15 December 2022
EMA/CHMP/3393/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Omblastys

International non-proprietary name: iodine (131I) omburtamab

Procedure No. EMEA/H/C/005499/0000

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:	Omblastys
Applicant:	Y-mAbs Therapeutics A/S Agern Alle 11 DK-2970 Hoersholm DENMARK
Active substance:	Iodine (^{131}I) omburtamab
International Non-proprietary Name/Common Name:	iodine (^{131}I) omburtamab
Pharmaco-therapeutic group (ATC Code):	other therapeutic radiopharmaceuticals, iodine (^{131}I) compounds (V10XA)
Therapeutic indication(s):	Omblastys is indicated for the treatment of central nervous system (CNS)/leptomeningeal (LM) metastasis of neuroblastoma in patients, who have previously received CNS-directed multi-modal therapy for their disease, such as chemotherapy, surgery, or radiation therapy
Pharmaceutical form(s):	Solution for infusion
Strength(s):	462.5 MBq/mL
Route(s) of administration:	Intracerebroventricular use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

%ID/g	percent injected dose per gram tissue
^{131}I	iodine-^{131}
^{131}I-omburtamab	iodine-^{131}-radiolabeled omburtamab
8H9	laboratory code for omburtamab
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
AM	alveolar macrophages
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-∞	area under the curve from Time 0 to infinity
AUCdata	area under the curve computed using trapezoidal integration of imaging measurements
AUCtail	area under the curve from the last time point onward
BSA	bovine serum albumin
CD	cluster of differentiation
CDR	complementarity-determining region
CED	convection-enhanced delivery
CE-SDS	capillary electrophoresis sodium dodecyl sulphate polyacrylamide gel electrophoresis
CFU	colony forming unit
cIEF	capillary isoelectric focusing
CGCCR	Central German Childhood Cancer Registry
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CNS	central nervous system
CNS/LM	central nervous system/leptomeningeal
CPP	critical process parameters
CPV	continued process verification
CQA	critical quality attribute
CSF	cerebrospinal fluid
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CV%	percent coefficient of variance
Cyno	cynomolgus monkey
DIPG	diffuse intrinsic pontine glioma
DNA	deoxyribonucleic acid
DP	drug product
DPI	drug product intermediate
DS	drug substance
DSRCT	desmoplastic small round cell tumour
E	epithelium
EBV	Epstein Barr virus
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
EOS	end of synthesis
EU	endotoxin unit
FAS	full analysis set
FDA	Food and Drug Administration
FEM	Erlenmeyer flasks
G	glial cells

GLP	good laboratory practice
GGT	γ-glutamyltransferase
GMP	good manufacturing practice
Grade 3+	Grade 3 or higher
HC	heavy chain
HCP	host cell protein
HDPE	high density polyethylene
HMW	high molecular weight
HTB119	small cell lung cancer cell line
HTB82	human rhabdomyosarcoma cell line
ICF	informed consent form
IgG	immunoglobulin G
ICH	International Council for Harmonisation
ID	identification
INDA	investigational new drug application
IHC	immunohistochemistry
IND	investigational new drug
INN	international non-proprietary name
INSS	international neuroblastoma staging system
IPC	in process controls
IRB	Institutional Review Board
IRB/PB	Institutional Review Board and Privacy Board
ISE	integrated summary of efficacy
i.t.	intrathecal
i.v.	intravenous
JPA	juvenile pilocytic astrocytoma
ka	association constant
kd	dissociation constant
KD	equilibrium dissociation constant
KM	Kaplan-Meier
LAL	limulus amebocyte lysate
LC	Leydig cells/light chain
LM	leptomeningeal
LMW	low molecular weight
MAA	marketing authorisation application
max	maximum
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MRI	magnetic resonance imaging
MRT	mean residence time
MSK/MSKCC	Memorial Sloan Kettering Cancer Center
MTD	maximum tolerated dose
mu8H9	murine 8H9 monoclonal antibody
MYCN v-myc	myelocytomatosis viral related oncogene
NA	not applicable
NB	neuroblastoma
NC	not collected
NCR	non-critical range
NE	not estimable
NF	national formulary
NHP	nonhuman primate
NLT	not less than
NMB7	human neuroblastoma cell line
NNAS	non-neuroblastoma analysis set

NNB	non-neuroblastoma
NOR	normal operating range
NT	not tested
OD280	optical density at 280 nm
OLINDA	organ level internal dose assessment
OS	overall survival
PAR	proven acceptable range
PBMC	peripheral blood mononuclear cell
PBS	phosphate-buffered saline
PETG	polyethylene terephthalate glycol
PFS	progression-free survival
Ph. Eur. E	European Pharmacopoeia
Pilocytic Ast	juvenile pilocytic astrocytoma
PK	pharmacokinetics
PI	principal investigator
PNET	primitive neuroectoderm
pPCS	preliminary process control strategy
PPQ	process performance qualification
psi	pounds per square inch
PUP	Protein A ProSep® Ultra Plus
PVDF	polyvinylidene fluoride
qPCR	quantitative polymerase change reaction
QTPP	quality target product profile
RD	radio detector signal from gamma rays of ^{131}-iodine
Res sd	residual standard deviation of curve fit
rHSA	recombinant human serum albumin
RIT	radioimmunotherapy
Rmax	maximum binding
RMIP	radiochemistry and molecular imaging probes
RMS	rhabdomyosarcoma
ROA	route of administration
ROI	region of interest
RRT	relative retention time
RT	room temperature
RU	response units
S	stroma
SAE	serious adverse event
SAF	safety analysis population
SAL	sterility assurance level
SAP	statistical analysis plan
SD	standard deviation
SDS-PAGE	sodium dodecyl sulfate polyacrylamide gel electrophoresis
SE-HPLC	size exclusion high performance liquid chromatography
SE-UPLC	size exclusion ultra-performance liquid chromatography
SMQ	standardized MedDRA queries
SOC	system organ class
SPECT	single-photon emission computed tomography
SPR	surface plasmon resonance
t1/2	half-life
t1/2(α)	alpha half-life (distributive half-life)
t1/2(β)	beta half-life (terminal half-life)
TAMC	total aerobic microbial count
TBD	to be determined
TBR	to be reported
TC	total aerobic microbial count

TEAE	treatment-emergent adverse event
TLC	thin layer chromatography
Tmax	time of maximum concentration
TOC	time of dose calibration
TYMC	total aerobic microbial count
U2OS	osteosarcoma cell line
U87	human glioblastoma cell line
ULN	upper limit of normal
USAN	United States adopted name
USP	United States Pharmacopoeia
UV	ultraviolet
WBC	white blood cell
Vd	volume of distribution
Y-mAbs	Y-mAbs Therapeutics A/S

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Y-mAbs Therapeutics A/S submitted on 27 April 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Omblastys, through the centralised procedure falling within the Article 3(1) and point 4 of Annex I of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 November 2019.

Omblastys, was designated as an orphan medicinal product EU/3/17/1839 on 27 February 2017 in the following condition: Treatment of neuroblastoma.

The applicant applied for the following indication:

Omblastys is indicated for the treatment of neuroblastoma with central nervous system (CNS)/leptomeningeal (LM) metastasis.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

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).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0322/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0322/2020 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4.2. New active substance status

The applicant requested the active substance iodine (^{131}I) omburtamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
18 May 2017	EMEA/H/SA/3528/1/2017/PA/PED/III	Prof. Brigitte Blöchl-Daum and Dr Alexandre Moreau

The protocol assistance pertained to the following clinical aspects:

- Adequacy of the historical data to demonstrate unmet medical need and to establish the historical rate of survival in paediatric patients with neuroblastoma CNS/LM metastasis.
- Acceptability of the historical data to serve as valid control for comparison with the ^{131}I-mu8H9 treated patients.
- Acceptability of the proposed analyses to provide clinical evidence that ^{131}I-mu8H9 provides substantial improvement over available therapies for the intended patient population.
- Acceptability of the proposed multicentre phase II clinical study design, in particular with regards to the primary and secondary endpoints, inclusion and exclusion criteria, criteria for assessment of efficacy, safety measures and the proposed evaluation of dosimetry.
- Acceptability of the sample size, the appropriateness of the statistical methods and the success criteria for effectiveness for the phase II study.
- Sufficiency of the existing ^{131}I-mu8H9 clinical data from study 03-133 together with the planned phase II study 101 to support a MAA.
- Proposed level of evidence at the time of the initial MAA versus data to be submitted as a post approval commitment.
- Orphan similarity.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: John Joseph Borg

The application was received by the EMA on	27 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 August 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	2 September 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 September 2021

The applicant submitted the responses to the CHMP consolidated List of Questions on	22 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	01 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	23 June 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 September 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 September 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	13 October 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 October 2022
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	08 November 2022
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 Omblastys on	15 December 2022
The CHMP adopted a report on similarity of Omblastys with Qarziba on	15 December 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	15 December 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Neuroblastoma (NB) is a rare paediatric cancer and is the most common solid extra-cranial solid tumour cancer in children. High-risk neuroblastoma is a life-threatening disease that is associated with poor long-term survival. For high-risk patients, 5-year overall survival (OS) rates have improved during the last two decades but are still below 50% (Pinto et al, 2015).

Neuroblastoma with CNS/LM metastasis is a neuroblastoma, that at initial staging or at relapse, has metastasised to the brain parenchyma and/or the LM, excluding tumours localised to the skull bone.

2.1.2. Epidemiology

Neuroblastoma represents about 10% of solid tumours in infants and children under the age of 15 with an annual incidence of about 1/70.000 in children in this class of age (orphanet reference). It is the third most common childhood cancer, after leukaemia and brain tumours, and is the most common solid extracranial tumour in children. Ninety percent of NB is found in children younger than 5 years of age (London, 2005; American Cancer Society, 2021). The median age at diagnosis is 17.3 months, and 40 percent of patients are diagnosed before one year of age. It is rare in people over the age of 10 years.

The population-based median annual age-standardised incidence rate of neuroblastoma per million children per year in Germany between 1980 and 2015 was 13.2 per million (Berthold et al, 2017). In the United States (US), 800 new cases of neuroblastoma are reported per year (American Cancer Society, 2021).

2.1.3. Aetiology and pathogenesis

Little is known about the events that predispose to the development of neuroblastoma. Certain risk factors are associated with a worse prognosis; these include v-myc myelocytomatosis viral related oncogene (MYCN) amplification, and >18 months of age at diagnosis.

2.1.4. Clinical presentation and diagnosis

The final diagnosis of neuroblastoma is based on pathology (tumour biopsy or tumour cytology combined with increased levels of urinary catecholamine metabolites) (Brodeur, 1993). The clinical presentation of CNS/LM neuroblastoma is dependent on the location and nature of the lesion. The diagnosis of CNS/LM neuroblastoma is based on clinical symptoms and imaging.

2.1.5. Management

Treatment options for neuroblastoma with CNS/LM metastasis

Current surgery and radiotherapy techniques for newly diagnosed patients, in conjunction with induction chemotherapy, have reduced the risk of local relapse. However, refractory, or recurrent disease occurs in most patients with high-risk neuroblastoma, and CNS/LM metastasis primarily occurs in the relapsed or recurrent setting (Kramer et al, 2001; Matthay et al, 2003). Conventional systemic treatment for newly diagnosed patients does not adequately prevent or treat the CNS/LM metastasis. Additionally, toxicity limits of high-dose chemotherapy appear to have been reached without further clinical benefit (Modak and Cheung, 2010).

The apparent increase in CNS/LM metastasis that has been observed is possibly related to the better treatment success for the primary disease. It is hypothesised that current treatments for the primary disease are not sufficiently treating micro-metastasis to the CNS. Therefore, the experience with this type of disease manifestation is also limited, since prior to the effective treatment of primary disease patients died by this "competing risk".

Various treatment combinations comprise one or more of the following standard options for metastatic CNS/LM neuroblastoma, all with the aim of reducing symptoms, but with modest chance of cure:

- Surgical debulking of tumour when feasible prior to irradiation, to reduce symptoms, oedema, and haemorrhage, or to correct cerebrospinal fluid (CSF) flow.
- Focal, whole brain irradiation, or craniospinal irradiation (where feasible) to alleviate symptoms, obtain disease control, and correct CSF flow in cases of obstruction.
- Systemic combination chemotherapy (e.g., irinotecan plus temozolomide).
- Myeloablative therapy and stem cell transplantation.

Data obtained from the Central German Childhood Cancer Registry (CGCCR) which include the majority of neuroblastoma patients enrolled in clinical trials in Germany, show that the treatment modalities for CNS/LM neuroblastoma are not uniform, even on a nationwide level in Germany. While most patients in Germany have received autologous stem cell transplantation, and radiation, around half of the patients have received chemotherapy, and less than that immunotherapy. Irrespective of treatment combinations used, data show only limited effects of current treatments (Kramer et al, 2001; Matthay et al, 2003; Berthold et al, 2017).

Unmet medical need

With specific treatments for neuroblastoma with CNS/LM metastasis yet to be approved, an area of high unmet medical need persists for patients with this very rare and life-threatening disease.

2.2. About the product

Y-mAbs Therapeutics A/S (Y-mAbs) has developed (^{131}I) omburtamab which is proposed by the company for the following indication:

Omburtamab is indicated for the treatment of neuroblastoma with central nervous system (CNS)/leptomeningeal (LM) metastasis.

Other names historically used for the drug product include burtomab, mu8H9, 8H9, and ^{131}I-8H9. Omburtamab is a murine IgG1κ monoclonal antibody (mAb) secreted by a hybridoma cell line issued from the fusion of Balb/C splenic lymphocytes and SP/2-0 myeloma cells. The secreted mAb recognizes a unique cell membrane neuroblastoma antigen 4Ig-B7-H3 (CD276) that is expressed on a wide range of paediatric and adult solid tumours and expressed as well on CNS/LM neuroblastoma tumour cells. The conjugated iodine-131 emits radiation, resulting in nearby tumour cell DNA damage and cell death. Memorial Sloan Kettering Cancer Center (MSK) initiated the developed of this radioimmunotherapy in 2001. The rights to the commercial development of omburtamab were licensed to Y-mAbs in 2015.

The nonclinical testing of (^{131}I) omburtamab relies on published data from studies conducted early in its development at Memorial Sloan Kettering Cancer Center (MSK) (New York, New York). Clinical evidence is derived from patients with paediatric neuroblastoma with CNS/LM metastasis during a single-site trial conducted at MSK (Trial 03-133). This is supplemented by data from an international, multisite clinical trial sponsored by Y-mAbs (Trial 101).

2.3. Type of application and aspects on development

Y-mAbs requested CHMP protocol assistance in 2017 for its orphan programme of omburtamab to seek advice related to the clinical data necessary to support a marketing authorisation application (MAA) for (^{131}I) omburtamab for the treatment of relapsed neuroblastoma with CNS/LM metastasis. Additionally, Y-mAbs requested to obtain feedback on specific clinical questions and endpoints to demonstrate significant benefit in relation to the orphan drug designation.

The feedback from CHMP was considered when designing the Phase 2/3 Trial 101. Furthermore, to accommodate CHMP's comments, the Paediatric Investigational Plan (PIP) initially submitted to EMA in 2017, included a detailed description of how external control data (especially historic control data from the German registry) would be defined to ensure adequately selected data as comparison for establishment of clinical evidence. The PIP also included a description of the measures to fulfil for the interim analysis of Trial 101 to be included as part of an MAA. The initial PIP decision was granted in 2019. A modification to the PIP was approved in August 2020 and a PIP compliance check was adopted in October 2020.

In preparation for the MAA submission in the EU, both an EMA MAA pre-submission meeting and a Rapporteur/Co-Rapporteur meeting were conducted during 2020 to discuss the format and content of the planned application.

2.4. Quality aspects

2.4.1. Introduction

Iodine-131 omburtamab is a radiolabelled murine monoclonal antibody (mAb) that recognises and binds selectively to the B7-H3 antigen expressed on CNS/LM neuroblastoma tumour cells. The iodine-131 emits beta radiation, resulting in DNA damage and tumour cell death.

Consequently, (^{131}I) omburtamab targets and kills the tumour with the combination of antibody binding affinity and beta decay from the radioisotope.

The manufacturing of the active substance (^{131}I) omburtamab is achieved by radiolabelling of omburtamab active substance intermediate using sodium iodide-^{131} active substance intermediate. An additional section describes the finished product intermediate which precedes the radiolabelling step to the finished product

The omburtamab finished product is provided in a sterile, 10 mL, borosilicate, clear, type I glass vial, sealed with an n-butyl rubber septum and secured by an aluminium crimp seal. The strength is defined as 462.5 MBq/mL at the time of administration as a solution for infusion.

2.4.2. Omburtamab mAb active substance intermediate

2.4.2.1. General information

Omburtamab is a murine IgG1κ monoclonal antibody (mAb) secreted by a hybridoma cell line issued from the fusion of Balb/C splenic lymphocytes and SP/2-0 myeloma cells. It binds to the glycoprotein antigen, 4Ig-B7-H3.

Molecular mass has been determined by intact mass spectrometry to confirm the theoretical molecular mass and the presence of lysine truncated- and glycoform variants. The most abundant variant contains one heavy chain C-terminal lysine and two N-glycans of the G0F type.

2.4.2.1. Manufacture, characterisation and process controls

Manufacturing process and control of critical steps

Omburtamab active substance (AS) intermediate is manufactured at an EU based Contract Manufacturer. Satisfactory demonstration of GMP compliance is provided.

Omburtamab active substance is a murine monoclonal antibody (IgG1κ mAb) secreted by a hybridoma cell line SP2/0. A cell culture process including cell expansion and production in a bioreactor with a fed-batch process resulting in a single crude harvest. For the production phase the culture is controlled by temperature, dissolved oxygen and pH. Nutrient supplement solutions are added to the culture at defined intervals. Production is stopped and harvested at a specified time or if cell viability drops below 50%. The population doubling level (PDL) should not exceed 40 from thawing of the WCB at the end of the production in bioreactor. The purification process starts with the removal of cells and cell debris from the harvested culture by depth filtration. The harvest material is clarified using depth filter. To obtain purified omburtamab active substance solution, all chromatography and filtration steps are performed at room temperature (15°C – 25°C). The purification process consists of the following steps: Protein A affinity chromatography, viral inactivation at low pH, anion exchange (AEX) chromatography, cation exchange (CEX) chromatography, Viral reduction filtration, and tangential flow filtration (TFF). The omburtamab active substance is microfiltered (0.5 µm/0.2 µm) and stored in polyethylene terephthalate glycol (PETG) bottles. In-process controls (IPCs) performed after each of the purification steps allow the monitoring of the performance of each step with respect to purity, yield and product integrity. No reprocessing is permitted but re-filtration may only be performed if the filter integrity test has failed. Overall, process description is of decent quality. The final control strategy is now provided, and the dossier updated accordingly. This control strategy definite (and not potential) classifications. Critical steps are identified and controlled with specific IPC. Based on criticality, IPCs are either controlled via-acceptance criteria (AC), IPC limits and monitoring. If an acceptance criterion is not met, after confirmation of the out-of-specification (OOS), the batch will be rejected. An IPC limit excursion results in an investigation.

The control strategy was considered to be preliminary, and this was raised as a major objection. The final commercial controls of critical steps and intermediates were provided following completion of validation activities.

Control of materials

All raw materials used for the manufacturing process of omburtamab active substance are received, identified, sampled, quarantined, tested, labelled and released according to established written procedures. All raw materials used in the manufacturing process are free of animal-derived components. Lists of compendial and non-compendial materials used in the upstream process (USP) and downstream process (DSP) are provided. Suppliers of resins and filters are indicated. Chromatographic resins and filters are single use.

Omburtamab is a murine IgG1κ monoclonal antibody (mAb) secreted by a hybridoma cell line issued from the fusion of Balb/C splenic lymphocytes and SP/2-0 myeloma cells. The cell banking system consists currently of a master cell bank (MCB) only.

An extended cell bank (ExCB) was generated covering a population doubling level (PDL) of +10.8 beyond the end of production and 40.4 from MCB-1 thawing. Both cell banks have been tested for the absence of adventitious agents according to (ICH Q5A(R1). The applicant states that MCB-1 and ExCB-1.1 underwent isoenzyme analysis and phenotypic characterisation to confirm identity, purity and stability of the cell line, according to ICH Q5B and ICH Q5D. The qualification of a future working cell bank (WCB) will be covered by a comparability study with the MCB-1. A new ExCB will be performed on a bioreactor run produced from one WCB vial to allow WCB & ExCB viral and phenotypic characterisations. The protocol for characterisation of future working and extended cell banks is acceptable. The maximum cell culture time is based on Population Doubling Level, and it has been classified as CPP.

Process validation and/or evaluation

The manufacturing and validation approach has been conducted for the omburtamab active substance. The preliminary control strategy was built on process experience throughout development (from small scale development studies to clinical manufacturing) and experience with similar processes. Operational and performance parameters were classified into potential critical and noncritical parameters in a risk assessment prior to process validation at full-scale. No formal process characterisation studies were performed. The control strategy is based on critical or key process parameters controls and associated in-process controls. Process validation for omburtamab active substance includes the identification and classification of (critical) quality attributes (CQAs), process risk assessment and a subsequent control strategy. For process verification the applicant proposes stage process validation, which, in principle, is acceptable. Data from process performance qualification (PPQ) runs: PPQ1, PPQ2, and PPQ3 have been included in the current submission. With regard to staging, the process validation the applicant refers to small scale model results and/or prior knowledge, The applicant provided details on the process risk assessment approach, e.g., definition of risk priority number (RPN) threshold. Results of the small-scale studies (process characterisation studies) supporting the process risk assessment are provided. The impact of investigated PP on certain CQAs is e shown. An overview about omburtamab critical quality attributes (CQAs) and the associated justification for the classification has been provided. The panel of CQAs listed is considered sufficient. Characteristics of mAbs such as low molecular weight (LMW) species, fragments, charged variants, glycosylated species were considered in the assessment.

To be able to demonstrate the fill homogeneity into the bottles, samples are taken before the first bottle, in the middle of the repartition and before the last bottle. The content by optical density (OD) and the high molecular weight (HMW) content by size exclusion high performance liquid chromatography (SE-HPLC) are performed respectively to confirm the homogeneity of the omburtamab active substance. The downstream process holding times were evaluated for their impact on stability indicating parameters at small scale during consistency to define the holding time for the production scale. Re-filtration studies on omburtamab active substance filtration will be formally evaluated to demonstrate the absence of impact on product quality in case the filtration step would be repeated. These studies were performed at laboratory scale using representative parameters of the production scale. Omburtamab active substance is shipped frozen (<–60°C) as per established shipping validation protocol. The omburtamab manufacturing process is shown to effectively and consistently remove process-related impurities (HCP, DNA, protein A, Poloxamer, antifoam) to acceptable safety levels.

Manufacturing process development

Development of the hybridoma cell line has been described leading to clinical and commercial scale manufacturing process. Characterisation and process controls, with comparability determined through the scale up activities during development have been described.

Characterisation

Omburtamab has been characterised by suitable analytical methods. The structure of the antibody has been confirmed. Post-translational modifications are sufficiently characterised. The N-glycosylation profile indicates that the most abundant N-glycan species observed is G0F, followed by G1F. Aglycosylated N-glycans (G0) is also present Omburtamab is a murine IgG1κ monoclonal antibody (mAb) secreted by a hybridoma cell line issued from the fusion of Balb/C splenic lymphocytes and SP/2-0 myeloma cells. The levels of HMW species and fragments are considered acceptable and are controlled by specifications. Biological activity was evaluated by binding activity of omburtamab to B7-H3. The biological characterisation of omburtamab is considered sufficient. It is noted that the intended mode of action (MoA) of Iodine-131 omburtamab is that the radiolabelled antibody recognises and binds selectively to the B7-H3 antigen expressed on CNS/LM neuroblastoma tumour cells and the iodine-131 emits radiation, resulting in DNA damage and tumour cell death. Omburtamab represents a full IgG1κ

monoclonal antibody and therefore characterisation of all biological properties including binding to Fc-gamma receptors, C1Q and Fc-mediated effector functions such as ADCC, ADCP, CDC is expected. With regard to ADCC in vitro tumour killing ADCC properties of the five IgG antibody constructs were investigated using neuroblastoma LAN-1 tumour cells as targets and human peripheral blood mononuclear cells as effector cells. The murine construct representing omburtamab had no ADCC function with human peripheral blood mononuclear cells. Characterisation of effector function activity was raised as a major objection; the characterisation has been satisfactorily demonstrated.

Process-related impurities such as host cell protein (HCP), host cell DNA (HCD), Protein A, Poloxamer 188, and anti-foam are removed by the process to acceptable limits. HCP, HCD, and ProtA are further controlled by specifications for which the limit for HCP should be tightened. Regarding extractable and leachables, the drug substance container was identified with the highest risk. An extractable study has been performed on the drug substance container using the formulation buffer. No organic extractables above analytical evaluation threshold and 3-fold above blank were detected in the extracts of the drug substance container

2.4.2.2. Specification

The release and shelf-life specifications for omburtamab AS include general tests, identity, concentration, potency, purity and impurities. Safety tests are controlled only at AS release.

Specifications cover the relevant Quality Attributes (QA) according to the characterisation.

The Acceptance Criteria were substantially tightened as requested: potency by surface plasmon resonance, SE-HPLC, capillary electrophoresis sodium dodecyl sulfate (CE-SDS), HCP, and Bioburden. Capillary isolelectric focusing (cIEF) is implemented as purity parameter and reported with numerical acceptance criteria. Stability specification acceptance criteria were aligned with the revised release.

Batch analysis

The batch release results for omburtamab drug substance batches were produced with the to-be-marketed manufacturing process. The data demonstrate that the acceptance criteria were met at the time of definition.

Reference materials

One interim reference standard and one primary reference standard have been established since the transfer of the omburtamab active substance manufacturing process. A working reference standard will be established from active substance and qualified against the primary reference standard. A two-tiered reference standard system will be implemented.

Container closure

Omburtamab active substance is filled in non-pyrogenic PETG bottles closed with high-density polyethylene (HDPE) screw caps. Materials are in compliance with relevant guidance documents mainly USP requirement. Considering the scattered guidance provided in European guidance documents, this is considered acceptable.

2.4.2.3. Stability

A 24-month shelf life is proposed for omburtamab active substance when stored at the recommended storage condition (–70°C ± 10°C). The batches placed on stability are considered representative. The proposed shelf life is based on 24 months long-term stability data at recommended storage conditions

and accelerated stability data at 5°C± 3°C for 12 months and stressed stability data at 25°C ± 2°C for 6 months. Overall, the data indicate a good stability profile of omburtamab.

2.4.3. Sodium Iodide-131 intermediate

The applicant submitted an ASMF (open part) of the radionuclide precursor sodium [^{131}I]iodide for radiolabelling. The restricted part of the ASMF for the radionuclide precursor sodium [^{131}I]iodide for radiolabelling is separately submitted by the ASMF holder.:

The ASMF open part covered the following areas: General information, Manufacture, Characterisation, Controls, Reference Standards or Materials, Container Closure System, Stability. The ASMF restricted part covered additional details on Characterisation, Control and Mnaufacture.

Iodine-131 is obtained by fission of uranium-235. The purification process ends with the trapping of iodine (I_2) in NaOH solution. This trapping occurs by dismutation and gives two oxidation stages (-1 for I^- and +5 for IO^{3-}). However, the radiolysis phenomenon due to the high activity of the mother solution results in the reduction of IO^{3-} to I^- (generally more than 99%). The stock solution is sodium iodide (NaI) in NaOH aqueous solution.

The oxidation stage [-1] of the iodine in the stock solution is confirmed by the routine radiochemical purity measurements, which indicate that more than 99% of the radioactivity is associated with the 'iodide' chemical form.

The fission of ^{235}U yields a large number of isotopes which form decay chains. During the process validation, only one other isotope of iodine was observed (^{133}I) meaning that iodine trapping and distillation are sufficient to remove all the other radio-contaminants.

Sodium iodide (^{131}I) solution for radiolabelling is only dedicated for the synthesis (radiolabelling) of a molecule to obtain a radio-iodinated clinically relevant active substance. Hence, the sodium iodide (^{131}I) solution for radiolabelling is not dedicated for use as an active substance in the manufacturing of a finished medicinal product as for e. g. sodium iodide (^{131}I) capsules.

With the radionuclide precursor sodium iodide (^{131}I) solution for radiolabelling, this ASMF does not describe an active substance but an intermediate dedicated for synthesis (radiolabelling) to obtain a clinically relevant active substance. The specification of the sodium iodide (^{131}I) solution for radiolabelling has more the character of a radiochemical substance than of a pharmaceutical substance. In this context it is also necessary to recognise that an ASMF is typically only used for clinically relevant active substances and not for intermediates as in this case. However, it was agreed that the detailed description of the manufacturing of a radionuclide using methods of nuclear physics and nuclear chemistry can be provided by ASMF in the marketing authorisation dossier.

With regard to the presented information about the manufacturing of sodium iodide (^{131}I) solution for radiolabelling no concerns are raised. The reason for this is on one side the fact that the sodium iodide (^{131}I) will be further processed to obtain the clinically relevant active substance and is from a chemical point of view only an intermediate in a synthesis sequence and on the other side it is recognised that sodium iodide (^{131}I) has manufactured for clinical use for more than 50 years, typically for thyroid therapy, and a wide practical knowledge about how to manufacture and handle sodium iodide (^{131}I) is widely available. Furthermore, the pharmacopoeia provides for sodium iodide (^{131}I) solution for radiolabelling a monograph and the sodium iodide (^{131}I) solution for radiolabelling is in compliance with this monograph.

2.4.4. Omburtamab mAb finished product intermediate

2.4.4.1. Description of the product and pharmaceutical development

Manufacture and partial release testing of omburtamab finished product intermediate is done by a fill/finish Contract Manufacturer (CMO) in EU. Additional release testing is performed by analytical Contract Research Organisations in EU and Switzerland. Satisfactory demonstration of GMP compliance is provided.

The omburtamab finished product intermediate is available as a solution ready for radio labelling composed of omburtamab active substance, citric acid/sodium phosphate dibasic buffer and water for injection with a pH of 4.2 ± 0.2. No novel excipients are used.

Omburtamab is formulated into the formulation buffer at the TFF step in the omburtamab active substance manufacturing process and is diluted in the omburtamab finished product intermediate fill process (with formulation buffer). All omburtamab finished product intermediate batches manufactured, have been made by dilution of omburtamab active substance, filtration and filling of omburtamab finished product intermediate into Type 1 glass vials without any modification. The batch size has varied according to clinical needs.

The omburtamab finished product intermediate batches manufactured on behalf of Y-mAbs have been filled in vials at the CMO in various batch sizes. This CMO is the chosen manufacturer for commercial supply of omburtamab finished product intermediate.

Compatibility studies were performed at the CMO to assess any potential incompatibility of the omburtamab finished product intermediate solution with the following material: polyvinylidene fluoride filters (PVDF filters); stainless steel; ultra low density polyethylene (ULDPE bag); Platinum cured silicon tubing. No significant changes were seen between the control sample and the samples in the compatibility study. In order to confirm the suitability of the omburtamab finished product intermediate container closure system a preliminary extractable and leachable assessment is provided for the glass vial and the rubber stopper. This includes the patient population and dosing regimen and the fact that the vial is made of Type I borosilicate glass and complies with the requirements of Directive 94/62/EC and Ph. Eur. 3.2.1. No basic qualification or specific extractables data are obtained from the supplier of the rubber stoppers but a product-specific extractable study was executed on the final vial and stopper (see below container closure system section).

The omburtamab finished product intermediate contains no preservatives and is manufactured using an aseptic process including sterilisation by filtration. In-process controls have been introduced to the manufacturing process to demonstrate the capability of the bioburden reducing steps. In addition, media fills have been executed to demonstrate the aseptic processing capability.

2.4.4.2. Manufacture of the product and process controls

The manufacturing process for omburtamab finished product intermediate includes thawing and dilution of the omburtamab active substance, mixing, followed by aseptic fill finish into glass vials. The vials are 100% visually inspected for product, particulate matter, closure and container defects. Omburtamab finished product intermediate is shipped frozen (−25°C to −15°C) CMO to warehouse and from warehouse to the designated radiolabelling facility.

The control strategy for the omburtamab finished product intermediate manufacturing process includes numerous process controls, which are classified as CPP or non-CPP. The CPPs defined for the Ab intermediate finished product manufacturing process are considered adequately justified. The majority

of CPPs is controlled by master batch record instructions. Process sampling points for finished product intermediate testing are indicated.

Periodical revalidation of the aseptic filling line is performed by executing a media fill worst-case process twice per year. Data for the last three worst-case media fill batches covering the omburtamab finished product intermediate process were presented. No contaminated units were observed in the media fill processes. The shipment is operated by an international shipping company who has completed a performance qualification on mock finished product intermediate material. The mock shipment was performed in a warm period of the year as a worst-case scenario and the temperature internal and external of the shipping container were monitored during the shipment. The data indicate that the shipping container maintains a temperature in the range of –25°C to –15°C during a shipment.

Process performance and control was demonstrated through three successful consecutive batches of omburtamab finished product intermediate. For the PPQ batches, all results conformed to the predefined acceptance criteria. No deviations occurred. A summary of in-process hold times at 15°C – 25°C observed during process performance qualification is provided.

Excipients are added during the omburtamab active substance manufacturing process and during dilution with formulation buffer in the omburtamab finished product intermediate process. All listed excipients are of compendial degree. There are no novel excipients in the omburtamab finished product intermediate. No excipients of human or animal origin are used in the manufacture of omburtamab finished product intermediate. According to the applicant the suppliers certify that the excipients are manufactured without the use of raw materials of animal origin and thus pose no risk of TSE.

2.4.4.3. Product specification

Five finished product intermediate batches were produced at the fill / finish CMO.

The release and shelf life specifications for omburtamab finished product intermediate include general tests, identity, concentration, potency, purity, impurities and microbial safety tests. The specifications for the finished product intermediate further include tests for visible and sub-visible particles, extractable volume, and container closure integrity.

Specifications cover the relevant quality attributes. Acceptance criteria (AC) for the following specifications were substantially tightened: potency by surface plasmon resonance, SE-HPLC, CE-SDS. cIEF was implemented as purity parameter and reported with numerical acceptance criteria. Stability specification acceptance criteria were aligned with the revised release AC. Compendial methods were successfully verified. It is acknowledged that since omburtamab active substance and omburtamab finished product intermediate are identical in terms of protein identity and formulation and has a similar protein concentration, the assay verifications and validations performed on omburtamab active substance as described in Section 3.2.S.4.3 also applies to omburtamab finished product intermediate. The acceptance criteria defined at the time of release were met for all finished product intermediate batches manufactured with the to-be-marketed manufacturing process. Product-related impurities in omburtamab finished product intermediate are the same as for the omburtamab active substance. Limits for the product-related impurities are included in the omburtamab finished product intermediate release specification. With regard to potential process-related impurities an extractables and leachables risk assessment was carried out to estimate whether potential leachables originating from polymeric single-use systems and containers pose any risk to the patient's safety. No items used during the omburtamab finished product intermediate manufacturing were identified as high-risk. The omburtamab finished product intermediate specification is set in accordance with the guidelines described in Q6B. For the definition of limits, it is acknowledged that it is not possible to use statistics for setting release acceptance criteria due to the limited number of lots.

Batch analysis

The batch release results for omburtamab finished product intermediate batches demonstrate that the acceptance criteria were met.

Reference materials

The reference standard used for omburtamab finished product intermediate testing is the same as the reference standard used for omburtamab active substance testing.

Container closure

The container closure system for omburtamab finished product intermediate 2 mg/mL consists of a sterile, clear 2R Type I glass vial sealed with a 13 mm bromobutyl stopper over sealed with an aluminium seal and white polypropylene cap. The components of the container closure system are in compliance with Ph. Eur. A product specific extractable study has been performed on the glass vial and stopper, using the formulation buffer (aqueous solution of citric acid and sodium phosphate dibasic, pH 4.2) as extraction solvent. No organic extractables above analytical evaluation threshold and 3-fold above blank were detected in the extracts of the glass vials/stopper combination. The glass vials are colourless, the rubber stoppers are made of bromobutyl rubber and primary packaging is in compliance with respective Ph. Eur. Requirements.

2.4.4.4. Stability of the product

A 36-month shelf life was proposed for omburtamab finished product intermediate when stored at the recommended storage condition (-20°C±5°C). The batches placed on stability are considered representative. The proposed shelf life was revised to 24 months long-term stability data at recommended storage conditions and accelerated stability data at 5°C± 3°C for 24 months and stressed stability data at 25°C ± 2°C for 6 months.

Overall, the data indicate a good stability profile of omburtamab finished product intermediate. Taking the comparability data into account it is agreed that currently 24 months stability data for three representative batches are available and support the proposed shelf life of 24 months for the omburtamab Finished Product Intermediate.

2.4.5. (^{131}I) omburtamab Finished Medicinal Product

2.4.5.1. Description of the product and pharmaceutical development

Radiolabelling of the cold omburtamab with iodine-131, sterile manufacturing and release testing of the finished product is performed by radiolabelling facility located in the USA. Satisfactory demonstration of GMP compliance is provided.

All excipients used for (^{131}I) omburtamab drug product: sodium dihydrogen phosphate, disodium phosphate, recombinant human serum albumin, sodium chloride, octanoic acid, polysorbate 80, hydrochloric acid, sodium hydroxide, water for injections, are tested per compendial methods.

There are no excipients of human or animal origin and no novel and no non-compendial excipients.

Omburtamab finished product intermediate is radiolabelled with iodine-131.

The radioactive active substance [^{131}I]Iodo-omburtamab is formulated in aqueous solution with a radioactive concentration (strength) to meet 462.5 MBq / mL (12.5 mCi/mL) at reference time. According the SmPC the reference time is defined as the time of use. The shelf-life is declared with 96

hours and one vial is dedicated for single use. To obtain clarity about the radioactive strength and the actual amount of product (radioactivity) per vial one binding reference time is defined.

According to the SmPC the fill volume of one product single dose vial is constant. Further, the strength of the product is acknowledged as being the radioactive concentration and amount present at the reference time.

For recombinant human serum albumin (rHSA), USP, the question was raised whether the rHSA is added as a pure substance or as a preparation containing its own excipients. The rHSA, Recombumin, is formulated with water for injection (Ph. Eur.), sodium chloride (USP/Ph. Eur.), octanoic acid (Ph. Eur.) and Polysorbate 80. These excipients are stated on the SmPC.

The applicant described the complete radiolabelling step which is the synthesis of the clinically relevant active substance [^{131}I]Iodo-omburtamab in the finished product part "P". It is clear that in radiopharmaceutical production, the active substance (radiolabelling) synthesis is directly connected to the finished product formulation, in this case the formulation of an injection.

The applicant initially presented a mainly narrative summary of development of the final product, with limited data. This was raised as a major objection, resolved during the procedure.

2.4.5.2. Manufacture of the product and process controls

The radiolabelling of the cold omburtamab with iodine-131, the purification of the [^{131}I]Iodo-omburtamab and its formulation in a sterile injection (finished product manufacturing) and the complete release testing of the finished product is done by the radiolabelling facility. A pre-approval inspection has been performed by FDA with outcome classification "Voluntary Action Indicated", and COMSTAT shows that the manufacturing site is acceptable for the activities related to Sterile-Filled Small Volume Parenteral Drugs. For market release the in the European Union seated manufacturer Y-mAbs Therapeutics A/S, Denmark, is declared. A GMP certificate covering the batch release of aseptically manufactured radiopharmaceuticals and biotechnological products issued by the Danish Medicinal Agency dated the 10th July 2020 is presented..

The (^{131}I) omburtamab finished product is produced in a continuous finished product manufacturing process by sterile filtration and aseptic filling. During this process, the precursor, the omburtamab finished product intermediate reacts with a solution of Na[^{131}I]I in a buffered solution and the use of Iodination beads. The product is purified by use of a purification column, immediately formulated *in situ*, sterile filtered and aseptically filled into a sterile vial and immediately stored at the recommended storage condition of −70 ± 10 °C. (^{131}I) Omburtamab finished product is shipped frozen <−60°C directly from the radiolabelling facility in USA to the hospital that ordered the dose. The individual process steps are described and IPCs are indicated in the process scheme and further described in section control of critical steps below. The preparation of the finished product is the purification of the after radiolabelling obtained [^{131}I]Iodo-omburtamab using a desalting column which works according to the size-exclusion principle letting inorganic ions and small molecules faster moving om the column than proteins with high molecular weight. By this the small molecules and non-reacted [^{131}I]iodine in the chemical form as iodide can be simply separated from the [^{131}I]Iodo-omburtamab, while the [^{131}I]Iodo-omburtamab elutes from the column much slower than the small molecules. As the eluent solution is aqueous phosphate buffer, the active substance [^{131}I]Iodo-omburtamab can be directly eluted in the finished product preparation which is an aqueous phosphate buffer which can be directly sterile filtered in the finished product vial. Because the size exclusion chromatography of proteins with high molecular weight does not allow separation of the radiolabelled proteins from the non-radiolabelled proteins, it is a technical fact that the complete amount of omburtamab whether radiolabelled or not remains in the finished product

The validation of the aseptic operations as for e.g., the media fill test belongs first of all into the GMP – area and is confirmed with the GMP certificate which covers the process. The stability of the manufacturing process is demonstrated by three consecutive process validation batches of [^{131}I]Iodo-omburtamab injection which were manufactured at the manufacturing site, which is common established praxis.

For manufacturing a "sterile fluid pathway" is described, meaning that beginning with the sterile filtration a closed connection from the sterile filter to a rubber stopper closed production vial using a syringe needle is used. This technique facilitates the demand for the cleanroom conditions for the filling area from class "A" to class "C". The disadvantage of this technique is that the rubber stopper of the vial is punctured by at least one needle, and in the case of a necessary ventilation needle by two needles. Furthermore, samples for release testing and retain samples must be withdrawn too. This means the original integrity of the rubber stopper is impaired by multiple insertion of syringe needles. The applicant has presented in the development part studies which show that the punctured rubber stoppers retain integrity. Nevertheless, this does not change the fact that the rubber stoppers are punctured, and this was raised as a Major Objection. The applicant agreed to revise the process, which is presented as a Recommendation to the final opinion. The simple closed vial filling technique derives from the in-house preparation of radiopharmaceuticals in hospitals where the injections are used "in-house" during few hours. For the classical Positron-Emission-Tomography (PET) Radiopharmaceuticals radiolabelled with the radionuclides Nitrogen-13, Carbon-11 and Fluorine-18 this technique is used and tolerated till today because these radiopharmaceuticals are used during few hours after their manufacturing because of their fast radioactive decay. In the case of [^{131}I]Iodo-omburtamab – injection the background is completely different. [^{131}I]Iodo-omburtamab is neither dedicated for use in few hours nor dedicated for in-house use. For [^{131}I]Iodo-omburtamab injection a shelf life of 4 days is proposed and the distribution is proposed throughout the world using air transport shipping. From (radio-)pharmaceutical manufacturing technology there is no reason to tolerate a filling method in contradiction to the standards of sterile solution filling by impacting the original integrity of the rubber stopper. For the filling of radiopharmaceuticals, the use of open-filling in a clean-room class A cabinet by closing of the vials after the filling without puncturing the stoppers is possible by remote controlled equipment to avoid radiation burden to the co-workers at the manufacturing facility. Argumentations that sterility testing and dye intrusion tests show the integrity of the punctured rubber stoppers cannot be accepted because the sterility assurance level (SAL) is defined according to the European pharmacopoeia with 10^{-6} meaning that only 1 to 1 million vial is allowed to be not sterile. The applicant describes his efforts to install two manufacturers which will be in the future capable to supply the finished product as usual for injections in glass vials closed with intact non - punctured rubber stoppers.

