27 February 2025
EMA/96948/2025
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Kizfizo

International non-proprietary name: temozolomide

Procedure No. EMEA/H/C/006169/0000

Note

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

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List of abbreviations

A	Anaemia
AAS	Atomic absorption spectrometry
AE	Adverse event
AIC	5-aminoimidazole-4-carboxamide
Amp	Amplified
ANC	Absolute neutrophil count
AP	Applicant's part (or open part) of an ASMF
API	Active pharmaceutical ingredient
AR	Assessment report
AS	Active substance
ASM	Active substance manufacturer
ASMF	Active substance master file = drug master file
ATC	Anatomical therapeutic chemical
AUC	Area under curve
AUC0-t	Area under the curve up to the last quantifiable concentration at time t
AUCextra	Extrapolated area under the curve
BCS	Biopharmaceutics classification system
BIT	Bevacizumab + irinotecan + temozolomide
BT	Bevacizumab + temozolomide
BTTo	Bevacizumab + temozolomide + topotecan
CEP	Certificate of suitability with the European Pharmacopoeia
CFU	Colony forming units
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
Cmax	Observed maximum plasma concentration
CMS	concerned member state
CNS	Central nervous system
CoA	Certificate of analysis
COJEC	Cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide
CPP	Critical process parameter
CQA	Critical quality attribute
CR	Complete response
CRS	Chemical reference substance (official standard)
CSR	Clinical study report
CV	Coefficient of variation
CVMP	Committee for Medicinal Products for Veterinary use
D	Day
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoE	Design of experiments
DoR	Duration of response
DP	Decentralised (application) procedure
DP	Drug product
DPM	Drug product manufacturer
DS	Drug substance
DSC	Differential scanning calorimetry
DSM	Drug product manufacturer
EC	European Commission
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EFS	Event-free survival
EMA	European Medicines Agency
EP/ Ph. Eur.	European Pharmacopoeia
EU	European Union
FDA	Food and Drug Administration
FMEA	Failure mode effects analysis
FPM	Finished product manufacturer
FPS	Finished product specifications
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas chromatography

GC-MS	Gas chromatography mass spectrometry
GMP	Good manufacturing practice
GN	Ganglioneuroma
GNB	Ganglion neuroblastoma
HCT	Hydrochlorothiazide
HDC	High dose chemotherapy
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSCT	Haematopoietic stem cell transplantation
i.v.	Intravenous/intravenously
IC	Ion chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IDRFs	Image-defined risk factors
INRC	The International Neuroblastoma Response Criteria
INRG	International Neuroblastoma Risk Group
IPA	Isopropyl alcohol
IPC	In-process control
IR	Infrared
IT	Irinotecan + temozolomide (in the text also reported as TEMIRI)
ITTS	Intent-to-treat set
IU	International units
IUPAC	International Union of Pure and Applied Chemistry
Kel	Elimination rate constant
KF	Karl Fischer titration
L1	Localised tumour confined to one body compartment and with absence of IDRFs
L2	Locoregional tumour with presence of one or more IDRFs
LCMS	Liquid chromatography mass spectrometry
LDPE	Low density polyethylene
LOA	Letter of access
LoD	Limit of detection
LOD	Loss on drying
LOQ	Limit of quantitation
LoQ	List of questions
LP	Lymphopenia
LT	Less than
M	Distant metastatic disease (except stage MS)
MA	Marketing authorisation
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
Max	Maximum
MEB	Medicines Evaluation Board
mIBG	Meta-iodo-benzyl-guanidine
Min	Minimum
MiR	Mixed response
MO	Major objection
MR	Minor response
MS	Mass spectrometry
MTD	Maximum tolerated dose
MTIC	Methyltriazenoimidazole-4-carboxamide
NA	Not amplified
NB	Neuroblastoma
ND	Not detected
NIR	Near infrared spectroscopy
NK	Natural killer
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
NOR	Normal operating range
NP	Neutropenia
NR	Not reported
OC	Other concern

OOS	Out of specification
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAR	Proven acceptable range
PCP	Pneumocystis jirovecii pneumonia
PCTFE	Polychlorotrifluoroethylene
PD	Progressive disease
PDE	Permitted daily exposure
PE	Polyethylene
Ped-TMZ	Paediatric temozolomide (Kizfizo)
PET	Polyethylene terephthalate
PF	Progression free
PFS	Progression-free survival
PIL	Patient information leaflet
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PK-pop	Population PK
PKS	PK set
po	per os (orally)
PP	Polypropylene
PR	Partial response
PSD	Particle size distribution
pts	Patients
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
q.s.	Quantum sufficit (as much as suffices)
Q1	First quartile
Q3	Third quartile
QbD	Quality by design
QC	Quality control
QOS	Quality overall summary
QP	Qualified person
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative humidity
RMS	Reference Member State
ROA	Route of Administration
RP	Restricted part (or closed part) of an ASMF
RR	Response rate
RRT	Relative retention time
SD	Stable disease
SIOPEN	International Society of Paediatric Oncology Europe Neuroblastoma
SmPC	Summary of product characteristics
StD	Standard deviation
T	temozolomide (in the text also reported as TMZ)
t1/2	Plasma elimination half life
TAMC	Total aerobic microbial count
TEAE	Treatment-emergent adverse event
TEMIRI	TMZ + irinotecan (in the text also reported as IT)
TGA	Thermo-gravimetric analysis
THCP	Thrombocytopenia
TLC	Thin layer chromatography
Tmax	Time to reach maximum plasma concentration
TMZ	Temozolomide
TOTEM	TMZ + topotecan (in the text also reported as TTo)
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of toxicological concern
TTo	Temozolomide + topotecan (in the text also reported as TOTEM)
TTP	Time-to-progression
TVD	Topotecan, vincristine and doxorubicin
TYMC	Total combined yeasts/moulds count
uHPLC	ultra-high performance liquid chromatography
USP	United States Pharmacopoeia

USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
VGPR	Very good partial response
w/v	Weight/volume
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Orphelia Pharma submitted on 31 July 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Kizfizo, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2022.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Kizfizo is indicated in monotherapy or in combination with a specific DNA inhibitor topoisomerase I (irinotecan or topotecan) for the treatment of patients aged 12 months and above with:

- refractory neuroblastoma or presenting an insufficient response to induction chemotherapy,

- recurrent neuroblastoma after at least partial response to induction chemotherapy followed by myeloablative therapy and stem cell transplantation.

Kizfizo, was designated as an orphan medicinal product EU/3/19/2188 on 21 August 2019, in the following condition: Treatment of neuroblastoma.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Temodal 100 mg hard capsules
- Marketing authorisation holder: Merck Sharp & Dohme B.V.
- Date of authorisation: 26-01-1999
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/98/096/16

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Temodal 100 mg hard capsules

- Marketing authorisation holder: Merck Sharp & Dohme B.V.
- Date of authorisation: 26-01-1999
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/98/096/16

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Temodal 100 mg hard capsules
- Marketing authorisation holder: Merck Sharp & Dohme B.V.
- Date of authorisation: 26-01-1999
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/98/096/16
- Bioavailability study number(s): ORP-TMZ-I-a / OP108319.ORP (EudraCT N° 2020-000293-23)

1.3. Information on paediatric requirements

Not applicable

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.

1.5. Scientific advice

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

Date	**Reference**
20 September 2018	EMEA/H/SA/3898/1/2018/SME/III
19 September 2019	EMEA/H/SA/3898/1/FU/1/2019/PED/SME/II

EMEA/H/SA/3898/1/2018/SME/III

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- The acceptability of the proposed pharmaceutical development plan to support evaluation of quality; the acceptability of the approach to waive a bioequivalence study between the proposed and the reference product
- The potential of the non-clinical pharmacodynamic and toxicological data to support an MAA in the sought indication.
- The potential of the available PK data together with published PK data of temozolomide to

support an MAA in the sought indication; The acceptability of using clinical literature to support the selected dose and regiment, and to evaluate efficacy and safety in the sought indication.

EMEA/H/SA/3898/1/FU/1/2019/PED/SME/I

The Protocol assistance pertained to the following clinical aspects:

- The acceptability of the proposed clinical development supported by published data to support an MAA in the sought indication.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig Co-Rapporteur: Alexandre Moreau

The Rapporteur appointed by the PRAC was:

Rapporteur: Martin Huber

The application was received by the EMA on	31 July 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 November 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 November 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 April 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	05 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 June 2024
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	27 June 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	16 September 2024
The CHMP Rapporteur 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	02 October 2024

The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	15 October 2024
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 Kizfizo on	14 November 2024
The CHMP adopted a report on similarity of Kizfizo with Qarziba on (Appendix on similarity)	14 November 2024

1.7. Steps taken for the re-examination procedure

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

Rapporteur: Peter Mol Co-Rapporteur: Filip Josephson

The Applicant submitted written notice to the EMA, to request a re-examination of Kizfizo CHMP opinion of 27 February 2025., on	4 December 2024
The CHMP appointed Peter Mol as Rapporteur and Filip Josephson as Co-Rapporteur on	11 December 2024
The Applicant submitted the detailed grounds for the re-examination on	10 January 2025
The re-examination procedure started on	11 January 2025
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP members on	10 February 2025
The CHMP Co-Rapporteur's assessment report was circulated to all CHMP members on	10 February 2025
SAG experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting	13 February 2025
The CHMP Rapporteurs circulated the updated CHMP Rapporteurs Joint Assessment Report on the detailed grounds for re-examination to all CHMP members on	20 February 2025
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	25 February 2025
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation on	27 February 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

2.1.1.1. Disease or condition

Initially claimed therapeutic indication

"Kizfizo is indicated in monotherapy or in combination with a specific DNA topoisomerase I inhibitor (irinotecan or topotecan) for the treatment of paediatric patients aged 12 months and above with:

- refractory neuroblastoma or presenting an insufficient response to induction chemotherapy,
- recurrent neuroblastoma after at least partial response to induction chemotherapy followed by myeloablative therapy and stem cell transplantation.

(see section 5.1)"

2.1.1.2. Epidemiology

Neuroblastoma accounts for approximately 5.5 % of all malignant diseases in childhood and adolescence, thereby representing one of the most frequent solid tumour types in this age group following tumours of the central nervous system (CNS tumours, brain tumours). It is an orphan disease with an annual incidence rate of 1.8 cases per million i.e., approximately 900 new cases are diagnosed per year in the European Union (Gatta et al, 2012).

Most children are diagnosed under the age of 5 years, with a median age at diagnosis of 17 months (London et al, 2005), with boys being (by 40%) more affected than girls (gender ratio: 1.4 : 1). Nevertheless, older children, adolescents and, seldom, adults may also be affected (Gatta et al, 2012).

Up to 30% of the high-risk neuroblastoma patients are refractory to induction chemotherapy, therefore requiring further chemotherapy, and over 50% of patients with high-risk neuroblastoma relapse with a dismal long-term outcome. These refractory and relapsed patients represent the target population for paediatric temozolomide (Ped-TMZ) accounting for approximately 220 patients per year in the EU.

2.1.1.3. Clinical presentation, diagnosis and stage/prognosis

Neuroblastoma is an embryonal tumour of the autonomic nervous system. The tumours arise in tissues of the sympathetic nervous system, typically in the adrenal medulla or paraspinal ganglia, and thus can present as mass lesions in the neck, chest, abdomen, or pelvis (Gatta et al, 2012).

Clinical symptoms vary depending on the location of the primary tumour, and may include an abdominal mass, abdominal pain, respiratory distress, or neurological symptoms from spinal cord involvement. Children with metastatic disease often appear ill at diagnosis, with fever, bone pain, and weight loss. While in some cases of neuroblastoma, lesions may regress spontaneously, in others, the disease may behave aggressively, with many patients succumbing to recurrent/ refractory metastatic disease (Luksch et al, 2016).

The diagnosis of neuroblastoma is based on the presence of characteristic histopathological features of tumour tissue or the presence of tumour cells in a bone marrow aspirate or biopsy accompanied by raised concentrations of urine catecholamines. Computed tomography and magnetic resonance imaging are the preferred methods for the assessment of tumour in the abdomen, pelvis, mediastinum, or in paraspinal lesions, respectively. For enhanced detection of tumour, radiolabelled metaiodobenzylguanidine (MIBG) scintigraphy is used. Other methods are used to detect minimal residual disease such as bone marrow aspirates and biopsy, pathological evaluation and polymerase-chain reaction-based techniques to identify GD2 synthase, tyrosine hydroxylase and protein gene product 9.5.

There have been substantial efforts to develop a risk-classification algorithm for patients with newly diagnosed neuroblastoma. An International Neuroblastoma Risk Group (INRG) classification system has been proposed in 2009 with four broad categories —very low risk, low risk, intermediate risk, and high risk — based on the assessment of the following prognostic factors: age at diagnosis (2 cut-offs, 12 and 18 months), INRG tumour stage (L1, L2, M, MS), histologic category, grade of tumour differentiation, DNA ploidy (hyperploidy/diploidy), MYCN oncogene status (amplified or not), aberrations at chromosome 11q (presence/absence) (Monclair et al, 2009).

In infants below 1 year of age the prognosis is very good with a 5-year overall survival (OS) of 91%, whereas it is less favourable in older children (1 to 14 years) with 5-year OS of 56 to 59% (Gatta et al, 2012). Amplification of the MYC gene family member, MYCN, is found in ~25% of cases and correlates with high-risk disease and poor prognosis (Tonini et al , 1997; Huang and Weiss, 2013).

2.1.1.4. Management

Therapy is stage- and risk-stratified. The therapeutic modalities include surgery, chemotherapy, radiotherapy and biotherapy; observation-only is undertaken in a few very low-risk patients. Focus for the description of the management of the disease is provided in line with the indication only for high-risk neuroblastoma:

First-line setting

For high-risk neuroblastomas (representing 40% of all newly diagnosed neuroblastomas), the current treatment can be divided into three distinct phases:

- **induction** of remission with intensive chemotherapy. The backbone of the most commonly used induction therapy includes dose-intensive cycles of cisplatin and etoposide alternating with vincristine, cyclophosphamide, and doxorubicin. Topotecan was added to this regimen based on the anti-neuroblastoma activity seen in relapsed patients. At the end of induction therapy, patients with high-risk disease typically undergo a full disease evaluation. Management of patients with residual disease at the end of conventional induction therapy is not standardised. After a response to chemotherapy, resection of the primary tumour is usually attempted.

- **consolidation** of the remission with myeloablative chemotherapy which attempts to eradicate minimal residual disease using lethal doses of chemotherapy followed rapidly by rescue with autologous hematopoietic progenitor cells to repopulate the bone marrow.

- and finally, a **maintenance** phase used to treat potential minimal residual disease (MRD) following haematopoietic stem cell transplantation (HSCT) to reduce the risk of relapse, e.g. with dinutuximab and isotretinoin, a molecule that induces terminal differentiation of neuroblastoma cell lines.

The SIOPEN protocol for high-risk neuroblastoma are derived from the front-line treatment in the SIOPEN HR-NBL1 study. The treatment consists of a rapid, dose intensive induction chemotherapy (rapid COJEC: carboplatin, etoposide, vincristine, cisplatin, cyclophosphamide) (Garaventa et al, 2021) with the recommended prophylactic use of granulocyte colony stimulating factor (filgrastim) to prevent infections (Ladenstein et al, 2010). Patients achieving complete or near complete response (CR) at metastatic sites on meta-iodo-benzyl-guanidine (mIBG) scanning (mIBG score <3) with no evidence of disease on bone marrow aspirates and no positive bone marrow biopsy (Ladenstein et al, 2018) then undergo peripheral blood stem cell harvest, attempted complete excision of the primary tumour, myeloablative therapy (busulfan and melphalan) followed by peripheral blood stem cell rescue (Ladenstein et al, 2017). Radiation treatment to the pre-operative extension of the primary tumour is given after the myeloablative therapy. Patients receive maintenance therapy comprising differentiation therapy with 13-cis retinoic acid and immunotherapy with anti-GD2 antibody (dinutuximab beta) (Yu et al, 2010; Ladenstein et al, 2018).

The new frontline protocol HR-NBL2 (NCT04221035) is derived from HR-NBL1 and opened in 2020. It aims at further improving frontline treatment by comparing 2 induction regimens (rapid COJEC (reference) vs GPOH), 2 HDC consolidation strategies (single HDC BuMel (reference) vs double HDC Thiotepa/BuMel), and 2 radiation protocols followed by maintenance therapy with 13-cis retinoic acid and immunotherapy with anti-GD2 antibody (dinutuximab beta). High-risk patients treated according to the SIOPEN HR-NBL2 protocol and who achieve insufficient response (PR<50% or SIOPEN score >3) after induction chemotherapy (i.e., refractory patients) receive 3 courses of TEMIRI as second line chemotherapy according to the HR-NBL2 amendment.

Of note, the VERITAS trial (NCT03165292), which aimed at defining the best therapeutic strategy for the "very high risk" refractory patients, also included two cycles of TEMIRI during the frontline treatment. The VERITAS trial was however stopped by the sponsor in 2023 due to limited recruitment as a consequence of difficulties accessing the mIBG therapy. All refractory patients are now treated according to HR-NBL2.

Relapsed and refractory neuroblastoma

Up to 30% of the high-risk neuroblastoma patients are refractory to induction chemotherapy, therefore requiring further chemotherapy (Ladenstein et al. 2010). Furthermore, half of the high-risk patients that initially respond to chemotherapy experience relapse within 3 years with a dismal prognosis (Ladenstein et al. 2017).

There are no uniform guidelines to direct the therapy of patients with refractory and recurrent neuroblastoma. Historically, recurrent and refractory neuroblastoma has been treated with a combination of chemotherapy and radiotherapy for the purposes of palliation only. In more recent times, treatment has evolved comprising salvage chemotherapy, radiotherapy and surgery, and 131I-MIBG therapy, and dinutuximab with interleukin-2 (IL-2) (De Sio et al, 2006; Rubic et al, 2006; Wagner et al, 2004; Kushner et al, 2006; Wagner et al, 2009; Bagatell et al, 2011; Rubie et al, 2010, Di Giannatale et al, 2014; Simon et al, 2007).

Second line chemotherapies with mild to modest toxicities that have not been included in frontline treatment are often considered for salvage. For the majority of patients with relapsed HR-NBL, initial treatment will comprise reinduction chemotherapy typically based around combinations of topotecan or irinotecan, with temozolomide or cyclophosphamide. The relative efficacy of these combinations is difficult to ascertain since the majority of published studies have been single-arm Phase II trials, with no comparison of treatment strategies, endpoints of response rates (rather than survival) and heterogeneous populations in terms of the extent of disease at relapse (such as measurable soft-tissue lesions vs. evaluable metaiodobenzylguanidine (MIBG)-avid skeletal disease or bone marrow only disease) (Morgenstern et al, 2021).

Long-term survival after relapse of high-risk neuroblastoma is uncommon and although therapy may be able to prolong survival, careful consideration needs to be given to the individual needs of patients, balancing toxicity and burden of therapy with likelihood of benefit.

2.1.2. About the product

The active substance in Kizfizo is temozolomide (TMZ), a cytotoxic alkylating agent (ATC code: L01AX03). TMZ is a triazene and is a prodrug which undergoes rapid chemical conversion at physiologic pH to methyltriazenoimidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to DNA alkylation at the O6 position of guanine with additional alkylation also occurring at the N7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adducts. Aberration in O6-methylguanine-DNA methyltransferase (MGMT) is a key factor that determines drug susceptibility. MGMT protein is an enzyme encoded by the MGMT gene that repairs DNA adducts at the O6 position of guanine. Repair of TMZ-induced O6-MeG adducts by MGMT prevents cytotoxicity and inhibition of MGMT activity enhances the cytotoxicity of TMZ (Baer et al. 1993).

Another driver for TMZ activity seems to be an intact mismatch repair (MMR) system as defects in MMR result in cellular resistance to TMZ (Liu et al. 1996). Correspondingly, in patients with malignant glioma, there is a relationship between MMR deficiency, as well as high MGMT activity, and poor response to TMZ (Friedman et al. 1998).

The initial proposed indication was: Kizfizo is indicated in monotherapy or in combination with a specific DNA inhibitor topoisomerase I (irinotecan or topotecan) for the treatment of patients aged 12 months and above with:

- refractory neuroblastoma or presenting an insufficient response to induction chemotherapy,

- recurrent neuroblastoma after at least partial response to induction chemotherapy followed by myeloablative therapy and stem cell transplantation.

The latest proposed indication is:

Kizfizo in combination with irinotecan or topotecan is indicated for the treatment of paediatric patients aged 12 months and above with:

- refractory high-risk neuroblastoma as second line chemotherapy after insufficient response to induction chemotherapy, to proceed to consolidation,

- actively progressing recurrent high-risk neuroblastoma after at least partial response to induction chemotherapy followed by myeloablative therapy and stem cell transplantation.

Proposed posology

Kizfizo is supplied as a ready-to-use 40 mg/mL oral suspension intended for use in patients aged 12 months and above to treat refractory and/or relapsed neuroblastoma as monotherapy or in combination with irinotecan or topotecan.

The Ped-TMZ dosing, which depends on whether treatment is used in combination with specific DNA topoisomerase I inhibitor topotecan or irinotecan, is summarised hereafter.

Combination therapy with topotecan

Cycle duration in combination with topotecan: 28 days

Ped-TMZ is administered orally at a dose of 150 mg/m² body surface once a day during 5 days and then stopped during 23 days. Topotecan is administered intravenously (i.v.) over 30 min, at least 1 h after administration of TMZ, at a dose of 0.75 mg/m^2 during the same 5 days and then stopped during 23 days. Dosing should be adapted in case of toxicity.

Combination therapy with irinotecan

Cycle duration in combination with irinotecan: 21 days

Ped-TMZ is administered orally at a dose of 100 mg/m² body surface once a day during 5 days and then stopped during 16 days. Irinotecan is administered i.v. over 1 h, at least 1 h after administration of TMZ, at a dose of 50 mg/m^2 during the same 5 days and then stopped during 16 days.
Dosing should be adapted in case of toxicity.

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

Rational behind the development of a paediatric formulation

The present Marketing Authorisation Application (MAA) is in accordance with Article 10(3) of Directive 2001/83/EC, so called hybrid application, with Temodal hard capsules, approved in the European Union on 26 January 1999, as reference medicinal product (EU/1/98/096/16). Temodal is indicated for the treatment of malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy in adults and children from the age of three years, and for newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment in adults (Temodal, EMA Product information).

Off-label use of TMZ in patients with neuroblastoma is currently based on oral TMZ-containing drug products, which are commercially available in the form of hard capsules (5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg). However, the administration of hard capsules is not recommended for paediatric patients (e.g., up to 6 years) and caregivers therefore open the capsules and mix the content with soft food or drink for administration. As TMZ is a bitter, highly toxic and unstable substance, this method of administration is not satisfactory, neither for the caregiver (drug exposure), nor the child (imprecise dosage, poor compliance, unknown stability of the drug substance in the food), or the environment (waste). In addition, in the section 4.2 of Temodal SmPC it is stated that the capsules must not be opened and should be swallowed whole. The need for an oral pharmaceutical form of TMZ adapted to children is therefore acknowledged.

Kizfizo is a new oral formulation of temozolomide (TMZ), developed as a ready-to-use 40 mg/mL oral suspension with the aim of providing a formulation more appropriate for the paediatric population that is not able to swallow capsules. It consists of a taste-masked oral suspension of 40 mg of TMZ per mL in a sealed bottle and will be filled extemporaneously by caregivers at home into syringes for oral administration.

Clinical development

Based on the recommendations provided by the EMA CHMP, a bioequivalence study (ORP-TMZ-1-a) has been conducted to compare oral bioavailability of the two formulations of TMZ (Ped-TMZ oral suspension and Temodal capsules) in adults with primary central nervous system (CNS) malignancies. The bioequivalence aimed at bridging existing Temodal data with those of Ped-TMZ.

In addition, a population pharmacokinetic (Pop-PK) (ORP-TMZ-1-b, TEMOkids), acceptability and safety study has been conducted in paediatric patients in need of TMZ (all indications) aged 1 year to less than 18 years. A Pop-PK model has been developed to provide insight on the TMZ exposure in young children, especially in the age range between 1 and 3 years, and to assess the potential effects of covariates including age on TMZ pharmacokinetics.

Regulator interactions in Europe

The applicant did receive CHMP Scientific Advice pertinent to the clinical investigation on September 20th, 2018 (EMA/CHMP/SAWP/599403/2018), and follow-up advice for the clinical development plan was requested in 2019 (EMA/CHMP/SAWP/493967/2019).

In the first advice the following issues were identified:

- bioequivalence between Ped-TMZ and Temodal should be demonstrated;
- combination between Temodal and topoisomerase I inhibitors should be further substantiated; as neither irinotecan nor topotecan are approved for relapsed or refractory neuroblastoma, the CHMP recommended that the Applicant includes the recommended dosage of irinotecan and topotecan when combined with TMZ in the MAA for Ped-TMZ, if the benefits of the doublets are shown to outweigh the risks compared to TMZ single agent. The CHMP acknowledged that single agent TMZ had established off-label use in relapsed or refractory neuroblastoma, and that TMZ in combination with irinotecan is a preferred salvage regimen for this disease, however, indicating that available data were exploratory;
- the potential local toxicity in the upper GI tract should be explored;
- extension of age range between 1 to 3 years of age would require efficacy and safety data;
- efficacy of TMZ in neuroblastoma would require additional clinical data.

In the follow-up scientific advice the proposal of the company for three new clinical studies (BE study, pop-PK acceptability and safety study and retrospective efficacy and safety study) as a part of the clinical development program of temozolomide oral suspension was presented. Overall, it was concluded that the amount of randomised trial data is foreseen to be limited and the applicant will have to rely heavily on the modelling to allow extrapolation of adult information to the lower age ranges.

In addition, a prospective meta-analysis of relevant studies as a part of the review of the literature was recommended. The PFS as a primary endpoint of the retrospective study (ORP-TMZ-4) has been questioned, considering it might be problematic to define the starting time point for the historical control group, if this would be used for comparison. Duration of response (DoR) was recommended to be added as an endpoint to the study plan.

In general, the applicant has followed the recommendations of these scientific advices. Of note, DoR was not added as an endpoint of the retrospective study (ORP-TMZ-4) and time to progression (TTP) has been chosen as primary endpoint of the study.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an oral suspension containing 40 mg/mL of temozolomide.

Other ingredients are: xanthan gum (E415), citric acid (E330), silicon dioxide (E551), sucralose (E955), cola flavour, sodium benzoate (E211) and purified water.

The product is available in a 30 mL transparent polyethylene terephthalate (PET) bottle with tamper evident child-resistant closure made of an outer cap in white polypropylene (PP) and a screw closure in clear high-density polyethylene (HDPE). A clear low-density polyethylene (LDPE) bottle-syringe adapter is preinstalled in the neck of the bottle. The bottle contains 18 mL of oral suspension.

Each pack of the finished product contains one bottle and two syringes, a 5 mL oral dosing syringe with white plunger (0.1 mL dose graduations) and a 10 mL oral dosing syringe with white plunger (0.25 mL dose graduations). The oral syringes have a CE mark.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazol[5,1-d]-as-tetrazine-8-carboxamide corresponding to the molecular formula $C_6H_6N_6O_2$. It has a relative molecular mass of 194.15 and the following structure:

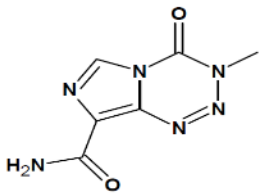


Figure 1. Active substance structure

The active substance is a white or slightly brown or slightly pink powder, sparingly soluble in water. It is not hygroscopic, and it is stable at acidic pH below 5 and labile at pH above 7. Temozolomide has a non-chiral molecular structure. Polymorphism has been observed for temozolomide.

As there is a monograph of temozolomide in the European Pharmacopoeia (Ph. Eur.), the two manufacturers of the active substance have been granted a Certificate of Suitability (CEP) to the monograph of the European Pharmacopoeia (CEP) for temozolomide, which have been provided within the current Marketing Authorisation Application.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by two manufacturers. The relevant information has been assessed by the EDQM before issuing the CEPs.

Both manufacturers possess a valid GMP certificate from their competent authorities.

2.2.2.3. Specification(s)

The active substance specification, as applied by the finished product manufacturer, includes tests for appearance, identity by IR and HPLC (Ph. Eur.), assay by HPLC (Ph. Eur.), impurities by HPLC (Ph. Eur.), residual solvents by GC, water content (Ph. Eur.), and sulphated ash (Ph. Eur.). The specifications are those of the Ph. Eur. monograph 2780 except for the additional control of one related

substance for the active substance of one of the manufacturers, and for the residual solvents, which are limited according to ICH Q3C and tested by the finished product manufacturer using the gas chromatography methods described in the CEPs.

The proposed specification tests and limits are acceptable and justified. The absence of control of other quality attributes has been discussed and justified, as described below.

Since temozolomide is a BCS class 1 active substance with rapid and nearly complete oral bioavailability, the particle size is not considered to have any impact on the dissolution properties. Therefore, in line with the guideline ICH Q6A, no specification for particle size distribution was defined for temozolomide.

Temozolomide shows polymorphism. Both active substance suppliers constantly yield one single polymorphic form. Representative X-ray diffraction spectra from both active substance suppliers of temozolomide have been provided. Different polymorphic forms of temozolomide have similar properties in terms of melting point, intrinsic dissolution profiles and non-clinical pharmacokinetics profiles. Therefore, in line with ICH Q6A guideline, it was agreed that there is no need to control the polymorphism of the active substance.

The applicant justified the absence of microbiological control from the active substance specification based on the low water activity and on the antimicrobial properties of temozolomide itself. This was considered acceptable, in line with ICH Q6A guideline.

The evaluation of the elemental impurities (EI) in the active substance was conducted by both manufacturers and it’s summarised in the CEPs. As concluded in the risk assessment, no additional tests are necessary for the control of elemental impurities in the active substance.

A risk evaluation of nitrosamines presence in the active substance was provided. The structure of temozolomide contains a secondary amide and an imidazotetrazine group (monocarboxylic acid amid and a triazene derivative) that could be an amine precursor. Also, the impurities of temozolomide described in Ph. Eur. monograph contain groups that can be secondary amine precursors. Thus, they contain nitrosable groups that can be converted into nitrosamines in presence of nitrosating agents. A nitrosamine risk assessment was performed by both active substance manufacturers, including the analytical testing of nitrosamine impurities on temozolomide batches using LC/MS or LC/MS/MS, confirming that the risk of presence of nitrosamines in the active substance from both manufacturers was excluded.

The analytical procedures comply with the Ph. Eur. Monograph 2780 and the current versions of the CEPs.

During the procedure, it was requested to the applicant to confirm that the internal HPLC method used by one of the active substance manufacturer and the finished product manufacturer to control one specific related substance in the active substance had already been assessed by the EDQM, since it was not reflected in the presented version of the CEP. The applicant confirmed it and provided an updated version of the CEP, including a description of the analytical method.

Active substance batch analyses data from both manufacturers have been provided. The results comply with the proposed specifications and are consistent from batch to batch.

Information related to the reference standards and materials has been provided: the applicant confirmed the use of EDQM CRS for identification, related substances, and assay testing. Satisfactory information has been presented.

2.2.2.4. Stability

For the active substance of one manufacturer, a re-test period of 5 years, if stored in double polyethylene bags in an aluminium bag with desiccant in between, placed in a paper drum, is defined in the CEP.

For the active substance of the other manufacturer, a re-test period of 36 months, if stored at a temperature between 2°C and 8°C in a double polyethylene bag placed in a fibre drum, is defined in the CEP.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is presented as a ready-to-use non-sterile oral aqueous, white or slightly pink or slightly brown suspension, containing 40 mg of temozolomide per mL. It is presented in a multidose bottle containing 18 mL of suspension containing 720 mg of temozolomide.

The finished product is a new oral dosage form of temozolomide, which is already available in EU in hard capsules. It was developed based on the reference product Temodal 100 mg hard capsules, to achieve an optimised formulation for the treatment of relapsed or refractory neuroblastomas in children.

A liquid formulation, rather than a powder for reconstitution, was chosen to minimise exposure of caregivers during handling operations of a cytotoxic drug used at home. Then, the Quality Target Product Profile (QTPP) was defined to develop a ready-to-use palatable oral suspension formulation at a concentration of 40 mg/mL, which can facilitate oral administration and dose adjustment, particularly in children. A minimum of shelf life of 24 months was required.

2.2.3.2. Manufacture of the product and process controls

The finished product was developed in collaboration with a cancer-research hospital, which originally prepared a paediatric formulation of temozolomide as a powder for reconstitution for oral suspension from the commercial capsules of temozolomide (Temodal).

The formulation studies have been properly described. The formulation used during clinical studies is the same as that proposed for marketing.

Particle size distribution of temozolomide was demonstrated to be a non-critical quality attribute and is not tested in the finished product. This was considered acceptable.

The finished product is a non-sterile aqueous suspension. The microbiological quality is assessed at release of each product batch, as well as in stability studies as per the requirements of the Ph. Eur. 5.1.4 monograph for aqueous preparations for oral use. The need of a preservative (benzoate sodium) was justified. Its concentration was defined on the basis of the Ph. Eur. test of efficacy of antimicrobial preservation (Ph. Eur. 5.1.3). It was demonstrated that the product without preservative has no intrinsic antimicrobial activity, and the proposed concentration of sodium benzoate is the minimal amount that ensures preservation at the end-of shelf-life of the finished product.

The properties of the active substance and the choice of the excipients have been satisfactorily described. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards or the United States Pharmacopoeia/National Formulary. There are no novel

excipients used in the proposed finished product formulation. The only non-pharmacopeial excipient of the formula is the cola flavour and its qualitative composition has been provided upon request.

The dissolution conditions for routine quality control testing of the proposed finished product have been adequately justified. The discriminatory power of the dissolution method could not be demonstrated since temozolomide is a highly soluble substance (BCS class 1). Due to differences in the dosage form between the finished product and the reference product (Temodal 100 mg capsule), a modified dissolution method was developed to carry-out the comparative analysis of the dissolution profiles between the bio-batches of test and reference products all over the pH range (pH 1, 4.5 and 6.8). Despite the modified dissolution method, it was not possible to show in vitro similarity of dissolution profiles between the test and reference product. Nonetheless, since bioequivalence between the test product and the reference product was demonstrated in vivo, the in vivo results prevail to those generated in vitro (as indicated in guideline CPMP/EWP/QWP/1401/98) and consequently, the lack of demonstration of the similarity of the dissolution profiles between the test product and reference product with the biobatches is not relevant for this product.

Manufacturing process development has been adequately explained for the different scales and for the process optimisation at commercial scale. Based on results obtained on the Design of Experiments (DoE) at pilot scale, scaling up and manufacturing process improvement, critical process parameters (CPPs) were established for the critical steps.

The primary packaging is a 30 mL PET bottle, closed with a two-piece tamper-evident child-resistant closure made of an outer cap in white PP and a screw closure in clear HDPE. A clear LDPE bottle-syringe adapter is preinstalled in the neck of the bottle. The primary packaging was chosen to avoid contact with the highly toxic active substance and to facilitate the administration. The suitability of the selected container closure system was properly addressed with respect to protection (photostability; physical container closure integrity, storage and shipping), safety and compatibility with the formulation as well as performance (delivery dose reproducibility study). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Each pack of the finished product contains one bottle and two syringes, a 5 mL oral syringe (graduated in 0.1 mL increments from 0.5 to 5.0 mL) and a 10 mL oral syringe (graduated in 0.25 mL increments from 1.0 mL to 10.0 mL). The oral syringes have a CE mark. Initially, the applicant intended to provide only the 5 mL oral syringe with the finished product. The 10 mL oral syringe has been included, following a request from CHMP, to avoid a potential dosing error when the daily volume intake is higher than 5 mL which would require two consecutive uses of the 5 mL syringe, to comply with the principles of the Guideline on Pharmaceutical Development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012).

Appropriate studies were conducted showing the compatibility of the finished product with the oral syringes as well as with nasogastric tubes.

Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Satisfactory information regarding GMP compliance of the manufacturing site has been provided.

The manufacturing process is a standard process, consisting of manufacturing steps covering addition and mixing of the excipients in a sequential order followed by the addition and dispersion of the active substance and filling in bottles.

The only intermediate in the manufacturing process of the finished product is the bulk suspension of temozolomide. The holding time of the bulk suspension has been appropriately validated.

Adequate details have been provided regarding the process steps, including the critical process parameters.

The in-process controls (IPC) and in-process monitoring (IPM) applied during the manufacturing process have been sufficiently described and are considered adequate for this type of manufacturing process.

Process validation has been satisfactorily conducted on three consecutive commercial scale batches of finished product using active substance from the two manufacturers. It has been demonstrated that the manufacturing process is capable of producing finished product of the intended quality in a reproducible manner.

2.2.3.3. Product specification(s)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification of temozolomide (HPLC-UV), identification of sodium benzoate (HPLC-UV), assay of temozolomide (HPLC-UV), assay of sodium benzoate (HPLC-UV), dissolution (paddle apparatus-UV), degradation products of temozolomide (HPLC-UV), pH (Ph. Eur.), uniformity of mass of delivered dose (Ph. Eur.), and microbiological quality (Ph. Eur.).

The proposed finished product release and shelf-life specifications are considered acceptable. During the procedure, the applicant was requested to revise the acceptance criteria for some specification parameters. An updated acceptable specification was provided. With regard to the limit of the dissolution test, the applicant should consider tightening the specification limits after the manufacturing of 10 commercial batches.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Following CHMP request, batch analysis data on one batch manufactured at commercial scale of finished product using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity (class 1 and 2A) was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The applicant proposed a waiver of nitrosamines testing, which was not initially accepted by CHMP. A question was raised to request testing of nitrosamines impurities in the finished product according to ICH Q3B, considering the advanced cancer indication and ICH S9. The applicant updated and submitted the nitrosamine risk assessment to determine the potential for nitrosamine contamination in the finished product according to EMA/369136/2020. Based on the information provided, it was accepted that the risk of nitrosamine impurities in the active substance or the related finished product is negligible. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the

reference standards for testing of assay of temozolomide, dissolution, degradation products and assay of sodium benzoate has been presented.

Batch analysis results have been provided for at least three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from at least three commercial scale and 2 two supportive pilot scale batches of finished product stored for up to 24 months under long term conditions (5°C ± 3°C / 60% RH) and for up to 6 months under accelerated conditions (25°C ± 2°C/60% ± 5) according to the ICH guidelines were provided. The batches of Kizfizo were manufactured using active substance from both manufacturers. The primary stability batches are representative of those proposed for marketing. They were manufactured using the proposed commercial manufacturing process, but were packaged in the primary packaging used during clinical development (30-mL bottle in transparent PET with a PP28 neck diameter and POM-HDPE-LDPE tamper evident and child-resistant closure). As the material in contact with the product is the same as in the proposed commercial packaging, the clinical primary packaging is considered equivalent to that proposed for marketing.

In addition, one batch packaged in the primary packaging intended for the commercial phase and manufactured at commercial scale was placed under stability studies under long term conditions (5°C ± 3°C / 60% RH) and under accelerated conditions (25°C ± 2°C / 60% ± 5). The results of this batch were not initially presented and during the procedure the CHMP requested the results from 6 months study from this batch. The applicant provided satisfactory ongoing long-term stability data at 5°C ± 3°C for 9 months. The applicant also provided accelerated stability data at 25°C ± 2°C / 60% ± 5 for 3 months. All results were consistent with the results of the primary stability batches, described below.

Samples were tested for appearance, assay of temozolomide, assay of sodium benzoate, dissolution, degradation products of temozolomide, pH and microbiological quality.

The shelf-life specification limits are the same as for release, with the exception of the ones for temozolomide assay and degradation products. The analytical procedures used are stability indicating.

No significant changes have been observed at long term conditions. Some significant changes (e.g. in appearance, assay, related substances or dissolution) were observed when the finished product was stored under accelerated storage condition. Since all results comply with shelf-life specification limits at long term conditions, the claimed shelf-life period with the storage condition 'store in a refrigerator (2 °C - 8 °C)' is considered acceptable.

Forced degradation studies were conducted on one pilot scale batch to test the impact of the following stress conditions: acidic and alkaline pH, oxidation, temperature and light. The major degradation products were identified in all tested stress conditions.

Further, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Only minor changes were observed. All parameters remained within the specification limits and therefore is considered not photosensitive.

In addition, in-use stability studies were performed to demonstrate that the finished product can be used at ambient temperature during the 5-day chemotherapy cycle without any impact on the finished product quality within the claimed shelf life of 24 months. Data from two commercial scale batches (one at release and the other at shelf-life) were provided in line with the "Note for guidance on in-use stability testing of human medicinal products" (CPMP/QWP/2934/99). The study was performed by

sampling finished product, after homogenisation of the suspension, once daily at room temperature over 5 days using a 5 mL syringe. After sample discarding, the bottles were stored at 5°C ± 3°C. At the end of the study, after the last 5th sampling, the finished product remaining in the bottles was tested for appearance, pH, temozolomide assay, sodium benzoate assay, degradation products and microbiological control. The results of both batches complied with specifications at the end of the in-use stability study. Therefore, it can be concluded that sampling of the finished product once daily at ambient temperature over the 5-day chemotherapy cycle has no impact on the finished product quality within the claimed finished product shelf-life. Thus, the relevant SmPC recommendation (section 6.3) is supported.

Moreover, the effect of short-term temperature excursions outside the label storage conditions during shipment and handling was also studied. The results revealed that the temperature excursion cycles did not have any impact on the quality of the finished product in the tested conditions which were defined according to the supply chain steps.

Based on available stability data, the proposed shelf-life of 2 years and storage conditions to store in a refrigerator (2°C-8°C), as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.2.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Kizfizo is a ready-to-use oral suspension developed to facilitate the administration of temozolomide, (cytotoxic alkylating agent) to children facilitating its dosing, improve treatment compliance, and minimise the contact of the caregivers and patients during dose preparation and administration over the current off-label use of the existing hard capsules formulation.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During evaluation, no major objection was raised by the CHMP in relation to quality aspects.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the benefit/risk ratio of the product, which pertain to tightening the acceptance criteria for the dissolution test. This point should be considered for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the proposed SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

N.A.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

The activity of temozolomide alone and in combination with irinotecan in neuroblastoma xenograft mouse models representing the proposed indication has been documented in several peer-reviewed publications. This is also reflected in the non-clinical overview. The data presented are briefly summarised below.

Temozolomide markedly induced apoptosis in the SH-SY5Y neuroblastoma cell line in vitro at 5 mM [Citisli et al. 2015]. The efficacy of temozolomide was assessed in six human neuroblastoma xenograft mouse models in vivo [Middlemas et al. 2000]. Temozolomide induced complete responses (CRs) that were maintained throughout the study period (12 weeks) in all mice bearing NB-1382 and NB-1771 neuroblastomas. Temozolomide also induced CR in all mice bearing NB-1643 tumours, although 2 out of 7 mice (29 %) relapsed during the study. CRs or partial responses (PRs) (≥50 % regression) were obtained against two additional neuroblastoma lines, NB-EB and NB-SD. NB-1691 was poorly responsive to temozolomide which induced PRs or no response in this model. The data are presented in Table 1.

Table 1. Efficacy of temozolomide in neuroblastoma xenograft models [Middlemas et al. 2000].

Tumour cell lines	N	Tumour growth delay in weeks, temozolomide vs placebo (adjusted *P*)	No. of PR	No. of CR	Maintained CR	Time to recover to initial tumour volume (weeks)[d]
NB-EB	7	6.0 (0.003)	3	4	1	5
NB-1771	7	>9.2 (0.001)	0	7	7	≥ 12
NB-1382	7	>9.9 (0.001)	0	7	7	≥ 12
NB-1643	7	>8.8 (0.001)	0	7	5	≥.12
NB-1691	7	4.3 (0.005)	5	0	NA	6
NB-SD	7	>8.7 (0.001)	3	1	1	11

CR: complete response; PR: partial response. Ps were obtained using exact log-rank tests (with Bonferroni correction procedure). Maintained CR: number of CR maintained through week 12.

Houghton et al. studied the antitumour efficacy of temozolomide combined with irinotecan on four mouse neuroblastoma xenograft models [Houghton et al. 2000]. Dose levels of irinotecan and temozolomide were chosen so that neither drug alone caused complete response (CR). The combination induced complete responses in the four neuroblastoma xenograft models demonstrating

improved response compared to single agents in three out of four models. The results are shown in Table 2.

Table 2. Efficacy of temozolomide in neuroblastoma xenograft models [Houghton et al. 2000].

Tumour	Treatment	Dose (mg/kg)	Growth delay *vs* placebo (weeks)	*p* of exact log rank *vs* placebo (unadjusted)
NB-SD	Temozolomide	66	3.75	0.033
	Irinotecan	0.4	2.25	0.015
	Temozolomide+ irinotecan	66 / 0.4	≥ 9.25	0.012
	Temozolomide	42	3.55	0.043
	Temozolomide+ irinotecan	42 / 0.4	≥ 9.25	0.002
NB-SD	Temozolomide	33	3.3	0.004
	Irinotecan	0.4	6.3	0.002
	Temozolomide+ irinotecan	33 / 0.4	≥ 9.3	0.002
	Irinotecan	0.26	5.6	0.004
	Temozolomide+ irinotecan	33 / 0.26	≥.9.3	0.002
	Temozolomide	22	≥.9.3	0.012
	Temozolomide+ irinotecan	22 / 0.4	≥.9.3	0.002
	Temozolomide+ irinotecan	22 / 0.26	≥.9.3	0.001
NB-1771	Temozolomide	19	4.1	0.010
	Irinotecan	1.25	8.2	0.004
	Irinotecan	0.61	7.3	0.005
	Temozolomide+ irinotecan	19 / 1.25	≥.8.5	0.002
	Temozolomide+ irinotecan	19 + 0.61	≥.8.5	0.004
NB-1643	Temozolomide	28	≥.8.2	0.002
	irinotecan	0.61	≥.8.2	0.002
	Temozolomide+ irinotecan	28 / 0.61	≥.8.2	0.002
	Temozolomide+ irinotecan	28 / 0.4	≥.8.2	0.002

Cai et al. evaluated the cytotoxicity of temozolomide and irinotecan, either alone or in combination, in five neuroblastoma cell lines. Temozolomide showed activity with IC_{90} < 50 µg/ml (0.26 mM) in two out of five cell lines, SN-38, the active metabolite of irinotecan, had IC_{90} < 20 ng/ml (51 nM) in four cell lines. For the combination, the fold of reduction in the temozolomide concentration required for 90% cell death was higher than 2 in four cell lines. Temozolomide addition improved the efficacy of SN-38 only in one out of five cell lines. These findings are consistent with the in vivo data. Temozolomide alone (25 mg/kg/day for 5 days every 3 weeks for 4 courses) did not significantly improve mouse survival of SMS-KCNR, CHLA-136 or CHLA-119 xenografts. Irinotecan alone improved the survival in all three xenograft models and addition of temozolomide did not further improve irinotecan activity [Cai et al. 2010].

As topotecan is concerned, the work of Daniel et al. showed that both topotecan and temozolomide alone caused dose-dependent inhibition of growth in three cell lines in vitro (NB-1691, SH-SY-5Y, and SKNBE). All cell lines exhibited similar levels of sensitivity to topotecan (GI_{50}, 3.5-5.5 nM) or temozolomide alone (GI_{50}, 162-210 µM). Topotecan was more potent than temozolomide as was the case with irinotecan. In the NB-1691 neuroblastoma xenograft models in mouse, temozolomide (68 mg/kg/day for 5 days) caused a transient regression followed by regrowth and an overall tumour growth delay of 19 days. Treatment of NB-1691 xenografts with topotecan alone (1 mg/kg, daily ×5) similarly resulted in transient regression followed by regrowth and an overall tumour growth delay of 10 days. SH-SY-5Y xenografts were more sensitive to topotecan and temozolomide than NB-1691 xenografts, and treatment of mice with topotecan or temozolomide alone resulted in tumour growth delays of 53 and 60 days, respectively, compared with controls [Daniel et al. 2009].

Regarding the combination of temozolomide and topotecan, no non-clinical data demonstrating the efficacy of this combination are available. This is acceptable since this combination has been evaluated clinically.

2.3.3. Toxicology

Of note, one publication reports impaired learning in juvenile mice treated intraperitoneally at 25 mg/kg/day (75 mg/m^2/day) for 3 days consecutive days per week during 4 weeks starting at 1 month of age; a similar finding was not observed in older animals. It was postulated that temozolomide may have altered hippocampal development in juvenile mice via suppression of neurogenesis. This triggers some concern for the youngest paediatric patients who may not be covered by the clinical experience in children from 3 years of age. Although the study was not GLP-compliant, the prescriber should be aware of the possible effects on cognition (learning) in patients aged 1-3 years. The following text for section 5.3. of the SmPC was thus adopted:

In juvenile mice treated intraperitoneal at 25 mg/kg/day for 3 consecutive days per week during 4 weeks starting at 1 month of age impaired learning was reported in a non-GLP study.

The applicant committed to monitor and discuss this issue in the PSURs.

2.3.4. Ecotoxicity/environmental risk assessment

Table 3. Summary of main study results

Substance (INN/Invented Name): Temozolomide			
CAS-number (if available): 85622-93-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-1.24	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-1.24	not B
Persistence	DT50 or ready biodegradability	-/-	Not assessed
Toxicity	NOEC or CMR	-/-	Not assessed
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00165	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			N

2.3.5. Discussion on non-clinical aspects

No new non-clinical studies have been conducted with temozolomide. The proposed indication is generally supported by the data from peer-reviewed scientific publications. The overall pharmacological, pharmacokinetic and toxicological profile of temozolomide is well known.

The applicant submitted an ERA including Phase I PEC calculation. The assessor does agree with the provided PEC calculation and the applicant's conclusion. The PEC I trigger of 0.01 µg/L is not met. Thus, a Phase II ERA is deemed not necessary. The applicant provided a study report of a study according to OECD TG 107 to determine the logKow of temozolomide. The logKow remains below 4.5. Therefore, no PBT assessment is deemed necessary.

Thus, Kizfizo is not considered to pose any unacceptable risk to the environment.

The non-clinical sections of the drafted SmPC are considered acceptable.

2.3.6. Conclusion on the non-clinical aspects

There are no objections to the approval of temozolomide in the applied indication from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is a hybrid application for ready-to-use 40 mg/mL oral suspension containing temozolomide. To support the marketing authorisation application, the applicant has conducted a bioequivalence study (ORP TMZ-1-a), a Pop-PK study, acceptability and safety study (ORP-TMZ-1-b, TEMOkids) and submitted the available clinical data from published literature, from the specific BEACON-CHEMO study data, from a relevant meta-analysis and from a real-life retrospective data collection study (ORP-TMZ-4/RETROTMZ). In addition, the safety data from the early access authorisation and compassionate use in France has been presented.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of temozolomide based on published literature and applicant new studies. The SmPC is in line with the SmPC of the reference product.

CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

GCP aspect

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

Tabular overview of clinical studies

To support the application, the applicant has submitted the following studies:

Type of Study	**Study Identifier**	**Location of study report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen;** **Route of Administration**	**Number of Patients**	**Diagnosis of Patients**	**Duration of Treatment**	**Study Status;** **Type of Report**
BE	ORP-TMZ-I-a	M 5.3.1.2	To evaluate BE between TMZ oral suspension and Temodal (100 mg) capsules	Phase I, multi-centre, open label, randomised, crossover, 2-period study	Ped-TMZ 40 mg/mL Oral route TEMODAL TMZ 100 mg capsules, Oral route	36 male and/or femal e patients aged 18-70 years (PK set: 30 patients)	Glioblastoma multiforme or low-grade glioma (grade 2 or 3) and patients with recurrent or progressive malignant glioma	Single oral administration in 2 different study periods	Completed; Full CSR
BA	AO18-050	M 5.3.1.4	BA method validation	Validation of LC-MS/MS method PKH/MOA/1229 for TMZ quantification in human plasma	TMZ as analyte and TMZ-D3 as internal standard	N/A	N/A	N/A	Completed; Validation report

Type of Study	**Study Identifier**	**Location of study report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen;** **Route of Administration**	**Number of Patients**	**Diagnosis of Patients**	**Duration of Treatment**	**Study Status;** **Type of Report**
Pop-PK	ORP-TMZ-I-b (TEMOkids)	M 5.3.3.5	PK parameters in paediatric patients aged 1 year and over	Phase I, multi-centre, non-randomised, open-label, single-arm study	Ped-TMZ 40 mg/mL; 75 to 200 mg/m2/day for 5 consecutive days; oral route	43 paediatric patients (40 children +30 adults from BE study for Pop-PK analysis)	Paediatric patients with malignant gliomas or other cancers such as neuroblastoma, medulloblastoma, rhabdo-myosarcoma, or Ewing sarcoma.	One treatment cycle (5 days of treatment, 21 or 28 days in total) Additional treatment cycles optional	Ongoing; Interim CSR
Efficacy and safety	BEACON-CHEMO (sub analysis of BEACON study)	M 5.3.5.2	Efficacy of TMZ as monotherapy and in combination with irino-tecan or topotecan	Phase II, multi-centre, randomised, open label	TMZ TEMIRI TOTEM (3 arms included in the sub-analysis)	80 patients (1 to ≤ 21 years) 36 TMZ 30 TEMIRI 14 TOTEM	Refractory or relapsed neuroblastoma	6-12 treatment cycles	Completed; Partial CSR

Type of Study	**Study Identifier**	**Location of study report**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Patients**	**Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
Efficacy	Meta-analysis	M 5.3.5.3	Efficacy of TMZ	Systematic review and meta-analysis	TMZ TEMIRI TOTEM	288	Refractory or relapsed neuroblastoma	Treatment cycles of 21/28 days	Completed; Full report
Efficacy and safety (tolerance)	ORP-TMZ-4 (RETRO TMZ)	M 5.3.5.4	Describe the population treated with TMZ and evaluate the time from start to first progression	Observational, retrospective, multicentre study	TMZ used as monotherapy or in combination with other treatments, mostly TOTEM and TEMIRI	196 paediatric patients	Patients <18 years of age with refractory or relapsed neuroblastoma	1-60 months (mean 5.2 months)	Completed; Full CSR
Safety	EAP summary report	M 5.3.6	Report data collected for patients included in the EAP	N/A	Ped-TMZ 40 mg/mL As monotherapy, TOTEM or TEMIRI	15 included (2 patients confirmed as treated)	Patients aged 1-6 years or patients aged >6 years unable to swallow TMZ capsule with high-risk, refractory or relapsed neuroblastoma	31 March 2022 to 01 February 2023	Ongoing; periodic report

Type of Study	Study Identifier	Location of study report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	CUP summary report	M 5.3.6	Report data collected for patients included in the CUP	N/A	Ped-TMZ 40 mg/mL As monotherapy or in combination	33 included (3 patients confirmed as treated)	Patients aged 1-6 years or patients aged >6 years unable to swallow TMZ capsule with refractory or relapsed cancer (malignant gliomas or other cancers such medulloblastoma, rhabdo-myosarcoma, or Ewing's sarcoma)	22 May 2022 to 01 February 2023	Ongoing; periodic report

2.4.2. Clinical pharmacology

The summary of PK and PD of TMZ provided by the Applicant is based on the known data with the reference medicinal product Temodal, together with a Phase 1 bioequivalence study in adult patients (ORP-TMZ-1-a) and a Pop-PK study in paediatric patients (ORP-TMZ-1-b).

