprehensive to mitigate the risks inherent in the fact that the BEACON efficacy results for patients with advanced breast cancer that has metastasised to the brain need to be confirmed. The BEACON study

demonstrated that an unprecedented 50% of BCBM patients treated with Onzeald survive for 10 months (95%CI: 7.8, 15.7 months) as compared to 4.8 months (95%CI: 3.7, 7.3 months) with TPC. A doubling of median OS benefit is unprecedented for any therapy in the treatment of patients with BCBM. External validity of these results is supported by the consistency of the observed median OS of 4.8 in the TPC arm with those from previously published clinical studies (ranging from 5 to 6.4 months), and consistency of the OS results among the individual TPC agents. Thus, overall, in the context of the urgent unmet medical need of patients with BCBM and a conditional MAA, any remaining residual uncertainty pertaining to the results in the overall ITT and BCBM Populations is outweighed by the potential benefits. Patients with a current diagnosis of BCBM will not survive to see the outcome of the ongoing ATTAIN confirmatory Study (15-102-14)—an open-label, randomised, parallel, two-arm, multicentre, international Phase 3 study of Onzeald versus TPC in male or female adult patients with metastatic breast cancer and stable brain metastases—due to report in approximately Q2 2020. The incidence of metastases to the brain is reported to be about 15-30% in patients with metastatic breast cancer (Tabouret 2012; Witzel 2016). Hence, with approximately 464,000 new breast cancer cases in the EU each year, 20-30% of which will relapse with metastatic disease, and 15-30% of those progressing to the brain, an estimated 14,000-42,000 patients in the EU will be diagnosed with brain metastases in any given year. Given the percentage of patients with brain metastases alive at one year with Onzeald treatment is 44.4% (95% CI: 28.0, 59.6) as compared to 19.4% (95% CI: 7.9, 34.6) with TPC, the availability of Onzeald in the EU offers the potential to prolong the lives of 3,500-10,500 patients with breast cancer and brain metastases each year. Thus, overall, in the context of the urgent unmet medical need of patients with advanced breast cancer that has metastasised to the brain and a conditional MAA, any remaining residual uncertainty pertaining to the results in the overall ITT and BCBM Populations is far outweighed by the potential benefits. This opinion of the Applicant on the benefits of the immediate availability of Onzeald outweighing any risks is supported by expert opinion letters provided by the following practising oncologists in the EU.

Applicant's conclusions

The Applicant continues to strongly believe that Onzeald falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims to treat a lifethreatening disease and seriously debilitating disease and all four conditions of a CMA per Articles 4(a-d) of Regulation (EC) 507/2006 have been dully substantiated. Specifically, pursuant to:

• Article 4 (a) of Regulation (EC) 507/2006, The data package for Onzeald supports a positive benefit-risk in that the therapeutic effects of Onzeald are positive in relation to the risks relating to the uncertainties due to the lack of comprehensive clinical efficacy data. Considering the relative strength of the randomised evidence—compared to what is published for other chemotherapies available to patients with advanced breast cancer that has metastasised to the brain for OS, HRs, response rates, quality of life, and toxicity; and the dire prognosis of patients with this condition, results from the BEACON study represent an overall high likelihood for clinical benefit in this group of patients.

• Article 4(b) of Regulation (EC) 507/2006, Comprehensive clinical data will be provided within a reasonable time-period from the ongoing confirmatory ATTAIN Phase 3 Study (15-102-14). This study has begun enrolling patients, with top-line results available in approximately Q2 2020.

• Article 4(1c) of Regulation (EC) 507/2006, Advanced breast cancer that has metastasised to the brain is a fatal condition and there is an undisputed critical need for new, active treatments. In the opinion of the Applicant, Onzeald fulfils this with a major therapeutic advantage over the standard of care based on the following: (i) a median OS in the predefined subgroup of patients with advanced breast cancer that has metastasised to the brain of the Phase 3 BEACON study that was double that of the current standard of care (Onzeald: 10.0 months vs TPC: 4.8 months, p = 0.010; HR = 0.51, 95% CI: 0.30- 0.86), (ii) a

predictable, manageable, differentiated, and more favourable safety profile versus TPC, with fewer Grade ≥3 toxicities than the current standard of care, (iii) less deterioration in HRQoL than the current standard of care, (iv) more favourable dosing schedule of once every 3-weeks (vs weekly), and (v) an unprecedented level of documented evidence of efficacy using a randomised and controlled trial in a patient population that has been routinely excluded from such trials.