The technical deficiency in the manufacturing process can be simply solved by using adequate production equipment from radiopharmaceutical technology and a commitment is made by the applicant that the manufacturing process of the finished product will be shifted from "closed" filling technique leading to punctured rubber stoppers to "open" filling technique leading to intact non punctured rubber stoppers at the latest 10 months after the issue of the marketing authorisation should be made (post authorisation measure). The applicant aims to introduce an alternative radiolabelling facility in the EU as the future finished product filling site to be filed as a variation post approval. A restricted access barrier system (RABS) and dispensing system is in place at this facility, ensuring a satisfactory aseptic filling process.

In-vivo stability of iodinated tyrosine moieties could be worse because the body possess enzymes specialised on the deiodination of iodo-tyrosine moieties in the context of the steering of the thyroid hormones thyroxine. About the in-vivo stability of the radioiodinated omburtamab no data is submitted by the applicant regarding deiodination. As iodine in ortho position to a hydroxyl group in an aromatic system is not perfectly stable towards deiodination, alternative processes were considered. para-

radioiodo– phenylalanine was also developed which can be first radioiodinated and then conjugated with the protein assuring that the protein is not damaged by harsh radiolabelling conditions. The applicant should use for the radiolabelling of omburtamab a method which produce an against deiodination stable [^{131}I]Iodo-omburtamab, as for e. g. by using radioiodinated Phenylalanine-derivatives. In this context the applicant is invited to provide data in view to the in-vivo stability of [131I]Iodo-omburtamab, for e. g. in blood plasma.

2.4.5.3. Product specification

The release and shelf life specifications for ^{131}I-omburtamab finished product include general tests, radiochemical identity, concentration, strength, potency, radiochemical purity and impurities, radionuclidic identity and purity, protein purity and microbial safety tests.

Specifications are set in accordance with ICH Q6A and Q6B and cover the characteristics to be controlled. Three consecutive process validation batches of ^{131}I-omburtamab were produced in which the quality of the product has been analysed. Clear references to analytical procedures are added to the specifications. Analytical procedures have been briefly described. Most of the specifications and their limits are founded on pharmacopeia monographs and are in the usual frame for radiopharmaceuticals and does not need to be discussed.

Potential process- and product-related impurities that may be present in ^{131}I-omburtamab finished product are described and would be detected by methods used for release testing.

Extractable samples were analysed for volatile, semi-volatile, non-volatile organic compounds and inorganic elements by HS-GC-FID/MS, GC-FID/MS, LC-DAD/MS, and ICP-MS. No compounds above the AET were observed. The radiochemical purity of ^{131}I-omburtamab should be aligned to ≥ 90% for the monomer at T0 and at expiry. To ensure the accurate potency of iodine - ^{131} the radiochemical purity of the [^{131}I]Iodo-omburtamab should be as high as possible. Because of [^{131}I]Iodo-omburtamab injection is a therapeutic radiopharmaceutical the reliable determination of the radioactivity amount filled is essential. The applicant describes the use of a by the German national meterologic institute physikalisch technische bundesanstalt (PTB) calibrated Iodine-131 reference standard in the same geometry and packaging of the finished product. Furthermore, the applicant describes that the calibration and operational tests for the dose calibrators are done according to the pharmacopeia. The radioactivity calibration of [^{131}I]Iodo-omburtamab was initially not sufficiently assured and raised as a Major Objection. The described methods used for calibration of the activimeters used at both relevant manufacturing sites are acceptable and assure a reliable determination of the radioactivity amount filled per vial.

A risk assessment to evaluate potential nitrosamine impurities in the ^{131}I-omburtamab finished product is provided. The risk assessment was satisfactory.

Batch analysis

Three consecutive process validation batches of ^{131}I-omburtamab were produced in which the quality of the product has been shown to meet the acceptance criteria.

Reference materials

A list of reference standards or reference materials used for quality control testing of the ^{131}Iomburtamab final finished product is provided. These materials are primarily used for calibration purposes and their use is justified. Reference standards are always connected to the analytical method they are used for. If an analytical method needs to be changed typically different reference standards are needed too. This is

in the case for the measurement of the radioactive concentration which is detailed described in the discussion of the validation of the method to determine the radioactive concentration.

Container closure

The container closure system used for the radiolabelled finished product is a pre-assembled, sterile empty vial (Type I borosilicate glass vial), which is closed with a n-butyl rubber elastomer septa and aluminium crimp seal. The glass used for the sterile empty vial is a USP Type I, borosilicate glass. The closure is a 20 mm butyl rubberstopper. The seal is an aluminium seal. An extractable study has been performed on the final product vial, using the final formulation buffer as extraction solvent. No extractable compounds were detected. The usual primary packaging material for sterile aqueous solutions is used which would be acceptable in the case that the rubber stopper is not punctured by filling needles using a for a sterile solution non adequate filling process. The filling process is assessed deeply before in the assessment of the manufacturing process. Specifications and description of analytical procedures used (and their validation, where relevant), and compendial confirmation for each element of packaging is provided. The actual used secondary packaging material are sufficiently described.

2.4.5.4. Stability of the product

^{131}I-omburtamab finished product is shipped frozen <–60°C directly from the CMO in the USA to the hospital that ordered the dose. Therefore it is acknowledged that a certain time is required for shipment and the proposed shelf-life of the final finished product ^{131}I-omburtamab of 96 hours at ≤-60°C, protected from light in a shielded lead container was not initially accepted due to lack of stability data.. To overcome the potential issues with the limited shelf-life, Y-mAbs proposed to transfer the manufacturing process to a European based CMO. Supportive stability batches were manufactured at a European based CMO, (to be added post-approval). The provided data support the proposed 96 hours shelf-life for ^{131}I-omburtamab finished product when stored at ≤-60°C.

When thawed for use, the finished product should be stored below 25°C and must be used within 3 hours.

2.4.5.5. Adventitious agents

TSE compliance

All raw materials used in the manufacture process of omburtamab are received, identified, sampled, quarantined, tested, labelled and released according to established written procedures. The whole production process of Omblastys, including the omburtamab fermentation and purification process as well as the radiolabelling process, is free of animal- or human derived materials. The omburtamab master cell bank has been established to grow in chemically-defined serum-free medium and has therefore been produced without materials of animal or human origin. Only during early cultivation of host cells before adaption to the serum-free growing, cells were cultivated in the presence of foetal bovine serum. TSE safety is demonstrated through the sourcing of the serum from geographical low risk country. In summary, compliance of the manufacture of Omblastys with TSE-Guideline EMEA 410/01 rev03 has been sufficiently demonstrated.

Virus safety

The omburtamab monoclonal antibody is produced in a hybridoma cell line derived from the fusion of mouse myeloma cells Sp2/0-Ag14 and splenic lymphocytes from BALB/c mice. No animal- or human-derived reagents are used in the manufacture of the omburtamab active substance or finished product, the corresponding master cell bank or the radiolabelling process of the antibody. The serum is gamma-irradiated. No more information on the serum is provided which is acceptable because the master cell

bank has been tested sufficiently and found to be negative for bovine viruses. None of the excipients are of human or animal origin. The omburtamab master cell bank and a corresponding extended cell bank have been tested sufficiently for adventitious viruses as well as retroviruses in accordance with ICH Q5A. As confirmed on certificates of analysis, no viruses except retrovirus-like particles as well as infectious amphotropic/xenotropic retroviruses were detected which is acceptable as hybridoma cells are known to produce such particles. The use of the MCB for omburtamab production is acceptable. The unprocessed bulk harvest is also tested routinely in compliance with ICH Q5A for adventitious viruses including a specific assay for MVM and Vesivirus detection. No viruses may be found by these assays for further processing of the batch. Detection of infectious retroviruses and the counting of retrovirus-like particles is not a routine assay, but has been performed on several batches produced according to the commercial process in line with ICH Q5A. Infectious retroviruses have been found in one of the batches analysed and retrovirus-like particles in all tested batches which is not unexpected. The maximum number detected has been used for calculation of the retrovirus safety margin. The virus reduction for the parvovirus is considered sufficient. A retrovirus risk assessment was performed demonstrating sufficient clearance for the hybridoma cell-derived retrovirus-like particles (RVLP). In summary, the virus safety of Omblastys has been shown to be suitable at the level of raw materials used in the production processes as well as the excipients, however, the virus reduction capacity of the process was initially demonstrated only to a limited extent and more information and data were provided to confirm a robust virus reduction capacity of the omburtamab purification process.

2.4.6. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The dossier is structured in order to reflect the stages of manufacture: omburtamab mAb intermediate active substance, omburtamab mAb intermediate finished product, Sodium Iodide-131 ASMF, and ^{131}I-omburtamab finished product.

Iodine-131 omburtamab is a radiolabelled murine monoclonal antibody that recognises and binds selectively to the B7-H3 antigen expressed on CNS/LM neuroblastoma tumour cells. The iodine-131 emits radiation, resulting in DNA damage and tumour cell death.

An ASMF (open part) of the radionuclide precursor sodium [^{131}I]iodide for radiolabelling is submitted by the applicant. The restricted part of the ASMF for the radionuclide precursor sodium [^{131}I]iodide for radiolabelling is separately submitted by the ASMF holder

Omburtamab finished product intermediate is radiolabelled with iodine-131 to produce ^{131}I-omburtamab Finished product.

While the omburtamab determines the biodistribution of the active substance, the strong β-emitter Iodine-131 with a physical half-life of around 8 days is suitable for therapeutic cancer treatment by irradiation.

In the submitted documentation the synthesis (radiolabelling) of the active substance [^{131}I]Iodo-omburtamab is not described in its own active substance part 3.2.S. In the manufacturing sequence from the active substance [^{131}I]Iodo-omburtamab to the finished product [^{131}I]Iodo-omburtamab injection (Omblastys) no isolation of the active substance [^{131}I]Iodo-omburtamab is foreseen.

The radionuclide iodine-131 is manufactured at a research reactor and used in the chemical form sodium iodide (^{131}I) solution for radiolabelling. Furthermore, the sodium iodide (^{131}I) solution for radiolabelling is specified in conformity with the corresponding Pharmacopoeia Monograph no. 2121.

After radioiodination obtained reaction solution is purified using size exclusion chromatography to separate the [^{131}I]Iodo-omburtamab / omburtamab from the smaller molecules, i.e. non-reacted [^{131}I]iodine, buffer salts etc.

A number of major objections on quality were raised during the procedure: control strategy for mAb intermediate was considered to be preliminary; characterisation of effector function activity; initially a mainly narrative summary of development of the final product was presented; radioactivity calibration of [^{131}I]Iodo-omburtamab was initially not sufficiently assured. These were resolved during the procedure.

The former major objection concerning the not state-of-the-art filling technology used in the manufacturing process leading to finished product vials where the closing stoppers are impacted in their integrity from the filling process with two needles for filling and venting can be solved with a recommendation. The applicant agreed to revise the process, which is now presented as a Recommendation for future quality development.

Overall, it is concluded that the provided quality information is considered sufficient and therefore from quality point of view the application for ^{131}I-omburtamab could be approvable.

2.4.7. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Omblastys is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

2.4.8. Recommendation(s) for future quality development

In the context of the obligation to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

The applicant should switch from a "closed" filling technique leading to punctured rubber stoppers to "open" filling technique leading to intact non punctured rubber.

2.1. Non-clinical aspects

2.1.1. Introduction

The nonclinical data package supporting the application to market ^{131}I-omburtamab relies on information in the published literature from studies conducted early in its development, as well as more recent studies that have characterized its specificity of binding, biodistribution and dosimetry, and mechanisms of radiation-induced toxicity.

2.1.2. Pharmacology

2.1.2.1. Primary pharmacodynamic studies

The identification of B7-H3 as a potential therapeutic target and its expression in tumour tissue is based on literature. It was demonstrated that Omburtamab bound to human and cynomolgus monkey B7-H3

with comparable high affinity (1.1 and 1.6 pM K_D for human and cynomolgus monkey B7-H3, respectively).

Table 1. The binding kinetic information of omburtamab to B7-H3 from different species

B7H3 (3ug/ml)	No. of replicates	Mean ka (M-1 S-1)	ka SD	Mean kd (S-1)	kd SD	Mean K_D (pM)	K_D SD (pM)	Mean Rmax (RU)	Rmax SD	Mean Res sd	Res sd SD
cyno	3	$6.5x10^6$	$9.6x10^5$	$1.0x10^{-5}$	0.0	1.6	0.23	210	42	4.8	1.3
human	3	$8.9x10^6$	$5.9x10^5$	$1.0x10^{-5}$	0.0	1.1	0.076	562	59	9.3	2.5
mouse	3	Na	na	na	na	na	na	5.2	2.2	3.7	1.5
rat	3	Na	na	na	na	na	na	2.2	3.8	6.5	3.2

No detectable binding was observed with mouse or rat B7-H3. In conclusion the cynomolgus monkey is considered the relevant species.

It was determined whether Omburtamab binds to human tumour tissues including non-small cell lung carcinoma, ovarian cancer, neuroblastoma, medulloblastoma, glioblastoma, sarcoma, liver cancer and melanoma. Positive staining was evident in all tumour types whereas no staining was observed in normal control tissues.

Table 2. Summary of Experimental Design

Tissue	FFPE	Frozen	Antibody
Non-Small Cell Lung Carcinoma	√	√	OMBURTAMAB
Ovarian Cancer	√	√	
Neuroblastoma	√	NA	
Medulloblastoma	√	NA	
Glioblastoma	√	√	
Sarcoma	√	√	
Melanoma	√	√	
Non-Small Cell Lung Carcinoma	√	√	Isotype Control Mouse IgG1
Ovarian Cancer	√	√	
Neuroblastoma	√	√	
Medulloblastoma	√	√	
Glioblastoma	√	√	
Sarcoma	√	√	
Melanoma	√	√	

Table 3. Summary of Histopathologic Scoring with OMBURTAMAB

Tissue (FFPE)	Distribution	Staining Incident/Intensity	Comment
Non-small cell lung carcinoma	diffuse	4/4	granular, cell surface, some intracellular
Ovarian Cancer	multifocal	2/2	granular, cell surface, some intracellular
Neuroblastoma	diffuse	4/3	granular, cell surface, some intracellular
Medulloblastoma	diffuse	4/4	granular, cell surface, some intracellular
Glioblastoma	multifocal	4/4	granular, cell surface, some intracellular
Sarcoma	multifocal	2/2	granular, cell surface, some intracellular
Melanoma	diffuse	4/4	granular, cell surface, some intracellular
Liver Cancer	diffuse	3/3	granular, cell surface, some intracellular
Liver Normal	NA	0/0	NA
Tissue (Frozen)	**Distribution**	**Staining Incident/Intensity**	**Comment**
Non-small cell lung carcinoma	diffuse	2/3	granular, cell surface, some intracellular
Lung Cancer	multifocal	2/2	granular, cell surface, some intracellular of glandular epithelial cells
Ovarian Cancer	diffuse	4/3	granular, cell surface, some intracellular
Glioblastoma	diffuse	3/3	granular, cell surface, some intracellular
Sarcoma	diffuse	4/4	granular, cell surface, some intracellular
Melanoma	multifocal	3/3	granular, cell surface, some intracellular

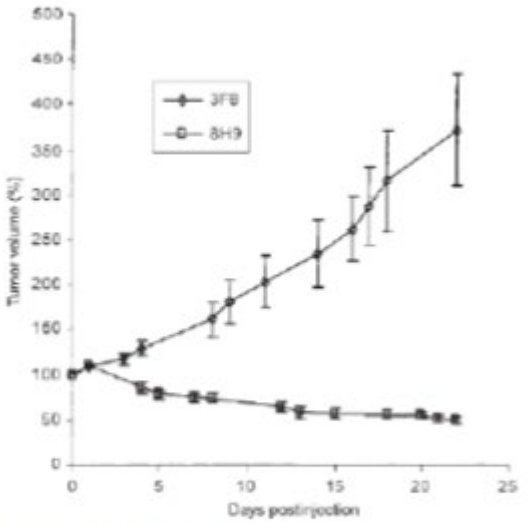
In the only GLP compliant tissue cross-reactivity study using a set of approximately forty specified tissues of human origin specific on-target binding to B7-H3, was seen in the epithelium of the skin, prostate, eye, endometrium, adrenal, fallopian tube, and cervix, as well as in the supporting stroma of most tissues. Potential off-target binding was seen in cytoplasmic staining of the Leydig cells of the testis, in cytoplasmic staining in glial cells of the spinal cord of one donor, and in cytoplasmic staining of alveolar macrophages in the lungs.

Inhibition of tumour growth by ^{131}I-Omburtamab compared to unlabelled Omburtamab was demonstrated in two different xenograft models.

The potential effectiveness of ^{131}I-omburtamab as an antitumor agent in vivo was evaluated in nude mice with established subcutaneous rhabdomyosarcoma (HTB82) or medulloblastoma (DAOY) cell xenografts, instead of the well-established mouse model of neuroblastoma.

Rhabdomyosarcoma tumour volume diminished to less than 50% of initial volume 21 days after injection without any adverse effects; however, tumour growth was noted 50 to 60 days after administration of ^{131}I-omburtamab.

Figure 1. Antitumor Effect of ^{131}I-omburtamab on RMS Xenografts



Source: Modak et al., 2005.[7]
Note: 3F8 is a murine anti-disialoganglioside IgG3 that binds to neuroblastoma cells but not RMS cells. 3F8 = iodine-131 murine 3F8 monoclonal antibody (^{131}I-3F8); 8H9 = iodine-131 murine monoclonal antibody (^{131}I-omburtamab); Ig = immunoglobulin; RMS = rhabdomyosarcoma.

In athymic, subcutaneous DAOY xenograft tumour bearing nude mice, ^{131}I-Omburtamab appears to inhibit tumour growth when compared to unlabelled omburtamab with a significant effect on survival (percent change in tumour volume was greater in the omburtamab group (97.1% ±22%) than in the ^{131}I-omburtamab group (30.9% ±19%) at all time points starting on Day 13).

In athymic, subcutaneous DAOY xenograft tumour bearing nude mice, ^{131}I-Omburtamab inhibits tumour growth when compared to unlabelled Omburtamab with a significant effect on survival as 6 out of 7 animals had to be euthanised due to tumour volume increase.

Table 4. Cause of Death for All Animals on Study per Group

Group	N per group	Reason for Euthanasia (n)			
		Weight loss	Tumor Volume > 2,000 mm^3	Study end point[a]	Other
Unlabeled Omburtamab (control)	7	0	6	0	1[b]
^{131}I-Omburtamab	7 (+1 extra)	0	0	6	2[c]

[a] Terminal end point defined as the date all animals from the unlabeled Omburtamab group were removed from study due to tumor size.
[b] Due to swelling of the eye.
[c] Due to poor health post-injection.

2.1.2.2. Secondary pharmacodynamic studies

No dedicated secondary safety pharmacodynamic studies have been conducted.

Safety pharmacology programme

In accordance with ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals no stand-alone safety pharmacology studies with ^{131}I-omburtamab have been conducted.

2.1.2.3. Pharmacodynamic drug interactions

Considering the MoA no pharmacodynamic drug interaction studies have been conducted.

2.1.3. Pharmacokinetics

Pharmacokinetic studies to characterise biodistribution and dosimetry of radiolabelled omburtamab were conducted after either intrathecal or intravenous dosing with ^{125}I-omburtamab in naïve rats or in tumour-bearing mice.

According to the Guideline on the non-clinical requirements for radiopharmaceuticals, in case of radiotherapeutics "the only additional aspect to consider in these cases is that the dosimetry study might be performed in an animal model of disease, if appropriate, to support that the targeted area will be reached adequately". The in vivo PK studies have been performed in rats (without tumour) and mice bearing medulloblastoma and rhabdomyosarcoma tumours. No in vivo studies have been performed in xenograft animal model with neuroblastoma.

Biodistribution analyses, conducted by single-photon emission computed tomography (SPECT) and computed tomography (CT) imaging, were used to quantify concentration over time in organs of interest, mean residence times (MRT), and organ and whole-body dosimetry estimates.

Figure 2. Blood Kinetics of ^{125}I-8H9 in nude mice with RMS xenografts

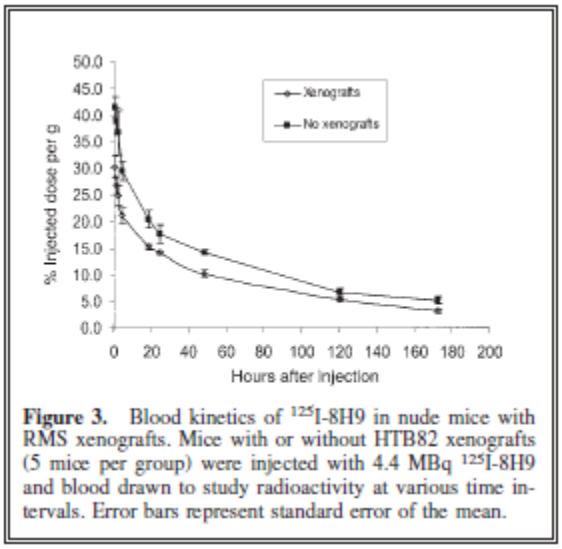


Figure 3. Blood kinetics of ^{125}I-8H9 in nude mice with RMS xenografts. Mice with or without HTB82 xenografts (5 mice per group) were injected with 4.4 MBq ^{125}I-8H9 and blood drawn to study radioactivity at various time intervals. Error bars represent standard error of the mean.

Table 5. Percent Injected Dose/Gram of ^{125}I-8H9 Distributed in HTB82 Xenografts and Normal Tissues 4, 24, 48 and 172 Hours After Injection

	4 hours (n = 7 mice) *Mean ± SD*	*24 hours (n = 9 mice)* *Mean ± SD*	*48 hours (n = 9 mice)* *Mean ± SD*	*172 hours (n = 8 mice)* *Mean ± SD*
Adrenal	5.0 ± 1.6	1.4 ± 1.6	1.4 ± 0.5	0.4 ± 0.3
Bladder	4.5 ± 1.6	2.6 ± 1.2	2.9 ± 0.8	0.9 ± 0.6
Blood	26.6 ± 2.1	14.1 ± 3.0	10.7 ± 2.1	3.2 ± 0.9
Brain	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.1 ± 0.0
Femur	1.2 ± 0.9	1.4 ± 0.5	1.1 ± 0.5	0.4 ± 0.1
Heart	10.3 ± 2.9	4.3 ± 1.9	2.9 ± 0.5	0.9 ± 0.2
Kidney	7.3 ± 3.1	3.9 ± 1.6	3.0 ± 0.7	0.8 ± 0.3
Large intestine	1.1 ± 0.7	1.7 ± 0.6	1.2 ± 0.3	0.2 ± 0.1
Liver	7.7 ± 1.3	4.0 ± 1.7	2.2 ± 0.3	0.7 ± 0.3
Lung	17.7 ± 7.8	5.7 ± 3.5	5.3 ± 1.1	1.4 ± 0.5
Muscle	0.7 ± 0.2	1.2 ± 0.6	1.1 ± 0.4	0.3 ± 0.1
Skin	3.2 ± 1.6	2.3 ± 1.6	2.5 ± 1.5	0.6 ± 0.4
Small intestine	2.8 ± 0.6	1.5 ± 0.4	1.1 ± 0.2	0.3 ± 0.1
Spine	2.8 ± 1.2	2.1 ± 0.8	1.7 ± 0.7	0.5 ± 0.2
Spleen	5.5 ± 2.2	5.8 ± 2.4	3.3 ± 0.8	0.5 ± 0.2
Stomach	2.4 ± 1.0	2.4 ± 2.1	1.6 ± 0.7	0.5 ± 0.4
Tumor	**7.0 ± 1.8**	**11.5 ± 3.9**	**15.1 ± 3.7**	**5.4 ± 1.2**

It is noted that no PK studies were performed regarding the antibody compound. Such analysis is expected including description and validation of the methods to characterise the antibody kinetics as well as potential ADAs. The applicant is asked to provide information regarding the antibody kinetics (^{131}I-omburtamab, free omburtamab) including potential ADA development.

In Sprague Dawley rats, dosimetry estimates indicate that the dose-limiting organ for ^{131}I-omburtamab in the adult male and female models was the heart wall followed by liver and the kidneys (0.53 and 0.69; 0.51 and 0,61; 0,38 and 0,46 respectively for the organs and animal gender). Effective doses for ^{131}I-omburtamab in adults were estimated at 0.20 and 0.28 mSv/MBq in males and females, respectively.

In Tumour-Bearing Mice selective tumour uptake was demonstrated at 4 to 172 hours after intravenous administration of 125I-omburtamab. Absorbed doses in tumours ranged from 797 mGy/MBq in small tumours up to 1,157 or 1,216 mGy/MBq in larger tumours. The dose-limiting organ was the skeleton (based on myelosuppression), followed by the liver and kidneys.

The overall pharmacokinetic characteristics of ^{131}I-omburtamab is driven by its antibody component and being a protein, omburtamab will undergo standard metabolism. Therefore, no dedicated studies to investigating the metabolism of ^{131}I-omburtamab are considered warranted. The applicant has not conducted any nonclinical excretion studies with ^{131}I-omburtamab, which is acceptable for the antibody part as it will undergo normal protein metabolism. It is stated that free iodine-131 will mainly undergo renal clearance which is agreed. Accumulation of free Iodine-131 possibly expected in the thyroid and the gastrointestinal tract has been analysed and clinical measures such as "Blockade of ^{131}I-uptake in the thyroid gland is to be ensured by administration of stable iodine e.g., potassium iodide" are indicated in the SmPC to counter act thyroid accumulation. Regarding the gastrointestinal tract only low levels of iodine-^{131} were detected by dosimetry in the various compartments.

2.1.4. Toxicology

The nonclinical toxicology programme has been conducted early in development at MSK in mice, rats, and Cynomolgus monkeys. Additional studies have been conducted more recently in mice and rats to better understand the radiation-induced toxicity associated with the ^{131}I-omburtamab treatment and the recovery after exposure.

Table 6. Overview of Toxicology Studies

Type of Study	Method of Administration	Test System Species/Strain	Test Article
Radiation-induced toxicity studies	Intrathecal, single-dose	SD rats	^{131}I-omburtamab
	Intrathecal, repeat-dose	SD rats	Omburtamab or ^{131}I-omburtamab
		Cynomolgus monkeys	^{131}I-omburtamab
	Intravenous, single-dose	Naïve athymic nude mice	Omburtamab or ^{131}I-omburtamab
		Athymic nude mice with MB (DAOY) xenografts	Omburtamab or ^{131}I-omburtamab
		Nude mice with or without RMS xenografts	^{131}I-omburtamab
	Intraperitoneal, single-dose	Athymic nude mice	^{131}I-omburtamab
Other toxicity studies	CED, single-dose	SD rats or athymic rats with U87 xenografts	Biotinylated-omburtamab
	CED, single-dose	SD rats	^{131}I-omburtamab (toxicity) or ^{124}I-omburtamab (dosimetry)
	CED, single-dose	Cynomolgus monkeys	^{124}I-omburtamab

CED = convection-enhanced delivery; GLP = Good Laboratory Practice; i.p. = intraperitoneal; i.t. = intrathecal; i.v. = intravenous; MB = medulloblastoma; MOA = method of administration; RMS = rhabdomyosarcoma; SD = Sprague Dawley; U87 = human glioblastoma cell line.

2.1.4.1. Single dose toxicity

Study YMAB-2019-CR14 radiotoxicity, biodistribution and dosimetry of radiolabeled omburtamab derivatives delivered intrathecally to Sprague Dawley Rats

After delivering a single intrathecal dose of ^{131}I-omburtamab to naïve Sprague Dawley rats (451 ±37.6 µCi; 20 µg mass dose), all animals experienced a transient decrease in white blood cells 1 week after treatment; however, there was no other evidence of treatment-related toxicity in blood count, serum chemistry, or histopathology assessments.

One rat treated with ^{131}I-Omburtamab was found dead one week after treatment and no cause of death was apparent on post-mortem evaluation. A second rat treated with ^{131}I-omburtamab was euthanised prematurely due to lab error associated with an erroneous weight measurement. White blood cell counts transiently decreased from baseline values in all treatment groups at week one treatment.

Table 7. Cause of Death Summary

Group	N per group	Reason for Euthanasia (n)			
		Found dead	Weight loss	Other	End of Study
^{131}I-Omburtamab	6	1*	0	1#	4^

Systemic radiotoxicity, namely myelosuppression in the first few weeks after treatment, was investigated after intravenous or intraperitoneal exposure to ^{131}I-omburtamab in mice.

Study YMAB-2019-CR16 Single-Dose Radiotoxicity Study of Iodine-^{131} Labelled Omburtamab in Athymic Nude Mice

To determine any radiotoxic effects of intravenous (IV) delivered omburtamab derivatives, mice were dosed IV at two dose levels with ^{131}I-Omburtamab (n=8 per group at 103.8 ± 1.9 μCi and 201.2 ± 5.1 μCi, 20 μg). A control cohort (n=8) was also dosed with unmodified omburtamab (20 μg). Following dosing, mice were monitored for 8 weeks with twice-weekly bodyweights and clinical observations, bi-weekly complete blood counts (CBC, one-half of animals per group per week), and serum chemistry at baseline and termination of the study (8 weeks).

There were no unexpected deaths or unscheduled euthanasia of any mice over the 8 weeks of the study. Compared to controls, mice in the ^{131}I-Omburtamab, groups experienced a transient decrease in haematocrit, red blood cell concentration, and white blood cell concentration that rebounded to baseline within 4 weeks post injection.

Study YMAB-2019-CR11 Efficacy of ^{131}I-omburtamab in DAOY Xenograft Athymic Nude Mice

In athymic, subcutaneous DAOY xenograft tumor bearing nude mice there appears to be a reversible effect on haematopoietic cells, particularly red and white blood cells. Specifically, a transient decrease in red blood cells and haematocrit was observed.

Table 8. Red Blood Cell concentration

Group	Baseline (10^6 cells/mm)	Week 2 (10^6 cells/mm)	Week 4 (10^6 cells/mm)
Omburtamab	8.4 ± 0.9	8.6 ± 0.6	8.8 ± 0.1
^{131}I-Omburtamab	9.9 ± 0.7	6.0 ± 1.6	7.4 ± 0.6

Table 9. White Blood Cell Concentration

Group	Baseline (10^3 cells/mm)	Week 2 (10^3 cells/mm)	Week 4 (10^3 cells/mm)
Omburtamab	2.9 ± 0.5	4.3 ± 0.9	5.3 ± 1.3
^{131}I-Omburtamab	3.3 ± 0.3	0.12 ± 0.06	3.8 ± 1.1

Table 10. Haematocrit Values

Group	Baseline (%)	Week 2 (%)	Week 4 (%)
Omburtamab	44.9 ± 2.6	41.9 ± 2.9	42.6 ± 0.4
^{131}I-Omburtamab	47.3 ± 3.7	29.7 ± 8.0	38.5 ± 3.3

Study YMAB-2019-CR07 Assessment of radiotoxicity of omburtamab derivatives delivered intraperitoneally into athymic nude mice.

To determine any radiotoxic effects of intraperitoneally delivered Omburtamab derivatives, groups of mice were dosed IP with ^{131}I-omburtamab. Following dosing, mice were monitored for five weeks with bi-weekly bodyweights and clinical observations, weekly CBC and urinalysis, and serum chemistry every three-weeks. Humane endpoints were defined as follows: greater than 20% decrease in bodyweight from peak weight on-study, greater than 10% weight gain from ascites, any sign of pain or distress. Survival, changes in bodyweight, blood and urine biomarker levels following dosing were compared to baseline measurements for each animal.

Six of the seven animals dosed with ^{131}I-omburtamab did not survive past day 16. Of the 6 mice dosed with ^{131}I-omburtamab, only one animal died due to study-specific endpoints. The majority of deaths on study were due to weight loss. The ^{131}I-omburtamab group had low haematocrit levels (<20%), low red blood cell counts (<5 x10^3/mm^3), and low white blood cell counts (<0.5 x 10^3/mm^3).

2.1.4.2. Repeat dose toxicity

Study YMAB-2019-CR17 Assessment of radiotoxicity of radiolabelled omburtamab following repeat intrathecal dosing to Sprague Dawley rats

To determine any radiotoxic effects of IT delivered omburtamab, groups of rats (n=6 per group) underwent repeat dosing (500 µCi, 20 µg) with ^{131}I-omburtamab for a total of three doses. Doses were separated by 20 days.

Table 11. Summary of Dosing in Study YMAB-2019-CR17

Group	Dose No.	Animal Information		Dosing Information[a]		
		N (M/F)	Weight (g)	Mass (µg)	Radioactivity (µCi)	Volume (µL)
Omburtamab	1	6 (3/3)	295 ±19	20	NA	30
	2	6 (3/3)	354 ±34	20	NA	30
	3	6 (3/3)	382 ±42	20	NA	30
^{131}I-Omburtamab	1	6 (3/3)	275 ±23	20	440.7 ±31.6	30
	2	6 (3/3)	348 ±34	20	460.0 ±13.6	30
	3	6 (3/3)	387 ±40	20	466.5 ±14.2	30

	Main/additional cohort	Dose No. and Inj. Date	Purified radiochemical purity, %	Immunoreactivity, %
Omburtamab	M	1: Oct 11, 2019	N/A	N/A
	M	2: Oct 31, 2019	N/A	N/A
	M	3: Nov 21, 2019	N/A	N/A
^{131}I-Omburtamab	M	1: Oct 11, 2019	>99%	86.4 ± 2.7
	M	2: Oct 31, 2019	98.3%	86.2 ± 1.0
	M	3: Nov 21, 2019	>99%	87.0 ± 2.6

After repeated intrathecal dosing of omburtamab (20-µg mass dose) or ^{131}I-omburtamab (441–467 µCi/dose) in Sprague Dawley rats, three doses given as one treatment every 20 days, deaths were noted in both dosing groups due to paraplegia caused by inflammation from the catheter placement, spontaneous tumor development, or other unknown causes; however, there were no clinically significant

findings in blood counts, serum chemistry, or histopathological evaluations suggestive of systemic radiotoxicity.

Subject ID	Group	Date of death/ Date euthanized	Cause	Notes
326	Omburtamab	Euthanized – Day 57	Paraplegia	Most likely caused by inflammation associated with the catheter
327	Omburtamab	Euthanized – Day 50	Spontaneous tumor	Inguinal mass and abrasions from self-mutilation
347	^{131}I-Omburtamab	Found dead – Day 45	Unknown	No abnormal findings
348	^{131}I-Omburtamab	Found dead – Day 51	Unknown	Bladder distended normal and erythematous / hemorrhagic
330	^{131}I-Omburtamab	Euthanized – Day 53	Paraplegia	Most likely caused by inflammation associated with the catheter

Study 92-01-001 A repeat-dose toxicity study with intrathecal administration of ^{131}I-omburtamab in cynomolgus monkey

Two monkeys were administered intrathecal injections of ^{131}I-omburtamab into the cisternal space at doses ranging from approximately 3.6 to 8.3 mCi on each of Days 1, 3, and 6; NHP2 also received injections on Days 8 and 10. NHP2 was preimmunised with ^{131}I-omburtamab (210 days and 127 days prior to study initiation, using 4.6 and 4.7 mCi, respectively, i.v.). Blood and cerebrospinal fluid (CSF) were obtained throughout the dosing period.

Table 12. Dosing Schedule

Animal	Injection Number	Day	Dose (mCi)	ROA
NHP1	1	1	7.32	i.t.
	2	3	8.34	i.v.
	3	6	3.62	i.t.
	4	8	Failed attempt*	–
	5	10	Failed attempt*	–
NHP2	Pre 1	–210	4.4	i.v.
	Pre 2	–127	4.77	i.v.
	1	1	7.44	i.t.
	2	3	8.04	i.t.
	3	6	7.5†	i.t.
	4	8	Not specified	i.t.
	5	10	Not specified	i.t.

Both animals achieved high levels of ^{131}I-omburtamab radioactivity counts per minute (CPM) in the CSF after intrathecal injections. Lower levels of CPM were detected in the blood after intrathecal injections in both monkeys. In preimmunised NHP2, a monkey anti-mouse antibody response had no effect on CPM measured in the CSF but did result in decreased CPM measured in the serum. On CNS single-photon emission computed tomography (SPECT) scans, there was no focal or ventricular retention at 24 or 72 hours after intrathecal administration.

One monkey died on Day 12 of the study after receiving three of five intended doses. The animal died from surgical complications that arose during the first injection; necropsy findings revealed a brainstem haemorrhage with old and new clots filling the fourth ventricle due to a traumatic cisternal puncture. All other organ systems, including the liver, were grossly normal. Scarring and haemorrhaging at the injection site were observed under histopathological assessment. The second monkey received all five doses and was euthanised on Day 1,301. No significant acute toxicities were observed during the

treatment period and no treatment-related toxicities were observed during the extended follow-up of this animal. At necropsy, all tissues examined appeared grossly normal.

High levels of radioactivity were achieved in the CSF of animals. In general, after i.t. administration, total radioactivity was eliminated from the CNS rapidly and was nearly complete by 48 hours after dosing. Dosing with ^{131}I-omburtamab had no apparent effect on CBC for either monkey. Dosing was associated with slight increases in BUN and serum Cr levels, which may have resulted from a postprocedural reduction in food intake. In the CSF, a rise in total protein and pleocytosis, predominantly eosinophilia, was observed with ^{131}I-omburtamab dosing; these lab values resolved or were recovering by Day 16.

2.1.4.3. Genotoxicity

According to (ICH) S6(R1), genotoxicity studies are generally not necessary to support marketing of biotechnology-derived pharmaceuticals; therefore, Y-mAbs does not consider genotoxicity testing with ^{131}I-omburtamab to be warranted.

2.1.4.4. Carcinogenicity

Y-mAbs has not conducted carcinogenicity studies with ^{131}I-omburtamab. As discussed in ICH S6(R1) and ICH S9, standard carcinogenicity studies are generally not necessary to support marketing of biotechnology products without cause for concern or to support therapeutics intended to treat advanced cancer; therefore, Y-mAbs does not consider carcinogenicity testing with ^{131}I-omburtamab to be warranted.

2.1.4.5. Reproductive and developmental toxicity

According to ICH S9, generally no fertility or pre- and postnatal toxicity studies are warranted to support the treatment of patients with late-stage or advanced cancer. As the age of the target population of ^{131}I-omburtamab is not expected to allow pregnancy to occur during the treatment or the subsequent exposure period, conduct of embryo-fetal development studies are not considered warranted.

2.1.4.6. Local Tolerance

Y-mAbs has not conducted local tolerance studies with ^{131}I-omburtamab. Local effects at injection sites were evaluated in toxicity studies.

2.1.4.7. Other toxicity studies

Not applicable

2.1.5. Ecotoxicity/environmental risk assessment

For (^{131}I-omburtamab) consisting of a protein a radionuclide, ERA is only performed for the radionuclide since the protein part is considered as not posing an environmental risk. The worst-case calculated $PEC_{SURFACEWATER}$ for (^{131}I-omburtamab) was calculated 44.4 Bq/L and compared to the $PEC_{SURFACEWATER}$ calculated for the main source of ^{131}I discharge from patients/hospitals to the environment, which are ^{131}Iodine thyroidal treatment indications. The calculated environmental impact resulting from ^{131}I exposure from thyroidal therapies therefore is about 60-fold higher than the one expected from ^{131}I-omburtamab therapy (2740 Bq/L vs. 44.4 Bq/L) and therefore it is acceptable to apply the same

conclusion that direct hospital discharge after ^{131}iodine therapeutic procedures is safe and exposure to medicinal staff and the public will remain under the threshold of 1 mSv/year.

2.1.6. Discussion on non-clinical aspects

The nonclinical data package supporting the application to market ^{131}I-omburtamab relies on information in the published literature from studies conducted early in its development, as well as more recent studies that have characterised its specificity of binding, biodistribution and dosimetry, and mechanisms of radiation-induced toxicity.

Pharmacodynamic

In pharmacology studies, the binding characteristics of unlabelled omburtamab were evaluated, and the effectiveness of ^{131}I-omburtamab as an antitumor agent was tested in an in vivo mouse xenograft model bearing omburtamab-reactive tumours. Nonclinical studies have shown that omburtamab specifically targets the membrane of cancer cells on B7-H3 (Cluster of Differentiation [CD] 276) which is a member of the B7 (CD28) and that it has preferential affinity for a spectrum of cancerous tissues with marginal binding to normal tissues and that it does not cross-react with normal human brain tissue.

According to the Guideline on the non-clinical requirements for radiopharmaceuticals "the selectivity and specificity of the non-radioactive part as well as secondary pharmacodynamics, defined as effects on other than the desired therapeutic targets, should be critically evaluated and documented". In vitro target/receptor profiling studies with omburtamab performed by the applicant are considered sufficient.

Absence of dedicated secondary safety pharmacodynamic studies is considered acceptable considering that ^{131}I activity is the driving MoA.

Pharmacokinetic

In pharmacokinetic (PK) studies conducted in the same xenograft mouse model, tissue distribution and clearance were evaluated with ^{125}I-omburtamab the difference in radionuclide use is not expected to affect the PK of the radiolabelled antibody, results obtained with ^{125}I-omburtamab are considered relevant to ^{131}I-omburtamab.

No nonclinical analytical methods were available to summarise and refers to the respective reports for descriptions of the methods used in imaging and dosimetry studies. The applicant proposes to conduct a human pharmacokinetics study employing validated analysis methods to assess the pharmacokinetics of ^{131}I-omburtamab. Taking this into account and in line with the 3R policy it is considered acceptable to not performing additional non-clinical work.

Stability of the ^{131}I-omburtamab conjugation is considered of concerns and data on such stability would be important to be collected. Impact of such data may be seen in the context of the benefit-risk of the product and would possibly trigger regulatory action.

Toxicology

In toxicology studies, the safety and feasibility of dosing were evaluated in several species using either unlabelled or radiolabelled omburtamab (including 124I-omburtamab and ^{131}I-omburtamab) delivered by several different routes of administration (including intraperitoneal, intrathecal or intravenous infusion, or by convection-enhanced delivery of the antibody directly into the brain parenchyma or to an implanted tumour).

The nonclinical toxicity programme is considered sparse and is focused on radiation-induced toxicity. The only GLP conform non-clinical study is the tissue cross reactivity study in human tissues. The applicant is asked to justify why toxicity studies were conducted under non-GLP conditions.