The data from both studies in patients treated with Ped-TMZ were used to perform a Pop-PK analysis, describing pharmacokinetics of the 40 mg/mL oral suspension in the whole population.

2.4.2.1. Pharmacokinetics

- **Bioequivalence**

Study ORP-TMZ-I-a: Bioequivalence study between Temozolomide Oral Suspension (Ped-TMZ) and Temodal capsules (study code: 17-136B) Methods

Study design

This was a Phase I, multi-centre, open label, randomised, crossover, 2-period study in 30 male/female patients with primary CNS malignancies.

Patients were randomised to receive, under fasting conditions, 200 mg/m² of either TMZ 40 mg/mL Oral Suspension (Ped-TMZ), or Temodal 100 mg capsules, as single oral administration in 2 different study periods depending on the randomisation, with no wash out period between administrations owing to the short half-life of TMZ. Treatment allocation occurred using an Interactive Web Response System (IWRS), allowing to allocate the treatments to patients according to the randomisation list.

Single oral administration of Ped-TMZ or Temodal capsules on D1 or D2 according to randomisation, followed by a glass of 240 mL of water in a sitting position and under fasting condition for at least 8 hours before dosing. Water was not allowed for one hour before drug administration and until one-hour post-dose (except for the 240 mL rinsing water). Fasting was continued for 4 hours post-administration (i.e. until a standardised lunch was served). The administration took place at around 8:00 a.m.

Table 4. Test and reference products

Product Characteristics	Test product	Reference Product
Name	Ped-TMZ (Temozolomide Oral suspension)	Temodal
Strength	40 mg/mL	100 mg
Dosage form	Oral suspension	Capsule
This product was used in the following trials:	ORP-TMZ-Ia	ORP-TMZ-Ia

Population(s) studied

The study population consisted of 30 male and/or female patients aged 18-70 years.

Main inclusion criteria:

- Patients with newly diagnosed glioblastoma multiforme or low-grade glioma (grade 2 or 3) treated with TMZ (200 mg/m^2) as monotherapy and patients with recurrent or progressive malignant glioma treated with TMZ as monotherapy (200 mg/m^2).
- Male and female patients at least 18 of age.
- Non-pregnant, non-breast feeding female.
- Body mass index (BMI) in the range of 18.5 to 30 kg/m².
- Having given a written informed consent.

Main exclusion criteria:

- Co-administration of sodium valproate, as administration of valproic acid decreases the clearance of TMZ.
- Patients with (naso)gastric tubes were excluded.
- Patients receiving 150 mg/m² and not eligible to the 200 mg/m² dose were excluded.

Patients were hospitalised for 10h (from 8:00 a.m. to 6:00 p.m.) for each period at D1 and D2 (successive days) or for 48 h (from D-1 evening to D2 evening).

Outside the scope of the protocol, from Day 3 (D3) to Day 5 (D5) of the treatment cycle, patients received their usual dose of Temodal, according to the physician's prescription. These doses were adjusted, according to the doses administrated on D1 and D2, which are multiple of 100 mg, to reach the total dose of up to 1000 mg/m² for the 5-day treatment cycle.

Sampling schedule

A total of 28, 6 mL blood samples were drawn per patient (14 blood samples per period). Blood samples were collected at T0 (pre-dose), and at 10 min, 20 min, 30 min, 45 min, 1 h, 1 h 30 min, 2 h, 2 h 30 min, 3 h, 4 h, 6 h, 8 h, and 10 h after administration in each period (to be compatible with daytime hospitalisation).

Analytical methods

Blood samples were collected in prechilled heparinised tubes and immediately placed in an ice-water bath. Samples were centrifuged at 4 ºC. After centrifugation, 10% acetic acid was added to plasma sample. Plasma samples were frozen and stored at -80°C +/-10°C until shipment to the analytical facility.

After thawing, the samples were further processed (protein precipitation) and analysed by LC-MS/MS.

TMZ concentrations were measured in human plasma according to the validated LC-MS/MS method prior to sample analysis.

Pharmacokinetic variables

The pharmacokinetic variables included C_{max}, AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , t1/2 (h), Kel (1/h), and percentage of AUC extrapolated.

Statistical methods

The different analysis sets were defined as follows:

- Intent-to-treat set (ITTS): All randomised patients of the study.
- Pharmacokinetic set (PKS): Patients from the ITTS having completed the study without protocol deviations or violations thought to significantly affect the pharmacokinetic analysis.
- Safety set (SS): Patients from the ITTS who received at least one study treatment dose.

Drug plasma concentrations were measured, and pharmacokinetic parameters were calculated for temozolomide. Pharmacokinetic parameters were calculated using Phoenix WinNonlin software (Version 8.1, Pharsight) for all patients who completed the study and who were not excluded due to deviations that could impact the pharmacokinetic analysis.

The statistical analysis was performed on log-transformed AUC_{0-t} and C_{max} of temozolomide using ANOVA.

The bioequivalence between test product and reference product was concluded if the 90% confidence interval fell within the [0.80-1.25] bioequivalence limits for Cmax and AUCt.

Results

A total of 36 patients from 7 different sites in France were screened and randomised in the study, until 30 patients with evaluable PK data were available. All 36 patients presented a glioblastoma multiforme, low-grade glioma (grade 2 or 3) or recurrent or progressive malignant glioma, all treated with temozolomide as monotherapy, as required for inclusion in the study.

Patient characteristics in the Intent-to-treat set (ITTS) were as follows:

- 25% were female and 75% were male.
- Age ranged from 20 to 79 years with a mean of 52.3 ± 14.8 years.
- BMI ranged from 19.8 to 30.6 kg/m² with a mean of 24.79 ± 2.91 kg/m².
- Karnofsky score ranged from 60 to 100 with a mean of 85.3 ± 11.3.

Three patients were discontinued, including 1 patient with major protocol deviation. Four other major deviations involving 3 patients were detected during the course of the study and led to the exclusion and replacement of these patients. Finally, 30 patients completed the study as per protocol and were included in the PK set (PKS).

Figure 2. Patient disposition

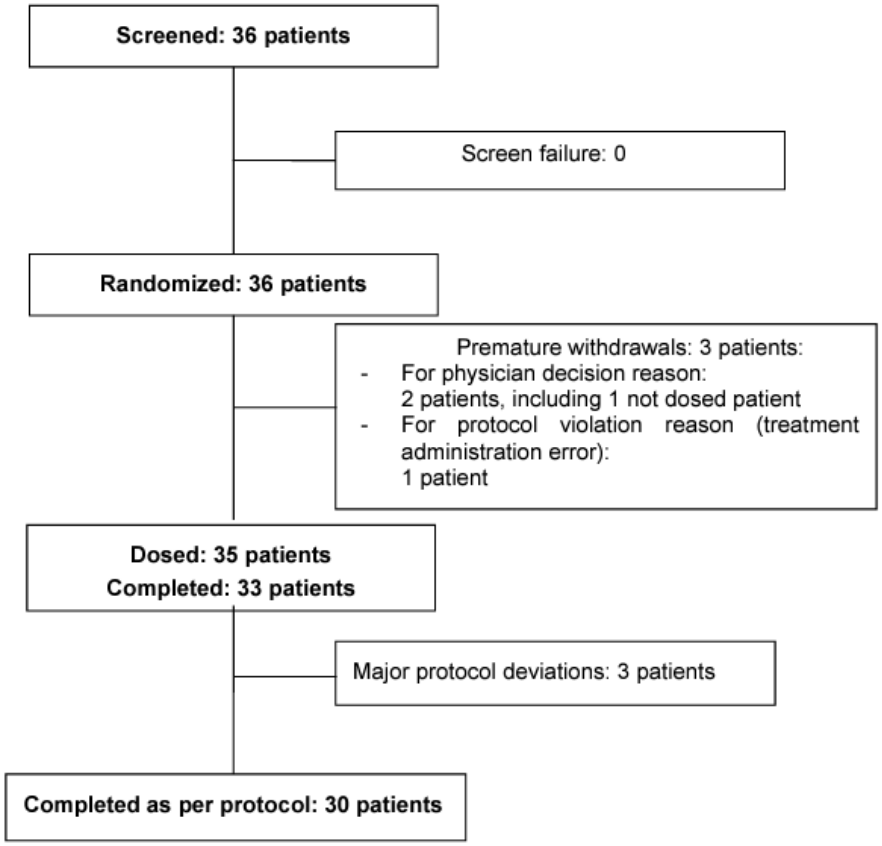


Figure 3. Mean TMZ plasma concentration-time profiles for Ped-TMZ oral suspension (Test) and Temodal capsules (Reference)

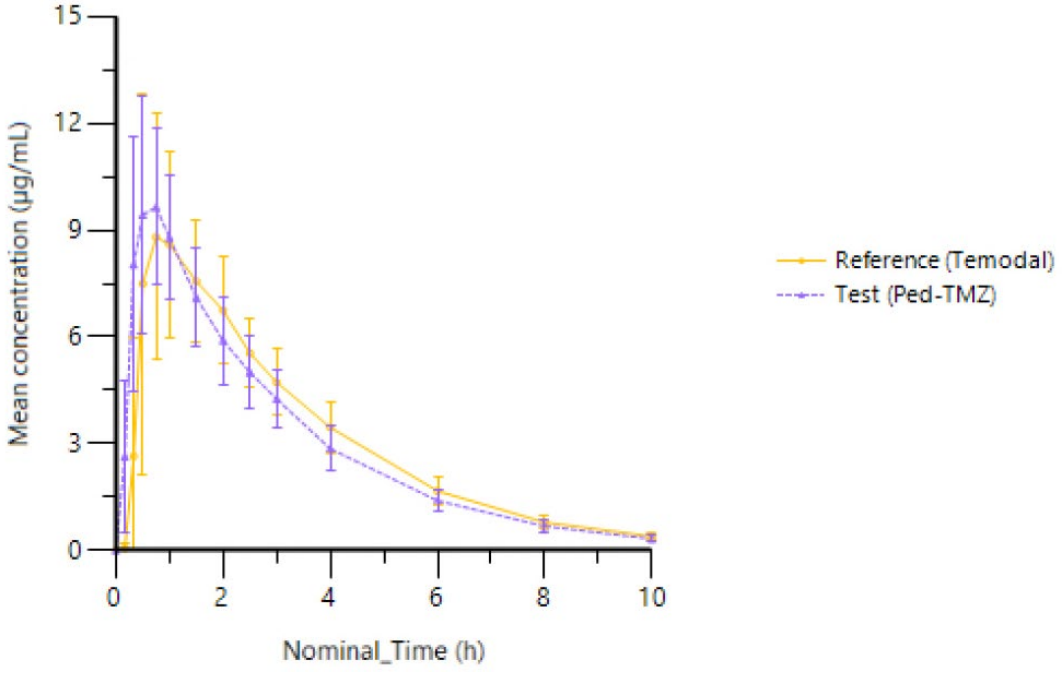


Table 5. PK parameters of TMZ after administration of Ped-TMZ oral suspension (Test) and Temodal capsules (Reference), n=30

		Cmax	**Tmax**	**AUC_{0-t}**	**$AUC_{0-\infty}$**	**Kel**	**t1/2**	**%AUCextra**
		(µg/mL)	(h)	(h*µg/mL)	(h*µg/mL)	(1/h)	(h)	(%)
Ped-TMZ	Mean	10.939	0.649	30.467	31.376	0.367	1.909	2.901
	SD	2.540	0.302	4.939	5.062	0.035	0.205	0.895
Temodal	Mean	10.506	0.909	31.471	32.584	0.362	1.928	3.454
	SD	3.894	0.405	5.727	5.840	0.031	0.163	0.954

Table 6. Bioequivalence evaluation of TMZ after administration of Ped-TMZ oral suspension (Test) and Temodal capsules (Reference), n=30

	Test/Reference ratio of geometric means (%)	**90% CI**		**Intra-Patient %CV**
		Lower	Upper	
$Ln(AUC_{0-t})$	97.18	95.05	99.35	0.25%
$Ln(C_{max})$	107.62	98.07	118.09	4.47%

- **Temozolomide pharmacokinetic from reference product:**

Pharmacokinetic properties of TMZ have been well studied in adults and have been described in a Pop-PK analysis including data from three Phase I and three Phase II studies conducted with the reference product Temodal, which included plasma samples from 359 patients a total. In the Phase I studies, patients with advanced cancer without bone marrow involvement were enrolled. In the Phase II studies, patients with glioblastoma or anaplastic astrocytoma were enrolled.

Absorption and Bioavailability

Oral TMZ is considered to be rapidly (Tmax of approximately 1 h) and nearly 100% bioavailable and rapidly eliminated (t1/2 of 1.8 h). After oral administration of Ped-TMZ to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 35 minutes post-administration (tmax ranging between 0.33 and 1.53 hours) and the half-life (t1/2) in plasma is approximately 1.9 hours.

TMZ can cross the blood brain barrier with a concentration in the cerebral spinal fluid of approximately 20% to 40% of that found in plasma. After absorption, TMZ was rapidly converted to the metabolite MTIC, and subsequently to active substance diazomethane, and the end-product 5-aminoimidazole-4-carboxamide (AIC). Mean Tmax values for MTIC were 1.5 to 2.0 hr after a single dose, and mean Tmax of AIC was 2.5 hr. Cmax values for MTIC and AIC were 2.5 – 4.7% and 13% of those for TMZ, respectively. The data indicate complete oral bioavailability of the drug. Mean AUC values ranged from 14.3-15.5 µg.hr/mL for a dose of 100 mg/m² to 176 µg.hr/mL for a dose of 1,000 mg/m².

Influence of food

Administration of TMZ after taking a meal (rich in modified fats) influences the rate and extent of its absorption, compared to taking it on an empty stomach:

- Tmax (time to maximum plasma concentration) increases from 1.07 to 2.25 hours.
- Cmax (maximum plasma concentration) decrease from 9.55 $\mu g.ml-1$ to 6.51 $\mu g.ml^{-1}$, or -33%.
- AUC_{0-24} decreases from 30.8 to 28.1 $\mu g.h.ml^{-1}$, or - 9%.

To substantiate the risk associated with mixing capsule in food, the applicant in collaboration with Gustave Roussy Cancer centre conducted an in-vitro study, which demonstrated that dispensing Temodal capsule content with soft food may result in significant underexposure: the delivered dose of TMZ is systematically under the lower specifications of 95%, whether using apple sauce (mean dose = 91.6%, range = 90-93%) or apple juice (mean = 91.0%, range = 89-93%).

No specific food effect studies were performed with Ped-TMZ.

Distribution

The mean apparent volume of distribution (Vd) ranged from 0.35 L/kg to 0.63 L/kg on day 1 of cycle 1 and was independent of the dose. TMZ demonstrates low protein binding (10% to 20%), and thus it is not expected to interact with highly protein bound agents. In plasma, TMZ undergoes non-enzymatic hydrolysis to MTIC, which further degrades to AIC and the reactive diazomethane. AIC is an intermediate of the biosynthesis of purines and expected to be non-toxic.

Positron emission tomography studies in humans and preclinical data suggest that TMZ crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient. CSF exposure based on AUC of TMZ was approximately 30% of that in plasma, which is consistent with animal data.

Elimination

Excretion

After oral administration of 14C -labelled TMZ, mean faecal excretion of 14C over 7 days post-dose was 0.8% and the half-life (t1/2) in plasma of adult patients is approximately 1.9 hours. The total recovery of 14C is low, probably because of the incorporation of AIC into the tissue purine pool. Following oral administration, approximately 5% to 10% of the dose is recovered unchanged in the urine over 24 h, and the remainder excreted as TMZ acid, AIC or unidentified polar metabolites.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of the dose.

Metabolism

TMZ is a prodrug that spontaneously hydrolyses at physiological pH primarily to the species, MTIC (t1/2 = 1.24 h at pH=7.4) which in turn, decomposes into the methyl diazonium ion (diazomethane) (t1/2 = 8 min) and AIC.

The intermediate MITC is not metabolised by the liver. Negligible metabolism of TMZ to temozolomide acid (1 to 2%) has been observed [Baker et al. 1999].

Special populations

Impaired renal function

No PK trials in patients with renal dysfunction have been performed. However, based on the pharmacokinetic properties of TMZ, it is unlikely that dose reductions are required in patients with any degree of renal impairment.

Impaired hepatic function

The pharmacokinetics of TMZ were comparable in patients with normal hepatic function and in those with mild or moderate hepatic impairment (data not shown). No data are available on the administration of TMZ in patients with severe hepatic impairment (Child's Class C) and caution should be exercised when TMZ is administered in these patients. A benefit/risk assessment should be performed prior to treatment initiation and after each treatment cycle.

Gender

In a population PK analysis of clinical trial experience with the reference product Temodal there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of grade 4 neutropenia (ANC < 0.5 x 109/L), 12 % vs 5 %, and thrombocytopenia (< 20 x 109/L), 9 % vs 3 %, in women versus men in the first cycle of therapy.

In a 400 subject recurrent glioma data set, grade 4 neutropenia occurred in 8 % of female vs 4 % of male subjects and grade 4 thrombocytopenia in 8 % of female vs 3 % of male subjects in the first cycle of therapy. In a study of 288 subjects with newly diagnosed glioblastoma multiforme, grade 4 neutropenia occurred in 3 % of female vs 0 % of male subjects and grade 4 thrombocytopenia in 1 % of female vs 0 % of male subjects in the first cycle of therapy.

No sub-analysis by gender was conducted in either the prospective BEACON-CHEMO study or the retrospective ORP-TMZ-4 study.

Elderly

In the bioequivalence study (ORP-TMZ-1-a), six elderly patients (65 to 74 years) were included in the study. No specific subgroup pharmacokinetic analysis was performed for this elder population.

Elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia.

Based on a Pop-PK analysis in patients 19-78 years of age, clearance of TMZ is not affected by age.

The Pop-PK analysis with Ped-TMZ suspension confirmed that TMZ pharmacokinetics was as expected based on allometric weight scaling principles. Clearance was decreased in patients with higher than age and sex adjusted creatinine and the absorption rate constant was slower than would be expected from allometric principles.

Paediatric patients

In the original paediatric phase I study, enclosed in the Temodal MAA dossier, 19 paediatric patients (3 to 17 years) were evaluated for PK. TMZ was found to be rapidly absorbed with a mean T_{max} ranging from 1.27 to 1.87 h in the different dose groups. The C_{max} (9.5-17 mg/L) and AUC (24.0-48.7 µg.h/mL) were higher than in adults (by 40%). However, this did not result in a higher myelotoxicity probably due to a higher bone marrow reserve in children. C_{max} and AUC of TMZ were found to be directly related to the dose. The mean terminal phase half-life, the mean body clearance and the mean volume of distribution were independent of the dose and comparable to the values in adults. Mean urinary recovery of unchanged TMZ and mean renal clearance were also consistent with results in adults. Following multiple dosing, no accumulation of TMZ in plasma was observed.

TMZ (100 mg/m²/day for 5 days, every 28 days) given in combination with intravenous irinotecan (10 mg/m²/day at day 1-5 and 8-12, every 28 days) to 12 children and adolescents (median age 12.5 [1–23] years) with recurrent or refractory cancer (including 2 neuroblastomas), showed a proportionate increase in drug and metabolite exposures for both agents with larger dosages [Wagner et al. 2004]. The median apparent TMZ clearance was 4.9 L/h/m2 (range, 1.3 to 7.4 L/h/m2). No PK interaction was observed and no change in TMZ or MTIC PK parameters was observed between treatment day 1 and day 5.

Wagner et al. then conducted similar study with the combination in 14 relapsed or refractory high-risk neuroblastoma patients (median 7 [3-22] years) using TMZ (75-100 mg/m²/day for 5 days every 21 days) and oral irinotecan (60 mg/m²/day at day 1-5 and 8-12, every 21 days). Twelve (12) patients were evaluable for pharmacokinetics. In general, drug and metabolite exposures for both agents were increased at larger dosages. The median apparent TMZ clearance was 6.7 L/h/m2 (range, 2.1 to 12.3

L/h/m2). The dosages recommended in this study were 75 mg/m²/day TMZ and 60 mg/m²/day irinotecan.

In the study performed with the combination topotecan and TMZ (TOTEM) in 16 children and adolescents (median age 8.5 [3–19] years) with relapsed or refractory solid malignancies, TMZ was administered orally, 100 or 150 mg/m2/d, and topotecan intravenously over 30 min, at 0.75 or 1 mg/m2/d over 5 consecutive days every 28 days [Rubie et al. 2010]. Fifteen (15) patients were evaluable for pharmacokinetics. There was no significant difference between apparent clearance at Day 1 and Day 5. The inter-individual variability in clearance was partly explained by BSA with a decrease from 45% (Day 1) or 53% (Day 5) to 26% (Day 1) or 32% (Day 5) when CL was expressed per m2. The mean CL was higher for patients at 150 mg (n= 12) than that of the 3 patients treated with 100 mg (3.70 versus 2.31 L/h/m2) resulting in similar AUC between the two dose levels (i.e. 43 mg h/L). The same pattern was shown for topotecan, and thus the lack of significant differences observed between plasma TMZ and topotecan concentrations on Day 1 and Day 5 indicated the absence of pharmacokinetic interaction between the drugs.

- ***ORP-TMZ-I-b - TEMOkids Population PK study***

Study title: Population pharmacokinetic, acceptability and safety study for Kizfizo, a paediatric oral suspension of temozolomide (TEMOkids) (EudraCT: 2020-003733-38).

This was a non-randomised, international, multi-centre, open-label, single-arm study, conducted in paediatric oncology patients aged 1-17. Patients received one 21 or 28-day treatment cycle involving administration of Ped-TMZ for five consecutive days followed by 16 or 23-days resting period. An optional treatment extension phase was allowed according to the protocol design. The prescribed Ped-TMZ dose was at the discretion of the principal investigator and depended on the indication and the most appropriate therapeutic protocol and ranged from 75 mg/m^2 to 200 mg/m^2 for 5 consecutive days. Based on the reference product [Temodal SmPC] and/or the clinical recommendations by European and International Medical Associations, the following regimens were recommended:

- As single agent: 150 mg/m2/day for 5 days, with subsequent dose escalation to 200 mg/m2/day in the absence of significant myelosuppression, every 28 days
- In combination with topotecan: 150 mg/m2/day for 5 days, every 28 days
- In combination with irinotecan: 100 mg/m2/day for 5 days, every 21 days

Pharmacokinetic sampling was performed on Day 1. A pre-dose and five post-dose blood samples were taken from each patient: t-1h (pre first dose), t0.1-0.2h (6-12 min), t0.33-0.66h (20-40min), t0.75-1.5h (45-90min), t2-3h and t6-8h.

For the Pop-PK modelling, the pharmacokinetic data from the 30 adult patients taking part in the bioequivalence study ORP-TMZ-I-a were also included. Each adult patient provided 13 samples following a single dose of Ped-TMZ.

Objectives:

Primary objective:

To evaluate PK parameters of Ped-TMZ in paediatric patients aged 1 year and over.

Secondary objectives:

- To evaluate the safety of Ped-TMZ
- To evaluate the acceptability of Ped-TMZ
- To describe the activity of Ped-TMZ over the course of a 6-month treatment period (complete or partial response, disease progression, stable disease) according to the standard follow-up exams and tests recommended for each indication.

Evaluation criteria:

Primary endpoint:

Pharmacokinetics: TMZ apparent clearance (CL/F), distribution volume (V/F), and absorption rate constant (Ka) were estimated from the PK analysis. These parameters were used to derive TMZ key exposure estimates: area under the curve between two intakes (AUC0-t), maximum concentration (Cmax) for each included patient, elimination half-life (t1/2), and the total AUC0-∞.

Secondary endpoints:

Acceptability was evaluated using a standardised assessment tool: CAST – ClinSearch Acceptability Score Test®. A paper diary was completed to assess acceptability of Ped-TMZ on days 1 and 5 of the first treatment cycle.

Safety events recorded by the caregiver in the patient diary were controlled monthly by the principal investigator prior to data entry into the CRF.

Safety follow-up: 21 or 28 days (or up to the next Ped-TMZ cycle), including buccal tolerance (at day 5 and until day 21 or 28), with data collected within the patient diary.

Activity: The clinical activity of Ped-TMZ during the optional treatment extension phase was described according to the standard follow-up exams and tests (i.e., complete or partial response, disease progression, stable disease).

Statistical analyses

Sample size:

Initial stochastic simulation for sample size yielded a minimum of 40 patients required for performing pharmacokinetic modelling, with a total of 240 blood samples (or 200 post-dosing blood samples) collected on day 1 (D1) (five to six blood samples/patient).

Descriptive analysis:

The analyses of the sample general characteristics, including study population, patients' status, study drug exposure, laboratory test results, clinical activity, and safety evaluation, were performed using the SAS® software (version 9.4 or above) to generate standard summary statistics (mean, SD, proportions) and perform standard statistical test (e.g., Student t-test, ANOVA, Kruskall-Wallis, χ^2 test).

Acceptability analysis:

Ped-TMZ acceptability was analysed *via* CAST, a standardised assessment tool collecting objective measures including events/behaviours that can be observed during the medicine administration and using multivariate analyses to yield a medicine acceptability score considering the many aspects of this multi-faceted concept. This standardised acceptability tool is supported by EMA which provided qualification advice for its use in relative acceptability testing for oral medicines in children under 12 years of age.

Study population

The population included in the study consisted of paediatric patients already receiving commercially available TMZ-based treatment or naïve paediatric patients requiring TMZ-based treatment as per investigator's decision. Indications included those described in the Temodal SmPC (*i.e.*, malignant gliomas such as glioblastoma and anaplastic astrocytoma). In individuals with no therapeutic alternatives, the investigational medicinal product (Ped-TMZ) was used in off-label indications in accordance with current treatment protocols recommended by European and International Medical

Associations. Such indications include, but are not limited to, neuroblastoma, and also medulloblastoma, rhabdomyosarcoma, or Ewing sarcoma. Other inclusion criteria were:

- Male and female individuals aged 1-17 years
- Individuals who have signed the signed informed consent or for which one, both parents or legal guardian(s)/representative(s) (depending on local legislation) have signed the informed consent
- Individuals having records of coverage by a health insurance
- Life expectancy ≥ 3 months
- Adequate haematological function:
    - Haemoglobin ≥ 80 g/L (transfusion support authorised)
    - Neutrophil count ≥ 1.0 x 10^9 cells/L
    - Platelet count ≥ 100 x 10^9 cells/L (without transfusion support)
    - In case of bone marrow involvement: neutrophils ≥ 0.5 x 10^9 cells/L and platelets ≥ 75 x 10^9 cells/L
- Adequate renal function:
    - Creatinine clearance ≥ 60 mL/min.1.73m^2 according to the Schwarz formula or its modified form
- Adequate hepatic function:
    - Bilirubin ≤ 1.5 x ULN
    - AST and ALT ≤ 2.5 x ULN (AST, ALT 5xULN in case of liver metastases)
- Lansky Score ≥ 70%

Patients were excluded if they met any of the following exclusion criteria:

- Patients treated with sodium valproate within two weeks prior to receiving Ped-TMZ, or enrolled individuals co-administrated at day 1 with Ped-TMZ and sodium valproate, the latter decreasing TMZ clearance.
- Patients requiring (naso)gastric tube administration
- Patients already enrolled in studies investigating TMZ or other investigational new drugs
- Post-menarche female individuals with a positive blood/urine pregnancy test at inclusion (D-7 to D-1)
- Known contraindication or hypersensitivity to TMZ or any chemically close substance
- Individuals living in a facility by order of a court or an administrative order
- Individuals infected by a SARS-CoV-2 variant

Male or female individuals of reproductive potential were not allowed to participate unless they agreed to use a highly effective contraceptive method (i.e., failure rate <1% per year in case of correct and consistent use) for the duration of the trial and for up to 6 months after the last dose of study drugs.

Results summary

Figure 4. Study population flow chart

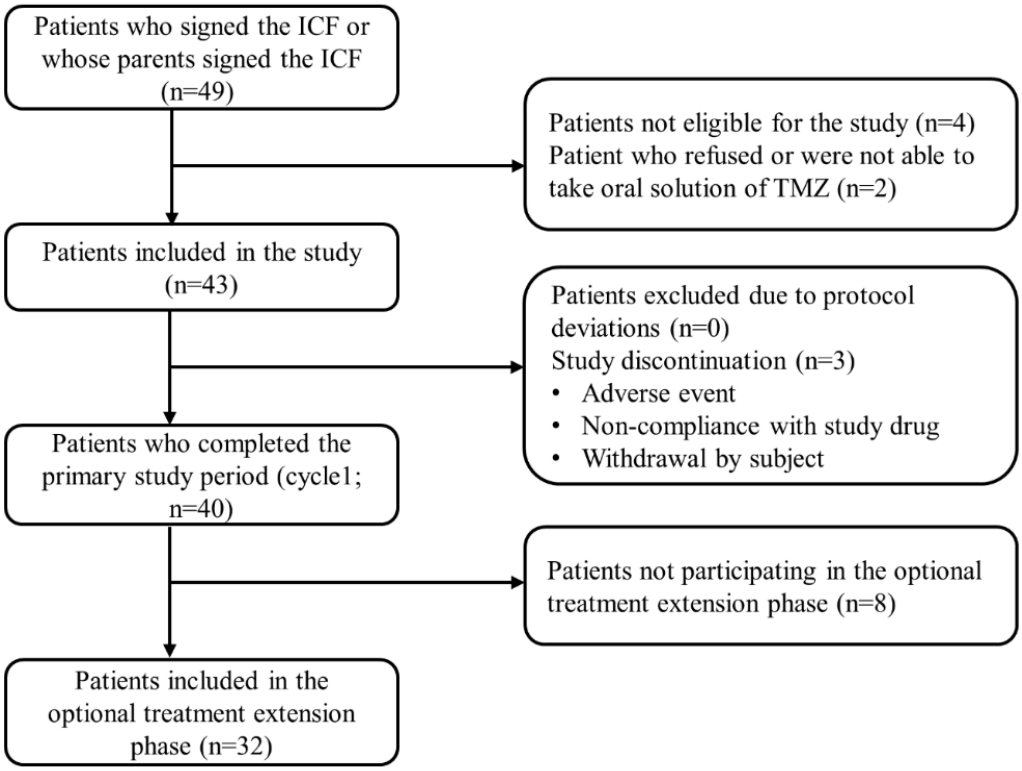


Table 7. Demographic characteristics of paediatric patients at inclusion (N=43 patients)

Variable	n (%)
Sex	
Female	20 (46.5)
Male	23 (53.5)
Age (years)	
Mean (SD)	5.9 (3.4)
Median	5.4
Q1 - Q3	3.4 - 8.0
Min - Max	1.2 - 14.8
Age group	
1-3 years [a]	13 (30.2)
4-11 years	27 (62.8)
12-17 years	3 (7.0)
Time from diagnosis to inclusion (months)	
Mean (SD)	20.7 (23.5)
Median	11.8
Q1 - Q3	6.0 - 28.1
Min - Max	1.6 - 118.1
Country	
France	32 (74.4)
Spain	6 (14.0)
Netherlands	1 (2.3)

Variable	n (%)
United Kingdom (UK)	4 (9.3)

[a] Nine patients aged < 36 months (20.9%)

Of the 43 patients included, 20 (46.5%) had neuroblastoma, 6 (14%) had medulloblastoma, 6 (14%) had rhabdomyosarcoma, 4 (9.3%) had glioblastoma/glioma, 2 (4.7%) had Ewing's sarcoma, and 5 (11.6%) presented other brain embryonal tumours, including 2 cases of embryonal tumour with multi-layered rosettes, 2 frontal tumours, and 1 case of primitive neuroectodermal tumour. Finally, among the 43 included patients, 21 (48.8%) displayed a metastatic indicator, 33 (76.7%) were naïve to prior medication by TMZ and 20 (46.5%) were prescribed TMZ in monotherapy.

Pharmacokinetics

The total dataset contained 43 paediatric patients. Two paediatric patients were excluded as they did not swallow the whole dose and one patient was excluded as no concentrations were reported due to insufficient sample collection.

One suspected sample switch in one patient, whereby the pre-dose sample was quantifiable but the first sample was below the limit of detection was reversed in the dataset. The other suspected switch samples were both post-dose and so could not definitively be called switched, hence left in for sensitivity analysis. One post-dose below limit of quantification value was excluded from the adult data.

For the Pop-PK analysis, data from 40 paediatric patients in study ORP-TMZ-I-b and the 30 adult patients administered Ped-TMZ in study ORP-TMZ-I-a were used to build the database.

Table 8. Demographics of patients included in the Pop-PK analysis

Variable	All patients	Paediatric	Adult
Number of patients	70	40	30
Number of samples	589	200	390
Number of validated samples	559	169	390
Age (years)	9.46 (1.25-79)	5.46 (1.25-14)	53.5 (20-79)
Sex (female/male)	25/45	17/23	8/22
Dose (mg/m^2)	156 (95-222)	136 (95-192)	200 (167-222)
Weight	30.35 (10-102)	18.4 (10-71)	73 (58-102)
Height	132.5 (74.5-188)	109.25 (74.5-173)	173.5 (157-188)
BSA (m2)	1.05 (0.49-2.3)	0.74 (0.49-1.9)	1.9 (1.6-2.3)
Creatinine (µmol/L)	44.5 (9-117)	31.5 (9-64)	78.5 (36-117)
eGFR ($mL/min/1.73m^2$)	119.5 (61-341)	125 (80-341)	107 (61-233)
Neuroblastoma	18	18	0
Other tumours	52	22	30

Time windows for PK sampling were t-1h (pre first dose), t0.1-0.2h (6-12 min), t0.33-0.66h (20-40min), t0.75-1.5h (45-90min), t2-3h and t6-8h. Plots of the raw data versus covariates along with concentration-time data were inspected prior to analysis.

A summary of the non-compartmental pharmacokinetics for adults and children is given in the tables below, respectively. As expected, due to the relatively sparse sampling, only 20 paediatric patients had sufficient elimination-phase samples to calculate $AUC_{0-\infty}$, Vd and CL.

Table 9. Summary results of the noncompartmental analysis in adults

	T_{max} (h)	C_{max} (µg/mL)	T_{last} (h)	C_{last} (µg/mL)	AUC_{0-t} (µg*h/mL)	$AUC_{0-\infty}$ (µg*h/mL)	Vd (L)	CL (L/h)
N	30	30	30	30	30	30	30	30
Mean	0.649	10.90	10.00	0.324	30.10	31.00	33.40	12.20
SD	0.302	2.54	0.0313	0.0841	4.86	4.99	5.81	2.14
Min	0.333	6.78	10.00	0.1600	21.80	22.30	19.80	7.55
Median	0.625	10.20	10.00	0.3270	29.60	30.60	33.40	11.90
Max	1.530	17.60	10.10	0.4980	38.80	39.80	44.50	16.50
Geo mean	0.593	10.70	10.00	0.3130	29.70	30.60	32.90	12.00

AUC: area under the plasma concentration-time curve; Clast: last observed concentration, Cmax: observed maximum plasma concentration; CL: clearance; Tlast: time of the last observed concentration; Tmax: first time to reach Cmax; Vd: Volume of distribution.

Table 10. Summary results of the noncompartmental analysis in children

	T_{max} (h)	C_{max} (µg/mL)	T_{last} (h)	C_{last} (µg/mL)	AUC_{0-t} (µg*h/mL)	$AUC_{0-\infty}$ (µg*h/mL)	Vd (L)	CL (L/h)
N	40	40	40	40	40	20	20	20
Mean	0.800	9.10	6.040	0.950	21.40	24.3	9.54	4.14
SD	0.486	3.84	0.525	0.296	6.45	6.2	3.33	1.43
Min	0.130	1.94	3.750	0.447	7.46	14.4	4.45	1.97
Median	0.685	9.10	6.080	0.948	20.80	23.6	8.86	3.92
Max	2.470	19.50	7.330	1.600	36.60	34.4	18.00	8.28
Geo mean	0.673	8.23	6.010	0.903	20.30	23.5	9.04	3.93

AUC: area under the plasma concentration-time curve; Clast: last observed concentration, Cmax: observed maximum plasma concentration; CL: clearance; Tlast: time of the last observed concentration; Tmax: first time to reach Cmax; Vd: Volume of distribution.

The developed final population PK model was a two-compartment model with first order absorption, with allometric weight scaling on all clearance and volume parameters and on Ka, additional categorical reduction of Ka in children and increase in proportional error in children, and a continuous allometric term associating decreased clearance with increasing age-corrected serum creatinine.

The final model parameter estimates are shown in the Table below. The parameter precision was below 20% for all primary pharmacokinetic parameters. Empirical Bayesian estimate shrinkage was less than 30% for clearance and central volume and less than 20% for Ka.

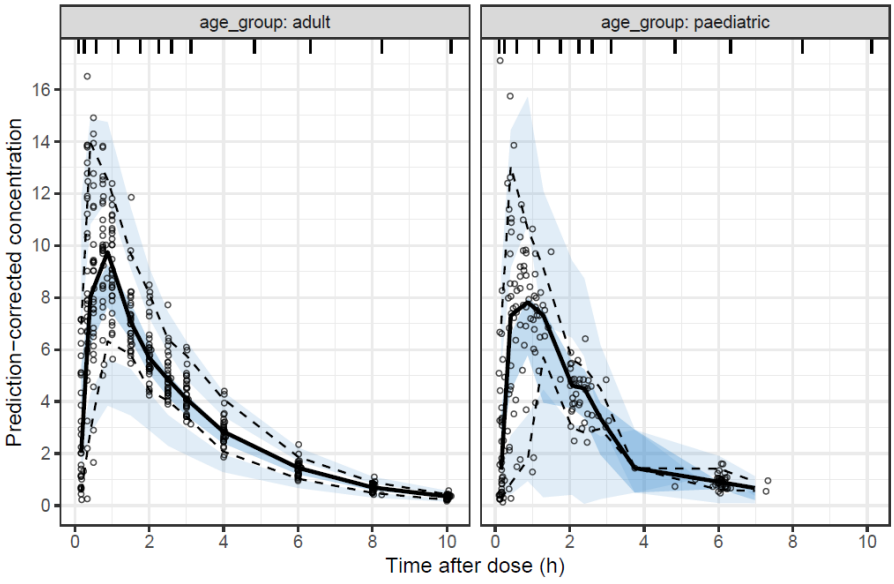
Table 11. Parameter estimates from the final model (parameters are scaled allometrically to a 70 kg individual).

Parameter	Estimate	Lower 95%CI	Upper 95%CI	IIV (%CV)	%RSE	Shrinkage %
Ka (h^{-1})	1.980	1.640	2.380	41.2	13.900	14.4
CL (L/h)	12.000	11.600	12.500	12.7	0.797	22.8
Vd (L)	20.900	17.600	24.700	21.6	2.840	24.6
Q (L/h)	8.700	5.440	13.900		11.100	
Vp (L)	8.890	6.440	12.300		7.540	
Beta child	-0.755	-0.988	-0.522		15.800	
Beta renal	-0.145	-0.239	-0.0501		33.300	
Beta error	0.826	0.515	1.140		19.200	
Proportional error	0.235	0.205	0.264		6.370	

Beta child is the proportional decrease in Ka in children, Beta renal is the allometric exponent on age-corrected serum creatinine, Beta prop is the proportional increase in proportional error in paediatric data. CL: clearance; Ka: Absorption constant; Q: Intercompartmental clearance; Vd: Volume of distribution; Vp: Peripheral volume of distribution

The prediction-corrected concentration versus time curves for adult and paediatric patient data are shown in the Figure below.

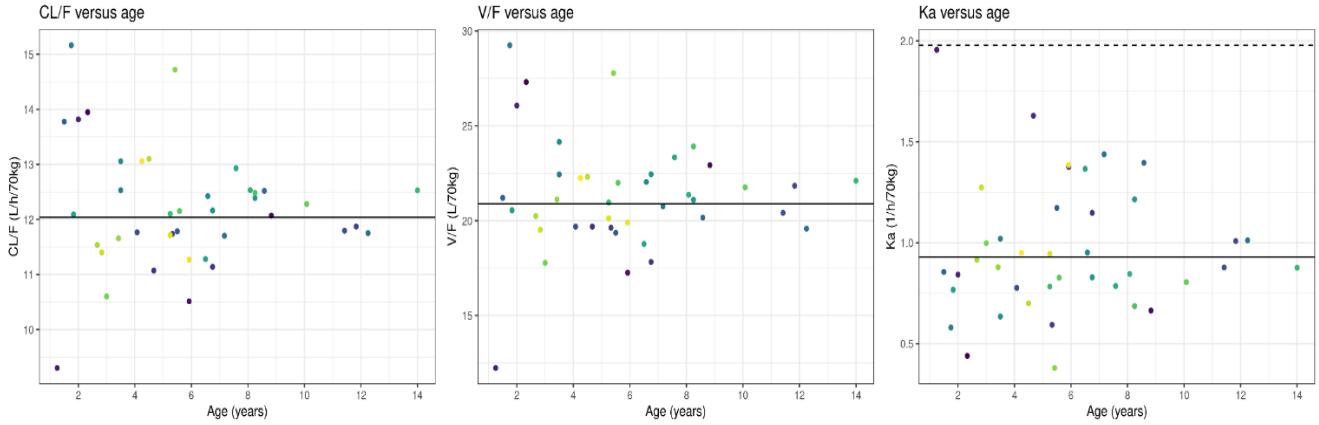
Figure 5. Prediction-corrected VPC for adult and paediatric patient data



Shaded areas correspond to the 95% prediction intervals for the 5th, 50th and 95th percentiles and the lines are the corresponding percentiles.

Whilst allometrically standardised CL/F and V/F did not change with age (and testing age in the model on clearance did not improve model fit), the decrease in absorption rate after standardising for expected increasing with allometric weight is shown in Figure below.

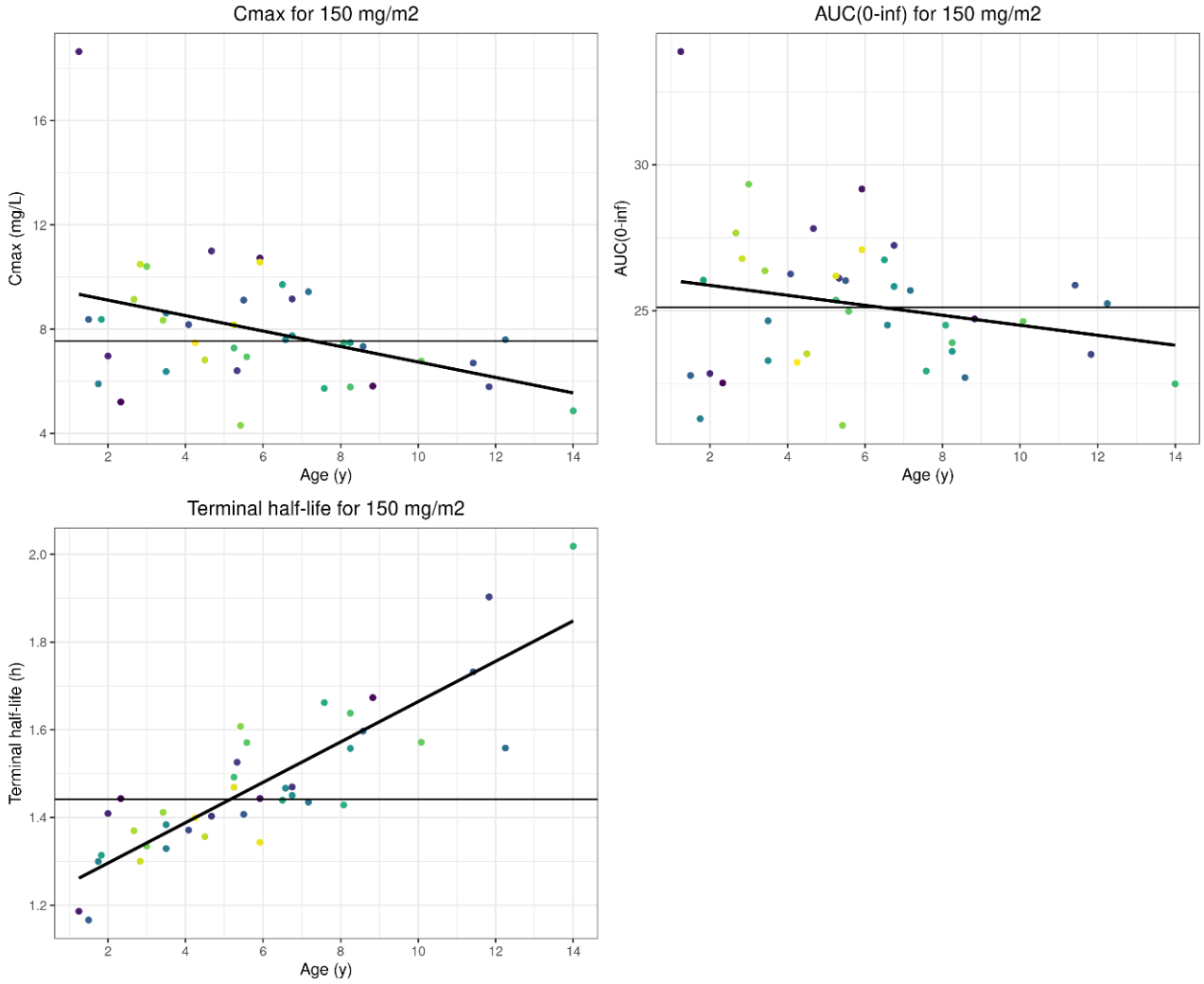
Figure 6. Plot of allometrically standardised parameters versus age



Solid lines represent the population typical value. For Ka a dashed line shows the typical value for adults.

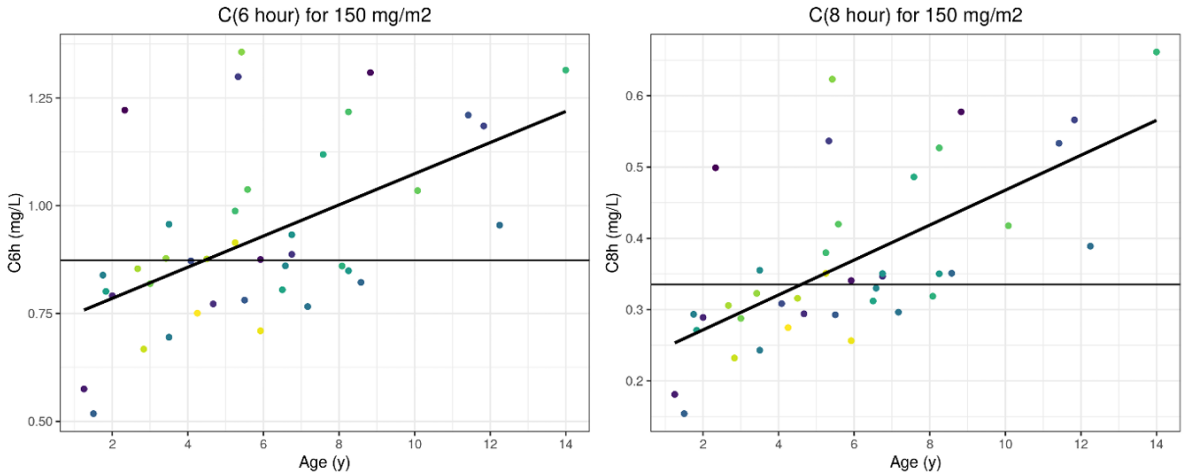
Secondary pharmacokinetic parameters were calculated for a constant dose of 150 mg/m^2. Plots of $AUC_{0-\infty}$ and C_{max} and terminal half-life and C_{6h} and C_{8h} versus age are given in the Figure below.

Figure 7. Plot of derived Cmax, AUC and terminal half-life versus age



Horizontal line is the population median, the black line represents a linear regression.

Figure 8. Plot of derived C_{6h} and C_{8h} versus age



Horizontal line is the population median, the black line represents a linear regression.

Ped-TMZ pharmacokinetics were described with a two-compartment model with first order absorption. Allometric scaling was used to describe CL/F and V/F across the age range.

Scaling V/F with body weight would ordinarily imply that BSA based dosing may yield higher C_{max} values in children compared with adults when dosing is by BSA since this implies higher mg/kg doses in smaller patients. However, this was potentially off-set by the lower Ka than would be expected from allometric principles, despite similar bioavailability (as implied by similar allometrically-scaled CL/F and V/F).

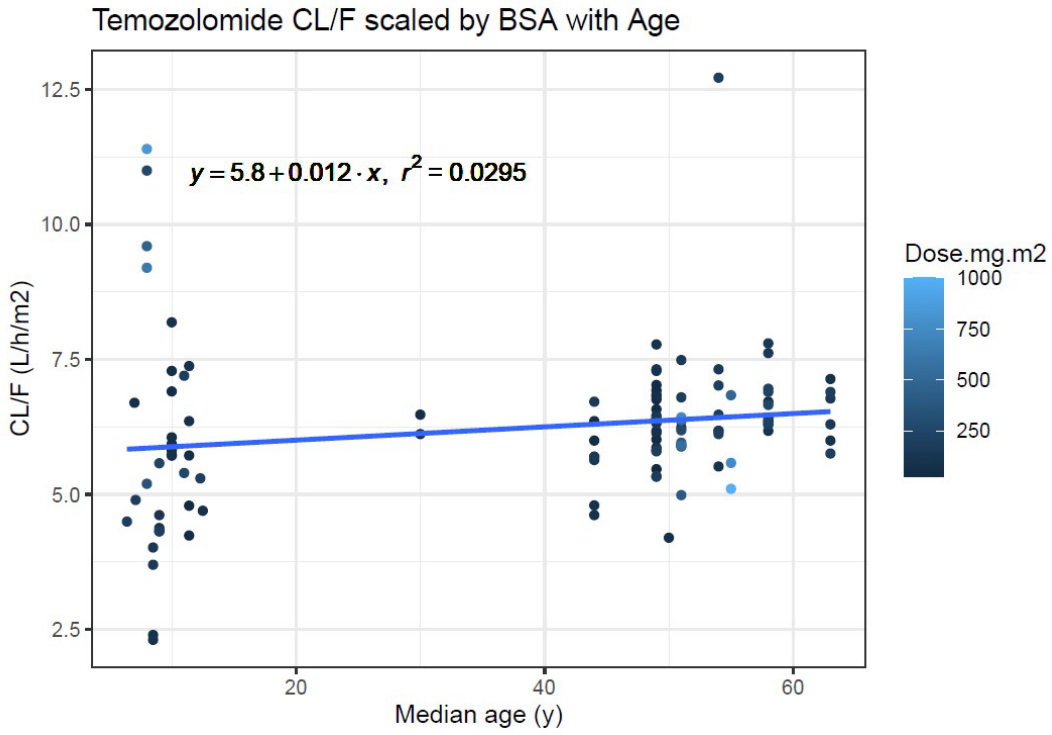
Allometric scaling of Ka predicts absorption rate constant should increase with decreasing weight, and BSA dosing also means that higher per kg doses are given to smaller children, which is also expected to increase C_{max}. In this study the increase in Ka with decreasing weight was not as pronounced as expected from allometric principles but nevertheless C_{max} is expected to increase with decreasing weight.

Allometric principles would imply a shorter terminal half-life in patients with lower body weight. This is what was observed with concentrations at 6 and 8 hours falling with increasing weight.

A covariate analysis showed that age was not a significant covariate on either clearance or volume but children did have significantly slower Ka than would be expected from allometric principles. Age adjusted serum creatinine was also correlated with clearance and paediatric patients had higher residual error than adults.