• Article 4(d) of Regulation (EC) 507/2006, As supported by multiple practising clinical oncologists, who are experts in their respective fields, the benefits to public health of the immediate availability of Onzeald for the treatment of patients with advanced breast cancer that has metastasised to the brain far outweighs the risks inherent in the fact that additional data are required to confirm the efficacy of Onzeald in this patient population. The risk due to lack of a comprehensive clinical data package is mitigated by the ongoing confirmatory ATTAIN study and represents a minimal loss of chance (loss of survival ofat most 6 days if the OS result in the ITT Population represented the true treatment effect) if Onzeald was used over a current standard of care (TPC) chemotherapy. Thus, overall, in the context of the urgent unmet medical need of patients with advanced breast cancer that has metastasised to the brain and a conditional MAA, any remaining residual uncertainty pertaining to the results in the overall ITT and BCBM Populations is outweighed by the potential benefits for these patients.

CHMP Assessment

The Applicant maintains that Onzeald falls within the scope of Article 2(1) of Regulation (EC) No 507/2006 and the requirements for the grant of a conditional marketing authorisation, as laid down by Article 4(1) of the Regulation are fulfilled. In accordance with this framework, it bears recalling that each of the following requirements must be culmatively met: (1) the benefit/risk of the drug is positive; (2) it is likely that the Applicant will be in a position to provide comprehensive data; (3) fulfilment of an unmet medical need; and (4) the benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

In the case of Onzeald the requested CMA is still not considered acceptable as the benefit-risk of the drug is not considered positive at this time. On the basis of all the evidence made available, the efficacy of Onzeald in the proposed indication has not been sufficiently substantiated. The proposed indication is based on the results of a subgroup analysis conducted in a study that failed to convincingly show increased OS compared to a comparator of treatment of physician's choice. The focus on this subgroup is not substantiated by a sound biological rationale supported by non-clinical and clinical data, and appears to be data-driven. The analysis included a very limited number of patients with history of brain metastases (67 patients), of which 51% did not have evidence of current brain metastases at the time of enrolment. Potential imbalances in unidentified factors able to affect study results cannot be excluded. An imbalance in post-treatment therapies and in the use of eribuline, the only drug that have demonstrated an improvement in OS in this setting, has been identified in favour of Onzeald, with a potential confounding effect on OS results. The lack of correction for multiplicity further hampers any conclusion from a statistical point of view. From a clinical point of view the lack of intern validity (i.e., absence of supportive effect of key secondary endpoints, like PFS) raises concerns over reliability of the results. Moreover, in the absence of comparative in-brain ORR and PFS data, there is no confirmatory radiological evidence that Onzeald has superior efficacy to TPC and that this would translate into the observed OS improvement. In view of this major uncertainty the results regarding the BCBM subgroup are not considered sufficiently reliable. As efficacy cannot be considered demonstrated, the benefit risk balance of the drug cannot be considered positive.

In relation to the requirement to demonstrate that the product fulfils an unmet medical need this has not been established. In this regard, it has not been demonstrated that Onzeald constitutes a major therapeutic advantage over existing therapies in the target indication.

The results presented should be considered hypothesis generating at best and warrant replication in a well designed and adequately powered clinical study.

Furthermore, as the benefit-risk balance cannot be considered positive at this time, the benefits to public health of the immediate availability of Onzeald for the treatment of patients with advanced breast cancer that has metastasised to the brain is not considered to outweigh the risks inherent in the fact that additional data are required to confirm the efficacy of Onzeald in this patient population.

In light of all of the above, it is considered that the Applicant has not duly substantiated why all of the requirements laid down pursuant to Article 4(1) of Regulation (EC) No 507/2006 are expected to be fulfilled.

Point not resolved.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the Applicant.

The available evidence for efficacy of Onzeald in the following indication: “Treatment of adult patients with advanced breast cancer that has metastasised to the brain, who also have extra-cranial metastases, and who have previously received systemic anthracycline, taxane, and capecitabine therapy, unless patients were not suitable for these treatments. Brain metastases must have been previously treated with prior local therapy surgery and/or radiotherapy)”, remain insufficient to demonstrate a positive benefit risk balance in the target population.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

The applicant’s proposed indication is the following: Onzeald monotherapy is indicated for the treatment of adult patients with advanced breast cancer that has metastasised to the brain, who also have extra-cranial metastases, and who have previously received systemic anthracycline, taxane, and capecitabine therapy, unless patients were not suitable for these treatments. Brain metastases must have been previously treated with prior local therapy (surgery and/or radiotherapy).

Breast cancer is the most common cancer in women in Europe with approximately 464,000 new cases diagnosed in 2012 and metastatic breast cancer is the leading cause of cancer-related death in women. As approximately 15-30% of patients with metastatic breast cancer will have brain metastasis, an estimated 14000 to 42000 patients in the EU will be diagnosed with brain metastases from breast cancer in any given year. Patients with brain metastasis generally also have disease localised to other sites. The prognosis is poor with approximately 80% mortality within 9 months of diagnosis.

The aim of Onzeald therapy is to prolong life while reducing symptoms of disease and/or the speed by which they occur.