All studies but the cross reactivity one described in the Pharmacology part (D84VS) were not conducted in GLP. Although it is recognised that some studies employing specialised test systems which are often needed for biopharmaceuticals, may not be able to comply fully with GLP (as per ICHS6 and guideline on radiopharmaceuticals).

The main animal model selected to test radiotoxicity was the naïve rat. ^{131}I-omburtamab dosimetry estimates after intrathecal dosing in indicated that the dose-limiting organ was the heart wall followed by liver and kidney.

No single-dose general toxicity studies evaluating cold (unlabelled) omburtamab monoclonal antibody have been conducted in a species with a similar cross-reactivity profile as for human tissues.

Systemic radiotoxicity was investigated after intravenous or intraperitoneal administration. In several studies, deaths in animals treated with radiolabelled omburtamab were associated with evidence of non-recoverable myelosuppression such as excessive bodyweight loss with reductions in haematocrit and red and white blood cell counts). Systemic administration of radiolabelled omburtamab causes bone marrow toxicity and non-recovering myelosuppression, which can be expected from radioimmunotherapy.

Absence of clinical or neurotoxicity, as well as absence of histological findings was observed both in rats (after direct infusion into brain parenchyma) and in monkeys (following CED single dose administration of 124I-omburtamab and over a period of 6, 7 and 9 months - Histological analysis - of postoperative examination). Moreover, ^{131}I-omburtamab was considered to be well tolerated in monkeys when administered via a non-traumatic cisternal injection.

Omburtamab demonstrated high affinity for B7-H3 antigen from human or monkey but not from mouse or rat indicating that the cynomolgus monkey is the relevant animal model to investigate potential on-target adverse effects of omburtamab binding. After repeated intrathecal administration in a very limited number of cynomolgus monkeys (2), unfortunately one animal died most probably due to surgical complications. This leaves just the results of one animal for which no significant acute toxicities were observed during the treatment period and no treatment-related toxicities were observed during the extended follow-up.

Taking into account that omburtamab binds with high affinity to B7-H3 of human or monkey origin the cynomolgus monkey is considered the relevant animal model to investigate potential on-target adverse effects of omburtamab binding and a an adequate GLP-conform toxicity study is expected for a MAA. Such a study should include a control group, "cold" omburtamab and ^{131}I-omburtamab. A GLP-conform toxicity study is expected for a MAA. This study should include a control group, "cold" omburtamab and ^{131}I-omburtamab.

In general, it is acceptable that genotoxicity testing was not performed with ^{131}I-omburtamab, but the absence of such studies should be adequately justified. Referring to the (ICH) S6(R1), where it is stated that genotoxicity studies are generally not necessary to support marketing of biotechnology-derived pharmaceuticals is not considered adequate as the MoA is based on the radio nucleotide which is actually genotoxic. ^{131}I-Omburtamab is a radioimmunotherapeutic for relapsed or refractory paediatric metastatic neuroblastoma. Therefore, in accordance with ICH S9 it is acceptable that no standard carcinogenicity studies were performed with ^{131}I-Omburtamab. The absence of dedicated reproductive and developmental toxicity studies is considered acceptable considering the age of the target population.

Local tolerance was assessed in other toxicity studies, in particular in such studies reflection the mode of administration. Omburtamab derivatives were administered by direct interstitial infusion or CED into the brain parenchyma to rats and monkeys. Finding in these studies were related to infusion site histological observations such as haemorrhaging, mild neuronal loss, gliosis.

In a GLP compliant tissue cross-reactivity study using a set of approximately forty specified tissues of human origin specific on-target binding to B7-H3, was seen in the epithelium of the skin, prostate, eye, endometrium, adrenal, fallopian tube, and cervix, as well as in the supporting stroma of most tissues. Potential off-target binding was seen in cytoplasmic staining of the Leydig cells of the testis, in cytoplasmic staining in glial cells of the spinal cord of one donor, and in cytoplasmic staining of alveolar macrophages in the lungs.

2.1.7. Conclusion on the non-clinical aspects

From non-clinical point of view, the MAA for ^{131}I-omburtamab is in general insufficiently characterised. Clinical data may be more informative and complement such deficiency, provided that the stability of the coupled antibody can be demonstrated. Indeed, concerns on non-targeted delivery of [^{131}I]Iodine, which could pose a risk to patient safety, are raised in regard to stability of the ^{131}I-omburtamanb conjugation for which data would be expected to be collected. Upon analysis of such data impact of it should be considered on the benefit risk of the product.

2.2. Clinical aspects

2.2.1. Introduction

GCP aspects

The cClinical 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**

Study ID	No. of study centres ~~/ locations~~	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
03-133	1	Phase 1 trial is a two-part, single-arm, open-label, non-randomized, single-centre efficacy, safety, and dosimetry trial of intracerebro-ventricular (ICV) administration of ^{131}I-omburtamab	Part 1 investigated escalating radioactivity of ^{131}I-omburtamab with the goal of identifying the maximum tolerated dose. Part 2 investigated dosing at the selected dose of 50 mCi (1850 MBq) determined in Part 1. Subjects without objective disease progression (as determined by neurologic or radiographic examination) four weeks after the last intracerebroventricular infusion and	Definition of clinical toxicities of intra-thecal ^{131}I-ombur-tamab	109 subjects with NB; 37 paediatric subjects with malignancies other than NB (included in SAE analysis only)	Cycle of 5 weeks included pre-medi-cation, ^{131}I-omburta-mab admini-stration (one dosimetry dose administered during Week 1 and one treatment dose administered during Week 2). If a subject received an additional	Male 72 67,3% Female 35 32,7% Age Mean – 5,149 SD 2,645 Median 4,709 Min max	Subjects with a histologically confirmed diagnosis of a NB with CNS/LM disease	Interim analysis OS at 3 years PFS (CNS/LM) at 12 months Follow – up duration Dosi-metry, blood, brain, and CSF dosi-metry radiation PK activity in blood and CSF

			without unexpected Grade 3 or 4 toxicity were eligible for a repeat dosing cycle.			cycle of treatment, the subsequent cycle started with a dosimetry dose >4 weeks after the treatment dose of the previous cycle.	0,85 13,03		Freuence and type of severe AE and SAE
101	4	Single-arm, open-label, nonrandomized trial included a screening period followed by treatment and observation periods. 4 periods spanning 3 years	FIRST DOSE ^{131}I-omburtamab was administered via an indwelling intracerebroventricular access device (e.g., Ommaya reservoir) with adequate CSF flow SECOND DOSE 5 weeks after first	Overall survival at 3 years	50	Screening – 4 weeks Followed by first dose, Second dose 5 weeks after first dose Follow up at 26th week Long term follow-up at 6 months for 3 years	Male 29 58% Female 21 42% Mean age 4,7 yrs Median 4 yrs Range 0 – 11 years	confirmed diagnosis of NB with relapse in the CNS or LM	CNS/LM PFS (primary interim endpoint) will be estimated at 6 months based on the time from first dose of ^{131}I-omburtamab to CNS/LM progression or death from any cause.

2.2.2. Clinical pharmacology

2.2.2.1. Pharmacokinetics

The clinical pharmacology programme for ^{131}I-omburtamab comprised two clinical studies (trial 03-133 and trial 101) enrolling paediatric subjects with neuroblastoma and CNS/LM metastasis. Clinical pharmacology investigations included radiation dosimetry, based on imaging and samples (CSF and blood), and PK based on radioactivity counts data from CSF and blood samples instead of protein-quantification-based PK analysis.

The intended posology is two intracerebroventricular doses of 1850 MBq (50 mCi; or the equivalent based on a dose reduction of 33% and 50% for children less than 3 years and 1 year of age, respectively) with a minimum of 4 weeks in between.

It should be noted that the proposed indication is not limited by age group, while in both presented trials the target population were children, please see clinical efficacy discussion.

Analytical Methods

Radioactivity measurements were conducted using a gamma or well counter according to Kramer et al., Journal of Clinical Oncology, 2007. Biodistribution was assessed by dosimetry using the same methods as for PK, while imaging-based dosimetry was based on whole-body gamma scans. Analytical methods used for quantification of pharmaceuticals must be validated to ensure that the methods are suitable for

their intended purpose. For ^{131}I-omburtamab, no data on method validation have been found for the radioactivity measurements performed for dosimetry and analysis of PK of ^{131}I-omburtamab.

The following PK parameters were tabulated for subjects in trial 03-133 (n=27 in PK population) and trial 101 (n=23 in PK population): CSF volume of distribution (mL), CSF clearance half-life (minutes), CSF maximum (peak) drug concentration (activity) (C_{max}) (Bq/mL), CSF time to maximum concentration (activity) (T_{max}) (hr), blood Cmax (Bq/mL), blood T_{max} (hr), whole body clearance half-life (hr) (Trial 101 only), brain clearance half-life (hr) (Trial 101 only). The following dosimetry endpoints were calculated: CSF absorbed dose (Gy), CSF absorbed dose per mCi (Gy/mCi), blood absorbed dose (Gy), blood absorbed dose per mCi (Gy/mCi), brain surface absorbed dose (Gy), brain surface absorbed dose per mCi (Gy/mCi), absorbed doses by ROI (mGy/MBq). Dosimetry data and PK parameters were summarised with descriptive statistics. Absorbed doses by ROI were listed and presented as bar graphs.

Adsorption, Distribution, Metabolism and Elimination.

Locally administered omburtamab was demonstrated to be primarily absorbed through the arachnoid granulations, where CSF is reabsorbed into the blood.

Biodistribution

In study 03-133, after a dosimetry dose of 2 mCi, mean absorbed radiation dose measured at brain surface was 0.394 Gy. Mean absorbed radiation doses in the CSF and blood were 0.787 Gy and 0.0469 Gy, respectively. No data are available on absorbed radiation doses after treatment doses.

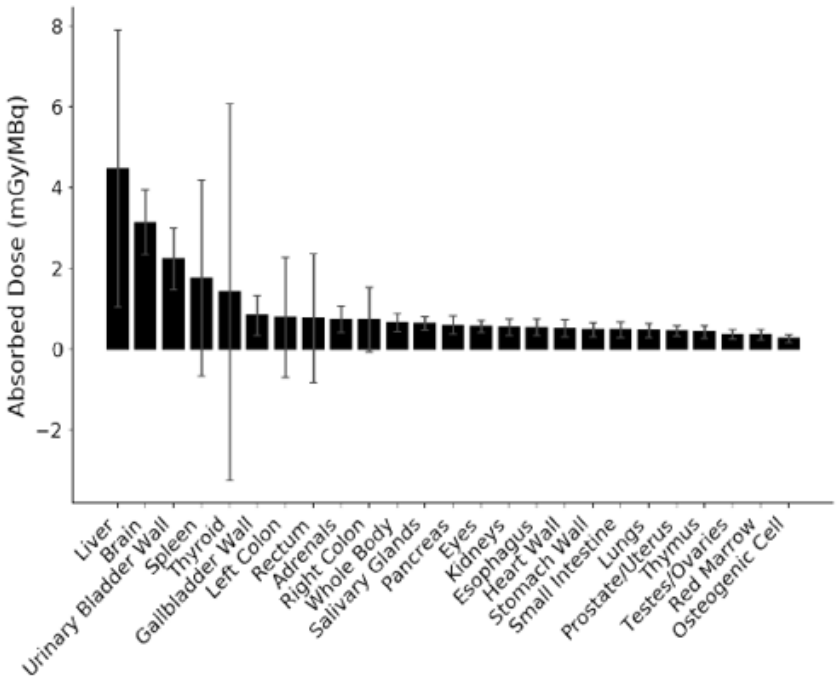
In study 101, mean absorbed radiation doses measured at brain surface, in CSF and in blood after the dosimetry dose (2mCi) were 0.61 Gy, 1.219 Gy and 0.016 Gy, respectively. After the treatment dose, mean absorbed radiation doses measured at brain surface, in CSF and in blood were 12.77 Gy, 25.54 Gy and 0.360 Gy, respectively. Absorbed doses were higher for the 50 mCi treatment dose than for the 2 mCi dosimetry dose, but similar mean values of absorbed doses were obtained in brain, blood, and CSF if corrected for mCi dose. As anticipated due to the intracerebroventricular route of administration, CSF absorbed a much higher (76-fold) radiation dose than the blood.

Table 13. Dosimetry and Pharmacokinetic Results from Clinical Trials

Trial ID	Primary Objective	Trial Design	No. of NB Subjects	Dose	Dosimetry and Source	Absorbed dose per mCi *(Gy/mCi)*	Absorbed dose *(Gy)*
Pediatric Neuroblastoma Subjects with CNS/LM Metastases							
03-133[c]	Define clinical toxicities of intrathecal ^{131}I-omburtamab	Single-center, single-arm, non-randomized, open-label trial Part 1: dose-escalation Part 2: cohort expansion	Safety: 109 Efficacy: 107 PK/dosimetry: 27	Dose escalation: 10-70 mCi/ treatment dose Dosimetry: 2 mCi Expansion phase: 50 mCi/treatment dose [d, e]	CSF	NC	0.787 (0.3664)
					Blood	NC	0.047 (0.0303)
					Brain surface	NC	0.394 (0.1832)
101[f]	Overall survival at 3 years	Multi-center, single-arm, non-randomized, open-label trial	Safety: 24 Efficacy: 24 PK/dosimetry: 23	Dosimetry: 2 mCi 50 mCi/treatment dose [d]	CSF	0.580 (0.3322)	1.219 (0.7248)
					Blood	0.009 (0.0034)	0.016 (0.0050)
					Brain surface	0.290 (0.1670)	0.610 (0.3632)
					Whole body	NC	NC

Imaging-based dosimetry revealed brain and liver as primary target organs with highest absorbed radiation doses, followed by urinary bladder wall and spleen.

Figure 3. Total Absorbed Treatment Dose by Organ



Organ dosimetry was analysed for whole body and regions-of-interest during Cycle 1 only.

Volume of distribution

In study 03-133, CSF volume of distribution was 63.2 mL and in study 101, CSF volume of distribution was 28.9 mL, with a relatively high degree of variability (range: 0.6–234 mL).

Elimination

Referring to radioactivity measurements in CSF, radioactivity left the CSF space with a geometric mean clearance half-life of 237.1 minutes and 127.74 minutes in study 03-133 and study 101, respectively.

The geometric mean whole-body clearance half-lives determined in study 101 were similar for the dosimetry dose (47 hours) and treatment dose (41 hours).

PK of ^{131}-iodine

The PK properties of free iodine-^{131} have been summarised in the EMA Guideline on core SmPC and Package Leaflet for sodium iodide (^{131}I) for therapeutic use. In brief, iodine-^{131} is absorbed rapidly from the upper GI tract (90% in 60 minutes). In case the thyroid is not protected, iodine-^{131} is predominantly taken up by the thyroid or excreted renally. Urinary excretion is 37-75%, faecal excretion is about 10%, with almost negligible excretion in sweat. The effective half-life of radioiodine is about 12 hours in blood plasma.

Dose proportionality and time dependency

Sample-based and imaging-based dosimetry revealed similar absorbed radioactive doses in CSF and blood if corrected for mCi/MBq administered to patients. Relationship appears to be dose-proportional (see Table 14).

Table 14. Dosimetry Absorbed Dose Parameters

Parameter	Dosimetry	Treatment
Full Analysis Set (N)	24	
CSF Absorbed Dose (Gy)		
N	23	22
Mean (SD)	1.219 (0.7248)	25.541 (16.1072)
Median	1.070	18.665
Min - Max	0.29 - 2.67	6.70 - 60.31
CSF Absorbed Dose per mCi (Gy/mCi)		
N	23	22
Mean (SD)	0.580 (0.3322)	0.563 (0.3309)
Median	0.500	0.495
Min - Max	0.15 - 1.25	0.15 - 1.25
Blood Absorbed Dose (Gy)		
N	23	22
Mean (SD)	0.016 (0.0050)	0.360 (0.1232)
Median	0.020	0.320
Min - Max	0.01 - 0.02	0.16 - 0.57
Blood Absorbed Dose per mCi (Gy/mCi)		
N	23	22
Mean (SD)	0.009 (0.0034)	0.009 (0.0035)
Median	0.010	0.010
Min - Max	0.00 - 0.01	0.00 - 0.01
Brain Surface Absorbed Dose (Gy)		
N	23	22
Mean (SD)	0.610 (0.3632)	12.770 (8.0541)
Median	0.540	9.330
Min - Max	0.14 - 1.34	3.35 - 30.15
Brain Surface Absorbed Dose per mCi (Gy/mCi)		
N	23	22
Mean (SD)	0.290 (0.1670)	0.282 (0.1650)
Median	0.250	0.250
Min - Max	0.07 - 0.63	0.07 - 0.62

Source: Table 14.2.4.1.
CSF = cerebrospinal fluid; Max = maximum; Min = minimum; N = Number of subjects; SD = standard deviation.

In both study 03-133 and study 101, sampling and imaging for PK and dosimetry were done during the first cycle only. PK data are only available for the dosimetry dose (2 mCi/74 MBq), PK characteristics after the first and second treatment dose have not been investigated.

Pharmacokinetics in the target population

Trial 03-133

Trial 03-133 was an open-label, single-arm, single-site Phase 1 clinical trial in paediatric patients with CNS/LM relapse from a known or confirmed omburtamab-reactive malignancy (i.e., expressing B7-H3 (CD276)). Trial 03-133 included two parts: a Part 1 (dose escalation phase) to evaluate the maximally tolerated dose (MTD) of intracerebroventricular ^{131}I-omburtamab (dose range 10 – 70 mCi) and a Part 2 (expansion phase) with 50 mCi as treatment dose established during the dose escalation phase. In both parts, subjects entered at Week 1 for the ^{131}I-omburtamab dosimetry dose (2 mCi/74 MBq) followed by Week 2 for the ^{131}I-omburtamab treatment dose at the dose levels specified.

Dose reduction was foreseen in patients aged between 1 – 3 years and patients younger than 1 year based on a publication by Bleyer, Cancer Treat Rep 1977 (see Table 15).

Table 15. Treatment Dose Directed by Age

Age (years)	Dosimetry Dose (mCi)[a]	Therapeutic Dose Reduction	Therapeutic Dose (mCi)[a]
<1	2.0	50% reduction	25.0
1 to <3	2.0	33% reduction	33.5
≥3	2.0	No reduction	50.0

[a] 2.0 mCi=74 MBq; 25.0 mCi=925 MBq; 33.5 mCi=1,239 MBq and 50.0 mCi=1,850 MBq.

Thyroid protection was ensured by adequate stable iodide saturation (by use of oral potassium iodide and Cytomel).

Sampling schedule for dosimetry and PK is presented in Table 16.

Table 16. CSF and Blood Sampling and Imaging Scans in Cycle 1 of Trial 03-133

Timing of Sampling	Dosimetry Dose	
	Blood and CSF[a]	Whole-Body Gamma Scan[b]
Baseline	X	
1 hr	X	
2-4 hr	X	
3-6 hr		X
18-24 hr	X	X
36-48 hr	X	
44-49 hr		X

CSF = cerebrospinal fluid

a: Blood and CSF samples: used both for PK and dosimetry (sample-based) investigations.

b: Whole-Body Gamma Scan: data are not available from MSK and imaging-based dosimetry results from Trial 03-133 are therefore not included in this application.

^{131}I-omburtamab PK CSF and blood parameters are presented in Table 17and Table 18, respectively.

Table 17. Summary of ^{131}I-omburtamab Pharmacokinetic CSF Parameters

Summary Statistic	T_{max} (h)	C_{max} (Bq/mL)	CL $t_{1/2}$ (min)	V_d (mL)
n	27	27	23	23
Mean	1.93	788497.4	237.0623	63.23213
SD	0.718	372400.81	162.85092	36.607077
Median	2.00	696340	198.7200	61.51520
Min, Max	1.0, 3.3	418840, 2090500	67.872,744.978	9.5238,146.4286

Source: Table 14.2.7.1

CL $t_{1/2}$ = clearance half-life; C_{max} = maximum concentration; CSF = cerebrospinal fluid; max = maximum; min = minimum; T_{max} = time to maximum concentration; V_d = volume of distribution.

Table 18. Summary of ^{131}I-omburtamab Pharmacokinetic Blood Parameters

Summary Statistic	T_{max} (h)	C_{max} (Bq/mL)
n	27	27
Mean	24.39	7152.662
SD	9.081	4383.9355
Median	22.00	6555.660
Min,Max	2.2, 46.5	307.47, 20553.5

Source: Table 14.2.7.1

C_{max} = maximum concentration; max = maximum; min = minimum; T_{max} = time to maximum concentration.

The median T_{max} in the CSF was 2.0 h with a range of 1.0 to 3.3 h. CSF exposure to ^{131}I-omburtamab (mean Cmax) was 788497.4 Bq/mL (corresponding to 0.0213 mCi/mL). Mean CL $t_{1/2}$ and V_d were 237 min and 63 mL, respectively.

Compared to ^{131}I-omburtamab in the CSF, ^{131}I-omburtamab was absorbed slowly in the blood, with a median T_{max} of 22.0 h (ranging from 2.2 to 46.5 h). This was expected due to the intracerebroventricular administration of ^{131}I-omburtamab. Systemic exposure to ^{131}I-omburtamab (mean Cmax of 7152.662 Bq/mL, corresponding to 0.193 µCi/mL) was approximately 110-fold lower than CSF exposure.

Trial 101

Trial 101 is an ongoing, single-arm, open-label, non-randomised, multisite Phase 2/3 clinical trial in paediatric patients who have a histologically confirmed diagnosis of neuroblastoma with relapse in the CNS/LM and who have progression or relapse in the CNS/LM after induction therapy.

Treatment with ^{131}I-omburtamab in Trial 101 followed a regimen similar to that described for Part 2 of Trial 03-133. The dosimetry and treatment dose levels (2 mCi and 50 mCi, respectively) and reductions based on age, the treatment cycles, the method of administration and thyroid protection treatment are consistent.

It should be noted that the dosimetry dose was used only to assess dosimetry and PK, not to individualise treatment doses, and dosimetry was discontinued as of 01 January 2020. All PK results included in this summary are from subjects enrolled prior to 01 January 2020 and who received both a dosimetry and treatment dose (one treatment cycle).

There was a more frequent sampling schedule in Trial 101 compared to Trial 03-133 and an additional sampling was conducted after the treatment dose (50 mCi) in Trial 101 only. Sampling schedule for dosimetry and PK is presented in Table 19.

Table 19. CSF and Blood Sampling and Imaging Scans in Cycle 1 of Trial 101

Timing of Sampling	Dosimetry Dose		Treatment Dose	
	Blood and CSF[a]	Whole-Body Gamma Scan[b]	Blood and CSF[a]	Whole-Body Gamma Scan[b]
Baseline	X			
30 minutes (± 5 min)	X			
1 hr (± 10 min)	X			
4 hr (± 10 min)	X			
4-5 hr (4 hr + 1 hr)		X		
24 hr (± 30 min)	X			
24 hr (± 2 hr)		X		
48 hr (± 1 hr)	X			
48 hr (± 2 hr)		X		X
72 hr (± 4 hr)	X			
7 days (± 1 day) post-infusion only			X	

CSF = cerebrospinal fluid.
a: Blood and CSF samples: used both for PK and dosimetry (sample-based) investigations.
b: Whole-Body Gamma Scan: used for dosimetry (imaging-based) investigations.

^{131}I-omburtamab infused directly into the CSF compartment and measured as radioactive counts is distributed relatively quickly in the CSF with a mean T_{max} of 0.642 hours. The median volume of distribution in the CSF compartment was 40.65 mL, exhibiting a relatively high degree of variability. This variability may be the result of sampling issues, or it may reflect variations in the degree of tumour target binding sites. The radioactivity left the CSF space with a geometric mean clearance half-life of 127.74 min. Upon entering the blood, the maximum radioactivity count was orders of magnitude lower than in CSF and occurred later with a mean T_{max} in blood of 24.88 hours.

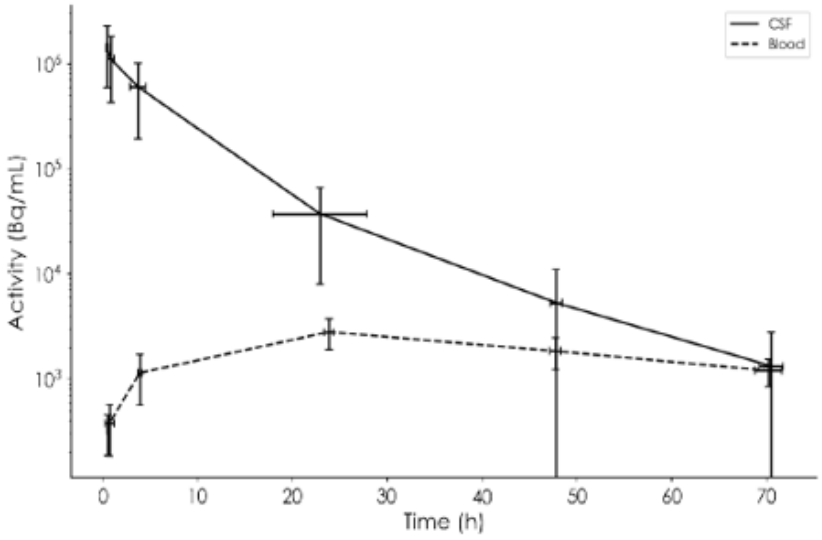
The geometric mean whole-body clearance half-lives were similar for the dosimetry dose (47 hours) and treatment dose (41 hours). The geometric mean brain clearance half-life was 24 hours.

Table 20. Pharmacokinetic Parameters

Parameter	Dosimetry	Treatment
Full Analysis Set (N)	24	
CSF C_{max} (Bq/mL)		
N	23	–
Geometric Mean (%CV)	1292386.8 (89.03)	–
Median	1413002.1	–
Min - Max	249643 - 7089229	–
CSF T_{max} (h)		
N	23	–
Mean (SD)	0.642 (0.2441)	–
Median	0.500	–
Min - Max	0.43 - 1.12	–
Blood C_{max} (Bq/mL)		
N	23	–
Geometric Mean (%CV)	2755.2 (38.48)	–
Median	3162.7	–
Min - Max	1315.8 - 4639.3	–
Blood T_{max} (h)		
N	23	–
Mean (SD)	24.88 (4.922)	–
Median	23.97	–
Min - Max	22.7 - 47.4	
CSF Volume of Distribution (mL)		
N	23	–
Geometric Mean (%CV)	28.90 (253.843)	–
Median	40.65	–
Min - Max	0.6 - 234.0	–
CSF Clearance Half-life (m)		
N	23	–
Geometric Mean (%CV)	127.74 (172.618)	–
Median	163.64	–
Min - Max	6.9 - 766.0	–
Whole Body Half-life (h)		
N	23	22
Geometric Mean (%CV)	47.26 (41.219)	41.07 (40.422)
Median	46.51	38.92
Min - Max	21.4 - 94.9	20.9 - 138.8
Brain Clearance Half-life (h)		
N	23	
Geometric Mean (%CV)	23.72 (40.251)	–
Median	22.01	–
Min - Max	11.8 - 50.6	–

Source: Table 14.2.4.1.
CSF = cerebrospinal fluid; CV = geometric coefficient of variation; h = hour; m = minutes; Max = maximum; Min = minimum; N = number of subjects; SD = standard deviation.

Figure 4. Mean Time-Activity Profiles in CSF and Blood – Trial 101



Activity and timepoint means with SD error bars.

PK in special populations

No PK studies of ^{131}I-omburtamab have been performed to assess differences among populations varying in renal or hepatic function, or across populations varying in sex, ethnicity, or age (other than children less than 3 years and 1 year of age).

As ^{131}I-omburtamab is primarily cleared via the kidneys, an increased radiation exposure is possible in patients with impaired renal function. However, due to exclusion of subjects with severe major organ toxicity (including renal and hepatic systems) greater than Grade 2 (Trial 03-133) or greater than Grade 3 (Trial 101), safety and efficacy in subjects with renal or hepatic impairment have not been established.

For study 03-133, ^{131}I-omburtamab PK CSF and blood parameters are presented by weight in Table 29. Most subjects belonged to the 0 to <15 kg or 15 to <30 kg groups. Only three subjects were ≥30 kg.

Table 21. Pharmacokinetic Parameters of Dosimetry Dose by Weight Group in Trial 03-133

PK Parameter	Statistic/Category	Weight (kg)			All Subjects (N=27)
		0 to <15 (N=11)	15 to <30 (N=13)	≥ 30 (N=3)	
CSF T_{max} (hr)	N	11	13	3	27
	Mean	1.80	2.16	1.43	1.93
	SD	0.527	0.822	0.666	0.718
	Median	1.70	2.10	1.10	2.00
	Min, Max	1.1, 2.9	1.2, 3.3	1.0, 2.2	1.0, 3.3
CSF C_{max} (Bq/mL)	N	11	13	3	27
	Mean	856381.8	758756.2	668466.7	788497.4
	SD	483420.69	291376.99	268855.69	372400.81
	Median	744070	669700	560180	696340
	Min, Max	418840, 2090500	432900, 1435230	470640, 974580	418840, 2090500
CSF CL $t_{1/2}$ (minutes)[a]	N	10	10	3	23
	Mean	182.6040	284.0646	261.9160	237.0623
	SD	108.66104	212.99995	87.35317	162.85092
	Median	129.8460	239.1480	307.0920	198.7200
	Min, Max	88.476, 415.800	67.872, 744.978	161.23, 317.430	67.872, 744.978
CSF V_d (mL)	N	10	10	3	23
	Mean	58.23767	61.65916	85.12357	63.23213
	SD	44.555616	29.941069	30.288524	36.607077
	Median	46.13075	60.75240	80.00000	61.51520
	Min, Max	9.5238, 146.4286	15.8692, 104.5000	57.7236, 117.6471	9.5238, 146.4286
Blood T_{max} (hr)	N	11	13	3	27
	Mean	26.25	21.79	28.87	24.39
	SD	9.260	8.314	11.645	9.081
	Median	22.80	21.00	24.80	22.00
	Min, Max	19.5, 46.5	2.2, 42.0	19.8, 42.0	2.2, 46.5
Blood C_{max} (Bq/mL)	N	11	13	3	27
	Mean	8140.774	6888.062	4676.183	7152.662
	SD	3868.3510	5121.0513	1627.6874	4383.9355
	Median	7773.700	5535.200	3742.920	6555.660
	Min, Max	2349.5, 17293.8	307.47, 20553.5	3730.0, 6555.66	307.47, 20553.5

Source: Trial 03-133 Table 14.2.7.2
CL = clearance; C_{max} = maximum concentration; CSF = cerebrospinal fluid; hr = hour; Max = maximum; Min = minimum; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = half-life; T_{max} = time of maximum concentration; V_d = volume of distribution.
a The unit in the source table was incorrectly stated as L/hr.

Summaries of absorbed doses to the CSF, blood, and brain by weight are provided in Table 22.

Table 22. Summary of Radioactive Absorbed Dosimetry Dose in Regions of Interest by Weight Group in Trial 03-133

Dosimetry Parameter	Statistic/Category	Weight (kg)			All Subjects (N=27)
		0 to <15 (N=11)	15 to <30 (N=13)	≥30 (N=3)	
CSF Radioactive Absorbed Dose (Gy)	N	11	13	3	27
	Mean	0.7980	0.8246	0.5870	0.7874
	SD	0.45756	0.31962	0.12379	0.36637
	Median	0.6970	0.8070	0.5420	0.7070
	Min, Max	0.380, 2.040	0.403, 1.394	0.492, 0.727	0.380, 2.040
Blood Radioactive Absorbed Dose (Gy)	N	10	13	3	26
	Mean	0.04555	0.05209	0.02860	0.04686
	SD	0.018230	0.039241	0.004927	0.030259
	Median	0.04500	0.04130	0.02920	0.04130
	Min, Max	0.0128, 0.0699	0.0099, 0.1535	0.0234, 0.0332	0.0099, 0.1535
Brain Surface Radioactive Absorbed Dose (Gy)	N	11	13	3	27
	Mean	0.39900	0.41231	0.29350	0.39369
	SD	0.228779	0.159809	0.061897	0.183183
	Median	0.34850	0.40350	0.27100	0.35350
	Min, Max	0.1900, 1.0200	0.2015, 0.6970	0.2460, 0.3635	0.1900, 1.0200

Source: Trial 03-133 Table 14.2.7.2
CSF = cerebrospinal fluid; Max = maximum; Min = minimum; SD = standard deviation.

For study 03-133, ^{131}I-omburtamab PK CSF and blood parameters are presented by age in Table 23.

Table 23. Pharmacokinetic Parameters of Dosimetry Dose by Age Group in Trial 03-133

PK Parameter	Statistic/Category	Age (years) 0 to <1 (N=2)	1 to <3 (N=6)	≥ 3 (N=19)	All Subjects (N=27)
CSF T_{max} (hr)	n	2	6	19	27
	Mean	1.75	2.22	1.86	1.93
	SD	0.354	0.655	0.763	0.718
	Median	1.75	2.20	1.70	2.00
	Min, Max	1.5, 2.0	1.4, 3.0	1.0, 3.3	1.0, 3.3
CSF C_{max} (Bq/mL)	n	2	6	19	27
	Mean	581455.0	1065662	722765.8	788497.4
	SD	229972.34	583676.12	260418.42	372400.81
	Median	581455	925925	606430	696340
	Min, Max	418840, 744070	426610, 2090500	432900, 1435230	418840, 2090500
CSF CL $t_{1/2}$ (minutes)[a]	N	2	6	15	23
	Mean	188.7030	168.8680	270.7880	237.0623
	SD	126.96951	110.37206	180.62920	162.85092
	Median	188.7030	105.2670	220.3440	198.7200
	Min, Max	98.922, 278.484	88.476, 352.158	67.872, 744.978	67.872, 744.978
CSF V_d (mL)	N	2	6	15	23
	Mean	88.58745	44.13272	67.49119	63.23213
	SD	81.799739	39.022187	28.573541	36.607077
	Median	88.58745	26.44875	71.09270	61.51520
	Min, Max	30.7463, 146.4286	9.5238, 107.5676	15.8692, 117.6471	9.5238, 146.4286
Blood T_{max} (hr)	N	2	6	19	27
	Mean	21.50	26.40	24.06	24.39
	SD	2.828	9.901	9.436	9.081
	Median	21.50	22.40	21.00	22.00
	Min, Max	19.5, 23.5	21.0, 46.5	2.2, 42.8	2.2, 46.5
Blood C_{max} (Bq/mL)	N	2	6	19	27
	Mean	8769.000	6925.968	7054.108	7152.662
	SD	1407.5668	2380.3973	5075.3241	4383.9355
	Median	8769.000	6997.810	5928.510	6555.660
	Min, Max	7773.7, 9764.30	3863.2, 10610.9	307.47, 20553.5	307.47, 20553.5

Source: Trial 03-133 Table 14.2.7.1
CL = clearance; C_{max} = maximum concentration; CSF = cerebrospinal fluid; hr = hour; Max = maximum; Min = minimum; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = half-life; T_{max} = time of maximum concentration; V_d = volume of distribution.
a The unit in the source table was incorrectly stated as L/hr.

Summaries of absorbed doses to the CSF, blood, and brain by age are provided in Table 24.

Table 24. Summary of Radioactive Adsorbed Dosimetry Dose in Regions of Interest by Age Group in Trial 03-133.

Dosimetry Parameter	Statistic/Category	Age (years) 0 to <1 (N=2)	1 to <3 (N=6)	≥3 (N=19)	All Subjects (N=27)
CSF Radioactive Absorbed Dose (Gy)	N	2	6	19	27
	Mean	0.5130	0.9960	0.7504	0.7874
	SD	0.18809	0.54577	0.29130	0.36637
	Median	0.5130	0.9120	0.7070	0.7070
	Min, Max	0.380, 0.646	0.455, 2.040	0.403, 1.394	0.380, 2.040
Blood Radioactive Absorbed Dose (Gy)	N	2	5	19	26
	Mean	0.04930	0.04366	0.04745	0.04686
	SD	0.011172	0.019072	0.034352	0.030259
	Median	0.04930	0.03500	0.04130	0.04130
	Min, Max	0.0414, 0.0572	0.0243, 0.0699	0.0099, 0.1535	0.0099, 0.1535
Brain Surface Radioactive Absorbed Dose (Gy)	N	2	6	19	27
	Mean	0.25650	0.49800	0.37518	0.39369
	SD	0.094045	0.272887	0.145649	0.183183
	Median	0.25650	0.45600	0.35350	0.35350
	Min, Max	0.1900, 0.3230	0.2275, 1.0200	0.2015, 0.6970	0.1900, 1.0200

Source: Trial 03-133 Table 14.2.7.1
CSF = cerebrospinal fluid; Max = maximum; Min = minimum; SD = standard deviation.

The studies contributing to the clinical pharmacology package of ^{131}I-omburtamab have solely been conducted in children. Thus, PK data provided fully refer to the paediatric population.

Exposure relevant for safety evaluation

No information available, as PK data for the intended treatment dose are lacking and the therapeutic dose range has not been adequately assessed.

2.2.2.2. Pharmacodynamics

No clinical data on PD are available.

Mechanism of action

^{131}I-omburtamab is an iodine-^{131} radiolabelled murine monoclonal antibody that recognises and binds selectively to the B7-H3 (CD276) antigen. B7-H3 is a member of the B7 (CD28) immunoglobulin superfamily, which regulates T-cell function, and is a tumour-associated antigen that is overexpressed on the cell membrane of a range of solid tumours, including CNS/LM neuroblastoma tumour cells. The iodine-131 emits ionizing radiation, resulting in DNA damage and tumour cell death.

Immunogenicity

As of the cut-off date for this MAA, no immunogenicity assessments have been conducted during the clinical programme. However, Trial 101 was amended to collect samples for immunogenicity detection from three to six subjects who received two treatment doses. This will necessitate the enrolment of up to 12 subjects to obtain the required samples. Results from a to be developed assay will investigate if there is any effect of ^{131}I-omburtamab antidrug antibodies on PK and safety and these analyses will be provided in the final CSR for Trial 101 (captured as REC).

Primary and Secondary pharmacology

N/A

2.2.3. Discussion on clinical pharmacology

Pharmacokinetics

In both studies contributing to the clinical pharmacology package for this submission (trial 03-133 and trial 101), clinical pharmacology investigations included radiation dosimetry, based on imaging and samples (CSF and blood), and PK based on radioactivity counts data from CSF and blood samples instead of protein-quantification-based PK analysis.

Radioactivity measurements were conducted using a gamma counter or well counter according to Kramer et al., Journal of Clinical Oncology, 2007. Biodistribution was assessed by dosimetry using the same methods as for PK, while imaging-based dosimetry was based on whole-body gamma scans. Method validation for the radioactivity measurements is considered acceptable. While the development and validation of assays to measure the PK of omburtamab monoclonal antibody are not acceptable this issue is not further pursued. In clinical trials (Trials 101 and 03-133), PK and dosimetry were only investigated in the first dosing cycle. The applicant refers to patient derived data, demonstrating that 20 patients from Trial 03-133 had CSF and blood samples collected, following both the dosimetry dose and the treatment dose. The data did not indicate any difference in absorbed dose per unit administered radioactivity across administered doses in the CSF, with a treatment CSF absorbed dose of 52.5 ±31.6 cGy/mCi vs. a dosimetry CSF absorbed dose of 55.5 ±75.8 cGy/mCi (data provided as median ±SD). Currently the data are accepted, and an additional PK study is not requested.

The applicant had been asked to provide more detailed information on the stability of ^{131}I-iodine binding to the antibody as well as on kinetics of the antibody. This issue is also considered unresolved as no stability testing of ^{131}I-omburtamab has been performed and thus, no sufficient information on the systemic stability of iodine-131 binding to the antibody in patients with malfunctioning blood-brain-barrier can be provided. The applicant proposes studies to investigate the in vitro stability of ^{131}I-omburtamab in CSF and human plasma performed as a commitment by Y-mAbs, with an estimated timeframe for reporting the data by end of Q4 2022. This proposal is acceptable for the time being, however, if stability is not demonstrated serious concerns regarding efficacy will be raised that may lead to a reconsideration of the benefit risk of the product.

Route of administration

The route of administration of ^{131}I-omburtamab is intracerebroventricular infusion via an intracerebroventricular access device (e.g., Ommaya catheter/reservoir). Intracerebroventricular administration has been used for decades in the clinic to provide treatment for adult and paediatric populations suffering from a variety of conditions, including varying cancer types.

The brain is a highly sensitive and fragile neuronal organ system that needs a regular supply of fuels, gases, and nutrients to maintain homeostasis and other vital functions. The blood brain barrier (BBB) acts as a physical barrier and imposes various obstacles. It inhibits delivery of therapeutic agents to the CNS and imposes obstruction for delivery of a large number of drugs, including antibiotics, antineoplastic agents, and neuropeptides, to pass through the endothelial capillaries to brain. Many different drug delivery methods have been developed for targeted brain delivery. Some of them are neurologically invasive and found unsafe for drug delivery.

Ommaya reservoir is a highly effective implant that provides long term access to the cerebrospinal fluid and has simplified administration of antimicrobials, antifungals, antineoplastic, and analgesic medications directly into the brain. Though initially conceived for delivery of antifungal medications into the cerebrospinal fluid (CSF), this device is commonly used today for chemotherapeutic central nervous system (CNS) delivery and CSF sampling. For the placement of the Ommaya catheter, the arachnoid epithelium is pierced resulting in a lowering of the integrity of one of the normal biological barriers. The contribution of this to the overall potential for physiological abnormal exchange between blood and brain is however considered insignificant. Contraindications for the use of this device are usually – scalp infection, brain abscess, known allergy to silicone. These specific contraindications are not proposed by the applicant.

Dosimetry/Biodistribution

Preclinical studies have demonstrated that omburtamab has marginal reactivity in most normal tissues. The ^{131}I-omurtamab is administered locally via an intraventricular catheter placed into the ventricular system of the brain. No specific omburtamab binding was detected in cerebral cortex or in cerebellum, or in endothelial cells in a Y-mAbs conducted GLP-compliant human tissue cross-reactivity immunohistochemistry study testing approximately 40 specified human tissues from 3 different human donors.

Absorbed doses, as reported above, were higher for the 50 mCi treatment dose than for the 2 mCi dosimetry dose, but similar mean values of absorbed doses were obtained in CSF and blood if corrected for mCi dose. As anticipated due to the intracerebroventricular route of administration, CSF absorbed a much higher (76-fold) radiation dose than the blood. The CSF to blood absorbed doses differs substantially in studies 101 and 03-133 (76 versus 16.78 times higher in CSF to compared to blood). One possible explanation could be an overestimation of the blood absorbed doses in Trial 03-133 using the modelling approach. If the blood clearance of ^{131}I-omburtamab is in fact faster (e.g., due to HAMA effects) and correctly described by the finding of a relatively low blood activity at the 72-hour sampling point in Trial 101, this would drive some of the difference. The CSF absorbed doses could be also underestimated, if ^{131}I-omburtamab was retained longer in the CSF compartment than what a 48-hour sample in Trial 03-133 indicate, and an artefactually low CSF activity would be the result of the modelling.