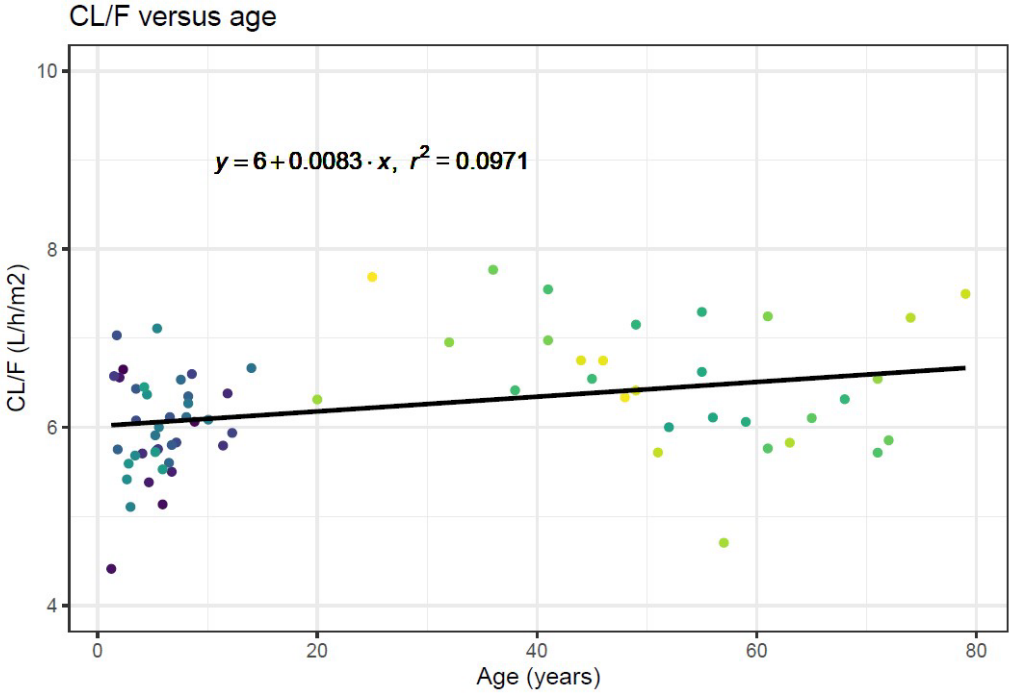
A literature review and analysis was undertaken by the Applicant in 2019 to study extracted clearance values for TMZ scaled by BSA. These are shown in the Figure below for comparison with the results obtained in the Pop-PK study with Ped-TMZ. The slope of the line obtained with literature data was not significantly different to zero but presented a slight trend upwards with age. It was similar to the slope found in the present study, which was significantly different to zero.

Figure 9. Plot of clearance scaled by BSA as analysed from literature data



The results found are consistent with those expected from the literature, and because clearance scales allometrically with weight$^{0.75}$, this is the reason that $AUC_{(0-\infty)}$ rises slightly with decreasing age when dosing is by BSA.

Figure 10. Plot of clearance scaled by BSA in the current study with Ped-TMZ data



In summary, younger children (including youngest patients of 1-2 years) had higher AUC and Cmax but lower Cmin values (at 6 and 8 h).

Acceptability

Over the course of the TEMOkids study, acceptability evaluations were collected for 41 subjects. Observable events or behaviours describing the many aspects of medicine acceptability had to be collected for medicine intake at day 1 (D1) of the treatment cycle and day 5 (D5) using a standardised questionnaire. The questionnaire was completed for all the 41 subjects at D1, but only 35 at D5. In total, there were 76 intakes of Ped-TMZ assessed.

According to the acceptability reference framework, Ped-TMZ oral suspension is considered as accepted in children aged 1 to 11 years of age.

- **Pharmacokinetics interactions studies**

No specific permeability, plasma protein binding, hepatic metabolism or drug-drug interaction studies have been performed with Ped-TMZ and all available data are from the reference product Temodal.

No studies have been conducted to determine the effect of TMZ on the metabolism or elimination of other drugs, including topotecan or irinotecan, however, it is considered unlikely that it would affect the pharmacokinetics of other medicinal products, considering TMZ does not require hepatic metabolism and exhibits low protein binding.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented. Overall, the mechanism of action of TMZ is known and independent of the tumour type and thus relevant to neuroblastoma as well.

TMZ belongs to the pharmacotherapeutic group of antineoplastic agents - other alkylating agents (ATC code: L01AX03). It is a prodrug which undergoes nonenzymatic hydrolysis at physiological pH to the metabolite 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC), which in turn decompose to diazomethane, the active metabolite.

2.4.3. Discussion on clinical pharmacology

Pharmacokinetics

A bioequivalence study (ORP-TMZ-1-a) has been conducted to compare oral bioavailability of the two formulations of TMZ (Ped-TMZ oral suspension and Temodal capsules) in adults with primary central nervous system (CNS) malignancies, under fasting conditions. The aim of the BE was to allow for the bridging of existing Temodal data with those of Ped-TMZ. Overall, the design of BE studies is acceptable. A bioequivalence study in patients is considered acceptable since temozolomide is a cytotoxic substance and not suitable for administration in healthy volunteers. A study under fasting conditions is adequate given that the reference product should be administered without food. Blood-samples were collected pre-dose and up to 10 hours post-dose in each period. A wash-out period of about 24 hours separated each period. Temozolomide in plasma was determined with a validated LC/MS/MS method.

Overall 4 major protocol deviations have been identified in 3 patients, which led to exclusion of these patients. Two deviations in one patient included missing data for blood samples at T0h20min and T0h30min, and additional two deviations included not fasting at D1 (before blood sampling for PK). The exclusion of these patients from the study is considered acceptable.

Based on the results of the submitted bioequivalence study, Ped-TMZ is considered bioequivalent with the reference medicinal product Temodal 100 mg hard capsules. Bioequivalence was demonstrated for C_{max} and AUC_{0-t} using the conventional acceptance range of 80-125%.

PK parameters of TMZ have been well described in literature both in adults and in children over the age of 3 years.

A specific population PK analysis of Ped-TMZ was undertaken by the Applicant, as part of the ORP-TMZ-1-b clinical study (TEMOkids study) to extrapolate PK parameters to the children from 1 to 3-year age range and to determine the doses for 1-3 years paediatric patients. The PK of TMZ was best described by a two-compartment model with first order absorption. Allometric weight scaling was included on absorption rate constant (Ka) as well as on all clearance and volume parameters. Additionally, a categorical reduction of Ka in children, an increase in proportional error in children, and a continuous allometric term associating decreased clearance with increasing age-corrected serum creatinine were included.

The impact of the bodyweight- and age-related changes in (Ka) remained unclear. According to the categorical factor reducing Ka in children, normalised Ka (to a 70 kg body weight) appeared to be about half as high in children compared to adults without any increase over the age range up to 14 years. The physiological basis was questioned and with this, the transition of Ka values from adolescents to adults, because it is not assumed that there could be a hard cut in Ka between the two populations. In addition, Ka was also allometrically scaled to weight. This was considered unusual and the physiological rationale unclear. The overall consequences of these factors on Ka over the course from low to high body weight up to adult weight as well as the physiological rationale were discussed and the influence on exposure (AUC) is considered limited. Additional discussions have been provided and some additional explanation given. The data indicate that variability in Cmax was especially high in 1-2 year-olds. This could not be explained by a food effect. The impact of body weight related changes

in ka on Cmax, as stated by the applicant is not large. Thus, these differences in Ka are not further pursued, even if the physiological rationale is still vague.

In regard to adequacy of administration of same BSA-based doses for patients aged 1-2 years, PK data were available in n=8 patients aged 1.25 to 2.85 years. The comparison of exposures between different paediatric age groups (1-2 years, 3-6 years and 7-14 years) was difficult, since different doses were administered, and limited data are available for most doses. Comparison of exposure for the dose range with most data in the youngest population (1-2 years: doses 125-<150 mg/m^2) reveals that AUC was most variable in the 1-2 years-old but in the median, AUC was comparable, Cmax increased with decreasing age and C6 decreased with decreasing age. Thus, the doses investigated are considered acceptable since AUC was comparable between age groups.

When comparing dosing data between all age groups (including adults), it is clear that the range of doses given to patients included in the PopPK dataset were different between age groups. In the youngest paediatric patients, aged 1-2 years, doses given were 95 – 150mg/m^2. Thus, even if same BSA based doses are claimed, doses administered in the respective studies did not overlap between adults (167 – 222 mg/m^2) and infants/toddlers (95 – 150 mg/m^2). This is due to different indications/respective dosing schedules. The PK and the safety of doses of 200mg/m^2 were not investigated in the youngest age group and in addition, doses administered were lower than intended. Therefore, the safety information available is limited to lower doses (maximally 150 mg/m^2). In addition, since the popPK model is based on very limited data in the youngest age cohort and variability in exposure is very high, the model is not considered to be fit for the purpose of extrapolation to higher doses than investigated. Therefore overall, doses higher than 150 mg/m^2 cannot be approved for the age below 3 years. Furthermore, the applicant revised the proposed indication of Kizfizo in response to the D180 LoOI to the use of the medicinal product only in combination with irinotecan or topotecan, excluding the use in monotherapy. The recommended doses of temozolomide when administered with irinotecan or topotecan never exceed 150 mg/m².

Pharmacodynamics

No new pharmacodynamic studies were presented. Overall, the mechanism of action of TMZ is known and independent of the tumour type and thus relevant to neuroblastoma as well.

The rationale for the combination of temozolomide and irinotecan or topotecan is based on the synergistic activity of temozolomide in combination with topoisomerase I inhibitors observed in preclinical studies due to their distinct mode of action (see non-clinical assessment).

The topoisomerase I inhibitors have demonstrated a broad spectrum of antitumour activity. However, neither topotecan nor irinotecan are approved for the treatment of neuroblastoma, although they have been clinically evaluated as monotherapy in patients with neuroblastoma. Anti-tumour activity of combination of temozolomide and irinotecan or topotecan in patients with neuroblastoma was demonstrated in several published phase I/II studies (some presented and discussed in the clinical efficacy part of the AR).

2.4.4. Conclusion on clinical pharmacology

Ped-TMZ 40 mg/mL oral suspension is bioequivalent with Temodal capsules based on the presented bioequivalence study ORP-TMZ-1-a.

Pharmacokinetic data on temozolomide has already been established in adults and paediatrics above the age of 3 years based on the literature data. As part of the TEMOkids study, the specific population PK analysis of Ped-TMZ has been performed to extrapolate PK parameters to the children from 1 to 3-year age range and to determine the doses for 1-3 years paediatric patients. Since model is not

considered to be fit for the purpose of extrapolation to higher doses than investigated, the doses higher than 150 mg/m^2 cannot be approved for the age below 3 years. However, the recommended doses of temozolomide when administered with irinotecan or topotecan never exceed 150 mg/m^2.

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.5. Clinical efficacy

To support the use of Ped-TMZ in relapsed or refractory neuroblastoma, the Applicant presented the efficacy results from the following studies with TMZ:

- **BEACON-CHEMO study**, a sub-study of the BEACON Phase II randomised, open label, multinational study investigating the activity of several TMZ regimens in paediatric relapsed or refractory neuroblastoma patients.

- **ORP-TMZ-4 study (Retro TMZ),** an international, multicentre retrospective study evaluating the use of TMZ in paediatric refractory or relapsed neuroblastoma.

In addition, the Applicant presented the results of a **meta-analysis** of data from all prospective studies evaluating TMZ monotherapy, TEMIRI, and TOTEM in children with refractory or relapsed neuroblastoma within the proposed indication for Ped-TMZ**.**

A systematic literature search conducted by the applicant on May 26, 2023 identified 8 published studies, investigating the efficacy of TMZ monotherapy, TMZ in combination with irinotecan (TEMIRI) and TMZ in combination with topotecan (TOTEM) in a total of 208 patients with refractory or relapsed neuroblastoma [De Sio et al. 2006, Rubie et al. 2006, Wagner et al. 2004, Kushner et al. 2006, Wagner et al. 2009, Bagatell et al. 2011, Rubie et al. 2010, Di Giannatale et al. 2014].

Furthermore, with the response to D120 LoQ, the applicant submitted a CSR (dated 17 April 2024) of the IC-TMZ STUDY - Indirect Comparison of BEACON-CHEMO and retroTMZ survival data versus historical cohorts survival data for relapsed high-risk neuroblastoma.

2.4.5.1. Dose response study(ies)

Currently, in patients 3 years of age or older, TMZ is authorised for the treatment of recurrent or progressive malignant glioma and it is given orally at the same dose as that used for adults. When given orally, TMZ is administered once daily and the capsules should be swallowed intact with a full glass of water.

No formal dose response study has been conducted for Ped-TMZ in the proposed indications.

Proposed posology and dosing schedules

Dosing depends on whether treatment is in monotherapy or in combination with specific DNA topoisomerase I inhibitors (topotecan or irinotecan). In the response to D180 LoOI, however, the proposed indication was revised to the use of the medicinal product only in combination with irinotecan or topotecan, which is why the proposed posology as monotherapy is no longer relevant.

The dose schedule for Ped-TMZ combination with topotecan is based on the dosing in the BEACON-CHEMO study and the phase II neuroblastoma study [Di Giannatale et al., 2014]. The dose schedule for Ped-TMZ combination with irinotecan (TEMIRI) is based on the dosing in the BEACON-CHEMO study. Dosing adjustments in case of toxicity used for cycle delays and dose reductions for combination treatment are the ones from the BEACON-CHEMO study.

Dosing recommendations and dosing adjustments for Ped-TMZ in case of toxicity are as follows:

Ped-TMZ in combination with topotecan (TOTEM)

Cycle duration in combination with topotecan: 28 days

Ped-TMZ is administered orally at a dose of 150 mg/m² body surface once a day during 5 days and then stopped during 23 days. Topotecan is administered intravenously over 30 min, at least 1 h after administration of TMZ, at a dose of 0.75 mg/m^2 during the same 5 days and then stopped during 23 days.

During treatment, a complete blood count and liver function tests should be obtained between Day 25 and Day 28. The new cycle of treatment should be delayed, the dose reduced, or administration discontinued according to the Tables below.

Table 12. Different dose levels of temozolomide and topotecan for treatment in combination with topotecan

Dose level	**Temozolomide dose (mg/m^2/day)**	**Topotecan dose (mg/m^2/day)**	**Remarks**
0	150	0.75	Dose during cycle 1
n-1	120	0.50	Reduction for toxicity at Dose level 0
n-2	90	0.25	Reduction for toxicity at Dose level n-1

Table 13. Temozolomide and topotecan cycle lengthening, dose reduction or discontinuation during treatment in combination with topotecan

Toxicity	**Ongoing cycle lengthening**	**Dose modification at first occurrence**	**Dose modification at second occurrence**
Haematological toxicity			
- ANC < 0.75 x 10^9/l [a, b] - Thrombocytes < 75 x 10^9/l [a b] recovered on day 28 after the start of a cycle	No	No dose modification	No dose modification
- ANC < 0.75 x 10^9/l [a, b] - Thrombocytes < 75 x 10^9/l [a, b] recovered between day 29 to 35 after the start of a cycle	Yes	No dose modification	Temozolomide Dose level n-1
- ANC < 0.75 x 10^9/l [a, b] - Thrombocytes < 75 x 10^9/l [a, b]	Yes		Temozolomide and topotecan

recovered between day 36 to 42 after the start of a cycle		Temozolomide and topotecan Dose level n-1	Dose level n-2
- ANC < 0.75 x 10^9/l [a, b] - Thrombocytes < 75 x 10^9/l [a, b] On day 43 after the start of a cycle	Treatment discontinuation		
Hepatic toxicity			
Liver function: Elevation of AST/ALT grade ≥3 that recovers to grade ≤1 before day 28 after the start of a cycle	No	No dose modification	No dose modification
Liver function: Elevation of AST/ALT grade ≥3 not recovered to grade ≤1 before day 28 after the start of a cycle	No	Temozolomide dose level n-1	Treatment discontinuation
Other toxicity			
Other grade ≥3 non haematological toxicity not recovered to grade ≤2 before day 28 after the start of a cycle	No	Temozolomide and topotecan Dose level n-1	Treatment discontinuation

Ped-TMZ in combination with irinotecan (TEMIRI)

Cycle duration in combination with irinotecan: 21 days

Ped-TMZ is administered orally at a dose of 100 mg/m² body surface once a day during 5 days and then stopped during 16 days. Irinotecan is administered intravenously over 1 h, at least 1 h after administration of TMZ, at a dose of 50 mg/m^2 during the same 5 days and then stopped during 16 days. Dosing should be adapted in case of toxicity.

During treatment, a complete blood count and liver function tests should be obtained between Day 18 and Day 21 before the initiation of the next cycle. The new cycle of treatment should be delayed, the dose reduced, or administration discontinued according to the tables below.

Table 14. Different dose levels of temozolomide and irinotecan for treatment in combination with irinotecan

Dose level	**Temozolomide dose (mg/m^2/day)**	**Irinotecan dose (mg/m^2/day)**	**Remarks**
0	100	50	Dose during cycle 1
n-1	80	40	Reduction for toxicity at Dose level 0
n-2	60	30	Reduction for toxicity at Dose level n-1

Table 15. Temozolomide and irinotecan cycle lengthening, dose reduction or discontinuation during treatment in combination with irinotecan

Toxicity	**Ongoing cycle lengthening**	**Dose modification at first occurrence**	**Dose modification at second occurrence**
Haematological toxicity			
- ANC < 0.75 x 10^9/l [a, b] - Thrombocytes < 75 x 10^9/l [a, b] recovered on day 21 after the start of a cycle	No	No dose modification	No dose modification
- ANC < 0.75 x 10^9/l [a, b] - Thrombocytes < 75 x 10^9/l [a, b] recovered between day 22 to 28 after the start of a cycle	Yes	No dose modification	Temozolomide Dose level n-1
- ANC < 0.75 x 10^9/l [a, b] - Thrombocytes< 75 x 10^9/l [a, b] recovered between day 29 to 35 after the start of a cycle	Yes	Temozolomide and irinotecan Dose level n-1	Temozolomide and irinotecan Dose level n-2
- ANC < 0.75 x 10^9/l [a, b] - Thrombocytes < 75 x 10^9/l [a, b] On day 36 after the start of a cycle	Treatment discontinuation		
Hepatic toxicity			
Liver function: Elevation of AST/ALT grade ≥3 that recovers to grade ≤1 before day 21 after the start of a cycle	No	No dose modification	No dose modification
Liver function: Elevation of AST/ALT grade ≥3 not recovered to grade ≤1 before day 21 after the start of a cycle	No	Temozolomide Dose level n-1	Treatment discontinuation
Other toxicity			
Grade 3 and 4 diarrhoea >3 days despite maximum loperamide therapy, and recovered on day 21 after the start of a cycle	No	Irinotecan Dose level n-1 If the same level of toxicity persists > 2 weeks despite suitable symptomatic	Irinotecan Dose level n-2 If the same level of toxicity persists > 2 weeks despite suitable symptomatic

		treatment, treatment discontinuation	therapy, treatment discontinuation
Grade 3 and 4 diarrhoea >3 days despite maximum loperamide therapy, and ongoing on day 21 after the start of a cycle	Yes	Irinotecan Dose level n-1 Delay next cycle for up to 2 weeks until diarrhoea resolves to grade ≤1 If the diarrhoea does not resolve after a 2-week delay, treatment discontinuation	Irinotecan Dose level n-2 Delay next cycle for up to 2 weeks until diarrhoea resolves to grade ≤1 If the diarrhoea does not resolve after a 2-week delay, treatment discontinuation
Other grade ≥3 non haematological toxicity not recovered to grade ≤2 before day 21 after the start of a cycle	No	Temozolomide and irinotecan Dose level n-1	Treatment discontinuation

Proposed duration of treatment

Treatment with Ped-TMZ shall be limited to the treatment objectives. For refractory patients, treatment is usually restricted to 6 cycles, with the objective to obtain sufficient response to proceed to consolidation therapy. For relapsed patients, treatment can also be targeted initially for 6 cycles; nevertheless, after the initial 6 cycles, upon treating paediatric oncologist decision, treatment can be continued for patients responding to treatment or at least stabilised with manageable toxicity, until objective disease progression or the development of unacceptable toxicity. In any case, it is recommended to evaluate the patient response to treatment after the first two courses of therapy and every 2 cycles thereafter.

2.4.5.2. Main study(ies)

Title of the study: BEACON-CHEMO chemotherapy arms sub-analysis of the Beacon-Neuroblastoma Trial: A randomized phase IIb trial of BEvACizumab added to Temozolomide ± IrinOtecan for children with refractory/relapsed Neuroblastoma

- **Methods**

The BEACON-CHEMO study is a sub-study of the BEACON-Neuroblastoma Trial (EudraCT# 2012-000072-42), which is a prospective randomised Phase II trial assess the activity of backbone chemotherapy regimens (TMZ monotherapy, TEMIRI (irinotecan-temozolomide [IT])) or TOTEM

(topotecan-temozolomide [TTo])) for children with relapsed or refractory high-risk neuroblastoma, to determine if inhibiting angiogenesis with bevacizumab adds to the activity of this chemotherapy and to assess if anti-GD2 antibody dinutuximab beta demonstrates activity when added to chemotherapy.

For full information, the Beacon-Neuroblastoma study is a phase II, randomised, open label, international multicenter 3x2 factorial trial. Patients were randomised to bevacizumab or not, to Irinotecan or Topotecan or neither, with a backbone of temozolomide. Thus, there were 6 arms:

1) Temozolomide alone (T)

2) Temozolomide + Bevacizumab (BT)

3) Irinotecan + Temozolomide (IT)

4) Irinotecan + Temozolomide + Bevacizumab (BIT)

5) Temozolomide + Topotecan (TTo)

6) Temozolomide + Topotecan + Bevacizumab (BTTo)

Only the Temozolomide-based chemotherapy arms (T, IT and TTo) are presented in this BEACON-CHEMO clinical study report.

The Sponsor of the BEACON-Neuroblastoma study has not planned to report the results of patients treated with TMZ monotherapy, TEMIRI or TOTEM without bevacizumab or dinutuximab beta. For this reason, and in order to support TMZ efficacy in relapsed or refractory neuroblastoma, the Applicant collaborated with Birmingham University (Sponsor the BEACON-Neuroblastoma study) to access the clinical database for the patients randomised in the TMZ monotherapy, TEMIRI and TOTEM treatment arms without any biologic, to include them in the BEACON-CHEMO sub-study.

The BEACON-CHEMO CSR V1.0, dated 20 July 2023, was submitted with the initial dossier. In the responses to the D12O LoQ the BEACON-CHEMO CSR V2.0, dated 12 April 2024, was submitted with the results of the analyses that included data from the TMZ backbone chemotherapy arms of the dinutuximab beta randomisation (additional 22 patients). As the updated results do not differ considerably from the results previously reported in the CSR V1.0, the originally reported results are not replaced by the new results. Only a brief description of the results from the CSR V2.0 are included (see section Updated analyses).

- **Study Participants**

Eligible patients were aged ≥1 to ≤21 years and had histologically proven neuroblastoma as per International Neuroblastoma Staging System either relapsed (any relapsed or progressed high-risk neuroblastoma) or refractory high-risk disease (lack of adequate response to frontline therapy). Patients had measurable disease by cross sectional imaging (RECIST) or evaluable disease (uptake on MIBG scan). Patients with only bone marrow detectable disease (bone marrow aspirate or trephine) were NOT eligible. Patients had Performance Status: Lansky ≥ 50%, Karnofsky ≥ 50% or ECOG ≤3. For patients without bone marrow disease, haematological parameters were Platelets ≥ 75 x 109/L, ANC ≥ 0.75 x 109/L and Haemoglobin > 7.5 g/dL. In the presence of bone marrow disease: Platelets ≥ 50 x 109/L, ANC ≥0.5 x 109/L and Haemoglobin > 7.5 g/dL. Renal and liver function were among inclusion/exclusion criteria. Prior treatment with temozolomide and/or irinotecan was not allowed.

Eighty patients were randomised: 36 in the TMZ, 30 in the TEMIRI and 14 in TOTEM treatment groups. For the overall ITT population, the median age was 5 years (1-18 years). 51% were males, 49% females. 41% of patients had refractory disease, 59% had relapsed disease. MYCN was amplified in 21% of patients and non-amplified in 79%.

Among the 80 patients, 5 did not receive investigational treatments and 4 patients had no response

data, i.e., the evaluable (EVA) population consisted in 71 patients (TMZ: 31, TEMIRI: 27, TOTEM: 13).

- **Treatments**

Within the BEACON-CHEMO, patients were randomised to three different treatment arms (TMZ arm, TEMIRI arm, and TOTEM arm).

TMZ was administered by the oral route once daily using commercially available capsules of temozolomide (Temodal or generics) from hospital stocks. Depending on the treatment arm TMZ was administered at:

- 200 mg/m^2/d for 5 consecutive days every 4 weeks (TMZ arm)
- 100 mg/m^2/d for 5 consecutive days every 3 weeks (TEMIRI arm)
- 150 mg/m^2/d for 5 consecutive days every 4 weeks (TOTEM arm)

Dose modifications for adverse events (AE) were decided using predefined rules: at dose level of -1 and -2, temozolomide was administered at the dose of 160 mg/m^2/d or 120 mg/m^2/d respectively in the TMZ arm, at the dose of 80 mg/m^2/d and 60 mg/m^2/d in the TEMIRI arm and at the dose of 120 mg/m^2/d and 90 mg/m^2/d in the TOTEM arm.

Irinotecan was administered at the dose of 50 mg/m^2/d intravenously for 5 consecutive days every 3 weeks in combination with temozolomide. In case of AE, the dose of irinotecan was reduced to 40 mg/m^2/d and 30 mg/m^2/d at dose level of -1 and -2 respectively.

Topotecan was administered at the dose of 0.75 mg/m^2/d intravenously for 5 consecutive days every 4 weeks in combination with temozolomide. In case of AE, the dose of topotecan was reduced to 0.50 mg/m^2/d and 0.25 mg/m^2/d at dose level of -1 and -2 respectively.

Commercial batches of irinotecan and topotecan were used.

Treatments were administered for 6 cycles followed by 6 additional cycles in case of patient benefit. Treatment was stopped in case of disease progression, unacceptable toxicity, or consent withdrawal.

- **Objectives**

The primary objective of the BEACON-CHEMO study is to describe the activity of the chemotherapy treatment arms (TMZ monotherapy, TEMIRI or TOTEM) in children with relapsed or refractory neuroblastoma.

The secondary objective is to describe the safety of TMZ monotherapy, TEMIRI or TOTEM in children with relapsed or refractory neuroblastoma.

- **Outcomes/endpoints**

Primary endpoint is Best Overall Response Rate (Best-ORR) defined as complete response [CR] or partial response [PR]) at any time during the first 6 cycles of trial treatment.

Secondary endpoints include: ORR at 2 cycles (defined as CR or PR after the first 2 cycles of trial treatment); Bast DCR (defined as the percentage of patients who have achieved CR, PR or SD at any time during the first 6 cycles of treatment), DCR at 2 cycles (defined as CR or PR after the first 2 cycles of trial treatment; PFS (defined as the time from randomisation until first event e.g. progression, recurrence following response or death without progression or recurrence); EFS (defined as the time from randomisation until first event e.g. progression, recurrence following response, second malignancy or death without progression or recurrence); OS (defined as the time from randomisation until death from any cause); Duration of response; Treatment duration and extent of

exposure: Dose/cycle, dose delay and dose reduction; Nature, incidence, severity of AEs; Nature, incidence of SAEs) and relationship to study treatment.

Evaluation criteria

Measurable tumours were evaluated using MRI (preferred) or CT (including brain) scans; Non measurable tumours were evaluated using mIBG (or PET if mIBG negative) according to the SIOPEN score and bilateral bone marrow assessment and trephines (assessed by local morphology). RECIST 1.1 criteria were used to evaluate response in patients with measurable tumours. The new INRC (International Neuroblastoma Response Criteria) criteria were used for patients with evaluable disease

- **Sample size**

The number of patients assessed in the sub-group analysis BEACON-CHEMO has not been prespecified. All patients accrued in the TMZ, TEMIRI and TOTEM arms at the time of the bevacizumab randomisation completion were included in the statistical analysis: 36 patients were randomised in the TMZ arm, 30 patients in the TEMIRI arm and 14 patients in the TOTEM arm. The smaller number of patients randomised in the TTo treatment group is explained by the fact that topotecan randomisation only started after a protocol amendment introduced in July 2015.

- **Randomisation and Blinding (masking)**

Randomisation in the Beacon-Neuroblastoma trial was done via a secured on-line computer-based system at the CRCTU, University of Birmingham, UK. Minimisation was used to ensure balance across the arms for the important prognostic factors: prognostic factors, early relapse (<18 months), late relapse (≥18 months) and measurable versus evaluable disease (i.e. disease evaluated according to RECIST versus disease detectable only by MIBG scanning with or without bone marrow involvement as detected by local morphology).

- **Statistical methods**

No statistical hypotheses were tested. The analyses were descriptive only.

Results

- **Participant flow**

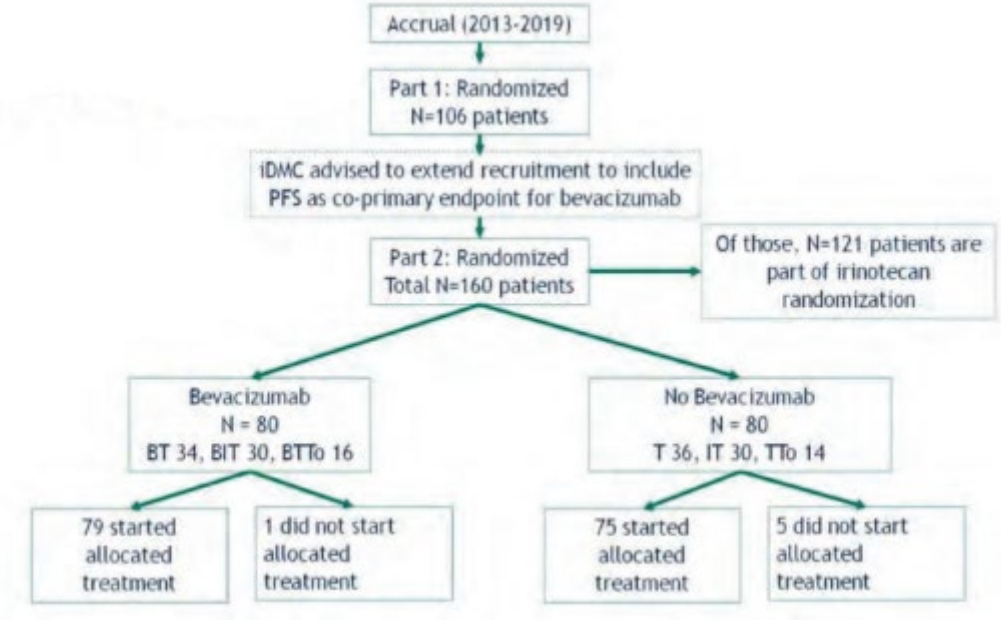


Table 16. Patient population (CSR V1.0)

	T (N=36)	IT (N=30)	Tto (N=14)	Total (N=80)
ITT Population	36 (100%)	30 (100%)	14 (100%)	80 (100%)
Safety Population	34 (94.4%)	28 (93.3%)	13 (92.9%)	75 (93.8%)
Evaluable Population	31 (86.1%)	27 (90.0%)	13 (92.9%)	71 (88.8%)

T: Temozolomide; IT: Irinotecan + Temozolomide; TTo: Temozolomide + Topotecan

- **Recruitment**

Study Period of BEACON-CHEMO (Beacon Bevacizumab randomisation)

8 years of patient recruitment, 5 years of patient follow up post-trial treatment period.

The first patient of the Beacon-Neuroblastoma (bevacizumab randomisation) was randomised on 11 July 2013, and the last patient End of Treatment Visit was on 27 May 2019.

- **Conduct of the study**

Protocol Version 5.0a dated 23 Sep 2015, Version 7.0 dated 07-Feb-2020 and last available Version 8.0 dated 07-Mar-2023 were provided together with the tables of Protocol Revisions. Protocol amendments are acceptable. Protocol deviations were not reported. GCP inspections were not reported.

- **Baseline data**

Table 17. Demographic and Baseline Characteristics in the ITT population (CSR V1.0)

		T N= 36	IT N= 30	TTo N=14	Total N=80
Age (years)	Mean (sd)	5.4 (3.3)	5.1 (3.0)	5.7 (4.0)	5.4 (3.3)
	Median	5.0	4.5	5.0	5.0
	Min-Max	1 – 18	1 – 13	1 – 17	1 – 18
Age < 3 years	Yes n (%)	6 (16.7%)	6 (20.0%)	1 (7.1%)	13 (16.3%)
	No n (%)	30 (83.3%)	24 (80.0%)	13 (92.9%)	67 (83.8%)
Age <4 years	Yes n (%)	9 (25.0%)	12 (40.0%)	3 (21.4%)	24 (30.0%)
	No n (%)	27 (75.0%)	18 (60.0%)	11 (78.6%)	56 (70.0%)
Height	Mean (sd)	109.4 (18.3)	108.4 (20.3)	115.4 (21.8)	110.1 (19.6)
	Median	109.5	104.0	111.0	109.5
	Min-Max	75.0 - 162.0	78.0 - 162.0	92.0 - 172.0	75.0 - 172.0
Weight	Mean (sd)	19.8 (9.3)	19.4 (8.1)	21.3 (12.4)	19.9 (9.4)
	Median	18.0	17.0	18.0	18.0
	Min-Max	10.0 - 55.0	11.0 - 44.0	12.0 - 59.0	10.0 - 59.0
BMI	Mean (sd)	15.9 (1.9)	15.9 (1.7)	15.0 (2.0)	15.7 (1.9)
	Median	15.7	15.5	14.9	15.5
	Min-Max	13.0 - 21.0	13.0 - 20.1	12.2 - 19.9	12.2 - 21.0
Sex: n (%)	Male	20 (55.6)	14 (46.7)	7 (50)	41 (51.3)
	Female	16 (44.4)	16 (53.3)	7 (50)	39 (48.7)
		T N= 36	**IT N= 30**	**TTo N=14**	**Total N=80**
Relapse or Refractory	refractory	15 (41.7)	14 (46.7)	4 (28.6)	33 (41.3)
	Early relapse	14 (38.9)	11 (36.7)	7 (50.0)	32 (40.0)
	Late relapse	7 (19.4)	5 (16.7)	3 (21.4)	15 (18.8)
Measurable or evaluable disease	Measurable disease n (%)	25 (69.4)	22 (73.3)	9 (64.3)	56 (70.0)
	Evaluable disease n (%)	11 (30.6)	8 (26.7)	5 (35.7)	24 (30.0)

T: Temozolomide; IT: Irinotecan + Temozolomide; TTo: Temozolomide + Topotecan; sd: standard deviation

Table 18. Disease characteristics (CSR V1.0)

		T N= 36	IT N= 30	TTo N=14	Total N=80
	50	0 (0.0%)	0 (0.0%)	1 (8.3%)	1 (1.5%)
Performance status at inclusion (Lansky)	60	0 (0.0%)	0 (0.0%)	1 (8.3%)	1 (1.5%)
	70	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (1.5%)
	80	0 (0.0%)	2 (8.0%)	1 (8.3%)	3 (4.5%)
	90	6 (20.7%)	3 (12.0%)	4 (33.3%)	13 (19.7%)
	100	23 (79.3%)	19 (76.0%)	5 (41.7%)	47 (71.2%)
	Missing data	7	5	2	14
INSS stage at diagnosis	1	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	2	-	-		-
	3	3 (8.6%)	2 (6.9%)	1 (7.1%)	6 (7.7%)
	4	30 (85.7%)	26 (89.7%)	13 (92.9%)	69 (88.5%)
	4S	1 (2.9%)	1 (3.4%)	0 (0.0%)	2 (2.6%)
	Missing	1	1	0	2
MYCN at diagnosis	Amplified	3 (8.3%)	9 (32.1%)	4 (28.6%)	16 (20.5%)
	Not amplified	33 (91.7%)	19 (67.9%)	10 (71.4%)	62 (79.5%)
	Missing	0	2	0	2
Segmental chromosomal aberration at diagnosis	No	7 (21.9%)	7 (29.2%)	1 (8.3%)	15 (22.1%)
	Yes	25 (78.1%)	17 (70.8%)	11 (91.7%)	53 (77.9%)
	Missing	4	6	2	12

New site of disease after initial complete or partial response	No	3 (15.0%)	4 (25.0%)	1 (9.1%)	8 (17.0%)
	Yes	17 (85.0%)	12 (75.0%)	10 (90.9%)	39 (83.0%)
	Missing	16	14	3	33
Number of relapses	1	14 (73.7%)	15 (93.8%)	10 (90.9%)	39 (84.8%)
	2	3 (15.8%)	0 (0.0%)	1 (9.1%)	4 (8.7%)
	3	1 (5.3%)	1 (6.3%)	0 (0.0%)	2 (4.3%)
	4	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
	Missing	17	14	3	34
Measurable soft tissue lesions at entry	No	9 (25.0%)	8 (26.7%)	5 (35.7%)	22 (27.5%)
	Yes	27 (75.0%)	22 (73.3%)	9 (64.3%)	58 (72.5%)

		T N= 36	IT N= 30	TTo N=14	Total N=80
		11 (30.6%)	5 (16.7%)	5 (35.7%)	21 (26.3%)
Bone site at entry	No				
	Yes	25 (69.4%)	25 (83.3%)	9 (64.3%)	59 (73.8%)
Bone marrow site at study entry	No	20 (55.6%)	17 (56.7%)	7 (50.0%)	44 (55.0%)
	Yes	16 (44.4%)	13 (43.3%)	7 (50.0%)	36 (45.0%)
CNS site at entry	No	33 (91.7%)	28 (93.3%)	13 (92.9%)	74 (92.5%)
	Yes	3 (8.3%)	2 (6.7%)	1 (7.1%)	6 (7.5%)
Liver site at entry	No	31 (86.1%)	24 (80.0%)	12 (85.7%)	67 (83.8%)
	Yes	5 (13.9%)	6 (20.0%)	2 (14.3%)	13 (16.3%)
Lung at entry	No	33 (91.7%)	27 (90.0%)	14 (100%)	74 (92.5%)
	Yes	3 (8.3%)	3 (10.0%)	0 (0.0%)	6 (7.5%)
Regional lymph nodes at entry	No	26 (72.2%)	25 (83.3%)	10 (71.4%)	61 (76.3%)
	Yes	10 (27.8%)	5 (16.7%)	4 (28.6%)	19 (23.8%)
Distant lymph nodes at entry	No	31 (86.1%)	24 (80.0%)	12 (85.7%)	67 (83.8%)
	Yes	5 (13.9%)	6 (20.0%)	2 (14.3%)	13 (16.3%)
Primary at entry	No	19 (52.8%)	12 (40.0%)	7 (50.0%)	38 (47.5%)
	Yes	17 (47.2%)	18 (60.0%)	7 (50.0%)	42 (52.5%)
Other at entry	No	29 (85.3%)	23 (82.1%)	12 (85.7%)	64 (84.2%)
	Yes	5 (14.7%)	5 (17.9%)	2 (14.3%)	12 (15.8%)
	Missing	2	2	0	4

T: Temozolomide; IT: Irinotecan + Temozolomide; TTo: Temozolomide + Topotecan

Table 19. Previous neuroblastoma treatments in the ITT population

	T N= 36	IT N= 30	TTo N=14	Total (N=80)
Induction - 1st Line				
COJEC	17 (47.2%)	9 (30.0%)	10 (71.4%)	36 (45.0%)
Other	5 (13.9%)	4 (13.3%)	4 (28.6%)	13 (16.3%)
Unknown	14 (38.9%)	17 (56.7%)	0 (0.0%)	31 (38.8%)
Induction - 2nd Line				
No	7 (19.4%)	4 (13.3%)	5 (35.7%)	16 (20.0%)
Yes	15 (41.7%)	9 (30.0%)	9 (64.3%)	33 (41.3%)
Unknown	14 (38.9%)	17 (56.7%)	0 (0.0%)	31 (38.8%)
Previous myeloablative chemotherapy with autologous stem cell rescue	20 (55.6%)	15 (50.0%)	11 (78.6%)	46 (57.5%)
Previous surgery	26 (72.2%)	19 (63.3%)	8 (57.1%)	53 (66.3%)
Previous 13-cis-Retinoic Acid therapy	20 (55.6%)	13 (43.3%)	6 (42.9%)	39 (48.8%)
Previous immunotherapy	16 (44.4%)	9* (31.0%)	7 (50.0%)	32 (40.5%)
Previous MIBG therapy	1 (2.8%)	3 (10.0%)	1 (7.1%)	5 (6.3%)
Previous radiotherapy	21 (58.3%)	16 (53.3%)	7 (50.0%)	44 (55.0%)

*1 missing data. T: Temozolomide; IT: Irinotecan + Temozolomide; TTo: Temozolomide + Topotecan.

- **Numbers analysed**

See above participants flow.

- **Outcomes and estimation (CSR V1.0)**

Primary efficacy endpoint results: Best Overall Response Rate (Best ORR)

Table 20. Best ORR in the overall evaluable (EVA) population

Best response **Overall population**	**TMZ** **N=31**	**TEMIRI** **N=27**	**TOTEM** **N=13**	**Total** **N=71**
Overall Best Response				
Complete Response (CR)	0 (0.0%)	0 (0.0%)	1 (7.7%)	1 (1.4%)
Partial Response (PR)	5 (16.1%)	5 (18.5%)	3 (23.1%)	13 (18.3%)
Stable Disease (SD)	15 (48.4%)	14 (51.9%)	4 (30.8%)	33 (46.5%)
Progressive Disease (PD)	11 (35.5%)	8 (29.6%)	5 (38.5%)	24 (33.8%)
ORR				
n (%)	5 (16.1%)	5 (18.5%)	4 (30.8%)	14 (19.7%)
95% CI	[7.1%;32.6%]	[8.2%;36.7%]	[12.7%;57.6%]	[12.1%;30.4%]

ORR: Overall response rate, TMZ: Temozolomide, TEMIRI: TMZ + irinotecan; TOTEM: TMZ + topotecan.

Table 11. Best ORR in children with relapsed neuroblastoma

Best response **Relapsed**	**TMZ** **N=17**	**TEMIRI** **N=14**	**TOTEM** **N=10**	**Total** **N=41**
Overall Best Response				
Complete Response (CR)	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (2.4%)
Partial Response (PR)	2 (11.8%)	3 (21.4%)	2 (20.0%)	7 (17.1%)
Stable Disease (SD)	7 (41.2%)	8 (57.1%)	3 (30.0%)	18 (43.9%)
Progressive Disease (PD)	8 (47.1%)	3 (21.4%)	4 (40.0%)	15 (36.6%)
ORR				
n (%)	2 (11.8%)	3 (21.4%)	3 (30.0%)	8 (19.5%)
95% CI	[3.3%;34.3%]	[7.6%;47.6%]	[10.8%;60.3%]	[10.2%;34.0%]

ORR: Overall response rate, TMZ: Temozolomide, TEMIRI: TMZ + irinotecan; TOTEM: TMZ + topotecan.

Table 22. Best ORR in children with refractory neuroblastoma

Best response **Refractory**	**TMZ** **N=14**	**TEMIRI** **N=13**	**TOTEM** **N=3**	**Total** **N=30**
Overall Best Response				
Complete Response (CR)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Partial Response (PR)	3 (21.4%)	2 (15.4%)	1 (33.3%)	6 (20.0%)
Stable Disease (SD)	8 (57.1%)	6 (46.2%)	1 (33.3%)	15 (50.0%)
Progressive Disease (PD)	3 (21.4%)	5 (38.5%)	1 (33.3%)	9 (30.0%)
ORR				
n (%)	3 (21.4%)	2 (15.4%)	1 (33.3%)	6 (20.0%)
95% CI	[7.6%;47.6%]	[4.3%;42.2%]	[6.1%;79.2%]	[9.5%;37.3%]

ORR: Overall response rate, TMZ: Temozolomide, TEMIRI: TMZ + irinotecan; TOTEM: TMZ + topotecan.

Secondary efficacy endpoint results

Disease Control Rate (DCR) after 6 cycles (Best DCR)

Table 23. Best DCR

DCR		**TMZ**	**TEMIRI**	**TOTEM**	**TOTAL**
Overall population	n	31	27	13	71
	DCR, n (%)	20 (64.5%)	19 (70.4%)	8 (61.5%)	47 (66.2%)
	95%CI	46.9% - 78.9%	51.5% - 84.1%	35.5% - 82.3%	54.6% - 76.1%
Relapsed	n	17	14	10	41
	DCR, n (%)	9 (52.9%)	11 (78.6%)	6 (60.0%)	26 (63.4%)
	95%CI	31.0% - 73.8%	52.4% - 92.4%	31.3% - 83.2%	48.1% - 76.4%
Refractory	n	14	13	3	30
	DCR, n (%)	11 (78.6%)	8 (61.5%)	2 (66.7%)	21 (70.0%)
	95%CI	52.4% - 92.4%	35.5% - 82.3%	20.8% - 93.9%	52.1% - 83.3%

DCR: Disease control rate, ORR: Overall response rate, TMZ: Temozolomide, TEMIRI: TMZ + irinotecan; TOTEM: TMZ + topotecan.

Response, ORR and DCR after 2 cycles

Table 24. Response, ORR and DCR at 2 cycles

Response at 2 cycles		**TMZ**	**TEMIRI**	**TOTEM**	**TOTAL**
Overall population	n	31	27	13	71
ORR	n (%)	1 (3.2%)	5 (18.5%)	1 (7.7%)	7 (9.9%)
	95%CI	0.6% - 16.2%	8.2% - 36.7%	1.4% - 33.3%	4.9% - 19.0%
DCR	n (%)	20 (64.5%)	19 (70.4%)	8 (61.5%)	47 (66.2%)
	95%CI	46.9% - 78.9%	51.5% - 84.1%	35.5% - 82.3%	54.6% - 76.1%
Relapsed	n	17	14	10	41
ORR	n (%)	1 (5.9%)	3 (21.4%)	0 (0.0%)	4 (9.8%)
	95%CI	1.0% - 27.0%	7.6% - 47.6%	0.0% - 27.8%	3.9% - 22.5%
DCR	n (%)	9 (52.9%)	11 (78.6%)	6 (60.0%)	26 (63.4%)
	95%CI	31.0% - 73.8%	52.4% - 92.4%	31.3% - 83.2%	48.1% - 76.4%
Refractory	n	14	13	3	30
ORR	n (%)	0 (0.0%)	2 (15.4%)	1 (33.3%)	3 (10.0%)
	95%CI	0.0% - 21.5%	4.3% - 42.2%	6.1% - 79.2%	3.5% - 25.6%
DCR	n (%)	11 (78.6%)	8 (61.5%)	2 (66.7%)	21 (70.0%)
	95%CI	52.4% - 92.4%	35.5% - 82.3%	20.8% - 93.9%	52.1% - 83.3%

DCR: Disease control rate, ORR: Overall response rate, TMZ: Temozolomide, TEMIRI: TMZ + irinotecan; TOTEM: TMZ + topotecan.

Progression Free Survival (PFS)

Table 25. Progression-free survival (PFS)(EVA population)

PFS		**TMZ**	**TEMIRI**	**TOTEM**	**TOTAL**
Overall	n	31	27	13	71
	Median (months) [95%CI]	3.9 [2.3-17.2]	8.7 [1.6-12.6]	5.6 [1.8-38.0]	6.1 [3.2 ;12.6]
	At 1 year % [95%CI]	41.94 [24.67-58.30]	44.44 [25.56-61.75]	46.15 [19.16-69.64]	43.66 [31.99-54.75]
	At 2 years % [95%CI]	32.26 [16.93-48.64]	25.93 [11.48-43.09]	30.77 [9.50-55.43]	29.58 [19.48-40.36]
	At 5 years % [95%CI]	25.40 [11.79-41.55]	13.89 [3.95-29.94]	0	18.40 [9.98-28.85]
Relapsed	n	17	14	10	41
	Median (months) [95%CI]	3.5 [1.8-5.9]	10.0 [1.2-12.6]	5.1 [0.5-23.2]	5.3 [2.0 ;11.3]
	At 1 year % [95%CI]	23.53 [7.31-44.92]	42.86 [17.73-66.04]	40.00 [12.27-67.02]	34.15 [20.27-48.51]
	At 2 years % [95%CI]	5.88 [0.39-23.50]	21.43 [5.21-44.79]	20.00 [3.09-47.47]	14.63 [5.94-27.03]
	At 5 years % [95%CI]	0	0	0	0
Refractory	n	14	13	3	30
	Median (months) [95%CI]	43.3 [2.3-NE]	6.1 [1.3-NE]	NE [2.1-N]	23.1 [2.3-NE]
	At 1 year % [95%CI]	64.29 [34.33-83.31]	46.15 [19.16-69.64]	66.67 [5.41-94.52]	56.67 [37.33-72.08]
	At 2 years % [95%CI]	64.29 [34.33-83.31]	30.77 [9.50-55.43]	66.67 [5.41-4.52]	50.00 [31.30-66.12]
	At 5 years % [95%CI]	48.98 [21.61-71.71]	30.77 [9.50-55.43]	0	43.08 [25.26-59.72]

PFS: Progression-free survival; TMZ: Temozolomide, TEMIRI: TMZ + irinotecan; TOTEM: TMZ + topotecan.

Overall Survival (OS)

Table 26. Overall survival (OS)(EVA population)

OS		TMZ N= 31	TEMIRI N= 27	TOTEM N=13	TOTAL (N=71)
Overall	n	31	27	13	71
	Median (months) [95%CI]	17.1 [9.9; 72.8]	17.1 [6.5; 40.3]	13.4 [8.4; NE]	15.9 [12.5; 34.3]
	At 1 year % [95%CI]	61.29 [42.02 ;75.85]	66.67 [45.71 ;81.06]	61.54 [30.83 ;81.84]	63.38 [51.07 ;73.38]
	At 2 years % [95%CI]	38.71 [22.01 ;55.15]	44.44 [25.56 ;61.75]	38.46 [14.05 ;62.80]	40.85 [29.40 ;51.94]
	At 5 years % [95%CI]	35.48 [19.43 ;51.93]	25.40 [10.96 ;42.76]	30.77 [9.50 ;55.43]	30.23 [19.81 ;41.33]
Relapsed	n	17	14	10	41
	Median (months)	15.5 [8.0; 17.5]	17.5 [3.1; 37.8]	12.9 [1.1; 38.0]	14.8 [11.0; 17.5]
	At 1 year % [95%CI]	52.94 [27.62; 73.03]	71.43 [40.63; 88.19]	60.00 [25.27; 82.72]	60.98 [44.42; 73.97]
	At 2 years % [95%CI]	17.65 [4.35; 38.30]	42.86 [17.73; 66.04]	30.00 [7.11; 57.79]	29.27 [16.37; 43.42]
	At 5 years % [95%CI]	11.76 [1.96; 31.20]	7.14 [0.45; 27.52]	20.00 [3.09; 47.47]	10.98 [3.45; 23.46]
Refractory	n	14	13	3	30
	Median (months)	72.8 [5.1; NE]	13.0 [3.7; NE]	NE [3.5; NE]	72.8 [7.5; NE]
	At 1 year % [95%CI]	71.43 [40.63; 88.19]	61.54 [30.83; 81.84]	66.67 [5.41; 94.52]	66.67 [46.92; 80.47]
	At 2 years % [95%CI]	64.29 [34.33; 83.31]	46.15 [19.16; 69.64]	66.67 [5.41; 94.52]	56.67 [37.33; 72.08]
	At 5 years % [95%CI]	64.29 [34.33; 83.31]	46.15 [19.16; 69.64]	0	56.67 [37.33; 72.08]

OS: Overall survival; TMZ: Temozolomide, TEMIRI: TMZ + irinotecan; TOTEM: TMZ + topotecan.

Duration of response

The median duration of response was 15.6 months (95% CI: 8.6 – NE) in the 14 patients with response (EVA population). It was 10.0 months (95% CI: 2.0 - 17.7) in relapsed and not evaluable in the refractory neuroblastoma.