6.1.2. Available therapies and unmet medical need

There is no curative treatment for patients with breast cancer with brain metastasis (BCBM). All available treatments are palliative. Local treatments include surgery and radiotherapy, including stereotactic radiotherapy, which are generally associated with important toxicity affecting quality of life, including focal neurological and cognitive side effects. Systemic therapy may also be given before or after surgery/radiotherapy. The efficacy of systemic therapy for breast cancer with brain metastasis is not very well described, as patients with known brain metastasis have generally been excluded from pivotal clinical trials. The most frequently used chemotherapeutic agent in patients with brain metastases is capecitabine. Case reports and case series have been also reported in the literature regarding intracranial response in breast cancer patients with brain metastases treated with eribulin or other cytotoxic drugs. However, activity is considered limited and prognosis of patients with brain metastases remains poor, with median overall survival less than 1 year. Patients with progressive brain metastases despite treatment present even worse prognosis. However, these patients were not included in the pivotal BEACON study.

There are a number of agents approved for use in metastatic breast cancer, including those used as comparator in the pivotal study. Among the treatment in the comparator arm, ixabepilone is not approved in the EU, but is approved in the US. Gemcitabine is approved as single agent in the US, but only in combination with paclitaxel in the EU. In the advanced treatment setting of the present pivotal trials, there is little evidence of efficacy for the different treatment options that are in use, with the exception of eribulin, for which a survival improvement has been shown in a similar setting.

6.1.3. Main clinical studies

The pivotal trial is Study 11-PIR-11 (BEACON). This was an open-label, randomized, parallel, two-arm, multicentre, international Phase 3 study of etirinotecan pegol versus treatment of physician's choice (TPC) in patients with locally recurrent or metastatic breast cancer previously treated with at least two prior and a maximum of five cytotoxic chemotherapy regimens including an anthracycline, taxane, and capecitabine (ATC). The primary endpoint was overall survival (OS). The Intent-to-treat (ITT) (full study) population consisted of 852 patients and the predefined subgroup of patients with a history of brain metastasis (BCBM), upon which the application rests, consisted of 67 patients. The most common TPC agents given were eribulin, vinorelbine and gemcitabine, followed by taxanes as group.

6.2. Favourable effects

The median overall survival in the full study population was 2.1 months longer in the etirinotecan arm compared with the TPC arm (12.4 vs 10.3 months), with a hazard ratio (HR) of 0.87 (95% CI: 0.75-1.02); this was not statistically significant (p=0.08).

In the BCBM subgroup, consisting of 67 patients, the median OS was 5.2 months longer in the etirinotecan arm compared with the TPC arm (10.0 vs 4.8 months), with HR 0.51 (95% CI: 0.30- 0.86). The p-value, unadjusted for multiplicity, was 0.01.

In the full study population, the secondary efficacy results were consistently very similar across arms. Median progression-free survival (PFS) was 2.4 and 2.8 months (Q3 estimate 5.7 and 5.6 months) for etirinotecan and TPC, respectively, with PFS HR 0.93 (n.s.). Furthermore, no significant difference in objective response rate (ORR, 16.4 and 17.0%, respectively), duration of response (DoR, 3.9 vs 3.7 months), and clinical benefit rate (CBR, i.e. objective responses + stable disease for ≥ 6 months, 20.5 vs 19.6%) was reported.

As eribulin is an approved drug in metastatic breast cancer, results in relation to prior eribulin exposure were explored even though this was not required for study participation. In the full study population, the OS HR point estimate was the same (0.87) in the subgroups of patients with and without prior eribulin. In the BCBM subpopulation, the HRs were 0.58 and 0.36 in patients without and with prior eribulin, respectively.

6.3. Uncertainties and limitations about favourable effects

The single pivotal trial failed to demonstrate superiority for etirinotecan pegol compared with treatment of physician's choice in the ITT population, where only eribulin has demonstrated an OS improvement in a reasonably similar population. Furthermore, ORR was similar in both arms. Similarly to the ITT population, no significant difference in PFS was observed between the two study arms in the BCBM subpopulation (HR 0.84, p=0.523, median PFS 3.1 vs 2.7 months). This creates an inherent uncertainty about the reliability of any subgroup analysis establishing the efficacy of etirinotecan pegol.

The BCBM subgroup was one of two prespecified subsets selected for further analysis among 24 baseline factors predefined for consistency analysis. Some of these factors resulted in two or more analyses and p-values (e.g., receptor status: TNBC versus HER2+ versus other), such that altogether, 57 subgroup analysis were performed. In the statistical analysis plan, no hypothesis was specified and no attempt to control the type-1 error was made upon subgroup evaluation. Thus the analysis conducted in the BCBM population is not statistically compelling. Furthermore, the subgroup consisted of only 67 patients, 51% of which did not have any macroscopic evidence of brain metastases at time of enrolment. The limited small sample size increases the risk that the results could be confounded by an imbalance in unidentified prognostic factors. The presence of brain metastases was also not used as stratification criterion, therefore potential imbalances in (un)identified prognostic factors able to affect study results cannot be excluded.