Use of radioactivity measurements in CSF and blood is an interesting approach. The long-term indwelling of the application and the continuous use of the device could affect these measurement (local inflammatory response, local injury of the endothelium, leakage of blood, lowered BBB integrity). The ICV catheter is one of several potential risk factors which could influence the BBB integrity, but a factor which may be considered as minimal. One would expect information on the effect of locally (to the cerebral ventricular system) administered ^{131}I-labelled markers demonstrating an effect especially since

it has been noted that with respect to clearance, after the treatments of omburtamab, a consistent decline in percent of the antibody present in CSF to less than 0.01% at 168 hours was observed. Imaging-based dosimetry revealed brain and liver as primary target organs with highest absorbed radiation doses, followed by urinary bladder wall and spleen. Absorbed doses in the liver were even higher than absorbed doses in the brain, which is unexpected given the intracerebroventricular route of administration and significantly lower radiation doses determined in blood as compared to CSF. Based on the submitted dossier the targeted administration provides an opportunity for therapeutic effect in the CNS with diminished systemic impact. The unbound ^{131}I-omburtamab quickly leaves the CSF compartment with a clearance half-life ($T_{½}$) of ~1 hour and the subsequent whole body clearance $T_{½}$ of ~48 hours is expected to be dependent on the normal physiological degradation of endogenous and recombinant antibodies via mononuclear cells abundantly located in the liver and spleen. This explains the presence of radioactivity in circulation and liver. Despite this fact, no treatment emergent adverse events (TEAEs) suggestive of significant liver dysfunction have been reported.

Uptake of ^{131}I-iodine in the thyroid was protected by stable iodide saturation and thus, absorbed doses in the thyroid were low. Thyroid protection is also foreseen in the label. Thyroid protection was initiated one week prior to ^{131}I-omburtamab dosimetry doses and continued until two weeks after each ^{131}I-omburtamab treatment dose.

CSF volume of distribution ranged between 28.9 – 63.2 mL, with a high degree of variability. Based on the normal CSF volume of 150 mL reached at the age of 5 years, ^{131}I-omburtamab distributes in less than 50% of the CSF.

PK of ^{131}I-iodine: For the PK properties of free iodine-131 it was referred to the EMA Guideline on core Summary of Product Characteristics for sodium iodide (^{131}I). Intracerebroventricular administered ^{131}I-omburtamab which has not bound to B7-H3 expressing tumour cells will be detectable in systemic circulation relatively quickly. When it thus enters the systemic circulation, omburtamab as a mAb is mainly metabolised and eliminated through proteolytic degradation that results in formation of smaller peptides and amino acids. Any free iodide will be distributed and eliminated.

It has been observed, after oral administration, that urinary excretion is 37 to 75%, faecal excretion is about 10%, and there is almost negligible excretion in sweat. Urinary excretion is characterised by the renal clearance, which constitutes about 3% of the renal blood flow. Clearance is affected by the impaired renal function and also affected by the state of the functional status of thyroid gland. It was clarified that the renal clearance of iodide was also found to be higher in the young similar to the thyroidal clearance of iodide, particularly between the age of 3 weeks to 6 months. When normalised for body weight, the young excrete iodide in urine at a greater rate than adults which is inconsistent with maturation of the glomerular filtration. This explanation can be accepted.

Elimination

With regard to PK of ^{131}-iodine, the applicant refers to the SmPC for sodium iodide (^{131}I) for therapeutic use for which PK properties have already been adequately characterised in the past. However, it remains uncertain how far binding to omburtamab would change PK characteristics of ^{131}I-iodine.

Referring to radioactivity measurements in CSF, radioactivity left the CSF space with a geometric mean clearance half-life of 2 – 4 hours in study 03-133 and study 101. The movement of molecules between the intrathecal space and the blood is prevented by the BBB. Elimination of the antibody portion itself (omburtamab) has not been determined but is expected to be mediated by intracellular proteolytic catabolism as known for other mAbs. Geometric mean whole-body clearance half-lives determined in study 101 were 47 hours after the dosimetry dose and 41 hours after the treatment dose.

The determination of whole-body clearance half-life and brain clearance half-life is welcomed. The applicant provided in detail main PK characteristics, absorption, distribution and elimination of ^{131}I-

omburtamab in humans but did not collect excreta samples and therefore cannot detail if the excretion of ^{131}I-omburtamab follows that for free iodine-131.

Dose proportionality and time dependency

Similar values are observed for dose-normalised absorbed radiation doses, indicating dose-proportionality with regard to dosimetry. Data reported in the assessment above show that absorbed doses per target organ are similar for dosimetry (2 mCi) and treatment dose (50 mCi) if corrected for MBq administered.

Due to the absence of PK data for the treatment dose (50 mCi), dose proportionality with regard to PK parameters cannot be assessed. PK parameters have solely been determined for the dosimetry dose (2 mCi).

No data for assessment of time-dependent effects and PK characteristics of ^{131}I-omburtamab after the first and second treatment dose are available. Considering that omburtamab is a full IgG1 antibody with anticipated half-life of approximately 3 weeks, accumulation is expected for the treatment dose given 1 week after the dosimetry dose. In this regard, information on target saturation and binding and distribution of ^{131}I-omburtamab in case of sustained target saturation due to the preceding dosimetry dose had been required. The potential for time-dependent effects and change in PK, in particular after the second ^{131}I-omburtamab treatment dose was discussed and judged to be minimal for both the CSF and the systemic compartments. Detailed information about the kinetics of the antibody part of the molecule is pending and this question needs to be re-addressed when these data will be further generated.

PK in the target population

Study 03-133

PK in study 03-133 was solely analysed for the dosimetry dose, since CSF and blood sampling for PK was restricted to the 36 – 48 hours period post dosimetry dose. Data are reported above in the report.

Only 27 patients contributed to PK data for this study, and these were patients consecutively enrolled over 3 years (2016-2018). The emphasis of PK results is based on Trial 101 analyses, and PK and dosimetry data from Trial 03-133 should be regarded as supplemental which is acknowledged and will be judged as such.

Study 101

Compared to study 03-133, PK sampling in CSF and blood in this study was conducted more frequently after the dosimetry dose (7 samples collected at baseline, 30 minutes, 1 hour, 4 hours, 24 hours, 48 hours and 72 hours post dosing). An additional sample was collected 7 days after the treatment dose (50 mCi). The dosimetry dose was only used to assess dosimetry and PK, not to individualise treatment doses, and dosimetry was discontinued as of 01 January 2020. All PK results included in this summary are from subjects enrolled prior to 01 January 2020 and who received both a dosimetry and treatment dose (one treatment cycle). In contrast, approval of ^{131}I-omburtamab is sought for two treatment doses of 1850 MBq without the preceding dosimetry dose.

Median T_{max} in CSF and blood after the dosimetry dose was 0.5 hours and 23.97 hours, respectively. Median CSF T_{max} in Trial 03-133 was 2.0 hours and thus, longer than what was observed in Trial 101 (0.5 hours); however, this could have resulted from inclusion of an earlier sampling time (30 minutes) in Trial 101. The median blood T_{max} was similar across both studies (23.97 hours in Trial 101 and 22.0 hours in Trial 03-133). The observed differences in median T_{max} between the studies could be caused by many factors, including extent of diseases, volume of tumour, BBB integrity, indwelling time of the device, and differences in sampling times etc. Geometric mean for Cmax in CSF and blood was

1,292,386.8 Bq/mL and 2755.2 Bq/mL. As expected, the maximum radioactivity count in blood was about 470-fold lower than in CSF and occurred significantly later as seen in values for T_{max}.

A high degree of variability was observed for the PK parameters analysed. This is supposed to be caused by the differences in tumour binding or sampling issues. An overview of potential factors influencing the CSF V_d was provided by the applicant and the different parameters with potential to affect PK findings and sample-based dosimetry are discussed. Differences in dosimetry approach, sampling schedule and PK analyses performed in both trials hamper the assessment of the presented data due to lack of uniformity. The applicant has no data on the analytical performance in Trial 03-133 as conducted by MSK, the qualification of equipment and standardisation of processing and analysis was not done by an independent vendor, and a retrospective qualification of MSK's analysis set-up is not feasible.

Neither study 03-133 nor study 101 provided PK data for the actual treatment dose of 1850 MBq ^{131}I-omburtamab. Therefore, PK data described in section 5.2 of the SmPC refers to kinetics observed with the dosimetry dose (2 mCi/74 MBq), which is not considered appropriate. PK should be adequately characterised after the treatment dose, which is actually 25-fold higher than the dosimetry dose. In this regard, it would be relevant to define a therapeutic exposure range accounting for exposure levels needed for efficacy with – at the same time – acceptable tolerability. For adequate characterisation of PK at the ^{131}I-omburtamab treatment dose, a post-authorisation PK study would be required.

Special populations

No PK studies of ^{131}I-omburtamab analysing differences in patients due to impaired renal or hepatic function, sex, ethnicity, or age were conducted. Subjects with impaired kidney function were not eligible for inclusion in the clinical trial programme with ^{131}I-omburtamab. Therefore, the effect of impaired kidney function on the exposure/PK of ^{131}I-omburtamab was not studied. A comparison of exposure in different subgroups of weight (0 to <15 kg; 15 to <30 kg; ≥30 kg) and age (0 to <1 year; 1 to <3 years; ≥3 years) was provided. Most subjects belonged to the 0 to <15 kg or 15 to <30 kg groups. Only three subjects were ≥30 kg. Median CSF T_{max} and blood T_{max} were similar across weight groups. Despite the applied dose reduction in children aged <1 year and 1 to <3 years, higher exposure as described by C_{max} in CSF and blood was seen in patients with lower body weight. Given that the applied dose reduction regimen is based on literature reference from 1977. Doses according to weight were discussed with the aim to avoid myelosuppression. The data indicate that dosing according to weight does not add further value to the safety if compared to dosing according to age.

The majority of subjects (70%) providing PK or dosimetry data were over the age of 3 years. Median CSF T_{max} was similar among age groups, with each age group having a median CSF T_{max} of about 2.0 hours. Median blood T_{max} was also similar among age groups, with each age group having a median blood T_{max} between 21.0 and 22.4 hours. No clear differences were seen in exposure comparing the different age groups and no valid conclusions may be drawn given the small numbers of subjects who were 0 to <1 years of age (n = 2) and 1 to <3 years of age (n = 6).

Based on the data provided, ^{131}I-omburtamab has been administered to 170 paediatric patients in Trial 03-133 and Trial 101 without any indication of acute adverse effects on the major physiological systems (e.g., cardiovascular, respiratory, renal, and CNS). The population being a paediatric one limits this conclusion. Prolonged toxicity of other factors – on the brain tissue affecting the BBB could be a major contributing factor. There are no safety reports suggesting adverse long-term neurological effects following treatment with ^{131}I-omburtmab. Neurocognitive functioning and QoL testing were performed where feasible before and after treatment with ^{131}I-omburtamab. The assessment of the results is ongoing; however, it should be noted that only a few patients have a baseline assessment of neurocognitive function. Given the lack of information, 'long-term safety including neurocognitive development' will be included as missing information in the Summary of safety concerns presented in the Risk Management Plan for ^{131}I-omburtamab. An assessment is currently ongoing to understand the

feasibility of establishing a patient registry to collect additional safety data on the important risks and explore the areas of missing information presented in the Risk Management Plan for ^{131}I-omburtamab. The registry study has been proposed as category 3 study in the RMP.

Pharmacodynamics

No data on clinical pharmacodynamics are available. Likewise, the relationship between radioactive dose/exposure and response (efficacy/safety) has not been investigated. Furthermore, a therapeutic exposure range accounting for maximum efficacy whilst maintaining minimal risk of toxicity has not been defined. No data on ^{131}I-omburtamab exposure after the treatment dose of 50 mCi (1850 MBq) that may be used for analysis of these relationships are available.

No data on immunogenicity have been provided. Study 101 was, however, amended to collect samples for immunogenicity detection from three to six subjects who received two treatment doses. Lack of immunogenicity data is a serious drawback of this application. The results on ADA in the above-mentioned patients are planned to be provided with the final CSR together with a bioanalytical method report and a validation report for the assay used for detection of anti-drug anti body.

2.2.4. Conclusions on clinical pharmacology

Overall, PK of ^{131}I-omburtamab is not considered to be sufficiently characterised to support approval of the intended two ^{131}I-omburtamab doses at 1850 MBq in paediatric neuroblastoma patients with CNS/LM metastasis. In particular, all dosimetry and PK results are based on analytical methods, which have not been validated to prove that these methods are suitable for their intended purpose. Collectively, the reliability of dosimetry and PK data is questionable.

2.2.5. Clinical efficacy

Table 25. Efficacy studies submitted in support of this procedure

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
03-133	Single center, initiated 2004, closed 2018	Single arm	Combined dose escalation cohort and expansion cohort	Toxicity of intrathecal ^{131}I-omburtumab	Safety: 109 neuroblastoma, 37 non-neuroblastoma Efficacy: 107 neuroblastoma	1-2 doses, long term follow-up ongoing	Neuroblastoma with CNS/LM metastasis	OS at 3 years (not prespecified at trial initiation)
101	3 US sites, 1 European site, initiated 2018, ongoing	Single arm	1850 MBq / dose	Efficacy as determined by OS	Efficacy: 50	1-2 doses	Neuroblastoma with CNS/LM metastasis	CNS/LM PFS at 6 months

2.2.5.1. Dose response study(ies)

The recommended dosing for ^{131}I-omburtamab in the proposed label is two 1850 MBq (50 mCi) infusions. Support for this recommended dosing comes from the 94 subjects in the Part 2, expansion phase of Trial

03-133 who received a treatment dose of 50 mCi. Part 1 of Trial 03-133 was a dose escalation phase. However, the maximum tolerated dose was not reached, and no dose-limiting toxicities were reported. Instead, the ^{131}I-omburtamab 50 mCi dose was selected for Part 2 of Trial 03-133, because myelosuppression observed at that dose level was found to be manageable.

The route of administration of ^{131}I-omburtamab is intracerebroventricular infusion via an intracerebroventricular access device (e.g., Ommaya catheter). Intracerebroventricular administration has been used for decades in the clinic to provide treatment for adult and paediatric populations suffering from a variety of conditions, including varying cancer types (Kramer et al, 2014; Cohen-Pfeffer et al, 2017). Kramer et al., assessed the safety and complication rate associated with ventricular access devices in patients receiving compartmental intraventricular radioimmunotherapy and concluded that minimal acute complications are observed and that long-term complications are rare. In addition, a literature review conducted by Cohen-Pfeffer and colleagues concluded that the intracerebroventricular route of administration appears to be a safe and well-tolerated method of long-term drug delivery in both paediatric and adult patients.

2.2.5.2. Main study(ies)

This submission is based on two trials. The 03-133 was a single centre "basket" trial in the US intended to investigate dose-finding and the toxicity of intrathecal administration of iodinated omburtamab. The majority of patients had neuroblastoma with leptomeningeal/parenchymal metastasis. The trial was initiated in 2004 and data were recorded over more than a decade, enrolment was stopped in 2018. This trial provides most of the efficacy data with respect to OS including long-term outcomes.

The 101 study is a multi-centre single-arm trial that is still ongoing. This trial recruits only neuroblastoma patients with LM/CNS metastasis. An interim analysis was conducted on data from patients recruited up to 01 January 2020. Further data were submitted during the procedure and currently 50 patients have been recruited (instead of 32 planned).

To provide context for both trials and for the evaluation of efficacy several external controls were provided. These controls are derived from registries (Central German Childhood Cancer Registry, CGCCR), SIOPEN, literature review and single-centre experiences prior to the start of the trial (Memorial Sloan-Kettering Cancer Center, MSKCC).

Title of study

Phase I Study of Intrathecal Radioimmunotherapy using ^{131}I-omburtamab for Central Nervous System/Leptomeningeal Neoplasms

Methods

- **Study Participants**

This trial included:

- Patients with malignancies that stained positive with omburtamab i.e., bound the monoclonal antibody, no confirmation of staining was required for patients with neuroblastoma.
- Subjects which have CNS/LM disease which is refractory to conventional therapies or for which no conventional therapy exists OR a recurrent brain tumour with a predilection for leptomeningeal dissemination (primitive neuroectodermal tumour, rhabdoid tumour).
- Patients were required to be clinically stable and not have rapidly progressing or deteriorating neurological examination.
- Bone marrow function was required to be stable.

The trial was initiated and run at a single site, the Memorial Sloan-Kettering Cancer Center in NYC.

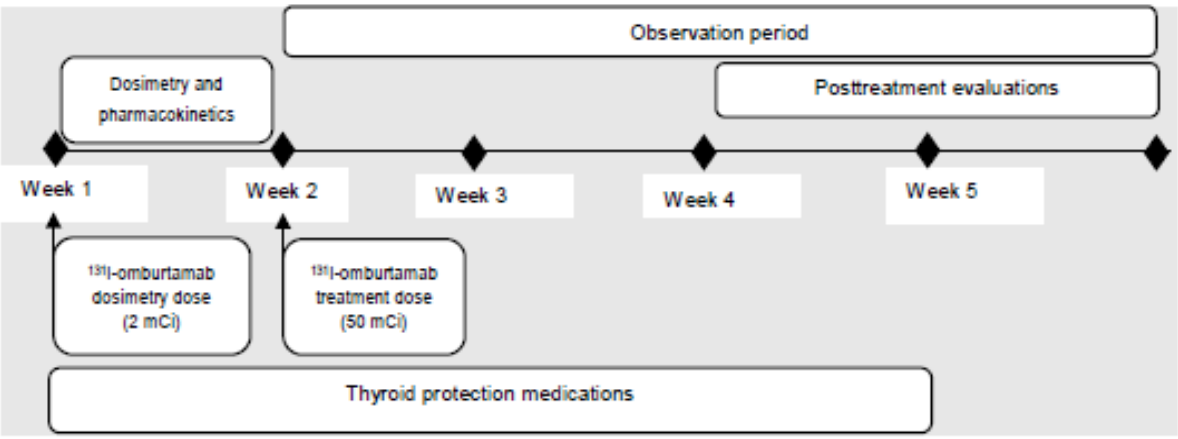
The trial excluded:

- Patients with obstructive or symptomatic communicating hydrocephalus.
- Patients with an uncontrolled life-threatening infection.
- Patients who are pregnant: Pregnant women are excluded for fear of danger to the foetus. Therefore, negative pregnancy test is required for all women of child-bearing age, and appropriate contraception is required during the study period.
- Patients who have received cranial or spinal irradiation less than 3 weeks prior to the start of this protocol.
- Patients who have received systemic chemotherapy (corticosteroids and immunotherapies not included) less than 3 weeks prior to the start of this protocol.
- Patients with severe major organ toxicity. Specifically, renal, cardiac, hepatic, pulmonary, and gastrointestinal system toxicity should all be less than Grade 2. Patients with stable neurological deficits (because of their brain tumour) are not excluded. Patients with ⩽3 hearing loss are not excluded.

- **Treatments**

^{131}I-omburtamab was administered via intrathecal access (e.g., Ommaya reservoir). Each patients received one cycle with a single dosimetry dose at week 1 and a single treatment dose at week 2. Subjects without objective disease progression 5 weeks after the first dose and no grade 4 toxicities could receive a second dose at the discretion of the investigator. The treatment dose that was administered to the majority of patients was 1850 MBq (50 mCi).

Figure 5. Treatment schedule



Doses were reduced in patients less than three years of age:

Table 26. Dose Reduction

Age (years)	Dose Reduction	^{131}I-omburtamab Dose (mCi)[a]
Less than 1	50% reduction	25.0
1 to less than 3	33% reduction	33.5
3 and above	No reduction	50.0

a 25.0 mCi = 925 MBq; 33.5 mCi = 1,239 MBq; 50.0 mCi = 1,850 MBq.

All patients received thyroid protection (oral potassium iodide, liothyronine) one week prior to ^{131}I-omburtamab dosimetry dose until 2 weeks after the treatment dose. In addition, oral or intravenous

dexamethasone was started 24 hours prior to ^{131}I-omburtamab twice daily for three days. Anti-pyretic (e.g., paracetamol) and an antihistamine (e.g., diphenhydramine) were administered hours prior to intrathecal infusion and as needed after infusion.

- **Objectives**

This was an exploratory trial intended to investigate toxicity of intrathecal administration of ^{131}I-omburtamab. The plan for interim analysis for the evaluation of efficacy was developed after the majority of patients were recruited. The changed objectives as stated in amendment 25 (see list below as per synopsis submitted) was to evaluate the OS rate at 3 years and compare to external controls:

Overall Objectives:

- Primary Objective - Define the clinical toxicities of intrathecal ^{131}I-omburtamab
- Secondary Objectives - To evaluate efficacy in terms of survival rate at 3 years
    - To evaluate efficacy in terms of overall response rate (ORR) 6 months after the first treatment dose
    - To evaluate efficacy in terms of CNS/LM progression 6 months after the first treatment dose
    - To evaluate long term safety
    - To collect neurocognitive and long term follow up data

Interim Analysis Objectives:

- Primary objective - To assess the overall survival at 3 years after the first treatment dose of ^{131}I-omburtamab

- Secondary objective
    - To evaluate CNS/LM progression-free survival (CNS/LM PFS) at 12 months
    - To evaluate duration of follow-up

- **Outcomes/endpoints**

The *primary efficacy endpoints* were introduced via amendment 25 (dated 05 June 2019).

- Overall survival rate at 3 years

Overall survival, defined as the time from first date of diagnosis of CNS relapse to the date of death. The survival time was calculated from the date of first diagnosis of CNS relapse until the date of death (event) or until the latest date confirmed alive (censored observation).

- CNS/LM PFS at 12 months

CNS/LM PFS time was calculated from the date of first dose of ^{131}I-omburtamab until the date of CNS/LM progression or death (event) or until the latest date confirmed to be progression-free (censored observation).

- Duration of follow-up

Duration of follow-up for OS and for CNS/LM PFS was estimated by the reverse Kaplan-Meier method, the median follow-up time with 95% CI is presented.

Secondary efficacy endpoint

Baseline CSF cytology was used as a secondary efficacy measurement. CSF cytology was assessed at screening as positive/negative. If positive, it was to be repeated within 3 weeks of the first and eventually second ^{131}I-omburtamab treatment infusions and during follow-up.

- **Sample size**

With Amendment 25 (dated 05 June 2019) the sample size was justified as follows. Assuming an OS rate at 3 years of 40% and a sample size of 100 patients in this trial, the statistical power to show that the OS rate at 3 years is >30% was estimated as 80%. The maximum 3-year OS rates to which omburtamab can be found superior, which can be excluded with 80% power for several assumed OS rates at 3 years are shown in the table below.

Table 27. statistical power

Power	Assumed omburtamab 3 year OS rate		
	30%	35%	40%
80%	20%	25%	30%

The numbers reported were derived based on simulations, which could not be fully reproduced and understood.

- **Randomisation and Blinding (masking)**

Not applicable. This is a single-arm, dose escalation and dose expansion study.

- **Statistical methods**

Analysis sets

Three analysis sets were defined. The full analysis set (FAS) was to include all patients enrolled in the trial who begin an infusion of ^{131}I-omburtamab; the per-protocol set (PPS) was to include all FAS patients who have no major protocol violations (patients with other protocol violations might have been uniformly excluded on the basis of data review, which was to be fully defined and documented before data lock); and the safety analysis set was to include all enrolled patients who receive at least one dose of IMP. The FAS was defined as primary efficacy analysis set and the PPS will be used for supplementary analyses.

Statistical analyses

The survival rate at 3 years including its 95% confidence interval, was to be estimated using the Kaplan-Meier method. Additionally, the median OS time were to be estimated, and 95% confidence intervals were to be calculated. Additionally, a multiple Cox-regression analysis including all or a reasonable subset of the most important prognostic factors: Age at diagnosis of CNS/LM relapse (≤18 months vs >18 months), INSS stage at diagnosis (4 vs non-4), isolated CNS/LM metastasis (yes vs no), MYCN amplification status, time from NB diagnoses, prior irradiation therapy for CNS/LM relapse (yes vs no), prior debulking surgery for CNS/LM relapse (yes vs no), and prior chemotherapy for CNS/LM relapse (yes vs no), was to be used to estimate the hazard ratio of survival in the contemporary CGCCR data vs. 03-133 data.

ORR and CNS/LM progression will be calculated and presented by the same subgroups, waterfall plots for response will be presented.

Subgroup analyses

OS was also to be analysed and presented by age above and below 18 months, MYCN amplification, and degree of salvage therapy.

Interim Analysis

An interim analysis, evaluating the survival rate at 3 years as well as a comparison of OS to external controls, was to be conducted when 6 months follow-up data was available for all neuroblastoma patients accrued to the protocol before 1st of January 2019. The interim analyses were to follow the same lines as described above.

Missing data

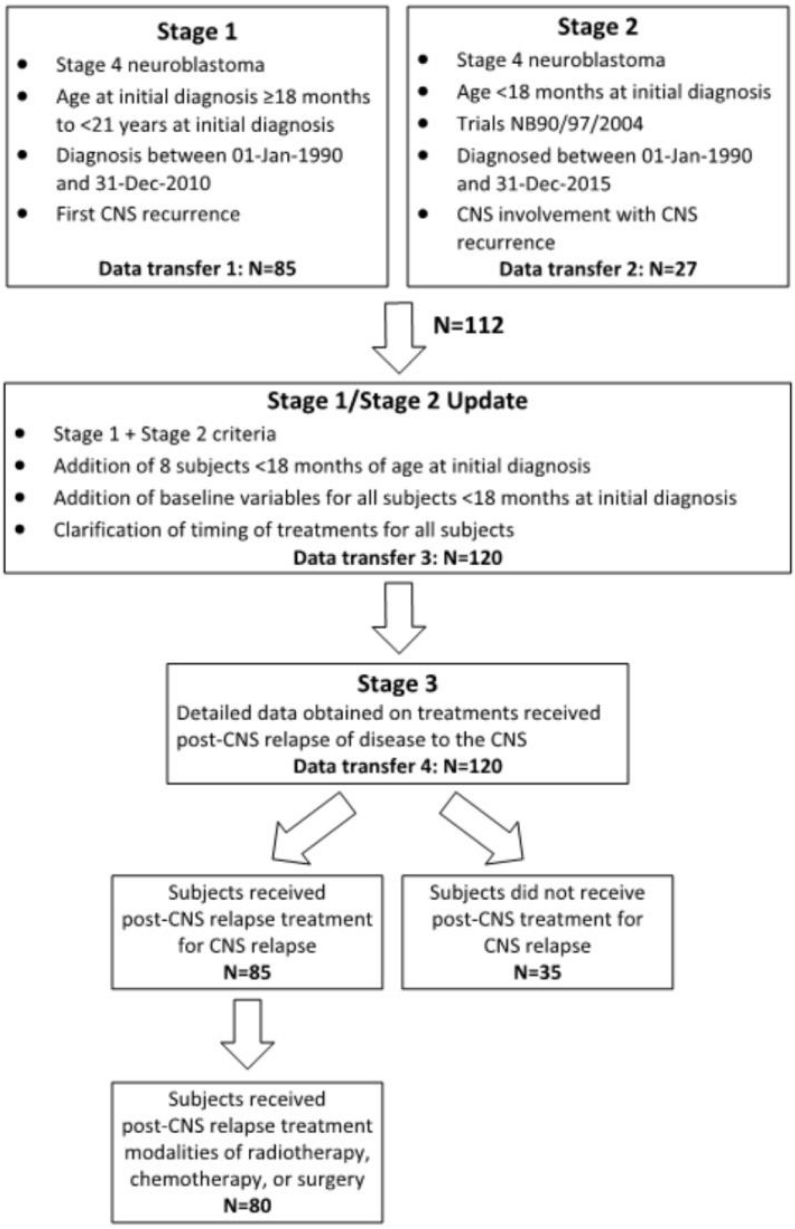
For OS, patients who do not have an event were to be censored at their date of their last evaluation. It was considered unlikely that missing of safety data will occur in the targeted patient population, but in case it happened the data was not to be imputed. No other data was to be imputed.

External control

An additional external control group was defined. External controls were to be primarily obtained from a query to the Central German Children's Cancer Registry (CGCCR). CGCCR initiated in 1980, registers approximately 2,000 children per year who are diagnosed with a malignant disease. CGCCR receives patient data from all paediatric oncology centres across Germany. 99% of all paediatric patients diagnosed with cancer in Germany were included in the national trials, with continuous update of the clinical data within the CGCCR. The CGCCR data was to be used to obtain an estimate of the 3-year survival rate in a contemporary systemically treated cohort of children. To explore the development of systemic treatment cut-offs in 2000 and 2004 were employed.

The database contains information on a total of 112 NB patients with CNS/LM relapse. Subjects were selected in multiple stages from the CGCCR data base according to the following flow chart (Figure 12).

Figure 6: Flow chart of selection process for ECA



Using cut-offs for CNS relapse diagnosis in 2000 or later and in 2004 or later, a total of 71 and 44 subjects remained respectively (updated later to 78 and 49 patients with cut-offs ≥2000 and ≥2004). The proportion of the youngest children ≤18 months at CNS/LM relapse diagnosis was approximately 27%. The estimated 3-year survival rates from the CGCCR data were to be used to support the estimates obtained from published literature, and the superiority of the estimate obtained from the 03-133 data.

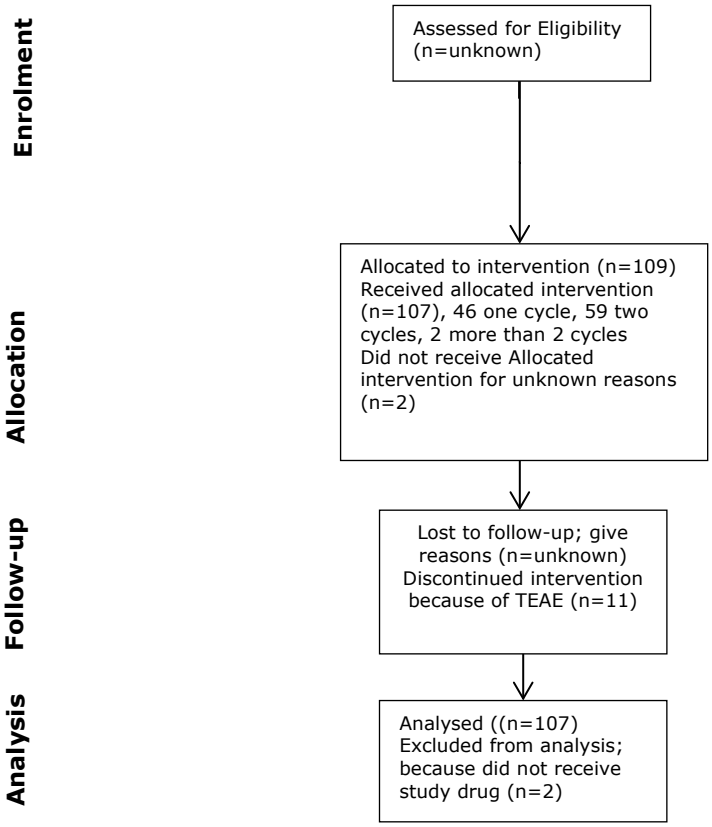
A propensity score weighted analysis for OS comparing CGCCR data with trial 03-133 was defined post-hoc. The analyses were conducted by an external CRO in a two-stage process including external control arm (ECA) construction (Stage 1) and subsequent ECA usage as a comparator in outcome analysis (Stage 2). In Stage 1, baseline composition of the ECA was aligned to that of the Trial 03-133 subjects using propensity score weighting. Despite the outcome data having been provided to the CRO during the creation of the harmonised dataset, the ECA construction was solely based on the baseline demographics and disease characteristics as specified in a dedicated ECA SAP (dated 28 Feb 2022). No outcome variables were considered in the ECA construction. No outcome analyses were conducted until the ECA

construction was completed by the CRO and subsequently reviewed and approved by the applicant. Comparison of Trial 03-133 and the ECA was carried out using methods specified in the SAP (Stage 2).

The primary propensity score weighted analysis included subjects who received radiotherapy and at least one other treatment modality (i.e., chemotherapy or surgery). The primary index date was defined as the start date of the last post-CNS relapse treatment (i.e., radiotherapy, chemotherapy, or surgery). Average treatment effect on the treated (ATT) weighting by propensity score was utilised to create a comparison of Trial 03-133 and the external control in a 3:1 ratio and to balance baseline composition of prognostic factors. Prognostic factors with less than 15% missing data were included in the estimation of propensity scores, and missing values were imputed.

Results

- **Participant flow**



- **Recruitment**

The trial was initiated on 5 Feb 2004 and enrolment was finished 31 October 2018. Follow-up is intended for the full life-span of the recruited patient.

- **Conduct of the study**

The trial was planned as a safety trial using dose escalation. The trial ran over a very long time and

multiple changes were made to the protocol, including changes to the objectives, the primary endpoint, the analysis populations and sample size.

- **Baseline data**

Median age for the FAS population (N=107) at consent was 4.7 years (Min 0.85, Max 13), 72 (67%) were male, 84 (79%) where Caucasian.

46 patients received one cycle, 59 patients received 2 cycles and 2 patients received more than 2 cycles of treatment. 55 patients received two treatment doses.

The median age at diagnosis for subjects in the FAS was 2.3 years with a range of 0.02 to 12.1 years. A total of 84 subjects (78.5%) were older than 18 months. The INSS stage at diagnosis for the majority of subjects in the FAS was Stage 4 in 78 patients (72.9%). 61 (57%) had no prior relapses. For 24 patients the stage of disease was unknown.

For the FAS the site of disease reported was "unifocal parenchymal site" in 51 patients, "multifocal parenchymal site" in 16 patients, "leptomeningeal" in 10 patients and "parenchymal and leptomeningeal" in 9 patients. It was reported as not known or not reported in 21 patients. MYCN amplification was reported in 55 FAS subjects (51.4%), and MYCN gain was reported in two subjects (1.9%).

In line with the inclusion criteria the majority had received prior therapy for CNS/LM disease (radiation 102 (95%), chemotherapy 107 (100%) or surgery.

- **Numbers analysed**

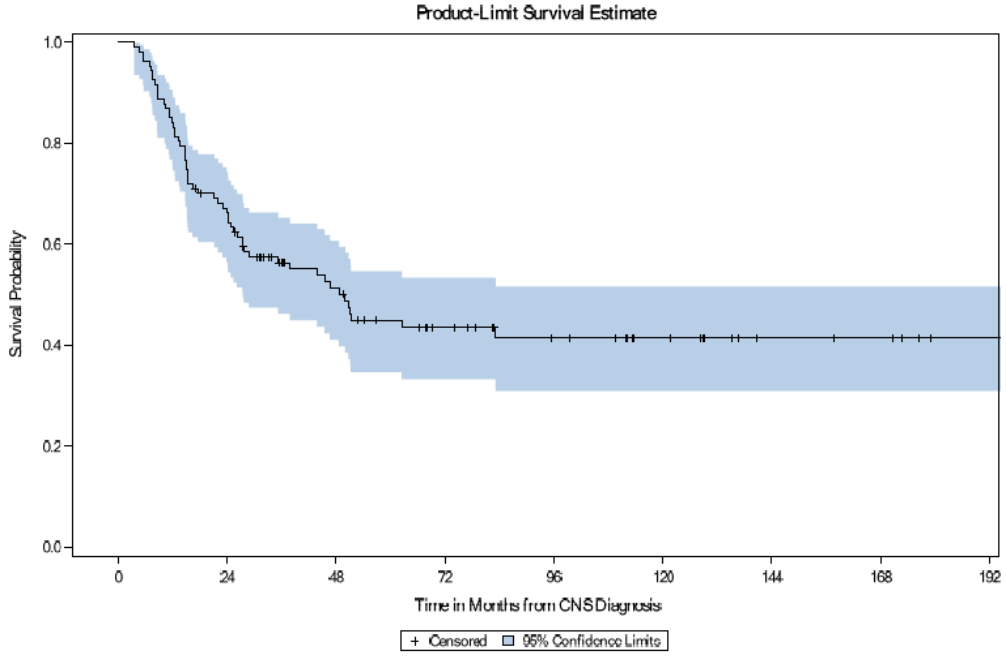
The trial had two parts, a dose escalation part and a cohort expansion part. In part 1 patients received one dosimetry dose (2 mCi) and varying treatment doses (up to 70 mCi). In part 2 all patients received a 50 mCi dose (with age adaptation in children less than 3 years). The applicant defines the FAS including patients that received at least one cycle of treatment, this includes 107 patients and excludes those that did not receive treatment (n=2). This population either received one cycle (n=46), two cycles (n=59) or >2 cycles (n=2).

- **Outcomes and estimation**

Primary endpoint: 3-year survival rate estimates from the time of CNS diagnosis in the FAS

The three-year OS rate (KM estimate) in the FAS was 0.56 (95%CI 0.46, 0.65). Death was observed in 57 cases, 40 cases were censored in the KM analysis. The following figure shows the respective KM plot.

Figure 6. Kaplan-Meier plot of OS (FAS) - Product-Limit Survival Estimate

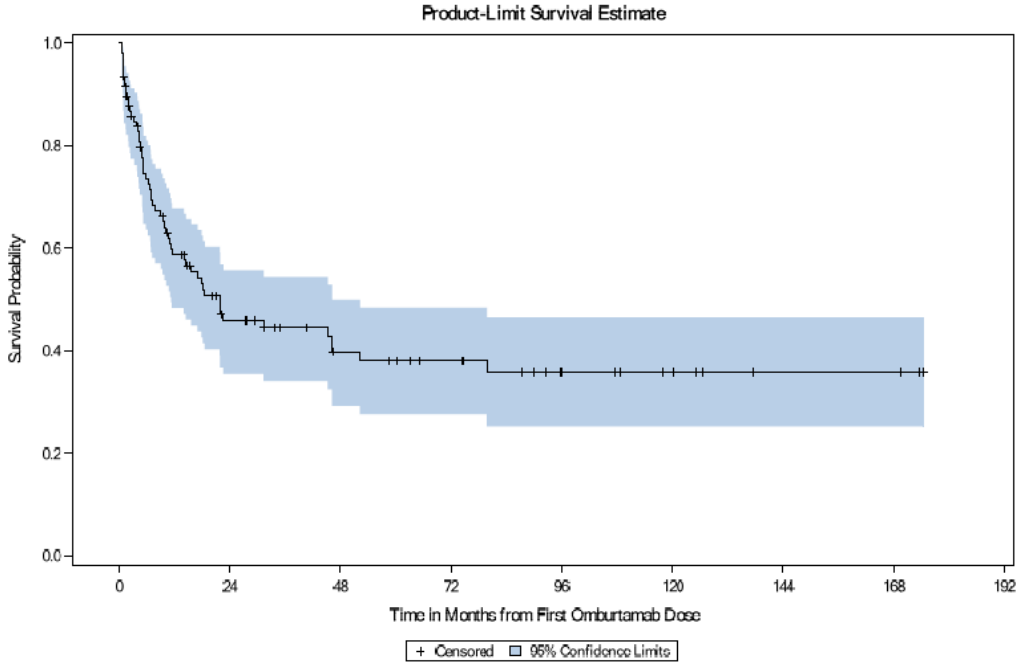


Secondary endpoint: 12 months CNS/LM progression free survival rate from first dose of ^{131}I-omburtamab in the FAS

The estimate for the 12 months CNS/LM progression free survival rate was 0.59 (95% CI: 0.44, 0.68). 58 subjects reached the endpoint, 30 subjects had CNS/LM progression and 28 subjects had died. 49 subjects were censored in the analysis.

The following figure shows the respective Kaplan-Meier plot of CNS/LM PFS (FAS).

Figure 7. Product-Limit Survival Estimate



Secondary endpoint: duration of follow-up

The median duration of follow-up was 75.0 (95% CI 49.3, 104.0) months, with a minimum duration of follow-up of 0.7 months and a maximum duration of follow-up of 176.0 months. For the 94 Trial 03-133 neuroblastoma subjects at the 50 mCi dose group, the median duration of follow-up was 63.3 (95% CI 46.3, 90.1) months, with a minimum duration of follow-up of 0.7 months and a maximum duration of follow-up of 133.2 months.

- **Ancillary analyses**

Subgroup analyses

The 3-year survival probability for the whole FAS of 107 patients in study 03-133 was 0.56 and the median survival estimate 50 months. Unifocal parenchymal site was diagnosed in 51 patients, multifocal parenchymal sites in 16, leptomeningeal involvement in 10, parenchymal and leptomeningeal in 9, not known in 11 and not reported in 10. The trial was not powered for subgroup analysis of the various metastases and the number of patients in the subgroups were small and variable (ranging from 9 to 51 subjects). It was observed that about 50% of the neuroblastoma subjects of the FAS (51 of 107 patients 48%) demonstrated unifocal parenchymal site type of disease. For these subjects the 3-year probability survival estimate was 0.65 and median survival estimate 83.2 months. Ten subjects (9%) had only leptomeningeal disease. The 3-year survival estimate for this group was 0.60 and the median survival estimate 46.6 months. 8% of the 107 FAS patients demonstrated parenchymal and leptomeningeal disease. The 3-year survival probability for these patients was 0.56 and the median survival estimate was 46.6 months. Sixteen of the 107 FAS patients had a multifocal parenchymal site of disease (15%). The 3-year survival probability was 0.42, and the median survival estimate was 27.7 months. 21 patients consisted of two categories – 11 in whom the type of disease reported by site was unclear, and 10 where this value was not reported.

The majority of the FAS subjects (77 of 107) had isolated CNS/LM disease prior to treatment in Trial 03-133. The 3-year survival probability was 0.66 and median survival estimate of 83.2 months. In patients with CNS relapse and systemic refractory disease (28 of 107) had a 3 year survival probability 0.32 and the median survival estimate 23.4 months. Similar to the OS results the 12-month CNS/LM PFS probability and median PFS estimates were numerically greater for Trial 03-133 FAS subjects with isolated CNS/LM disease prior to treatment in Trial 03-133.