- **Ancillary analyses**

Table 27. Overall summary of efficacy in relapsed vs. refractory patients (from BEACON CHEMO study)

		Refractory				Relapsed			
		Overall	**TMZ**	**TEMIRI**	**TOTEM**	**Overall**	**TMZ**	**TEMIRI**	**TOTEM**
Patients (n)		30	14	13	3	41	17	14	10
Best ORR		20.0%	21.4%	15.4%	33.3%	19.5%	11.8%	21.4%	30.0%
Best DCR		70.0%	78.6%	61.5%	66.7%	63.4%	52.9%	78.6%	60.0%
ORR, after 2 cycles		10.0%	0.0%	15.4%	33.3%	9.8%	5.9%	21.4%	0.0%
DCR, after 2 cycles		70.0%	78.6%	61.5%	66.7%	63.4%	52.9%	78.6%	60.0%
OS	**Median OS (months)**	72.8	72.8	13.0	NE	14.8	15.5	17.5	12.9
	1Y OS	67%	71%	62%	67%	61%	53%	71%	60%
	2Y OS	57%	64%	46%	67%	29%	18%	43%	30%
	3Y OS	57%	64%	46%	67%	24%	18%	29%	30%

PFS	**Median PFS (months)**	23.1	43.3	6.1	NE	5.3	3.5	10.0	5.1
	1Y PFS	57%	64%	46%	67%	34%	24%	43%	40%
	2Y PFS	50%	64%	31%	67%	15%	6%	21%	20%
	3Y PFS	47%	57%	31%	67%	12%	6%	14%	20%

Table 28. Overall summary of survival data according to the best response – Relapsed vs. refractory patients

		Refractory				**Relapsed**			
		CR	**PR**	**SD**	**PD**	**CR**	**PR**	**SD**	**PD**
Patients (n)		0	6	15	9	1	7	18	15
OS	**Median OS (months)**	-	72.8	NE	3.7	NE	19.8	17.3	9.9
	1Y OS	-	100%	93%	0	100%	100%	72%	27%
	2Y OS	-	83%	80%	0	100%	43%	44%	0
	3Y OS	-	83%	80%	0	100%	29%	39%	0
	4Y OS	-	83%	80%	0	100%	0	28%	0
	5Y OS	-	83%	80%	0	100%	0	19%	0
PFS	**Median PFS (months)**	-	NE	NE	1.3	23.2	12.6	7.7	1.6
	1Y PFS	-	100%	73%	0	100%	71%	39%	7%
	2Y PFS	-	83%	67%	0	0	14%	28%	0
	3Y PFS	-	67%	67%	0	0	14%	22%	0
	4Y PFS	-	67%	59%	0	0	0	11%	0
	5Y PFS	-	67%	59%	0	0	0	0	0

- **Updated analyses (from BEACON-CHEMO CSR V2.0)**

Table 29. Patient populations in BEACON-CHEMO CSR V2.0

	TMZ (N=39)	**TEMIRI (N=30)**	**TOTEM (N=33)**	**Total (N=102)**
ITT population, n (%)	39 (100)	30 (100)	33 (100)	102 (100)
Safety population, n (%)	37 (94.9)	28 (93.3)	32 (97.0)	97 (95.1)
Evaluable population, n (%)	34 (87.2)	27 (90.0)	32 (97.0)	93 (91.2)

TMZ: Temozolomide; TEMIRI: Irinotecan +Temozolomide; TOTEM: Temozolomide +Topotecan

Table 30. Demographic and baseline characteristics (ITT population)

		T N=39	**IT N=30**	**TTo N=33**	**Total N=102**
Age (years)	Mean (SD)	5.3 (3.2)	5.1 (3.0)	5.6 (4.3)	5.3 (3.5)
	Median	5.0	4.5	5.0	5.0
	Min-max	1.0-18.0	1.0-13.0	1.0-17.0	1.0-18.0
Age <3 years	Yes, n (%)	6 (15.4)	6 (20.0)	7 (21.2)	19 (18.6)
	No, n (%)	33 (84.6)	24 (80.0)	26 (78.8)	83 (81.4)
Age <4 years	Yes, n (%)	10 (25.6)	12 (40.0)	11 (33.3)	33 (32.4)
	No, n (%)	29 (74.4)	18 (60.0)	22 (66.7)	69 (67.6)
Height	Mean (SD)	109.1 (17.6)	108.4 (20.3)	112.7 (24.5)	110.1 (20.7)
	Median	109.0	104.0	110.0	109.0
	Min-max	75.0-162.0	78.0-162.0	76.0-172.0	75.0-172.0
Weight	Mean (SD)	19.5 (9.0)	19.4 (8.1)	22.2 (14.0)	20.3 (10.6)

		T N=39	IT N=30	TTo N=33	Total N=102
	Median	18.0	17.0	18.0	18.0
	Min-max	10.0-55.0	11.0-44.0	10.0-71.0	10.0-71.0
BMI	Mean (SD)	15.8 (1.9)	15.9 (1.7)	16.1 (2.5)	15.9 (2.0)
	Median	15.6	15.5	15.7	15.6
	Min-max	13.0-21.0	13.0-20.1	12.2-24.0	12.2-24.0
Sex, n (%)	Male	22 (56.4)	14 (46.7)	17 (51.5)	53 (52.0)
	Female	17 (43.6)	16 (53.3)	16 (48.5)	49 (48.0)
Relapse or refractory disease, n (%)	Refractory disease	16 (41.0)	11 (36.7)	7 (21.2)	34 (33.3)
	Relapsed disease	23 (59.0)	19 (63.3)	26 (78.8)	68 (66.7)
Measurable or evaluable disease, n (%)	Measurable disease n (%)	26 (66.7)	22 (73.3)	26 (78.8)	74 (72.5)
	Evaluable disease n (%)	13 (33.3)	8 (26.7)	7 (21.2)	28 (27.5)

SD: standard deviation; T: Temozolomide; IT: Irinotecan + Temozolomide; TTo: Temozolomide + Topotecan; BMI: Body Mass Index.

Table 31. Best ORR and DoR (EVA population)

Best ORR		T	IT	TTo	Total
Overall population	n	34	27	32	93
	ORR, n (%)	5 (14.7)	5 (18.5)	8 (25.0)	18 (19.4)
	95% CI	[6.4; 30.1]	[8.2; 36.7]	[13.3; 42.1]	[12.6;28.5]
	mDoR, months				15.6
	95% CI				[8.6–37.3]

Best ORR		T	IT	TTo	Total
Patients with relapsed disease	n	19	17	25	61
	ORR, n (%)	2 (10.5)	3 (17.6)	6 (24.0)	11 (18.0)
	95% CI	[2.9; 31.4]	[6.2; 41.0]	[11.5; 43.4]	[10.4; 29.5]
	mDoR, months				9.3
	95% CI				[2.0-17.7]
Patients with refractory disease	n	15	10	7	32
	ORR, n (%)	3 (20.0)	2 (20.0)	2 (28.6)	7 (21.9)
	95% CI	[7.0; 45.2]	[5.7; 51.0]	[8.2; 64.1]	[11.0; 38.8]
	mDoR, months				not evaluable
	95% CI				[11.7-not evaluable]

CI, confidence interval; ORR, overall response rate; T: Temozolomide; IT: Irinotecan + Temozolomide; TTo: Temozolomide + Topotecan.

Table 32. Best ORR and DoR in relapsed patients (ITT population)

Endpoint	Overall (N=68)	T arm (N=23)	IT arm (N=19)	TTo arm (N=26)
ORR (95% CI)	16.2% (9.3%-26.7%)	8.7% (2.4%;26.8%)	15.8% (5.5%;37.6%)	23.1% (11.0%;42.1%)
DoR Median (months) (95% CI)	9.3 (2.0-17.7)	7.8 (2.0 ;NE*)	8.6 (6.4 ;NE*)	13.5 (1.8 ;NE*)

**NE: Not Evaluable*

Table 33. Best ORR and DoR in refractory patients (ITT population)

Endpoint	Overall (N=34)	T arm (N=16)	IT arm (N=11)	TTo arm (N=7)
ORR (95% CI)	20.6% (10.3%-36.8%)	18.8% (6.6%;43.0%)	18.2% (5.1%;47.7%)	28.6% (8.2%;64.1%)
DoR Median (months) (95% CI)	NE* (11.7-NE*)	NE* (29.2 ;NE)	NE* (11.7 ;NE)	NE* (37.3 ;NE)

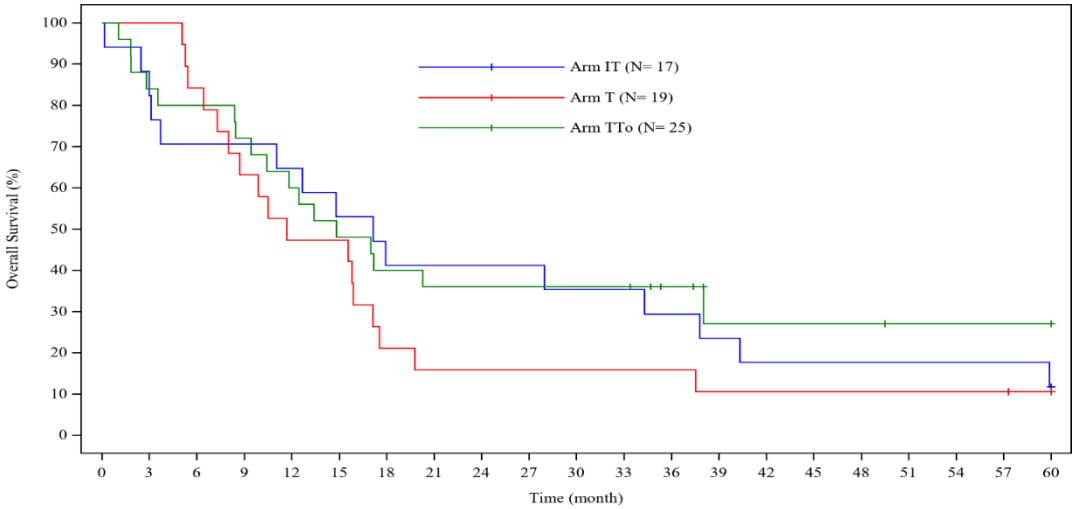
**NE: Not Evaluable*

Table 34. Best DCR (EVA population)

Best DCR		T	IT	TTo	Total
Overall population	n	34	27	32	93
	DCR, n (%)	23 (67.6)	19 (70.4)	21 (65.6)	63 (67.7)
	95% CI	[50.8; 80.9]	[51.5; 84.1]	[48.3; 79.6]	[57.7; 76.4]
Patients with relapsed disease	n	19	17	25	61
	DCR, n (%)	10 (52.6)	12 (70.6)	16 (64.0)	38 (62.3)
	95% CI	[31.7; 72.7]	[46.9; 86.7]	[44.5; 79.8]	[49.7; 73.4]
Patients with refractory disease	n	15	10	7	32
	DCR, n (%)	13 (86.7)	7 (70.0)	5 (71.4)	25 (78.1)
	95% CI	[62.1; 96.3]	[39.7; 89.2]	[35.9; 91.8]	[61.2; 89.0]

CI, confidence interval; DCR, disease control rate; T: Temozolomide; IT: Irinotecan + Temozolomide; TTo: Temozolomide + Topotecan.

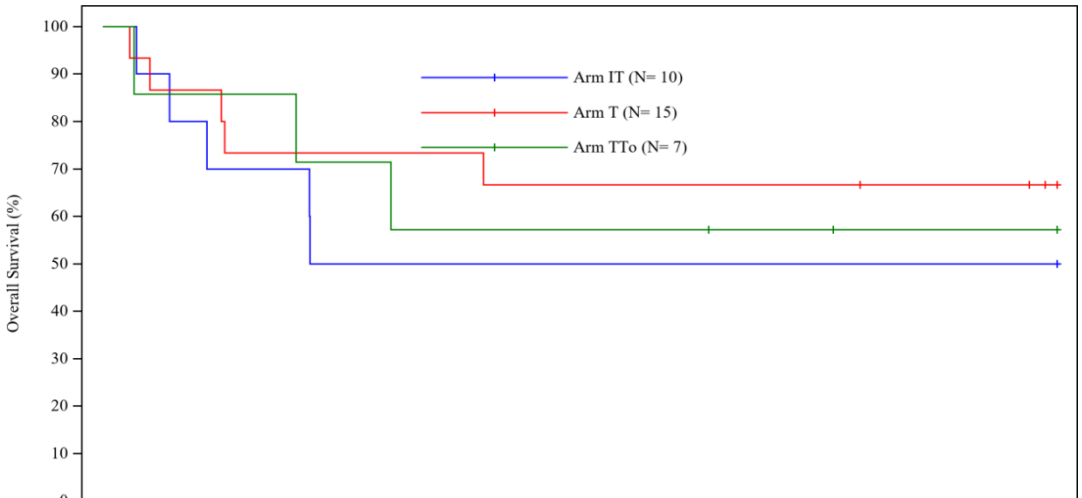
Figure 11. OS according to treatment in patients with relapsed neuroblastoma (EVA population)



Number of subjects at risk
(Number of censored subjects)

Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Arm IT	17	14	12	12	11	9	7	7	7	7	6	6	5	4	3	3	3	3	3	3	1
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
Arm T	19	19	16	12	9	9	4	3	3	3	3	3	3	2	2	2	2	2	2	2	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)
Arm TTo	25	21	20	18	15	12	10	9	9	9	9	9	6	3	3	3	3	2	2	2	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)	(5)	(5)	(5)	(5)	(6)	(6)	(6)	(8)

Figure 12. OS according to treatment in patients with refractory neuroblastoma (EVA population)



Number of subjects at risk
(Number of censored subjects)

Months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Arm IT	10	9	8	7	7	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(5)
Arm T	15	13	13	11	11	11	11	11	10	10	10	10	10	10	10	10	9	9	9	9	1
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(1)	(9)
Arm TTo	7	6	6	6	6	5	5	4	4	4	4	4	4	3	3	3	2	2	2	2	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(1)	(1)	(2)	(2)	(2)	(2)	(4)

Efficacy endpoints in patients <3 years versus patients ≥3 years

Table 35. Best response, best ORR and best DCR according to age (EVA population)

	Age (years)		
	<3 (N=17)	>=3 (N=76)	Total (N=93)
Overall Best Response			
n	17	76	93
(CR) Complete Response	0 (0.0%)	2 (2.6%)	2 (2.2%)
(PR) Partial Response	2 (11.8%)	14 (18.4%)	16 (17.2%)
(SD) Stable Disease	7 (41.2%)	38 (50.0%)	45 (48.4%)
(PD) Progressive Disease	8 (47.1%)	22 (28.9%)	30 (32.3%)
ORR			
n	17	76	93
ORR	2 (11.8%)	16 (21.1%)	18 (19.4%)
95% CI	[3.3%;34.3%]	[13.4%;31.5%]	[12.6%;28.5%]
DCR			
n	17	76	93
DCR	9 (52.9%)	54 (71.1%)	63 (67.7%)
95% CI	[31.0%;73.8%]	[60.0%;80.0%]	[57.7%;76.4%]

ORR: overall response rate; DCR: disease control rate; CI: confidence interval.

- **Results only for the combination therapy (TEMIRI and TOTEM)**

Given the different prognosis of relapsed and refractory neuroblastoma and given the more limited activity of TMZ monotherapy in these 2 populations, the efficacy results are further summarised for patients with relapsed versus refractory neuroblastoma treated with temozolomide combined with a topoisomerase inhibitor (TEMIRI or TOTEM) in BEACON-CHEMO study.

For both relapsed and refractory neuroblastoma populations, the best ORR was 22.0% and disease control was achieved in 67.8% of the patients.

Table 36. Best ORR of the IT and TTo arms in the ITT population of BEACON-CHEMO

ORR [95% CI]	IT (N=30)	TTo (N=33)	IT+TTo (N=63)
ITT	16.7% [7.3%;33.6%]	24.2% [12.8%;41.0%]	20.6% [12.5%;32.2%]
ITT, relapsed (N=45)	15.8% [5.5%;37.6%]	23.1% [11.0%;42.1%]	20.0% [10.9%;33.8%]
ITT, refractory (N=18)	18.2% [5.1%;47.7%]	28.6% [8.2%;64.1%]	22.2% [9.0%;45.2%]

Access to consolidation for refractory patients treated with TEMIRI or TOTEM (from BEACON CHEMO - FINAL ANALYSIS TFL v3.0)

In BEACON-CHEMO, 66.7% [43.7%; 83.7%] of refractory patients in the ITT population, treated with TMZ combined with a topoisomerase inhibitor achieved response or disease stabilisation and became eligible to access to consolidation. 10/18 (56%) of the patients proceeded to consolidation therapy.

Table 37. Consolidation - ITT population refractory (N=18)

	Group Treatment		
	Arm IT: Temozolomide + Irinotecan (N=11)	Arm TTo: Temozolomide + Topotecan (N=7)	Total (N=18)
Consolidation			
n	11	7	18
No	3 (27.3%)	5 (71.4%)	8 (44.4%)
Yes	8 (72.7%)	2 (28.6%)	10 (55.6%)
Missing data	0	0	0

Disease stabilisation and access to immunotherapy for relapsed patients treated with TEMIRI or TOTEM (from BEACON CHEMO - FINAL ANALYSIS TFL v3.0)

In BEACON-CHEMO, 62.2% [51.6%; 79.0%] of relapsed patients in the ITT population, treated with TMZ combined with a topoisomerase inhibitor achieved response or disease stabilisation (i.e. DCR) and became eligible to receive further treatment with dinutuximab beta. 2/5 of patients who achieved CR or PR as best response and 9/11 of patients who achieved SD as best response received further treatment with anti-GD2 immunotherapy.

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 38. Summary of efficacy for trial BEACON-CHEMO

Title: BEACON-CHEMO, chemotherapy arms sub-analysis of the BEACON-Neuroblastoma Trial: A randomized phase IIb trial of BEvACizumab added to Temozolomide ± IrinOtecan for children with refractory/relapsed Neuroblastoma	
Study identifier	BEACON-Neuroblastoma trial Sponsor Protocol Number: RG_11-087 EudraCT number: 2012-000072-42 ISRCTN Reference Number: 40708286 ClinicalTrials.gov Identifier: NCT02308527
Design	The BEACON-Neuroblastoma study is a phase II, randomised, open label, international, multicentre, 3x2 factorial trial to evaluate whether bevacizumab was sufficiently active. There were 6 arms in the initial Bevacizumab randomisation: 1) Temozolomide alone (TMZ) 2) Temozolomide + Bevacizumab (BT) 3) Irinotecan + Temozolomide (TEMIRI) 4) Irinotecan + Temozolomide + Bevacizumab (BIT) 5) Temozolomide + Topotecan (TOTEM) 6) Temozolomide + Topotecan + Bevacizumab (BTTo) Efficacy was assessed by the Objective Response Rate (ORR); then it was continued with Progression Free Survival (PFS) as the primary endpoint. Responses were categorised as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), further to changes in tumour size according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria for measurable disease or according to a semi-quantitative score (International Neuroblastoma Response Criteria [INRC]) for evaluable only disease. The BEACON-CHEMO study is a sub-analysis of the temozolomide-based chemotherapy arms (TMZ, TEMIRI and TOTEM).

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		5 years -July 2013- May 2019 (Beacon bevacizumab randomisation including TMZ, TEMIRI and TOTEM arms) Not applicable Not applicable
Hypothesis	Exploratory: For the bevacizumab randomisation of the BEACON-Neuroblastoma study, assuming 40% PFS at 1 year in the control arm, with 160 patients and 80 events in total, there was a 80% power to detect a difference of 15% at p=0.15. The number of patients assessed in the descriptive sub-group analysis BEACON-CHEMO was not prespecified and resulted from the 80 patients accrued in the TMZ, TEMIRI and TOTEM arms at the time of the bevacizumab randomisation completion: 36 patients were actually randomised in the TMZ Arm, 30 patients in the TEMIRI Arm and 14 patients in the TOTEM Arm.		
Treatments groups BEACON-CHEMO subanalysis	TMZ arm		TMZ dosing cycle: oral dose of 200 mg/m^2 body surface area once a day for 5 consecutive days, every 4 weeks (dose modifications allowed following predefined rules). Up to 6 cycles for patients with a response (CR, PR) or SD, possibly extended up to 12 cycles in CR, PR or SD patients with acceptable toxicity. 36 patients randomised; 34 patients treated. Actual treatment duration in cycles: Mean (sd): 3.8 (2.6); Median: 3; Min; Max: 1; 12.
	TEMIRI arm		TEMIRI dosing cycle: oral TMZ dose of 100 mg/m^2 body surface area once a day (+ IV irinotecan at a dose of 50 mg/m^2) for 5 consecutive days, every 3 weeks (doses modifications allowed following predefined rules). Up to 6 cycles for patients with a response (CR, PR) or SD, possibly extended up to 12 cycles in CR, PR or SD patients with acceptable toxicity. 30 patients randomised; 28 patients treated. Actual treatment duration in cycles: Mean (sd): 4.4 (3.0); Median: 4; Min; Max: 1; 12.
	TOTEM arm		TOTEM dosing cycle: oral TMZ dose of 150 mg/m^2 body surface area once a day (+ IV topotecan at a dose of 0.75 mg/m^2) for 5 consecutive days, every 4 weeks (doses modifications allowed following predefined rules). up to 6 cycles for patients with a response (CR, PR) or SD, possibly extended up to 12 cycles in CR, PR or SD patient with acceptable toxicity. 14 patients randomised; 13 patients treated. Actual treatment duration in cycles: Mean (sd): 6.1 (4.2); Median: 6; Min; Max: 1; 12.
Endpoints and definitions *BEACON-CHEMO subanalysis*	Primary endpoint	Best ORR	Best Overall Response Rate (Best ORR) was defined as the highest category of response (CR or PR) achieved by a patient at any time during the first 6 cycles of trial treatment.
	Secondary endpoint	ORR at 2 cycles	ORR at 2 cycles was defined as the highest category of response (CR or PR) achieved by a patient within the considered time period of 2 cycles.
	Secondary endpoint	Best DCR	Best Disease Control Rate (Best DCR) was defined as the percentage of patients who have achieved CR, PR or SD at any time during the first 6 cycles of trial treatment.
	Secondary endpoint	PFS	Progression Free Survival (PFS) was defined as the time from randomisation until first event (progression, recurrence following response or death without progression or

			recurrence). For those patients who did not experience any first event during the course of the trial, PFS times were censored at the date of their last available trial assessment.
	Secondary endpoint	EFS	Event Free Survival (EFS) was defined as the time from randomisation until first event (progression, recurrence following response, second malignancy or death without progression or recurrence). For those patients who did not experience an event during the course of the trial, EFS times were censored at the date of their last available trial assessment.
	Secondary endpoint	OS	Overall survival (OS) was defined as the time from randomisation until death from any cause. Patients who did not die during the course of the trial were censored at the date of their last available trial assessment.
Database lock	29 March 2023 (BEACON-Neuroblastoma patient data extraction for BEACON-CHEMO sub analysis)		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Two analysis sets were defined: Intent to treat (ITT) population: defined as all patients randomised. Patients are retained in their randomised treatment groups which include patients who have not been exposed to treatment for any reason, were protocol deviations, or found ineligible. Evaluable (EVA) population: defined as all randomised patients having received at least one dose of treatment with one evaluation at baseline and at least one evaluation under treatment. The primary endpoint (Best ORR) is presented in both populations, the secondary endpoints are only presented in the EVA population. Time points: ORR and DCR at 2 cycles are reported after 2 treatment cycles (cycles of 28 days for TMZ and TOTEM arms and cycles of 21 days for TEMIRI arm). Best ORR and Best DCR are reported after up to 6 cycles of treatment (cycles of 28 days for TMZ and TOTEM arms and cycles of 21 days for TEMIRI arm). PFS, EFS and OS are reported as median and at 1 year, 2 years and 5 years.

Descriptive statistics and estimate variability	Treatment group **ITT**	Overall	TMZ arm	TEMIRI arm	TOTEM arm
	Number of subjects	80	36	30	14
	Best ORR (%)	17.5	13.9	16.7	28.6
	95% CI (%)	10.7 – 27.3	6.1 - 28.7	7.3 - 33.6	11.7 - 54.6
Descriptive statistics and estimate variability	Treatment group **EVA**	Overall	TMZ arm	TEMIRI arm	TOTEM arm
	Number of subjects	71	31	27	13
	Best ORR (%)	19.7	16.1	18.5	30.8
	95% CI (%)	12.1 – 30.4	7.1 - 32.6	8.2 - 36.7	12.7 - 57.6
	ORR at 2 cycles (%)	9.9	3.2	18.5	7.7
	95% CI (%)	4.9 – 19.0	0.6 - 16.2	8.2 - 36.7	1.4- 33.3
	Best DCR (%)	66.2	64.5	70.4	61.5
	95% CI (%)	54.6- 76.1	46.9 - 78.9	51.5 - 84.1	35.5 - 82.3
	PFS Median (months)	6.1	3.9	8.7	5.6
	95% CI (months)	3.2 – 12.6	2.3 - 17.2	1.6 - 12.6	1.8 - 38.0
	1-year PFS (%)	43.7	41.9	44.4	46.2
	95% CI (%)	32.0 - 54.8	24.7 – 58.3	25.6 – 61.8	19.2 – 69.6
	2-year PFS (%)	29.6	32.3	25.9	30.8
	95% CI (%)	19.5 – 40.4	16.9 – 48.6	11.5 – 43.1	9.5 – 55.4

	5-year PFS (%)	18.4	25.4	13.9	0
	95% CI (%)	10.0 – 28.9	11.8 – 41.6	4.0 – 29.9	-
	EFS Median (months)	6.1	3.9	8.7	5.6
	95% CI (months)	3.2 – 12.6	2.3 - 17.2	1.6 - 12.6	1.8 - 38.0
	1-year EFS (%)	43.7	41.9	44.4	46.2
	95% CI (%)	32.0 - 54.8	24.7 – 58.3	25.6 – 61.8	19.2 – 69.6
	2-year EFS (%)	28.2	32.3	22.2	30.8
	95% CI (%)	18.3 – 38.9	16.9 – 48.6	9.0 – 39.0	9.5 – 55.4
	5-year EFS (%)	18.4	25.4	13.9	0
	95% CI (%)	10.0 – 28.9	11.8 – 41.6	4.0 – 29.9	-
	OS Median (months)	15.9	17.1	17.1	13.4
	95% CI (months)	12.5 – 34.3	9.9 - 72.8	6.5 - 40.3	8.4 - NE*
	1-year OS (%)	63.4	61.3	66.7	61.5
	95% CI (%)	51.1 – 73.4	42.0 – 75.9	45.7 – 81.1	30.9 – 81.8
	2-year OS (%)	40.9	38.7	44.4	38.5
	95% CI (%)	29.4 – 51.9	22.0 – 55.2	25.6 – 61.8	14.1 – 62.8
	5-year OS (%)	30.2	35.5	25.4	30.8
	95% CI (%)	19.8 – 41.3	19.4 – 51.9	11.0 – 42.8	9.5 – 55.4
Notes	-				
Analysis description	**Sub-group analysis:** All efficacy analyses were repeated in the sub-groups of refractory patients versus relapsed patients (analyses not pre-specified)				
Analysis population and time point description	The primary endpoint (Best ORR) is presented in both ITT and EVA populations, the secondary endpoints are only presented in the evaluable (EVA) population. <u>Time points</u>: ORR and DCR at 2 cycles are reported after 2 treatment cycles (cycles of 28 days for TMZ and TOTEM arms and cycles of 21 days for TEMIRI arm). Best ORR and Best DCR are reported after up to 6 cycles of treatment (cycles of 28 days for TMZ and TOTEM arms and cycles of 21 days for TEMIRI arm). PFS, EFS and OS are reported as median and at 1 year, 2 years and 5 years.				
Descriptive statistics and estimate variability	Treatment group **ITT Refractory**	Overall	TMZ arm	TEMIRI arm	TOTEM arm
	Number of subjects	33	15	14	4
	Best ORR (%)	18.2	20.0	14.3	25.0
	95% CI (%)	8.6 – 34.4	7.0 - 45.2	4.0 - 39.9	4.6 - 69.9
	Treatment group **ITT Relapsed**	Overall	TMZ arm	TEMIRI arm	TOTEM arm
	Number of subjects	47	21	16	10
	Best ORR (%)	17.0	9.5	18.8	30.0
	95% CI (%)	8.9 – 30.1	2.7 - 28.9	6.6 - 43.0	10.8 - 60.3
Descriptive statistics and estimate variability	Treatment group **EVA Refractory**	Overall	TMZ arm	TEMIRI arm	TOTEM arm
	Number of subjects	30	14	13	3
	Best ORR (%)	20.0	21.4	15.4	33.3
	95% CI (%)	9.5 – 37.3	7.6 - 47.6	4.3 – 42.2	6.1 – 79.2
	ORR at 2 cycles (%)	10.0	0.0	15.4	33.3
	95% CI (%)	3.5 – 25.6	0.0 - 21.5	4.3 – 42.2	6.1 - 79.2
	Best DCR (%)	70.0	78.6	61.5	66.7
	95% CI (%)	52.1 – 83.3	52.4 – 92.4	35.5 – 82.3	20.8 - 93.3
	PFS Median (months)	23.1	43.3	6.1	NE*
	95% CI (months)	2.3 – NE*	2.3 – NE*	1.3 – NE*	2.1 – NE*
	1-year PFS (%)	56.7	64.3	46.2	66.7
	95% CI (%)	37.3 – 72.1	34.3 - 83.3	19.2 – 69.6	5.4 – 94.5
	2-year PFS (%)	50.0	64.3	30.8	66.7
	95% CI (%)	31.3 – 66.1	34.3 – 83.3	9.5 – 55.4	5.4 – 94.5
	5-year PFS (%)	43.1	49.0	30.8	0

	95% CI (%)	25.3 – 59.7	21.6 – 71.7	9.5 – 55.4	-
	EFS Median (months)	23.1	43.3	6.1	NE*
	95% CI (months)	2.3 – NE*	2.3 – NE*	1.3 – NE*	2.1 – NE*
	1-year EFS (%)	56.7	64.3	46.2	66.7
	95% CI (%)	37.3 – 72.1	34.3 - 83.3	19.2 – 69.6	5.4 – 94.5
	2-year EFS (%)	50.0	64.3	30.8	66.7
	95% CI (%)	31.3 – 66.1	34.3 – 83.3	9.5 – 55.4	5.4 – 94.5
	5-year EFS (%)	43.1	49.0	30.8	0
	95% CI (%)	25.3 – 59.7	21.6 – 71.7	9.5 – 55.4	-
	OS Median (months)	72.8	72.8	13.0	NE*
	95% CI (months)	7.5 – NE*	5.1 – NE*	3.7 – NE*	3.5 - NE*
	1-year OS (%)	66.7	71.4	61.5	66.7
	95% CI (%)	47.0 – 80.5	40.6 – 88.2	30.9 - 81.8	5.4 – 94.5
	2-year OS (%)	56.7	64.3	46.2	66.7
	95% CI (%)	37.3 – 72.1	34.3 - 83.3	19.2 – 69.6	5.4 – 94.5
	5-year OS (%)	56.7	64.3	46.2	0
	95% CI (%)	37.3 – 72.1	34.3 – 83.3	19.2 - 69.6	-
Descriptive statistics and estimate variability	Treatment group **EVA Relapsed**	Overall	TMZ arm	TEMIRI arm	TOTEM arm
	Number of subjects	41	17	14	10
	Best ORR (%)	19.5	11.8	21.4	30.0
	95% CI (%)	10.2 – 34.0	3.3 – 34.3	7.6 – 47.6	10.8 – 60.3
	ORR at 2 cycles (%)	9.8	5.9	21.4	0.0
	95% CI (%)	3.9 – 22.5	1.0 - 27.0	7.6 – 47.6	0.0- 27.8
	Best DCR (%)	63.4	52.9	78.6	60.0
	95% CI (%)	48.1 – 76.4	31.0 – 73.8	52.4 – 92.4	31.3 - 83.2
	PFS Median (months)	5.3	3.5	10.0	5.1
	95% CI (months)	2.0 – 11.3	1.8 – 5.9	1.2 – 12.6	0.5 – 23.2
	1-year PFS (%)	34.2	23.5	42.9	40.0
	95% CI (%)	20.3 – 48.5	7.3 – 44.9	17.7 – 66.0	12.3 – 67.0
	2-year PFS (%)	14.6	5.9	21.4	20.0
	95% CI (%)	5.9 – 27.0	0.4 – 23.5	5.2 – 44.8	3.1 – 47.5
	5-year PFS (%)	0	0	0	0
	95% CI (%)	-	-	-	-
	EFS Median (months)	5.3	3.5	10.0	5.1
	95% CI (months)	2.0 – 11.3	1.8 – 5.9	1.2 – 12.6	0.5 – 23.2
	1-year EFS (%)	34.2	23.5	42.9	40.0
	95% CI (%)	20.3 – 48.5	7.3 – 44.9	17.7 – 66.0	12.3 – 67.0
	2-year EFS (%)	12.2	5.9	14.3	20.0
	95% CI (%)	4.5 – 24.1	0.4 – 23.5	2.3 – 36.6	3.1 – 47.5
	5-year EFS (%)	0	0	0	0
	95% CI (%)	-	-	-	-
	OS Median (months)	14.8	15.5	17.5	12.9
	95% CI (months)	11.0 – 17.5	8.0 – 17.5	3.1 – 37.8	1.1 – 38.0
	1-year OS (%)	61.0	52.9	71.4	60.0
	95% CI (%)	44.4 – 74.0	27.6 – 73.0	40.6 – 88.2	25.3 – 82.7
	2-year OS (%)	29.3	17.6	42.9	30.0
	95% CI (%)	16.4 – 43.2	4.4 – 38.3	17.7 – 66.0	7.1 – 57.8
	5-year OS (%)	11.0	11.8	7.1	20.0
	95% CI (%)	3.5 – 23.5	2.0 – 31.2	0.5 – 27.5	3.1 – 47.5
Notes	-				

*NE: Non Evaluable

ORP-TMZ-4 (RetroTMZ) study

Multicentre retrospective study of Temozolomide use in paediatric refractory / relapsed neuroblastoma

- **Methods**

Observational retrospective study. The study was conducted in 6 centres in France (3), Spain (2) and Switzerland (1).

- **Study Participants**

Inclusion/exclusion criteria

Inclusion criteria:

1. Confirmed diagnosis of neuroblastoma
    a. Either histologically
    b. Or tumour cells on bone marrow analysis, and either raised catecholamines or positive MIBG
2. Diagnosed with neuroblastoma between 1st January 2004 and 31st December 2017
3. Aged less than 18 years at diagnosis with neuroblastoma
4. Diagnosed with relapsed or refractory neuroblastoma
    a. Either high-risk at diagnosis with refractory or relapsed disease
    b. Or, not high-risk at diagnosis, but subsequently developed metastatic disease
5. Treated with TMZ-based chemotherapy before the 1st of May 2018

Non-inclusion criteria:

1. Children whose care is not managed at, or led by, the participating centre. For example:
    a. Attended centre for a single consultation for a second opinion only – no treatment directed by or given at participating centre
    b. Medical files reviewed at participating centre, e.g. for expert review of pathology or imaging only – child not seen clinically
2. TMZ given as holding chemotherapy

- **Treatments**

Children included on the study had received TMZ treatment as a single therapy or in combination with other chemotherapy drugs without change in the medical practice. All treatment episodes (where episode refers to a line of treatment with TMZ regardless of other treatments that may have preceded TMZ), were included. Data collected related to TMZ treatment included: treatment history with TMZ, prescription details, dosing details, response after 2 cycles and best response and TMZ withdrawal details.

The most frequent treatment regimen was TOTEM (81 patients), then TMZ monotherapy (59) and TEMIRI (39) accounting for 91.3% of treatments. In line with the dosing recommendations for each

regimen (TMZ: 150-200mg/m^2/d; TEMIRI: 100mg/m^2/d, TOTEM 150mg/m^2/d), 91.4% of patients receiving TOTEM had a dosing of temozolomide of 100-150mg/m^2; 81.4% of patients receiving TMZ monotherapy had a dosing of temozolomide of 100-150mg/m^2 or >150mg/m2 and 82.1% of patients treated with TEMIRI received a TMZ dose of 75-100mg/m^2. The starting doses of TMZ used in RetroTMZ are generally in line with the proposed posology of Kizfizo.

In Retro-TMZ, the patients received up to 69 cycles of therapy, with a maximum of 12 cycles for TMZ monotherapy (6 cycles for refractory, 12 cycles for relapsed patients), 37 cycles for TOTEM (29 cycles for refractory, 37 cycles for relapsed patients) and 69 for TEMIRI (8 cycles for refractory, 69 cycles for relapsed patients).

Overall 17 relapsed and 1 refractory patient, switched to TMZ monotherapy after initial combination therapy.

- **Objectives**

The primary objective was to describe the population treated with TMZ and evaluate the time taken from start of first TMZ to first progression (time-to-progression [TTP]).

The secondary objectives were to estimate the response rates at 2 cycles and the best response, the OS and the PFS at 1-, 2- and 5- years, to describe the tolerability profile of TMZ in neuroblastoma patients, the performance status for those children on TMZ for at least 6 months, and to evaluate the incidence of secondary malignancies including myelodysplastic syndrome.

- **Outcomes/endpoints**

TTP has been defined as the time from start date of first TMZ to first progression (as defined by formal disease evaluation or contemporaneous clinical assessment or death). For patients who died due to disease for whom a progression was recorded, but no date of progression noted, the date of death has been considered as the progression date.

PSF has been defined from the date of initiation of TMZ to progression/death or date of last follow-up.

OS is defined as the time from initiation of first TMZ episode to death (whatever the cause) or to the date of last news for alive patients.

Time to event data (TTP, PFS and OS) have been summarised using the Kaplan-Meier method and displayed graphically.

The evaluation of tumour response included both formal and clinical response after 2 cycles and best response. Formal response was an evaluation of disease status, that is, radiological (CT, MRI and/or ultrasound), nuclear medicine (MIBG scan or positron emission tomography) and pathology (bone marrow) examinations. Clinical response was a response assessment made by the treating clinician only. The response rates were calculated according to the formal evaluation for the first episode.

Primary endpoint

To describe the population treated with TMZ.

- Disease history (primary site, metastases, stage at diagnosis, histology)
- Treatment history prior to TMZ treatment
- Disease status necessitating TMZ treatment (indication – relapse or refractory, relapses number and site)

- Main TMZ treatment characteristics (number of distinct episodes of treatment with TMZ, chemotherapy protocol, dosage, total number of cycles, total duration of treatment)
- Number of patients exposed to TMZ for more than 12 months
- Evaluate the time from start date of first TMZ to first progression (time-to-progression, TTP)

Secondary endpoints:

- Response rates: best response and response at 2 cycles (according to formal evaluation), proportion of TMZ withdrawal for lack of efficacy (progression or death).
- Survival analyses (PFS, OS)

- **Statistical methods**

Descriptive analyses for patient characteristics, treatment indications, and treatment outcomes were conducted for the overall patient population, defined as all patients meeting the eligibility criteria and for some pre-specified subgroups. Patients were considered evaluable for efficacy if evidence of outcome evaluation was found in the notes, either formal (imaging, pathology), or clinical. The analysis was performed for the overall population and by subgroups (refractory or relapsed disease at time of first treatment with TMZ-based chemotherapy).

Follow-up data initially collected until the 31 October 2018, with a first update recording follow-up data until the 31 October 2019. A final follow-up was conducted until the 02 February 2021. Median follow-up was defined from the date of initiation of TMZ by using the reverse Kaplan-Meier method.

A *post-hoc* efficacy analysis (for formal and clinical response, DCR, duration of response (DoR), OS, and PFS) was performed per treatment regimen (*i.e.*, TMZ monotherapy, TOTEM and TEMIRI) and indication (relapsed or refractory). Notably, this analysis was carried out at the request of the French regulatory authorities in the context of the assessment of the Early Access Program for Ped-TMZ.

Results

- **Participant flow**

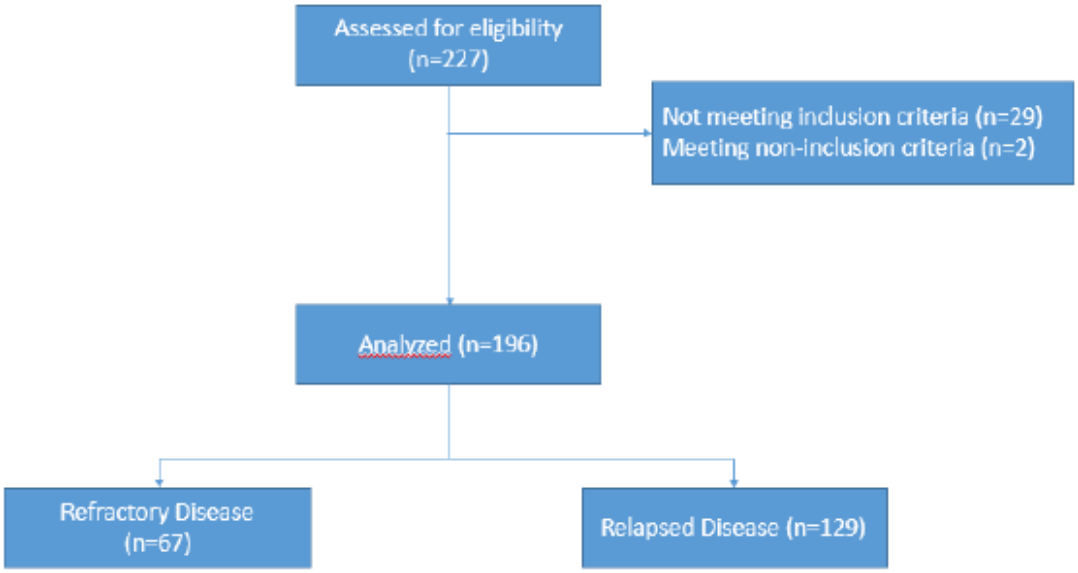


Figure 13. Flow chart

Table 39. Median follow-up (years) all patients and by TMZ indication

	Follow-up median	Minimum	Maximum
Refractory	5.2	0.3	12.8
Relapse	6.5	0.3	11.1
Overall	5.2	0.3	12.8

Fifteen patients (2 refractory and 13 treated for relapsed disease) electively stopped TMZ (*i.e.* not for progression), after at least 12 cycles. Of these, 7 remained in progression-free remission at a median 5.5 year follow-up, and 2.2 years after TMZ withdrawal.

- **Recruitment**

Data collection carried out from 01/01/04 to 02/02/21, for patients diagnosed from 01/01/04 to 31/12/17.

- **Baseline data**

Patient demographics

One hundred and ninety-six patients (196) were included; 67 children were treated for refractory neuroblastoma, and 129 for relapsed disease.

The mean age at diagnosis was 4.3 (StD 3.3) years and the median age was 4 years, with children aged between 1 and 5 years making up the majority of patients (34.2% and 34.7% aged >1.0-3.0 and >3.0-5.0 years old, respectively). There were more males than females (54.1% vs. 45.9%).

Disease characteristics at diagnosis of neuroblastoma

With regards to stage at diagnosis the metastatic non-MYCN amplified tended to be the most common diagnosis (62.7%), followed by metastatic MYCN amplified (24.9%). Loco-regional relapse was reported in 7.1%, most of the patients had a metastatic relapse (58.7%), and majority of relapsed patients were being treated following their first relapse (86.8%).

The mean time from diagnosis to description as relapsed/refractory disease was 1.3 (StD=1.1) years, specifically, 0.6 (StD=0.5) years for refractory patients and 1.7 (StD=1.1) years for relapsed patients.

All patients were treated for a first TMZ episode, 33 patients had a second episode and 2 patients had a third episode. Of these 33 patients, 16 were initially treated for refractory (1/33 still for a refractory disease and 15/33 for a subsequent relapsed disease) and 17 initially for relapsed disease. One of each, (1/16 and 1/17) subsequently received a third episode of TMZ for a subsequent relapse. Note that the patient who had two TMZ episodes for refractory disease, stopped single-agent TMZ for stable disease, before restarting TEMIRI.

The mean age at initiation of treatment with TMZ for the 67 refractory patients was 5.2 years (StD=3.8). The mean age at TMZ treatment initiation for the 129 relapsed patients was 6.4 years (StD=3.6). Among the 196 patients, 100 were ≤5.0 years at initiation of TMZ, including 38 aged ≤3.0 years.

Half of refractory patients with low/intermediate risk disease had not had prior treatment, whereas 89% of relapsed patients had previously received etoposide/carboplatin combination (VP16/Carbo). In the high-risk disease cohort, 74.6% of refractory patients had previously received topotecan-vincristine-doxorubicin (TVD) combination, and 81.7% patients had received cycled administration of cisplatin, vincristine, etoposide, cyclophosphamide and carboplatin (Induction COJEC).

Surgery and radiotherapy, both in management of initial and later relapsed disease, had been given to study subjects. Of the refractory patients, 19.4% (13/67) and 1.5% (1/66) patients had had surgery or radiotherapy prior to temozolomide, respectively. Refractory patients also had surgery or radiotherapy during and after temozolomide treatment. Of the relapsed patients, 78.3% (101/129) and 58.1%(75/129) patients had had surgery or radiotherapy prior to temozolomide, respectively. None of the relapsed patients were reported to have had surgery during temozolomide treatment or radiotherapy after temozolomide.

- **Outcomes and estimation**

Primary endpoint criteria

The median (95% CI) TTP from the first dose of TMZ was 5.8 months (3.8–8.1) for the overall population (n=196 and 161 progressions).

The median (95% CI) TTP from the first dose of TMZ was 13.7 months (4.8-18.7) for refractory patients (n=67 and 48 progressions).

The median (95% CI) TTP from the first dose of TMZ was 4.7 months (3.4-6.6) for relapsed patients (n=129 and 113 progressions).

Secondary endpoint criteria

Response and disease control rates (ORR and DCR)

Forty-five patients had no formal evaluation; most of them stopped treatment for progression (30/45) or death (7/45). Seven patients had neither formal nor clinical evaluations performed at any timepoint after the first episode of TMZ treatment.

Table 40. Tumour response following TMZ treatment, first and subsequent episodes*

Variable		First TMZ episode - Refractory		First TMZ episode - Relapse		Subsequent TMZ episodes - Refractory⊥		Subsequent TMZ episodes - Relapse⊥	
		N	%	N	%	N	%	N	%
Formal response after 2 cycles	n (m.d.)	52 (15)		72 (57)		0 (1)		20 (14)	
	Complete response	1	1.9%	3	4.2%			1	5.0%
	Partial response	19	36.5%	21	29.2%			7	35.0%
	minor response / stable disease	24	46.2%	29	40.3%			4	20.0%
	Progressive disease / mixed	8	15.4%	18	25.0%			8	40.0%
	Maintained CR			1	1.4%				
	Maintained PR								
Best formal response	n (m.d.)	56 (11)		95 (34)		1		23 (11)	
	Complete response	3	5.4%	13	13.7%			3	13.0%
	Partial response	25	44.6%	29	30.5%			6	26.1%
	minor response / stable disease	19	33.9%	27	28.4%	1	100.0 %	3	13.0%
	Progressive disease / mixed	9	16.1%	23	24.2%			10	43.5%
	Maintained CR			2	2.1%			1	4.3%
	Maintained PR			1	1.1%				
Best clinical response	n (m.d.)	67		128 (1)		1		34	
	Unknown/Not commented on	8	11.9%	7	5.5%			1	2.9%
	Clinically improved	11	16.4%	47	36.7%			9	26.5%
	No clinical progression	38	56.7%	40	31.3%	1	100.0 %	14	41.2%
	Clinical progression	8	11.9%	29	22.7%			7	20.6%
	N/A - i.e. already progressed/stopped after 2 cycles before assessment /or 2 cycles was best or stopped after 2	2	3.0%	5	3.9%			3	8.8%

*: Formal response corresponds to radiological and histological disease staging. Note: Maintained CR/PR includes patients with response prior to initiation of TMZ-based chemotherapy (e.g. following radiotherapy), that continues during treatment. ⊥: 33 patients have a second episode. Among these patients, 2 have third episode. The number of responses is based on considering the 35 episodes.

m.d.; missing data

The best response was available for 151 relapsed + refractory patients: 16 CR, 2 maintained CR, 54 PR, 1 maintained PR, i.e. Best ORR of 48.3%. 46 patients had minor response or SD, i.e. the best DCR was 78.8%.

The response after 2 cycles of therapy was available 124 relapsed + refractory patients: 4 CR, 1 maintained CR and 40 PR, i.e. ORR after 2 cycles of 36.3%. 53 patients had minor response or SD, i.e. the DCR after 2 cycles of therapy was 79.0%.

Overall survival (OS)

The median (95% CI) OS for the total population (refractory and relapsed patients) was 15.0 (12.2; 21.4) months.

Figure 14. Overall survival for refractory and relapsed patients

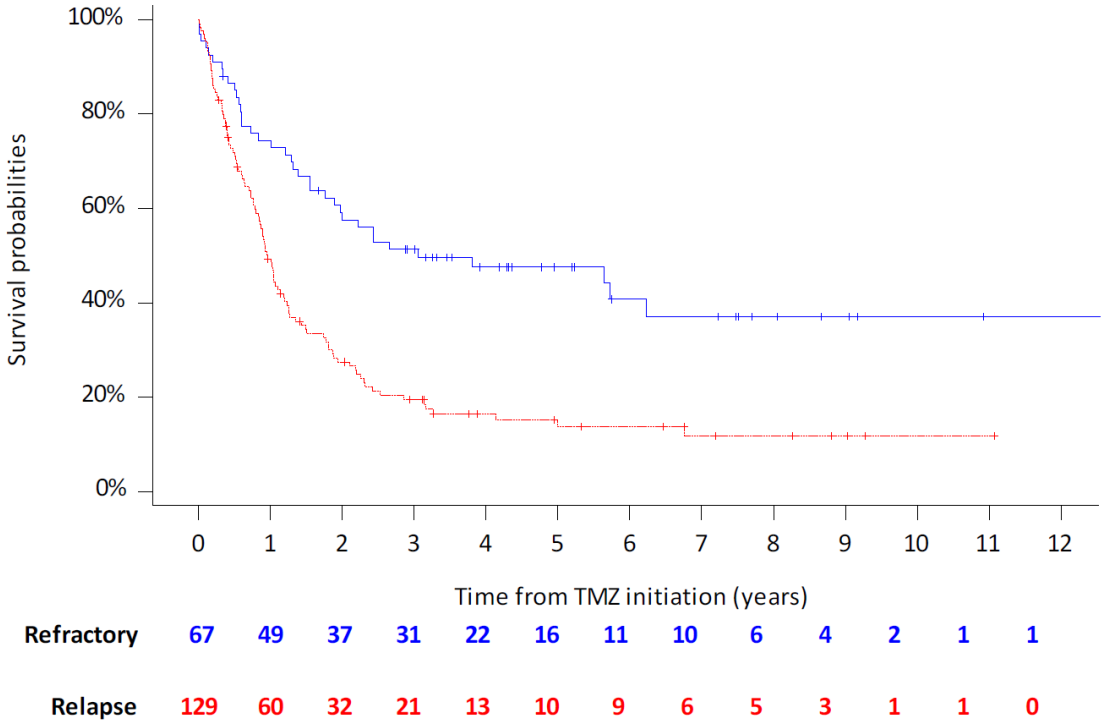


Table 41. Summary of efficacy for trial RetroTMZ (ORP-TMZ-4)

Title: RetroTMZ: Multicentre retrospective study of temozolomide use in paediatric refractory / relapsed neuroblastoma	
Study identifier	RetroTMZ Sponsor Gustave Roussy registration Number: MR004 N° 2207313 (18.09.18) ORPHELIA Pharma identifier: ORP-TMZ-4

Design	The RetroTMZ is an observational multicenter retrospective study. Clinical data were captured from established medical records without any change of clinical practice. Data collection was performed for all patients diagnosed with refractory or relapsed neuroblastoma from the 1st of January 2004 until the 31st of December 2017 and started on treatment with temozolomide (TMZ)-based chemotherapy (single-agent or combination therapy) before the 1st of May 2018. Full follow-up data was collected in 2020, with vital status only updated in February 2021. This study included 6 centres from 3 countries (France, Spain, Switzerland). A patient list was generated by each centre for the data collection in accordance with the condition that all children with high risk (either at diagnosis or subsequent metastatic disease) refractory or relapsed neuroblastoma should be identified, in order to retain for analysis those that received TMZ before the 1st of May 2018 and meeting eligibility criteria. Two-hundred and twenty-seven patients were assessed for eligibility. Thirty-one patients were excluded from the analysis because they did not meet inclusion criteria (n=29) or met non-inclusion criteria (n=2). One hundred ninety-six (196) patients treated with TMZ-based chemotherapy were analysed in the study, 67 patients with refractory disease and 129 patients with relapsed disease. Response to treatment was evaluated: Complete Response (CR), Partial Response (PR), Minor Response (MR) / Stable Disease (SD) or Progressive Disease (PD) Given that the refractory and relapsed populations have distinct characteristics, it was planned to present clinical outcomes for these two populations separately. A small number of initially refractory patients were later exposed for a second or further occasion for relapsed disease by TMZ-based treatment. Some relapsed patients were also treated for a second or further occasion for subsequent relapses. All outcomes are based on the initial treatment received, and groups defined by disease situation at time of initial treatment with TMZ. Additional post-hoc analysis per treatment regimen (TMZ monotherapy or TMZ in combination with irinotecan (TEMIRI) or topotecan (TOTEM)) and per indication (relapsed or refractory), not planned in the initial Statistical Analysis Plan, was carried out further to a request from the French regulatory authorities (ANSM) in the context of the assessment of the Early Access Program for the oral suspension of TMZ.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Not applicable Not applicable Not applicable
Hypothesis	Observational study: The available sample size was driven by the number of patients at the selected sites during the period of interest. The total number corresponds to the total number of patients with refractory or relapsed neuroblastoma treated in each of the 6 centres during the study period.	