As there were no target lesions in the CNS per RECIST, due to prior local therapy, and the study was not designed to evaluate intracranial objective response rates in the CNS, a direct measure of intracranial activity is not available. Potential signs of intracranial activity were reported in 3 etirinotecan-treated patients in BEACON study. Some indirect evidence for intracranial activity of Onzeald is supported by the results of two single arms studies performed with Onzeald in patients with pre-treated glioblastoma and NSCLC/SCLC and refractory brain metastases. However, due to biological and clinical differences, the relevance of the data presented for the breast cancer population is unknown. Therefore, there is uncertainty about the biological plausibility of the differential outcomes in the BCBM and the ITT population.

A larger fraction of patients in the Onzeald arm compared to the TPC arm received post-study therapy. In the BCBM, the mean number of post-study cancer therapies was twice as high in the etirinotecan arm compared with the TPC arm (1.7 vs 0.8). The frequency of patients with at least one post-study cancer therapy was 72% vs 48% (etirinotecan vs TPC), and 69% vs 42% received chemotherapy. In particular, a higher number of patients enrolled in the etirinotecan arm of the BCBM population received eribulin post study (42% vs 6%), a drug that has been associated with a clear improvement in OS in this setting. As this difference may also indicate that the patients in the Onzeald arm were better suited to receive post-study treatment, the overall impact of this on the OS outcomes is unclear.

The Health-related quality of life (HRQoL) and Patient-reported outcomes (PRO) results indicated less deterioration in Global health status in the etirinotecan compared with the TPC arm. However, interpretation of HRQoL/PRO results is challenged by the open-label design of the study and the lack of control for the type-1 error.

6.4. Unfavourable effects

The overall safety profile of etirinotecan pegol was consistent across the four studied safety populations (overall, N = 790; overall at target dose, N=644; BEACON, N = 425; and BCBM, N = 34).

In the pivotal BEACON study, the most common adverse events associated with the use of etirinotecan pegol were gastrointestinal toxicities manifested as diarrhoea (66%), nausea (60%), vomiting (41%), decreased appetite (31%), constipation (26%), abdominal pain (21%), and decreased weight (13%); and bone marrow suppression manifested as neutropenia (21%), anaemia (16%), thrombocytopenia (3%), and febrile neutropenia (0.7%).

Potentially related to these common GI and myelosuppression AEs, other clinically important AEs were observed. Dehydration occurred in 10% of patients, with Grade ≥ 3 reactions at 2% (4% in the Overall safety population at target dose). A serious potential consequence of dehydration is renal failure.

Renal failure AEs were reported in similar frequencies in the two treatment arms, etirinotecan: 1.6% vs TPC: 1.2%; and clinical laboratory results showed similar frequencies of creatinine and urea increases across study arms, and no shifts to x3 of upper limit of normal (ULN). An AE of acute renal failure was listed as primary cause of death in one patient in the etirinotecan arm of BEACON (0 in TPC arm).

Infections and infestations SOC AEs (all grades) occurred in 31%of etirinotecan-treated patients and 40% of TPC; Infection SOC serious adverse events (SAEs) were reported in 5.9 vs 7.1% of patients. The number of patients with an infection as primary cause of death was low; 1 (0.2%) vs 3 (0.7%) in etirinotecan vs TPC arm, respectively.

Cholinergic-like reactions are known to be associated with irinotecan and these occurred frequently (23% as a group). Only 2 patients (0.5%) had grade 3 reactions (blurred vision and cholinergic syndrome) and none had a cholinergic-like AE of higher toxicity grade. A majority of these AEs were eye disorders (73%), the most common blurred vision (57%). Cholinergic syndrome occurred in less than 1% (in total 4 patients, one grade 3)

The overall occurrence of SAEs was similar across treatment arms in the BEACON study, 30.1 vs 31.8% (etirinotecan vs TPC). The SAE frequencies for etirinotecan-treated patients were also similar to, or (numerically) lower than, the TPC arm in BEACON for most SAE items, with the exception of GI disorders SOC (9.2 vs 5.4%), Hepatobiliary disorders SOC (1.9 vs 0.7%) and Renal and urinary disorders SOC (1.2 vs 0.5%).

The frequency of AEs reported as the primary cause of death was similar across treatment arms of BEACON (numerically lower in etirinotecan arm).

The Health-related quality of life (HRQoL) and Patient-reported outcomes (PRO) showed worsening of symptom scales for diarrhoea, nausea and vomiting and appetite loss.