Comparison to external controls

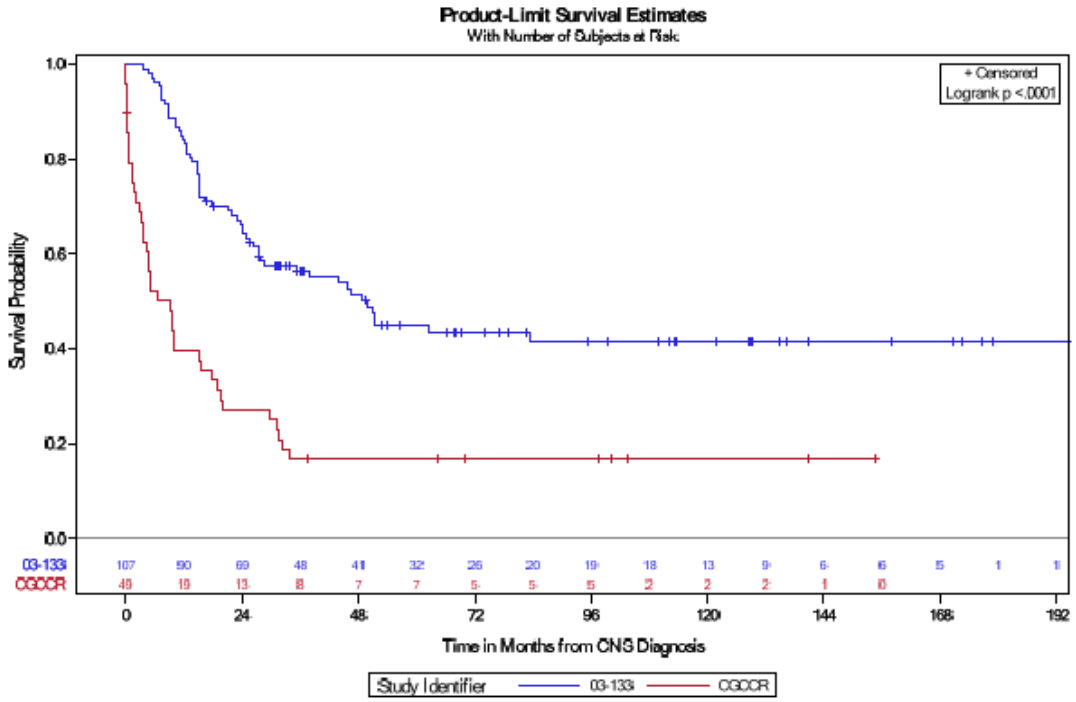
Comparisons of the survival data from the 03-133 trial with external data were provided. Four comparisons have been conducted: comparison to the CGCCR dataset, comparison to the SIOPEN dataset, literature review, MSK controls.

Central German Childhood Cancer Registry (CGCCR)

The CGCCR registers cases from all paediatric oncology units affiliated with the German Society for Paediatric Oncology and Haematology. It is estimated that more than 95% of all German children and adolescents under the age of 15 years with malignant diseases are reported to the CGCCR.

To account for a potential temporal effect on survival, estimates of survival were also evaluated in subsets of the population after applying CNS/LM relapse cut-off dates in the years 2000 and 2004. Trial 03-133 enrolled the first patient in 2004, and the latest subset grouping ("2004 and later") should therefore be regarded as a contemporaneous external comparator in these subsets. The following plot is representative of several KM analyses comparing different subgroups of 03-133 and CGCCR based on date of diagnosis, age (≤18 months, >18 months) and MYCN status amplified/non amplified.

Figure 8. Unadjusted Kaplan-Meier plot of OS, 03-133 vs CGCCR (Neuroblastoma diagnosis 2004 or later)



SIOPEN dataset

Patient-level data from SIOPEN could contribute to the understanding of survival in this population. In 2002 SIOPEN initiated a randomised Phase III trial (HR-NBL1/SIOPEN) in high-risk neuroblastoma (HR-NBL) patients. Patients with newly diagnosed stage 4 HR-NBL were enrolled in the HR-NBLI/SIOPEN trial (NCT00030719) from February 2002 to June 2015. Of the 1,977 Stage 4 HR-NBL patients enrolled in the trial, there were 1,161 recurrent patients (855 patients with metastatic relapse), including 53 patients with CNS involvement at first recurrence confirmed by central imaging review. Of the 53 patients with confirmed CNS relapse, 31 received at least one relevant post-relapse treatment for CNS disease (e.g., chemotherapy, surgery, or radiotherapy), or any combination of these.

Analysis according to treatment modalities (additional therapy administered for CNS/LM metastasis)

All patients in the trial 03-133 had received either radiotherapy, chemotherapy or surgery while this was only the case for 80 of the 120 patients from the CGCCR control group rendering these population not comparable. To account for different treatments and duration of prior treatments the applicant developed "treatment modality groups": Modality group 1 includes subjects who received at least one treatment modality of radiotherapy, chemotherapy, or surgery; modality group 2 includes subjects who received radiotherapy and at least one other treatment modality (chemotherapy or surgery); modality group 3 includes subjects who received three treatment modalities (radiotherapy, chemotherapy, and surgery).

The following table shows results of OS rate at 3 years by Treatment Modality group (Assessor's table derived from table 5-11 of additional statistical report). Of note, these analyses include also patients that were diagnosed prior to 2004 while the more relevant control is the concurrent external control.

Table 28. OS rate at 3 years by Treatment Modality group

	03-133	CGCCR	SIOPEN

	n	3y-OS rate (95%CI)	n	3y-OS rate (95%CI)	n	3y-OS rate (95%CI)
Modality group 1	107	0.56 (0.46, 0.65)	80	0.15 (0.08, 0.24)	31	0.13 (0.04, 0.27)
Modality group 2	99	0.56 (0.45, 0.65)	35	0.26 (0.13, 0.41)	18	0.22 (0.07, 0.43)
Modality group 3	77	0.58 (0.46, 0.68)	21	0.38 (0.18, 0.58)	8	0.38 (0.09, 0.67)

Propensity score modelling

In response to the concern that the external control population would not be comparable to the trial population with regard to many baseline characteristics further analysis methods were employed. In order to compensate for the lack of a randomised control a propensity score model was developed. The primary analysis includes subjects who received radiotherapy and at least one other treatment modality (i.e., chemotherapy or surgery). Average treatment effect on the treated (ATT) weighting by propensity score was utilised to create a comparison of Trial 03-133 and the external control in a 3:1 ratio and to balance baseline composition of prognostic factors. Prognostic factors with less than 15% missing data were included in the estimation of propensity scores, and missing values was imputed. The OS was compared between Trial 03-133 and the ECA using the weighted log-rank test. In comparison to the subjects in the ECA with well-balanced baseline characteristics by propensity score-based weighting, the Trial 03-133 cohort was associated with a numerical improvement in OS (HR=0.62, 95% CI: 0.34, 1.13; log-rank test p-value=0.084).

The applicant presented this analysis also at an Oral Explanation in front of CHMP and the strategy for the comparison was described. It was acknowledged by the applicant that not all known prognostic factors were included in the propensity score model (complete surgical resection, presence of systemic disease, number of recurrences). It was also acknowledged that craniospinal irradiation was considerably more common in the trial patients compared to the external controls. No new data were presented.

Trial 101

Title:

A Multicenter Phase 2/3 Trial of the Efficacy and Safety of Intracerebroventricular Radioimmunotherapy using ^{131}I-omburtamab for Neuroblastoma Central Nervous System/Leptomeningeal Metastases

Methods

- **Study participants**

This trial included:

- Patients with histologically confirmed neuroblastoma with CNS or LM metastasis either progressing through induction therapy or following induction therapy, i.e., relapsing.
- Stable systemic disease, stable neurologic function for three weeks prior to the first dose and sufficient function bone marrow and major organs was required.

This trial is ongoing in three academic sites in the USA and one site in Europe.

- **Treatments**

^{131}I-omburtamab was administered via intrathecal access (e.g., Ommaya reservoir). Each patients received one cycle with a single dosimetry dose at week 1 and a single treatment dose at week 2. Subjects without objective disease progression 5 weeks after the first dose and no grade 4 toxicities received a second dose at the discretion of the investigator.

The treatment administered was essentially identical to the treatment administered in trial 03-133 without the dose-escalation part.

- **Objectives**

Primary objective of the trial is to evaluate efficacy and safety of ^{131}I-omburtamab:

Primary Objective:

- Overall survival (OS) rate at 3 years.

Secondary Objectives:

- To evaluate central nervous system/leptomeningeal (CNS/LM) progression-free survival (PFS) at 6 and 12 months.
- To evaluate OS at 12 months.
- To evaluate the objective response rate at 6 months
- To evaluate dosimetry of ^{131}I-omburtamab
- To evaluate the pharmacokinetics (PK) of ^{131}I-omburtamab
- To evaluate safety of ^{131}I-omburtamab
- To evaluate the immunogenicity of ^{131}I-omburtamab

For the purpose of this submission an interim analysis was introduced in version 10 of the protocol that evaluates the data for patients that were enrolled prior to 01 January 2020.

- **Outcomes/endpoints**

The primary endpoint is OS rate at 3 years with starting time defined as the time of first treatment dose. Several secondary endpoints for evaluation of efficacy are proposed. These include CNS/LM PFS (time from first treatment dose to documented progression of CNS metastasis, leptomeningeal metastasis or death), OS (from the date of first ^{131}I-omburtamab infusion until the date of death by any cause), OS at 12 months (KM estimate) and ORR at 6 months. The objective response rate (ORR=CR+PR) at 6 months as defined by RANO criteria for CNS disease and EANO-ESMO guidelines for LM disease.

For the interim analysis amendment 10 introduced CNS/M PFS at 6 months as primary endpoint.

- **Sample size**

At least 32 and a maximum of 50 patients were to be enrolled in this trial. With an estimated screen failure rate of 25% it was considered likely that 40-50 patients were to be screened to reach 32 eligible. Assuming an OS rate at 3 years of 40%, a sample size of 32 patients in this trial provides statistical power of 99% to show that the lower limit of a 95% confidence interval of the OS rate at 3 years is >10%. The power for alternative assumed 3 years OS rates are shown in Table 37 below. Power was estimated by simulation using an exponential model and an assumed lost to follow-up rate of 10%.

Table 29. Assumed power for 3 years OS rate

Control 3 yr OS rate	Assumed 3 yr OS rate			
	30%	40%	50%	60%
10%	89%	99%	99.9%	99.9%

- **Randomisation**

Not applicable. This is a single-arm, open-label trial.

- **Blinding (masking)**

In principle this is an open-label trial. The "Independent Review Charter" describes that a central, blinded review of imaging would be performed by two independent reviewers using the RANO-BM and/or EANO/ESMO guideline. A third reviewer may be involved for the purpose of adjudication.

- **Statistical methods**

Analysis sets

Analyses sets were defined as for Trial 03-133. See Trial 03-133 for a description.

Statistical analyses

The primary endpoint of the OS rate at 3 years as well as OS at 12 months, and CNS/LM PFS at 6 and 12 months with corresponding 95% confidence intervals, was to be estimated using Kaplan-Meier methods using the FAS. The comparison to external controls (OS only) was to be exploratory and performed using multiple Cox regression taking into account the most important prognostic factors identifiable in the historic data. The median OS and CNS/LM time and associated 95% confidence interval was to be calculated.

ORR according to RANO criteria and CSF cytology as well as CSF cytology alone, will be assessed, 95% confidence intervals will be calculated using the Clopper-Pearson exact methodology.

Interim analyses

An interim analysis, evaluating the dosimetry and pharmacokinetic endpoints as well as available safety and efficacy data, was to be conducted on data from patients having received at least treatment cycle 1 prior to January 1st, 2020. Starting January 1st, 2020, no further patients were to be administered dosimetry doses. Progression in CNS/LM was to be assessed at 6 and 12 months for the full analysis. The primary efficacy endpoint for the interim analysis was to be CNS/LM PFS at 6 months.

Missing data

For the primary time to event efficacy endpoint, patients who do not have an event was to be censored at their date of their last evaluation. It was considered unlikely that missing of safety data will occur in the targeted patient population, but in case it happens the data was not to be imputed.

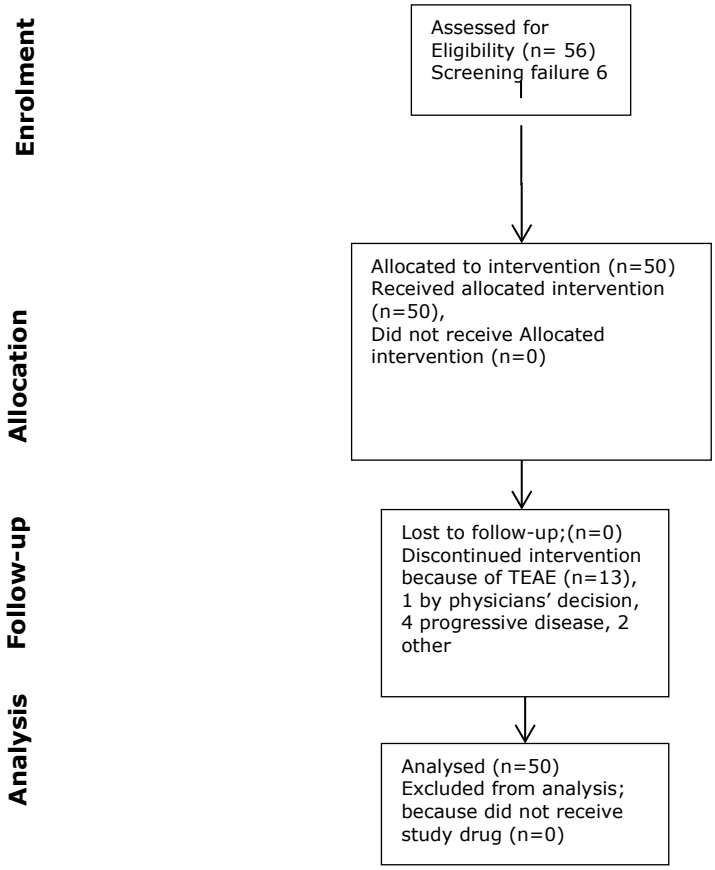
External control

External controls were defined as for Trial 03-133. See Trial 03-133 for a description.

Results

- **Participant flow**

Study Participant flow



- **Recruitment**

Several updated documents with different focus were provided during the procedure. For the interim analysis patients recruited between December 2018 until 20 October 2020 are included. Overall, 50 patients were recruited at the present time.

- **Conduct of the study**

With version 5 of the protocol issued on 12 April 2019 the trial objectives were changed to evaluate the objective response rate at 6 months instead of up to 3 years and evaluate CNS/LM progression instead of CNS progression-free survival. The objective to compare the overall survival with historical controls was deleted.

With version 7 issued 11 Sept 2019 an interim analysis for dosimetry, PK safety and efficacy was introduced.

Version 10 issued 01 May 2020 added two secondary efficacy objectives/endpoints (by request of U.S. FDA) 1) to evaluate CNS/LM progression-free survival (CNS/LM PFS) at 6 months and 2) to evaluate Overall Survival (OS) at 12 months at the interim analysis.

- **Baseline data**

Median age for the FAS population at the interim analysis (N=32) was 4.0 years (Min 0, Max 10), 21 (66%) were male, 25 (78%) where Caucasian.

The INSS stage at diagnosis for the majority of subjects in the FAS was Stage 4 in 27 patients (84%).

For the FAS the site of disease reported was "parenchymal metastasis" in 4 patients, "leptomeningeal metastasis" in 5 patients, "parenchymal and leptomeningeal" in 5 patients, "unadjudicated" 2 patients and "no parenchymal and leptomeningeal metastasis" in 16 patients. MYCN amplification was reported in 14 FAS subjects (46%), and MYCN gain was reported in two subjects (8%).

In line with the inclusion criteria the majority had received prior therapy for CNS/LM disease (irradiation 30 (94%), craniospinal irradiation 25 (78%), chemotherapy 29 (91%). The most frequently administered chemotherapy was temozolomide and irinotecan. 26 patients had surgery.

Many patients received additional therapy after ^{131}I-omburtamab administration. Eleven received Naxitamab, 17 received temozolomid and/or irinotecan.

- **Numbers analysed**

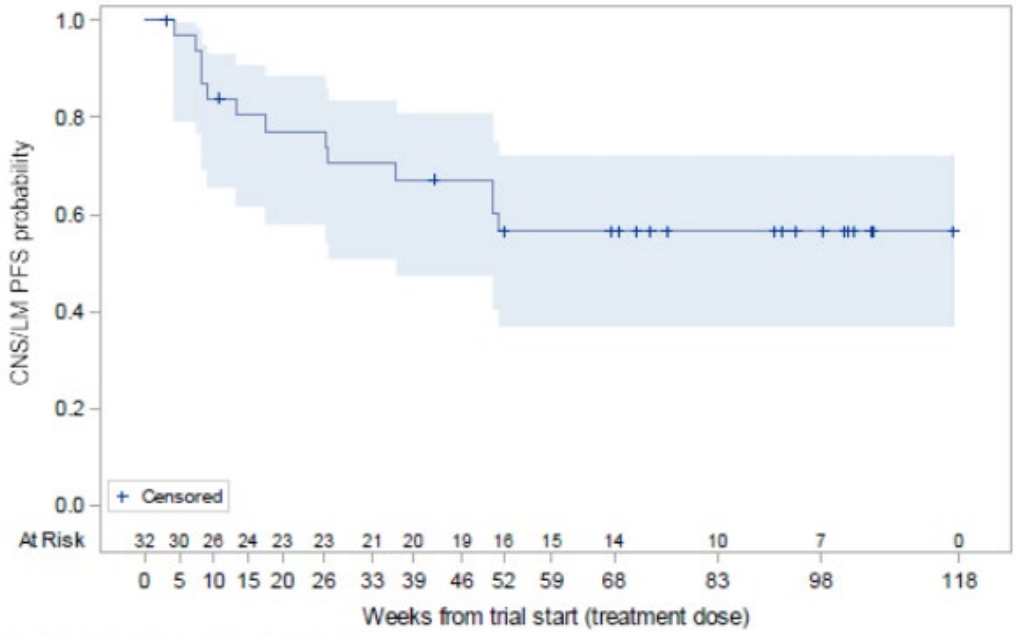
13 patients received one treatment dose, 19 patients received 2 treatment doses and no patients received more than 2 treatment doses.

- **Outcomes and estimation**

Primary endpoint: CNS/LM Progression Free Survival at 6 Month

The CNS/LM PFS rate (KM estimate) at week 26 was 0.77 (95%CL 0.58, 0.88). The following figure shows the corresponding KM plot.

Figure 8. CNS/LM Progression Free Survival Rate

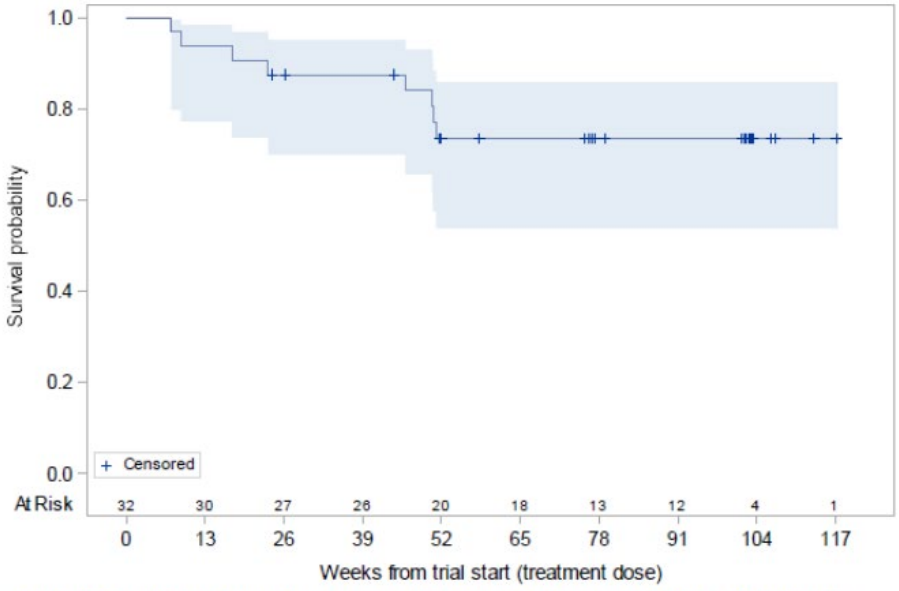


Survival curve with 95% confidence bands.
Subjects alive without progression are censored at last disease evaluation without CNS/LM progression.
Trial: 101
Program: fig_pfs.sas - output: fig_pfs.rtf - executed: 05JAN2022- Cut off date: 01JUN2021

Secondary endpoint: Overall survival at 12 months

The 12 months survival rate was 0.74 (95%CL 0.54;0.86). The following figure shows the corresponding KM-plot.

Figure 9. Overall survival



Survival curve with 95% confidence bands. Subjectss alive are censored at the date subject was last confirmed alive

Trial: 101

Program: fig_os.sas - output: fig_os.rtf - executed: 05JAN2022- Cut off date: 01JUN2021

Secondary endpoint: objective response rate at 6 months

Objective response was assessed 26 weeks after the first treatment dose of ^{131}I-omburtamab as a combination of best overall Partial Response or Complete Response. The evaluation followed the response assessment in the Neuro-Oncology (RANO) group criteria for brain metastases or in the guideline by EANO-ESMO for LM metastases.

The ORR at Week 26 was defined as the proportion of subjects with response (Complete Response or Partial Response) from the total population of subjects with radiographically evaluable disease at baseline. The following table shows details on responses.

Table 30. objective response rate

Full Analysis Set, N	32
Objective Response (CR and PR), N (%) [95% CI*]	5 (31.3) [11.0; 58.7]
Best Overall Response, N (%)	
Complete Response	3 (18.8)
Partial Response	2 (12.5)
Stable Disease	7 (43.8)
Progressive disease	3 (18.8)
Not evaluable	1 (6.3)
Total	16 (100.0)
No Evidence of Disease (N)	16
Duration of Response incl. Follow-up (Days)	
N	5
Mean (SD)	332.8 (300.80)
Median	280.0
Min – Max	37 - 715
[Mean 95% CI]	[-40.7; 706.3]

Source: Table 14.2.1.3.1

During the procedure, data were provided for all 50 patients recruited, 20 of which had evaluable disease at baseline. Overall, there were 7 patients who achieved an objective response, resulting in an ORR of 35.0% (95% CI: 15.4; 59.2) of which 5 with CR (25%) and 2 with PR (10%). Seven (7) patients achieved SD (35%), 5 PD and 1 not evaluable. Most patients with CR or PR received additional therapies after the omburtamab treatment either for systemic disease or as an experimental adjuvant treatment.

- **Summary of main efficacy results**

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

Table 31. Summary of efficacy for trial 03-133

Title: Phase I Study of Intrathecal Radioimmunotherapy using ^{131}I-omburtamab for Central Nervous System/Leptomeningeal Neoplasms		
Study identifier	Protocol number: 03-133 Clinicaltrials.gov identifier: NCT00089245 EudraCT: 2020-001590-68	
Design	Two-part, single-arm, open-label, non-randomised, single-centre. Part 1 investigated escalating doses of ^{131}I-omburtamab with the goal of identifying the maximum tolerated dose. Part 2 investigated dosing at the selected dose of 50mCi (1850 MBq) as determined in Part 1.	
	Duration of main phase:	A treatment cycle was 5 weeks, including premedication and ^{131}I-omburtamab

	Duration of Run-in phase: Duration of Extension phase:		administration (one dosimetry dose during Week 1 and one treatment dose during Week 2). A repeated cycle of treatment was initiated with a dosimetry dose at least 4 weeks after completion of the first cycle. Not applicable. Subjects were followed for assessment of Overall Survival (OS) at 3 years.
Hypothesis	Exploratory: Time-to-event endpoints were estimated by Kaplan-Meier methods and presented with corresponding 95% confidence intervals (CI)		
Treatment groups	03-133 FAS		^{131}I-omburtamab Up to two cycles (each including one dosimetry and one treatment dose). N= 107 (full analysis set, FAS).
	External controls (CGCCR)		Retrospective data collected from the Central German Childhood Cancer Registry (CGCCR) on patients with CNS neuroblastoma (N=120). Patients diagnosed in 2004 and later (N=49).
Endpoints and definitions	Primary	3 years OS	OS at 3 years after first treatment dose of ^{131}I-omburtamab.
	Secondary	12 months CNS/LM PFS	Central Nervous System/Leptomeningeal progression-free survival (CNS/LM PFS) at 12 months.
	Secondary	FU	Duration of follow-up (FU) for OS and CNS/LM PFS from first dose of ^{131}I-omburtamab.
Data cut-off	Enrolment cut-off date: 31 December 2018 Data cut-off date: 30 June 2019 12 March 2020 (survival follow-up)		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	03-133 Full Analysis Set (FAS): subjects who began an infusion of a treatment dose of ^{131}I-omburtamab. Timepoint: Not applicable.	
Descriptive statistics and estimate variability	Treatment group	03-133 FAS
	Number of subjects	107
	3 years OS (Rate) 95% CI	0.56 0.46 ; 0.65
	Median survival (months) 95% CI	50.0 27.4 ; NE *NE: Not estimable*

	12 months CNS/LM PFS (Rate) 95% CI	0.59 0.44, 0.68	
	Median CNS/LM PFS (months) 95% CI	21.8 11.3 ; 46.2	
	Median FU time (months) 95% CI Range (months)	75.0 49.3 ; 104.0 0.7–176.0	
Analysis description	**Exploratory analysis** Pre-specified exploratory analyses of OS comparing ^{131}I-omburtamab subjects with the external CGCCR control group using Cox regression models with adjustment for prognostic factors. Hazard ratio and 95% CI were estimated.		
Analysis population and time point description	- 03-133 FAS: subjects who began an infusion of a treatment dose of ^{131}I-omburtamab. - External controls (CGCCR): All patients diagnosed with CNS neuroblastoma in 2004 and later. Timepoint: Not applicable.		
Descriptive statistics and estimate variability	Treatment group	03-133 FAS	External controls (CGCCR)
	Number of subjects	107	49
	3 years OS (Rate) 95% CI	0.56 0.46 ; 0.65	0.17 0.08 ; 0,28
	Median survival (months) 95% CI	50.0 27.4 ; NE *NE: Not estimable*	9.1 3.6 ; 15.7
Effect estimate per comparison	03-133 FAS versus External controls (CGCCR)		
	Hazard ratio 95% CI	0.352 (p<0.0001) 0.228 ; 0.542	
Notes	Not applicable		

Table 32. Summary of efficacy for trial 101

Title: A Multicenter Phase 2/3 Trial of the Efficacy and Safety of Intracerebroventricular Radioimmunotherapy using ^{131}I-omburtamab for Neuroblastoma Central Nervous System/Leptomeningeal Metastases – Interim Analysis	
Study identifier	Protocol number: 101 Clinicaltrials.gov identifier: NCT03275402 EudraCT number: 2017-001828-22
Design	Single-arm, open-label, non-randomised, multi-centre.

	Subjects received up to two cycles of ^{131}I-omburtamab, each including one dosimetry dose [2 mCi =74 MBq] and one treatment dose [50 mCi = 1850 MBq].		
	Duration of main phase:		A treatment cycle was 5 weeks, including premedication and ^{131}I-omburtamab administration (one dosimetry dose during week 1 and one treatment dose during week 2), and a 3-week observation period (following the treatment dose). The subjects could receive up to two cycles.
	Duration of Run-in phase:		Not applicable.
	Duration of Extension phase:		Subjects will be followed for assessment of Overall Survival (OS) at 3 years.
Hypothesis	Exploratory: Time-to-event endpoints will be estimated by Kaplan-Meier methods and presented with corresponding 95% confidence intervals (CI).		
Treatment groups	Full Trial Population		^{131}I-omburtamab. Up to two cycles (each including one dosimetry and one treatment dose). 32 subjects (full analysis set, FAS).
Endpoints and definitions	Primary interim endpoint	6 months CNS/LM PFS	Central Nervous System/Leptomeningeal progression-free survival (CNS/LM PFS) at 6 months based on the time from first dose of ^{131}I-omburtamab to CNS/LM progression or death from any cause.
	Secondary	12 months OS	OS at 12 months after first dose of ^{131}I-omburtamab.
	Secondary	6 months ORR	6 months overall response rate (ORR) (combination of partial response and complete response) as defined by RANO group criteria for brain metastasis, or LM metastases as defined by EANO-ESMO criteria. ORR will be assessed at 6 months after the first dose of ^{131}I-omburtamab.
Data cut-off	Enrolment cut-off date:		20 October 2020
	Data cut-off date:		01 June 2021

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Full Trial population = FAS All 32 subjects enrolled who began an infusion of ^{131}I-omburtamab. Time point: Not applicable	
Descriptive statistics and estimate variability	Treatment group	Full Trial Population
	Number of subjects	32
	6 months CNS/LM PFS (Rate)	0.77
	95% CL	0.58; 0.88

	Median Follow-Up Time (weeks) 95% CI	91 69 ; 101
	12 months OS (Rate) 95% CL Median Follow-Up Time (weeks) 95% CL	0.74 0.54; 0.86 101 76 ; 103
	6 months ORR (Rate) 95% CI Median (SD) duration of response incl. Follow-up (days) Min–Max	0.31 0.11; 0.59 280 (33.23) 37-715
Notes	None	
Analysis description	**Other analyses** Not applicable	

2.2.5.3. Clinical studies in special populations

Not applicable

2.2.5.4. Supportive study(ies)

Not applicable

2.2.6. Discussion on clinical efficacy

General and methodological considerations on the clinical development plan

The demonstration of efficacy is based on data from two trials, 03-133 and 101.

Study 03-133 was a single centre, uncontrolled, exploratory "basket" trial in the US intended for dose-finding and to investigate the toxicity of intrathecal administration of iodinated omburtamab. The majority of patients had neuroblastoma with leptomeningeal/parenchymal metastases that had been pre-treated for their systemic disease as well as for their CNS disease. This trial generated the majority of the clinical data under discussion. It was initiated in 2004 and data were recorded over more than a decade. Enrolment was stopped in 2018. The analyses regarding the evaluation of efficacy in study 03-133 and its promotion to a trial for marketing authorisation purposes was introduced with amendment 25 in 2019 and is regarded as post hoc given the long history of the trial and its open-label nature. From the protocols and interim CSR of trial 03-133 it is apparent that no specific, falsifiable hypotheses were formulated. Descriptive analyses of OS and PFS were planned and comparisons to several external controls were planned post-hoc. The trial 03-133 is proposed as the main trial supporting the MAA. This cannot be accepted for the above reasons.

The 101 study is an ongoing multi-centre single-arm trial recruiting only neuroblastoma patients with LM/CNS metastasis. An interim analysis was conducted on data from patients recruited up to 01 January 2020, an update was provided during the procedure including data up to 01 June 2021 and an expansion to 32 patients. In a further update, data from 20 patients with measurable disease at baseline were

submitted. Within this application the trial is regarded as supportive by the applicant. In comparison to study 03-133, study 101 is much closer to the current treatment landscape, appears to have a much better-defined plan for the evaluation of efficacy data, and response data was systematically collected which is considered potentially important for establishing efficacy in a single arm trial. Therefore, for the purpose of efficacy assessment, study 101 is in principle better suited to provide relevant data on the effect of the medicinal product. Overall, 50 patients have now been recruited in the study, but the data is currently limited especially regarding follow-up time. The study was only planned with descriptive analyses, again no success criteria (statistical hypotheses) were pre-planned.

Both clinical trials lack an internal control and therefore the evaluation of efficacy in this complex disease with several treatment options poses challenges. To provide context for both trials and for the evaluation of efficacy several external controls were investigated. These controls were derived from a registry (Central German Childhood Cancer Registry, CGCCR), SIOPEN, literature review and single-centre experiences (at MSKCC prior to the start of the trial 03-133).

The chosen endpoints (landmark analyses of time related endpoints, e.g., 3-year OS rate, 12-month CNS/LM PFS) are not appropriate to establish efficacy in single arm trials as the characteristic of the patient population and their importance for prognosis has a major influence on outcome. On the other hand, survival rate at 3 years when a plateau has been established could provide relevant information on long term efficacy in case efficacy has been established by other means.

Considering the difficulties in interpreting time-related endpoints in single-arm trials (unless extreme results are observed) evaluating response rates is of particular interest. Although it is stated that tumour response was not an objective of study 03-133, in other parts of the protocol ORR was mentioned as an efficacy endpoint. It was clarified during the procedure that responses were not systematically assessed in Study 03-133. Study 101 investigates ORR as a secondary endpoint with an appropriate methodology.

Study conduct

Study 03-133 was initially designed as a Phase 1 trial to evaluate the MTD in a 3 + 3 design. Later, the study design was modified and the patient population to be enrolled during dose escalation was increased. Only late in the trial the sample size was justified and a comprehensive description of efficacy analyses for neuroblastoma patients was added (Amendment 25). The statistical considerations hence can be considered rather ad hoc than pre-specified given the open label nature of the study and the duration of recruitment to the dose expansion cohorts which was initiated more than two and a half years earlier. Only one SAP was drafted one year after the protocol amendment 25. In this SAP further details regarding the historic controls were provided in addition to the very limited information from the protocol. Overall, the planning of the analyses cannot be considered agnostic of the outcome of study 03-133 and are not considered sufficient for a confirmatory trial.

The reasons for the termination of dose escalation part of study 03-133 were clarified in the responses and were related to myelotoxicity which was not included in the list of expected dose-limiting toxicities for the definition of an MTD.

It is unknown how many patients were screened for inclusion in study 03-133, even at the main trial site MSKCC. During the procedure, it was clarified that the majority of patients were referred from other centres in the USA but also internationally. The screening procedure in these external centres was not defined, it is unknown how many patients were screened. The recruited study population was therefore very likely highly selected, but the selection criteria are not explicit and cannot be established in hindsight. Any attempt to find a relevant external control cohort is therefore challenging. The proposed FAS population resembles a per protocol set. Two patients were not included in the FAS population.

For study 101 it is unclear how the multiple interim analyses are justifiable in this small trial even if the data are only considered supportive.

Population

In study 03-133 the majority of patients had parenchymal metastasis. As expected, the majority had stage 4 disease and MYCN amplification. For 24 patients the stage of underlying neuroblastoma was unknown. Even though the response of the tumour to the experimental therapy was investigated with MRI the results are not reported in a systematic fashion based on pre-specified criteria which constitutes a major shortcoming. It is evident from the line listings that in some patients there was no evidence of disease after surgery/radiotherapy at the baseline MRI prior to ^{131}I-omburtamab therapy. Other patients had documented treatment response at baseline, i.e., prior treatment had already resulted in a response and the contribution of the additional therapy with ^{131}I-omburtamab is unknown. It is not clear how many patients had objective evidence of CNS/LM disease at baseline. Even though cure is unlikely in this population at least two prognostically different subgroups are contained that could also be investigated separately: patients with (measurable) disease at baseline could show response to treatment while in patients without disease at baseline, prevention of relapse would be the treatment goal.

Different doses were applied with 8 subjects receiving doses <50 mCi and 5 subjects receiving higher doses (>50 mCi). The majority of the population received a dose of 1850 MBq/50 mCi (n = 94). This complicates the interpretation of results. Furthermore, patients received either a single administration or two administrations of the study drug. The requested analysis indicated that patients who received two doses appear to have a somewhat better prognosis. The choice for the number of cycles might be influenced by a number of factors including prognostic ones.

Study 101 also included a heterogeneous population. Most but not all subjects had received chemotherapy, radiotherapy and surgery for the CNS/LM disease. Of note 16/32 patients (30 out of 50 in the updated data cut-off 31 March 2022) had no evidence of disease at baseline. More than half of the patients received additional therapies including anti-GD2 antibody and chemotherapy after they had received ^{131}I-omburtamab.

External Control

It is a particular challenge to establish with reasonable certainty that the external control population is comparable to the trial population. As a general principle, external controls in single-arm trials are only considered supportive to further explore the derived efficacy, in case efficacy was established solely based on the single-arm trial itself. This is not considered to be the case in this application.

The analysis of the CGCCR population in comparison to the population from study 03-133 give some strong indication of differences. This is related to prognosis as evidenced by the different shape of the OS KM- curves in the initial phase after diagnosis of relapse when no therapeutic effect of ^{131}I-omburtamab therapy is to be expected. In addition, it is related to the treatments that were administered for CNS relapse. As a general observation the German neuroblastoma population received less therapies compared to the trial population. Comparing the populations which had received chemotherapy, radiotherapy and surgery, and that could be considered more homogenous than the full populations, diminished the assumed treatment effect by improving the survival of the external control. These observations, in addition to the general issue of selection bias as discussed above, make it likely that populations with different prognostic factors were included in the study and the external control. During the procedure, the applicant provided new propensity score (PS) weighted analyses for the comparison of study 03-133 and the CGCCR data. These various post hoc analyses intend to improve the balance between the cohorts and have become the main argument for concluding on efficacy for this application.

Propensity score methods and similar methods can only adjust for measured confounders. Unmeasured confounder and further differences in data quality cannot be incorporated. Hence, such approaches might reduce the bias but cannot completely remove it and make results comparable to the standard from a

randomised controlled trial. Thus, standard criteria to conclude on a statistically significant result are not applicable and a higher uncertainty is expected and should be taken into account.

The propensity score weighted analyses was based on time-to-event endpoints (OS as primary EP) as was the study 03-133 and the initial comparison to the external control. The considerations on the endpoint in single arm trials with external controls hence remain valid (see below). It is acknowledged that the implemented method intended to account for some of the issues (e.g., immortal time bias) by better aligned definitions of the index date and the choice of more homogenous patient populations (based on treatment modalities, see below). However, the fundamental issue remains that patients have to survive until inclusion in the trial whereas all patients are included in the external control.

The primary PS weighted analysis is based on a post hoc selected population with *at least* two (out of three) post CNS relapse treatment modalities. The size of the group in comparison to all eligible subjects in the cohorts varies and furthermore the number of subjects in the group which were treated with more than two (i.e., all three) treatment modalities vary substantially. This might induce significant bias. While the propensity score method further tried to take this into account, it remains unclear how successful this was. Furthermore, all decisions for the propensity score method were made post hoc when trial and external control data were already available. Some choices were even made in a data driven fashion; confounders used in the propensity score model were e.g., chosen based on a maximum number of missing values (and perceived clinical relevance).

Uncertainties with respect to the choice of analysis sets and the choice and definition of confounders remain. The sample sizes in treatment modality groups (MG) presented in the new ECA analysis differ from numbers previously reported in the CSR, sometimes to a large extent. The reasons for these deviations were not discussed by the applicant and are not understood. Furthermore, the algorithm to select subjects from CGCCR is not comprehensible. In Stage 1 of the selection process only older subjects (≥ 18 months of age) were selected but with cutoff for diagnosis on 31 December 2010. More recently treated subjects were selected in Stage 2 but only subjects younger than 18 months of age were extracted. Newer data, which is more relevant as comparator, were restricted to an exceptionally young population not reflected in Trial 03-133 where the median age was 4.7 years (Range 0.85 – 13). Which subjects ended up in the finally selected 80 subjects is not clear from the flowchart. This all underlines the uncertainties with respect to the database.

Overall, the presented analyses do not overcome the issues raised. The amount of remaining bias is unknown and not quantifiable. Given the relatively small difference between cohorts it cannot be excluded that this is a result of prognostic variables, differences in the data quality or other sources of bias.

Endpoints, Efficacy results

The choice of 3-year OS rate, 12-month CNS/LM PFS rate and follow-up time in itself is not suitable to establish efficacy in a single arm setting because the prognosis of the selected population cannot be separated from a possible effect of therapy. The obtained result for 3-year OS rate and CNS/LM PFS are not interpretable on their own. It has also to be noted that there were no prior definitions for a relevant survival rate to establish an efficacious treatment. No specific hypotheses were formulated a priori, and no proposals were brought forward for an effect to be considered relevant on a population level. Because of these issues the seemingly important observed 3-year OS rate cannot be regarded as a robust sign of efficacy. It is also entirely possible that the observed survival rates are achievable with the multimodal treatment (surgery, combination of radiation therapies, chemotherapy in various combinations) that patients received in a preselected population in a highly specialised treatment centre.

Based on further statistical analyses the applicant considers that an effect is shown overall, and across treatment modality groups and subgroups. Furthermore, a propensity score based inverse probability

weighting analysis for the treatment modality group 2 is interpreted as showing superiority while prognostic factors and post-CNS relapse treatments are balanced. It is understood that modality group 2 was chosen based on the pragmatic reasons to obtain relatively homogenous population with sufficient sample size. However, neither the pre-treatment is considered sufficiently homogenous nor the sample size optimal. Furthermore, these choices were all made post hoc. These analyses are hence regarded as exploratory and hypothesis-generating and not sufficient to establish efficacy (see also discussion above).

The same considerations apply to study 101, here the issue is even more prevalent as the result CNS/LM PFS rate at 6 months or OS rate at 12 months are rather short term and generated in a very small population. In an updated report five CR were observed in 20 patients with measurable disease at baseline. Based on the characteristics of the cases (e.g., only adjudication resulted in CR in at least two cases), the overall small numbers and the fact that additional therapies were administered to most patients, in some even prior to establishment/confirmation of CR these findings are not considered a robust demonstration of efficacy.

2.2.7. Conclusions on the clinical efficacy

The design of the trials, the choice of endpoints, the conduct of the trials, the recruited population and the obtained results do not allow to establish that there is a treatment effect that is attributable to ^{131}I-omburtamab therapy. Further analyses of the existing dataset and updates on the ongoing trial have been provided but were not able to alleviate the totality of concerns.

2.2.8. Clinical safety

The safety and tolerability data for ^{131}I-omburtamab in support of this application were collected from two clinical trials, i.e., Trial 03-133 and 101.

Trial 03-133: Ongoing single-site trial conducted at Memorial Sloan Kettering Cancer Center (MSK); the applicant presents interim report data of a safety analysis based on 109 paediatric neuroblastoma subjects. Enrolment for Trial 03-133 was closed in December 2018 for patients with neuroblastoma.
Trial 03-133 was open for enrolment of patients with CNS/LM malignancies known to be omburtamab-reactive [i.e., express B7-H3 (CD276)]. The majority of patients were neuroblastoma patients, but patients with several different brain tumour types were also enrolled. The CSR is based on the paediatric (neuroblastoma and non-neuroblastoma) subjects enrolled in Trial 03-133 by 31 December 2018.
The safety data cut-off was 30 June 2019 with follow-up survival data collected through 12 March 2020. Supportive serious adverse event (SAE) data for 37 paediatric non-neuroblastoma subjects were also provided. This report focuses on results of neuroblastoma patients.

Trial 101: Ongoing, international, multisite clinical trial sponsored by Y-mAbs with enrolment cut-off for the interim analysis 01 January 2020 and safety data cut-off of 01 June 2020 compiled in an interim CSR. The trial continued enrolment after 01 January 2020. Primary clinical safety analyses were based on 24 neuroblastoma subjects. An updated interim CSR including 32 patients with cut-off 01 June 2021 was provided with the responses to the D120 LOQ. These data are added in the respective sections.

The **pooled data** (both trials) were included in the initial submission and are still included in this overview for a better comparability of the results.