<table>
<tr><td></td><td colspan="3">Among the 196 patients assessed, 179 received any of the 3 main treatment regimens (TMZ, TOTEM or TEMIRI).
Note: the remaining 17 patients of the analysis set received at initial first treatment course any of these 3 backbone chemotherapies in combination with bevacizumab (10 patients), or other TMZ-based combinations (7 patients).
The breakdown of the main set of 179 patients per indication (refractory/relapsed) and per TMZ-based treatment regimen (TMZ, TOTEM, TEMIRI) are summarised below.
<table>
<tr><th>TMZ treatment regimen</th><th>First TMZ episode
Refractory patients</th><th>First TMZ episode
Relapsed patients</th></tr>
<tr><td>TMZ monotherapy</td><td>17</td><td>42</td></tr>
<tr><td>TOTEM</td><td>30</td><td>51</td></tr>
<tr><td>TEMIRI</td><td>13</td><td>26</td></tr>
</table></td></tr>
<tr><td rowspan="3">Treatments groups
(post-hoc analysis)</td><td colspan="2">TMZ monotherapy</td><td>TMZ dose and duration for first course as per reported physician’s prescription in patient’s file. 59 patients, starting dose of TMZ was in the range of 100-150 mg/m^2 for 23 patients (39%) and >150 mg/m^2 for 25 patients (42%); Treatment duration Median (Q1, Q3) (months): 2 (1; 3): Min; Max (months): 1; 12</td></tr>
<tr><td colspan="2">TOTEM</td><td>TOTEM doses and duration for first course as per reported physician’s prescription in patient’s file. 81 patients, starting dose of TMZ was in the range of 100-150 mg/m^2 for 74 patients (91%); Treatment duration Median (Q1, Q3) (months): 3 (1; 8): Min; Max (months): 1; 34</td></tr>
<tr><td colspan="2">TEMIRI</td><td>TEMIRI doses and duration for first course as per reported physician’s prescription in patient’s file. 39 patients, starting dose of TMZ was in the range of 75-100 mg/m^2 for 32 patients (82%); Treatment duration Median (Q1, Q3) (months): 3 (1; 6): Min; Max (months): 1; 60</td></tr>
<tr><td rowspan="3">Endpoints and definitions</td><td>Primary endpoint</td><td>TTP</td><td>Time To Progression (TTP): time from TMZ-based treatment start date to first progression (as defined by formal disease evaluation or contemporaneous clinical assessment). Formal evaluation corresponds to disease staging with radiological and/or nuclear medicine and/or histological evaluation.</td></tr>
<tr><td>Secondary endpoint</td><td>ORR at 2 cycles (formal evaluation)

DCR at 2 cycles (formal evaluation)</td><td>Responses at 2 cycles after formal evaluation defined as the highest category of response (CR, PR, MR/ SD or PD) achieved by a patient.
Overall Response Rate (ORR) at 2 cycles was derived as the percentage of patients who achieved CR or PR after 2 cycles of treatment.

Disease Control Rate (DCR) at 2 cycles was also derived as the percentage of patients who have achieved CR, PR or MR/SD after 2 cycles of treatment.</td></tr>
<tr><td>Secondary endpoint</td><td>Best ORR (formal evaluation)

Best DCR (formal evaluation)</td><td>Responses after formal evaluation defined as the highest category of response (CR, PR, MR/SD or PD) achieved at any time of the treatment course by a patient.
Best Overall Response Rate (Best ORR) was derived as the percentage of patients who achieved CR or PR at any time of the treatment course.

Best Disease Control Rate (Best DCR) was also derived as the percentage of patients who achieved</td></tr>
</table>

			CR, PR or MR/SD at any time of the treatment course
	Secondary endpoint	PFS	Progression Free Survival (PFS) was defined as the time from initiation of any TMZ-based treatment until progression or death without progression or date of last follow-up. *Note: if 2 separate treatment courses were administered to the same patient, 2 different PFS, i.e. PFS1 and PFS2 were calculated. Only "PFS1" data is considered in this summary table*.
	Secondary endpoint	OS	Overall survival (OS) was defined as the time from initiation of the first TMZ-based treatment until death from any cause, or date of last follow-up.
Database lock	31 May 2021		
Results and Analysis			
Analysis description	**Primary Analysis:** All patients (n=196) treated with any TMZ-based regimen. All efficacy analyses were completed for the total population and per indication (refractory/relapsed).		
Analysis population and time point description	Population evaluable for the efficacy criteria: patients were considered evaluable for efficacy if evidence of outcome evaluation was found in the patients' files, either formally (based on imaging, pathology), or clinically (not reported in this summary table). Results are presented for the overall group and for refractory/relapsed groups according to the disease indication at first TMZ-based treatment for the total of patients with available data for the specific efficacy criterion. Missing data for each efficacy criterion are only reported. Time points: ORR and DCR at 2 cycles are reported after 2 treatment cycles, for the first TMZ-based treatment episodes (potential subsequent treatment episodes excluded). Best ORR and Best DCR are reported at best response which can occur anytime during the treatment course, for the first TMZ-based treatment episodes (potential subsequent treatment episodes excluded). PFS and OS are reported as median and at 1 year, 2 years and 5 years. The median follow-up calculated from the date of the first TMZ-based treatment for the overall population was 5.2 years [min: 0.3- max: 12.8]. For refractory patients, the median follow-up was 5.2 years [0.3-12.8] and for relapsed patients, 6.5 years [0.3-11.1].		

Descriptive statistics and estimate variability	Study population	Overall	Refractory patients	Relapsed patients
	Number of subjects (N)	196	67	129
	TTP Number of events (censored data)	161 (35)	48 (19)	113 (16)
	Median TTP (month)	5.8	13.7	4.7
	95% CI (month)	3.8 – 8.1	4.8 – 18.7	3.4 – 6.6
	ORR at 2 cycles (%) Missing data (N)	36.3 (72)	38.5 (15)	34.7 (57)
	DCR at 2 cycles (%) Missing data (N)	79.0 (72)	84.6 (15)	75.0 (57)
	Best ORR (%) Missing data (N)	46.4 (45)	50.0 (11)	44.2 (34)
	Best DCR (%) Missing data (N)	76.8 (45)	83.9 (11)	72.6 (34)
	PFS Number of events (censored data)	165 (31)	49 (18)	116 (13)
	PFS Median (months)	-	12.9	4.6

	95% CI (months)	-	4.8 – 18.7	3.4 – 6.6
	1-year PFS (%)	-	50.7	25.3
	95% CI (%)	-	38.8—62.7	17.7 – 32.8
	2-year PFS (%)	-	35.8	14.7
	95% CI (%)	-	24.3 – 47.3	8.5 - 20.9
	5-year PFS (%)	-	27.6	9.1
	95% CI (%)	-	16.6 – 38.6	3.8 – 14.3
	OS Number of events (censored data)	142 (54)	37 (30)	105 (24)
	OS Median (months)	15.0	36.7	11.5
	95% CI (months)	12.2 – 21.4	21.1 – NE*	9.6 – 14.3
	1-year OS (%)	-	74.4	49.3
	95% CI (%)	-	63.9 – 84.9	40.6 – 58.1
	2-year OS (%)	-	57.5	27.5
	95% CI (%)	-	45.6 – 69.5	19.5 – 35.4
	5-year OS (%)	-	47.5	13.8
	95% CI (%)	-	35.2 – 59.9	7.1 – 20.4
Notes	-			
Analysis description	**Post-hoc analyses:** All efficacy analyses were also completed per indication (refractory/relapsed) and per TMZ-based treatment regimen (TMZ, TOTEM, TEMIRI) for the secondary endpoints.			
Analysis population and time point description	Population evaluable for the efficacy criteria: patients were considered evaluable for efficacy if evidence of outcome evaluation was found in the patients' files, either formally (based on imaging, pathology), or clinically (not reported in this summary table). Results are presented for refractory and relapsed patients' groups separately per first TMZ-based treatment groups (TMZ, TOTEM, TEMIRI) for the total of patients with available data for the specific efficacy criterion. Missing data for each efficacy criterion are only reported. <u>Time points</u>: ORR and DCR at 2 cycles are reported after 2 treatment cycles, for the first TMZ-based treatment episodes (potential subsequent treatment episodes excluded). Best ORR and Best DCR are reported at best response which can occur anytime during the treatment course, for the first TMZ-based treatment episodes (potential subsequent treatment episodes excluded). PFS and OS are reported as median and at 1 year, 2 years and 3 years. The median follow-up calculated from the date of the first TMZ-based treatment for the overall population was 5.2 years [min: 0.3- max: 12.8]. For refractory patients, the median follow-up was 5.2 years [0.3-12.8] and for relapsed patients, 6.5 years [0.3-11.1].			
Descriptive statistics and estimate variability	Treatment group **Refractory**	TMZ	TOTEM	TEMIRI
	Number of subjects	17	30	13
	ORR at 2 cycles (%) Missing data (N)	36.4 (6)	48.0 (5)	30.0 (3)
	DCR at 2 cycles (%) Missing data (N)	63.6 (6)	96.0 (5)	70.0 (3)
	Best ORR (%) Missing data (N)	38.5 (4)	59.3 (3)	50.0 (3)
	Best DCR (%) Missing data (N)	61.5 (4)	96.3 (3)	70.0 (3)
	PFS Number of events (censored data)	15 (2)	19 (11)	11 (2)
	PFS Median (months)	3.6	26.4	2.4
	95% CI (%) (month)	2.4 – 13.2	13.2 – NE*	0.0 -8.4
	1-year PFS (%)	29.4	70.0	23.1
	95% CI (%)	13.3 – 53.1	52.1 – 83.3	8.2 – 50.3
	2-year PFS (%)	17.6	53.3	15.4

	95% CI (%)	6.2—41.0	36.1 – 69.8	4.3 – 42.2
	3-year PFS (%)	11.8	43.3	15.4
	95% CI (%)	3.3 – 34.3	27.4 – 60.8	4.3 – 42.2
	OS Number of events (censored data)	14 (3)	12 (18)	8 (5)
	OS Median (months)	14.4	NE*	19.2
	95% CI (months)	3.6 – 28.8	37.2 – NE*	1.2 – NE*
	1-year OS (%)	58.8	82.9	61.5
	95% CI (%)	36.0 – 78.4	65.6 – 92.5	35.5 – 82.3
	2-year OS (%)	29.4	76.0	46.2
	95% CI (%)	13.3 - 53.1	58.0 – 87.8	23.2 – 70.9
	3-year OS (%)	23.5	72.5	38.5
	95% CI (%)	9.6 – 47.3	54.4 – 85.4	17.7 – 64.5
Descriptive statistics and estimate variability	Treatment group **Relapsed**	TMZ	TOTEM	TEMIRI
	Number of subjects	42	51	26
	ORR at 2 cycles (%) Missing data (N)	30.8 (29)	39.0 (10)	30.0 (16)
	DCR at 2 cycles (%) Missing data (N)	61.5 (29)	80.5 (10)	80.0 (16)
	Best ORR (%) Missing data (N)	28.6 (21)	59.1 (7)	50.0 (6)
	Best DCR (%) Missing data (N)	66.7 (21)	79.5 (7)	80.0 (6)
	PFS Number of events (censored data)	41 (1)	41 (10)	25 (1)
	PFS Median (months)	2.4	8.4	6.0
	95% CI (%) (month)	1.2 – 3.6	3.6 – 12.0	3.6 – 8.4
	1-year PFS (%)	7.1	36.6	23.1
	95% CI (%)	2.5 – 19.0	24.6 – 50.4	11.0 – 42.1
	2-year PFS (%)	2.4	26.4	15.4
	95% CI (%)	0.4 – 12.3	16.2 – 40.0	6.2 – 33.5
	3-year PFS (%)	2.4	22.0	7.7
	95% CI (%)	0.4 -12.3	12.7 – 35.4	2.1 – 24.1
	OS Number of events (censored data)	38 (4)	37 (14)	22 (4)
	OS Median (months)	8.4	14.4	10.8
	95% CI (months)	4.8 – 12.0	9.6 – 22.8	9.6 – 26.4
	1-year OS (%)	35.6	58.4	48.5
	95% CI (%)	22.6 – 51.2	44.7 – 71.0	30.4 – 66.9
	2-year OS (%)	12.7	33.7	32.3
	95% CI (%)	5.6 – 26.5	22.1 – 47.7	17.4 – 51.9
	3-year OS (%)	7.6	27.0	24.2
	95% CI (%)	2.6 – 20.2	16.4 – 40.9	11.6 – 43.7
Notes	-			

*NE: Non Evaluable

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

Meta-analysis of efficacy data

A meta-analysis of all relevant clinical studies (i.e., randomised/controlled studies, observational and non-comparative studies) in patients with refractory or relapsed neuroblastoma treated with TMZ monotherapy, TEMIRI or TOTEM was performed to generate supportive evidence on TMZ efficacy.

Objectives

The primary objective was to assess the objective response rate (ORR) according to best response at any time of treatment (Best ORR).

Secondary objectives were to assess:

- Disease control rate (DCR) according to best response at any time of treatment (Best DCR).
- ORR according to the response after 2 cycles of treatment.
- DCR according to the response after 2 cycles of treatment.
- Median overall survival (OS) and OS rates at 1, 2, and 3 years.
- Median progression-free survival (PFS) and PFS rates at 1, 2, and 3 years.
- Treatment duration (in days).
- Duration of response (in days).

Methods

A search of the literature published between 01 January 2004 (date of first study with TMZ) and 30 June 2022 was performed using MEDLINE (via PubMed), EMBASE (via ProQuest), SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL) in Cochrane Library, and EudraCT. The search terms used included: (Neuroblastoma) AND (Temozolomide OR TMZ) AND (Refractory OR relapsed) AND (patient* OR human OR clinical).

The study eligibility was assessed by 2 independent reviewers. The quality of all studies was assessed based on description of patient characteristics, reasons for study withdrawal, calculation of sample size, description of the procedure, description of measure of outcomes and measure of variability. For randomised/controlled studies, the risk of bias was assessed based on the Cochrane handbook/STROBE statement taking into account selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Studies presenting results for both patients treated with TMZ monotherapy/TEMIRI/TOTEM and patients who also received additional agents such as a biological product (*e.g.* dinutuximab) were taken into account only if results were presented for the subgroups of patients receiving TMZ monotherapy/TEMIRI/TOTEM.

Standardised data extraction forms were used to collect and record the data. Responses from literature studies were categorised according to the following **standardised response criteria:**

- CR: complete disappearance of all detectable sites of the disease
- PR: decrease of at least 50% in tumour size (i.e., includes VGPR reported in some published studies)
- SD: less than 50% decrease and less than 25% increase in tumour size (i.e., includes minor response and mixed response reported in some published studies)
- PD: at least 25% increase in tumour size or the appearance of a new lesion

For all studies fulfilling the inclusion criteria, a meta-analysis was performed to generate an overall estimate of the following criteria:

- Primary criterion: Best ORR, defined as the percentage of patients with a CR or PR according to best response at any time of treatment.
- Secondary criteria:

- Best DCR, defined as the percentage of patients with at least SD according to best response at any time of treatment.
- ORR at 2 cycles, defined as the percentage of patients with a CR or PR after 2 cycles of treatment.
- DCR at 2 cycles, defined as the percentage of patients with at least SD after 2 cycles of treatment.
- Median OS and OS rates at 1, 2 and 3 years, with OS defined as the time to event calculated from initiation of TMZ to death, or to time of last contact, if patient was alive.
- Median PFS and PFS rates at 1, 2 and 3 years, with PFS defined as the time to event calculated from initiation of TMZ to progression, recurrence following response or death without progression or recurrence, or to time of last contact, if no event occurred.
- Treatment duration (in days), defined as time from first day of first cycle to last day of last cycle.
- Duration of response (in days), defined as time from best response to progression or death in patients with complete or partial response.

Statistical Analysis

The meta-analysis was performed using summary data extracted from the eligible studies. The inverse variance weighted method (2-step approach) was used to estimate an overall effect and the corresponding 95% CIs. In the first step of the inverse variance weighted method, the effect size and its variance were estimated. In the second step, the overall effect size and its variance were estimated.

Primary endpoint methodology:

- Fixed or random effects models: The overall ORR, as best response at any time of treatment (Best ORR), resulting from the weighted combination of the ORRs observed in the studies were estimated using a fixed effects model or a random effects model.
- Study heterogeneity assessment In addition to the Q statistic and the between-study variance τ^2, the Higgins's index I^2 were computed to assess the heterogeneity between clinical studies.
- Publication bias assessment: A funnel plots to illustrate the presence of heterogeneity between studies and to detect potential publication bias were planned.

Secondary endpoint methodology:

Secondary qualitative criteria (DCR as best response at any time of treatment (Best DCR, ORR and DCR at 2 cycles) were analysed as for the primary endpoint.

For OS and PFS, individual patient data were reconstructed from the Kaplan-Meier curves. The median and the survival probabilities at different time points (1, 2, and 3 years) of survival curve of each study were estimated using the Kaplan-Meier method.

Results

A total of 9 prospective studies were included: 8 published studies and the BEACON-CHEMO study (which includes 3 treatment arms).

Primary outcome: Best ORR

Table 42. Overall best response rate (Best rate)

Study population	Number of studies	Number of patients	Best ORR, median (95% CI)	
			Fixed effects	**Random effects**
Overall (**primary outcome**)	8	248	18.24% (13.71%-23.53%)	18.32% (13.30%-23.94%)
According to TMZ treatment protocol				
TMZ alone	2	56	18.90% (9.82%-31.33%)	18.90% (9.96%-29.89%)
TMZ combined with irinotecan	5	133	14.40% (9.01%-21.39%)	14.40% (9.07%-20.73%)
TMZ combined with topotecan	3	59	28.06% (17.38%-40.91%)	28.06% (17.66%-39.80%)
Abbreviations: CI, confidence intervals; ORR, objective response rate (proportion of patients with complete response or partial response as best response during treatment); TMZ, temozolomide.				

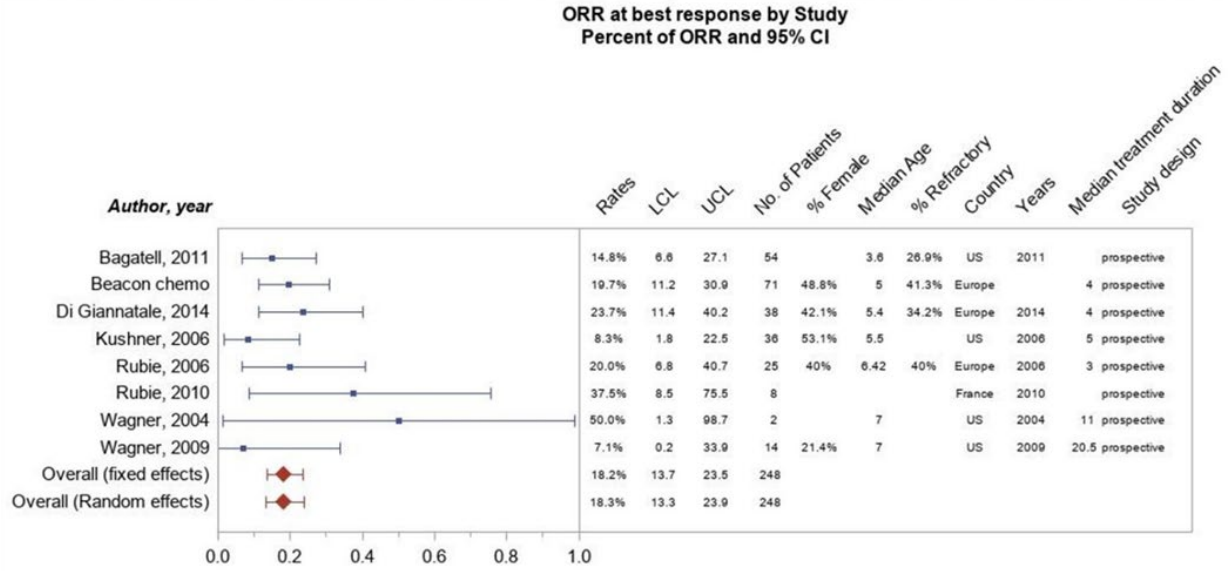


Figure 15. Forest plot showing ORR (95% CI) at best response by study – All prospective studies

Overall Survival

Table 43. Overall survival

Study population (N° of studies, N° of patients)	Median OS (95% CI), in months		1-year OS rate	2-year OS rate	3-year OS rate
	Fixed effects	**Random effects**			
Overall (4 studies, 190 patients)	18.14	18.07	60% (51%-71%)	40% (31%-52%)	37% (28%-48%)
According to TMZ treatment protocol					
TMZ alone (2 studies, 53 patients)	14.65	11.95	50% (26%-94%)	31% (15%-65%)	30% (14%-65%)

	TMZ combined with irinotecan (2 studies, 85 patients)	18.54	18.52	64% (52%-80%)	38% (24%-59%)	30% (18%-50%)
	TMZ combined with topotecan (2 studies, 52 patients)	20.17	19.86	58% (43%-78%)	46% (30%-69%)	44% (28%-68%)
Abbreviations: CI, confidence intervals; OS, overall survival; TMZ, temozolomide.						

Literature data from published trial

Patient populations

Table 44. Neuroblastoma patient population in literature studies

Publication or study	% refractory	% relapsed	Median age (years) (min/max)	Male (%)	Female (%)	MYCN amp (%)	MYCN non amp (%)	MYCN unknown
TMZ monotherapy								
De Sio, 2006	unknown	unknown	7.83 (2-16.92)	5 (29.4%)	12 (70.6%)			17 (100%)
Rubie, 2006	40%	60%	6.42 (1.67-15.83)	15 (60%)	10 (40%)	9 (36%)	15 (60%)	1 (4%)
TEMIRI								
Bagatell, 2011	26.9% (14/52)	73.1% (38/52)	3.6 (0.2-18.4)	unknown	unknown	11 (20%)	23 (41.8%)	21 (38.2%)
Kushner, 2006	unknown	unknown	5.5 (2.3-25.9)	23 (46.9%)	26 (53.1%)			49 (100%)
Wagner, 2004	unknown	unknown	7 (7-7)	unknown	unknown			2 (100%)
Wagner, 2009	unknown	unknown	7 (3-22)	11 (78.6%)	3 (21.4%)	5 (35.7%)	6 (42.9%)	3 (21.4%)
TOTEM								
Di Giannatale, 2014	34.2%	65.8%	5.4 (1-19.8)	22 (57.9%)	16 (42.1%)	10 (26.3%)	23 (60.5%)	5 (13.2%)
Rubie, 2010	unknown	unknown	16 patients/8 neuroblastoma – no neuroblastoma patient characteristics					

Abbreviations: TMZ, temozolomide, TEMIRI, TMZ + irinotecan; TOTEM, TMZ + topotecan
Source: 2.7.3 Table 33

Overview of efficacy results

Table 45. Overview of efficacy results from the Literature studies (relapsed and refractory patients)

Studies	ORR at 2 cycles, n (%)	DCR at 2 cycles, n (%)	Best ORR, n (%)	Best DCR, n (%)	OS				PFS			
					Median (months)	1 year	2 years	3 years	Median (months)	1 year	2 years	3 years
TMZ monotherapy												
De Sio, 2006	5.9%	64.7%	-	-	7	27%	18%	18%	4	12%	6%	6%
Rubie, 2006	16%	68%	20%	68%								
TEMIRI												
Bagatell, 2011	-	-	14.8%	68.5%		64%	30%	21%				
Kushner, 2006	-	-	8.3%	75%								
Wagner, 2004	-	-	50%	100%								
Wagner, 2009	-	-	7.1%	42.9%					4.2			
TOTEM												
Di Giannatale, 2014	18.4%	78.9%	23.7%	78.9%	25.8	58%	51%		10.3	45%		
Rubie, 2010	-	-	37.5%	100%								

Source: Module 2.7.3 Table 36, Table 37, Table 38 and Table 39.

2.4.5.4. Comparisons with historical control cohorts

The applicant performed the indirect comparison analysis of survival data for the relapsed/progressive high-risk neuroblastoma patients from the BEACON-CHEMO trial and from the retroTMZ trial versus survival data for relapsed/progressive high-risk neuroblastoma patients included in historical cohorts as reported by Simon at al, 2011 by Basta et al, 2016 and Garaventa et al, 2009.

The following historical control arms were selected:

- 60 relapsed high-risk neuroblastoma patients who were treated with supportive care only at relapse (Simon cohort, individual patient data)

- 17 matched relapsed high-risk neuroblastoma patients who were treated with supportive care only at relapse (Basta2 cohort, aggregated data)

- 17 matched relapsed high-risk neuroblastoma patients who were treated with etoposide at relapse (Basta1 cohort, aggregated data)

- 318 matched relapsed high-risk neuroblastoma patients who were actively treated at relapse using different chemotherapy regimens (Garaventa cohort, aggregated data).

Results

Table 26. Comparison of post-relapse OS of BEACON-CHEMO and retroTMZ with matched untreated historical cohorts

	SIMON (supportive care)		BASTA-2 (supportive care)
Type of data	Individual patient data (IPTW)	Aggregated data (MAIC)	Aggregated data (MAIC)
Hazard ratio [90% CI] (p value)			
BEACON (weighted)	0.40 [0.27-0.58] (**<0.001**)	0.39 [0.25-0.60] (<**0.001**)	0.17 [0.08-0.39] (**<0.001**)
TMZ (weighted)	0.33 [0.22-0.50] (**<0.001**)	*not performed*	*not performed*
TEMIRI (weighted)	0.48 [0.33-0.70] (**<0.001**)	0.44 [0.21-0.91] (**0.026**)	0.27 [0.10-0.74] (**0.010**)
TOTEM (weighted)	0.33 [0.22-0.50] (**<0.001**)	0.35 [0.21-0.58] (**<0.001**)	0.13 [0.05-0.38] (**<0.001**)

retroTMZ (weighted)	0.34 [0.23-0.50] (**<0.001**)	0.31 [0.20-0.47] (**<0.001**)	0.14 [0.07-0.25] (**<0.001**)
TMZ (weighted)	0.43 [0.29-0.62] (**<0.001**)	0.49 [0.31-0.79] (**0.003**)	0.26 [0.10-0.64] (**0.003**)
TEMIRI (weighted)	0.37 [0.25-0.54] (**<0.001**)	0.36 [0.22-0.60] (**<0.001**)	0.14 [0.05-0.41] (**<0.001**)
TOTEM (weighted)	0.27 [0.18-0.41] (**<0.001**)	0.27 [0.16-0.43] (**<0.001**)	0.11 [0.05-0.24] (**<0.001**)

Table 47. Comparison of post relapse OS of BEACON-CHEMO and retroTMZ with matched historical cohorts treated with 2nd line chemotherapy/ best standard of care

	BASTA-1 (etoposide)	**GARAVENTA (active therapy)**
Type of data	Aggregated data (MAIC)	Aggregated data (MAIC)
Hazard ratio [90% CI] (p value)		
BEACON (weighted)	0.38 [0.20-0.72] (**0.003**)	0.61 [0.43-0.88] (**0.009**)
TMZ (weighted)	*not performed*	0.67 [0.37-1.21] (0.19)
TEMIRI (weighted)	0.45 [0.19-1.08] (0.074)	0.61 [0.27-1.34] (0.22)
TOTEM (weighted)	0.32 [0.15-0.68] (**0.003**)	0.51 [0.30-0.86] (**0.011**)
retroTMZ (weighted)	0.29 [0.16-0.51] (**<0.001**)	0.56 [0.44-0.71] (**<0.001**)
TMZ (weighted)	0.48 [0.23-1.00] (**0.050**)	0.87 [0.57-1.31] (0.50)
TEMIRI (weighted)	0.31 [0.14-0.67] (**0.003**)	0.53 [0.33-0.86] (**0.010**)
TOTEM (weighted)	0.24 [0.12-0.48] (**<0.001**)	0.42 [0.28-0.62] (**<0.001**)

Table 48. Comparison of post relapse OS of BEACON-CHEMO and retroTMZ with untreated historical cohorts

	SIMON (supportive care)		**BASTA-2 (supportive care)**
Type of data			
	Individual patient data (IPTW)	Aggregated data (MAIC)	Aggregated data (MAIC)
Hazard ratio [90% CI] **(p value)**			
BEACON			
TOTEM/TEMIRI (weighted)	0.39 [0.26-0.57] **(<0.001)**	0.37 [0.23-0.60] **(<0.001)**	0.19 [0.09-0.40] **(<0.001)**
RetroTMZ			
TOTEM/TEMIRI (weighted)	0.30 [0.20-0.46] **(<0.001)**	0.29 [0.19-0.45] **(<0.001)**	0.12 [0.06-0.23] **(<0.001)**

Table 49. Comparison of post relapse OS of BEACON-CHEMO and retroTMZ with historical cohorts treated with 2nd line chemotherapy/ best standard of care

	BASTA-1 (etoposide)	**GARAVENTA (active therapy)**
Type of data		
	Aggregated data (MAIC)	Aggregated data (MAIC)
Hazard ratio [90% CI] **(p value)**		
BEACON		
TOTEM/TEMIRI (weighted)	0.37 [0.20-0.71] **(0.003)**	0.55 [0.36-0.85] **(0.007)**
RetroTMZ		
TOTEM/TEMIRI (weighted)	0.25 [0.14-0.48] **(<0.001)**	0.47 [0.35-0.64] **(<0.001)**

2.4.6. Discussion on clinical efficacy

Temozolomide oral suspension (Ped-TMZ) is a hybrid application of Temozolomide, which has been first authorised in 1999. It is a new oral dosage form of temozolomide, specifically adapted for the treatment of children and developed for the treatment of relapsed or refractory neuroblastoma. The efficacy of temozolomide in neuroblastoma has been evaluated in multiple published clinical trials. Currently, temozolomide is not authorised for the treatment of neuroblastoma and it is not indicated for use in paediatric patients under the age of 3 years. However, temozolomide-based regimens have been used off-label for the treatment of relapsed or refractory neuroblastoma in clinical trials conducted in Europe and in the US (e.g. HRNBS2 siopen protocol).

TMZ (as monotherapy or in combination) has been suggested as treatment option for relapsed or refractory high-grade neuroblastoma as per current guidelines/treatment recommendations [CCLG 2017, Parikh et al. 2015, Moreno et al. 2017, NIH 2023]. However, despite multimodality treatment, the overall survival and event-free survival in high-risk patients remain suboptimal. More than half of children diagnosed with high-risk neuroblastoma either do not respond to conventional therapies or relapse after treatment. Therefore, an unmet medical need for a more effective treatment options is obvious.

Design and conduct of clinical studies

No prospective clinical studies were carried out to demonstrate efficacy of Ped-TMZ in the proposed new orphan indication. To support the use of Ped-TMZ in relapsed or refractory neuroblastoma, the results from other studies with temozolomide (Temodal or generics) conducted by several academic groups published in the literature were submitted and are claimed pivotal: BEACON-CHEMO study (phase II randomised, open label multinational study) and Retro TMZ (observational retrospective study). In addition, a meta-analysis of data from studies evaluating TMZ monotherapy, TEMIRI, and TOTEM in children with refractory or relapsed neuroblastoma was also presented to support this MAA in accordance with SAWP recommendations. To further substantiate the clinical benefit of temozolomide in relapsed high-risk neuroblastoma, the Applicant has performed indirect comparisons of overall survival in the BEACON-CHEMO trial and retroTMZ trial with historical control cohorts.

Dosing recommendation

No formal dose response study has been conducted. The proposed posology and dosing schedule overall depends on whether treatment is as monotherapy or in combination with specific DNA topoisomerase I inhibitors (topotecan or irinotecan). However, none of these DNA topoisomerase I inhibitors (topotecan nor irinotecan) is approved for the treatment of neuroblastoma. During the procedure, the applicant has revised the proposed indication of Kizfizo to the use of the medicinal product only in combination with irinotecan or topotecan. The posology is therefore also revised to only include the dose schedule for Ped-TMZ in combination with topotecan or irinotecan.

Distinct approaches of treatment duration according to the disease status (refractory versus relapsed) have been proposed by the applicant. Considering the objective of TMZ-based chemotherapy in patients who are refractory to the initial induction therapy is to proceed to consolidation therapy, the recommendation for duration of therapy is proposed to be in line with the treatment duration in the Beacon-Neuroblastoma trial, i.e. up to 6 cycles with response evaluation every 2 cycles, before proceeding to consolidation therapy unless the patient experiences PD. In line with the different treatment objectives (i.e. achieving the highest achievable level of response) for relapsed patients, the recommended duration of treatment in line with the Beacon-Neuroblastoma trial, is an initial targeted duration of 6 cycles with response evaluation every 2 cycles. However, for CR, PR and SD patients treated with manageable toxicity, it is proposed to leave the decision to continue treatment to the treating paediatric oncologist, possibly up to disease progression or the development of unacceptable

toxicity. Considering that in Beacon-Chemo trial, the treatment could also be continued beyond 6 months (i.e. up to 12 months), the proposed treatment duration recommendation by the company for the relapsed patients seems reasonable and is agreed. In addition, it is recommended to evaluate patients after two courses of therapy and every 2 cycles thereafter.

BEACON-CHEMO study

The main evidence for efficacy of temozolomide as monotherapy or in combination with irinotecan/topotecan in the targeted population comes from the BEACON-CHEMO study, an uncontrolled trial with a complex design leading to small subgroups in 3 temozolomide arms (TMZ alone or in combination with irinotecan or topotecan). Moreover, this study was intended only as a sub-study for the exploratory analyses of the 3 backbone chemotherapy arms of a study which had originally aimed to assess the add-on effect of bevacizumab to these backbone chemotherapies. After dinutuximab beta amendment of the BEACON Neuroblastoma study protocol, additional 64 patients were included in the study thereby creating 4 treatment arms: Arm Temozolomide (T), Arm Dinutuximab beta + T (dBT), Arm TTo and Arm dBTTo. However, following urgent safety measure T and dBT were closed immediately leaving only TTo and dBTTo Arms open. The updated results for these treatment arms were also provided. The BEACON-CHEMO CSR V2.0 was submitted with the results of the analyses that included the data of the TMZ backbone chemotherapy arms of the dinutuximab beta randomisation (additional 22 patients). The number of patients in IT group has not changed, which is understandable as only T and TTo groups were opened in the dinutuximab beta randomisation. However, it appears that 3 patients that were previously included in the refractory group are now listed as relapsed patients, which led to slight differences in reported frequencies in V1.0 vs. V2.2 CSR. The applicant clarified that the observed discrepancy between the initial data in BEACON-CHEMO CSR V1 and the updated data in the CSR V2 regarding the number of patients with refractory neuroblastoma receiving IT was due to database entry issues.

The number of patients assessed in the sub-group analysis BEACON-CHEMO has not been prespecified considering the post-hoc setting. According to the Applicant, the irinotecan and topotecan randomisations were essentially free questions that were to provide some preliminary unbiased randomised evidence on whether irinotecan and topotecan are useful agents in relapsed/refractory neuroblastoma. Randomisation in the part 1 (bevacizumab) ratio was 1:1:1:1:1:1 and was done via IWRS. The prognostic factors used to ensure balance across the arms were: a) refractory disease, early relapse (<18 months), late relapse (≥18 months) and b) measurable versus evaluable disease (i.e. disease evaluated according to RECIST versus disease detectable only by MIBG scanning with or without bone marrow involvement as detected by local morphology).

The treatment of temozolomide received during the study was the commercially available capsules.

The inclusion and exclusion criteria are considered adequate for the intended population, i.e. patients ≥1 year with histologically proven relapsed or refractory neuroblastoma, measurable disease by RECIST or evaluable disease by MIBG scan.

The primary endpoint was Best Overall Response Rate (Best ORR), which allows in principle some determination of anti-tumour activity as accepted previously in phase I/II trial. However, best ORR was defined as the highest category of response achieved by a patient at any time during the first 6 cycles of trial treatment. Considering patients could have received up to 12 cycles of treatment, it is not clear why this was limited to the first 6 cycles only in a highly heterogeneous target-population. Due to the heterogenic number of cycles of TMZ, TEMIRI and TOTEM administered to patients in the literature it is challenging to confirm if the choice of 6 cycles is adequate to reflect the actual best ORR. Secondary endpoints included ORR at 2 cycles, Best Disease Control Rate, DCR at 2 cycles and time-to-event endpoints: overall survival, progression free survival and event free survival. However, it needs to be considered that outcome for harder endpoints (e.g. PFS and particularly OS) in this type of cancer also

depend significantly from the tumour location itself. Duration of response is considered informative for patients responding to the treatment. Overall, primary and secondary endpoints are endorsed. Nevertheless, it remains critical that no comprehensive analyses demonstrate that DCR adds to the value of response/activity endpoints in clinical trials.

The total population (ITT) in BEACON-CHEMO CSR V1 consisted of 80 patients (TMZ 36, TEMIRI 30 and TOTEM 14), 47 (59%) with relapsed disease and 33 (41%) refractory. Five (5) patients did not receive treatment, and 4 patients had no best response data, therefore, the evaluable population consisted of 71 patients (TMZ 31, TEMIRI 27 and TOTEM 13). Overall, the number of patients per arm is small. Percentage of refractory patients was lower in the TOTEM group than in the 2 other groups (TMZ and TEMIRI groups), other demographics and baseline were mostly balanced between the arms, probably due to the minimisation method used in the randomisation. Of note, as a result of including the additional patients to the analysis in the CSR V2, the initial imbalance between the randomised populations was adjusted as 19 additional patients were added to the TTo group.

There were some differences between arms regarding disease characteristics such as amplification of MYCN (lower in the T group), segmental chromosomal aberration (lower in the TTo group), number of relapses (higher in the T group), bone site (lower in the IT group) and Lansky score (lower in the TTo group). In addition, there were 2 patients in T and 1 patient in IT of favourable prognosis INSS stage (stage 1 and 4S) and none in the TTo group. Further, the information about the number of relapses was missing for almost half of the patients in the BEACON-CHEMO study. With regards to the baseline characteristics, considering identified prognostic factors that impact OS and its interpretability as well as interpretability of other study outcomes, patients should have been stratified according to these known risk factors such as early relapse or MYCN gene amplification, but also prior therapies received should be considered, response to prior therapies, and other molecular subtypes.

Efficacy data and additional analyses

The ORR at best response in the total EVA population in BEACON-CHEMO CSR V1 is rather not outstanding, particularly considering the impact of large heterogeneity regarding the included population and the disease characteristics. There was a trend for a higher response rate in TTo (30.8%) compared to the other 2 treatment groups (TMZ: 16.1%, TEMIRI: 18.5%). No marked difference in best ORR for each treatment arm was observed between relapsed and refractory patients; only a trend for a lower best ORR for T in relapsed patients (11.8%) and for TEMIRI in refractory patients (15.4%).

In a sensitivity analysis, the best ORR in the ITT population was overall slightly lower to that of the EVA population. Of note, there was only one complete response in the study (in TTo arm).

The updated analysis from the Beacon-Chemo CSR V2 including additional 22 patients (T=3; TOTEM=19) showed overall comparable best ORR of temozolomide as monotherapy or in combination with irinotecan/topotecan in the total EVA population and in the subgroup of patients with relapsed disease and with two complete responses (in TTo arm). In the total ITT population, the best ORR was overall slightly lower to that of the EVA population. It was 17.6% (95% CI: 11.5%-26.2) in the total ITT population and 16.2% (9.3%-26.7%) in the subgroup of patients with relapsed disease. In the subgroup of patients with refractory disease the best ORR in ITT population was 20.6% [95%CI 10.3%-36.8%] and was comparable to the EVA population.

In the total EVA population, the ORR at 2 cycles was much lower than the Best ORR, supporting the administration of temozolomide alone or combination with topotecan beyond 2 treatment cycles. However, for TEMIRI, the Best ORR and the ORR at 2 cycles are comparable, and suggest that patients with response to TEMIRI, respond already at second cycle. The small number of patients per arms,

however, hampers any robust conclusion and indicate remaining significant uncertainties with respect to the proof of clinical efficacy for the applied product.

In all patients with response (Partial response or above in EVA population) (n=14), the median duration of response is estimated at 15.6 months (95% CI: 8.6 – NE). It was, however, lower in relapsed patients (10.0 months), and not evaluable in patients with refractory neuroblastoma. In the updated analysis (EVA population), the median duration of response was similar to initially reported DoR and was 15.6 months (95% CI: 8.6–37.3) in the 18 patients with response. It was 9.3 (95% CI: 2.0 - 17.7) in relapsed and not evaluable (11.7- not evaluable) in the refractory neuroblastoma.

As often in small population, the results for PSF and EFS were identical. The median PFS was 6.1 months [3.2; 12.6] in the total EVA population; 5.3 months [2.0 ;11.3] for relapsed and 23.1 months [2.3-NE] for refractory patients. The median OS was 15.9 months [12.5; 34.3] in the total EVA population; 14.8 months [11.0; 17.5] for relapsed and 72.8 months [7.5; NE] for refractory patients. At 5 years, 30.23% [19.81 ;41.33] of patients were alive; 10.98% [3.45; 23.46] for relapsed patients and 56.67% [37.33; 72.08] for refractory patients. The patients with refractory neuroblastoma, which is expected, had a better prognosis than that of patients with relapsed neuroblastoma. Median OS was 72.8 months and median PFS was 23.1 months for patients with refractory neuroblastoma compared to 14.8 months and 5.3 months respectively for patients with relapsed neuroblastoma. These endpoints are however, uninterpretable without a control arm taken into account the large intraindividual variability in OS known in this disease.

Again, the contribution of each component of the proposed combination to the observed benefit is not possible to determine. The sample size is far too small for any robust conclusions. Moreover, although the majority of patients were followed for 5 years, this alone does not make the data robust.

The analysis by age group suggested a lower benefit for ORR, DCR PFS and OS, in the younger population (<3 years old). With respect to the relapse and refractory setting, a lower median PFS (95% CI) in refractory population in patients <3 years (4.3 months, 0.9; NE) compared to ≥3 years (39.3 months, 3.9; NE) as well as a lower OS (95%CI) in refractory population in patients <3 years compared to ≥ 3 years was observed. Further differences were observed according to treatment received as well. However, the results are hampered by a very limited number of patients <3 years old.

The applicant argues that the survival was markedly influenced by the best response achieved. This view is not shared by the CHMP. For refractory patients, >80% of patients achieving at least SD were alive at 5 years, compared to 0% at 1 year for patients with PD. For relapsed, >40% of patients achieving at least SD were alive at 2 years, compared to 0% for patients with PD. It is methodologically incorrect to claim that patients with best response achieved, also had longest survival meaning that survival is causally explained exclusively by treatment response. The same correlation may be explained also by the fact that the patients who responded have had a better prognosis independently from response at baseline.

Overall, a moderate clinical activity of all 3 temozolomide arms can be agreed considering the best ORR of approximately 20% in overall EVA population of both relapsed and refractory patients. However, further interpretation of the current data to conclude on a potential clinical benefit does not seem possible. Moreover, it does not indicate clearly an outstanding activity which is considered as a prerequisite for approval based on uncontrolled clinical data. Considering this limitation, it is however acknowledged that data may indicate that refractory patients (as expected) have a better outcome than relapsed patients.

Of note, all comparative efficacy analyses between treatment arms are considered purely descriptive with limitations due to the post-hoc nature of the BEACON-CHEMO study.

In conclusion, the design of the sub-study allows an unbiased comparison of TMZ alone with TMZ in combination with irinotecan or topotecan. However, as there is no control arm that does not include TMZ, the study does not allow to conclude reliably on a clinical benefit of TMZ. Even regarding evaluation of a potential add-on effect of irinotecan or topotecan, the study is too small for any robust conclusions. No valid direct comparisons (i.e. outcome differences by different treatment) can be reliably evaluated. Moreover, due to the small numbers included in the subgroups the corresponding confidence intervals are wide and overlapping. The main efficacy analysis was performed in the evaluable (EVA) population with additional efficacy analyses carried out in the ITT population. In general, the analysis should be based on the ITT population, particularly in an open-label study. Treated patients should not be excluded from the analysis, as it cannot be excluded that missing data are related to treatment. In general, it appears hardly acceptable to justify pivotal claims for the applied broad indication based on this data; even in an orphan disease entity.

ORP-TMZ-4 (RetroTMZ) study

The ORP-TMZ-4 (RetroTMZ) multicentre, **retrospective** study has been based on data captured from established medical records without any change of clinical practice. It was conducted by Gustave Roussy cancer centre with the support of the Applicant. The aim was to describe the current use and response to TMZ in children with refractory or relapsed neuroblastoma. Data collection was performed for all patients diagnosed with refractory or relapsed neuroblastoma from the 01 January 2004 until 31 December 2017 and had started on treatment with TMZ-based chemotherapy (single-agent or combination therapy) before 01 May 2018, with follow-up (vital status only) updated up to February 2021. The overall cohort comprises 196 relapsed and refractory neuroblastoma patients treated with any TMZ-based regimen. In addition, the TMZ-TEMIRI-TOTEM cohort was generated via a post-hoc efficacy analysis.

The primary endpoint was to describe the population treated with TMZ and time to first progression (TTP). TTP has been defined as the time from start date of first TMZ to first progression (as defined by formal disease evaluation or contemporaneous clinical assessment or death). Secondary efficacy endpoints include response rates (best response and response at 2 cycles); they may isolate treatment effects, if response is defined in a way that cannot be achieved without treatment, however, it indicates only activity which does not necessarily translate into clinically relevant benefit. Due to its retrospective nature, the results of the RetroTMZ study are hampered by progression or response not being systematically assessed using standardised criteria and follow-up times. Even if clinical practice with regard to treatment did not change in the centres, it is unclear whether there were differences within and between centres with regard to progression assessment. All analyses were descriptive. No statistical hypothesis was tested. No comparison to a control group was made. Therefore, no causal interpretation is possible for time to event endpoints, i.e. it is not possible to conclude whether treatment prolonged time to event, as it is unknown what would have been the outcome without treatment (or alternative relevant control treatment). Response endpoints may theoretically isolate treatment effects compared to no treatment, as response can usually not occur without treatment. However, practically, it is unclear whether responses could also be falsely claimed due to measurement errors (not all patients are consistently evaluated for progression, based on 'formal' evaluation or clinical evaluation, it is also unclear whether 'formal' evaluation and clinical evaluation was standardised.), or occur due to carry-over effect of previous treatments. Even if it could be justified that this is unlikely, response indicates activity of treatment but this does not necessarily translate into a clinically relevant benefit. Furthermore, evaluation of response is based on evaluable patients, patients were considered evaluable for efficacy if evidence of outcome evaluation was found in the notes, either formal (imaging, pathology), or clinical. As sensitivity analysis, an analysis of response in all patients meeting the eligibility criteria (i.e. in ITT population) was provided. The analysis of time to event endpoints is based on the assumption of non-informative censoring. Censoring reasons are not

provided and it remains unclear what proportions of patients was censored due to being known to be event-free at data cut-off, or due to loss to follow-up.

Descriptive comparisons between treatment regimens (i.e. TMZ, TOTEM, TEMIRI) cannot support conclusions of one regimen being 'better' than another as bias due to confounding or differences in assessment of endpoints cannot be excluded.

Considering the limitations of the time to event endpoints in the non-randomised/uncontrolled settings, it is hard to interpret the primary endpoint of the study. In overall population, TTP from the first dose of TMZ was 5.8 months whereas in refractory patient, as expected, it was longer (13.7 months), and in relapsed patients, it was 4.7 months. Of note, for this endpoint, patients who died for whom no prior progression was noted were censored. This is not supported, especially in cases where the underlying disease was listed as the cause of death.

Almost one-fourth of patients had no formal evaluation and according to the applicant, most of them stopped treatment for either progression (30/45) or death (7/45). For further 8 patients no information is provided.

Response to the therapy also includes maintained CR/PR i.e. patients with response prior to initiation of TMZ-based chemotherapy (e.g. following radiotherapy), that continues during treatment.

In the overall population, ORR after 2 cycles was 36.3%. DCR after 2 cycles of therapy was 79.0%. Best ORR was 48.3% and the best DCR was 78.8%. Of note, the rates are based on evaluable patients (those with formal evaluation); non-evaluable patients may have less favourable outcomes (as most stopped because of progression or death). When the rates are calculated for the ITT population, ORR after 2 cycles is actually 23% in overall population, and best ORR is 37.2%.

For the assessed refractory patients (77.6%), ORR after 2 cycles was 38.5% and DCR after 2 cycles was 84.6%. Best ORR was 50.0%, assessed in 83.6% of patients with refractory disease. The best DCR was 83.9%. According to the applicant, thirty-four patients (50.7%) in this cohort had sufficient responses to proceed to intensification with high-dose chemotherapy and stem cell rescue, a key part of curative treatment. Considering that overall 28 refractory patients had CR or PR, this would mean that also patients with e.g. minor response/stable disease might have proceeded to intensification. Of note, formal evaluation was not appropriate for all patients in this cohort, e.g. rapidly progressive disease or palliative context, so clinical evaluations were also recorded and only 11 relapsed patients (16.4%) were considered clinically improved according to these evaluations.

For the relapsed patients, ORR after 2 cycles was 34.7% and the DCR after 2 cycles of therapy was 75.0%. Best ORR was 47.7%, and the best DCR was 75.9%. Best clinical evaluation was available for 116 of 129 relapsed patients, and 47 patients (36.7%) were considered clinically improved according to clinical evaluations.

Therefore, according to this real-life cohort, patients with refractory disease (for whom the goal is to achieve response in order to proceed to consolidation) and patients with MYCN amplification (poorer prognosis) are more likely to be treated with the combinations, whereas relapsed patients (for whom the goal is to achieve disease control with the tolerability being an important parameter) are more likely to be treated with TMZ monotherapy.

Supportive evidence

A meta-analysis of relevant clinical studies in patients with refractory or relapsed neuroblastoma treated with TMZ monotherapy, TEMIRI or TOTEM was performed to generate supportive evidence on TMZ efficacy. Overall, 8 published studies and BEACON-CHEMO study were included in this study with total of 248 patients. The overall summary of the meta-analysis results show that the TMZ chemotherapy regimens have antitumour activity with Best ORRs of about 18%. The Best ORR exceeds

the ORR after 2 cycles, suggesting that some patients may benefit from the treatment beyond 2 cycles. The Best ORR and – to some extent – best DCR tend to be better for TOTEM vs TMZ and TEMIRI. There was a trend for better 2 and 3-year OS for TOTEM and no difference in PFS across the 3 treatment regimens. Given the limited information in the published literature, it was not possible to analyse efficacy endpoints according to relapsed versus refractory patient subgroups.

Literature data from published trials investigating the use of TMZ as single agent or in combination with irinotecan or topotecan in relapsed/refractory neuroblastoma, was provided as supportive evidence for this MAA. These trials were mostly small phase I and early phase II trials and have been included in the meta-analysis conducted by the applicant. These phase I/II trials are limited in their scope, as they report mostly on immediate outcomes (such as response to therapy). Therefore, the interpretation of data from these trials is difficult, as the lack of randomised trials hampers direct and scientifically robust comparisons. Different response criteria were utilised due to (at that time) the lack of updated internationally agreed response criteria. The population is heterogeneous and includes patients with measurable and evaluable disease as well as patients with relapsed and refractory neuroblastoma. This makes stratification and common response criteria critical for effective analysis. The response is a complex and difficult endpoint to measure and requires a central review for single arm studies. It is not clear if central review of computerised tomography (CT) and MIBG scans was done for all presented studies.

Overall, the activity that has been reported in these trials varied substantially, with Best ORR from 7.1% with TEMIRI in Wagner 2010 to 50% also with TEMIRI in study by Wagner 2006. ORR rates for T alone were approximately 20%.

Additional ad-hoc analyses and Comparison to external control retroTMZ

During the procedure, the applicant proposed different approaches to support the clinical benefit of TMZ-based treatments first in relapsed high-risk neuroblastoma patients and then in refractory high-risk neuroblastoma patients. To further substantiate the clinical benefit of temozolomide in relapsed high-risk neuroblastoma, indirect comparisons of overall survival in the BEACON-CHEMO trial and retroTMZ trial with historical control cohorts were submitted. In order to assess the clinical benefit of temozolomide for refractory patients included in the BEACON-Chemo and retroTMZ study, the following criteria were presented: the DCR, access-to-consolidation rate, and OS results for the refractory patient population.

The approach to evaluate these very different populations separately is supported.

However, the provided comparison with external control groups cannot constitute pivotal evidence of efficacy/clinical benefit for the claimed indication in relapsed patients, but could at best be considered as supportive data. This is due to the general inability to control bias for external control groups and the specific concerns regarding patient selection and analysis.

During the procedure, the indication for relapsed patients was reworded to add "actively progressing high risk recurrent neuroblastoma". This is justified by the fact that the focus is on the patients to be able to receive dinutuximab beta which has been shown to have a benefit in patients with stable disease (progressive disease was an exclusion criterion of the clinical trials included in the initial MAA) as specified in section 4.2 of Qarziba(dinutuximab beta)'s SmPC. Nevertheless, section 4.1 of the SmPC of Qarziba specify in addition that "In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, Qarziba should be combined with interleukin-2 (IL-2)." Therefore, it is understood that in the setting proposed by the Applicant, Qarziba is meant to be administered in combination and not in monotherapy, the claimed benefit would therefore lie on an off-label use.

In BEACON chemo study, 62.2% [47.6%;74.9%] in the ITT population (66.7% [51.6%;79.0%] of EVA population) achieved response or SD and became eligible to receive immunotherapy. On top of the 2/25 patients who achieved CR and the 3/25 patients who achieve PR as best response (of which 2 received dinutuximab beta, 11/25 achieved SD as best response (44%). On these 11 patients who achieved SD, 9 received an antiGD2 (dinutuximab beta, and naxitamab for one patient), 1 patient received a CART cell therapy, and 1 patient received lorlatinib and other kinase inhibitors related to ALK mutation. The remaining 9/25 had PD as best response. Among these patients who received a subsequent therapy, 3 had an OS > 60 months, 5 had an OS of at least 42 months (alive at cut off), the 3 remaining patients had a survival of 10, 17 and 21 months suggesting that IT or TTO could have contribute to a prolonged survival. Despite it could appear more important than initially claimed, the benefit in patient to receive Qarziba monotherapy is uncertain since it is not consistent with the current labelling.