Compared with the TPC arm, the patients in the etirinotecan arm of the BEACON trial had lower frequencies (at least numerically) of grade 3 AEs (48 vs 63%), SAEs (30 vs 32%), AEs leading to death (i.e. primary cause; 1.2% vs 2.0%), and AEs with fatal outcome (3.8 vs 6.2%), but higher frequencies of study drug-related AEs (93 vs 88%), study drug-related SAEs (12 vs 6%), and AEs leading to study drug discontinuation (11 vs 7%).

When selected AEs considered to have potential impact on quality of life were compared across arms, lower frequencies were generally seen for etirinotecan than TPC: Alopecia (10 vs 23%), Asthenia (22 vs 29%; grade ≥3: 1.9 vs 3.7%), Myalgia (6.1 vs 14.5%), Peripheral oedema (4.5 vs 10.6%), Neuropathy-related events (7.8 vs 25.6%; grade ≥3: 0.5 vs 3.7%). A numerically higher frequency was

only observed for Fatigue (34% vs 32%) among these selected items. However, the etirinotecan-induced AEs with the strongest impact on patients' QoL were the GI toxicities.

6.5. Uncertainties and limitations about unfavourable effects

The safety database is limited by the relatively short follow up.

6.6. Effects Table

Table 57: Effects Table for Onzeald (etirinotecan pegol) in the treatment of patients with breast cancer with brain metastasis (Data cut-off date 08 December 2014)

Effect	Short Description	Unit	Onzeald	TPC	Uncertainties / Strength of evidence
Favourable Effects					
BCBM subgroup (ITT) – sought indication					
		n	**36**	**31**	Small sample size Results not statistically compelling No strong support from mechanistic/ pharmacology perspective Clinically relevant difference in OS; p value unadjusted for multiplicity. OS HR < PFS HR
OS	Median Event rate	m %	10.0 74	4.8 78	
	Difference: HR (95%CI): p-value:	m	5.2 0.51 (0.30, 0.86) 0.010		
PFS	Median Event rate	m %	3.1 86	2.7 83	
	Difference: HR (95%CI): p-value:		0.4 0.84 (0.49, 1.43) 0.5		
		n	**32**	**27**	
ORR (RECIST 1.1 [a])	Proportion of patients	%	15.6	5.6	Relevant increase from low level Includes responses in all sites, not only BM Small sample size
DoR	Median	m	5.6	3.7	Longer DoR. Small sample size
ITT population					
		n	**429**	**423**	
OS	Median Event rate	m %	12.4 86	10.3 93	Not statistically significant OS HR < PFS HR No difference in PFS, but trend in OS
	Difference: HR (95%CI): p-value:	m	2.1 0.87 (0.75, 1.02) 0.08		
PFS	Median Event rate	m %	2.4 89	2.8 81	

	Difference: HR (95%CI): p-value:	m	-0.4 0.93 (0.80, 1.075) 0.3				
		n	**354**		**358**		
ORR (RECIST 1.1 [a])	Proportion of patients	%	16.4		17.0		No difference
DoR	Median	m	3.9		3.7		No difference

Effect	**Short Description**	**Unit**	**BEACON Safety population**		**BCBM Safety population**		**Uncertainties / Strength of evidence**
			Onzeald	**TPC**	**Onzeald**	**TPC**	
Unfavourable Effects							
Proportion of patients with:		**n**	**425**	**406**	**34**	**27**	
Grade 3 AE		%	48	63	50	70	
Study drug related AE		%	93	88	91	78	
AE leading to death [b]		%	1.2	2.0	0	3.7	
SAE		%	30	32	35	41	
Study drug related SAE		%	12	6	9	11	
AE leading to discontinuation		%	11	7	21	4	
Diarrhoea Grade 3		% %	66 10	20 1	56	19	
Renal failure (acute) [c]		%	1.6*	1.2	n.r.	n.r.	*1 fatal renal failure in Onzeald arm
Neutropenia -related AE [d] Grade ≥3		% %	26 10	43 31*	38 15	33 33	*1 fatal neutropenic sepsis in TPC arm
Myalgia		%	6	15	2	22	
Neuropathy-related events [e] Grade ≥3		% %	8 0.5	26 3.7	12 0	7 0	

Abbreviations: TPC = Treatment of physician's choice, OS = Overall survival, PFS = Progression-free survival, ORR = Objective response rate, DoR = Duration of response, n = numbers, n.r. = not reported, m = months, HR= hazard ratio, AE = Adverse event, SAE = Serious adverse event

[a] : RECIST 1.1 criteria do not require confirmation of responses

[b] : AE noted as primary cause of death

[c] : Grade 3 by definition.

[d] : Neutropenia-related events include the preferred terms of febrile neutropenia, neutropenia, neutropenic sepsis, and neutrophil count decreased

[e] : Neuropathy-related events include the preferred terms neuropathy peripheral, peripheral sensory neuropathy, paraesthesia, neurotoxicity, neuralgia, peripheral motor neuropathy, and polyneuropathy.