Table 33. Clinical Trials Providing Subject-Level Data Used for the Safety Analysis of ^{131}I-Omburtamab

Trial	Type of Data Provided in Support of the Application	Trial Design	Treatment[a]	Subjects Providing Safety Data	Population	Trial Status/Type of Report in Application
Trial 03-133	PK Safety Efficacy	Open-label, single arm, single-centre trial, dose escalation (Part 1) and expansion (Part 2)	Part 1: • i.c.v. ^{131}I-omburtamab: Week 1 at 2 mCi (74 MBq; dosimetry dose)[b] • i.c.v. ^{131}I-omburtamab: Week 2 at 10-80[c] mCi (370 – 2960 MBq; treatment dose) Part 2: • i.c.v. ^{131}I-omburtamab: Week 1 and 6 at 2 mCi (74 MBq; dosimetry dose)[b] • i.c.v. ^{131}I-omburtamab: Week 2 and 7 at 50 mCi (1850 MBq; treatment dose)[e]	Safety: 146 - 109 paediatric neuroblastoma subjects - 37 paediatric non-neuroblastoma subjects	Subjects with a histologically confirmed diagnosis of an omburtamab-reactive malignancy with CNS/LM disease	Ongoing/Interim CSR[d]
Trial 101	PK Safety Efficacy	Open-label, single arm, multicentre trial	• i.c.v. ^{131}I-omburtamab: Week 1 and 6 at 2 mCi (74 MBq; dosimetry dose) • i.c.v. ^{131}I-omburtamab: Week 2 and 7 at 50 mCi (1850 MBq; treatment dose)[e]	Safety: 24	Paediatric NB subjects with CNS/LM metastasis	Ongoing/Interim CSR[f]

CNS=central nervous system; CSR=clinical study report; i.c.v.=intracerebroventricular; LM=leptomeningeal; MSK=Memorial Sloan Kettering Cancer Center; NB=neuroblastoma; PK=pharmacokinetics; Y-mAbs=Y-mAbs Therapeutics, Inc.

a In Trial 03-133 (Part 1 and Part 2) and Trial 101, subjects were administered two cycles of i.c.v. ^{131}I-omburtamab (if tolerated and no progressive disease between the cycles).

b ^{124}I-omburtamab was administered for the dosimetry dose for some subjects. ^{131}I-omburtamab was administered for all treatment doses.

c The highest treatment dose level administered to any subject in Trial 03-133 was 80 mCi (2960 MBq); the highest treatment dose level administered to a neuroblastoma subject was 70 mCi (2590 MBq).

d Enrolment of NB subjects closed December 2018. The data cut-off for neuroblastoma subjects was 30 June 2019 for EU MAA. As per the protocol, follow-up for all subjects is ongoing. Although the CSR for 03-133 indicates that it is an interim report, this CSR is actually the final report with respect to data being included in the MAA. The CSR for Trial 03-133 includes a full assessment of safety and efficacy data collected for paediatric patients with neuroblastoma enrolled by 31 December 2018; safety data are presented as of a cut-off of 30 June 2019 with follow-up survival data collected through 12 March 2020 (CSR 03-133 Section 7.0). Pharmacokinetic (PK) and dosimetry data are also presented for the paediatric neuroblastoma patients dosed in the trial in years 2016-2018, inclusive. This report also includes serious adverse events (SAEs) from paediatric non-neuroblastoma subjects.

e Treatment doses were reduced by 50% for subjects less than 1 year of age, and by 33% for subjects between 1 and 3 years of age.

f Safety data cut-off was 01 June 2020 for this SCS.

2.2.8.1. Patient exposure

Subject Disposition and exposure to trial medication

Trial 03-133

As of 31 December 2018, there were 109 neuroblastoma subjects and 37 paediatric non-neuroblastoma subjects enrolled in Trial 03-133. Of the 109 neuroblastoma subjects, two subjects had an International Neuroblastoma Pathology Classification (INPC) classification of ganglioneuroblastoma and a sub-histology of ganglioneuroblastoma at diagnosis of systemic disease. However, both subjects had a sub-histology of neuroblastoma at the time of CNS/LM relapse.

Table 34. Summary of Radiolabelled Omburtamab Administration for Subjects in the Safety Analysis Set

	Statistic/ Category	<50 mCi (N=10)	50 mCi (N=94)	>50 mCi (N=5)	All Subjects (N=109)
Total actual dosage (mCi)	n	10	94	5	109
	Mean	43.685	75.032	71.324	71.986
	SD	28.4526	30.3896	18.5296	30.9466
	Median	44.235	69.935	61.750	65.500
	Q1, Q3	25.610, 67.430	52.890, 103.040	60.620, 71.930	52.450, 102.190
	Min, Max	1.87, 84.79	28.35, 218.33	59.10, 103.22	1.87, 218.33
No. of dosimetry doses [n (%)]	1	3 (30.0)	41 (43.6)	4 (80.0)	48 (44.0)
	2	6 (60.0)	51 (54.3)	1 (20.0)	58 (53.2)
	3	1 (10.0)	1 (1.1)	0	2 (1.8)
	4	0	1 (1.1)	0	1 (0.9)
No. of treatment doses [n (%)]	1	1 (10.0)	45 (47.9)	4 (80.0)	50 (45.9)
	2	7 (70.0)	47 (50.0)	1 (20.0)	55 (50.5)
	3	0	1 (1.1)	0	1 (0.9)
	4	0	1 (1.1)	0	1 (0.9)
Total actual treatment dosage (mCi)	N	8	94	5	107
	Mean	50.058	71.835	69.094	70.079
	SD	20.7407	29.4340	17.4617	28.8627
	Median	51.250	66.040	60.090	61.980
	Q1, Q3	34.825, 63.950	50.700, 98.910	59.030, 70.000	50.410, 98.410
	Min, Max	19.30, 81.11	26.30, 210.78	57.30, 99.05	19.30, 210.78

Source: Table 14.1.8.1.
Note: For subjects under 3 years of age, dose groups were assigned based on the treatment dose before age adjustment (i.e., 33% or 50% dose reduction).
SD = standard deviation; Min = minimum, Max = maximum.

All 109 enrolled neuroblastoma subjects are included in the SAF. Most subjects were in the 50 mCi group (94 subjects [86.2%]). 28 SAF subjects were documented as having discontinued treatment due to an intervening circumstance. For the SAF, progressive disease (12 subjects [11.0%]) and Other (11 subjects [10.1%]) accounted for the highest number of reasons for discontinuing treatment. 4 SAF subjects (3.7%) discontinued treatment due to excessive toxicity. The Other reasons were low platelets with or without low neutrophils (6 subjects [5.5%]), medical events that required treatment cessation (3 subjects [2.8%]), or investigator discretion for other treatments (2 subjects [1.8%]).
The majority of non-neuroblastoma analysis set (NNAS) subjects received a 50 mCi treatment dose (23 subjects [62.2%]. Of the 37 NNAS subjects, 13 were categorised in the clinical database as having completed treatment as of the data cut-off date. Progressive disease (11 subjects [29.7%]) was the most frequently documented reason for discontinuing treatment. One subject (2.7%) ended treatment due to excessive toxicity, and one subject (2.7%) ended treatment due to a reason in the category of "Other".

Trial 101
A total of 36 subjects were screened and enrolled in this ongoing trial from end-November 2018 to the enrolment cut-off date for this interim analysis, 20-Oct-2020. Three subjects failed screening and one subject was withdrawn by the physician before receiving any treatment. A total of 32 subjects were included in the full analysis set.

Of the eight deaths reported in the trial, one AE leading to death was reported (intracranial haemorrhage, received one treatment cycle). The remaining seven deaths were due to disease progression (4 Subjects received one treatment cycle. 3 Subjects received two treatment cycles). A total of 13 subjects discontinued treatment: ten due to AEs, two due to disease progression and one as a result of parents deciding to seek other treatment.

The subject disposition is summarised in Table 35.

Table 35. Subject Disposition

Disposition	N (%)
Screened subjects	36
Screening failures	3
Withdrawn before treatment	1
Eligible subjects included	32 (100)
Full analysis set	32 (100)
Safety analysis set	32 (100)
End of trial status	
Ended participation	9 (28.1)
Ongoing	23 (71.9)
Reason for end of trial participation	
Death	8 (88.9)
Withdrawal by parent/guardian	1 (11.1)
Discontinued treatment	13 (40.6)
Reason for discontinued treatment	
Adverse event	10 (76.9)
Other	1 (7.7)
Progressive disease	2 (15.4)

Source: Table 14.1.1.1 and Appendix 16.2.1.2.
N: Number of subjects; %: Percentage of subjects.
Other: refers to parents decided to pursue other possibilities for the subject and parents decided to seek other treatment, no formal withdrawal of consent.

Exposure by total number of ^{131}I-omburtamab infusions and number of cycles is presented for Trial 101 in Table 36. A total of 26 subjects were administered the full treatment dose of 50 mCi, whereas the remaining six subjects were administered a reduced treatment dose as they were below 3 years of age. A total of 92 infusions were administered up until the data cut-off date for this interim analysis.

Table 36. Exposure to ^{131}I-Omburtamab by Total Number of IMP Infusions and Number of Cycles (Safety Analysis Set)

	^{131}I-omburtamab N (%)
Dosimetry infusions	
1	11 (34.4)
2	15 (46.9)
Treatment infusions	
1	13 (40.6)
2	19 (59.4)
Number of Cycles[a]	
1	12 (37.5)
2	20 (62.5)
Total dosimetry exposure (mCi)	
N	26
Mean (SD)	3.27 (1.054)
Median	3.85
Min – Max	1.8 – 4.4
Total exposure (mCi)	
N	32
Mean (SD)	74.00 (25.220)
Median	69.45
Min – Max	31.7 – 107.5

Source: Table 14.1.4.1, Appendix 16.2.5.1
IMP= investigational medicinal product, N=number of subjects; % = percentage of treated subjects; SD = standard deviation.
[a] The number of cycles is calculated by initiated cycle.

Demographics and Other Characteristics of Study Population

Demographics

Trial 03-133

More subjects (72/109; 66.1%) were male. The median age of subjects was 4.74 years with a range of 1 to 15 years. The median weight of subjects was 15.10 kg, ranging from 6.9 to 71 kg. The majority of the subjects were White (86/109; 78.9%). The remaining subjects were Black/African American (9/109; 8.3%), Asian/Far East Indian Subcontinent (3/109; 2.8%), Unknown (6/109; 5.5%). The majority of the subjects were not Hispanic or Latino (79/109; 72.5%).

As with the Trial 03-133 SAF, the majority of subjects in the NNAS were White males and the majority were not Hispanic or Latino. Subjects in the NNAS were older and weighed more than those in the SAF with a median age of 8.42 years (mean age of 8.33 years) and a median weight of 24.45 kg, ranging from 11.1 to 78.2 kg. Most of the paediatric non-neuroblastoma subjects received ^{131}I-omburtamab for CNS cancer (31/37; 83.8%), with the remaining subjects receiving ^{131}I-omburtamab for sarcoma (3/37; 8.1%), retinoblastoma (2/37; 5.4%), and melanoma (1/37; 2.7%).

Trial 101

Of the 32 treated subjects, 21 were male (65.6%), and 11 were female (34.4%). At baseline, the mean and median age of subjects were 4.5 and 4.0 years, respectively. The majority of subjects included in the trial were 'White' (78.1%) followed by 'Asian' (15.6%). Subjects were recruited from four U.S. sites (MSK [New York, NY], Nationwide Children's Hospital [Columbus, OH], Riley Hospital for Children [Indianapolis, IN] and MD Anderson Cancer Center [Houston, TX]) that treated 26 subjects and one site in Spain (Hospital Sant Joan de Déu, Barcelona) that treated 6 subjects.

Baseline Subject and Disease Characteristics

Trial 03-133

The median age at neuroblastoma diagnosis for subjects in Trial 03-133 was 2.387 years with a range of 0.02 to 13.53 years. A total of 86 of 109 (78.9%) subjects were older than 18 months. The International Neuroblastoma Staging System (INSS) stage at diagnosis for the majority of subjects was Stage 4 (79/109; 72.5%). The site of disease reported most often was unifocal parenchymal site (52/109; 47.7%). MYCN amplification was reported for 55 of 109 (50.5%) subjects, and v-myc myelocytomatosis viral related oncogene (MYCN) gain was reported in two of 109 (1.8%) subjects. The tumour subtype for about half of the subjects was neuroblastoma poorly differentiated (56/109; 51.4%). For subjects in the NNAS, MYCN amplification was reported in one subject in the <50 mCi treatment group. INSS stage at diagnosis was not reported for any subject. Similar to the SAF in Trial 03-133, most subjects (94.6%) in the NNAS had prior radiation therapy. Thirty-four (91.9%) subjects had prior surgery and 34 (91.9%) subjects had prior chemotherapy.

Trial 101

The median age at neuroblastoma diagnosis for subjects in Trial 101 was 2.77 years with a range of 0 to 9 years. Most subjects (27/32; 84.4%) were INSS Stage 4 at diagnosis. MYCN amplification was reported for 14/32 (43.8%) and MYCN gain was reported in two of 32 (6.3%) subjects. Neither gain nor amplification was reported for the remaining 15 subjects. International Neuroblastoma Pathology Classification was reported for 25 subjects. A common tumour subtype for subjects was neuroblastoma poorly differentiated (13/32; 40.6%). The median time from neuroblastoma diagnosis to first relapse was 544 days, ranging from 65 to 1534 days. The median time from CNS/LM relapse until treatment with ^{131}I-omburtamab was 146 days, ranging from 70 to 513 days.

Prior and Concomitant Treatments

All Prior Treatments for Neuroblastoma

Trial 03-133

Exposure to all prior treatments with surgery, autologous stem cell transplantation (ASCT), and radiation for neuroblastoma for Trial 03-133 subjects are presented in Table 37.

Table 37. Summary of Other Prior Treatments for Study Disease in the Safety Analysis Set of Trial 03-133

Other Prior Treatments	Statistic/ Category	<50 mCi (N=10) [n(%)]	50 mCi (N=94) [n(%)]	>50 mCi (N=5) [n(%)]	All Subjects (N=109) [n(%)]
Any Prior Surgery?	Yes	10 (100.0)	94 (100.0)	5 (100.0)	109 (100.0)
Type of Surgery	Curative	2 (20.0)	3 (3.2)	0	5 (4.6)
	Palliative	0	3 (3.2)	0	3 (2.8)
	Not Reported	9 (90.0)	94 (100.0)	5 (100.0)	108 (99.1)
Any Prior ASCT?	Yes	8 (80.0)	68 (72.3)	4 (80.0)	80 (73.4)
Type of ASCT	Single	1 (10.0)	18 (19.1)	0	19 (17.4)
	Tandem	1 (10.0)	4 (4.3)	0	5 (4.6)
	Not Reported	6 (60.0)	53 (56.4)	4 (80.0)	63 (57.8)
Any Prior Radiation?	Yes	10 (100.0)	89 (94.7)	5 (100.0)	104 (95.4)

Source: CSR 03-133 Table 14.1.6.1.
ASCT=autologous stem cell transplantation.
Note: 50 mCi=1850 MBq.

While all Trial 03-133 subjects (N=109) underwent surgery as a prior treatment of neuroblastoma, 80 of 109 subjects (73.4%) had ASCT and 104 of 109 (95.4%) were exposed to radiation. Of the surgery types reported, 5 of 109 (4.6%) subjects underwent curative surgery and 19 of 109 (17.4%) had single ASCT. All subjects (109/109; 100.0%) had received antineoplastic and/or immunomodulating agents.

Trial 101

All subjects had received multiple types of treatment for NB prior to the treatment with ^{131}I-omburtamab. All subjects received prior chemotherapy (combination treatment: 32 subjects; single agent treatment: 10 subjects). Chemotherapy was for most subjects administered in 1-2 cycles, but a few subjects received up to 13 cycles of treatment.

A total of 22 subjects received immunotherapy. Most subjects (15 subjects) received autologous stem cell transplant (ASCT). The majority of subjects (31 subjects) received radiation therapy. A total of 30 subjects had 57 previous surgeries performed, with the majority being curative surgery (38 surgeries in 22 subjects).

Prior Treatments for Neuroblastoma: Period between CNS/LM Relapse and before ^{131}I-omburtamab Administration

Trial 03-133

The subset of the prior treatments (i.e., radiation therapy, surgery, and autologous stem cell transplantation [ASCT]) for neuroblastoma reported for the period between CNS/LM relapse and before ^{131}I-omburtamab administration for SAF subjects is summarised in Table 46.

Most subjects received radiation therapy (99/109; 90.8%), a majority of subjects had surgery (84/109; 77.1%), and a minority of subjects had ASCT (23/109; 21.1%) during this period. The vast majority of

subjects received chemotherapy during this period, 103 (94.5%) subjects received antineoplastic and/or immunomodulating agents.

Table 38. Summary of Other Prior Treatments for Neuroblastoma Between CNS/LM Relapse and ^{131}I-omburtamab Administration for Safety Analysis Set of Trial 03-133

		<50 mCi (N=10) [n(%)]	50 mCi (N=94) [n(%)]	>50 mCi (N=5) [n(%)]	All Subjects (N=109) [n(%)]
Any Prior Surgery?	Yes	5 (50.0)	76 (80.9)	3 (60.0)	84 (77.1)
Type of Surgery	Curative	2 (20.0)	2 (2.1)	0	4 (3.7)
	Palliative	0	2 (2.1)	0	2 (1.8)
	Not Reported	3 (30.0)	74 (78.7)	3 (60.0)	80 (73.4)
Any Prior ASCT?	Yes	3 (30.0)	18 (19.1)	2 (40.0)	23 (21.1)
Type of ASCT	Single	1 (10.0)	11 (11.7)	0	12 (11.0)
	Tandem	0	1 (1.1)	0	1 (0.9)
	Not Reported	2 (20.0)	6 (6.4)	2 (40.0)	10 (9.2)
Any Prior Radiation?	Yes	9 (90.0)	85 (90.4)	5 (100.0)	99 (90.8)
Total Radiation Dose (Gy)	n	9	84	5	98
	Mean	16.200	19.891	22.280	19.674
	SD	8.4427	38.2372	23.8108	35.8026
	Median	21.600	18.000	21.600	18.000
	Q1, Q3	10.800, 21.600	1.800, 21.600	2.000, 26.000	1.800, 21.600
	Min, Max	1.80, 21.60	1.20, 300.00	1.80, 60.00	1.20, 300.00

Source: CSR 03-133 Table 14.1.6.3
ASCT= autologous stem cell transplantation; Max=maximum; Min=minimum; n=number of subjects; SD=standard deviation
Note: 50 mCi=1850 MBq.
Note: Multiple responses are possible.

Trial 101

All subjects had received multiple types of treatment for neuroblastoma prior to the treatment with ^{131}I-omburtamab. Most subjects received chemotherapy, radiation therapy, and surgery in the period between CNS/LM relapse and before entering the screening period (i.e., before ^{131}I-omburtamab administration).

Chemotherapy was administered to 29 subjects (90.6%) (Table 39). A total of 30 subjects (93.8%) received radiation therapy during this period, and of these, 25 subjects received craniospinal irradiation (CSI). Surgery was performed in 26 subjects (81.3%).

Table 39. Prior Treatments (Chemotherapy, irradiation and surgery) for Target Indication Between CNS/LM Relapse and ^{131}I-Omburtamab Administration.

	^{131}I-omburtamab N (%)
Full analysis set (N)	32
Prior chemotherapy between CNS/LM relapse and ^{131}I-omburtamab administration	
No	3 (9.4)
Yes	29 (90.6)
Prior irradiation between CNS/LM relapse and ^{131}I-omburtamab administration	
No	2 (6.3)
Yes	30 (93.8)
CSI between CNS/LM relapse and ^{131}I-omburtamab administration	
No	7 (21.9)
Yes	25 (78.1)
Prior surgery between CNS/LM relapse and ^{131}I-omburtamab administration	
No	6 (18.8)
Yes	26 (81.3)

Source: Table 14.1.2.2 and Table 16.2.4.6
N = Number of subjects; % = Percentage of subjects; CSI = craniospinal irradiation

2.2.8.2. Adverse events

Trial 03-133

TEAEs were reported in 102/109 (93.6%) subjects and 97/109 subjects (89.0%) reported at least one related TEAE, as judged by the investigator (Table 48). 89/109 subjects (81.7%) reported at least one related TEAE of Grade 3 or greater. SAEs were reported in 53/109 (48.6%) subjects, with 35/109 (32.1%) subjects reporting at least one related SAE. TEAEs leading to drug discontinuation were reported for 11/109 subjects (10.1%). No TEAEs resulted in death.

Table 40. Overview of Treatment-emergent Adverse Events in the Safety Analysis Set of Trial 03-133

Parameter	<50 mCi (N=10) [n(%)]	50 mCi (N=94) [n(%)]	>50 mCi (N=5) [n(%)]	All Subjects (N=109) [n(%)]
Subjects with at least one TEAE	10 (100.0)	87 (92.6)	5 (100.0)	102 (93.6)
Subjects with at least one related TEAE	9 (90.0)	83 (88.3)	5 (100.0)	97 (89.0)
Subjects with at least one TEAE of Grade 3 or Greater	9 (90.0)	78 (83.0)	5 (100.0)	92 (84.4)
Subjects with at least one related TEAE of Grade 3 or Greater	8 (80.0)	76 (80.9)	5 (100.0)	89 (81.7)
Subjects with at least one TEAE leading to discontinuation of study treatment	2 (20.0)	7 (7.4)	2 (40.0)	11 (10.1)
Subjects with TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with at least one SAE	6 (60.0)	46 (48.9)	1 (20.0)	53 (48.6)
Subjects with at least one related SAE	2 (20.0)	32 (34.0)	1 (20.0)	35 (32.1)

Source: CSR 03-133 Table 14.3.1.1, Table 14.3.1.32, Table 14.3.1.33.
SAE=serious adverse events; TEAE=treatment-emergent adverse events.
Note: 50 mCi=1850 MBq.
Note: Safety Analysis Set consists of all neuroblastoma subjects who began an infusion of any dose of ^{131}I-omburtamab.
Note: For subjects under 3 years and 1 year of age, dose groups were assigned based on the treatment dose before age adjustment (i.e., 33% or 50% dose reduction).

Trial 101

All subjects reported at least one TEAE, with most events (253/269; 94%) being non-serious and the majority were CTCAE Grade 1 or 2 (204/269; 76%; see Table 41). 156/269 TEAEs (58%) were assessed as related, probably, or possibly related to treatment by the investigator.

16 SAEs were reported in 10/24 (41.7%) subjects; 15/16 SAEs were determined by the investigator to be at least possibly related. Eleven TEAEs leading to drug discontinuation were reported for 8/24 (33.3%) subjects. One TEAE resulted in death. The majority of reported TEAEs had the outcome recovered/resolved (237/269; 88%). There were 28 unresolved cases as of the data cut-off date for this interim report. Unresolved cases of Grade 3 and above included platelet count decreased/thrombocytopenia, WBC count decreased/leukopenia, and lymphocyte count decreased/lymphopenia.

Table 41. Overview of Treatment-emergent Adverse Events in the Safety Analysis Set of Trial 101

Overall TEAEs	^{131}I-omburtamab N (%) E
Safety Analysis Set (N)	24
TEAEs	24 (100.0) 269
Serious TEAEs	10 (41.7) 16
Nonserious TEAEs	23 (95.8) 253
Fatal TEAEs	1 (4.2) 1
Related TEAEs	24 (100.0) 156
TEAEs Leading to Discontinuation of ^{131}I-omburtamab	8 (33.3) 11
Toxicity Grade of TEAEs	
Grade 1	22 (91.7) 134
Grade 2	19 (79.2) 70
Grade 3	20 (83.3) 48
Grade 4	11 (45.8) 16
Grade 5	1 (4.2) 1
Outcome of TEAEs	
Not recovered/not resolved	12 (50.0) 28
Fatal	1 (4.2) 1
Recovered/resolved	23 (95.8) 237
Not reported	1 (4.2) 1
Recovered/resolved with sequelae	2 (8.3) 2

Source: CSR 101 Table 14.3.1.1 and Appendix 16.2.7.1.

N=Number of subjects experiencing the event at least once; E=Total number of reports of the event, TEAE=Treatment-emergent AE. A treatment-emergent adverse event is defined as an AE with onset at or after administration of infusion of ^{131}I-omburtamab. Related AEs: Events with drug relationship Related, Possibly related or Probably related. SAEs are reported until 3 weeks after last IMP administration. For SAEs occurring later than 3 weeks after last IMP treatment only events related to the trial drug are reported, hence some fatal events are not reported as SAEs.

The interim analysis with cut-off date of 01-Jun-2020 provided similar results, see Table 42.

Table 42. Overall Treatment-Emergent Adverse Events

Overall TEAEs	^{131}I-omburtamab N (%) E
Safety Analysis Set (N)	32
AEs in post-treatment follow-up period	14 (43.8) 92
TEAEs[a]	31 (96.9) 239
Serious TEAEs	13 (40.6) 19
Nonserious TEAEs	29 (90.6) 220
Fatal TEAEs	1 (3.1) 1
Related TEAEs	30 (93.8) 179
TEAEs Leading to Discontinuation of Drug	6 (18.8) 7
TEAEs Leading to Discontinuation of Study	1 (3.1) 1
Toxicity Grade of TEAEs	
Grade 1	26 (81.3) 132
Grade 2	21 (65.6) 41
Grade 3	23 (71.9) 51
Grade 4	11 (34.4) 14
Grade 5	1 (3.1) 1
Relationship of TEAEs	
Related	3 (9.4) 7
Probably related	20 (62.5) 74
Possibly related	25 (78.1) 98
Not related (unlikely)	10 (31.3) 15
Not related	17 (53.1) 45
Outcome of TEAEs	
Recovered/resolved	30 (93.8) 210
Recovered/resolved with sequelae	4 (12.5) 5
Not recovered/resolved	12 (37.5) 23
Fatal	1 (3.1) 1

Source: Table 14.3.1.1 and Appendix 16.2.7.1.
N: Number of subjects experiencing the event at least once; E: Total number of reports of the event; TEAE: Treatment emergent adverse event. A treatment emergent adverse event is defined as an AE with onset at or after administration of infusion of ^{131}I-omburtamab. Related AEs: Events with drug relationship Related, Possibly related or Probably related. All SAEs are reported until 3 weeks after last investigational medicinal product (IMP) administration. For SAEs occurring later than 3 weeks after last IMP treatment only events related to the trial drug are reported, hence some deaths are not reported as SAEs. AEs in post-treatment follow up period equals non-serious adverse events that occur more than 21+2 days after last treatment
[a] does not include non-serious AEs in post-treatment follow-up period

All Treatment-Emergent Adverse Events

A summary of TEAEs by preferred term (PT) reported for at least 5% of subjects in Trial 03-133 is presented in Table 43.

Table 43. Summary Treatment-Emergent Adverse Events Reported for at Least 5% of Subject in the Safety Analysis Set of Trial 03-133

System Organ Class Preferred Term	<50 mCi (N=10) [n(%)], #events	50 mCi (N=94) [n(%)], #events	>50 mCi (N=5) [n(%)], #events	All Subjects (N=109) [n(%)], #events
Number of TEAEs	213	1496	53	1762
Subjects with at least one TEAE	10 (100), 213	87 (92.6), 1496	5 (100), 53	102 (93.6), 1762
Blood and lymphatic system disorders	**8 (80.0), 57**	**60 (63.8), 387**	**4 (80.0), 10**	**72 (66.1), 454**
Lymphopenia	7 (70.0), 56	59 (62.8), 385	4 (80.0), 10	70 (64.2), 451
Cardiac disorders	**1 (10.0), 1**	**7 (7.4), 7**	**0**	**8 (7.3), 8**
Sinus tachycardia	1 (10.0), 1	7 (7.4), 7	0	8 (7.3), 8
Gastrointestinal disorders	**8 (80.0), 22**	**47 (50.0), 117**	**5 (100), 7**	**60 (55.0), 146**
Vomiting	5 (50.0), 8	31 (33.0), 53	2 (40.0), 3	38 (34.9), 64
Diarrhoea	1 (10.0), 1	17 (18.1), 28	0	18 (16.5), 29
Abdominal pain	1 (10.0), 2	10 (10.6), 11	1 (20.0), 1	12 (11.0), 14
Nausea	3 (30.0), 4	8 (8.5), 8	1 (20.0), 1	12 (11.0), 13
Abdominal pain upper	2 (20.0), 2	5 (5.3), 5	0	7 (6.4), 7
General disorders and administration site conditions	**4 (40.0), 8**	**22 (23.4), 40**	**2 (40.0), 4**	**28 (25.7), 52**
Pyrexia	2 (20.0), 4	13 (13.8), 13	0	15 (13.8), 17
Fatigue	0	5 (5.3), 7	1 (20.0), 1	6 (5.5), 8
Injury, poisoning and procedural complications	**2 (20.0), 3**	**23 (24.5), 32**	**3 (60.0), 3**	**28 (25.7), 38**
Contusion	2 (20.0), 3	18 (19.1), 24	3 (60.0), 3	23 (21.1), 30
Investigations	**8 (80.0), 90**	**65 (69.1), 669**	**5 (100), 13**	**78 (71.6), 772**
Platelet count decreased	7 (70.0), 48	49 (52.1), 243	3 (60.0), 5	59 (54.1), 296
White blood cell count decreased	5 (50.0), 23	44 (46.8), 196	2 (40.0), 4	51 (46.8), 223
Neutrophil count decreased	4 (40.0), 11	41 (43.6), 143	2 (40.0), 3	47 (43.1), 157
Haemoglobin decreased	2 (20.0), 2	30 (31.9), 78	1 (20.0), 1	33 (30.3), 81
Alanine aminotransferase increased	3 (30.0), 5	4 (4.3), 6	0	7 (6.4), 11
Metabolism and nutrition disorders	**2 (20.0), 2**	**24 (25.5), 28**	**1 (20.0), 1**	**27 (24.8), 31**
Decreased appetite	2 (20.0), 2	13 (13.8), 13	1 (20.0), 1	16 (14.7), 16
Musculoskeletal and connective tissue disorders	**4 (40.0), 5**	**13 (13.8), 19**	**0**	**17 (15.6), 24**
Pain in extremity	2 (20.0), 2	8 (8.5), 9	0	10 (9.2), 11
Nervous system disorders	**7 (70.0), 8**	**28 (29.8), 49**	**1 (20.0), 3**	**36 (33.0), 60**
Headache	6 (60.0), 6	20 (21.3), 29	1 (20.0), 3	27 (24.8), 38
Psychiatric disorders	**1 (10.0), 1**	**13 (13.8), 20**	**1 (20.0), 1**	**15 (13.8), 22**
Irritability	0	7 (7.4), 9	1 (20.0), 1	8 (7.3), 10
Respiratory, thoracic and mediastinal disorders	**4 (40.0), 8**	**35 (37.2), 57**	**2 (40.0), 4**	**41 (37.6), 69**
Cough	3 (30.0), 4	25 (26.6), 26	1 (20.0), 1	29 (26.6), 31
Rhinorrhoea	1 (10.0), 1	15 (16.0), 16	2 (40.0), 2	18 (16.5), 19
Skin and subcutaneous tissue disorders	**3 (30.0), 5**	**17 (18.1), 27**	**2 (40.0), 4**	**22 (20.2), 36**
Petechiae	1 (10.0), 2	5 (5.3), 5	1 (20.0), 1	7 (6.4), 8

Source: CSR 03-133 Table 14.3.1.2.
TEAEs=treatment-emergent adverse events.
Note: 50 mCi=1850 MBq.
Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects who reported at least one AE in that SOC or PT. Subjects reported more than one AE in a given SOC or PT were counted only once for that particular SOC or PT.
Note: For subjects under 3 years and 1 year of age, dose groups were assigned based on the treatment dose before age adjustment (i.e., 33% or 50% dose reduction).

More TEAEs were reported for the Investigations SOC than any other SOC. Within the Investigations SOC, 772/1762 (43.8%) events were reported for 78/109 (71.6%) subjects. Within the Blood and lymphatic system disorders SOC, 454/1762 (25.8%) events were reported for 72/109 (66.1%) subjects. Commonly reported TEAEs by preferred term (PT) were lymphopenia (451 events for 70 of 109 (64.2%) subjects), platelet count decreased (296 events for 59/109 (54.1% subjects), and WBC count decreased (223 events for 51/109 (46.8%) subjects). WBC count decrease and platelet count decrease are

consistent with myelosuppression. Myelosuppression was anticipated to be a significant risk resulting from exposure to radiation and ^{131}I-omburtamab (Kramer et al, 2010).

Trial 101

A summary of TEAEs by PT reported for at least 5% of subjects (three or more subjects) in Trial 101 is presented in Table 44:

Table 44. Treatment-Emergent Adverse Events Reported by at Least 5% of Subjects

System Organ Class Preferred Term	^{131}I-omburtamab N (%) E
Safety Analysis Set (N)	32
Any adverse event ≥ 5% on preferred term level	31 (96.9) 191
Investigations	
Platelet count decreased	17 (53.1) 20
White blood cell count decreased	13 (40.6) 18
Lymphocyte count decreased	12 (37.5) 13
Neutrophil count decreased	10 (31.3) 24
Gastrointestinal Disorders	
Nausea	11 (34.4) 12
Vomiting	8 (25.0) 11
Abdominal pain	2 (6.3) 2
Respiratory, Thoracic and Mediastinal Disorders	
Cough	6 (18.8) 6
Nasal congestion	4 (12.5) 4
Epistaxis	2 (6.3) 4
Nervous System Disorders	
Headache	8 (25.0) 12
Haemorrhage intracranial	3 (9.4) 3
Neuralgia	2 (6.3) 5
Blood and Lymphatic System Disorders	
Anaemia	10 (31.3) 13
Metabolism and Nutrition Disorders	
Decreased appetite	5 (15.6) 5
Hyperglycaemia	2 (6.3) 2
Hypokalaemia	2 (6.3) 2
General disorders and administration site conditions	
Fatigue	3 (9.4) 3
Pain	3 (9.4) 3
Pyrexia	2 (6.3) 3
Skin and subcutaneous tissue disorders	
Rash	2 (6.3) 3
Dermatitis acneiform	2 (6.3) 2
Dry skin	2 (6.3) 2
Rash maculo-papular	2 (6.3) 2
Injury, poisoning and procedural complications	
Contusion	3 (9.4) 3
Meningitis chemical	2 (6.3) 2
Vascular disorders	
Haematoma	3 (9.4) 4
Endocrine disorders	
Hypothyroidism	2 (6.3) 3
Infections and infestations	
Nasopharyngitis	2 (6.3) 3
Musculoskeletal and connective tissue disorders	
Pain in extremity	2 (6.3) 2

Source: Table 14.3.1.15 and Appendix 16.2.7.1.

Overall, 31/32 patients experienced any adverse event (96.9%). The most frequently reported SOC was Investigations, and the most common TEAEs by preferred term were platelet count decreased (17/32, 53.1%), white blood cell count decreased (13/32, 40.6%), and lymphocyte count decreased (12/32, 37.5%). One case of infection (sepsis) was reported as Grade 4, serious and not related to study drug (resolved). A total of 3/32 (9.4%) subjects experienced 3 events of intracranial

hemorrhage. The events were serious and of Grade 3, 4 and 5, respectively (possibly related to the study drug by the sponsor). One of the events was fatal.

Pooled Trial 03-133 and Trial 101

The most common TEAE were compatible with myelosuppression and anticipated given exposure to radiation and ^{131}I-omburtamab. Radiation exposure and treatment with cytotoxic drugs before trial initiation may confound the assessments of events such as myelosuppression as they may also promote the development of prolonged cytopenia following myelosuppression.

Treatment-Emergent Adverse Events by Intensity – Grade 3 and 4 TEAEs

Trial 03-133
92/109 (84.4%) subjects reported a total of 1220 TEAEs. that were CTCAE Grade 3 or higher (1220/1762; 69.2% of all TEAEs; Table 45).

Table 45. Summary of Treatment Emergent Adverse Events by Highest CTCAE Grade from Subjects in the Safety Analysis Set

	CTCAE Grade	<50 mCi (N=10)	50 mCi (N=94)	>50 mCi (N=5)	All Subjects (N=109)
Number of subjects by highest grade of TEAE	Grade 1	1 (10.0)	7 (7.4)	0	8 (7.3)
	Grade 2	0	2 (2.1)	0	2 (1.8)
	Grade 3	4 (40.0)	43 (45.7)	4 (80.0)	51 (46.8)
	Grade 4	5 (50.0)	35 (37.2)	1 (20.0)	41 (37.6)

Source: Table 14.3.1.4.
Note: For subjects under 3 years of age, dose groups were assigned based on the treatment dose before age adjustment (i.e., 33% or 50% dose reduction).
TEAE = treatment-emergent adverse events.

The majority of Grade 3 or higher TEAEs belonged to the SOC Investigations (731/1220 TEAEs; 60.0%). The Grade 3 or higher TEAEs reported for 5% of all subjects were lymphopenia (70/109, 64.2%), platelet count decreased (59/109, 54.1%), WBC decreased (51/109, 46.8%), neutrophil count decreased (47/109, 43.1%), haemoglobin decreased (33/109, 30.3%), ALT increased (7/109, 6.4%), and hypokalaemia (7/109, 6.4%).

Grade 4 TEAEs reported by at least two subjects included platelet count decreased (32/109, 29.4% subjects), neutrophil count decreased (18/109, 16.5%), WBC decreased (11/109, 10.1%), lymphopenia (8/109, 7.3%), haemoglobin decreased (6/109, 5.5%), myelodysplastic syndrome (3/109, 2.8%), and acute myeloid leukaemia (2/109, 1.8%). No subject had a Grade 5 (fatal) TEAE.

Trial 101
24/32 (75%) subjects reported a total of 66 TEAEs that were CTCAE Grade 3 to Grade 5 (see Table 46).

Table 46. Treatment-Emergent Adverse Events Grade 3 or Higher by System Organ Class and Preferred Terms (Safety Analysis Set)

System Organ Class Preferred Term	Grade 3 N (%) E	Grade 4 N (%) E	Grade 5 N (%) E	Total N (%) E
Safety Analysis Set, N=32				
Any adverse event of Grade 3 and above	23 (71.9) 51	11 (34.4) 14	1 (3.1) 1	24 (75.0) 66
Investigations	23 (71.9) 46	9 (28.1) 12	-	24 (75.0) 58
Platelet count decreased	7 (21.9) 7	7 (21.9) 7	-	13 (40.6) 14
White blood cell count decreased	10 (31.3) 12	1 (3.1) 1	-	10 (31.3) 13
Lymphocyte count decreased	10 (31.3) 10	1 (3.1) 1	-	10 (31.3) 11
Neutrophil count decreased	9 (28.1) 16	2 (6.3) 3	-	9 (28.1) 19
Alanine aminotransferase increased	1 (3.1) 1	-	-	1 (3.1) 1
Blood and Lymphatic System Disorders	3 (9.4) 3	-	-	3 (9.4) 3
Anaemia	2 (6.3) 2	-	-	2 (6.3) 2
Febrile neutropenia	1 (3.1) 1	-	-	1 (3.1) 1
Nervous System Disorders	1 (3.1) 1	1 (3.1) 1	1 (3.1) 1	3 (9.4) 3
Hemorrhage intracranial	1 (3.1) 1	1 (3.1) 1	1 (3.1) 1	3 (9.4) 3
Infections and infestations	-	1 (3.1) 1	-	1 (3.1) 1
Sepsis	-	1 (3.1) 1	-	1 (3.1) 1
Injury, Poisoning and Procedural Complications	1 (3.1) 1	-	-	1 (3.1) 1
Meningitis chemical	1 (3.1) 1	-	-	1 (3.1) 1

Source: Table 14.3.1.8 and Listing 14.3.2.3
N: Number of subjects; %: Percentage of subjects; E: Number of events. A treatment emergent adverse event is defined as an AE with onset at or after administration of infusion of ^{131}I-omburtamab. The summary does not include non-serious AEs that occur more than 21+2 days after last treatment

The majority of these events belonging to the SOCs 'Investigations' and 'Blood and lymphatic system disorders', were consistent with myelosuppression. Three subjects experienced intracranial haemorrhage: Grade 3 and 4 in two subjects and fatal (Grade 5) in one subject. This case was already reported in the initial submission, thus no further fatal cases occurred.

Pooled Trial 03-133 and Trial 101

Within pooled safety populations of Trial 03-133 and Trial 101, Grade 3 or greater TEAEs of low white blood cell counts were common. A total of 59.4% of subjects reported lymphocyte count decreased, 54.9% of subjects reported platelet count decreased, 46.6% of subjects reported white blood cell count decreased, and 42.1% of subjects reported neutrophil count decreased that were Grade 3 or greater.

Related Treatment-Emergent Adverse Events by Intensity

Trial 03-133

89/109 (81.7%) subjects reported at least one related Grade 3 or higher treatment-related TEAE. 67.7% reported treatment-related TEAEs of Grade 3 or higher. Related TEAEs of Grade 3 or higher reported for >5% of all subjects were lymphopenia (69/109, 63.3%), platelet count decreased (59/109, 54.1%), WBC decreased (51/109, (46.8%), neutrophil count decreased (47/109, 43.1%), haemoglobin decreased (32/109, 29.4%), and hypokalaemia (7/109, 6.4%). Two subjects reported a related Grade 3 event of chemical meningitis. Both subjects belonged to the 50 mCi group.

Related TEAEs of Grade 4 or higher reported for at least two subjects included platelet count decreased (31/109, 28.4%), neutrophil count decreased (17/109, 15.6%), WBC decreased (11/109, 10.1%),

lymphopenia (7/109, 6.4%), haemoglobin decreased (5/109, 4.6%), and myelodysplastic syndrome (2/109, 1.8%).

Trial 101

A summary of all TEAEs judged by the investigator as being related to ^{131}I-omburtamab is provided in Table 47.

There were 179 TEAEs in 30/32 (93.8%) subjects considered related to ^{131}I-omburtamab by the investigator. Similar to all TEAEs, the majority of the related events were preferred terms consistent with myelosuppression: Most frequent related TEAEs were platelet count decreased (17/32, 53.1%) subjects, white blood cell count decreased (12/32, 37.5%), lymphocyte count decreased (12/32, 37.5%), neutrophil count decreased (10/32, 31.3%) and anaemia (8/32, 25%) subjects. Additional frequently reported related TEAEs were nausea (10/32, 31.3%), headache (8/32, 25.0%) and vomiting (4/32, 12.5%).