The proposed indication in refractory patients is also rephrased to include the aim of the therapy (i.e. to proceed to consolidation). Although the results of temozolomide and combinations (with irinotecan or topotecan) reported in BEACON-CHEMO overall show responses after insufficient induction therapy, allowing about half of the refractory patients to proceed to consolidation therapy, the interpretation of these results is difficult. The main uncertainty relates to the lack of a control arm with which these results could be compared and the optimal temozolomide combination to recommend in this setting. As seen with the SIOPEN recommendation for the refractory patients, these have evolved from the earlier 2 courses of TVD (topotecan-vincristine-doxorubicin) combination, over recently 3 courses of TEMIRI, to currently 4 courses of TEMIRI with DB (dinutuximab beta). Clearly, the aim is to improve the response to second-line induction therapy by exploring new combinations, and these efforts are ongoing. Furthermore, the best ORR for temozolomide containing treatment arms in refractory patients is still considered modest, even when a monotherapy arm is excluded from the analysis (i.e. ORR of the IT and TTO arms in the ITT population is 22.2% [95% CI 9.0%;45.2%]). The applicant argues that patients who proceed to consolidation with autologous stem cell rescue (ASCR) after second-line therapy have comparable survival to patients who proceed to consolidation with ASCR after initial induction therapy. This may be considered reassuring, nevertheless, the unplanned post-hoc analysis of data to explore the eligibility to access to consolidation is not sufficiently robust for firm conclusions.

Demonstration of favourable effects on survival duration are the most convincing outcome of a clinical trial. In the current application, due to the uncontrolled design of the studies submitted in this MAA, the time to event endpoints (i.e. TTP, PFS and OS) cannot be interpreted. Efficacy in the studies presented was evaluated in an exploratory manner without comparing clinical benefits with other therapies available. ORR is considered a convincing measure of anti-tumour activity (EMA/CHMP/205/95 Rev.6) as it allows isolation of treatment effect. However, an ORR of approximately 20% in overall population of BEACON CHEMO study is not convincing nor outstanding as would be required for an uncontrolled clinical trial and cannot support the demonstration of clinical benefit.

During the procedure, the applicant has presented the information regarding the eligibility to access the anti-GD2 immunotherapy for relapsed patients and the eligibility to proceed to consolidation therapy for refractory patients in the BEACON-CHEMO study (data not shown). This unplanned post-hoc analysis of data represents all the patients with stabilised disease (i.e. best disease control rate) during the temozolomide containing treatment.

However, evidence that this modest clinical activity is indicative of patient benefit (i.e. access to consolidation) has not been sufficiently demonstrated.

In general, external (historical) controls to a single-arm trials (or in this case, a trial without a control group) aim to provide supportive evidence for further exploration of the derived efficacy. This is

considered appropriate when the efficacy has been established based on the single-arm trial itself, which is not considered to be the case for this application. The uncontrolled data from a SAT must be convincing on their own. Only endpoints that isolate treatment effects such as ORR are suitable for this purpose. A convincing/outstanding ORR is a necessary requirement. Only if this requirement is fulfilled, can contextualisation with external data provide supportive evidence.

2.4.7. Conclusions on clinical efficacy

Efficacy claims for temozolomide in combination with irinotecan or topotecan for the treatment refractory or recurrent high-risk neuroblastoma are based on the BEACON-CHEMO study (phase II uncontrolled study) and the Retro TMZ study (observational retrospective study). These studies were not designed to confirm efficacy for relapsed high-risk neuroblastoma patients or refractory high-risk neuroblastoma patients. Furthermore, due to the uncontrolled design of these studies, the time to event endpoints (i.e. TTP, PFS and OS) cannot be interpreted.

The exploratory data of the BEACON-CHEMO trial suggest only modest clinical activity of temozolomide in combination with irinotecan and topotecan in the treatment of the relapsed neuroblastoma (20.0% [10.9%;33.8%]) and treatment benefit cannot currently be established in this patient population. The comparison to external control groups that was provided during the procedure cannot establish pivotal evidence of efficacy/clinical benefit for the claimed indication but could at best be considered as supportive data. This is because of the general inability to control bias for external control groups, and the specific concerns with regard to patient selection and analysis.

The best response rate for refractory patients receiving temozolomide in combination with irinotecan or topotecan is also considered modest (ORR 22.2% [9.0%;45.2%]). About half of the refractory patients proceeded to consolidation therapy in the BEACON-CHEMO study, although in the post-hoc analysis of data, 2/3 of the refractory patients were considered eligible to proceed to consolidation therapy (i.e. all the patients with stabilised disease).

Overall, evidence that the modest clinical activity of Kizfizo is indicative of patient benefit (i.e. access to consolidation) has not been sufficiently demonstrated.

2.4.8. Clinical safety

The safety profile of TMZ is well documented. As Ped-TMZ has been shown to be bioequivalent to Temodal (Study ORP-TMZ-I-a), its safety profile (when given in monotherapy) is well characterised by the available clinical safety data with Temodal in the approved adult and paediatric indications in clinical trials and from post-marketing use with TMZ drug products since 1999. In addition, to underline respectively the safety profile in the intended targeted indications / paediatric population, the following safety information was provided and discussed by the applicant.

The results of *Study ORP-TMZ-I-b (TEMOkids)* provide safety data regarding the *new formulation of temozolomide* (in monotherapy as well as in combination therapy) in 43 children aged from 1 year to 17 years (with different indications). Of note, only 20 children with neuroblastoma were included.

The results of the *BEACON CHEMO study* provide the main understanding of the use of the *known formulation (capsule) of temozolomide in the targeted indication (Neuroblastoma) in paediatric population* (TMZ mono n=34, TEMIRI n=28, TOTEM n=13).

Supplementary, results from the retrospective study *ORP-TMZ-4* (RETROTMZ, TMZ mono n=59, TEMIRI n=39, TOTEMn=81) as well as from an *Early access Program* (pts. treated n=2) and a *Compassionate Use program* (pts. treated n=4) were presented and discussed.

Given the hybrid nature of the application, additionally published data concerning the use of TMZ for treating patients with refractory or relapsed neuroblastoma were identified by a *systematic review of the literature*.

The proposed dose schedule for Ped-TMZ monotherapy is the same as currently approved for reference product Temodal. It is also the dose schedule that was used in a phase II neuroblastoma study published by Rubie et al., 2006 and in the BEACON-CHEMO study except for the dosing of cycle 1 (where 200mg/m2/day was given).

The dose schedule for Ped-TMZ combination with Topotecan is based on the dosing in the BEACON-CHEMO study and on the results of a phase II neuroblastoma study published by Di Giannatale et al., 2014 and for the Ped-TMZ combination with Irinotecan (TEMIRI) on the dosing in the BEACON-CHEMO study and on the results published by Kushner et al., 2006.

Dosing adjustments in case of toxicity used for cycle delays and dose reductions proposed are the ones from the BEACON-CHEMO study (and the publications mentioned above) respectively from the approved reference product.

2.4.8.1. Patient exposure

ORP-TMZ-I-b - TEMOkids study.

Table 50. Study drug exposure by indication during the primary study period (Cycle 1) in the TEMOkids study

	Neuroblastoma (n=20)	Medulloblastoma (n=6)	Rhabdomyosarcoma (n=6)	Glioblastoma/ Glioma (n=4)	Ewing's Sarcoma (n=2)	Other brain embryonal tumours (n=5)	Total (n=43)
Duration of cycle (days)							
n	20	6	6	4	2	5	43
Mean (SD)	24.5 (8.4)	26.8 (1.8)	21.8 (3.3)	20.0 (11.1)	20.0 (0.0)	28.0 (1.9)	24.2 (7.0)
Median	27.0	28.0	21.0	24.0	20.0	28.0	27.0
Q1 - Q3	21.0 - 28.0	25.0 - 28.0	21.0 - 22.0	12.5 - 27.5	20.0 - 20.0	27.0 - 28.0	21.0 - 28.0
Min - Max	1 - 43	24 - 28	18 - 28	4 - 28	20 - 20	26 - 31	1 - 43
Dose prescribed (mg/m^2/day)							
n	20	6	6	4	2	5	43
Mean (SD)	122.5 (26.8)	145.0 (12.2)	129.2 (10.2)	137.5 (25.0)	122.5 (3.5)	145.0 (11.2)	130.6 (22.5)
Median	112.5	150.0	125.0	150.0	122.5	150.0	150.0
Q1 - Q3	100.0 - 150.0	150.0 - 150.0	125.0 - 125.0	125.0 - 150.0	120.0 - 125.0	150.0 - 150.0	100.0 - 150.0
Min - Max	75.0 - 150.0	120.0 - 150.0	125.0 - 150.0	100.0 - 150.0	120.0 - 125.0	125.0 - 150.0	75.0 - 150.0
Dose administered (mg/m^2/day) *							
n	20	6	6	4	2	5	43
Mean (SD)	128.7 (30.8)	142.1 (13.3)	131.2 (11.2)	137.5 (24.4)	121.3 (4.5)	145.3 (15.6)	133.3 (24.1)
Median	135.5	145.9	128.0	146.6	121.3	152.7	141.3
Q1 - Q3	101.9 - 151.8	127.6 - 152.7	126.2 - 130.3	123.2 - 151.8	118.1 - 124.5	144.0 - 155.0	118.1 - 152.7
Min - Max	79.8 - 199.5	124.7 - 156.1	121.7 - 153.3	101.4 - 155.4	118.1 - 124.5	118.7 - 156	79.8 - 199.5

So far, no data regarding further cycles was provided

BEACON CHEMO study

Table 51. Treatment Duration in the BEACON-CHEMO study

Treatment duration		TMZ	TEMIRI	TOTEM	Total
SAF Population	n	34	28	13	75
Cycles	Mean (SD)	3.8 (2.6)	4.4 (3.0)	6.1 (4.2)	4.4 (3.1)
	Median	3.0	4.0	6.0	4.0
	Range	1.0 - 12.0	1.0 - 12.0	1.0 - 12.0	1.0 - 12.0
Days	Mean (SD)	105.4 (73.6)	93.0 (62.7)	170.2 (116.3)	112.0 (82.4)
	Median	84.0	84.0	168.0	84.0
	Range	28.0 - 336.0	21.0 - 252.0	28.0 - 336.0	21.0 - 336.0
Relapse	n	20	14	10	44
Cycles	Mean (SD)	2.8 (1.5)	5.4 (3.2)	5.9 (4.1)	4.3 (3.1)
	Median	2.0	6.0	5.5	3.0
	Range	1.0 - 6.0	1.0 - 12.0	1.0 - 12.0	1.0 - 12.0
Days	Mean (SD)	78.4 (41.2)	112.5 (66.7)	165.2 (116.2)	109.0 (78.1)
	Median	56.0	126.0	154.0	84.0
	Range	28.0 - 168.0	21.0 - 252.0	28.0 - 336.0	21.0 - 336.0
Refractory	n	14	14	3	31
Cycles	Mean (SD)	5.1 (3.3)	3.5 (2.6)	6.7 (5.0)	4.5 (3.2)
	Median	4.5	2.0	6.0	4.0
	Range	1.0 - 12.0	1.0 - 9.0	2.0 - 12.0	1.0 - 12.0
Days	Mean (SD)	144.0 (92.4)	73.5 (53.9)	186.7 (140.9)	116.3 (89.4)
	Median	126.0	42.0	168.0	112.0
	Range	28.0 - 336.0	21.0 - 189.0	56.0 - 336.0	21.0 - 336.0

ORP-TMZ-4 (RETROTMZ) study

The duration of treatment for the first TMZ episode was influenced by the treatment indication, with refractory patients having a shorter treatment duration probably as the intention was to gain sufficient response of metastatic disease to proceed to intensification, rather than to obtain a sustained response.

Refractory: TMZ mono median = 2 month TEMIRI median = 2 month, TOTEM median = 4 month TMZ
Relapsed: TMZ mono median = 3 month TEMIRI median = 6 month, TOTEM median = 5.5 month

Table 52. Number of cycles of TMZ combination according to TMZ episodes and TMZ indication in the RETROTMZ study

	First TMZ episode						Subsequent TMZ episodes					
	Refractory			Relapse			Refractory			Relapse		
	Median	Min	Max	Median	Min	Max	Median	Min	Max	Median	Min	Max
Number of cycles assessed												
	3.0	1	29	4.0	1	69	9.0	9	9	3.5	1	37
Age at treatment with TMZ												
0-1.0 year	3.0	1	5									
>1.0-3.0 years	2.5	1	9	1.5	1	26	.	.	.	.	.	.
>3.0-5.0 years	3.5	1	29	3.0	1	69	9.0	9	9	2.0	1	34
>5.0-10.0 years	4.0	1	12	4.0	1	33	.	.	.	3.0	1	37
>10.0 years	3.5	2	20	5.5	1	13	.	.	.	5.0	1	16

2.4.8.2. Adverse events

ORP-TMZ-I-b - TEMOkids study

153 treatment-emergent adverse events (TEAE) were recorded in 40 patients (93%) during the primary study period (one cycle only). One was defined as adverse event of special interest (AESI, 0.65%). The majority of all recorded TEAE were related to Kizfizo (n=98, 64%). However, there were only seven instances of actions involving Kizfizo to resolve an AE (Kizfizo interrupted, withdrawn, or dose rate reduced). 40 actions involving concomitant medications, other pharmacological treatments (e.g., antibiotics, analgesics, antiemetics), and seven actions involving transfusion (red blood cells, platelets). A substantial proportion of adverse events involved no action with Kizfizo (n=128, 83.6%) nor with concomitant medications and other pharmacological. Of note, the single reported adverse event of special interest (AESI =oral inflammation and ulceration such as mucositis) had occurred 28 days after the beginning of the primary study period and was classified as not related to Kizfizo.

Table 53. Summary of treatment-related adverse events that occurred during the primary study period of ORP-TMZ-I-b

Treatment-related adverse events	During the primary study period (Cycle 1) (n=98)
Vomiting	18 (18.4%)
Neutropenia	7 (7.1%)
Thrombocytopenia	7 (7.1%)
Diarrhoea	6 (6.1%)
Abdominal pain	5 (5.1%)
Anaemia	5 (5.1%)
Lymphopenia	5 (5.1%)
White blood cell count decreased	5 (5.1%)
Neutrophil count decreased	4 (4.1%)
Alanine aminotransferase increased	3 (3.1%)
Asthenia	3 (3.1%)
Platelet count decreased	3 (3.1%)
Aspartate aminotransferase increased	2 (2.0%)
Blood creatinine increased	2 (2.0%)
Fatigue	2 (2.0%)
Leukopenia	2 (2.0%)
Nausea / Vomiting	2 (2.0%)
Affect lability	1 (1.0%)
Anaemia / Asthenia	1 (1.0%)
Blood phosphorus decreased	1 (1.0%)
Constipation	1 (1.0%)
Constipation / Rectal fissure / Haematochezia	1 (1.0%)
Cough	1 (1.0%)
Dysgeusia	1 (1.0%)
Febrile neutropenia	1 (1.0%)
Flushing	1 (1.0%)
Headache	1 (1.0%)
Lymphocyte count decreased	1 (1.0%)
Nausea	1 (1.0%)
Pain in extremity	1 (1.0%)
Pruritus	1 (1.0%)
Rash maculo-papular	1 (1.0%)
Retching	1 (1.0%)
Vomiting / Gastroenteritis Escherichia coli	1 (1.0%)

BEACON CHEMO study

Table 54. Incidence of AEs > 5% displayed by PT and treatment groups in the BEACON-CHEMO study

	TMZ N= 34		TEMIRI N= 28		TOTEM N=13		Total N=75	
At least one AE	Patients n(%)	Events n	Patients n(%)	Events n	Patients n(%)	Events n	Patients n(%)	Events n
At least one AE	31 (91.2%)	440	26 (92.9%)	695	12 (92.3%)	414	69 (92.0%)	1549
Platelet Count Decreased	12 (35.3%)	35	10 (35.7%)	30	9 (69.2%)	71	31 (41.3%)	136
Vomiting	8 (23.5%)	13	15 (53.6%)	47	7 (53.8%)	8	30 (40.0%)	68
Neutrophil Count Decreased	7 (20.6%)	33	12 (42.9%)	40	7 (53.8%)	71	26 (34.7%)	144
Anaemia	11 (32.4%)	31	9 (32.1%)	42	6 (46.2%)	25	26 (34.7%)	98
Diarrhoea	2 (5.9%)	2	18 (64.3%)	54	3 (23.1%)	5	23 (30.7%)	61
White Blood Cell Decreased	10 (29.4%)	36	8 (28.6%)	43	4 (30.8%)	23	22 (29.3%)	102
Lymphocyte Count Decreased	9 (26.5%)	29	9 (32.1%)	43	4 (30.8%)	16	22 (29.3%)	88
Fever	8 (23.5%)	11	7 (25.0%)	7	6 (46.2%)	14	21 (28.0%)	32
Nausea	5 (14.7%)	6	6 (21.4%)	19	5 (38.5%)	14	16 (21.3%)	39
Investigations – Other	6 (17.6%)	87	8 (28.6%)	91	0 (0.0%)	0	14 (18.7%)	178
Anorexia	2 (5.9%)	2	8 (28.6%)	14	4 (30.8%)	13	14 (18.7%)	29
Abdominal Pain	2 (5.9%)	2	9 (32.1%)	22	3 (23.1%)	13	14 (18.7%)	37
Alanine Aminotransferase Increased	6 (17.6%)	7	7 (25.0%)	30	0 (0.0%)	0	13 (17.3%)	37
Cough	4 (11.8%)	6	6 (21.4%)	8	3 (23.1%)	5	13 (17.3%)	19
Aspartate Aminotransferase Increased	4 (11.8%)	8	8 (28.6%)	18	0 (0.0%)	0	12 (16.0%)	26
Pain	5 (14.7%)	6	4 (14.3%)	4	3 (23.1%)	13	12 (16.0%)	23
Infections And Infestations – Other	5 (14.7%)	7	5 (17.9%)	6	2 (15.4%)	3	12 (16.0%)	16
Fatigue	4 (11.8%)	5	4 (14.3%)	8	3 (23.1%)	14	11 (14.7%)	27
Constipation	5 (14.7%)	6	3 (10.7%)	7	2 (15.4%)	4	10 (13.3%)	17
Blood And Lymphatic System Disorders – Other	3 (8.8%)	7	3 (10.7%)	16	1 (7.7%)	3	7 (9.3%)	26
Activated Partial Thromboplastin Time Prolonged	4 (11.8%)	12	2 (7.1%)	6	0 (0.0%)	0	6 (8.0%)	18
Skin And Subcutaneous Tissue Disorders – Other	1 (2.9%)	1	4 (14.3%)	5	1 (7.7%)	1	6 (8.0%)	7
Bone Pain	2 (5.9%)	2	2 (7.1%)	3	1 (7.7%)	6	5 (6.7%)	11
Creatinine Increased	3 (8.8%)	8	2 (7.1%)	2	0 (0.0%)	0	5 (6.7%)	10
Rhinitis Infective	1 (2.9%)	1	1 (3.6%)	1	3 (23.1%)	7	5 (6.7%)	9
Headache	3 (8.8%)	4	1 (3.6%)	1	1 (7.7%)	3	5 (6.7%)	8
GGT Increased	1 (2.9%)	1	4 (14.3%)	4	0 (0.0%)	0	5 (6.7%)	5
Metabolism And Nutrition Disorders – Other	2 (5.9%)	7	2 (7.1%)	25	0 (0.0%)	0	4 (5.3%)	32

Table 55. Incidence of severe AEs (grade 3-5) > 5% displayed by PT and treatment groups in the BEACON-CHEMO study

	TMZ N= 34		TEMIRI N= 28		TOTEM N=13		Total N=75	
At least one severe AE (G3, G4, G5)	Patients n(%)	Events n	Patients n(%)	Events n	Patients n(%)	Events n	Patients n(%)	Events n
At least one severe AE (G3, G4, G5)	14 (41.2%)	53	15 (53.6%)	85	11 (84.6%)	134	40 (53.3%)	272
Neutrophil Count Decreased	5 (14.7%)	13	9 (32.1%)	19	6 (46.2%)	47	20 (26.7%)	79
Platelet Count Decreased	5 (14.7%)	5	6 (21.4%)	12	9 (69.2%)	50	20 (26.7%)	67
White Blood Cell Decreased	3 (8.8%)	3	4 (14.3%)	5	2 (15.4%)	6	9 (12.0%)	14
Lymphocyte Count Decreased	2 (5.9%)	4	4 (14.3%)	6	1 (7.7%)	3	7 (9.3%)	13
Anaemia	3 (8.8%)	3	1 (3.6%)	3	2 (15.4%)	11	6 (8.0%)	17
Alanine Aminotransferase Increased	2 (5.9%)	2	2 (7.1%)	7	0 (0.0%)	0	4 (5.3%)	9
Blood and Lymphatic System Disorders – Other Specify	1 (2.9%)	2	2 (7.1%)	3	1 (7.7%)	2	4 (5.3%)	7
Vomiting	1 (2.9%)	1	3 (10.7%)	4	0 (0.0%)	0	4 (5.3%)	5

ORP-TMZ-4 (RETROTMZ) study

Adverse events *per se* were not described. However, tolerance effects, including dose discontinuation, delays and modifications were reported in the study. Certain toxicities including secondary malignancies and deaths were described as well.

Published studies

Table 59 summarises the safety data of 8 peer-reviewed published clinical studies which assessed the efficacy of TMZ alone or in combination with Irinotecan or Topotecan in 261 patients with solid tumours, including 208 patients with relapsed or refractory neuroblastoma. Across these 8 studies, the 3 treatment regimens (TMZ, TEMIRI, and TOTEM) were considered to be well tolerated with manageable adverse reactions, with treatment cycles up to 24 courses. The most common grade 3-4 adverse reactions were thrombocytopenia, neutropenia, anaemia, diarrhoea and emesis. They resolved within 2 weeks either spontaneously or were easily managed with dose reductions, treatment delays.

Table 56. Grade 3-4 toxicities reported in the 8 studies evaluating the safety of TMZ, TEMIRI and TOTEM in relapsed or refractory neuroblastoma

	Regimen	Evaluable patient/no. courses	Haematological toxicities				Infections	Non-haematological toxicity
			THCP	NP	LP	A		
[Rubie *et al.* 2006]	TMZ	25 patients / 94 courses	16%	12%	NR	9%	2%	NR
[De Sio *et al.* 2006]	TMZ	52 patients (17 NB) / 252 courses	21%	NR	NR	NR	NR	NR
[Wagner *et al.* 2004]	TEMIRI	12 patients (2 NB) / 56 courses	4%	7%	NR	NR	NR	13%
[Kushner *et al.* 2006]	TEMIRI	49 patients	Myelosuppression was manageable and clinically insignificant				8%	2%
[Wagner *et al.* 2009]	TEMIRI	14 patients / 75 courses	14%	29%	NR	NR	7%	29%
[Bagatell *et al.* 2011]	TEMIRI	55 patients	13%	35%	NR	15%	22%	33%
[Rubie *et al.* 2010]	TOTEM	16 patients (8 NB) / 84 courses	69%	75%	NR	NR	NR	6%
[Di Giannatale *et al.* 2014]	TOTEM	38 patients / 213 courses	47%	62%	31%	18%	0%	10%

2.4.8.3. Serious adverse event/deaths/other significant events

ORP-TMZ-I-b - TEMOkids study

Table 57. Serious adverse events by SOC during the primary study period of **ORP-TMZ-I-b**

SOC	PT	During the primary study period (Cycle 1) (n=9)
Infections and infestations		3 (33.3)
	Bacterial sepsis / Catheter site infection	1 (33.3)
	Catheter site cellulitis / Cellulitis staphylococcal	1 (33.3)
	Staphylococcal infection / Catheter site infection	1 (33.3)
Blood and lymphatic system disorders		2 (22.2)
	Febrile neutropenia	2 (100.0)
Infections and infestations / General disorders and administration site conditions		2 (22.2)
	Otitis media / Pyrexia	1 (50.0)
	Respiratory syncytial virus infection / Disease progression	1 (50.0)
Gastrointestinal disorders		1 (11.1)
	Vomiting	1 (100.0)
Nervous system disorders		1 (11.1)
	Headache	1 (100.0)

BEACON CHEMO study

Table 58. Incidence of SAEs displayed by PT and treatment groups in BEACON-CHEMO

	TMZ (N=34)		TEMIRI (N=28)		TOTEM (N=13)		Total (N=75)	
	Patients	Events	Patients	Events	Patients	Events	Patients	Events
At least one SAE	n(%)	n	n(%)	n	n(%)	n	n(%)	n
Serious AEs	11 (32.4%)	26	10 (35.7%)	23	5 (38.5%)	26	26 (34.7%)	75
Serious Drug Related AEs	7 (20.6)	16	9 (32.1)	20	2 (15.4)	17	18 (24.0)	53
Fever	6 (17.6%)	7	1 (3.6%)	1	2 (15.4%)	3	9 (12.0%)	11
Vomiting	3 (8.8%)	4	5 (17.9%)	6	0 (0.0%)	0	8 (10.7%)	10
Abdominal Pain	1 (2.9%)	1	2 (7.1%)	2	1 (7.7%)	3	4 (5.3%)	6
Diarrhoea	1 (2.9%)	1	3 (10.7%)	4	0 (0.0%)	0	4 (5.3%)	5
Febrile Neutropenia	2 (5.9%)	2	0 (0.0%)	0	1 (7.7%)	2	3 (4.0%)	4
Headache	2 (5.9%)	2	0 (0.0%)	0	1 (7.7%)	2	3 (4.0%)	4
Infections And Infestations – Other Specify	0 (0.0%)	0	2 (7.1%)	2	1 (7.7%)	1	3 (4.0%)	3
Lethargy	2 (5.9%)	2	0 (0.0%)	0	0 (0.0%)	0	2 (2.7%)	2
Catheter Related Infection	1 (2.9%)	1	1 (3.6%)	1	0 (0.0%)	0	2 (2.7%)	2
Back Pain	0 (0.0%)	0	1 (3.6%)	1	1 (7.7%)	2	2 (2.7%)	3

+

RETROTMZ study

No SAEs were provided within the documentation of the RETROTMZ study. The main cause of death was the disease itself. More deaths occurred in relapsed patients (105/129 (81.4%) compared to refractory patients (37/67 (55.2%).

2.4.8.4. Laboratory findings

No further details regarding the haematological changes or chemistry abnormalities were provided.

2.4.8.5. Safety in special populations

Age

In the *TEMOkids study*, the highest AE/patient ratio (non-SAE) was observed in the 12-17 years age group (r=4), followed by the 4-11 years age group (r=3.88), and the 1-3 years age group (r=3). Alternatively, the highest SAE/patient ratio was in the 1-3 years age group (r=0.46), followed by the 4-11 years age group (r=0.13). Specifically relating to the type of AE, all three age groups reported blood and lymphatic system disorders and gastrointestinal disorders as the main types of AE, whilst infections and infestations were more frequent in the 1-3 years age group, and general disorders and investigations in the 4-11 age group.

In the *BEACON CHEMO study*, in the TMZ monotherapy group, the incidence of the AEs by SOC was slightly higher in the children below 4 years of age compared to the children above 4 years of age. However, number of AEs/ severe AEs by patient was similar in the patients below 4 years (12.2 AE/patient / 2.0 severe AE/patient) as in the patients above 4 years (13.2 AE/patient / 1.4 severe AE/patient). In the TEMIRI group, the incidence of the AEs by SOC was similar in the children below 4 years of age compared to the children above 4 years of age. The number of AEs / severe AEs by child was slightly lower in the patients below 4 years (20.2 AE/patient / 2.3 severe AE/patient) than in the

patients above 4 years (28.3 AE/patient / 3.5 severe AE/patient). Of note, the populations of the subgroups (age categories, dose regimes) are very small and therefore results should be interpreted with caution.

Disease indication

With regard to the data presented in the CSRs of the *BEACON CHEMO and the RETROTMZ studies*, the safety profile of the active substance temozolomide seems to be the same in children with relapsed neuroblastoma and in children with refractory neuroblastoma. Of note, again the populations of the subgroups (disease indication, dose regimes) are very small. Thus, the results presented have to be interpreted with caution.

No specific safety assessment by the refractory or relapsed neuroblastoma was provided within the data submitted for the *TEMOkids study* and the data discussed within the *literature research*.

2.4.8.6. Immunological events

Not applicable.

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

No new studies have been conducted to determine the effect of Ped-TMZ on the metabolism or elimination of other drugs, including Topotecan or Irinotecan. However, since TMZ does not require hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products. The proposed draft SmPC contains the same information as for the reference product Temodal.

2.4.8.8. Discontinuation/cycle delay/dose reduction due to adverse events

In the *BEACON CHEMO study* cycle delays were seen in about 30% of the pts., dose reductions in 15%.

In the *published studies* the following information regarding cycle delays and dose reduction were reported:

- Rubie et al. 2006: cycle delay due to thrombocytopenia 24%, dose reduction 21% (10pts.)

- Di Giannatale et al. 2006: cycle delay 17% (20 pts.), dose reduction 16% (haematotoxicity)

- Kushner et al. 2014: no information regarding cycle delays and dose reduction is provided.

The following incidences of toxicity-related delays and dose reductions were reported within the results of the *RETROTMZ study*:

- 8.6% of cycles were delayed for toxicity with TMZ monotherapy, 9.6% (62/645) for TOTEM and 13.9% (43/309) for TEMIRI.

- For 1 % of cycles with TMZ monotherapy a dose reduction was reported and in 14% of cycles for TOTEM and 34% of cycles for TEMIRI.

From the *TEMOkids study,* only safety data from the first Cycle was provided within this submission. Thus, no delays of further cycles were reported. There were seven instances of actions involving Kizfizo to resolve an AE (Kizfizo interrupted, withdrawn, or dose rate reduced).

2.4.8.9. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.9. Discussion on clinical safety

The safety profile of TMZ is well documented. As Ped-TMZ has been shown to be bioequivalent to Temodal (Study ORP-TMZ-I-a), its safety profile (when given in monotherapy) is well characterised by the available clinical safety data with Temodal in the approved adult and paediatric indications in clinical trials and from post-marketing use with TMZ drug products since 1999.

While the number of subjects exposed to temozolomide in the target population (Neuroblastoma) is substantial, the evaluation of the safety profile, particular of the new formulation (Ped-TMZ), is hampered due to the uncontrolled nature of the study data, the heterogeneity of the underlying conditions of the patients to be treated and the mainly retrospective nature of the data analysis.

Clinical safety data was collected to include standard reporting of AEs, SAEs, vital signs, ECGs and laboratory data in clinical trials. In addition, a broad literature research was performed.

The primary focus of the safety analysis of the *new formulation of temozolomide* was based on the results from *Study ORP-TMZ-I-b* (TEMOkids, n=43, pts. with neuroblastoma n=20). However, it should be noted that the treatment regimen was up to the investigator's decision according to the more suitable recommendation for the patient. Thus, various treatment combinations were administered, making evaluation difficult.

Of note, due to required dose reductions, the actual dose received by the patients as well in the first cycle as in the optional extension treatment period was slightly lower than the intended dosage.

Overall, 40 (93%) patients experienced adverse events during the primary study period (Cycle 1), treatment-related adverse events were observed in 29 (67.4%) patients, serious adverse events in 7 (16.3%) patients. Moreover, one (2.3%) patient experienced an adverse event of special interest (AESI). The most common adverse event related to the new formulation Ped-TMZ and recorded during the primary study period of the TEMOkids study, were vomiting, which occurred 18 times (18.4%), neutropenia and thrombocytopenia (7.1%), diarrhoea (6.1%). Abdominal pain, anaemia, lymphopenia, and a decrease in white blood cell count occurred five times (5.1%), each. SAEs were within SOCs "infections and infestations" (3 SAEs of catheter site infection), "blood and lymphatic system disorders" (2 febrile neutropenia), "infection and infestation/ general disorders and administration site conditions" (1 otitis media/pyrexia and 1 respiratory syncytial virus infection/disease progression), "gastrointestinal disorders" (1 vomiting) and "nervous system disorders" (1 headache).

Of note, the tolerability within the first cycle seems to be better than the tolerability in the subsequent cycles: The overall incidence of treatment related AEs during the first cycle vs the subsequent cycles was 72.1% vs 81.3%. The incidence of SAEs (regardless the relatedness) during the first cycle vs the subsequent cycles was 16.3 % vs 21.9%. In summary, no concerns can be raised. No deaths were reported during the primary study period of the study.

In addition, treatment related SAEs were more frequent in relapsed population (60.0%) than in refractory population (37.5%). However, the very small number of patients precludes from any definitive conclusion.

Uncertainties remain particularly with regard to the safety profile in the youngest intended population. It is acknowledged that the sample size of the younger population (1-2 years) in TEMOkids was very limited (9 patients). However, 55.6% of patients <3 years vs 5.9% of patients ≥ 3 years experienced a SAE during the primary study period. During the optional treatment extension phase, SAEs were

more balanced between both populations, i.e. 11.1% in patients < 3 years and 17.6% in patients'≥ 3 years. As TEMOkids is currently the only study with the intended Ped-TMZ formulation a warning of close monitoring addressing these issues has been considered necessary.

Five patients reported an adverse events of special interest (AESI). All of them occurred during the optional treatment extension phase. Further pertaining to AESI and therefore to the buccal tolerance of Ped-TMZ formulation, a total of six events were recorded in five patients treated by Ped-TMZ formulation in combination with other anti-cancer drugs. Overall, all AESI were graded 1-2 on the CTCAE scale, occurred within periods of 0 to 40 days after the latest Ped-TMZ formulation intake, and with three AESI being related or possibly related to Ped-TMZ formulation (mucosal inflammation). Upper gastro-intestinal toxicity should be closely monitored.

Laboratory values and changes in clinical characteristics were analysed with respect to the mean change in value from baseline to predefined time-points (inclusion, end of primary study period, end of optional treatment extension phase when applicable). In summary, most laboratory chemistry parameters remained stable throughout the study. Of note, with regard to the haematological parameters notable changes were seen in the frame of the known haematotoxicity particular in the combination with Topotecan.

With regard to the vital signs, the great majority of patients displayed normal pulse rate and normal temperature throughout the examined periods (≥ 96%).

Lansky PS scores in TEMOKIDS study were consistent with results of RETROTMZ study, i.e., most of the patients had a score of 80-100% at inclusion visit and at the end of treatment.

Regarding the safety profile of the *known formulation of temozolomide in the target population*, the focus was based on the results of the *BEACON CHEMO study*. With regard to the data provided within the initial submission, 75 paediatric patients were exposed to temozolomide in monotherapy (TMZ, 34 patients), or in combination with irinotecan (TEMIRI, 28 patients) or topotecan (TOTEM, 13 patients). The median duration of treatment was similar in TMZ (3.0 cycles) and TEMIRI (4.0 cycles) groups and twice longer in TOTEM group (6.0 cycles), suggesting that additional toxicity from irinotecan did not lead to an increase in discontinuations. Nevertheless, the low number of patients in each group, particularly in TOTEM, limit the possibility to draw any firm conclusion.

Dose density was overall consistent with the planned doses in each group. To be noted that temozolomide in TMZ group was administered at a dose higher during cycle 1 in BEACON CHEMO (200mg/m²) than in Ped-TMZ recommended posology (150 mg/m² at the first cycle then 200mg/m² for subsequent cycles in absence of significant toxicity).

The safety population included all 75 paediatric patients who received at least one dose of study treatment. In this population, 90% of patients had an AE. As expected the incidence of AEs were lower in TMZ arm than in the TEMIRI and TOTEM arms. The safety profile of the TMZ mono therapy in the targeted population was comparable to the known safety profile of temozolomide in the approved indications. In the TEMIRI group, diarrhoea and vomiting were the most 2 frequent AEs (64.3% and 53.6% respectively). Thrombocytopenia and neutrocytopenia had the highest incidences in the TOTEM group (69.2% and 53.8% respectively). Incidence of severe (grade 3-5) AEs by SOC showed that severe AEs were more frequent in TOTEM group (84.6%) than in TMZ (41.2%) and TEMIRI (53.6%) groups. This likely reflects the highest incidence of AEs within SOC "investigations" in TOTEM group compared to TMZ and TEMIRI. The most frequent severe AEs by SOC were within the most frequent AEs by SOC (i.e. investigations, Blood and Lymphatic System disorders, infections and infestations), with the exception of "Gastrointestinal disorders". Most frequent severe AEs by PT were related to myelotoxicity (neutrophil count decreased, platelet count decreased, white blood cell decreased, lymphocyte count decreased, and anaemia).

The incidence of AEs were lower in TMZ arm than in the TEMIRI and TOTEM arms. The safety profile of the TMZ mono therapy in the targeted population was comparable to the known safety profile of Temodal in the approved indications. In the TEMIRI group, diarrhoea and vomiting were the most two frequent AEs (64.3% and 53.6% respectively). Thrombopenia and Neutropenia had the highest incidences in the TOTEM group (69.2% and 53.8% respectively). Of note, the entire population in the BEACON sub study is acceptable (n=75). However, the subpopulation are rather small (TMZ mono n=34, TEMIRI n=28, TOTEM n=13)

Overall, the most frequent AEs were consistent with the known safety profile of temozolomide, Irinotecan and Topotecan as from their respective SmPC.

In particular with regard to the updated data, the safety profile was similar in patients with relapsed and refractory neuroblastoma. Differences may be observed although the low number of patients precludes from any definitive conclusion. The incidence of AEs was lower in the relapsed patients group (90.6%), compared to the refractory patients group (97.0%), the proportion of patients with at least 1 severe AE (CTCAE grade ≥3) was lower in the relapsed patients group (54.7%) compared to the refractory patients group (69.7%). Overall, the incidence of SAEs was higher in the relapsed subgroup (45.3%) compared to in the refractory subgroup (36.4%). Finally, the incidence of drug-related SAEs was similar in the subgroups: 31.3% in the relapsed subgroup 30.3% in the refractory subgroup.

As expected more patients in the refractory population (approx. 50%) were still alive at their last follow-up whereas 87% of the relapsed patients had died. In the ITT population, 72.5% of the patients died, of which 96.6% from neuroblastoma and 2 patients from other causes. The two deaths related to another cause than neuroblastoma were related to a multisystem failure in the context of a metastasised neoplastic process and to an IL-2 related AE.

In summary, there was no obvious age effect and the subgroup analysis in children aged <3 years and ≥ 3 years did not identify any new safety signal in any age category.

Cycle delays were seen in about 30% of the patients, dose reductions in 15%. Of note, no detailed information regarding the cause of the delay (toxicity, familiar reasons etc.) was provided. More than a third of cycles were delayed for TMZ monotherapy and more than half of cycles were delayed in TOTEM group, while only 16.7% of cycles were delayed in TEMIRI. Dose modifications were mainly observed in the second cycle and especially in the monotherapy group and it seemed due to the higher dose of temozolomide in monotherapy compared to the approved dosing recommendation. In any case, dose modifications clearly occurred for toxicity.

In summary, it has to be noted that the populations of the subgroups looked at (age, disease indication, dose regimens) were very small. Thus, the results presented have to be considered with caution.

The applicant also provided a *broad literature research*. However, as only the dose regimens used in the studies published by Rubie et al., 2006 (n=25), Kushner et al., 2006 (n=49) and Di Giannatale et al., 2014 (n=38) are comparable with those used in the BEACON CHEMO study respectively intended for the marketing authorisation of the new formulation, the focus was laid on these publications. In summary, the safety profile is mainly comparable with the one observed in the BEACON study. Of note, the populations in the published studies are heterogeneous and small. Moreover, safety assessment from literature data is often limited and less precise; reporting bias cannot be sufficiently excluded from such source of information provided in publications. Thus, these results should be considered with caution.

The safety data from the *retrospective study ORP-TMZ-4* (RETROTMZ, TMZ mono n=59, TEMIRI n=39, TOTEMn=81)) is very limited as well (e.g. no AEs/SAEs were recorded). It seems that most of the patients received a dose >100-150 mg/m²/day and almost a third of the patients received a low dose

of TMZ (<100 mg/m²/day). Considering that the dose of TMZ varied according to the protocol used, the provided data are difficult to interpret.

The majority of patients had a Lansky/Karnofsky PS 80-100% score at baseline. Of note, at 6 months and at the end of treatment, the majority of patients still had an 80-100% score.

In addition, the population included was very heterogeneous and the subpopulations discussed (age groups, disease indication (refractory vs relapsed), dose regimens administered (monotherapy vs. combination therapy)), were very small. Thus, in summary, the assessment of the RETROTMZ study was significantly hampered. However, the results are mostly comparable with those of the BEACON study.

In summary, the following incidences of toxicity-related delays and dose reductions were reported:

- 8.6% of cycles were delayed for toxicity with TMZ monotherapy, 9.6% (62/645) for TOTEM and 13.9% (43/309) for TEMIRI.

- For 1 % of cycles with TMZ monotherapy a dose reduction was reported and in 14% of cycles for TOTEM and 34% of cycles for TEMIRI.

As expected, more deaths occurred in relapsed patients (105/129 (81.4%)) compared to refractory patients (37/67 (55.2%)). However, 4 patients died from an unknown cause. In addition, one patient died from complications related to the high dose chemotherapy during intensification/consolidation phase, one patient died from a fall resulting in subdural haemorrhage and one patient died from sepsis in an immunocompromised patient with progressive disease in the palliative phase of treatment.

In RETROTMZ, no difference was observed between the different classes of age (<3.0 years and ≥3.0 years) for treatment discontinuation. The main reason for discontinuation was progression (at least 50% in each age category) or end of course (around 30% in each cage category).

There were more delayed cycles in the younger population, but frequency of delayed cycles for toxicity was equivalent in all age category. Overall, there was no sign of a worse tolerance in younger patients (<3 years old) than in other age groups. The percentage of patients < 3 years and ≥ 3 years with dose modifications was similar, 17.4% (4/23) and 19.8% (32/162) respectively, but the limited number of patients below 3 years does not allow to draw definitive conclusions.

The data from the *French Early Access Program* (EA n=24) and the *Compassionate Use Program* (CUP, n=37) were limited. The submitted reports of both programmes cover periods until the beginning of 2024. In summary, the pharmacovigilance data reported so far is not leading to a change in the safety profile. In particular, only the EA program is aimed at patients with neuroblastoma, whereas CU program mainly includes patients with other tumours. In addition, only the dose regimens of the EA program are based on those sought by the applicant for approval.

The recommended dose regimens and dose adjustments of Kizfizo as monotherapy are based on the dosing protocols of temozolomide monotherapy in other oncology indications for which temozolomide has been already approved. Nevertheless, this is no more relevant as the latest proposed indication by the applicant does not include the use of temozolomide as monotherapy.

The recommended dose regimens and dose adjustments of Kizfizo in combination with Irinotecan or Topotecan are based on those standardised in the BEACON-CHEMO trial.

In summary, no new specific safety concern across age range was identified during clinical trials. The known safety risk for Temodal include "Gastrointestinal disorders" and myelotoxicity (neutrophil count decreased, platelet count decreased, white blood cell decreased, lymphocyte count decreased, and anaemia). However, as there is globally limited clinical experience with temozolomide in the youngest

children (1-2 years), a particular attention should be paid to this subpopulation due to the limited overall treatment exposure.

No new studies have been conducted to determine the effect of Ped-TMZ on the metabolism or elimination of other drugs, including Topotecan or Irinotecan. However, since TMZ does not require hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products.

2.4.10. Conclusions on clinical safety

Overall, considering the known safety profile of the approved TMZ, the safety profile of Ped-TMZ monotherapy as well as of the intended dose combinations (with Irinotecan and Topotecan) in the targeted paediatric population appears to be acceptable and manageable. However, the evaluation of the safety profile of Ped-TMZ in the targeted paediatric population is significantly hampered by the poor quality of the documentation considering the scarcity of the submitted data, the absence of controlled trials and the mainly retrospective nature of the data analysis.

Uncertainties remain particularly with regard to the safety profile in the youngest intended population as only 9 patients < 3 years received the intended formulation Ped-TMZ. Furthermore, Irinotecan and Topotecan are not authorised in the intended indication but for cancers occurring mainly in the adult population providing limited data on the safety of the combinations.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns

The applicant identified the following safety concerns in the RMP (latest version in the procedure: 0.3):

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Medication errors
Missing information	None

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Plans for post-authorisation efficacy studies

No post authorisation efficacy studies were proposed by the applicant.

2.5.4. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Medication errors	**Routine risk minimisation measures:** SmPC sections 4.2 where Method of administration, Dosing conversion tables are specified./caregivers SmPC sections 4.4, 4.6, 4.9 SmPC section 6.6 where special precautions for handling are given PL sections 2 and 3 where pictured instructions on how to prepare and take a dose of Kizfizo are given Labelling Pack size Legal status: restricted medicinal prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities: adverse reactions (including special situations such as medication error, …) reporting and signal detection : Specific adverse reaction follow up questionnaires Additional pharmacovigilance activities: None

2.5.5. Conclusion

The CHMP and PRAC, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan (latest version: 0.3) cannot be agreed at this stage.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. Periodic Safety Update Reports submission requirements

In light of the negative recommendation, the requirements for the Periodic Safety Update Reports submission are not applicable at this point in time.

2.7. Product information

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

2.7.1. User consultation

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

2.7.2. Additional monitoring

Not applicable

3. Benefit-risk balance

3.1. Therapeutic Context

This application concerns a hybrid version of temozolomide (oral suspension). The reference product Temodal is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment and for the treatment of children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy. From a clinical perspective, this application does contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance.

3.1.1. Disease or condition

The last applied indication was:

"Kizfizo in combination with irinotecan or topotecan is indicated for the treatment of paediatric patients aged 12 months and above with:

- refractory high-risk neuroblastoma as second line chemotherapy after insufficient response to induction chemotherapy, to proceed to consolidation,

- actively progressing recurrent high-risk neuroblastoma after at least partial response to induction chemotherapy followed by myeloablative therapy and stem cell transplantation (See section 5.1 for the definition of high-risk neuroblastoma)."

3.1.2. Available therapies and unmet medical need

Therapy for neuroblastoma is stage and risk stratified. The therapeutic modalities include surgery, chemotherapy, radiotherapy and biotherapy; observation-only is undertaken in a few very low-risk patients.

The management of neuroblastoma takes into consideration the risk stratification-based therapeutic modalities in accordance with the 2009 International Neuroblastoma Risk Group (INRG) Consensus Pre-treatment Classification Scheme. Treatment is based on 4 defined risk groups (very low risk, low risk, intermediate risk and high risk).

Up to 30% of the high-risk neuroblastoma patients are refractory to induction chemotherapy, therefore requiring further chemotherapy. Furthermore, half of the high-risk patients that initially respond to chemotherapy experience relapse within 3 years with a dismal prognosis.

High-risk patients treated according to the current SIOPEN HR-NBL2 protocol and who achieve insufficient response (PR<50% or SIOPEN score >3) after induction chemotherapy (i.e., refractory patients) receive 3 courses of TEMIRI as second line chemotherapy according to the HR-NBL2 amendment.

There are no uniform guidelines to direct the therapy of patients with recurrent neuroblastoma. Historically, recurrent neuroblastoma has been treated with a combination of chemotherapy and radiotherapy for the purposes of palliation only. In more recent times, treatment has evolved comprising salvage chemotherapy, radiotherapy and surgery, and 131I-MIBG therapy, and dinutuximab with interleukin-2 (IL-2) (De Sio et al, 2006; Rubic et al, 2006; Wagner et al, 2004; Kushner et al, 2006; Wagner et al, 2009; Bagatell et al, 2011; Rubie et al, 2010, Di Giannatale et al, 2014; Simon et al, 2007).

Second line chemotherapies with mild to modest toxicities that have not been included in frontline treatment are often considered for salvage. For the majority of patients with relapsed HR-NBL, initial treatment will comprise reinduction chemotherapy typically based around combinations of topotecan or irinotecan, with temozolomide or cyclophosphamide (Morgenstern et al, 2021).

Off-label use of TMZ in patients with neuroblastoma is currently based on oral TMZ-containing drug products, which are commercially available in the form of hard capsules.

Long-term survival after relapse of high-risk neuroblastoma is uncommon and although therapy may be able to prolong survival, careful consideration needs to be given to the individual needs of patients, balancing toxicity and burden of therapy with likelihood of benefit.

3.1.3. Main clinical studies

The main efficacy data come from a BEACON-CHEMO study, a sub-study of the BEACON Phase II randomised, open label, multinational study investigating the activity of several TMZ regimens in paediatric relapsed or refractory neuroblastoma patients (N=80); and ORP-TMZ-4 study (Retro TMZ), an international, multicentre retrospective study evaluating the use of TMZ in paediatric refractory or relapsed neuroblastoma (N=196).

In BEACON-CHEMO study the primary endpoint was Best Overall Response Rate (ORR, defined as Complete Response or Partial Response) at any time during the first 6 cycles of trial treatment. RECIST 1.1 criteria were used to evaluate response in patients with measurable tumours. Secondary endpoints included ORR at 2 cycles, PSF, EFS, OS and duration of response.

The primary endpoint of RetroTMZ study was to describe the population treated with TMZ and evaluate the time taken from start of first TMZ to first progression (time-to-progression [TTP]). Secondary endpoints included response rates (best response and response at 2 cycles), PSF and OS.

3.2. Favourable effects

The most important favourable effect is the Best ORR in overall population, in relapsed patients and in refractory patients in the BEACON-CHEMO study.

The ORR at best response in the total EVA population (updated analysis of all 3 temozolomide arms) was 19.4% (95% CI: 12.6%-28.5%). It was 18.0% (95% CI: 10.4%-29.5%) and 21.9% (95% CI: 11.0%; 38.8%) in the subgroup of patients with relapsed and refractory disease, respectively. The median duration of response was 15.6 months (95% CI: 8.6–37.3) in the 16 patients with response. It was 9.3 months (95% CI: 2.0 - 17.7) in relapsed and not evaluable (11.7- not evaluable) in the refractory neuroblastoma.

Excluding the monotherapy arm from the analysis, the ORR according to the best response (ITT population) remains in the same range, for overall population 20.6% (95% CI: 12.5%; 32.2%) for relapsed patients 20.0% (95% CI: 12.5%; 32.2%), and for refractory patients 22.2% (95% CI: 9.0%; 45.2%).

The rate of stable disease (SD), which could allow access to consolidation for patients with refractory disease is 66.7% [43.7%;83.7%], and to complementary treatment modalities in the relapsed disease setting (e.g. anti-GD2 antibody dinutuximab beta) is 62.2% [47.6%;74.9%].

In RetroTMZ study, the median (95% CI) TTP from the first dose of TMZ was 5.8 months (3.8–8.1) for the overall population, 13.7 months (4.8-18.7) for refractory patients and 4.7 months (3.4-6.6) for relapsed patients. In the overall population, ORR after 2 cycles was 36.3%. DCR after 2 cycles of therapy was 79.0%. Best ORR was 48.3% and the best DCR was 78.8%.

3.3. Uncertainties and limitations about favourable effects

The current available efficacy data are not considered comprehensive and robustness may be challenged due to potential baseline imbalances from the variable disease course, the small number of subjects included, the missing control and the post hoc analysis approach.

The main evidence for efficacy of temozolomide as monotherapy or in combination with irinotecan/topotecan in the targeted population comes from the BEACON-CHEMO study, a sub-study of BEACON neuroblastoma Phase II study investigating the activity of three TMZ regimens. However, the low level of activity observed in addition to the absence of a control arm without TMZ, limits the possibility to conclude on a clinical benefit of TMZ.

The clinical activity of temozolomide (in combination with irinotecan and topotecan) in the treatment of the relapsed neuroblastoma reported in the exploratory data of the BEACON-CHEMO trial is considered modest (20.0% [10.9%;33.8%] and no clinical benefit can be established in this patient population. The comparison to external control groups can be considered as supportive data at best, but cannot establish pivotal evidence of efficacy/clinical benefit in the claimed indication. This is because of the general inability to control bias for external control groups, and the specific concerns with regard to patient selection and analysis.

As with relapsed patients, the best response rate for refractory patients receiving temozolomide in combination with irinotecan or topotecan is also considered modest (ORR 22.2% [9.0%;45.2%]). Despite the fact that about half of the refractory patients proceeded to consolidation therapy in the BEACON-CHEMO study, and in the post-hoc analysis of data, 2/3 of the refractory patients were considered eligible to proceed to consolidation therapy (i.e. all the patients with stabilised disease), the modest clinical activity is not sufficiently robust to establish the clinical benefit of Kizfizo.

Time to event endpoint (OS and PFS) are uninterpretable without a control arm. Although the majority of patients were followed for 5 years, this alone does not make the data robust. The sample size is far too small for any robust conclusions. All comparative efficacy analyses between treatment arms are considered purely descriptive with limitations due to the post-hoc nature of the BEACON-CHEMO study.

Due to the retrospective nature of the study, the results of the RetroTMZ study are hampered by progression or response not being systematically assessed using standardised criteria and follow-up times. Even if clinical practice with regard to treatment did not change in the centres, it is unclear whether there were differences within and between centres with regard to progression assessment. All analyses were descriptive. No statistical hypothesis was tested. No comparison to a control group was made. Therefore, no causal interpretation is possible for time to event endpoints, i.e. it is not possible to conclude whether treatment prolonged time to event, as it is unknown what would have been the

outcome without treatment (or alternative relevant control treatment). Response endpoints may theoretically isolate treatment effects compared to no treatment, as response can usually not occur without treatment. However, practically, it is unclear whether responses could also be falsely claimed due to measurement errors, or occur due to carry-over effect of previous treatments. Considering the limitations of the time to event endpoints in the non-randomised/uncontrolled settings, it is hard to interpret the primary endpoint of the RetroTMZ study.