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

The condition of brain metastasis is characterised by pain, physical and cognitive losses of function, loss of autonomy, and frequently also personality change and associated with a poor prognosis. A prolongation of median overall survival by 5 months in breast cancer patients with previously treated brain metastases would constitue an important improvement in the treatment of this condition, provided that it could reliably be identified as a drug effect. In this way, etirinotecan pegol would address an unmet medical need, which is a requirement for the sought conditional marketing authorisation. However, the several identified major uncertainties (related to statistical issues and lack of internal and external validity and of solid justification of plausibility of the claimed effect from a non-clinical and clinical point of view) raise major concerns over the credibility of the efficacy results presented to date.

The safety of Onzeald appears in line with the class of compounds with gastrointestinal toxicity and myelosuppression being the most frequently observed adverse events.

6.7.2. Balance of benefits and risks

This application is based on a subgroup analysis from a study that failed to convincingly show increased OS compared to a comparator of treatment of physician's choice. The BCBM subgroup showed the largest treatment benefit of Onzeald compared with TPC among other subgroups, and was chosen as the target population based on the very high unmet need and the unprecedented treatment effect observed in this patient population, with a doubling of median OS from 4.8 to 10 months. However, the results in the BCBM subgroup were not statistically robust and several methodological concerns were identified. They were essentially related to the very limited sample size (67 patients), the presence of potential confounders in the analysis due to lack of adequate stratification, the identified imbalances in post study therapies (in particular eribuline), and the lack of internal consistency in terms of supportive data from key secondary endpoints (increased PFS could not be demonstrated, and ORR was similar across arms). Overall, the claimed efficacy has not been convincingly substantiated as the identified uncertainties could not be resolved with the data presented in the application. Furthermore, the relevance of the non-clinical data able to support the biological plausibility of a differential/improved activity of the drug in patients with brain metastases and how this would translate in a better OS is uncertain. Consequently, the results of BCBM subgroup are not considered sufficiently reliable.

In summary, the available evidence for efficacy is not considered sufficient to demonstrate a positive B/R in the target population.

6.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 2(1) of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease and seriously debilitating disease. Advanced breast cancer with brain metastases (BCBM) is end of line where patients have received prior local cranial therapy (surgery and/or radiotherapy), anthracycline, capecitabine and taxane, unless unsuitable. The presence of brain metastases dramatically worsens quality of life, with personality change and cognitive issues featuring prominently. The prognosis is extremely poor with

approximately 80% mortality at 9 months.

However, the CHMP considers that the product does not fulfil the requirements for a conditional marketing authorisation pursuant to Article 4(1) of the Regulation considering the benefit-risk balance cannot be considered positive, as discussed above.

6.8. Conclusions

The overall benefit/risk of Onzeald in monotherapy for the treatment of adult patients with advanced breast cancer that has metastasised to the brain, who also have extra-cranial metastases, and who have previously received systemic anthracycline, taxane, and capecitabine therapy, unless patients were not suitable for these treatments, is negative.

Divergent positions are appended to this report.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the efficacy of Onzeald is not sufficiently demonstrated and therefore recommends the refusal of the granting of the conditional marketing authorisation for the above mentioned medicinal product.

The CHMP considers that:

Evidence of therapeutic efficacy is insufficiently substantiated in the claimed indication for the “Treatment of adult patients with advanced breast cancer that has metastasised to the brain, who also have extra-cranial metastases, and who have previously received systemic anthracycline, taxane, and capecitabine therapy, unless patients were not suitable for these treatments. Brain metastases must have been previously treated with prior local therapy surgery and/or radiotherapy)”:

The efficacy claims are based on subgroup analysis from a single pivotal trial which failed to convincingly demonstrate efficacy. Given multiple tests, the subgroup findings are not statistically convincing. Furthermore they are not supported by a convincing biological rationale and/or corroborating clinical evidence from supportive studies.

Since the efficacy has not been sufficiently demonstrated the benefit risk balance cannot be considered positive.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Divergent positions to the majority recommendation are appended to this report.

Appendices

1. Divergent position to the majority recommendation 20 July 2017
2. Divergent position to majority recommendation 9 November 2017

APPENDIX 1

DIVERGENT POSITION

Divergent position – Onzeald (EMEA/H/C/003874)

The undersigned members of the CHMP did not agree with the CHMP's negative opinion recommending the refusal of the granting of the marketing authorisation of Onzeald indicated for treatment of adult patients with breast cancer that has metastasised to the brain, who have received prior local treatment for brain metastases (surgery and/or radiotherapy), and systemic anthracycline, taxane, and capecitabine, unless patients were not suitable for these treatments.