Table 47. Related (^{131}I-omburtamab) Treatment-Emergent Adverse Events

System Organ Class Preferred Term	^{131}I-omburtamab N (%) E
Safety Analysis Set (N)	32
Any related adverse event	30 (93.8) 179
Investigations	**25 (78.1) 77**
Platelet count decreased	17 (53.1) 20
White blood cell count decreased	12 (37.5) 16
Lymphocyte count decreased	12 (37.5) 13
Neutrophil count decreased	10 (31.3) 24
Alanine aminotransferase increased	1 (3.1) 1
Aspartate aminotransferase increased	1 (3.1) 1
Blood thyroid stimulating hormone increased	1 (3.1) 1
Red blood cell count decreased	1 (3.1) 1
Nervous System Disorders	**11 (34.4) 22**
Headache	8 (25.0) 12
Neuralgia	2 (6.3) 5
Dizziness	1 (3.1) 1
Dysaesthesia	1 (3.1) 1
Haemorrhage intracranial[1]	1 (3.1) 1
Hypoaesthesia	1 (3.1) 1
Peripheral sensory neuropathy	1 (3.1) 1
Gastrointestinal Disorders	**13 (40.6) 19**
Nausea	10 (31.3) 11
Vomiting	4 (12.5) 5
Abdominal pain	1 (3.1) 1
Diarrhoea	1 (3.1) 1
Dyspepsia	1 (3.1) 1
Blood and Lymphatic System Disorders	**9 (28.1) 12**
Anaemia	8 (25.0) 11
Febrile neutropenia	1 (3.1) 1
Metabolism and Nutrition Disorders	**6 (18.8) 11**
Decreased appetite	3 (9.4) 3
Hyperglycaemia	2 (6.3) 2
Hypokalaemia	2 (6.3) 2
Hyperphagia	1 (3.1) 3
Dehydration	1 (3.1) 1
General Disorders and Administration Site Conditions	**6 (18.8) 10**
Fatigue	3 (9.4) 3
Pyrexia	2 (6.3) 3
Xerosis	1 (3.1) 2

System Organ Class Preferred Term	^{131}I-omburtamab N (%) E
Malaise	1 (3.1) 1
Pain	1 (3.1) 1
Skin and Subcutaneous Tissue Disorders	**3 (9.4) 7**
Rash	2 (6.3) 3
Rash maculo-papular	2 (6.3) 2
Eczema	1 (3.1) 1
Rash erythematous	1 (3.1) 1
Vascular Disorders	**4 (12.5) 6**
Haematoma	2 (6.3) 3
Flushing	1 (3.1) 1
Hot flush	1 (3.1) 1
Peripheral coldness	1 (3.1) 1
Injury, Poisoning and Procedural Complications	**5 (15.6) 5**
Contusion	3 (9.4) 3
Meningitis chemical	2 (6.3) 2
Musculoskeletal and Connective Tissue Disorders	**3 (9.4) 3**
Arthralgia	1 (3.1) 1
Myalgia	1 (3.1) 1
Pain in extremity	1 (3.1) 1
Endocrine Disorders	**2 (6.3) 3**
Hypothyroidism	2 (6.3) 3
Respiratory, Thoracic and Mediastinal disorders	**1 (3.1) 3**
Epistaxis	1 (3.1) 3
Cardiac Disorders	**1 (3.1) 1**
Ventricular arrhythmia	1 (3.1) 1

Source: Table 14.3.1.12 and Appendix 16.2.7.2.

N: Number of subjects; %: Percentage of subjects; E: Number of events. A treatment emergent adverse event is defined as an AE with onset at or after administration of infusion of ^{131}I-omburtamab. Related AEs: Events with drug relationship Related, Possibly related or Probably related as assessed by the investigator. The summary does not include non-serious adverse events that occurred more than 21+2 days after last treatment

1) There were three events of intracranial hemorrhage in total (Appendix 16.2.7.1). One was considered related by the investigator. All three were considered possibly related by the sponsor (Section 14.3.3).

Infusion-related Treatment-Emergent Adverse Events

Trial 03-133

A total of 174 of 1353 (12.9%) related TEAEs had an onset on the same day as a ^{131}I-omburtamab infusion. Infusion-related TEAEs were reported for 61/109 (56.0%) subjects. Infusion-related TEAEs not associated with abnormal laboratory parameters reported for two or more subjects were vomiting (13 subjects), pyrexia (6 subjects), nausea (3 subjects), and chemical meningitis (2 subjects). The time from infusion of ^{131}I-omburtamab to the onset of infusion-related TEAEs is not available for Trial 03-133. Serious infusion-related TEAEs not associated with abnormal laboratory parameters were chemical meningitis (two subjects) and nausea, vomiting, pyrexia, headache (one subject each).

Trial 101

A total of 27/156 (17.3%) subjects related TEAEs had an onset on the same day as a ^{131}I-omburtamab infusion (Table 56). Infusion-related TEAEs were reported for 12/24 (50.0%) subjects. The mean (SD) time from infusion of ^{131}I-omburtamab to onset of infusion-related TEAEs was 25.6 (75.8) minutes, ranging from 0-300 minutes. The mean (SD) duration of the events were 4.4 (7.6) days, ranging from 0-33 days. Events of headache, pyrexia, vomiting and other events typically associated with infusion of antibodies had a duration of maximum two days.

Infusion-related TEAEs not associated with abnormal laboratory parameters reported for two or more subjects were headache (5 subjects), nausea (2 subjects), and chemical meningitis (2 subjects). One subject reported a serious infusion-related TEAE (Table 48). This was a single event of Grade 3 chemical meningitis (one of the two mentioned above). The SAE was reported for the investigator as probably related, and ^{131}I-omburtamab was discontinued.

Until the second data cut-off (June 2021), infusion-related TEAEs were reported for 13/32 (40.6%) subjects, there were no infusion-related TEAEs above Grade 3. Most of the infusion-related events (19/29) were Grade 1, of which 'headache' (five events in five subjects), 'nausea' (2 events in 2 subjects), and 'neuralgia' (3 events in 1 subject) were among the most frequently reported events by preferred term. 4 Grade 3 infusion-related TEAEs were reported for 3 subjects, i.e. chemical meningitis (SAE), platelet count decreased, neutrophil and WBC count decreased; all recovered.

Table 48. Summary of Infusion-Related TEAEs by System Organ Class and Preferred Terms in the Safety Analysis Set of Trial 03-133 and Trial 101

	Study 03-133	Study 101
System Organ Class/ Preferred Term	All (N=109) [n(%)], #events	All (N=24) [n(%)], #events
Number of Infusion-related TEAEs	174	27
Number of subjects with at least one infusion-related TEAE	61 (56.0)	12 (50.0)
Blood and lymphatic system disorders	37 (33.9), 60	1 (4.2), 1
Lymphopenia	37 (33.9), 60	0
Anaemia	0	1 (4.2), 1
Investigations	23 (21.1), 50	2 (8.3), 3
Platelet count decreased	14 (12.8), 20	1 (4.2), 1
White blood cell count decreased	11 (10.1), 15	1 (4.2), 1
Neutrophil count decreased	8 (7.3), 8	1 (4.2), 1
Haemoglobin decreased	6 (5.5), 7	0
Gastrointestinal disorders	17 (15.6), 21	3 (12.5), 3
Vomiting	13 (11.9), 15	1 (4.2), 1
Nausea	3 (2.8), 4	2 (8.3), 2
Abdominal pain	1 (0.9), 1	0
Abdominal pain upper	1 (0.9), 1	0
Nervous system disorders	14 (12.8), 18	6 (25.0), 9
Headache	13 (11.9), 14	5 (20.8), 5
Peripheral sensory neuropathy	2 (1.8), 2	0

System Organ Class/ Preferred Term	Study 03-133 All (N=109) [n(%)], #events	Study 101 All (N=24) [n(%)], #events
Nervous system disorders (continued)		
Cerebrospinal fluid leakage	1 (0.9), 2	0
Dizziness	0	1 (4.2), 1
Neuralgia	0	1 (4.2), 3
General disorders and administration site conditions	8 (7.3), 10	3 (12.5), 4
Pyrexia	6 (5.5), 6	1 (4.2), 1
Catheter site pain	2 (1.8), 2	0
Chills	0	1 (4.2), 1
Feeling cold	0	1 (4.2), 1
Hypothermia	1 (0.9), 1	0
Injection site pain	1 (0.9), 1	0
Malaise	0	1 (4.2), 1
Injury, poisoning and procedural complications	3 (2.8), 3	2 (8.3), 2
Meningitis chemical	2 (1.8), 2	2 (8.3), 2
Injection site haemorrhage	1 (0.9), 1	0
Skin and subcutaneous tissue disorders	3 (2.8), 3	2 (8.3), 4
Exfoliative rash	1 (0.9), 1	0
Pain of skin	1 (0.9), 1	0
Rash	0	1 (4.2), 2

System Organ Class/ Preferred Term	Study 03-133 All (N=109) [n(%)], #events	Study 101 All (N=24) [n(%)], #events
Skin and subcutaneous tissue disorders (continued)		
Rash erythematous	0	1 (4.2), 1
Rash maculo-papular	0	1 (4.2), 1
Urticaria	1 (0.9), 1	0
Psychiatric disorders	4 (3.7), 5	0
Agitation	1 (0.9), 1	0
Anxiety	1 (0.9), 1	0
Depression	1 (0.9), 1	0
Irritability	1 (0.9), 2	0
Respiratory, thoracic and mediastinal disorders	2 (1.8), 2	0
Oropharyngeal pain	1 (0.9), 1	0
Rhinitis allergic	1 (0.9), 1	0
Cardiac disorders	0	1 (4.2), 1
Ventricular arrhythmia	0	1 (4.2), 1
Metabolism and nutrition disorders	1 (0.9), 1	0
Hypokalaemia	1 (0.9), 1	0
Musculoskeletal and connective tissue disorders	1 (0.9), 1	0
Pain in extremity	1 (0.9), 1	0

Source: Appendix 13.5
%=Percentage of subjects; N=Number of subjects.
Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects reported at least one AE in that SOC or PT. Subjects wh reported more than one AE in a given SOC or PT were counted only once for that particular SOC or PT.

Table 49. Summary of Infusion-Related Adverse Events by System Organ Class and Preferred Terms in the Safety Analysis Set of Trial 03-133 and Trial 101

System Organ Class/ Preferred Term	Study 03-133 All (N=109) [n(%)], #events	Study 101 All (N=24) [n(%)], #events
Number of Infusion-related SAEs	7	1
Number of subjects with at least one infusion-related SAE	4 (3.7)	1 (4.2)
Injury, poisoning and procedural complications	2 (1.8), 2	1 (4.2), 1
Meningitis chemical	2 (1.8), 2	1 (4.2), 1
Gastrointestinal disorders	2 (1.8), 2	0
Nausea	1 (0.9), 1	0
Vomiting	1 (0.9), 1	0
General disorders and administration site conditions	1 (0.9), 1	0
Pyrexia	1 (0.9), 1	0
Investigations	1 (0.9), 1	0
Platelet count decreased	1 (0.9), 1	0
Nervous system disorders	1 (0.9), 1	0
Headache	1 (0.9), 1	0

Source: Appendix 13.24
%=Percentage of subjects; N=Number of subjects.
Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects reported at least one AE in that SOC or PT. Subjects who reported more than one AE in a given SOC or PT were counted only once for that particular SOC or PT.

Treatment-Emergent Adverse Events by Treatment Cycle

An analysis of TEAEs by treatment cycle was not performed for Trial 101 due to the small number of subjects in the trial.

Trial 03-133

Overall, the proportion of subjects with TEAEs is similar for subjects receiving one or 2+ treatment cycles (93.8% versus 93.4%). For related TEAEs a numerically higher proportion of subjects receiving 2+ cycles (31.1%) reported related TEAEs compared to subjects receiving only one cycle (18.8%). No differences were seen for related serious TEAEs. Most TEAEs occur for a comparable proportion of subjects, whether they had one or 2+ treatment cycles. Noticeable differences for related TEAEs include numerically higher proportions of subjects receiving 2+ cycles for WBC count decreased and for neutrophil count decreased, whereas there was no notable difference for platelet count decreased or for lymphopenia. Another observed numerical difference is a higher proportion of subjects receiving 2+ cycles reporting vomiting.

2.2.8.3. Serious adverse event/deaths/other significant events

Trial 03-133

1 Subject received the last treatment cycle of ^{131}I-omburtamab in July 2009 (total dose 104.75 mCi) and was subsequently treated with 3F8 and GM-CSF, Immunotherapy (not further specified) and temozolomide. The subject was diagnosed with acute myeloid leukaemia and died about 2 and half year after treatment with ^{131}I-omburtamab. The case was assessed as possibly related to ^{131}I-omburtamab.

Trial 101

4 deaths occurred during the study. 3 deaths were due to disease progression. One TEAE leading to death was reported (intracranial haemorrhage). A full narrative description of this fatal event was provided.

Other Serious Adverse Events

Trial 03-133

Almost half of the subjects (53/109; 48.6%) had at least one SAE (see Table 58). Most SAEs were in the SOC Investigations. Platelet count decreased, neutrophil count decreased, and WBC count decreased all occurred in more than 5% of the subjects and were attributable to myelosuppression. Other SAEs occurring in more than 2 subjects were haemoglobin decreased, alanine aminotransferase (ALT) increased, myelodysplastic syndrome, meningitis chemical, and vomiting.

The 65 treatment-related SAEs were reported for 35/109 (32.1%) subjects. Frequently reported (for >5% of subjects) treatment-related SAEs were platelet count decreased (21/109, 19.3%) followed by neutrophil count decreased (12/109, 11.0%) and WBC count decreased (8/109, 7.3%).

In addition to the SAEs, 19 SAEs with onset greater than 30 days after last dose were reported for 12 subjects. The majority of SAEs with onset greater than 30 days after last dose (12/109, 63.2%) were within the SOC Investigations, including platelet count decreased (4.6%), neutrophil count decreased (2.8%), haemoglobin and WBC decreased (each 0.9%). The 7 remaining SAEs with onset greater than 30 days after last dose were myelodysplastic syndrome (2.8%), acute myeloid leukaemia (1.8%), hypoglycaemia and seizure (each 0.9%).

Table 50. Summary of Serious Adverse Events Reported for Subjects in the Safety Analysis Set

System Organ Class Preferred Term	<50 mCi (N=10) [n (%)], #events	50 mCi (N=94) [n (%)], #events	>50 mCi (N=25) [n (%)], #events	All Subjects (N=109) [n (%)], #events
Number of SAEs	11	82	1	94
Subjects with at least one SAE	6 (60.0), 11	46 (48.9), 82	1 (20.0), 1	53 (48.6), 94
Blood and lymphatic system disorders	**2 (20.0), 2**	**2 (2.1), 2**	**0**	**4 (3.7), 4**
Lymphopenia	1 (10.0), 1	1 (1.1), 1	0	2 (1.8), 2
Febrile neutropenia	0	1 (1.1), 1	0	1 (0.9), 1
Immune thrombocytopenic purpura	1 (10.0), 1	0	0	1 (0.9), 1
Gastrointestinal disorders	**0**	**4 (4.3), 4**	**0**	**4 (3.7), 4**
Vomiting	0	3 (3.2), 3	0	3 (2.8), 3
Nausea	0	1 (1.1), 1	0	1 (0.9), 1
General disorders and administration site conditions	**1 (10.0), 1**	**1 (1.1), 1**	**0**	**2 (1.8), 2**
Pyrexia	1 (10.0), 1	1 (1.1), 1	0	2 (1.8), 2
Immune system disorders	**0**	**1 (1.1), 1**	**0**	**1 (0.9), 1**
Hypersensitivity	0	1 (1.1), 1	0	1 (0.9), 1
Infections and infestations	**0**	**6 (6.4), 6**	**0**	**6 (5.5), 6**
Device related infection	0	2 (2.1), 2	0	2 (1.8), 2
Gastric infection	0	1 (1.1), 1	0	1 (0.9), 1
Infectious colitis	0	1 (1.1), 1	0	1 (0.9), 1
Infectious colitis	0	1 (1.1), 1	0	1 (0.9), 1
Pneumonia	0	1 (1.1), 1	0	1 (0.9), 1
Sepsis	0	1 (1.1), 1	0	1 (0.9), 1
Injury, poisoning and procedural complications	**0**	**4 (4.3), 4**	**0**	**4 (3.7), 4**
Meningitis chemical	0	3 (3.2), 3	0	3 (2.8), 3
Upper limb fracture	0	1 (1.1), 1	0	1 (0.9), 1
Investigations	**4 (40.0), 6**	**29 (30.9), 52**	**1 (20.0), 1**	**34 (31.2), 59**
Platelet count decreased	1 (10.0), 1	21 (22.3), 24	1 (20.0), 1	23 (21.1), 26
Neutrophil count decreased	0	13 (13.8), 13	0	13 (11.9), 13
White blood cell count decreased	0	8 (8.5), 8	0	8 (7.3), 8
Haemoglobin decreased	0	5 (5.3), 5	0	5 (4.6), 5
Alanine aminotransferase increased	3 (30.0), 4	1 (1.1), 1	0	4 (3.7), 5
Aspartate aminotransferase increased	1 (10.0), 1	1 (1.1), 1	0	2 (1.8), 2
Metabolism and nutrition disorders	**0**	**1 (1.1), 1**	**0**	**1 (0.9), 1**
Hypoglycaemia	0	1 (1.1), 1	0	1 (0.9), 1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (10.0), 1**	**4 (4.3), 4**	**0**	**5 (4.6), 5**
Myelodysplastic syndrome	1 (10.0), 1	2 (2.1), 2	0	3 (2.8), 3
Acute myeloid leukaemia	0	2 (2.1), 2	0	2 (1.8), 2
Nervous system disorders	**1 (10.0), 1**	**6 (6.4), 7**	**0**	**7 (6.4), 8**
Headache	0	2 (2.1), 2	0	2 (1.8), 2
Nervous system disorder	0	2 (2.1), 2	0	2 (1.8), 2
Seizure	0	2 (2.1), 2	0	2 (1.8), 2
Cerebrospinal fluid leakage	1 (10.0), 1	0	0	1 (0.9), 1
Depressed level of consciousness	0	1 (1.1), 1	0	1 (0.9), 1

Source: Table 14.3.1.17.
Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects who experienced at least one AE in that SOC or PT. Subjects experienced more than one AE in a given SOC or PT were counted only once for that particular SOC or PT.
Note: For subjects under 3 years of age, dose groups were assigned based on the treatment dose before age adjustment (i.e., 33% or 50% dose reduction).
SAE = serious adverse event.

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (10.0), 1	4 (4.3), 4	0	5 (4.6), 5
Myelodysplastic syndrome	1 (10.0), 1	2 (2.1), 2	0	3 (2.8), 3
Acute myeloid leukaemia	0	2 (2.1), 2	0	2 (1.8), 2
Nervous system disorders	**1 (10.0), 1**	**6 (6.4), 7**	**0**	**7 (6.4), 8**
Headache	0	2 (2.1), 2	0	2 (1.8), 2
Nervous system disorder	0	2 (2.1), 2	0	2 (1.8), 2
Seizure	0	2 (2.1), 2	0	2 (1.8), 2
Cerebrospinal fluid leakage	1 (10.0), 1	0	0	1 (0.9), 1
Depressed level of consciousness	0	1 (1.1), 1	0	1 (0.9), 1

Source: Table 14.3.1.17.
Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects who experienced at least one AE in that SOC or PT. Subjects experienced more than one AE in a given SOC or PT were counted only once for that particular SOC or PT.
Note: For subjects under 3 years of age, dose groups were assigned based on the treatment dose before age adjustment (i.e., 33% or 50% dose reduction).
SAE = serious adverse event.

Trial 101

11/32 (34.4%) subjects experienced treatment-related SAEs (Table 51). The fatal SAE described above (Grade 5 intracranial hemorrhage) was reported as not related by the investigator but assessed as possibly related by the sponsor.

The majority of the related SAEs were consistent with myelosuppression as most frequently reported preferred terms were 'platelet count decreased' and 'lymphocyte count decreased'. Aside from SAEs of myelosuppression, one subject had a related SAE of 'chemical meningitis' (resolved), one subject had a

related SAE of 'intracranial haemorrhage' (recovered with sequelae) and one subject had a related SAE of 'alanine aminotransferase increased' (resolved).

Table 51 Related (^{131}I-Omburtamab) Serious Treatment -Emergent Adverse Event by Grade, System Organ Class and Preferred Term.

System Organ Class Preferred Term	Grade 3 N (%) E	Grade 4 N (%) E	Total N (%) E
Safety Analysis Set, N=32			
Any related serious adverse event	7 (21.9) 7	8 (25.0) 9	11 (34.4) 16
Investigations	**4 (12.5) 4**	**7 (21.9) 8**	**8 (25.0) 12**
Platelet count decreased	-	6 (18.8) 6	6 (18.8) 6
Lymphocyte count decreased	3 (9.4) 3	1 (3.1) 1	4 (12.5) 4
Alanine aminotransferase increased	1 (3.1) 1	-	1 (3.1) 1
Neutrophil count decreased	-	1 (3.1) 1	1 (3.1) 1
Blood and Lymphatic System disorders	**2 (6.3) 2**	-	**2 (6.3) 2**
Anaemia	1 (3.1) 1	-	1 (3.1) 1
Febrile neutropenia	1 (3.1) 1		1 (3.1) 1
Injury, Poisoning and Procedural Complication	**1 (3.1) 1**	-	**1 (3.1) 1**
Meningitis chemical	1 (3.1) 1	-	1 (3.1) 1
Nervous System Disorders	-	**1 (3.1) 1**	**1 (3.1) 1**
Hemorrhage intracranial[1]	-	1 (3.1) 1	1 (3.1) 1

Source: Table 14.3.1.5 and Listing 14.3.2.2.

N: Number of subjects; %: Percentage of subjects. E: Number of events. A treatment emergent adverse event is defined as an AE with onset at or after administration of infusion of ^{131}I-omburtamab. Related AEs: Events with drug relationship Related, Possibly related or Probably related as assessed by the investigator. Serious AEs have been extracted from the case report form (CRF) if answer to serious is Yes.

1): There were three serious events of intracranial hemorrhage. One was considered related by the investigator. All were considered possibly related by the sponsor.

Table 52 provides a summary of SAE by SOC for both trials (03-133 and 101, first data cut-off).

Table 52. Summary of SAEs by System Organ Class and Preferred Terms in the Safety Analysis Set of Trial 03-133 and Trial 101

	Study 03-133	Study 101
System Organ Class/ Preferred Term	All (N=109) [n(%)], #events	All (N=24) [n(%)], #events
Number of Serious TEAEs	94	16
Number of subjects with at least one Serious TEAE	53 (48.6)	10 (41.7)
Investigations	34 (31.2), 59	6 (25.0), 9
Platelet count decreased	23 (21.1), 26	5 (20.8), 5
Neutrophil count decreased	13 (11.9), 13	1 (4.2), 1
White blood cell count decreased	8 (7.3), 8	0
Alanine aminotransferase increased	4 (3.7), 5	1 (4.2), 1
Haemoglobin decreased	5 (4.6), 5	0
Aspartate aminotransferase increased	2 (1.8), 2	0
Lymphocyte count decreased	0	2 (8.3), 2
Nervous system disorders	7 (6.4), 8	2 (8.3), 2
Haemorrhage intracranial	0	2 (8.3), 2
Headache	2 (1.8), 2	0
Nervous system disorder	2 (1.8), 2	0
Seizure	2 (1.8), 2	0
Cerebrospinal fluid leakage	1 (0.9), 1	0
Depressed level of consciousness	1 (0.9), 1	0
Blood and lymphatic system disorders	4 (3.7), 4	4 (16.7), 4
Lymphopenia	2 (1.8), 2	2 (8.3), 2
Anaemia	0	1 (4.2), 1
Febrile neutropenia	1 (0.9), 1	0
Immune thrombocytopenic purpura	1 (0.9), 1	0
Thrombocytopenia	0	1 (4.2), 1
Infections and infestations	6 (5.5), 6	0
Device related infection	2 (1.8), 2	0
Gastric infection	1 (0.9), 1	0
Infectious colitis	1 (0.9), 1	0
Pneumonia	1 (0.9), 1	0
Sepsis	1 (0.9), 1	0
Injury, poisoning and procedural complications	4 (3.7), 4	1 (4.2), 1
Meningitis chemical	3 (2.8), 3	1 (4.2), 1
Upper limb fracture	1 (0.9), 1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (4.6), 5	0
Myelodysplastic syndrome	3 (2.8), 3	0
Acute myeloid leukaemia	2 (1.8), 2	0
Gastrointestinal disorders	4 (3.7), 4	0
Vomiting	3 (2.8), 3	0
Nausea	1 (0.9), 1	0
General disorders and administration site conditions	2 (1.8), 2	0
Pyrexia	2 (1.8), 2	0
Immune system disorders	1 (0.9), 1	0
Hypersensitivity	1 (0.9), 1	0
Metabolism and nutrition disorders	1 (0.9), 1	0
Hypoglycaemia	1 (0.9), 1	0

Source: Appendix 13.25

Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects reported at least one AE in that SOC or PT. Subjects who reported more than one AE in a given SOC or PT were counted only once for that particular SOC or PT.

Serious Adverse Events for Non-neuroblastoma Subjects in Trial 03-133

For all subjects in the NNAS, 15 of 37 subjects (40.5%) reported at least one SAE. Frequently reported (reported for ≥5% of subjects) SAEs in the NNAS were vomiting, platelet count decreased, and headache (3 subjects each).

Adverse events of special interest

Trial 03-133
There were no AESIs predefined in Trial 03-133.

Trial 101
For Trial 101, AESIs were predefined as presented in Table 53.

Table 53. Definition of Adverse Events of Special Interest

Predefined AESI	Collected and reported as AESIs according to protocol versions
Neurotoxicities of Grade 3 and above	From Protocol version 1
Severe infections related to placement of cerebroventricular device	From Protocol version 1
Chemical meningitis	From Protocol version 7
Liver toxicities Grade 3 and above	Applicable from Protocol versions 1 through 4
Worsening of performance test	Applicable from Protocol versions 1 through 4
Myelosuppression Grade 4 during treatment	Applicable from Protocol versions 1 through 4

TEAEs of special interest are summarised in Table 54.

A total of 13 AESIs were reported for 11/32 (34.4%) subjects. The majority of AESIs were related to myelosuppression.

Three events of intracranial hemorrhage were reported in three subjects:
• One event was the fatal Grade 5 event, as described above.

• One event was Grade 3, serious, assessed as not related to study drug by the investigator and possibly related to study drug by sponsor. The event was reported as resolved.

• One event was Grade 4, serious, assessed as possibly related to study drug by the investigator and sponsor and reported as resolved with sequelae.

In all three cases, disease progression was observed and considered to be a potential cause of the events, but concomitant low platelet counts (CTCAE grade 3-4) cannot be excluded as a potential contributing factor.

Two events of chemical meningitis occurred in two subjects. Both events were infusion-related, assessed as probably related to study drug by the investigator, and reported as resolved without sequelae. One event was Grade 3, serious, and led to discontinuation of further dosing with ^{131}I-omburtamab in one subject. The other event was Grade 2, non-serious.

Table 54. Treatment-Emergent Adverse Events of Special Interest by Grade, System Organ and Preferred Term.

System Organ Class Preferred Term	Grade 1 N (%) E	Grade 2 N (%) E	Grade 3 N (%) E	Grade 4 N (%) E	Grade 5 N (%) E	Total N (%) E
Safety Analysis Set, N=32						
Any adverse event of special interest	-	1 (3.1) 1	3 (9.4) 3	7 (21.9) 8	1 (3.1) 1	11 (34.4) 13
Investigations	-	-	**1 (3.1) 1**	**6 (18.8) 7**	-	**7 (21.9) 8**
Platelet count decreased	-	-	-	5 (15.6) 5	-	5 (15.6) 5
Lymphocyte count decreased	-	-	1 (3.1) 1	1 (3.1) 1	-	2 (6.3) 2
Neutrophil count decreased	-	-	-	1 (3.1) 1	-	1 (3.1) 1
Injury, poisoning and procedural complications	-	**1 (3.1) 1**	**1 (3.1) 1**	-	-	**2 (6.3) 2**
Meningitis chemical	-	1 (3.1) 1	1 (3.1) 1	-	-	2 (6.3) 2
Nervous System Disorders	-	-	**1 (3.1) 1**	**1 (3.1) 1**	**1 (3.1) 1**	**3 (9.4) 3**
Haemorrhage intracranial	-	-	1 (3.1) 1	1 (3.1) 1	1 (3.1) 1	3 (9.4) 3

Source: Table 14.3.1.10 and Listing 14.3.2.5.
N: Number of subjects; %: Percentage of subjects; E: Number of events.
A treatment emergent adverse event is defined as an AE with onset at or after administration of infusion of ^{131}I-omburtamab.
AE of special interest selected from the case report form (CRF) where AE of special interest is ticked. The summary does not include non-serious adverse events that occurred more than 21+2 days after last treatment.

Analysis of Adverse Events by Organ System or Syndrome

In order to better understand the safety profile of ^{131}I-omburtamab, investigations of AEs by organ systems or syndrome were undertaken. Searches for AEs in Trial 03-133 and Trial 101 relating to myelosuppression, hepatic toxicity, thyroid suppression, anaphylactic reactions, and haemorrhage were performed using MedDRA standardised MedDRA queries (SMQs). Secondary malignancies, neurotoxicity, and infections were investigated by summarizing AEs in the associated SOCs or selected relevant TEAE PTs. These data were not updated in the interim CSR with cut-off June 2021.

Myelosuppression

Myelosuppression and prolonged cytopenia is a side effect of exposure to ionizing radiation due to radiation-related adverse effects on bone marrow. A summary of TEAEs related to myelosuppression in Trial 03-133 and Trial 101 is provided in Table 63.

A total of 89/109 (81.7%) and 21/24 (87.5%) of subjects had at least one TEAE related to haematopoietic cytopenias in Trial 03-133 and Trial 101, respectively. Frequently reported (at least 30.0% of subjects in either trial) haematopoietic cytopenia events were lymphopenia, platelet count decreased, WBC count decreased, neutrophil count decreased, and anaemia. Specific haematopoietic cytopenia events were considered SAEs as follows: platelet count decreased, neutrophil count decreased, WBC count decreased, haemoglobin decreased, lymphopenia, myelodysplastic syndrome, lymphocyte count decreased, and anaemia, febrile neutropenia, thrombocytopenia.

In order to assess the possible association between myelosuppression and infection, all subjects who had Grade 3 or above haematopoietic cytopenia events of neutrophil count decreased, WBC count decreased, lymphopenia, myelodysplastic syndrome, lymphocyte count decreased, and/or febrile neutropenia were investigated for infections. The findings are presented below.

Table 55. Summary of TEAEs related to Myelosuppression as Identified by MEDRA SMQ Haematopoietic Cytopenias by Preferred Term in Trial 03-133 and Trial 101

SMQ/ Preferred Term	Study 03-133 All (N=109) [n(%)], #events	Study 101 All (N=24) [n(%)], #events
Haematopoietic cytopenias (SMQ)	89 (81.7), 1212	21 (87.5), 79
Lymphopenia	70 (64.2), 451	5 (20.8), 5
Platelet count decreased	59 (54.1), 296	14 (58.3), 17
White blood cell count decreased	51 (46.8), 223	9 (37.5), 10
Neutrophil count decreased	47 (43.1), 157	7 (29.2), 10
Haemoglobin decreased	33 (30.3), 81	0
Anaemia	0	8 (33.3), 12
Lymphocyte count decreased	0	5 (20.8), 6
Leukopenia	0	3 (12.5), 8
Myelodysplastic syndrome	3 (2.8), 3	0
Neutropenia	0	2 (8.3), 10
Febrile neutropenia	1 (0.9), 1	0
Thrombocytopenia	0	1 (4.2), 1

Source: Appendix 13.3
%=Percentage of subjects; N=Number of subjects.
Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in standardised MedDRA queries (SMQ) and preferred term (PT) rows are numbers of subjects reported at least one AE in that SMQ or PT. Subjects who reported more than one AE in a given SMQ or PT were counted only once for that particular SMQ or PT.
Note: Both broad and narrow terms were included.

Hepatic Toxicity

Organ dosimetry data show the CSF, brain, and the liver as the regions with the highest absorbed radiation dose. Subjects with severe hepatic impairment have thus been excluded from clinical trials. A summary of TEAEs related to hepatic disorders in Trial 03-133 and Trial 101 is provided in Table 64.

A total of 8/109 (7.3%) and 1/24 (4.2%) of subjects had at least one TEAE related to hepatic toxicity in Trial 03-133 and Trial 101, respectively. Specific hepatic toxicity events were considered SAEs as follows: ALT increased (five subjects) and AST increased (two subjects).

Table 56. SMQ Drug related Hepatic Disorders in Trial 03-133 and trial 101

SMQ/ Preferred Term	Study 03-133 All (N=109) [n(%)], #events	Study 101 All (N=24) [n(%)], #events
Drug related hepatic disorders (SMQ)	8 (7.3), 15	1 (4.2), 1
Alanine aminotransferase increased	7 (6.4), 11	1 (4.2), 1
Aspartate aminotransferase increased	3 (2.8), 3	0
Prothrombin time prolonged	1 (0.9), 1	0

Source: Appendix 13.3
%=Percentage of subjects; N=Number of subjects.
Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in standardised MedDRA queries (SMQ) and preferred term (PT) rows are numbers of subjects reported at least one AE in that SMQ or PT. Subjects who reported more than one AE in a given SMQ or PT were counted only once for that particular SMQ or PT.
Note: Both broad and narrow terms were included.

Secondary Malignancies

Secondary malignancies, especially haematological malignancies are a potential risk with the use of ^{131}I-omburtamab due to late myelotoxicity, especially in patients who have received significant amounts of chemotherapy and radiation therapy prior to treatment with ^{131}I-omburtamab.

In Trial 03-133, 6/109 (5.5%) subjects had one TEAE belonging to the SOC Neoplasms benign, malignant, and unspecified. In Trial 101, no subjects had a TEAE belonging to the Neoplasms benign, malignant, and unspecified SOC. Myelodysplastic syndrome was reported for three subjects, two subject had acute myeloid leukaemia, and one subject had skin papilloma. With the exception of skin papilloma (wart), all TEAEs belonging to the SOC Neoplasms benign, malignant, and unspecified were considered serious.

In addition to the 6 subjects described above, malignancies were reported for 5 subjects (all in Trial 03-133) more than 30 days after last infusion of ^{131}I-omburtamab (3 subjects with myelodysplastic syndrome and 2 subjects with acute myeloid leukaemia).

Neurotoxicity

Intracerebral exposure to therapeutic irradiation carries the risk of symptomatic neurological injury. The radiation emitted from a radiolabelled antibody bound to a tumour cell may also damage neighbouring cells since beta-emission penetration range in tissue can extend over several cell diameters. Neurotoxicity can also arise from local irritation of the meninges (e.g., chemical meningitis), and the origin of symptoms can hence be difficult to distinguish. TEAEs possibly associated with neurotoxicity include the following PTs: chemical meningitis, peripheral sensory neuropathy, and seizure. TEAEs possibly associated with neurotoxicity are listed in Table 65.

A total of 7/109 (6.4%) and 3/24 (12.5%) of subjects had at least one TEAE possibly associated with neurotoxicity in Trial 03-133 and Trial 101, respectively. Of these, 5 subjects had chemical meningitis, 4 subjects had peripheral sensory neuropathy and 2 subjects had seizures. Specific neurotoxicity events were considered SAEs as follows: seizure (2 subjects) and chemical meningitis (4 subjects).

In Trial 101, performance testing was conducted and analysed using the Lansky Play-Performance Scale for children less than 16 years and the Karnovsky Scale for children at least 16 years to evaluate gross neurologic function and measure subjects' overall function. For Trial 101, the mean Lansky Play-Performance Score at baseline was 93.3. At Week 26, mean change from baseline in Lansky Play-Performance Score was 0.0, range was -20 to 20. Note: All children in Trial 101 were less than 16 years. Therefore, only the Lansky Play-Performance Score was used in Trial 101. In total, five subjects had a worsening of their screening performance score at follow-up. The remaining subjects had improvement or no change in score during the trial. In general, subjects were high functioning at baseline and had little or no deterioration in follow-up performance scores.

Table 57. Summary of TEAEs Possibly Associated with Neurotoxicity in Trial 03-133 and Trial 101

Subject No.	Dose group	Preferred Term	Grade	Serious
xxxxxxxxxx	50 mCi	Peripheral sensory neuropathy	2	No
xxxxxxxxxx	50 mCi	Peripheral sensory neuropathy	1	No
xxxxxxxxxx	<50 mCi	Peripheral sensory neuropathy	2	No
xxxxxxxxxx	50 mCi	Seizure	2	Yes
xxxxxxxxxx	50 mCi	Seizure	3	Yes
xxxxxxxxxx	50 mCi	Meningitis chemical	2	Yes
xxxxxxxxxx	50 mCi	Meningitis chemical	3	Yes
xxxxxxxxxx	50 mCi	Meningitis chemical	3	Yes
xxxxxxxxxxx	50 mCi	Peripheral sensory neuropathy	1	No
xxxxxxxxxxx	50 mCi	Meningitis chemical	3	Yes
xxxxxxxxxxx	50 mCi	Meningitis chemical	2	No

Source: Appendix 13.11 and Appendix 13.12.
Note: 50 mCi=1850 MBq.

Thyroid Suppression

Thyroid suppression is a potential risk with ^{131}I-omburtamab due to the effects of radioactive iodine on the thyroid. The risk is mitigated by treating all subjects with thyroid-blocking agents from one week before treatment until 14 days after the last therapeutic dose.

No subjects in Trial 03-133 and 2/24 (8.3%) of subjects in Trial 101 had at least one TEAE related to thyroid suppression. A TEAE of blood thyroid stimulating hormone increased (Grade 1, possibly related to IMP, onset 20 days after latest infusion, not recovered at data cut-off) and hypothyroidism (Grade 2, probably related to treatment, onset 21 days after latest infusion, not recovered at data cut-off) was reported for one subject each.

While there were few measurements (at baseline or during treatment), there were no obvious trends in changes from baseline across visits for T4, free T4 or for TSH.

Anaphylactic Reactions

No AEs met the criteria for anaphylactic reactions.

Infections

A total of 20/109 (18.3%) and 5/24 (20.8%) of subjects had at least one TEAE belonging to the Infections and Infestations SOC in Trial 03-133 and Trial 101, respectively. Specific infection events were considered SAEs as follows in six subjects: device related infection and gastric infection, infectious colitis, pneumonia, and sepsis. Each of the serious infections was considered unrelated to study treatment by the investigator.

Of the 6 subjects with a serious infection, 3 had a Grade 3 or above decrease in WBCs (i.e., decrease WBC count, lymphopenia, or decreased neutrophil count). One subject (serious devise-related infection) had Grade 3 lymphopenia. Another subject (serious gastric infection) had Grade 3 lymphopenia. A further subject (serious pneumonia) had Grade 3 lymphopenia and Grade 3 neutrophil count decrease.

The risk of serious infections due to low white blood cell counts was quantified by pooling all subjects with a TEAE in the Infections and Infestations SOC from Trial 03-133 and Trial 101. Within this pool, a total of 18.8% of subjects had at least one TEAE and 3.8% had a TEAE of Grade 3 or higher belonging to the Infections and Infestations SOC.

Haemorrhage

There is a risk of haemorrhage due to low platelet count. A summary of TEAEs related to haemorrhage in Trial 03-133 and Trial 101 is provided in Table 66.

A total of 32/109 (29.4%) and 8/24 (33.3%) of subjects had at least one TEAE related to haemorrhage in Trial 03-133 and Trial 101, respectively. Specific haemorrhage events were considered SAEs. 2 subjects had serious intracranial haemorrhage. Both subjects had platelet count decrease of Grade 3 or above and the primary reason for haemorrhage was considered to be disease progression. A third subject had serious thrombocytopenic purpura.

The risk of haemorrhage was quantified by pooling all subjects with a TEAE in the SMQ of haemorrhage from Trial 03-133 and Trial 101. Within this pool, a total of 30.1% of subjects had at least one TEAE, and 2.3% had a TEAE CTCAE Grade ≥3 related to haemorrhage.

Table 58. Summary of TEAEs Related to Haemorrhage as Identified by MedDRA SMQ Haemorrhage Terms in Trial 03-133 and Trial 101

SMQ/ Preferred Term	Study 03-133 All (N=109) [n(%)], #events	Study 101 All (N=24) [n(%)], #events
Haemorrhage terms (excl laboratory terms) (SMQ)	32 (29.4), 49	8 (33.3), 11
Contusion	23 (21.1), 30	2 (8.3), 2
Petechiae	7 (6.4), 8	0
Epistaxis	4 (3.7), 4	1 (4.2), 3
Haematoma	0	3 (12.5), 4
Haemorrhage intracranial	0	2 (8.3), 2
Angina bullosa haemorrhagica	1 (0.9), 1	0
Catheter site haemorrhage	1 (0.9), 1	0
Central nervous system haemorrhage	1 (0.9), 1	0
Ecchymosis	1 (0.9), 1	0
Haematochezia	1 (0.9), 1	0
Immune thrombocytopenic purpura	1 (0.9), 1	0
Injection site haemorrhage	1 (0.9), 1	0

Source: Appendix 13.3

%=Percentage of subjects; N=Number of subjects.

Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in standardised MedDRA queries (SMQ) and preferred term (PT) rows are numbers of subjects reported at least one AE in that SMQ or PT. Subjects who reported more than one AE in a given SMQ or PT were counted only once for that particular SMQ or PT.

Note: Both broad and narrow terms were included.

2.2.8.4. Laboratory findings

Trial 03-133

Lymphocytes

Mean values for lymphocytes were close to the lower reference range value for all dose groups and cycles. Changes from baseline in lymphocyte values were variable; however, decreases in lymphocytes were observed for all dose groups around Day 8 during Cycle 1 or 2. In such cases, mean lymphocyte values dropped below the lower reference range value between Day 11 to Day 14. Following this drop, lymphocyte values remained close to the lower reference range value.

Neutrophils

In general, mean values for neutrophils were close to the lower reference range value for all dose groups and cycles. Changes from baseline in neutrophil values were highly variable. Mean neutrophil values dropped below the lower reference range value at least once for all dose groups and cycles, with the exception of the 50 mCi dose group for Cycle 3 and 4.

Platelets
Mean values for platelet were consistently below the lower reference range value for all dose groups and cycles. Changes from baseline in platelet values were highly variable. Platelet values dropped below the lower reference range value for the <50 mCi and 50 mCi dose groups on Day 11 during Cycle 1. Following this drop, platelet values for both dose groups generally remained below the normal reference range for the remainder of the cycle.

Trial 101
Across both trials (Trial 03-133 and Trial 101) trends in haematology lab values over time as well as reported TEAEs related to laboratory parameters (i.e., decreases in blood cell counts and occurrences of blood and lymphatic disorders such as lymphopenia and thrombocytopenia) indicate myelosuppression. Trends in laboratory values generally align with TEAEs in both trials. A decrease in platelet count led to the discontinuation of study treatment for eight subjects in Trial 03-133.

Liver Function Tests

Liver Function Test Values over Time
In Trial 03-133 mean values for laboratory parameters indicative of liver function (ALT and AST) were typically close to, or above the upper reference range value for all dose groups and there were no pronounced trends in changes from baseline in ALT and AST values across visits.
In Trial 101, one subject had a Grade 3 abnormally high value for ALT on a single assessment. No subjects had Grade 3 abnormally high values for AST.

Individual Clinically Meaningful Liver Function Test Abnormalities
In Trial 03-133, five subjects reported treatment-related Grade 3 or higher ALT increased (3 subjects) and AST increased (two subjects). ALT increased was reported as a nonserious lab toxicity in five subjects, and AST in one subject. In Trial 101, one subject reported a treatment-related Grade 3 event of ALT increased.

Summary of Liver Function Tests
Although there were increases in ALT and AST lab values in subjects across both trials, no TEAEs associated with liver dysfunction were reported. Thus, there is no indication of liver dysfunction in subjects.