Almost one-fourth of patients had no formal evaluation and most of them stopped treatment for either progression (30/45) or death (7/45). For further 8 patients no information is provided. Of note, response to the therapy besides CR and PR also included maintained CR/PR i.e. patients with response prior to initiation of TMZ-based chemotherapy (e.g. following radiotherapy), that continues during treatment.

In the overall population, ORR after 2 cycles was 36.3%. DCR after 2 cycles of therapy was 79.0%. Best ORR was 48.3% and the best DCR was 78.8%. However, these rates are based on evaluable patients (those with formal evaluation); non-evaluable patients may have less favourable outcomes (as most stopped because of progression or death).

3.4. Unfavourable effects

As the new formulation Ped-TMZ has been shown to be bioequivalent to Temodal in Study ORP-TMZ-I-a, its safety profile (when given in monotherapy) is in principle well characterised by the available clinical safety data with Temodal in the approved adult and paediatric indications in clinical trials and from post-marketing use with TMZ drug products since 1999. The known safety risk of Temodal include, but are not limited to "Gastrointestinal disorders" and myelotoxicity (neutrophil count decreased, platelet count decreased, white blood cell decreased, lymphocyte count decreased, and anaemia).

The most common adverse events related to the *new formulation Ped-TMZ* and recorded during the primary study period of the *TEMOkids study*, were vomiting, which occurred 18 times (18.4%), neutropenia and thrombocytopenia (7.1%), diarrhoea (6.1%). Abdominal pain, anaemia, lymphopenia, and a decrease in white blood cell count occurred five times (5.1%), each.

Of note, 55.6% of patients <3 years vs 5.9% of patients ≥ 3 years experienced a SAE during the primary study period. During the optional treatment extension phase, SAEs were more balanced between both populations, i.e.. 11.1% in patients < 3 years and 17.6% in patients' ≥ 3 years.

Treatment related SAEs were more frequent in relapsed population (60.0%) than in refractory population (37.5%).

Of note, 6 adverse events of special interest (AESI =oral inflammation and ulceration such as mucositis) were reported.

As shown in the results of the *BEACON CHEMO study*, the safety profile of the *Temozolomide therapy in the targeted population respectively indication* was comparable to the known safety profile of Temozolomide in the approved paediatric indications. In the TEMIRI group, diarrhoea and vomiting were the most frequent AEs (64.3% and 53.6% respectively). Thrombopenia and Neutropenia had the highest incidences in the TOTEM group (69.2% and 53.8% respectively).

As expected more patients in the refractory population (approx. 50%) were still alive at their last follow-up whereas 87% of the relapsed patients had died.

There was no obvious age effect and the subgroup analysis in children aged < 3 years and ≥ 3 years did not identify any safety signal in any age category. Cycle delays were seen in about 30% of the pts., dose reductions in 15%.

The safety profile according to the *literature data* is comparable with that observed in the BEACON study.

The results provided with regard of the *RETROTMZ study* are mostly comparable with those of the BEACON study as well. In summary, the following incidences of toxicity-related delays and dose reductions were reported:

- 8.6% of cycles were delayed for toxicity with TMZ monotherapy, 9.6% (62/645) for TOTEM and 13.9% (43/309) for TEMIRI.

- For 1 % of cycles with TMZ monotherapy a dose reduction was reported and in 14% of cycles for TOTEM and 34% of cycles for TEMIRI.

3.5. Uncertainties and limitations about unfavourable effects

The evaluation of the safety profile of *the new formulation* (Ped-TMZ), is significantly hampered due to the uncontrolled nature and the scarcity of the study data, the heterogeneity of the underlying conditions of the patients to be treated and the mainly retrospective nature of the data analysis.

With regard to the *TEMOkids study*, the subpopulations looked at (age, neuroblastoma status, treatment group, grades) are rather small and no scientific meaningful conclusion regarding the safety profile can be drawn. Thus, uncertainties remain particular with regard to the safety profile in the youngest intended population.

Despite an acceptable number of subjects exposed to *temozolomide in the target population* (in the frame of *the BEACON CHEMO study and the published studies*) the populations of the several subgroups (age, disease indication, dose regimens) are considered small. Thus, the results presented in such subbgroups have to be considered with caution.

The safety data from the *retrospective study ORP-TMZ-4* (RETROTMZ) is very limited and less reliable (e.g., no AEs/SAEs were recorded) due to heterogeneity and the small size of the analysed subgroups . Thus, in summary, the assessment of the RETROTMZ study does not add significant information regarding safety.

Similarly, the information provided by the *French Early Access Program* and the *Compassionate Use Program* is very limited.

Overall, no new specific safety concern across age range was identified during clinical trials. However, as there is globally limited clinical experience with temozolomide in the youngest children (1-2 years), special attention is to be given in order to take into consideration that close monitoring on safety should be taken in this subpopulation due to the limited overall treatment exposure.

3.6. Effects Table

Table 59. Effects table for Kizfizo

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Best ORR of combined IT and TTo arms	CR or PR at any time during the first 6 cycles of trial treatment	% (95% CI)	20.6% [12.5%;32.2%] 20.0% [10.9%;33.8%] 22.2% [9.0%;45.2%]	None	No control, total ITT population (n=63) Relapsed patients, ITT population (n=45) Refractory patients, ITT population (n=18)	BEACON CHEMO - FINAL ANALYSIS TFL _v3.0_06SEP2024
DoR in combined Arm IT and Arm TTO	Time (in months) from the date of the first initial occurrence of a CR or PR to the PFS event or censoring date.	Months (95%CI)	11.7 (6.4–37.3) 9.3 (1.8-NE*) NE* (11.7-NE*)	None	No control, ITT population in Arm IT and Arm TTO (N=63) Relapsed patients in Arm IT and Arm TTO (N=45), ITT population Refractory patients in Arm IT and Arm TTO (N=18), ITT population	BEACON CHEMO - FINAL ANALYSIS TFL _v3.0_06SEP2024
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Three main AEs by PT	Vomiting Diarrhoea Neutropenia / Thrombocytopenia	% % %	Cycle 1: 18,4 % Cycle1: 6,1 % Cycle1: 7,1 %	None	Data is limited. Subgroups looked at (i.e. age, neuroblastoma status) are very small	**TEMOkids**
	TEMIRI Vomiting Diarrhoea Neutropenia Thrombocytopenia *TOTEM* Vomiting Diarrhoea Neutropenia Thrombocytopenia	% % 	 53,6 % 64,3 % 42,9% 35,7 % 53,8 % 23,1 % 53,8 % 69,2 %	None None		**BEACON**
Cycle delay	 *TEMIRI* *TOTEM*	% % %	30 % 13,9 % 9,6 %	None	No information regarding the cause of the delay was provided Heterogeneous population, rather small subgroups (age, disease indication, dose regimens)	**BEACON** **RETROTMZ**
Dose reduction	 *TEMIRI* *TOTEM*	% % %	/15 % 34 % 14 %	None	 Heterogeneous population, rather small subgroups (age, disease indication, dose regimens)	**BEACON** **RETROTM**Z

**NE: Not Evaluable*

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

In the current application, due to the uncontrolled design of the studies submitted in this MAA, the time to event endpoints (i.e. TTP, PFS and OS) cannot be interpreted. As a consequence, ORR is the only endpoint that can be relied upon as it is considered a convincing measure of anti-tumour activity. Nevertheless, it is not considered to be an appropriate endpoint to measure clinical benefit.

ORR of 20.6% [95%CI: 12.5-32.2] for temozolomide regimens (TEMIRI and TOTEM) in the overall population of BEACON-CHEMO study and associated with two complete responses (in TOTEM arm) is not convincing nor outstanding as would be required for an uncontrolled clinical trial.

The exploratory data of the BEACON-CHEMO trial suggest only modest clinical activity of temozolomide (in combination with irinotecan and topotecan) in the treatment of the relapsed neuroblastoma (ORR 20.0% [10.9%;33.8%]) and the treatment benefit currently cannot be established in this patient population. Comparison to external control groups provided by the Applicant cannot establish pivotal evidence of efficacy/clinical benefit for the claimed indication but could at best be considered as supportive data. This is because of the general inability to control bias for external control groups, and the specific concerns with regard to patient selection and analysis.

As with relapsed patients, the best response rate for refractory patients receiving temozolomide in combination with irinotecan or topotecan is also considered modest (ORR 22.2% [9.0%;45.2%]). Despite the fact that about half of the refractory patients proceeded to consolidation therapy in the BEACON-CHEMO study, and in the post-hoc analysis of data, 2/3 of the refractory patients were considered eligible to proceed to consolidation therapy (i.e. all the patients with stabilized disease), the modest clinical activity is not sufficiently robust to establish the clinical benefit of Kizfizo.

Unfavourable effects

The evaluation of the safety profile, particular of *the new formulation* (Ped-TMZ), is significantly hampered due to the uncontrolled nature of the study data, the heterogeneity of the underlying conditions of the patients to be treated and the mainly retrospective nature of the data analysis.

However, as Ped-TMZ has been shown to be bioequivalent to Temodal in *Study ORP-TMZ-I-a*, its safety profile (when given in monotherapy) is in principle well characterised by the available clinical safety data with Temodal in the approved adult and paediatric indications in clinical trials and from post-marketing use with TMZ drug products since 1999.

The primary focus of the safety analysis of the *new formulation of temozolomide* was based on the results from *Study ORP-TMZ-I-b* (*TEMOkids study*). However, it should be noted that the treatment regimen was up to the investigator's decision according to the more suitable recommendation for the patient. Thus, various treatment combinations were administered, making evaluation difficult. The most common adverse events reported during the primary study period of the *TEMOkids study*, were vomiting, (18.4%), neutropenia and thrombocytopenia (7.1%), diarrhoea (6.1%). Abdominal pain, anaemia, lymphopenia and a decrease in white blood cell count occurred five times (5.1%), each.

Six adverse events of special interest (AESI =oral inflammation and ulceration such as mucositis) were reported. Overall, all AESI were graded 1-2 on the CTCAE scale, occurred within periods of 0 to 40 days after the latest Ped-TMZ formulation intake. Close monitor of upper gastro-intestinal toxicity is agreed as considered necessary.

As shown in the results of the *BEACON CHEMO study*, the safety profile of the *temozolomide therapy in the targeted population respective indication* was comparable to the known safety profile of temozolomide in the approved paediatric indications. In the TEMIRI group, diarrhoea and vomiting were the most frequent AEs (64.3% and 53.6% respectively). Thrombocytopenia and neutropenia had the highest incidences in the TOTEM group (69.2% and 53.8% respectively).

Overall, no new specific safety concern across the age range was identified in the clinical studies submitted for this MAA. As there is globally very limited clinical experience with temozolomide in the youngest children (1-2 years), a warning was added to the drafted SmPC, including the information that particular attention should be paid to this subpopulation due to the limited overall treatment exposure in the younger population

3.7.2. Balance of benefits and risks

The magnitude of patient benefit that is attributed to the temozolomide regimens cannot be determined at this point as there are no studies with a control arm in which patients were not treated with temozolomide.

The information from the non-randomised Phase II ad-hoc sub-study BEACON-CHEMO, the meta-analysis and the retrospective study ORP-TMZ-4 (RetroTMZ) was considered not sufficient due to the heterogeneity of data, the exploratory nature and the uncontrolled design of these studies that hampered a clear evaluation of the magnitude of the effect of both TMZ treatment regimens as assessed by best ORR, duration of response and time-to-event endpoints.

It is considered that ORR of 20.6% [95%CI: 12.5-32.2] for temozolomide regimens (TEMIRI and TOTEM) in the overall population of BEACON CHEMO study and associated with two complete responses (in TOTEM arm) is not convincing nor outstanding as would be required for an uncontrolled setting. Furthermore, evidence that this modest clinical activity is indicative of patient benefit (i.e. access to consolidation) has not been sufficiently demonstrated.

Despite the poor quality of the documentation and the scarcity of the data presented (which hamper the assessment significantly), the safety profile of Ped-TMZ as combination therapy (with irinotecan or topotecan) appears to be acceptable and manageable. The main risks include, among others, myelotoxicity and gastro-intestinal toxicity.

Overall, in absence of a clinically relevant benefit to outweigh the risks of Kizfizo, which include among others myelotoxicity and gastro-intestinal toxicity, the benefit-risk balance of Kizfizo (temozolomide) in the applied indication is negative.

3.7.3. Additional considerations on the benefit-risk balance

Marketing authorisation under exceptional circumstances

Since it is not possible to produce a fully comprehensive dataset on the clinical efficacy (and safety) in relapsed or refractory neuroblastoma under normal conditions of use of Kizfizo, the applicant considered the possibility to discuss a Marketing authorisation under exceptional circumstances, as mentioned by the applicant during the oral explanation in the last phase of the procedure without providing a justification that the criteria of MA under EC would be fulfilled.

However, the benefit-risk balance of Kizfizo as concluded by the CHMP based on the data submitted is considered negative and does not support the granting of a marketing authorisation for Kizfizo. Considering that a positive benefit-risk balance is an essential requirement for the granting of a

marketing authorisation under exceptional circumstances and that this requirement is not met in the case of Kizfizo, such type of authorisation was not further discussed.

3.8. Conclusions

The overall benefit /risk balance of Kizfizo is negative.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kizfizo is not similar to Qarziba within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Kizfizo in the proposed indication in combination with irinotecan or topotecan for the treatment of paediatric patients aged 12 months and above with:

- refractory high-risk neuroblastoma as second line chemotherapy after insufficient response to induction chemotherapy, to proceed to consolidation,

- actively progressing recurrent high-risk neuroblastoma after at least partial response to induction chemotherapy followed by myeloablative therapy and stem cell transplantation (see section 5.1 for the definition of high-risk neuroblastoma);

the CHMP considers by consensus that the efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and therefore, recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

- Efficacy results from the BEACON-CHEMO study (phase II uncontrolled study) and the Retro TMZ study (observational retrospective study) show only modest clinical activity of temozolomide in combination with irinotecan or topotecan in relapsed / refractory high-risk neuroblastoma patients. Evidence that this modest clinical activity is indicative of patient benefit (i.e. access to consolidation) is not sufficiently robust for firm conclusions. Furthermore, the impact of temozolomide on time-dependent endpoints cannot be ascertained based on the submitted studies.

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

5. Re-examination of the CHMP opinion of 27 February 2025

Following the CHMP conclusion that Kizfizo was not approvable considering that:

Efficacy results from the BEACON-CHEMO study (phase II uncontrolled study) and the Retro TMZ study (observational retrospective study) show only modest clinical activity of temozolomide in combination with irinotecan or topotecan in relapsed / refractory high-risk neuroblastoma patients. Evidence that this modest clinical activity is indicative of patient benefit (i.e. access to consolidation) is not sufficiently robust for firm conclusions. Furthermore, the impact of temozolomide on time-dependent endpoints cannot be ascertained based on the submitted studies.

the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the applicant

5.1.1. Ground #1.1: TMZ-based chemotherapy has meaningful clinical activity in the context of relapsed or refractory high-risk neuroblastoma

Applicant´s position on the first Ground for re-examination:

The Applicant respectfully believes that the natural course of the condition was not fully understood and has resulted in the CHMP making the following misinterpretations:

- choosing to evaluate Overall Response Rate (ORR) as the "only endpoint that can be relied upon" as a "convincing" measure of anti-tumour activity;
- mischaracterising the observed ORR treatment effect as "modest" and "not convincing" in the context of the condition; and
- failing to embrace disease stabilisation as a relevant and key endpoint for this indication.

The Applicant will therefore:

- explain the natural course of the disease to be treated;
- demonstrate that the ORR reflects meaningful clinical activity in this condition; and
- demonstrate that Disease Control Rate (DCR), including Stable Disease (SD), is a treatment effect and reflects large and meaningful clinical activity in the treatment of the condition.

Natural course of the condition

The natural course of the disease is discussed in detail in the Kizfizo MAA, in particular in the Clinical overview. To summarise, neuroblastoma is a tumour arising from the embryonal remnants of the sympathetic nervous system. Neuroblastoma is an extracranial solid tumour in childhood cancers. It is an orphan disease with an annual incidence rate of 1.8 cases per million [Gatta et al, 2012], i.e., approximately 900 new cases are diagnosed per year in the European Union (EU). About 90% of tumours arise in children below 5 years of age; the median age at diagnosis is 18 months [London et al, 2005 and 2011] and occurrence in adolescents and adults is unusual [Gatta et al, 2012].

The current management of neuroblastoma takes into consideration the risk-stratification-based-therapeutic modalities in accordance with the 2009 International Neuroblastoma Risk Group (INRG) Consensus Pre-treatment Classification Scheme [Cohn et al, 2009; Liang et al, 2020]. Treatment is based on 4 defined risk groups (very low risk, low risk, intermediate risk and high risk). Treatment of these four groups takes into account INRG stage, age, histologic category, grade of tumour differentiation, MYCN status, presence/absence of 11q aberrations, and tumour cell ploidy.

The high-risk neuroblastoma patients represent 40% of all newly diagnosed neuroblastomas and have the poorest prognosis. Up to 30% of the patients with high-risk neuroblastoma are refractory to induction chemotherapy, therefore requiring further chemotherapy [Ladenstein et al, 2010]. Furthermore, despite intensive multimodal treatment (chemotherapy, surgery, radiotherapy, autologous stem cell transplantation, and immunotherapy), half of the high-risk patients experience relapse within 3 years with a dismal prognosis [Ladenstein et al, 2017].

Relapse typically occurs in the bone and bone marrow, but soft tissue, lymph nodes, liver, or the central nervous system (CNS) may also be involved. Most of relapses are widespread. Early relapses (within 6 months to 1 year) generally indicate more aggressive disease, while later relapses might suggest a different tumour biology or clonal evolution. These refractory and relapsed high-risk neuroblastoma patients represent the target population of Kizfizo and account for approximately 220 patients per year in the EU, thus representing an ultra-rare indication for Kizfizo.

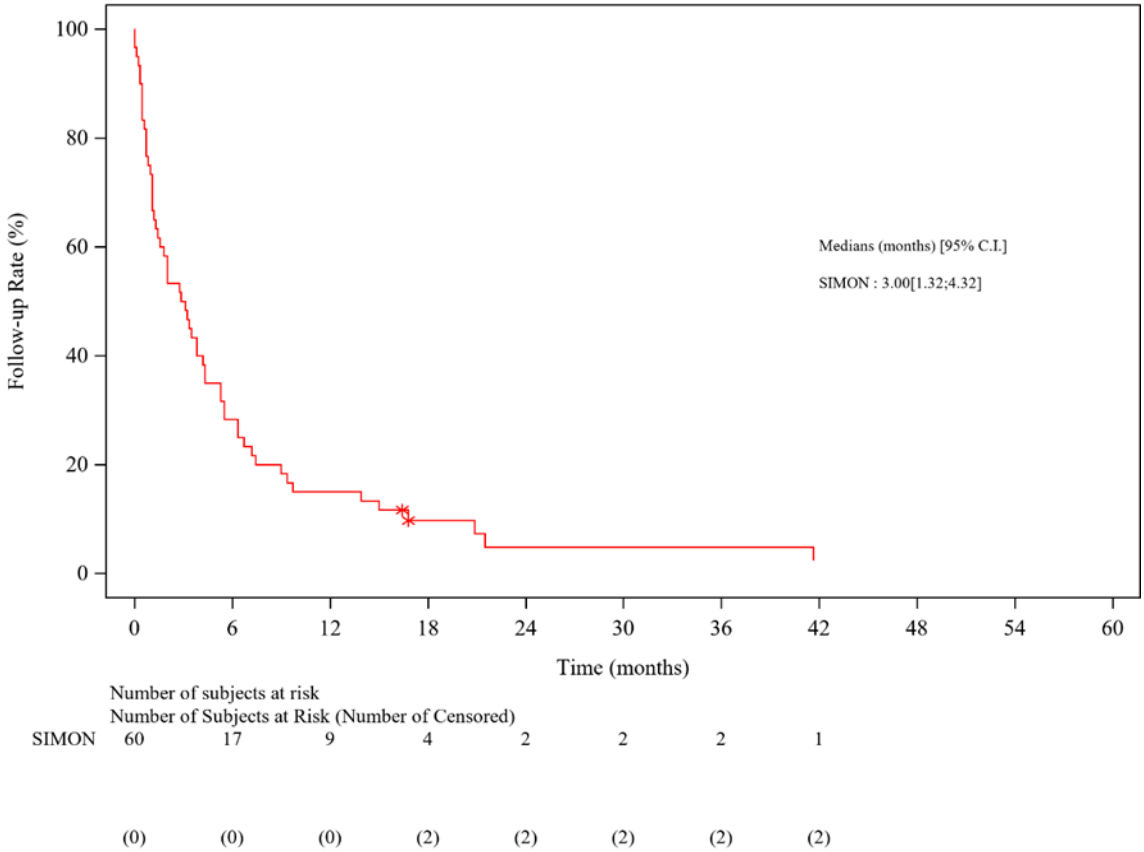
It is well recognised by the medical community that refractory and relapsed high-risk neuroblastoma patients exhibit very rapid progression and have a very dismal prognosis, leading to death within a few weeks if left untreated. It reflects the very aggressive nature of this paediatric cancer, which shall be fully appreciated when assessing the clinical benefit of Kizfizo. The expert opinion provided in the submission dossier by the applicant confirms that without proper treatment, refractory and relapsed high-risk neuroblastoma always progress rapidly within weeks and that spontaneous disease stabilisation or regression never occurs: "Until the early 2000s, a disease progression occurring during the induction phase after a first or a second line of conventional chemotherapy where all the classical drugs had been administered was constantly fatal within few weeks" and "a relapse after consolidation with HDC and ASCR was until the early 2000s considered as always fatal in a short period of time because of a rapidly progressive disease".

Historical (untreated) cohorts confirm the dismal natural progression of disease

In the Kizfizo MAA, the Applicant provided post-relapse Overall Survival (OS) data from 2 untreated cohorts of progressing or relapsed neuroblastoma patients (the Simon and Basta2 historical cohorts, fully described in the CSR, version V1.0, of the IC-TMZ study). These cohorts illustrate the natural course of the relapsed high-risk neuroblastoma patients, notably in respect of OS. The cohorts were also used as external controls to perform Indirect Comparisons (IC) of post relapse survival (see above initial AR).

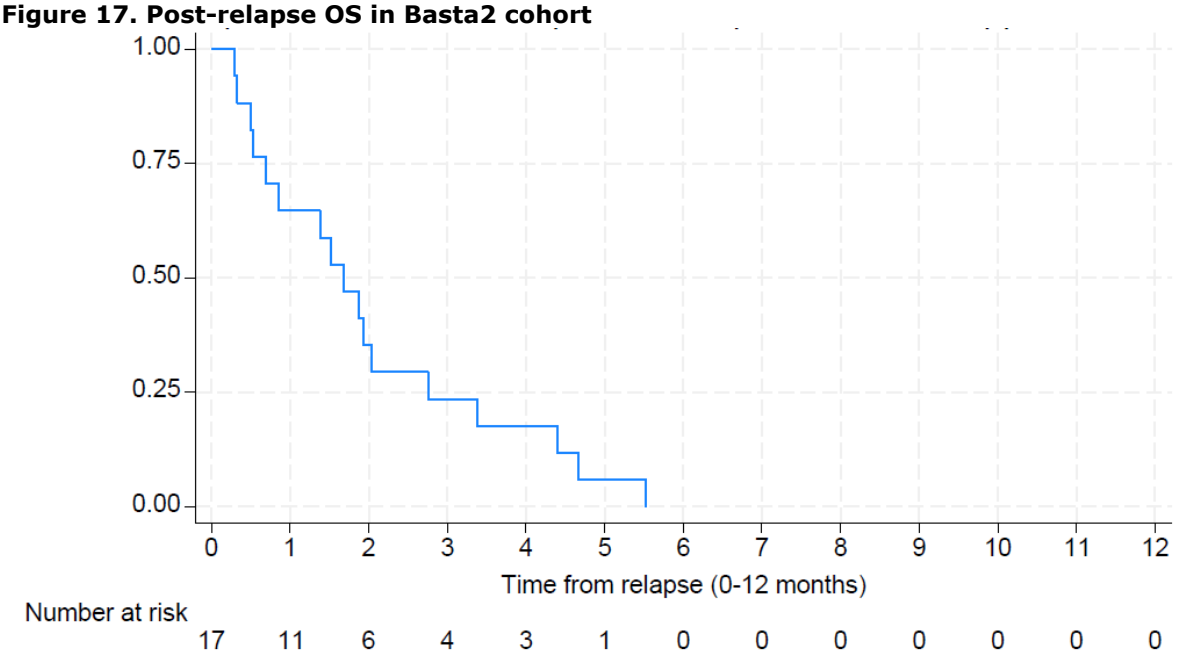
The Simon cohort is the one described by Simon et al. 2011. In this retrospective cohort, patients of the German neuroblastoma trials NB90, NB97, and NB2004 diagnosed between January 1990 and December 2007 were included in the analysis when they fulfilled all of the following criteria: (1) age at diagnosis 1 year or older, (2) first diagnosis between 1990 and 2007, (3) stage 4 disease or stage 3 neuroblastoma with MYCN amplification, and (4) relapse or progression after successful first-line ASCT. This cohort is representative of the high-risk neuroblastoma population in Germany during the reporting period as the German neuroblastoma trials registered more than 98% of all national neuroblastoma patients. Follow-up data for these patients were collected according to the protocol guidelines with cut-off date of February 2010. From this cohort, individual data of 72 patients who did not start any second-line chemotherapy further to recurrence were retrieved to assess the natural course of the disease. Among these 72 patients, 60 patients were finally assessed for the purpose of IC analyses as 12 patients had missing values for at least 1 predefined confounder covariate (age at diagnosis, MYCN amplification status and time to progression/first relapse). 32 patients (53%) were male and 28 patients (47%) were female, the median age was 3.0 years (Q1-Q3: 2.3 – 5.3) and 24 patients (40%) had MYCN amplification. The median post-relapse OS [95% CI] is 3.00 [1.32 ;4.32] months and the 1-year OS is 15.00% [7.38 ;25.13]. The post-relapse OS curve for the 60 patients is provided in Figure 16.

Figure 16. Post-relapse OS in Simon cohort



The Basta2 cohort is a smaller cohort of non-treated patients. This cohort is described by Basta et al. 2016. In this retrospective cohort, all cases of relapsed and progressive neuroblastoma diagnosed during 1990–2010 were identified from four UK Paediatric Oncology principal treatment centres. Follow-up was censored on 31 March 2014. Aggregate data of 17 patients treated only with palliative or supportive care for their progressive or relapsed condition have been extracted. 11 patients (65%) were male and 6 patients (35%) were female, the median age was 2.7 years (Q1-Q3: 1.7 – 3.6) and among the 7 patients with available MYCN status, 4 (57%) were MYCN amplified. The median post-relapse OS [95% CI] was 1.68 [0.69 – 2.76] months and 6-month OS was 0%. The Post-relapse OS curve for the 17 relapsed patients is provided in figure 17.

Figure 17. Post-relapse OS in Basta2 cohort



In conclusion, it is well documented that patients with relapsed or progressing neuroblastoma experience inevitable and very rapid progression with rapid death. The Applicant has provided 2 historical patients cohorts in the MAA (Simon and Basta2 cohorts), which clearly demonstrate and validate the course of this high-risk disease in the absence of effective therapy.

Spontaneous disease stabilisation (or regression) cannot occur as evidenced by clinical trial data (Vassal 2008)

During the MAA evaluation, the Rapporteur expressed concerns regarding the untreated cohorts, notably regarding the fact that it cannot be excluded that the decision to not actively treat the patients in Simon and Basta2 cohorts may have been influenced by non-specified reasons, such as poor health condition (Rapporteurs' Day 150 Joint Assessment Report of the responses to the List of Questions – Clinical: "patients with a very poor health status are usually not included in a clinical study, while no such restriction existed for patients with a relapse that were retrospectively selected to be included in the control groups from larger cohorts of patients. Notably, patients in these larger cohorts were not included because of relapse or at the time of relapse; rather, they were included at earlier time points based on other selection criteria").

While the Applicant believes that these cohorts accurately describe the spontaneous evolution of the disease of relapsed patients, and to provide further perspective to conclusively address the Rapporteur's comment, we would like to quote additional published historical data from clinical trial(s) in relapsed or refractory high-risk neuroblastoma for which the investigated drug was later shown, by multiple studies, to have no or minimal activity (such as irinotecan monotherapy). This addresses the Rapporteur's concerns as the patients enrolled in a clinical trial have disease characteristics and minimal life expectancy required for the clinical trial enrolment, excluding patients who would not comply with the inclusion/exclusion criteria, such as very poor health status. Such "negative" trial therefore provides the results of various endpoints of interest in a relapsed and refractory patient population in the absence of effective therapy. A review of relevant literature was performed as detailed in the re-examination dossier.

The output of this literature search led to the identification of the publication of a phase II clinical trial entitled "A phase II study of irinotecan in children with relapsed or refractory neuroblastoma: A

European cooperation of the Société Française d'Oncologie Pédiatrique (SFOP) and the United Kingdom Children Cancer Study Group (UKCCSG)" [Vassal et al, 2008]. This publication provides the results of a prospective, open label, multicentre phase II study designed to evaluate the efficacy of the cytotoxic medicinal product irinotecan at 600 mg/m2 over 60 min as a single injection every 3 weeks in neuroblastoma, rhabdomyosarcoma, and medulloblastoma. The Vassal 2008 publication specifically details the clinical efficacy and safety data in the relapsed or refractory neuroblastoma cohort. A significant number of patients with this ultra-rare condition, n=37, aged between 6 months and 20 years were included in the trial. Patients were eligible based on histologically confirmed neuroblastoma, which was relapsed or refractory to standard treatments. Other inclusion criteria included: measurable or evaluable primary and/or metastatic disease by meta-iodobenzylguanidine (mIBG) scan; World Health Organisation (WHO) performance status ≤2; life expectancy ≥8 weeks. Tumour response was evaluated by conventional radiological and mIBG scans and anti-tumour activity was assessed according to the WHO criteria (used at the time of the study conduct and shown to provide consistent results compared to the more recent RECIST criteria) every two cycles and/or at the end of treatment, then, during follow-up, every 2 months. The initial target lesions were measured by baseline method. Disease staging was defined according to the International Neuroblastoma Staging System (INSS) criteria including mIBG evaluation. An External Response Review Committee (ERRC), consisting of independent experts in the evaluation of paediatric tumours, reviewed all data.

The patients' characteristics of the Vassal 2008 are summarised in Table 63 below. The patient set is representative of the relapsed or refractory high-risk neuroblastoma patient population targeted in the indication of Kizfizo. In particular, the main demographic and baseline characteristics of these patients are compared to the ones in the main piece of efficacy data in the present dossier, the BEACON-CHEMO study (all TMZ-chemotherapy arms).

In the Vassal study, a total of 37 patients were enrolled; 26 were males and 11 were females. As expected for this condition, the patients are young children with a median age [min-max] of 4.0 [1–14] years, and a majority of the included patients are relapsed (28 patients, 76%), which is consistent with the relapsed and refractory settings incidences described in the literature [Ladenstein et al, 2010, Ladenstein et al, 2017] and the figures reported in the large European retrospective retroTMZ study included in the MAA (Module 5.3.5.4: 129 relapsed out of 196 patients, i.e., 66%).

Besides, focusing on the comparison of the characteristics of the patients in BEACON-CHEMO and Vassal 2008 studies, they are also similar in terms of age, relapsed versus refractory status, performance status at time of study randomisation and prior therapy in terms of induction chemotherapy, surgery and consolidation. There are, however, 2 differences:

i) 37% of patients in BEACON-CHEMO had received maintenance treatment with immunotherapy, whereas immunotherapy was not available at the time of the Vassal study (it is unlikely that the patients received immunotherapy as the evaluation of dinutuximab beta in HRNBL1 SIOPEN study started in 2009); although this therapy was shown to reduce the risk of recurrence, it is unlikely to alter the course of the disease once a patient relapses and it is of no impact for refractory patients; and

ii) a more important difference regarding the INSS stage at time of diagnosis, a key prognostic factor [London et al, 2011]. Indeed, there are more stage 3 patients enrolled in the Vassal study (86%) compared to 6% in the BEACON-CHEMO study (in which most patients (85%) were stage 4). Although this represents a difference in an important characteristic, all patients in Vassal 2008 had metastatic stage 3 or 4 disease (i.e. of poor prognosis) and, should this staging difference impact the prognosis, it should anyway result in a better prognosis of the patients included in the Vassal study compared to the BEACON-CHEMO study. This is therefore considered an acceptable bias for the projected use of the data.

Table 60. Demographics and baseline characteristics in BEACON-CHEMO and VASSAL study

	BEACON-CHEMO N= 102		**VASSAL 2008 N= 37**	
Gender, [N (%)]				
Male	53 (52)		26 (70)	
Female	49 (48)		11 (30)	
Age				
Median (years)	5.0		4.0	
Min, max (years)	1 - 18		1 – 14	
INSS (International Neuroblastoma Staging System) stage at initial diagnosis, [N (%)]				
1	1 (1)		0	
2	3 (3)		0	
3	6 (6)		32 (86)	
4	87 (85)		5 (13)	
4S	3 (3)		0	
Missing	2 (2)		0	
Relapse / Refractory status [N (%)]				
Refractory	34 (33)		9 (24)	
Relapsed	68 (67)		28 (76)	
Performance status [N (%)]	**Lansky**		**WHO**	
	100	63 (62)	0	25 (69)
	80-90	20 (20)	1	9 (24)
	60-70	3 (3)	2	2 (5)
	40-50	1 (1)	3	1 (3)
	Missing	15 (15)	Missing	0
Prior therapy, [N (%)]				
Induction chemotherapy	102 (100)		37 (100)	
Radiation therapy	53 (52)		10 (27)	
Surgery	65 (64)		29 (78)	
Consolidation/transplantation	54 (53)		19 (51)	
Immunotherapy	38 (37)		(missing)	

No objective response was observed, and stable disease was reported only in 4 evaluable patients (13% as reported by the authors in the evaluable (EVA) population, i.e., 10.8% in the ITT population). The median time to progression (TTP), i.e. the time from first administration to progression or death, was 1.38 months (95% CI range: 1.22 - 1.45 months) and the median OS was 8.8 months (95% CI range: 6.70 - 11.24 months). Of note, this post-relapse OS in Vassal 2008 is slightly higher than the post-relapse OS in Basta2 and Simon untreated cohorts (median post-relapse OS (months) [95% CI] of 1.68 [0.69 – 2.76] and 3.00 [1.32 ;4.32], respectively). This could be due to a slightly poorer condition of the patients receiving palliative care only in the untreated cohorts and/or some minimal activity of irinotecan monotherapy.

In conclusion, all patients included in the Vassal 2008 phase II trial progress within a maximum of 1.5 months and no patient remained alive at 1 year after the diagnosis of relapsed or refractory disease and randomisation in the study [Vassal et al, 2008]. Given the lack of activity of the investigational drug (irinotecan monotherapy) in this clinical trial and the rigorous evaluation of activity and survival endpoints, it provides valuable insights regarding spontaneous evolution and prognosis of the condition. These patients never experience spontaneous stabilisation or regression of their disease and always experience progression within the first 2 months, leading to death.

Activity data from pivotal BEACON-CHEMO study

The Applicant presents here the key activity data of the pivotal BEACON-CHEMO study, a sub-analysis of chemotherapy arms of the ITCC-SIOPEN Phase IIb Beacon-Neuroblastoma study, comprising 3 arms: the TMZ monotherapy arm (T), the TMZ + irinotecan arm (IT) and the TMZ + topotecan arm (TTo), with patients accrued from 2013 to 2021. In the BEACON trial, as per protocol, "patients with a

response (CR, PR) or stable disease (SD) were to receive 6 cycles of trial treatment. As per protocol, patient response was evaluated every 2 cycles, and if the patient has achieved a satisfactory response (i.e. CR, PR or SD), with acceptable toxicity, treatment could be extended beyond 6 cycles (up to 12 cycles), showing that SD constitutes for the clinicians of the BEACON trial a treatment response.

The results for

- ORR (defined as the percentage of patients who have achieved CR or PR within the considered first 6 cycles),
- DCR (disease control rate) at Best Response (defined as the percentage of patients who have achieved CR, PR and SD within the considered first 6 cycles) and
- DCR at end of therapy (CR, PR and SD without any progression throughout the whole treatment)

are provided and discussed below for the ITT analysis set in the context of the condition.

- **ORR, which is an acknowledged reliable endpoint of clinical activity, reflects meaningful clinical activity in this condition**

The ORR according to the best response in pivotal BEACON-CHEMO (ITT population) is summarised below and in the table. The ORR by treatment arm was ranging from 12.8% (95% CI: 5.6%-26.7%) in the T group and 16.7% (95% CI: 7.3%-33.6%) in the IT group, to 24.2% (95% CI: 12.8%-41.0%) in the TTo group. In the relapsed patients' subgroup more specifically, there was a trend for a lower ORR in the T group, 8.7% [2.4%;26.8%], compared to 15.8% [5.5%;37.6%] for IT and 23.1% [11.0%;42.1%] for TTo group, suggesting a superior activity of the combination regimens versus monotherapy.

For the 18 patients who had CR or PR at Best Response, the median duration of response (DoR defined as the time (in months) from the date of the first occurrence of a CR or PR to the first event date (progression, recurrence or death without progression or recurrence) or censoring date), was 15.6 months (95% CI: 8.6–37.3). It was 9.3 months (95% CI: 2.0-17.7) in the 11 patients with relapsed neuroblastoma and was not evaluable (95% CI: 11.7-not evaluable) in the 7 patients with refractory neuroblastoma.

For the IT and TTo arms together, the ORR was 20.6% [95%CI: 12.5-32.2] and the median DoR was 11.7 months [95% CI: 6.4 ;37.3].

Table 31. ORR in the T, IT and TTo arms of the ITT population of BEACON-CHEMO

ITT, relapsed/refractory	**T arm (n=39)**	**IT arm (n=30)**	**TTo arm (n=33)**
ORR [95% CI]	12.8% [5.6%;26.7%]	16.7% [7.3%;33.6%]	24.2% [12.8%;41.0%]
ITT, relapsed	**T arm (n=23)**	**IT arm (n=19)**	**TTo arm (n=26)**
ORR [95% CI]	8.7% [2.4%;26.8%]	15.8% [5.5%;37.6%]	23.1% [11.0%;42.1%]
ITT, refractory	**T arm (n=16)**	**IT arm (n=11)**	**TTo arm (n=7)**
ORR [95% CI]	18.8% [6.6%;43.0%]	18.2% [5.1%;47.7%]	28.6% [8.2%;64.1%]

T: TMZ; IT: TMZ + Irinotecan; TTo: TMZ + Topotecan

ORR is a reliable endpoint and reflects meaningful activity

During the evaluation, it has been acknowledged by the CHMP that the ORR is a reliable endpoint of clinical activity ("ORR is the [only] endpoint that can be relied upon as it is considered a convincing measure of anti-tumour activity").

However, the CHMP ground for refusal state that "efficacy results from the BEACON-CHEMO study (phase II uncontrolled study) and the Retro TMZ study (observational retrospective study) show only modest clinical activity of TMZ in combination with irinotecan or topotecan in relapsed / refractory high-risk neuroblastoma patients". In particular, the CHMP considers that "ORR of 20.6% [95%CI: 12.5-32.2] for TMZ regimens (TEMIRI and TOTEM) in the overall ITT population of the single arm trial (SAT) BEACON CHEMO study and associated with two complete responses (in TOTEM arm) is not convincing nor outstanding as would be required for an uncontrolled setting".

Although the Applicant understands the concerns raised by the Rapporteur in the context of a SAT in most oncology conditions, the Applicant respectfully disagrees with the CHMP evaluation in the context of treatment of patients with relapsed or refractory high-risk neuroblastoma. Indeed, the Applicant understands that for uncontrolled studies, there is no concurrent (randomised) control group to provide context for the outcomes in the treatment arm. It also means there is no way to fully avoid any possible selection bias, i.e., avoid any risk that the study has recruited patients more likely to achieve a desirable clinical outcome. In order to mitigate risks of selection bias, it is understandable that CHMP wishes generally to see higher ORR rates with a new therapy when a 10-15% ORR can be achieved with a standard of care. In settings however, where there is no possibility of spontaneous disease regression and no standard of care, risks associated with selection bias in an uncontrolled study are minimal and the observed rates of ORR should be evaluated accordingly.

Relapsed or refractory high-risk neuroblastoma is such a very aggressive condition. As described in Section 2.1.1, the natural evolution of the disease can be appreciated in particular thanks to the results of the publication from Vasal et al. [Vassal et al, 2008]. This publication reporting the (negative) results of a phase II study evaluation irinotecan as monotherapy adequately confirm the dreadful prognosis of relapsed and refractory high-risk neuroblastoma when no adequate chemotherapy is administered. That study was conducted in the early 2000's at a time when TMZ was not already considered as standard of care (SoC) for the treatment of relapsed and refractory neuroblastoma patients, but intensive front-line treatment was already used to treat these patients.

The Table below provides a comparative tabulation of ORR, DoR and TTP results of BEACON-CHEMO (IT and TTO arms of interest for the claimed indication) versus Vassal 2008 study. Taking into account that patients invariably progress within the first 2 months, the 20.6% [95%CI: 12.5-32.2] ORR shall be compared to the 0% ORR in the Vassal 2008 study, for which spontaneous regression never occurs and for which no approved treatment exists for the active disease. As it has been acknowledged that ORR is a reliable endpoint of clinical activity, the Applicant respectfully reiterates that achieving response in 20.6% [95%CI: 12.5-32.2] of patients, compared to 0% response rate in case of administration of an ineffective chemotherapy, is a meaningful clinical activity. As a further line of evidence, for the IT and TTo arms together of the BEACON-CHEMO, the patients experiencing response have durable response (median DoR was 11.7 months [95% CI: 6.4 ;37.3]). This, again, is to be assessed in the context of the inevitable (in 100% of the patients) and rapid (TTP < 1.5 months) progression, as exemplified in the Vassal 2008 study [Vassal et al, 2008].

Table 62. ORR, DoR and TTP in BEACON-CHEMO and VASSAL study

	BEACON-CHEMO (IT and TTo arms)	**VASSAL 2008**
ITT (N)	63	37
ORR [95% CI]	20.6% [12.5-32.2]	0.0%
Median DoR: months [95% CI]	11.7 [6.4 ;37.3]	-
Median TTP: months [95% CI]	6.5 [3.5 ;12.1]	1.38 [1.22–1.45]

Another concern raised by the Rapporteur is that "ORR of 20.6% […] is not convincing nor outstanding as would be required for an uncontrolled setting". In other words, the ORR of 20.6% [95%CI: 12.5-32.2] would not meet the threshold for a "convincing" or "outstanding" ORR, which would be expected for a SAT.

Again, the Applicant respectfully disagrees with the Rapporteur's Opinion. There is no definition or threshold for a "convincing" or "outstanding" ORR, nor is there a regulatory or legal basis for requiring such "convincing" or "outstanding" ORR in a SAT. The fact that the CHMP used different wordings interchangeably to qualify the antitumour activity of TMZ in the negative Opinion and Assessment Report illustrates that, in the absence of definition, threshold or regulatory requirement, the qualification as "modest", "moderate", "convincing" or "outstanding" is subjective.

A 20.6% [95%CI: 12.5-32.2] ORR with a median DoR of 11.7 months [95% CI: 6.4–37.3] shall be considered convincing in the context of relapsed or refractory neuroblastoma, which lacks any alternative therapeutic option and with inevitable progression in less than 1.5 months (1.4 months (95%; CI; range, 1.2–1.4 months), see Vassal 2008 in Section 2.1.1).

To merely illustrate the approval of an oncology medicinal product based on a 20% ORR, among others, atezolizumab (Tecentriq) European approval in 2017 as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma was based on a pivotal phase II SAT IMvigor 210 with ORR of 22.7% [15.5, 31.3] in a first cohort of 119 patients and 15.8% [11.9, 20.4] in a larger cohort of 310 patients. One important comment made by the CHMP in the assessment report [Tecentriq EPAR] was that a "single-arm trial design as pivotal study can be appropriate for a setting where there is no approved or acceptable therapeutic option", which is the case for high-risk refractory and relapsed neuroblastoma.

In conclusion, ORR is a reliable endpoint of activity, as acknowledged by the CHMP. There is no regulatory basis setting a minimum threshold for ORR, which shall rather be specifically assessed in the context of the condition to be treated and potential alternative treatment options. The 20.6% [95%CI: 12.5-32.2] ORR, with a median DoR of 11.7 months [95% CI: 6.4–37.3], shall be deemed meaningful and convincing in the absence of alternative therapeutic options in view of the aggressive and rapidly progressing nature of the condition, and taking into account the acceptable and easy manageable toxicity of TMZ regimens.

- **Disease control rate (DCR) is a treatment effect based on the natural course of the condition and reflects large and meaningful clinical activity in the treatment of the condition**

In the Assessment Report and in the CHMP Opinion, the CHMP did not consider the stabilisation of the disease (SD) or the Disease Control Rate (DCR) as relevant endpoints of activity in the context of the very aggressive refractory and relapsed high-risk neuroblastoma. Therefore, the CHMP does not evaluate stabilisation of the disease (which occurs in most patients after treatment) but only refers to ORR as a convincing measure of anti-tumour activity: "In the current application, due to the uncontrolled design of the studies submitted in this MAA,(…), ORR is the only endpoint that can be relied upon as it is considered a convincing measure of anti-tumour activity".

The Applicant respectfully disagrees. In addition to the ORR as a convincing measure of anti-tumour activity, the Applicant will demonstrate that stabilisation of the disease (SD) with TMZ regimens can, with a very low degree of uncertainty, be attributed to a treatment effect in the context of the condition to be treated and that DCR shall, as ORR, be considered as an endpoint that can, and should, be relied upon for quantification of the treatment effect.

DCR can be a relevant endpoint of activity in advanced cancer

Disease stabilisation refers to a situation where the tumour neither shrinks nor grows significantly over a defined period, remaining largely unchanged or showing minimal progression, as assessed per the criteria of RECIST 1.1 specifically in the BEACON-CHEMO study. Disease control rate (DCR), including disease stabilisation, may be an important clinical endpoint, especially in cases of advanced cancers where achieving tumour shrinkage may be difficult in hard-to-treat cancers, such as pancreatic cancer, glioblastoma, or paediatric high-risk neuroblastoma. For example, DCR has been found to predict subsequent survival in extensive stage small cell lung cancer in phase II clinical trials [Lara et al, 2016]. In these very aggressive cancers, disease stabilisation becomes an important indicator of treatment benefit, particularly when the therapy has a well-established and easily manageable safety profile, as acknowledged by the CHMP for TMZ ("temozolomide has low and manageable toxicity and is administered orally without requiring hospitalisation" [Temodal EPAR]). Also, for the Kizfizo target population of patients with an advanced/metastatic disease, maintaining disease stability for extended periods can significantly improve patient outcomes by delaying disease progression, reducing symptoms, and improving quality of life, while importantly offering access to otherwise inaccessible additional EU-approved or recommended treatments.

In the EMA guideline on the clinical evaluation of anticancer medicinal products [EMA/CHMP/205/95 Rev.6] referring to the sub-section "Endpoints" of the section "Phase III, confirmatory ("pivotal") trials, the following is recognised in case of advanced/metastatic disease: "In advanced/metastatic disease irrespective of the choice of primary endpoint, ORR, DoR and if relevant, rate of tumour stabilisation for, e.g. 3 or 6 months should be reported ". In the context of the high-risk relapsed or refractory neuroblastoma, an advanced/metastatic disease, and in compliance with this guideline recommendation, the Applicant will further rely on the relevant rate of tumour stabilisation (i.e., the DCR) for the above-mentioned duration, in addition to ORR and DoR already discussed.

Thus, it is clear from the EMA's own guidelines that there is a strong disease-specific recognition of the value of prolonged disease stabilisation as an endpoint of activity. For advanced/metastatic cancer, in addition to ORR and DoR, DCR and Duration of Disease Control (DoDC) shall be reported.

DCR in the pivotal BEACON-CHEMO study

The DCR at Best Response (defined as the percentage of patients who have achieved CR, PR and SD within the considered first 6 cycles) and the DCR at end of therapy (CR, PR and SD without any progression throughout the whole treatment) in pivotal BEACON CHEMO (ITT population) are summarised below.

The DCR at Best Response was large across all TMZ-based treatment arms (59.0% [43.4%;72.9%] for T, 63.3% [45.5%;78.1%] for IT and 63.6% [46.6%;77.8%] for TTo).

For the IT and TTo arms together (arms of interest in the indication), the DCR was similar for relapsed (62.2% [47.6%;74.9%]) and refractory (66.7% [43.7%;83.7%]) patients. As the for the ORR in relapsed setting, there was a trend for lower DCR in relapsed setting for the T monotherapy arm.

The Duration of Disease Control (DoDC), defined as the time from randomisation to the first event date (progression, recurrence or death without progression or recurrence) or censoring date, was specifically calculated for this re-examination dossier to assess the duration of disease control. For the 63 patients who had Disease Control at Best Response, the duration of disease control was prolonged, with a median DoDC of 13.0 months (95% CI: 8.7–33.1) for the 3 chemotherapy arms (similar to the median DoR of 15.6 months (95% CI: 8.6–37.3)). The median DoDC was 11.7 months (95% CI: 5.7-14.8) in the 38 patients with relapsed neuroblastoma and was not evaluable (95% CI: 12.0-not evaluable) in the 25 patients with refractory neuroblastoma. By treatment arm, median DoDC was 14.0 months [3.9 ;NE] in the T am (n=23), 12.1 months [7.6 ;40.3] in the IT arm (n=19), and 23.2

months [5.7 ;39.3] in the TTo arm (n=21). For the IT and TTo arms together (arms of interest for the claimed indication), the median DoDC was 12.8 months [95% CI: 11.3 ;38.0]; 12.3 months (95% CI: 6.7-27.4) in the 28 patients with relapsed neuroblastoma and 39.3 months (95% CI: 6.1-not evaluable) in the 12 patients with refractory neuroblastoma.

Further to the pre-submission meeting held on January 7th 2025 with the Rapporteur and Co-Rapporteur, it was also decided to provide the DCR at end of therapy, i.e. for patients achieving CR, PR or SD and without any progression throughout the whole treatment period. This is another way to evidence the long-term benefit of disease stabilisation. At the end of therapy, the DCR was large with 60.0% [42.3%;75.4%] for the IT arm and 39.4% [24.7%;56.3%] for the TTo arm, and was 30.8% [18.6%;46.4%] for the T arm. The DCR for the relapsed patients was 57.9% [36.3%;76.9%] for the IT arm and 34.6% [19.4%;53.8%] for the TTo arm, but only 17.4% [7.0%;37.1%] for the T arm. For refractory patients, the DCR at the end of therapy was large and comparable for the 3 arms (50.0% [28.0%;72.0%] for T, 63.6% [35.4%;84.8%] for IT and 57.1% [25.0%;84.2%] for TTo).

Table 63. DCR in the T, IT and TTo arms of the ITT population of BEACON-CHEMO

ITT, relapsed/refractory	**T arm (n=39)**	**IT arm (n=30)**	**TTo arm (n=33)**
DCR at Best Response [95% CI]	59.0% [43.4%;72.9%]	63.3% [45.5%;78.1%]	63.6% [46.6%;77.8%]
DCR end of therapy [95% CI]	30.8% [18.6%;46.4%]	60.0% [42.3%;75.4%]	39.4% [24.7%;56.3%]
ITT, relapsed	**T arm (n=23)**	**IT arm (n=19)**	**TTo arm (n=26)**
DCR at Best Response [95% CI]	43.5% [25.6%;63.2%]	63.2% [41.0%;80.9%]	61.5% [42.5%;77.6%]
DCR end of therapy [95% CI]	17.4% [7.0%;37.1%]	57.9% [36.3%;76.9%]	34.6% [19.4%;53.8%]
ITT, refractory	**T arm (n=16)**	**IT arm (n=11)**	**TTo arm (n=7)**
DCR at Best Response [95% CI]	81.3% [57.0%;93.4%]	63.6% [35.4%;84.8%]	71.4% [35.9%;91.8%]
DCR end of therapy [95% CI]	50.0% [28.0%;72.0%]	63.6% [35.4%;84.8%]	57.1% [25.0%;84.2%]

T: TMZ; IT: TMZ + Irinotecan; TTo: TMZ + Topotecan

In conclusion, when focusing on the patients who received TMZ combined treatment with topoisomerase 1 inhibitors (in line with the target indication), approximately 2 out of 3 patients (ITT population) had at least SD at Best Response (DCR), regardless of their relapsed or refractory neuroblastoma status. DCR at end of therapy was also large (60% for the IT arm and 39.4% for the TTo arm). The median DoDC was 12.8 months [11.3 ;38.0] for IT and TTo arms together. Most patients had maintained DC until the end of therapy, although there was a trend for lower DCR at the end of treatment in relapsed patients treated with TTo.

<u>DCR in BEACON-CHEMO "SAT" isolates a large treatment effect</u>

As sustained DCR is an endpoint of interest in advanced cancers (such as relapsed or refractory neuroblastoma) and as the pivotal uncontrolled BEACON-CHEMO study can be considered to present the characteristics of a SAT, it must be established whether such endpoints isolate a treatment effect. To address this question, the Applicant relies on the reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a MAA [EMA/CHMP/458061/2024] to demonstrate that the BEACON-CHEMO pivotal trial as a SAT can isolate the TMZ-based treatment effect on DCR as a specific endpoint with a very low degree of uncertainty.