The reason for divergent opinion was the following:

Evidence to support the proposed indication in adult patients with breast cancer that has metastasised to the brain (BCBM) is derived from a single pivotal trial in which a borderline effect on overall survival in the broader ITT population was generated: hazard ratio 0.87, 95% CI: 0.75-1.02, p=0.08 in comparison to treatment of physician's choice (TPC). An estimate of effect in the BCBM sub-population can be drawn directly from a subgroup analysis, but making inferences from this subgroup analysis must be approached with great caution. Specifically, a strong biological rationale for an increased and clinically relevant treatment effect in this sub-population of patients is sought, through pharmacological considerations and through further interrogation of the clinical trial data.

Several lines of evidence were provided. To support evidence of in-brain activity of Onzeald, the Applicant provided results of exploratory pre-clinical studies in three mouse models of BCBM; radiological evidence of in-brain activity for Onzeald in a small number of BCBM patients; and supportive evidence of in-brain activity from patients with primary brain tumours and lung cancer patients with progressive brain metastases, considered to be relevant due to Onzeald's physical targeting and mechanism of action. Direct clinical proof of principle that PEGylated macromolecules can accumulate in cerebral metastases is provided from a recently published study (Lee *et al*, June 7 2017, Clinical Cancer Research, published online in advance of print). Given that the indication is defined by presence of brain metastases it is proportionate to expect sufficient evidence that in-brain anti-tumour activity contributes to overall survival benefit. It is not considered a requirement that the contribution to overall survival made by pharmacodynamic activity of Onzeald in brain metastases is higher than the contribution made by activity of Onzeald in metastases outside brain; or that Onzeald should be demonstrably superior compared to TPC in terms of intracranial objective responses. A number of lines of evidence support that in-brain anti-tumour activity translates into overall survival benefit including analysis of "in-brain" progression-free survival; overall survival benefit in patients with tumour burden below the median is lower in the BCBM sub-population (HR=0.50) versus the overall breast cancer population (HR=0.97); fewer intracranial progressions leading to death; and relevance of Onzeald's resistance to Pglycoprotein (one of the main efflux transporters at the blood brain barrier) to survival benefit.

The clearest evidence against survival benefit in BCBM patients being a chance finding derives from evidence of survival benefit for Onzeald over TPC in a number of additional subgroups with metastases where the Applicant's rationale for accumulation and retention of etirinotecan pegol would also apply.

Onzeald is proposed to accumulate and be retained by metastases associated with a leaky vasculature. Onzeald is a large hydrophilic macromolecule that can only exit blood vessels through

fenestrations in neovasculature formed during angiogenesis. Although the control of angiogenesis is complex, a fundamental trigger is that angiogenesis occurs in response to tumour hypoxia when tumours grow to a size where they outstrip their normal blood supply. The clinical evidence supports this, with Onzeald demonstrating greater overall survival benefit in subgroups with multiple metastatic sites involved (OS HR 0.77), tumour burden at baseline above the median (OS HR 0.71) and in patients with hepatic metastases (OS HR 0.73). Larger and more life-threatening metastases can be understood to be more sensitive to revelation of survival benefit for Onzeald; whereas progressing but not extensively neovascularised metastases (e.g. due to good organ perfusion) could be understood as less able to reveal benefit expressed in terms of non-lethal progression events. This is consistent with the clinical data which consistently demonstrate benefit on overall survival, the gold standard for outcome in oncology trials. These additional analyses give strong support, aligned to clinical expectation of an ideal systemic therapy for breast cancer in association with brain metastases, that Onzeald is active in both intracranial and extracranial sites.

The consistent OS benefit across several subgroups underpinned by analyses in patients with high tumour burden and pharmacological considerations on neovascularisation makes it highly unlikely that the finding in the BCBM sub-population is entirely due to chance and whilst the treatment effect taken directly from the sub-group analysis might be over-estimated, the weight of evidence can be concluded to support a demonstration of therapeutic efficacy. The benefits for immediate availability of Onzeald based on these trial data are demonstrated not only by the overall survival benefit – likely to reflect an unprecedented effect at any level in this patient population - but also by a differentiated toxicity profile to microtubule modulating drugs in particular, including taxanes and eribulin, which provides an important potential therapeutic option in patients who have reached end of line through toxicity. Uncertainties remain as to the precise magnitude of overall survival benefit in the BCBM population which can be resolved by the forthcoming ATTAIN study. In the meantime, given the exceptionally high level of unmet need in this patient population it is considered that the available evidence supports a Conditional Marketing Authorisation.

London, 20 July 2017

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Andrea Laslop (Austria)

Katarina Vučić (Croatia)

Dana Gabriela Marin (Romania)

Robert Hemmings (Co-Opted)

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APPENDIX 2

DIVERGENT POSITION

Divergent position – Onzeald (EMEA/H/C/003874)

The undersigned members of the CHMP did not agree with the CHMP's negative opinion recommending the refusal of the granting of the marketing authorisation of Onzeald indicated for treatment of patients with breast cancer that has metastasised to the brain, who also have extra-cranial metastases, and who have previously received systemic anthracycline, taxane, and capecitabine, unless patients were not suitable for these treatments. Brain metastases must have been previously treated with prior local therapy (surgery and/or radiotherapy).