Kidney Function Tests

Kidney Function Test Values over Time
In Trial 03-133 mean lab values for creatinine were typically close to or below the lower reference range value for all dose groups and cycles. There were no apparent trends in changes from baseline in creatinine across visits.
In Trial 101, abnormal creatinine values were all Grade 1.

Individual Clinically Meaningful Kidney Function Test Abnormalities
No TEAEs associated with kidney dysfunction were reported in either trial.

Summary of Kidney Function Tests
There is no indication of kidney dysfunction in subjects.

Other Blood Chemistry

For Trial 03-133, other blood chemistry parameters typically fluctuated within normal range. In addition, there were no apparent trends in changes from baseline across visits for these parameters. While there were few assessments (at baseline or during treatment), there were no obvious trends in changes from baseline across visits for free T4 or for TSH.
For Trial 101, increases in T4, free T4, and thyrotropin above the normal reference range in individual subjects was observed. Given the small number of assessments, there was a high degree of variability of mean thyroid hormones without obvious trends.
There was no change from baseline in urine protein levels from baseline to Cycle 1 Day 37.

Vital Signs and physical findings

Vital signs measured during Trial 03-133 and Trial 101 included heart rate, temperature, and blood pressure.

A number of findings were reported as TEAEs: The 6 cases of hypertension were all unrelated and patients have recovered. 11 cases of pyrexia were diagnosed, 8 thereof were possibly or probably related to the study drug and resolved. 9 unrelated cases with Grade 1-2 hypotension have resolved, too. All 15 events of tachycardia were assessed unrelated.

Physical Examination

Abnormal findings at physical examination were monitored during the course of Trial 03-133 and Trial 101. For Trial 101 specifically, physical examination included assessment of general appearance, mental status, and various organ systems (skin, head, eyes, ears, nose, mouth, throat, neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, and neurologic systems). Clinically significant changes in physical examination were to be reported as AEs. One case of weight decreased was reported.

In trial 03-133 there were subjects who had abnormal physical examination findings associated with various organ systems, but they were predominately minor in nature (e.g., dry cough, constipation, stuffy nose, etc.).

Radiographic Examination
Trial 03-133
In Trial 03-133, neurotoxicity was assessed clinically and radiographically. Assessment and grading of cortical atrophy, cerebral ventricular size, white matter changes or other abnormalities were performed by a neuroradiologist. Altered CSF flow was interpreted by the study nuclear medicine physicians. Results were abnormal for only one subject in which a mid-delay in CSF flow with no evidence of significant obstruction was observed.

Trial 101
In Trial 101, neurotoxicity assessments occurred as scheduled according to the National Cancer Institute clinical neurotoxicity criteria. All neurological abnormalities were recorded (at pre-treatment baseline and during the trial). Grade 3 or 4 neurotoxicity was assessed by trial physicians as being unrelated, possibly related, probably related, or related to trial drug. Predefined AESIs included neurotoxicities Grade 3 and above. None of the AESIs were related to neurotoxicities.

2.2.8.5. Safety in special populations

Intrinsic Factors

Incidence of Adverse Events by Age Group
For Trial 03-133, a numerically higher proportion of subjects aged 3 to 5 years had events related to myelosuppression (lymphopenia, reduced platelet count, reduced WBC count, and reduced neutrophil count) compared to the children <3 years. There were no other clinically meaningful differences in incidences of TEAEs between the age groups in Trial 03-133 and Trial 101.

Incidence of Adverse Events by Body Weight
Similar to what is seen for incidence of AEs by age, for Trial 03-133, a numerically higher proportion of subjects in the 15-25 kg group had reduced WBC and neutrophil counts compared to the children <15 kg. There were no other clinically meaningful differences in incidences of TEAEs between the age groups in Trial 03-133 and Trial 101.

Incidence of Adverse Events by Gender
There were no clinically meaningful differences between incidence of TEAEs by gender in Trial 03-133 and Trial 101.

Incidence of Adverse Events by Race
There were no clinically meaningful differences between incidence of TEAEs by race in Trial 03-133 and Trial 101.
Because of the limited number of subjects in subgroups based on age, body weight, gender, and race, it is difficult to draw any firm conclusions on safety in subgroups.

Given that neuroblastoma is a paediatric malignancy, the lack of data related to elderly subjects, pregnant women and lactation is a limited concern.

Extrinsic Factors

During the clinical development there has been a shift of drug product intermediate (DPI). For Trial 03-133 107 of 109 subjects in 03-133 were treated with ^{131}I-omburtamab produced from a MSK DPI batch for at least part of their treatment during the trial. 6 subjects (4 paediatric neuroblastoma subjects and 2 paediatric non-neuroblastoma subjects) received ^{131}I-omburtamab from Y-mAbs-produced DPI. All subjects in Trial 101 received treatment with ^{131}I-omburtamab from Y-mAbs-produced DPI. Given the similarity in types of AEs reported, frequency, severity and seriousness between Trial 03-133 and Trial 101, the change in DPI does not seem to have had any impact on the safety profile of ^{131}I-omburtamab.

Drug Interactions
No drug-drug interaction studies have been conducted with ^{131}I-omburtamab. It is recommended that live vaccines are not given concurrently with ^{131}I-omburtamab.

Use in Pregnancy and Lactation
^{131}I-omburtamab is contraindicated during pregnancy. Based on its mechanism of action, ^{131}I-omburtamab may cause foetal harm when administered to a pregnant woman, and monoclonal antibodies are known to be transported across the placental barrier. There are no data from the use of ^{131}I-omburtamab in pregnant women. No animal reproductive toxicology studies of ^{131}I-omburtamab have been conducted.

Breast-feeding should be discontinued during treatment with ^{131}I-omburtamab and for 1.5 months after end of treatment. It is unknown whether ^{131}I-omburtamab is excreted in breast milk. A risk to the new-borns/infants cannot be excluded.

Overdose

^{131}I-omburtamab must be used by authorised personnel in a hospital setting. The risk of overdose is therefore theoretical.

In the event of administration of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition and by forced diuresis and frequent bladder voiding. Additionally, blockade of the thyroid gland is recommended (e.g., with potassium perchlorate) in order to reduce the radiation exposure of the thyroid gland.

Drug Abuse

^{131}I-omburtamab abuse was not formally studied in clinical or nonclinical investigations.

^{131}I-omburtamab is administered by qualified healthcare professionals and is not for in-home use.

There have been no reports of drug abuse for ^{131}I-omburtamab. The risk abuse potential for ^{131}I-omburtamab is considered low.

Withdrawal and Rebound

Y-mAbs did not formally evaluate the effect of ^{131}I-omburtamab on withdrawal and rebound effects.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

It is considered unlikely that ^{131}I-omburtamab will affect a patient's ability to drive or to use machines; however, the patient's general condition and the possible side effects to treatment must be taken into account to assess this ability before driving or using machines.

2.2.8.6. Immunological events

As of the cut-off date for this MAA, no immunogenicity assessments have been conducted during the clinical programme.

Trial 101 was amended to collect samples for immunogenicity detection, and evaluation of immunogenicity is a secondary objective of the trial. Results from a to be developed assay will enable an investigation if there is any effect of ^{131}I-omburtamab antidrug antibodies on PK and safety and these analyses will be provided in the final CSR for Trial 101.

2.2.8.7. Adverse drug reactions

Information on Adverse Drug Reactions were provided with the responses. The methodology is described as causality assessment for each PT including an evaluation of potential biological plausible mechanism, potential temporal relationship, and established class effects. The assessment was performed by the sponsors safety and medical experts and were based on all reported AEs for ^{131}I-omburtamab (all doses) regardless of investigator assessment of investigational medicinal product (IMP) relationship. ADR calculation of frequencies is based on all TEAEs, which is acceptable as regards the heavily-pretreated patient population.

2.2.8.8. Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been conducted with ^{131}I-omburtamab. It is recommended that live vaccines are not given concurrently with ^{131}I-omburtamab.

2.2.8.9. Discontinuation due to adverse events

Adverse Events Leading to Discontinuation

Trial 03-133

Treatment-emergent adverse events that led to discontinuation of ^{131}I-omburtamab are summarised in Table 59. 11/109 (10.1%) subjects reported at least one TEAE leading to discontinuation of ^{131}I-omburtamab.

Table 59. Summary of Treatment Emergent Adverse Events Leading to Discontinuation of Study Treatment

System Organ Class Preferred Term	<50 mCi (N=10) [n(%)], #events	50 mCi (N=94) [n(%)], #events	>50 mCi (N=5) [n(%)], #events	All Subjects (N=109) [n(%)], #events
Number of TEAEs leading to discontinuation	3	7	2	12
Subjects with at least one TEAE leading to discontinuation	2 (20.0), 3	7 (7.4), 7	2 (40.0), 2	11 (10.1), 12
Blood and lymphatic system disorders	1 (10.0), 1	0	0	1 (0.9), 1
Immune thrombocytopenic purpura	1 (10.0), 1	0	0	1 (0.9), 1
Injury, poisoning and procedural complications	0	3 (3.2), 3	0	3 (2.8), 3
Meningitis chemical	0	3 (3.2), 3	0	3 (2.8), 3
Investigations	2 (20.0), 2	4 (4.3), 4	2 (40.0), 2	8 (7.3), 8
Platelet count decreased	2 (20.0), 2	4 (4.3), 4	2 (40.0), 2	8 (7.3), 8

Source: CSR 03-133 Table 14.3.1.32.
%=Percentage of subjects; N=Number of subjects.
Note: Adverse events (AEs) are coded using MedDRA v20.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects who experienced at least one AE in that SOC or PT. Subjects who experienced more than one AE in a given SOC or PT were counted only once for that particular SOC or PT.

Trial 101

Treatment-emergent adverse events that led to the discontinuation of ^{131}I-omburtamab are summarised in Table 60.

Table 61. Treatment-Emergent Adverse Events Leading to Discontinuation of ^{131}I-Omburtamab Treatment by System Organ Class and preferred Term.

System Organ Class Preferred Term	^{131}I-omburtamab N (%) E
Safety Analysis Set	32
Any adverse event leading to discontinuation from treatment	6 (18.8) 7
Investigations	**5 (15.6) 6**
Platelet count decreased	5 (15.6) 5
Lymphocyte count decreased	1 (3.1) 1
Injury, Poisoning and Procedural Complications	**1 (3.1) 1**
Meningitis chemical	1 (3.1) 1

Source: Table 14.3.1.11 and Listing 14.3.2.6.
N: Number of subjects; %: Percentage of subjects. E: Number of events. A treatment emergent adverse event is defined as an AE with onset at or after administration of infusion of ^{131}I-omburtamab. The summary does not include non-serious adverse events that occurred more than 21+2 days after last treatment.

According to Table 61, 6/32 (18.8%) discontinued ^{131}I-omburtamab due to 7 TEAEs. Six of these seven TEAEs were consistent with myelosuppression with the most frequent TEAE being 'platelet count decreased'. In addition to the myelosuppression events, an event of chemical meningitis led to discontinuation of study drug of one enrolled subject.

28 SAF subjects were documented as having discontinued treatment due to an intervening circumstance. For the SAF, progressive disease (12 subjects [11.0%]) and Other (11 subjects [10.1%]) accounted for the highest number of reasons for discontinuing treatment. 4 SAF subjects (3.7%) discontinued treatment due to excessive toxicity. The Other reasons were low platelets with or without low neutrophils (6 subjects [5.5%]), medical events that required treatment cessation (3 subjects [2.8%]), or investigator discretion for other treatments (2 subjects [1.8%]).

The majority of non-neuroblastoma analysis set (NNAS) subjects received a 50 mCi treatment dose (23 subjects [62.2%]. Of the 37 NNAS subjects, 13 were categorised in the clinical database as having completed treatment as of the data cut-off date. Progressive disease (11 subjects [29.7%]) was the most frequently documented reason for discontinuing treatment. One subject (2.7%) ended treatment due to excessive toxicity, and one subject (2.7%) ended treatment due to a reason in the category of Other.

2.2.8.10. Post marketing experience

There are no post-marketing data for ^{131}I-omburtamab.

2.2.9. Discussion on clinical safety

The heterogenous nature and quality of the safety data was discussed in the Pre-submission meeting with Rapporteur teams on 23 November 2020. The MAA acknowledged that: "*Trials 03-133 and 101 have been initiated and conducted at different time periods. Therefore inevitably, there are differences in trial design, data capturing, and procedures between the two trials*." The Rapporteur team agreed with the presented strategy not to pool the clinical safety data from Trial 03-133 and Trial 101 for the MAA and that any similarities and differences across studies would be discussed as side-by-side comparisons.

Study population and exposure
Safety data were collected in two ongoing open-label, single-arm trials 03-133 and 101. The applicant initially presented interim report data of 109 and 24 paediatric neuroblastoma subjects, respectively, with CNS/LM metastasis expressing B7-H3 (CD276). An updated clinical interim report of study 101 with cut-off date June 2021 was submitted with the responses. Supportive serious adverse event data come from 37 paediatric non-neuroblastoma patients (03-133). The safety analysis population (SAF) of trial 03-133 consists of 109 enrolled neuroblastoma patients and the SAF of trial 101 includes all enrolled subjects who received at least one dose of ^{131}I-omburtamab.

Subjects in both Trial 03-133 and Trial 101 had received various types of prior treatments. In both trials, the majority had received a combination of surgery, chemotherapy, irradiation and ASCT, thus constituting a heavily pre-treated population. In the period between relapse and before initiation of ^{131}I-omburtamab administration, the same treatments with similar frequencies were applied suggesting that all available treatment options were exhausted.

Trial 03-133 employed a two-part dosing regimen: In Part 1 (dose-escalation part) patients received an icv infusion of ^{131}I-omburtamab ranging from 10 to 80 mCi administered at week 2 by icv infusion preceded by a 2 mCi ^{124}I-omburtamab or ^{131}I-omburtamab dosimetry dose of 2mCi. In part 2 (cohort expansion part) all subjects were treated at 50 mCi icv at week 2 and 7, also preceded by a 2 mCi ^{124}I-omburtamab or ^{131}I-omburtamab. This Part 2 dosing regimen was also applied in trial 101 and is the intended posology for the claimed indication. Age-dependent dose reductions were performed for infants.

In trial 03-133, the mean exposure was lower than in trial 101; patients had fewer treatment cycles and a lower mean dosage (70 vs. 75.4 mCi).

Treatment-emergent Adverse Events
In both trials, almost every patient experienced treatment-emergent as well as treatment-related adverse events across all administered doses, and the majority had events ≥Grade 3. Serious adverse events were common, and about a third had treatment-related serious adverse events.

In trial **03-133**, most study subjects experienced TEAEs in SOCs Investigations (71.6%), Blood and lymphatic system disorders (66.1%), Gastrointestinal disorders (55.0%), Respiratory, thoracic and mediastinal disorders (37.6%) and Nervous system disorders (33%).
The most frequent PTs were lymphopenia (64.2%), platelet count decreased (54.1%), and WBC count decreased (46.8%), suggesting a myelosuppressive side effect, an anticipated risk of omburtamab treatment. Moreover, vomiting was reported by 34.9% and Headache by 24.8% as central nervous secondary effects. 69.2% of all TEAEs were ≥CTCAE Grade 3/4 with a similar distribution across SOCs as listed above. Grade 4 TEAEs were of similar quality, furthermore myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) were diagnosed in 2.8% and 1.8% of the patients, respectively. TEAE intensity seemingly increased with doses >50 mCi, however, in this dose group only 5 patients were included limiting significance of the results, thus, a treatment-by-subgroup effect is difficult to identify.

Throughout **trial 101**, most TEAEs were reported in SOCs Investigations (87.5%), Gastrointestinal disorders (50.0%), Respiratory, thoracic and mediastinal disorders (50%), Nervous system disorders (45.8%), and General disorders and administration site conditions (45.8%). The most frequently reported PTs were platelet count decreased (62.5%), WBC count decreased (50.0%), lymphocyte

decreased (41.7%), neutrophil count decreased (37.5%), and anaemia (33.3%), Nausea (33.3%), and Headache (33.3%). Thus, results were relatively similar across both studies.

Based on the listing of concomitant therapies and procedures, only one patient had simultaneous radiotherapy and two concomitant chemotherapies, thus, it is likely that these observed effects were related to the IMP itself and to the extensive pre-trial treatments, respectively. Due to the lack of control groups, it is doubtful if any further data can substantially improve the understanding of whether pre-trial treatments or ^{131}I-omburtamab are causing the adverse reactions. The 3-week treatment wash-out period implemented in both trials hardly excludes pre-trial treatments as causally involved in the myelosuppression and its consequences.

The most frequently reported related TEAE was cytopenia with a similar incidence in both trials. Infusion-related TEAEs were reported in about half of the patient population in both studies. Several cases with chemical meningitis occurred throughout both studies, an adverse reaction already known to be associated with intracerebroventricular injections.

Serious Adverse Events
Proportions of patients that experienced SAEs were similar in both trials (48.6% vs. 41.7%), treatment-related SAEs had 32.1% vs. 41%, respectively. The SAE profile was broadly similar in studies 03-133 and 101, and as described above, most TEAEs were reported in SOC Investigations due to myelosuppression and elevated liver enzymes. Apart from SOC Investigations, no specific SAE cluster is evident.
In trial 101 further SAEs were reported, i.e. lymphocyte count decreased, intracranial haemorrhage, and lymphopenia. One patient died due to intracranial haemorrhage. The cause is difficult to identify based on the narratives and may have been associated with disease progression or the concurrent thrombocytopenia.

Adverse Events of Special Interest
Only for trial 101 AESIs were predefined including myelosuppression ≥ Grade 4, liver and neurotoxicities ≥Grade 3, device related infections, chemical meningitis, and worsening of performance test. These data were supplemented by investigations of AEs by organ systems for both trial 03-133 and 101 including general signs of myelosuppression, liver and neurotoxicities, thyroid suppression, anaphylactic reactions, secondary malignancies, infections and haemorrhage.
As described above, AESI associated with myelosuppression prevailed in both trials affecting all three haematopoietic cell lines. It is known that ionizing radiation impairs haematopoiesis, inter alia, through dose-dependent declines in circulating haematopoietic cells caused by reduced bone marrow production, redistribution and apoptosis of mature cells, in some cases resulting in leukaemia as long-term effect.
Secondary malignancies were reported for 5.5% of the patients in trial 03-133, 6 patients developed MDS (one of these was fatal after five years) and 4 AML and at least 3 cases were assessed as possibly related to omburtamab. No cases occurred in trial 101. Every third patient had TEAEs related to haemorrhage, most likely due to decreased platelet counts, and 2 cases of serious haemorrhage occurred. A potential relationship between myelosuppression and infections cannot be ruled out, however the frequency of infections ≥Grade 3 was relatively low. Neurotoxic effects were common in both trials. Hepatic toxicities occurred in some patients without associated TEAEs.

The applicant referred to earlier studies assessing the safety and complication rate associated with ventricular access devices in patients receiving compartmental intraventricular radioimmunotherapy and concluded that minimal acute complications are observed, and long-term complications are rare.
Intracerebroventricular route of administration appears to be a safe and well-tolerated method of long-term drug delivery in both paediatric and adult patients. It is acknowledged that no short-term dose-

limiting toxicities were reported. Long-term effects could not have been investigated. In addition, the safety of the medical device used seems well documented (low complication rate, low long – term complications). Based on submitted data, the variability in the rates of Ommaya reservoir non-infectious complications is influenced by the improved neuroguidance for placement of an ICV device.

Laboratory findings/Vital signs
The laboratory abnormalities recorded throughout the studies are consistent with the clinical condition of the patient population and treatment effects. No additional safety concern has been identified by analysing laboratory parameters, however, the assessment of related harmful therapeutic effects is only possible with restrictions as this population is heavily pre-treated and no comparative, but concomitant treatment was administered. Data on vital signs need to be prepared and presented differently.

Immunogenicity
No immunogenicity results are hitherto available. In trial 03-133, two patients experienced each ≥Grade 3 and ≥Grade 4 Hypersensitivity assessed in both cases as related. However, causality assessment is hampered by the fact that immunogenicity detection is only part of ongoing trial 101.

Discontinuation due to TEAEs
In study 03-133, the AEs leading to treatment discontinuation in 10 patients were decreases in platelet count (8/109 subjects; 7.3%), chemical meningitis (3/109 subjects; 2.8%), and immune thrombocytopenic purpura (1/109 subjects; 0.9%).
In study 101 a third of the study subjects discontinued omburtamab treatment. Decreased platelet count was the only TEAE leading to withdrawal that occurred in 7/24 (29.2%) patients, all other TEAEs were reported for single patient only.

Safety results included in the submitted updated interim report of clinical trial 101 are consistent with those of the primary safety analysis.

Long-term post-marketing safety data with a specific focus on neurocognitive adverse effects are deemed important as the drug has potential curative intent. Assessment of the long-term safety of ^{131}I-Omburtamab was not planned in both studies, however, some data on neurocognitive function will be available when trial 101 will have been finalised. The inclusion of 'long-term safety including neurocognitive development' as Missing Information in the Summary of Safety Concerns of the RMP was proposed by the applicant and is endorsed.

In conclusion, myelosuppression is an important identified risk, and the proposed PI provides advice regarding suspension of treatment until acceptable blood counts return. Chemical meningitis is an important identified risk, and the proposed PI provides advice regarding monitoring, pre-treatment with dexamethasone and permanent discontinuation in patients experiencing this adverse reaction. Adverse events related to hepatic toxicity were based solely on laboratory values; there were no clinical signs of impaired hepatic function. If a patient shows hepatic toxicity, it is recommended to suspend or delay the administration until toxicities return to acceptable levels. Neurotoxicity was observed in a small number of children; patients experiencing neurotoxicity CTCAE grade 4 should be permanently discontinued from the treatment. Thyroid suppression is a potential risk with ^{131}I-omburtamab due to the effects of radioactive iodine on the thyroid. The risk is mitigated by treating all subjects with thyroid-blocking agents from one week before treatment until two weeks after the last therapeutic dose. ^{131}I-omburtamab may cause serious infusion reactions. In order to mitigate the risk of such reactions, the patient should prophylactically be given dexamethasone (or equivalent) and an oral antihistamine, moreover ^{131}I-omburtamab should be permanently discontinued in patients who develop serious infusion reactions including CTCAE Grade 3 or higher anaphylaxis. Increased susceptibility to infections can occur in patients with myelosuppression. Thus, blood counts should be monitored in order to mitigate the risk of

infections as stated in the Product Information. Due to radiation exposure to bone marrow, serious haemorrhage is a potential risk with ^{131}I-omburtamab due to low platelet counts. In the Product Information, patients are advised to seek immediate medical attention if unexpected bleeding or other signs develop.

Due to the radioactive properties of the product, ^{131}I-omburtamab is only to be handled and administered by specialised health care professionals.

2.2.10. Conclusions on the clinical safety

Most frequently reported related TEAEs were consistent with myelosuppression, neurotoxicity and infusion related reactions. Respective risk-mitigation measures have been reflected in the proposed Product Information. The summary of safety concerns in the RMP was amended accordingly.

Overall, the heterogeneous nature and quality of safety data issuing from differences in trial designs, data capturing, and procedures between the two trials render a comparison of safety results difficult. The single-arm designs including limited patient numbers as well as the considerable number of treatment discontinuations impede the evaluation of the safety profile, especially in light of the fact that comparable treatments are lacking.

Long-term post-marketing safety data with a specific focus on neurocognitive adverse effects are deemed important as the drug has potential curative intent. Considering the unmet medical need, a post-authorisation study would be warranted (see section 2.3 Risk Management Plan). However, similar to the pivotal single arm trial the interpretation of data from a post-authorisation study would be challenging if the product is used as a second line treatment in patients having been exposed to first line treatments (radiation and cytotoxic drugs). Thus, only a study of infusion related reactions may be possible but considering the indication, it is questionable if this safety concern can be classified as important. Without controls only severe toxicities would be detected whereas mild ones would probably go undetected. However, even under the given circumstances, every effort should be made to characterise the safety profile as precisely as possible.

Safety data from this heavily pre-treated patient population were collected in the context of two open-label and single-arm trials yielding data that are difficult to interpret. However, the described uncertainties related to data acquisition and interpretation may be tolerable if the efficacy of the product could have been clearly demonstrated.

The CHMP considers the following measures would be necessary to address issues related to safety:

A long-term, observational cohort study of children with neuroblastoma who are new users of Omblastys following other central nervous system (CNS)- directed multi-modal therapy for the treatment of CNS/leptomeningeal (LM) metastasis in the real-world setting.

2.3. Risk Management Plan

2.3.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None

Summary of safety concerns	
Important potential risks	• Myelosuppression and prolonged cytopenia • Chemical meningitis. • Secondary malignancies
Missing information	• Use in patients who have received systemic chemotherapy and/or cranial or spinal irradiation less than 3 weeks prior to the start of the treatment. • Immunogenicity. • Long-term safety including neurocognitive development.

2.3.2. Pharmacovigilance plan

Table Part III.3: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
Voluntary PASS	A long-term, observational cohort study of children with neuroblastoma who are new users of Omblastys following other central nervous system (CNS)-directed multi-modal therapy for the treatment of CNS/leptomeningeal (LM) metastasis in the real-world setting.	Myelosuppression and prolonged cytopenia (and potentially associated (non-opportunistic infections and bleeds), Chemical meningitis Secondary malignancies	To be determined	To be determined

2.3.3. Risk minimisation measures

Table 62 Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Myelosuppression and prolonged cytopenia	***Routine risk minimization measures:*** SmPC section 4.2 and 4.4 PL section 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.2 and 4.4 and PL Section 3 where requirements are given for haematology tests before each administration and every week for four weeks after administration. • SmPC section 4.2 where criteria are given for dose modification based on haematology test results. • SmPC section 4.4 informing that severe myelosuppression may be treated with transfusions or growth factors in accordance with local medical practice. • SmPC section 4.4 instructing to withhold initial treatment or delay second treatment with Omblastys in patients with a grade 4 infection. PL Section 2 which informs patients to tell the doctor if having a life-threatening infection. • PL Section 2 which informs patients to immediately tell the doctor if experiencing	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Post-marketing follow-up questionnaire. ***Additional pharmacovigilance activities:*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	unexpected bleedings or severe headache. ***Additional risk minimization*** ***measures:*** None ***Legal status:*** Medicinal product subject to restricted medical prescription	
Chemical meningitis	***Routine risk minimization measures:*** SmPC section 4.4 and 4.4 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.2 and 4.4 where pre-medication with dexamethasone is described. • SmPC Section 4.2 where instruction is given to permanently discontinue Omblastys in event of chemical meningitis. • SmPC Section 4.4 where instructions are given to monitor blood counts and to not initiate or resume Omblastys until lab values are at acceptable ranges. • PL Section 2 which informs patients about early signs and symptoms of chemical meningitis and to	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Post-marketing follow-up questionnaire ***Additional pharmacovigilance*** ***activities:*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	immediately tell the doctor if such occur. ***Additional risk minimization*** ***measures:*** None ***Legal status:*** Medicinal product subject to restricted medical prescription	
Secondary malignancies	***Routine risk minimization measures:*** SmPC section 4.2 and 4.4 PL section 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 and 4.4 and PL Section 3 where treatment with potassium iodide and liothyronine sodium prior to and after Omblastys administration is described. • SmPC Section 4.4 where it is described that it must be ensured that the risks of the radiation exposure are less than the risks from the disease itself, especially for patients having received prior radiation/chemotherapy. ***Additional risk minimization*** ***measures:*** None ***Legal status:***	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** Post-marketing follow-up questionnaire. ***Additional pharmacovigilance*** ***activities:*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Medicinal product subject to restricted medical prescription	
Missing Information		
Use in patients who have received systemic chemotherapy and/or cranial or spinal irradiation less than 3 weeks prior to the start of the treatment	***Routine risk minimization measures:*** SmPC section 4.4 PL section 2 ***Additional risk minimization measures:*** None ***Legal status:*** Medicinal product subject to restricted medical prescription	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Immunogenicity	***Routine risk minimization measures:*** SmPC section 4.4 ***Additional risk minimization measures:*** None ***Legal status:*** Medicinal product subject to restricted medical prescription	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Long-term safety including neurocognitive development	***Routine risk minimization measures:*** None	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: Medicinal product subject to restricted medical prescription	***Additional pharmacovigilance activities:*** None

2.3.4. Conclusion

The CHMP, 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.

2.4. Pharmacovigilance

2.4.1. Pharmacovigilance system

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

2.4.2. Periodic Safety Update Reports submission requirements

Not applicable

2.5. Product information

In light of the negative recommendation, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.5.1. User consultation

In light of the negative recommendation, a satisfactory package leaflet cannot be agreed at this stage, therefore no user testing consultation has been assessed.

2.5.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The Group accepted the proposed translation exemption to have English-only outer carton and vial label.

However, the Group didn’t reach an agreement on the proposed translation exemption of the package leaflet. Therefore, the applicant is requested to liaise with the NCAs to discuss requirements and

alternatives at national level. The applicant should explore the feasibility of including a QR code on the package leaflet to provide information in all EU official languages. Alternatively, a printed package leaflet in national language could be distributed alongside the supplies of the product, under the responsibility of the MAH.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.5.3. Additional monitoring

Not Applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The initially sought indication for ^{131}I-omburtamab is "OMBLASTYS is indicated for the treatment of neuroblastoma with central nervous system (CNS)/leptomeningeal (LM) metastasis."

Neuroblastoma is a rare paediatric cancer and is the most common extra-cranial solid tumour cancer in children. High-risk neuroblastoma is a life-threatening disease that is associated with poor long-term survival. For high-risk patients, 5-year overall survival (OS) rates have improved during the last two decades but are still below 50%.

Neuroblastoma with CNS/LM metastasis is neuroblastoma that at initial staging or at relapse, has metastasised to the brain parenchyma and/or the leptomeninges. The clinical presentation of CNS/LM neuroblastoma is dependent on the location and nature of the lesion. The diagnosis of CNS/LM neuroblastoma is based on clinical symptoms and imaging.

3.1.2. Available therapies and unmet medical need

Surgery, chemotherapy, immunotherapy, differentiation therapy and radiotherapy techniques for newly diagnosed patients have improved the prognosis of patients with stage 4, high-risk neuroblastoma. However, recurrent disease occurs in many patients with high-risk neuroblastoma, and CNS/LM metastasis primarily occurs in the relapsed or recurrent setting.

Various treatment combinations comprise one or more of the following standard options for metastatic CNS/LM neuroblastoma, all with the aim of reducing symptoms, but with modest chance of cure:

- Surgical debulking of tumour when feasible prior to irradiation, to reduce symptoms, oedema, and haemorrhage, or to correct cerebrospinal fluid (CSF) flow.
- Focal, whole brain irradiation, or craniospinal irradiation (where feasible) to alleviate symptoms, obtain disease control, and correct CSF flow in cases of obstruction.
- Systemic combination chemotherapy (e.g., irinotecan plus temozolomide).
- Myeloablative therapy and stem cell transplantation.

Data obtained from the Central German Childhood Cancer Registry (CGCCR) which include the majority of neuroblastoma patients enrolled in clinical trials in Germany, show that the treatment modalities for CNS/LM neuroblastoma are not uniform, even on a nationwide level in Germany.

Currently there are no approved medicinal products for the treatment of neuroblastoma metastasised to the CNS/LM. There exists an unmet medical need for these patients as the prognosis with available therapies is still unsatisfactory. The current aim of treatment is prolongation of survival.

3.1.3. Main clinical studies

The application is mainly based on trial 03-133. This single arm trial recruited patients with a histologically-confirmed diagnosis of an omburtamab-reactive-malignancy with CNS/LM disease but the majority of patients had relapsed neuroblastoma with CNS/LM disease (n=109). The majority of patients received a total dose of 1850 MBq in one or two doses.

Trial 101 is a smaller trial in neuroblastoma with CNS/LM disease that is considered supportive (n=50).

3.2. Favourable effects

The most important favourable effect to consider is the 3-year OS rate that is derived from the trial 03-133. The 3-year OS rate (KM estimate) for the FAS was 0.56 (95%CI 0.46, 0.65). The median survival is estimated as 50 months (95% CI 27.4, not estimable).

Supportive information can be derived from the 12-month CNS/LM PFS rate. This is estimated as 0.59 (95%CI 0.48, 0.68).

To further support the conclusion of efficacy a propensity score model was developed. Using this model to compare OS in the trial population to the selected external control a final HR of 0.58 (95%CI: 0.31, 1.09) was derived.

In the supportive trial 7 objective responses have been observed resulting in an ORR of 35% if only patients with measurable disease at baseline (n=20) are used as the denominator.

3.3. Uncertainties and limitations about favourable effects

Data for efficacy are derived from an exploratory trial without pre-specified hypothesis or analysis plan. The trial was subject to many modifications. The supportive trial is too small to allow conclusions. There is no confirmatory element to the clinical development plan.

The chosen endpoints (landmark analyses of time related endpoints, e.g., 3-year OS rate, 12-month CNS/LM PFS) are unsuited to establish efficacy in single arm trials. Analysis and comparison to controls is indispensable in a complex disease with complex, non-standardised treatments. The tumour response to treatment was not analysed in the main dataset from trial 03-133.

As this was a single centre trial, many patients were referred after additional unspecified/non-explicit selection in the referring centres. The process that led to selection and referral of patients is unknown. Aside from selection bias, this also has impact on the external validity of the results.

Patients received additional treatments (irradiation, chemotherapy, surgery) in varying combinations and the impact of the different treatments on the endpoints cannot be differentiated. The population is heterogenous, also with respect to the presence or absence of CNS/LM disease at baseline, i.e., prior to the administration of the experimental therapy.

The population was selected based on clinical course and presence of stable disease. Comparison to an external control emphasised differences in treatments administered to patients prior to the administration of the experimental treatment. The performed comparison of OS between patients from trial 03-133 and the external CGCCR patients show important differences in the shape of the KM-plots that are not compatible with a treatment effect but point to prognostically distinct populations and an immortal time bias.

The use of subgroups from external controls to make the results comparable with the finalised study 03-133 raise serious issues on the reliability of the results and their clinical relevance. In order to further explore the data and enable the use of the collected time-related endpoint a propensity score method was used. The employed advanced statistical methods do not allow the establishment of efficacy as they cannot address the fundamental uncertainties related to selection and unmeasured confounding. In any case, even despite this major effort in the development of the model the obtained results are not considered compelling.

3.4. Unfavourable effects

In the two studies 03-133 and 101, respectively, using the recommended dosing regimen with *ICV* administration of ^{131}I-Omburtamab almost every patient (93.6%* and 100%) experienced treatment-emergent adverse events (TEAEs). The most frequent TEAEs were cytopenia such as decreased lymphocyte, platelet, WBC, and neutrophil count, as well as decreased haemoglobin, consistent with myelosuppression. Further frequently reported TEAEs were vomiting, nausea, cough, headache and pyrexia.

As to AESI, hepatic toxicities were experienced by 7.3% and 4.2% of patients, respectively for each of the two studies. Serious adverse events (SAEs) included elevated liver enzymes. Secondary malignancies were reported for 5.5% and 0% of patients respectively; overall, 6 patients developed MDS and 4 AML and at least 3 cases were assessed as possibly related to omburtamab. 6.4% and 12.5% of patients, respectively had symptoms of neurotoxicity such as seizures (2 were SAEs), meningitis (3/4 were SAEs) and sensory neuropathy. Worsening of performance was noted in 20.8% of the patients in trial 101. Overall, 18.3% and 20.8% reported infections in each of the two studies, 6 patients experienced unrelated serious infections and 3 thereof had reduced WBC. 29.4% and 33.3% of patients, respectively for each of the two studies, had TEAEs related to haemorrhage, and 2 cases of serious haemorrhage occurred (see above, 1 presented with serious thrombocytopenic purpura. Pooled data of both trials yielded a frequency of 2.3% for ≥Grade 3 haemorrhage.

Most patients (84.4% and 87.5% respectively for each of the two studies) experienced at least one severe (grade 3/4) AE. The most frequent severe AEs were related to myelosuppression, moreover, patients had elevated liver enzymes and some developed myelodysplastic syndrome and acute myeloid leukaemia.

SAEs were experienced by 48.6% and 47.7% of patients respectively for each of the two studies; the vast majority of the SAEs was assessed as treatment-related. Most TEAEs were reported in SOC Investigations due to myelosuppression and elevated liver enzymes. Apart from SOC Investigations, no specific SAE cluster is evident. As to PTs, reported SAEs for >2 patients were WBC/platelet/neutrophil count decreased, haemoglobin decreased, ALT increased, vomiting, MDS and chemical meningitis.

In the whole safety database 5 deaths occurred, 2 due to haemorrhagic events possibly related to ^{131}I-omburtamab; 3 were the result of disease progression.

25.7% and 33.3% of patients respectively for each of the two studies, discontinued the study drug due to TEAEs such as progressive disease, excessive toxicity, low platelets with or without low neutrophils, medical events that required treatment cessation or investigator discretion for other treatments.

Data on long-term effects assessing the safety and complication rate associated with ventricular access devices in patients receiving compartmental intraventricular radioimmunotherapy are missing.

3.5. Uncertainties and limitations about unfavourable effects

The methodological issues described under 'uncertainties and limitations about favourable effects' also affect the data validity and interpretability of the safety profile.

The size of the safety database is currently limited with many withdrawals in both studies. As Study 101 is considered to have more prospective elements, this database could provide more reliable information, however, effects of ^{131}I-Omburtamab treatment cannot be determined properly on the basis of 50 patients.

The single-arm trial design contributes to a difficult interpretation of safety data as it hampers conclusions on treatment-related AEs and especially the distinction between treatment-related TEAEs

and disease-related events. Included patients seem not to have been standardised regarding the pre-treatments and some patients received concomitant therapies which makes it difficult to disentangle side effects.

Lacking immunogenicity data hinder the characterisation of the safety profile as well as missing long-term safety data with a specific focus on neurocognitive and developmental adverse effects.

Inaccuracies relating to the data processing and presentation hamper the overall interpretation of the results. These findings lead to uncertainties on the safety profile, which is already difficult to determine in light of the fact that maximally 2 cycles in 6 weeks are administered in a heavily pre-treated patient population.

Thus, a full assessment of the safety profile is not possible.

3.6. EFFECTS Table

Table 63. Effects Table for ^{131}I-Omburtamab for the treatment of paediatric patients with central nervous system (CNS)/leptomeningeal metastasis from neuroblastoma (data cut-offs: 30 June 2019 for trial 03-133 and 01 June 2020 for trial 101).

Effect	Short Description	Unit	Treatment ^{131}Omburtamab	Uncertainties/ Strength of evidence	References
Favourable Effects (study 03-133)					
3-year overall survival rate (trial 03-133)	KM estimate of OS rate three years after diagnosis		0.56 95%CI (0.46, 0.65)	Methodological: exploratory trial, single arm, no hypothesis, no pre-specified planning of data analysis; inherent difficulty to establish efficacy on the basis of time-related endpoint in single arm trial Data assessment: Selected population; external control not comparable with differing treatment intensity; possible immortal time bias; prior and concomitant treatments with possible effect on LM/PM.	

Effect	Short Description	Unit	Treatment ^{131}Omburtamab	Uncertainties/ Strength of evidence	References
12month CNS/LM progression free survival rate	KM estimate of OS rate three years after diagnosis (FAS)		0.59 (95% CI: 0.44, 0.68)	See above, in addition magnitude of effect cannot be assessed without control	
Unfavourable Effects					
TEAE	Patients with at least 1 treatment-related TEAE of ≥Grade 3	%	81.7[1] 83.3[2]	No control	
TE-SAE	At least 1 treatment-emergent serious AE	%	48.6[1] 41.7[2]	No control	
Death	TEAEs leading to death	%	1[1] 4[2]	No control	

Abbreviations: AE: Adverse event, TEAE: Treatment- emergent AE, SAE: Serious AE

Notes: [1]source: CSR 03-133, [2]source: CSR trial 101, 3: CSR 03-133, App.13.31, Pooled data

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

3-year OS rate is a clinically relevant endpoint as it could indicate longer term survival in patients with a malignant disease such as neuroblastoma. 12-month CNS/LM PFS is an unusual endpoint but could be accepted in these specific circumstances. Nevertheless, the interpretation of OS and PFS without a comparator group is not possible. The original purpose of the pivotal study 03-133 was dose-finding and safety of an experimental targeted radiotherapy. From a confirmatory perspective the insufficient planning and fundamental flaws in the trial design, the questionable choice of endpoints for the chosen single-arm trial, the changes in the conduct and the analysis while the trial was ongoing, are obvious concerns. The provided analyses to the external control cannot address the issues that were observed for the pivotal trial. Selection bias and confounders are likely to be present and comparability of the populations is not accepted.

Overall, the study design as well as the data processing of both trials prohibit any thorough assessment of the safety profile. The restricted sample size renders it difficult to detect rare adverse events, so nearly every treatment-emergent adverse event is considered related and listed as adverse drug reaction. Due to the relatively large number of treatment discontinuations the safety profile is difficult

to characterise in an already small study population, even if it seems that 50% of TEAEs resolved in trial 101 (no information available as to trial 03-133). However, this aspect per se may be an expression of poor tolerance towards ^{131}I-omburtamab. Considering the dismal prognosis of the investigated study population, the described uncertainties related to data collection and interpretation could have been acceptable if the efficacy of the product was clearly demonstrated which is not the case with the data provided. Taken together, more prospective and unified (long-term) data are needed to provide meaningful results regarding the characterisation of a safety profile in the claimed indication. Currently, the quality of the data submitted merely enables a descriptive data interpretation.

3.7.2. Balance of benefits and risks

A favourable effect of ^{131}I-omburtamab has not been demonstrated and the safety profile cannot be sufficiently characterised for the reasons stated above. The benefit-risk balance of ^{131}I-Omburtamab is unfavourable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk balance of Omblastys is negative.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Omblastys in the treatment of central nervous system (CNS)/leptomeningeal (LM) metastasis of neuroblastoma in patients, who have previously received CNS-directed multi-modal therapy for their disease, such as chemotherapy, surgery, or radiation therapy, the CHMP considers by consensus that the safety and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for Omblastys. The CHMP considers that:

- The trial design and subsequently conducted analyses do not allow to isolate a treatment effect that can be attributed to ^{131}I-omburtamab. In analyses of time related endpoints where trial data are compared to an external control in a post-hoc manner, it cannot be ascertained with reasonable certainty, that underlying prognosis in the respective groups is sufficiently similar. The response data from the supportive trial are not considered robust enough to ameliorate the identified concerns concerning the pivotal data set. These concerns are based on confounding by additionally administered therapies and divergent imaging assessments.
- It should be noted that concerns remain regarding the stability of the ^{131}I-omburtamab drug product in artificial cerebrospinal fluid (aCSF) as well as human plasma/human serum. Non-targeted delivery of ^{131}Iodine poses a risk to patient safety, therefore the stability of ^{131}I-omburtamab must be demonstrated.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as previously outlined in the list of outstanding issues cannot be agreed at this stage.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Omblastys is not similar to Qarziba within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

New active substance

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is that ^{131}I omburtamab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.