The reason for divergent opinion was the following:

Evidence to support the proposed indication in adult patients with breast cancer that has metastasised to the brain (BCBM) is derived from a single pivotal trial in which a borderline effect on overall survival in the broader ITT population was generated: hazard ratio 0.87, 95% CI: 0.75-1.02, p=0.08 in comparison to treatment of physician's choice (TPC). An estimate of effect in the BCBM sub-population can be drawn directly from a subgroup analysis, but making inferences from this subgroup analysis must be approached with great caution. Specifically, a strong biological rationale for an increased and clinically relevant treatment effect in this sub-population of patients is sought, through pharmacological considerations and through further interrogation of the clinical trial data.

Several lines of evidence were provided. To support evidence of in-brain activity of Onzeald, the Applicant provided results of exploratory pre-clinical studies in three mouse models of BCBM; radiological evidence of in-brain activity for Onzeald in a small number of BCBM patients; and supportive evidence of in-brain activity from patients with primary brain tumours and lung cancer patients with progressive brain metastases, considered to be relevant due to Onzeald's physical targeting and mechanism of action. Direct clinical proof of principle that PEGylated macromolecules can accumulate in cerebral metastases is provided from a recently published study (Lee *et al*, June 7 2017, Clinical Cancer Research, published online in advance of print). Given that the indication is defined by presence of brain metastases it is proportionate to expect sufficient evidence that in-brain anti-tumour activity contributes to overall survival benefit. It is not considered a requirement that the contribution to overall survival made by pharmacodynamic activity of Onzeald in brain metastases is higher than the contribution made by activity of Onzeald in metastases outside brain; or that Onzeald should be demonstrably superior compared to TPC in terms of intracranial objective responses. A number of lines of evidence support that in-brain anti-tumour activity translates into overall survival benefit including analysis of "in-brain" progression-free survival; overall survival benefit in patients with tumour burden below the median is higher in the BCBM sub-population (HR=0.50) versus the overall breast cancer population (HR=0.97); fewer intracranial progressions leading to death; and relevance of Onzeald's resistance to Pglycoprotein (one of the main efflux transporters at the blood brain barrier) to survival benefit.

The clearest evidence against survival benefit in BCBM patients being a chance finding derives from evidence of survival benefit for Onzeald over TPC in a number of additional subgroups with metastases where the Applicant's rationale for accumulation and retention of etirinotecan pegol would also apply.

Onzeald is proposed to accumulate and be retained by metastases associated with a leaky vasculature. Onzeald is a large hydrophilic macromolecule that can only exit blood vessels through fenestrations in neovasculature formed during angiogenesis. Although the control of angiogenesis is complex, a fundamental trigger is that angiogenesis occurs in response to tumour hypoxia when tumours grow to a size where they outstrip their normal blood supply. The clinical evidence supports this, with Onzeald demonstrating greater overall survival benefit in subgroups with multiple metastatic sites involved (OS

HR 0.77), tumour burden at baseline above the median (OS HR 0.71) and in patients with hepatic metastases (OS HR 0.73). Larger and more life-threatening metastases can be understood to be more sensitive to revelation of survival benefit for Onzeald; whereas progressing but not extensively neovascularised metastases (e.g. due to good organ perfusion) could be understood as less able to reveal benefit expressed in terms of non-lethal progression events. This is consistent with the clinical data which consistently demonstrate benefit on overall survival, the gold standard for outcome in oncology trials. These additional analyses give strong support, aligned to clinical expectation of an ideal systemic therapy for breast cancer in association with brain metastases, that Onzeald is active in both intracranial and extracranial sites.

The consistent OS benefit across several subgroups underpinned by analyses in patients with high tumour burden and pharmacological considerations on neovascularisation makes it highly unlikely that the finding in the BCBM sub-population is entirely due to chance and whilst the treatment effect taken directly from the sub-group analysis might be over-estimated, the weight of evidence can be concluded to support a demonstration of therapeutic efficacy. The benefits for immediate availability of Onzeald based on these trial data are demonstrated not only by the overall survival benefit – likely to reflect an unprecedented effect at any level in this patient population - but also by a differentiated toxicity profile to microtubule modulating drugs in particular, including taxanes and eribulin, which provides an important potential therapeutic option in patients who have reached end of line through toxicity. Uncertainties remain as to the precise magnitude of overall survival benefit in the BCBM population which can be resolved by the forthcoming ATTAIN study. In the meantime, given the exceptionally high level of unmet need in this patient population it is considered that the available evidence supports a Conditional Marketing Authorisation.

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