Indeed, the reflection paper states in the definition of "Isolation of treatment effect" that "if observed individual outcomes in a SAT for the defined endpoint within the designated follow-up could not have occurred without active treatment in any patient who entered the trial, the SAT is able to isolate the treatment effect on that specific endpoint. Conceptually, this can allow a causal interpretation of the effect of the treatment, despite the limitations in study design. This is a theoretical concept which

requires qualitative reasoning that leaves no doubt about the causal relationship between the treatment and outcome measured by the chosen endpoint. This will only be perfectly satisfied in exceptional cases. However, in general this concept enables systematic assessment of the uncertainties involved in attributing observed outcomes to the investigational treatment. This systematic assessment ultimately aids to determine whether causal conclusions can be drawn with sufficient certainty from the SAT on the effect of the treatment".

To leave no doubt about the causal relationship between the treatment and the outcome measured by the chosen endpoint (DC), i.e. that the Disease Control in the target condition is very likely a treatment effect, it is of importance to assess it taking into account the natural progression of the condition. As described above, the natural course of the disease can be appreciated in particular thanks to the results of the publication by Vassal et al. [Vassal et al, 2008]. This publication reports the "negative" results of a phase II study in high-risk relapsed and refractory neuroblastoma. The Table below provides a comparative tabulation of the main activity results of BEACON-CHEMO IT and TTo arms (treatment arms of interest for the claimed indication) versus Vassal 2008 study. Among the 37 patients (30 assessed for response), SD occurred in 4 patients (i.e., DCR of 13.3% as reported by the authors in the evaluable population, or 10.8% in the ITT population). This shall be considered at best as the "spontaneous" DCR in relapsed or refractory neuroblastoma, with a median TTP of 1.38 months [range: 1.22–1.45]. In other words, every patient experienced progression within less than 1.5 months and disease stabilisation cannot occur without active treatment. In BEACON-CHEMO, for the IT and TTo arms together, the DCR according to the best response was 63.5% [51.1%;74.3%], and the median DoDC was 12.8 months [11.3;38.0]. The very large and sustained DCR seen in BEACON-CHEMO necessarily reflects the effect of the treatment.

Table 64. DCR, DoDC and TTP in BEACON-CHEMO and VASSAL study

	BEACON-CHEMO (IT and TTo arms)	**VASSAL 2008**
ITT (N)	63	37
DCR [95% CI]	63.5% [51.1%;74.3%]	10.8%
Median DoDC: months [95% CI	12.8 [11.3;38.0]	-
Median TTP: months [95% CI]	6.5 [3.5 ;12.1]	1.38 [1.22–1.45]

In conclusion, in the BEACON-CHEMO study, for the patients treated with TMZ combined with irinotecan or topotecan, DCR at Best Response was large (63.5% [51.1%;74.3%]) and sustained (median DoDC of 12.8 months [11.3 ;38.0]). Such a large and sustained rate of DC cannot happen in the absence of active treatment and, therefore, it leaves no doubt about the causal relationship between the treatment and outcome measured by the chosen endpoint (DCR).

- **Additional considerations regarding key activity results in BEACON-CHEMO**

Use of follow-up therapies

As part of the evaluation of the duration of response or disease control, it is relevant to point out that the calculation of the DoR and the DoDC may have been influenced by potential follow-up therapies that some patients may have received after the completion of the BEACON study. The potential use of subsequent treatments is perfectly justified in the treatment pathway of these patients and is expected, as TMZ-based treatments enable access to consolidation for refractory patients and to immunotherapy. It is thus relevant to quantify the effects of the treatment sequence in total and hence subsequent treatments capture the effects of interest.

However, if we want to also assess separately the TMZ-based treatment effect, it can be highlighted that the median duration of treatment (a period during which patients were not allowed to receive any other therapy) for the patients with Disease Control at Best Response (n=63 patients), a median of 4 cycles (Q1-Q3: 4.0-6.0) -corresponding to 4.0 months of treatment- was administered in the T arm, 6 cycles (Q1-Q3: 4.0-7.0) -corresponding to 4.3 months of treatment- was administered in the IT arm and a median of 6 cycles (Q1-Q3: 6.0-8.0)– corresponding to 5.6 months of treatment- was administered in the TTo arm (see Table below).

Table 65. Treatment duration in patients with disease control at best response in BEACON-CHEMO (safety population)

	Group Treatment			
	Arm T: Temozolomide (N=23)	Arm IT: Temozolomide + Irinotecan (N=19)	Arm TTo: Temozolomide + Topotecan (N=21)	Total (N=63)
Treatment Duration (cycles)				
n	23	19	21	63
Mean (SD)	5.0 (2.5)	5.8 (2.7)	7.0 (2.6)	5.9 (2.7)
Median	4.0	6.0	6.0	6.0
Q1 - Q3	4.0 - 6.0	4.0 - 7.0	6.0 - 8.0	4.0 - 6.0
Range	2.0 - 12.0	2.0 - 12.0	4.0 - 12.0	2.0 - 12.0
Missing data	0	0	0	0
Treatment Duration (days)				
n	23	19	21	63
Mean (SD)	146.5 (73.4)	131.4 (58.2)	204.2 (79.7)	161.2 (77.0)
Median	119.0	130.0	169.0	144.0
Q1 - Q3	112.0 - 171.0	90.0 - 176.0	167.0 - 233.0	113.0 - 181.0
Range	71.0 - 362.0	42.0 - 256.0	112.0 - 385.0	42.0 - 385.0
Missing data	0	0	0	0

Percentages are based on all participants excluding those with missing values.
Program: 3.0_SAFETY.SAS, Date & time program was run: 12DEC2024 11:22, Source dataset(s): ADRESP

These prolonged treatment durations in most achieving DC indicate a lasting treatment activity of TMZ. Therefore, although there might be some degree of uncertainty regarding the maximum duration of the DC which is attributable to the TMZ-based chemotherapy only, a clear and prolonged DC can undoubtedly be evidenced in all treatment arms of BEACON-CHEMO.

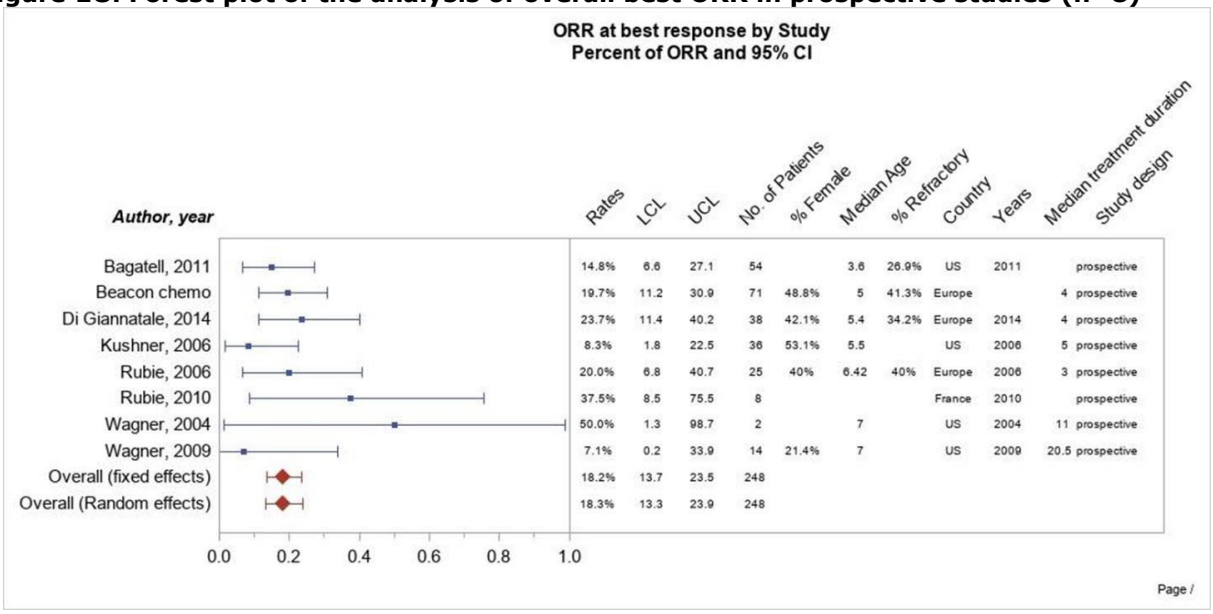
Robustness of the BEACON-CHEMO results

Relapsed and refractory high-risk neuroblastoma being an ultra-rare condition, clinical studies conducted in this condition cannot enrol very large cohorts of patients. Even if the BEACON study is the largest ever conducted study in refractory and relapsed high-risk neuroblastoma, the Applicant would like to highlight the results of the meta-analysis already included in the MAA, and conducted by the Applicant as recommended in the initial CHMP SA (EMA/CHMP/SAWP/599403/2018) and follow-up SA (EMA/CHMP/SAWP/493967/2019). This meta-analysis allows providing more precise estimates of the treatment effect by reducing random error compared to small individual studies.

As detailed in the Clinical Overview of the Kizfizo MAA (Module 2.5), published data concerning the use of TMZ, alone or in combination with irinotecan or topotecan, for treating relapsed or refractory neuroblastoma patients were identified by a systematic review of the literature. No Phase III trial has been conducted in the target indication; however, 8 uncontrolled studies, including 3 Phase II trials, have been identified (2 studies with TMZ in monotherapy, 4 studies with IT/TEMIRI and 2 studies with TTo/TOTEM. Their summary is presented in the clinical overview; ORR and DCR at Best Response were reported in all studies, except for one study where only ORR and DCR at 2 cycles were provided [De Sio et al, 2006]. Excluding one reference (2 patients only) [Wagner et al, 2004], the ORR (CR+PR) at Best response ranged from 7.1% to 37.5% and DCR (CR+PR+SD) at Best response ranged from 42.9% to 100%, and was 64.5%-68% for TMZ, 42.9%-75.0% for TEMIRI and 78.9% - 100% for TOTEM. In the 3 Phase II studies, the best ORR were 20%, 15% and 24%, and DCR at Best response were 68%, 68.5% and 78.9% for TMZ, TEMIRI, TOTEM, respectively [Rubie et al, 2006; Bagatell et al, 2011; Di Giannatale et al, 2014].

The prospective meta-analysis comprises the 8 published studies reported above and the BEACON-CHEMO study (data from the 80 patients of the bevacizumab randomisation as reported in the 1st version of the CSR included in the MAA). Overall, in 248 relapsed or refractory patients, the Best ORR (best response during treatment) was estimated to be 18.2% (95% CI: 13.7%-23.5%) using fixed effects and 18.3% (95% CI: 13.3%-23.9%) using random effects, and the DCR according to the best response during treatment was estimated to be 70.3% (95% CI: 64.3%-75.9%) using fixed effects and 71.3% (95% CI: 62.5%-79.4%) using random effects.

Figure 18. Forest plot of the analysis of overall best ORR in prospective studies (n=8)



Applicant General Conclusion

Given,

- the very predictable course of the disease with an impossibility to see stabilisation or regression in the absence of active treatment,
- the large and sustained effect (DCR=ORR+SD) after the treatment with TMZ regimens
- the qualitative reasoning leaving no doubt about the causal relationship between the treatment and outcome measured, deemed to be acceptable for a SAT

The Applicant concludes that:

- As ORR is a treatment effect, DCR is also a treatment effect
- DCR (and DoDC), together with ORR and DoR, are reliable endpoints of clinical activity
- Based on these endpoints (ORR, DoR, DCR and DoDC), the clinical activity of TMZ regimens (temozolomide combined with irinotecan or topotecan) is meaningful and convincing.

5.1.2. Ground #1.2: TMZ-based chemotherapy clinical activity translates into quantifiable patient benefit

Applicant´s position on the second Ground for re-examination:

For the purpose of this section, the Applicant will focus on DCR. The Applicant will demonstrate that the reported clinical activity (based on DCR) translates into clinical benefit:

- Given the course of the disease, large and sustained DCR is highly likely to translate into clinical benefit in the context of high-risk relapsed or refractory neuroblastoma and given the favourable toxicity profile;
- Large and sustained DCR allows access to consolidation which is the treatment goal for the refractory patients; and
- Large and sustained DCR allows access to the dinutuximab beta immunotherapy – the only approved drug in this condition - which is the treatment goal for the relapsed patients.

Prolonged DCR is likely to translate into clinical benefit for high-risk relapsed or refractory neuroblastoma

Evidence of clinical benefit based on BEACON-CHEMO pivotal study

According to the EMA guideline on the clinical evaluation of anticancer medicinal products [EMA/CHMP/205/95 Rev.6], section "Studies in small study populations, very rare cancers", subsection "Non-randomised trials", "resorting to non-randomised trials (e.g. SAT) should be duly justified (including e.g. a predictable course of the disease [1] in combination with a large treatment effect on endpoints [2] such as ORR and duration of response reasonably likely to translate in true clinical benefit, and acceptable toxicity [3])."

[1] As described above, the course of the disease in the absence of active treatment is very predictable, with for the Vassal study, 10.8% DCR and inevitable rapid progression in less than 1.5 months (the median TTP was 1.38 months [95% CI: 1.22–1.45]). The resulting median OS was 8.8 months [95% CI: 6.70–11.24], with a 1-year OS of 0%.

[2] The TMZ regimens (TMZ combined with irinotecan or topotecan) treatment effect is large: DCR was 63.5% [95% CI: 51.1%;74.3%] for the ITT population of BEACON-CHEMO (63.3% [95% CI: 45.5%;78.1%] for IT and 63.6% [46.6%;77.8%] for TTo), and sustained: median DoDC was 12.8 months [95% CI: 11.3 ;38.0] (12.1 months [95% CI: 7.6 ;40.3] in the IT arm and 23.2 months [95% CI: 5.7 ;39.3] in the TTo arm). Accordingly, the median TTP was 6.5 months [3.5 ;12.1] and the median OS was 15.9 months [11.8 ;34.3] for the IT and TTo arms together. The 1-year OS was 62.9% [49.7 ;73.6], 2-year OS was 40.3% [28.2 ;52.2] and the 5-year OS was 28.3% [17.1 ;40.5].

[3] Furthermore, the true clinical benefit of the TMZ-based treatment is further substantiated by the cumulated safety clinical evidence available. TMZ regimens have a favourable safety and manageable toxicity profiles as already acknowledged by the CHMP in the Assessment Report. The low and manageable toxicity profile was also emphasised in the Temodal EPAR ("temozolomide has low and manageable toxicity and is administered orally without requiring hospitalisation").

Thus, it can be concluded that it is legitimate to consider the results of the BEACON-CHEMO "SAT" as strongly convincing for the approval of Kizfizo MAA.

Supporting evidence of clinical benefit from published clinical trials

The large DCR and favourable safety profile have also consistently been emphasised in clinical trials. Since TMZ has been first assessed in clinical trials, investigators consistently emphasised that the actual clinical benefit of TMZ-based treatment lies in the sustained control of the disease progression, while presenting with a good and easily manageable safety profile. In the first publication on salvage TMZ monotherapy from a compassionate use study [De Sio et al, 2006], DCR was achieved in 11/17 (65%) relapsed or refractory neuroblastoma patients at 2 cycles, including 7 patients with at least 6 treatment cycles (up to 24 cycles in 1 patient) and prolonged survival; the authors concluded that "temozolomide demonstrated activity in neuroblastoma patients with prolonged stable disease achieved" and "that temozolomide appears to be well tolerated and the low incidence of major toxicity along with its oral formulation make it an attractive choice for long-term maintenance chemotherapy".

Likewise, in the first Phase 2 study with TMZ monotherapy [Rubie et al, 2006], DCR was achieved in 17/25 (68%) relapsed or refractory neuroblastoma patients at best response, including 7 patients with at least 6 treatment cycles (up to 9 cycles in 1 patient); the toxicity was considered moderate in these heavily pretreated patients. Finally, in the first publication on combined treatment of TMZ with irinotecan in the relatively large number of 49 relapsed or refractory neuroblastoma patients [Kushner et al, 2006], DCR at best response was reported in 75% of patients. The authors concluded that "multiple courses (up to 15 cycles in 1 patient) entailed no cumulative toxicity and controlled disease for prolonged periods in many patients, including some who were unable to complete prior treatments because of hematologic, infectious, cardiac, or renal problems". Therefore "this treatment regimen does not exacerbate preexisting toxic effects on vital organs from extensive prior therapy, is feasible in patients with poor hematologic status, and allows good quality of life".

Supportive evidence of clinical benefit from the retrospective RetroTMZ cohort

The favourable safety profile is further substantiated with the real-world data from the study ORP-TMZ-4 / RetroTMZ, which includes 196 patients diagnosed with relapsed or refractory high-risk neuroblastoma from the 1 January 2004 until 31 December 2017 and treated with TMZ-based chemotherapy. For a significant number of children (n=46) on prolonged TMZ-based regimens (at least 6 months), the performance scale prior to initiation of therapy and at 6 months was collected (see Table below).

Table 66. Lanksy/Karnofsky performance scale scores for patients treated for at least 6 months in RetroTMZ

Variable		First TMZ episode		Subsequent TMZ episodes	
Prior TMZ	n (m.d.)	46 (3)		10 (1)	
	Unknown	6	13.0%	2	20.0%
	0-20%				
	30-50%			1	10.0%
	60-70%	3	6.5%	1	10.0%
	80-100%	37	80.4%	6	60.0%
At 6 months	n (m.d.)	46 (3)		10 (1)	
	Unknown	5	10.9%	2	20.0%
	0-20%				
	30-50%				
	60-70%				
	80-100%	41	89.1%	8	80.0%

m.d., missing data; TMZ: temozolomide.

Results are available for 40/46, i.e., 87% of concerned patients at TMZ treatment initiation, and for 41/46, i.e., 89% at 6 months. The Lanksy/Karnofsky performance scale scores of patients treated for 6 months were very good (treated patients fully active or suffering only minor physical restrictions after 6 months), supporting the notion that prolonged TMZ-based regimens are well tolerated and allows good quality of life.

Expert opinion on the clinical benefit of TMZ regimens in the management of relapsed or refractory neuroblastoma

Lastly, this is further corroborated by clinicians using TMZ in routine clinical care for almost 20 years. In the expert statement as provided by the applicant emphasis is made as follow: for refractory patients, "during the first part of treatment or after consolidation, allowing to induce tumor stabilization or regression and thus to propose complementary treatments that could not have been safely and usefully administered in the first instance (…). For induction failures, temozolomide combination with chemotherapy or chemo-immunotherapy is currently the only proposal identified to be able in a significant number of patients to control the disease progression after administration of classical chemotherapy or to reduce the metastatic burden and allow access to an intensified consolidation with a tandem HDC that has been demonstrated to be a key proposal to improve the survival". For refractory patients, "temozolomide combinations are well tolerated and have changed this dramatic situation landscape. In case of relapse, we can propose with caution a strategy that is not palliative and explain to parents that we will manage the situation step by step. A disease stabilization is the first objective compatible with a prolonged good quality of life because of the treatment good tolerance. For patients with a tumor response, a prolonged treatment can be proposed or a consolidation with immunotherapy with the objective of a curative treatment".

In conclusion, the data from BEACON-CHEMO, further supported by the data from published clinical trials, real-world evidence (retrospective data collection) and opinion by clinical experts, collectively show TMZ-based salvage therapy is very likely to translate in true clinical benefit for relapsed or refractory neuroblastoma patients with improved rate and duration of disease control, while exhibiting an acceptable toxicity profile (as already acknowledged by CHMP) and allowing good quality of life.

Having demonstrated the intrinsic clinical benefit of TMZ-based therapy, the Applicant will provide below further supportive evidence of the overall clinical benefits by discussing the access to consolidation therapy, which is the treatment goal for the refractory patients; discussing the access to immunotherapy, the only approved drug in this condition, and providing IC of post relapsed OS with external controls

Supportive evidence of clinical benefit: access to consolidation

Patients treated in the HRNBL1 SIOPEN study with insufficient metastatic response at the end of induction chemotherapy (refractory), defined as SIOPEN score > 3 or less than 50% reduction in mIBG score (or > 3 bone lesions or less 50% reduction in number of FDG-PET-avid bone lesions for mIBG-non avid tumours) have a poorer prognosis with a 5-year Event Free Survival (EFS) of 14 % [Ladenstein et al, 2018]. The current SIOPEN recommendation in HRNBL2 is to give a 2nd line induction therapy and to proceed to an intensified consolidation therapy with high-dose chemotherapy (HDC) and autologous stem cell rescue (ASCR) unless the patient experiences progressive disease (PD) or major toxicity (High-Risk Neuroblastoma Study 2 of SIOP-Europa-Neuroblastoma (SIOPEN) protocol, V4.1 dated 08/03/2024). Thus, there is a major unmet medical need for an approved salvage therapy to achieve disease control (response or disease stabilisation) and to allow the refractory patients to progress to the consolidation.

In BEACON-CHEMO, in the ITT population of refractory patients treated with TMZ combined with a topoisomerase inhibitor, 66.7% [43.7%;83.7%] achieved disease control (response or SD) based on the best response and 61.1% [38.6%;79.7%] had DCR at end of therapy and became eligible to access to consolidation. Data on 18 refractory patients treated with IT and TTo from the BEACON-CHEMO study, including the best response and the response at the end of treatment with IT or TTo, the access to consolidation therapy, and the patient follow-up have been provided. All patients experiencing PD (n=8) at the end of therapy did not receive consolidation. 12 patients had response or SD and 10/12 (83%) received consolidation therapy; the 2 other patients with DC electively decided to

be enrolled in a lorlatinib trial. For the patients treated with IT or TTo regimens and who proceeded to consolidation, the survival rate was very high, with 5-year OS of 70.0% [32.9 ;89.2].

In conclusion, 66.7% [43.7%;83.7%] (ITT population) of the refractory patients treated with TMZ combined with a topoisomerase inhibitor achieved response or disease stabilisation, which is a requirement to proceed to consolidation therapy according to the current SIOPEN HRNBL2 treatment protocol. Follow-up data of BEACON-CHEMO patients confirmed that 83% (10/12) of these high-risk refractory patients with disease control at the end of therapy proceeded successfully to consolidation, the other 2 eligible patients electively deciding not to proceed to consolidation but to receive another experimental protocol.

Supportive evidence of clinical benefit: access to immunotherapy

Disease Control (at least SD) is required for access to Qarziba which is approved for patients with relapsed and refractory neuroblastoma [Qarziba SmPC]. Qarziba (dinutuximab beta) is currently the only EU approved therapy for patients with relapsed or refractory disease. Dinutuximab beta is not effective on active or bulky disease [Yu et al, 1998] and – in the context of relapsed or refractory disease - was approved only in patients having demonstrated prior disease stabilisation by other suitable measures [Qarziba SmPC].

Indeed, the clinical evidence provided at the time of dinutuximab beta (a new active substance) approval in Europe was based on data from one single-arm study (APN311-202) and data from a compassionate use program (APN311-303), with progressive disease (PD) being a main exclusion criterion. Overall, the ORR in the global refractory/relapsed population was 36% [25; 48]; 41% [23; 57] in refractory patients and 29% [95% CI: 15; 46] in relapsed patients. Noteworthy, details regarding the prior treatment received by the patients of the registrational study APN311-303 is provided in [Mueller et al, 2018]. Among the 48 patients with relapsed or refractory disease in APN-11-303, the most frequent systemic chemotherapy received to stabilise their relapsed or progressive disease was TOTEM or TEMIRI in 22/33 (66%) of the patients who received chemotherapy, the other chemotherapies much less frequently used being topotecan/ vincristine/ doxorubicin (TVD) or topotecan/cyclophosphamide/etoposide. The registrational results of Qarziba in relapsed or refractory neuroblastoma were confirmed in the single arm open label phase 2 APN311-304 study [Lode et al, 2023]: dinutuximab beta monotherapy in 40 high-risk refractory/relapsed neuroblastoma patients having achieved prior disease stabilisation with a second line treatment as per the SmPC indication demonstrated an ORR at best response of 37% in the global population of 38 evaluable patients, and 29% in the 21 relapsed patients, specifically. Consequently, access to dinutuximab beta as an EU approved treatment for relapsed and refractory neuroblastoma requires prior disease stabilisation by appropriate chemotherapy.

In BEACON-CHEMO, 62.2% [47.6%;74.9%] of the relapsed patients and 66.7% [43.7%;83.7%] of the refractory patients in the ITT population treated with IT or TTo achieved disease control (response or disease stabilisation) and thus became eligible to receive dinutuximab beta (Qarziba), which has been approved in these indications.

Whereas the main treatment goal for refractory patients is to receive consolidation therapy, access to immunotherapy with dinutuximab beta, the only approved product, is of paramount importance for the relapsed patients. As mentioned above, 62.2% of the 45 relapsed patients treated with IT or TTo qualify for anti-GD2 immunotherapy.

To further substantiate the access to immunotherapy after relapse, the Applicant provides further analyses on the follow-up immunotherapy with dinutuximab beta as suggested by the Rapporteur during the clarification meeting held on July 9th 2024. Twelve (12) relapsed patients of the BEACON-

CHEMO study treated with TMZ combined with irinotecan or topotecan received dinutuximab beta (Qarziba) as a follow-up therapy. For these patients, the 5-year OS was 50.0% [20.9; 73.6].

Of note, whereas 28/45 patients achieved DC and theoretically qualified for Qarziba immunotherapy, the number of patients who effectively received Qarziba was limited (12/45). This can be explained by the fact that

i) access to immunotherapy was not part of the BEACON study and was provided at the decision of the treating physician and,

ii) all patients who received immunotherapy after relapse have been treated with Qarziba after March 2017 which corresponds to the date of the CHMP positive opinion of this product, i.e. towards the end of the accrual period in BEACON-CHEMO 2013-2021.

The 2 reasons presented above may explain the overall limited number of patients effectively treated with Qarziba during the follow up-period. In fact, if we focus on the 2017-2021 period (during which treatment with Qarziba was recommended), 11 of the 25 (44%) relapsed patients received Qarziba immunotherapy.

In conclusion, 62.2% [47.6;74.9] (ITT population) of the BEACON-CHEMO relapsed patients treated with TMZ combined with irinotecan or topotecan achieved response or disease stabilisation and became eligible to receive dinutuximab beta (Qarziba SmPC), which is approved in this indication provided the patients have been stabilised by other suitable measures.

Applicant General Conclusion

The TMZ regimens treatment effect (DCR), which reflects the clinical activity, is reasonably very likely to translate in true clinical benefit with improved duration of disease control and survival, further supported by

- allowing the access to consolidation which is the treatment goal for the refractory patients; and
- enabling the access to immunotherapy, the only approved drug in this condition

while exhibiting an acceptable and manageable toxicity (the latter point being already acknowledged by CHMP).

It can be concluded that it is legitimate to consider the results of the BEACON-CHEMO SAT as convincing for the approval of Kizfizo MAA.

5.1.3. Ground #1.3: Impact of TMZ on time-dependent endpoints provides supportive evidence of the patients' clinical benefit

Applicant´s position on the third Ground for re-examination:

The Applicant demonstrated above that ORR and DCR are reliable endpoints of activity and observed results on these endpoints reflect a large and sustained treatment effect, which is likely to translate into meaningful clinical benefit with improved duration of disease control and survival, access to consolidation therapy for refractory patients and access to immunotherapy with Qarziba. Given the single arm nature of the pivotal BEACON-CHEMO, the Applicant is providing in this section further insight on time-to-event endpoints as supportive evidence of the clinical benefit of the medicinal product.

Indirect comparisons of post-relapse OS

In the MAA, the Applicant provided indirect comparisons (IC) of post-relapse OS of relapsed patients from the BEACON-CHEMO study and from 4 different cohorts of high-risk relapsed or progressive neuroblastoma retrospective cohorts. The purpose of performing the IC of post-relapse OS was to provide supportive evidence of the patient's benefit in the context of BEACON-CHEMO being a SAT, which is in line with the CHMP comment in the Assessment Report: "In general, external (historical) controls to a single-arm trials (or in this case, a trial without a control group) aim to provide supportive evidence for further exploration of the derived efficacy".

However, during the evaluation, the CHMP considered that the efficacy of the product, based on endpoints that isolate treatment effects, had not been established: according to the initial evaluation, only ORR could be considered as a suitable endpoint and the ORR was considered not convincing nor outstanding, precluding any further interpretation of the OS data (in the CHMP Assessment Report: "In general, external (historical) controls to a single-arm trials (or in this case, a trial without a control group) aim to provide supportive evidence for further exploration of the derived efficacy. This is considered appropriate when the efficacy has been established based on the single-arm trial itself, which is not considered to be the case for this application. The uncontrolled data from a SAT must be convincing on their own. Only endpoints that isolate treatment effects such as ORR are suitable for this purpose. A convincing/outstanding ORR is a necessary requirement. Only if this requirement is fulfilled, can contextualisation with external data provide supportive evidence."

In this ground for re-examination dossier, the Applicant has demonstrated that, in the context of high-risk relapsed or refractory neuroblastoma, ORR and DCR are endpoints that isolate treatment effects of TMZ in BEACON-CHEMO; that the clinical activity of TMZ combined with a topoisomerase inhibitor is large and sustained; and that it is highly likely to translate into patients' clinical benefit . Furthermore, the clinical benefit is supported by the fact that the treatment allows the patients to qualify for the next phase of their SoC therapy, i.e. consolidation for the refractory patients according to SIOPEN recommendations and immunotherapy according to Qarziba SmPC.

With the above provided evidence, the Applicant respectfully disagrees and believes that the efficacy has been established and that the requirements raised by the CHMP for using time to event data are now fulfilled, helping to give context to the clinical benefit of the TMZ combined treatments, even if effects on survival endpoints are supportive only in order for the CHMP to reach a positive opinion.

Furthermore, the Applicant would also like to, again, point to the very specific condition (high-risk relapsed or refractory neuroblastoma) being an ultra-rare condition. According to the EMA guideline on the clinical evaluation of anticancer medicinal products [EMA/CHMP/205/95 Rev.6], section "Studies in small study populations, very rare cancers", subsection "Use of external control", "in situations where a single-arm trial is justified, contextualisation of the results is a key issue. In some cases, when the response is dramatic, occurs rapidly following initiation of treatment, and is unlikely to have occurred spontaneously (e.g., measurable tumour shrinkage), assessment may be based on general knowledge. However, in less evident cases, specific external controls should be sought".

In the context of high-risk relapsed or refractory neuroblastoma, which is an ultra-rare condition, as the DCR

a) allows to isolate a large and sustained treatment effect (most high-risk relapsed and refractory patients experienced DC, which is by no means comparable to the course of the disease without effective treatment;

b) occurs very rapidly (all patients experiencing DC had DC at their first response evaluation);

c) is very unlikely to occur in the absence of treatment; and

d) is reasonably very likely to translate in true clinical benefit;

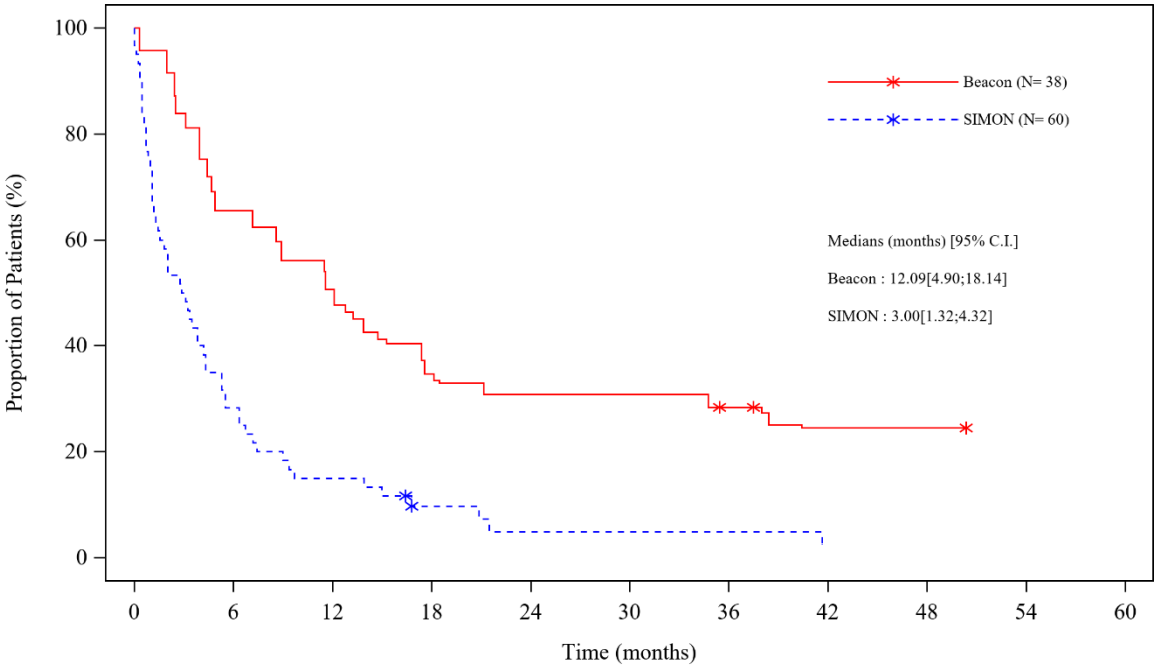
it can be concluded that it is legitimate to contextualise the results of the BEACON-CHEMO SAT with external data to provide further supportive evidence of the patients' clinical benefit.

For this purpose, Indirect Comparison (IC) of post-relapse OS data of patients treated with TMZ combined with irinotecan or topotecan are compared to the post-relapse OS data of relevant and rigorously selected historical control arms.

For indirect comparisons analyses, in addition to the disease stage (high-risk only), 3 confounder covariates reported to be independently predictive of post-relapse OS in multivariable analysis [London et al, 2011] have been pre-defined: age at diagnosis, MYCN amplification status and time to progression/first relapse (defined as the length of time between neuroblastoma diagnosis and progression/first relapse).

The IC of post-relapse OS for the BEACON-CHEMO patients was first performed against cohorts of untreated relapsed high-risk neuroblastoma patients to merely compare the post-relapse OS to the natural progression of the disease. Thus, these IC provide valuable insight into the order of magnitude of the treatment benefit in this patient population. Patients with high-risk neuroblastoma treated with TMZ combined with irinotecan or topotecan showed a large survival benefit compared to individual patient data from 60 relapsed high-risk neuroblastoma patients treated with supportive care only at relapse (Simon cohort, individual patient data [Simon et al, 2011] using Inverse Probability of Treatment Weighting (IPTW) (HR 0.39 [0.26; 0.57], $p<0.001$, see figure below), and compared to aggregated data of 17 high-risk relapsed neuroblastoma patients treated with supportive care only at relapse (Basta2 cohort, aggregated data [Basta et al, 2016] using Matched Adjusted Indirect Comparison (MAIC) (HR 0.19 [0.09 ;0.40], $p<0.001$, see figure below).

Figure 19. OS from progression/first relapse, BEACON-CHEMO (IT+TTO) vs Simon cohort (IPTW)

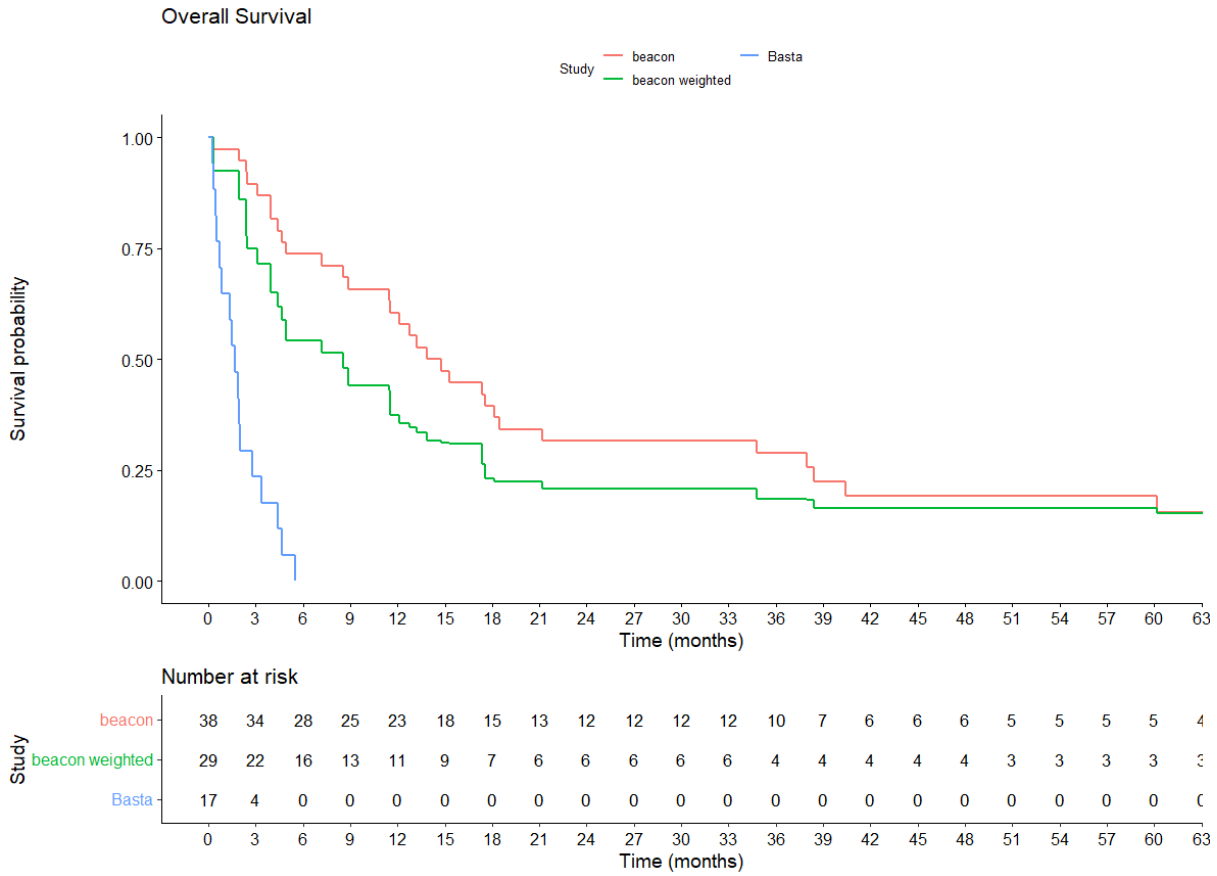


Weighted LogRank p-value [a] = <.001

Number of Subjects at Risk (Number of Censored)

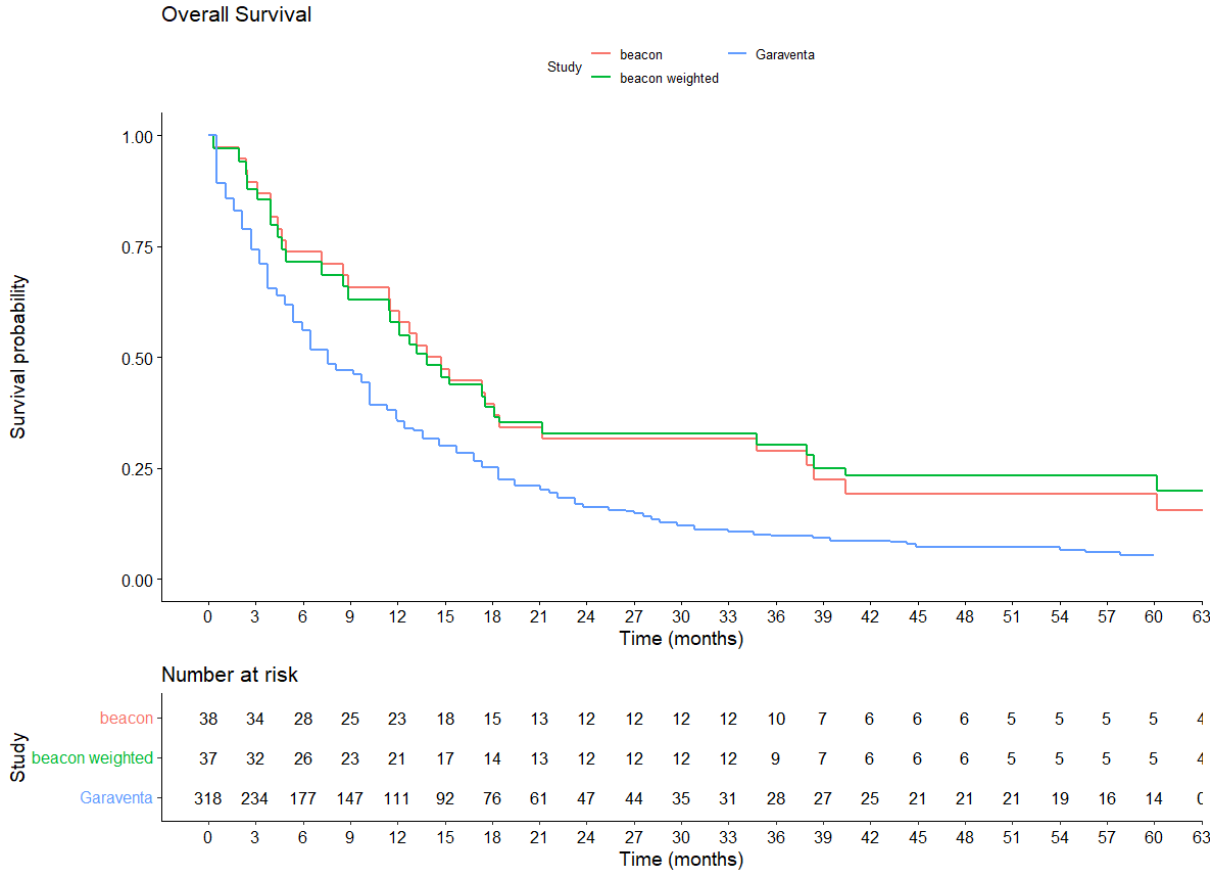
Beacon	62	41	31	22	19	19	14	10	10	9
	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(2)	(2)	(3)
SIMON	60	17	9	4	2	2	2	1	1	1
	(0)	(0)	(0)	(2)	(2)	(2)	(2)	(2)	(2)	(2)

Figure 20. OS from progression/first relapse, BEACON-CHEMO (IT+TTO) vs Basta 2 cohort (MAIC)



The TMZ treatment regimens also compared very favourably to the treated GARAVENTA historical cohort (HR 0.55 [0.36 ;0.85], p=0.007, see figure below); the Italian cohort comprises 318 patients treated until December 2006 according to the best standard of care at that time (most frequently, topotecan-vincristine-doxorubicin (TVD) or ifosfamide-carboplatin-etoposide (ICE)) but excluding any TMZ-based therapy.

Figure 21. OS from progression/first relapse, BEACON-CHEMO (IT+TTO) vs Garaventa cohort (MAIC)



Noteworthy, these IC of post-relapse OS for the BEACON-CHEMO patients versus 4 relevant and rigorously selected historical control arms were also performed with the post-relapse OS of the patients included in the retrospective data collection RetroTMZ study (Real World Evidence). Efficacy and safety data generated within the context of a retrospective study may suffer numerous biases, but post-relapse OS are robust data and can be considered for IC. IC with RetroTMZ data are very consistent when compared to the IC with the BEACON-CHEMO and further strengthen the robustness of the conclusions.

In the CHMP negative opinion on the granting of the MA for Kizfizo, it is stated that "comparison to external control groups provided by the Applicant cannot establish pivotal evidence of efficacy/clinical benefit for the claimed indication but could at best be considered as supportive data. This is because of the general inability to control bias for external control groups, and the specific concerns with regard to patient selection and analysis".

Although Orphelia recognises that the IC data shall be definitely considered as supportive data in the global assessment of the totality of the scientific evidence, we would like to contest the main methodological concerns related to patient selection and analysis.

The Applicant agrees that IC analyses were not prospectively planned, but:

- Analyses were decided after an initial comment made by the Co-Rapporteur in the Rapporteur Day 80 critical assessment report stating that we would suggest the Applicant to discuss in what extent the available efficacy data on TMZ, TEMIRI and TOTEM could demonstrate a clinical benefit in patients with refractory and relapsed high risk neuroblastoma (e.g. indirect comparison with historical control).

- The Indirect Comparison SAP was validated before analyses, so design and analysis decisions were made without knowledge of the results.
    - The SAP followed as much as possible EMA and other relevant national guidance documents on single arm trials and indirect comparisons (https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing-authorisation-application_en.pdf and https://arxiv.org/pdf/2206.09669) (https://research-information.bris.ac.uk/en/publications/nice-dsu-technical-support-document-18-methods-for-population-adj)
- Data sources were exhaustively searched for, and the list of data sources would have been the same prospectively or retrospectively.

All the biases described in the EMA guidance have been carefully considered and taken into account when applicable or feasible.

The Applicant agrees that randomisation and blinding are the best methods to avoid bias, but would like to make the following comments:

- In ICH E10, it is stated that indirect comparisons are acceptable when the course of illness is in fact predictable in a defined population (which is the case for high-risk relapsed or refractory neuroblastoma), and it may be possible to use a similar group of patients previously studied as a historical control.
- In addition, ICH E10 mentions: "Externally controlled trials are most likely to be persuasive when the study endpoint is objective, when the outcome on treatment is markedly different from that of the external control and a high level of statistical significance for the treatment-control comparison is attained, when the covariates influencing outcome of the disease are well characterised, and when the control closely resembles the study group in all known relevant baseline, treatment (other than study drug), and observational variables".

The analyses provided in the dossier are in accordance with these recommendations. A high level of statistical significance for the treatment-control comparison is attained in most sensitivity analyses with HR<0.5.

The choice of covariates is justified in the dossier using the publication by London [London 2011] and already fully acknowledged by the CHMP in the Qarziba assessment report in 2017 in which it is mentioned that following CHMP request, two studies in the relapsed setting [of high-risk neuroblastoma] were compared to historical controls; additional data on the relapses were collected to strengthen the evidence that these are reasonably matched with the patients treated in the APN311 studies for the most relevant baseline characteristics that are known from the literature. Two historical cohorts were identified: one from the Italian Neuroblastoma Registry (Garaventa et al, 2009) (…) and relapsed patients extracted from the SIOPEN high risk neuroblastoma study (HRNBL1), and that "based on the literature [i.e. London 2011], there are four key individual prognostic factors of survival in the relapsing patients: age at diagnosis, INSS stage of the tumour, time to first relapse and MYCN amplification status."

These prognostic factors have been considered in our historical comparison. INSS was not used in the model because primary estimand population focused only on INSS stage 4.

The indirect comparisons in the Qarziba dossier considered adequate by the CHMP were made with the individual patient data from the Garaventa and HRNBL1 historical cohorts by a multivariate model adjusted on prognosis variables (naïve indirect treatment comparison against a historical control), but without use of:

- Estimand approach
- Propensity score or MAIC approaches

- No consideration of the NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE (Technical Support Documents). NICE Decision Support Unit unlike the ICs made for Kizfizo, as recommended by the different guidance documents.

As per the previous round of assessment, the assessment team considered that the selection criteria and selection mechanisms for the BEACON-CHEMO study and the external control groups were substantially different, which is likely to have an important impact on the prognosis of patients: patients with a very poor health status are usually not included in a clinical study, while no such restriction existed for patients with a relapse that were retrospectively selected to be included in the control groups from larger cohorts of patients; notably, patients in these larger cohorts were not included because of relapse or at the time of relapse; rather, they were included at earlier time points based on other selection criteria.

This specific concern was already addressed above. The Applicant recognises that IC with cohorts of patients receiving only palliative care for their relapsed condition may suffer from inherent bias related to patient selection, but given the fact the Vassal clinical trial has demonstrated OS results consistent with the 2 cohorts of patients receiving only palliative care, this validates that the natural progression of the disease can be legitimately extrapolated from the data of the Simon and Basta2 cohorts.

Orphelia recognised that the external control groups are relatively old cohorts because of the need to identify neuroblastoma patient cohorts before the introduction of TMZ as SoC for the treatment of high-risk refractory and relapsed neuroblastoma. Nevertheless, these cohorts are recent enough for having received intensive first-line treatment protocols.

As per SAP, the 4 historical cohorts of interest have been carefully selected based on the main following characteristics:

- comprehensive neuroblastoma patients' data (either individual patient data or aggregated data, whichever could be made available) from national or international registries either i) collected before the introduction of TMZ (2004) as preferred salvage high-risk treatment of relapsed neuroblastoma in Europe or ii) including patients who have not been actively treated at relapse
- staging of high-risk neuroblastoma performed as per the INSS or INRGSS staging systems
- evaluation of MYCN amplification
- intensive first-line treatment protocols (combination chemotherapy and high-dose myeloablative therapy routinely used to treat high-risk neuroblastoma).
- European cohorts (i.e., patients treated according to European first line therapy for consistency with the patients enrolled in the Beacon-Neuroblastoma trial and the patients' data collected in the retrospective study RetroTMZ).

The Applicant agrees with the CHMP that for time to event endpoints, the choice of the appropriate time 0 is particularly challenging. This is the reason why in the SAP, the day of relapse was chosen as T0 for all analyses to limit biases (in particular, immortal bias).

The Applicant respectfully believes that the main methodological concerns have been addressed in an adequate manner.

In conclusion, despite the inherent biases in any indirect comparison analyses which the Applicant minimised as much as possible, post-relapsed OS data for relapsed patients treated with TMZ combined with irinotecan or topotecan in BEACON-CHEMO (as well in RetroTMZ) consistently showed a significant survival benefit over all available and relevant European historical cohorts (untreated or treated). These data support, with high plausibility, that achieving objective response and prolonged stable disease, allowing most relapsed patients to receive dinutuximab immunotherapy, results in extending survival times. The IC data provide strong supportive evidence of the clinical benefit of TMZ

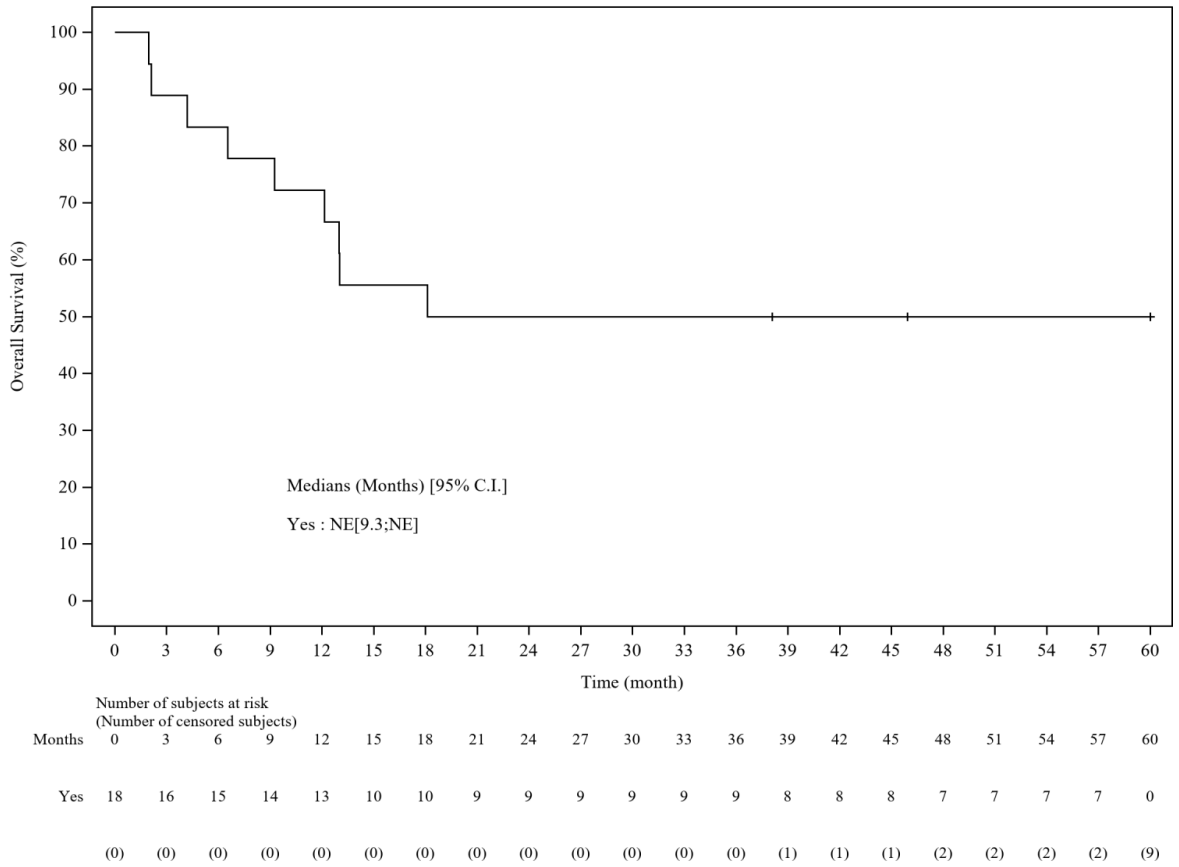
combined with irinotecan or topotecan for relapsed neuroblastoma. The theoretical risk of biases is not sufficient to set aside these compellingly positive results in an area of unmet medical need.

OS of refractory patients receiving consolidation

There is no historical OS data available specifically for refractory neuroblastoma patients to allow performance of IC analyses. Although time-to-event data from SATs need to be interpreted with caution, it is however of interest to comment on the OS for such a deadly and rapidly progressive disease in the context of OS of frontline (i.e., non-refractory) high-risk patients.

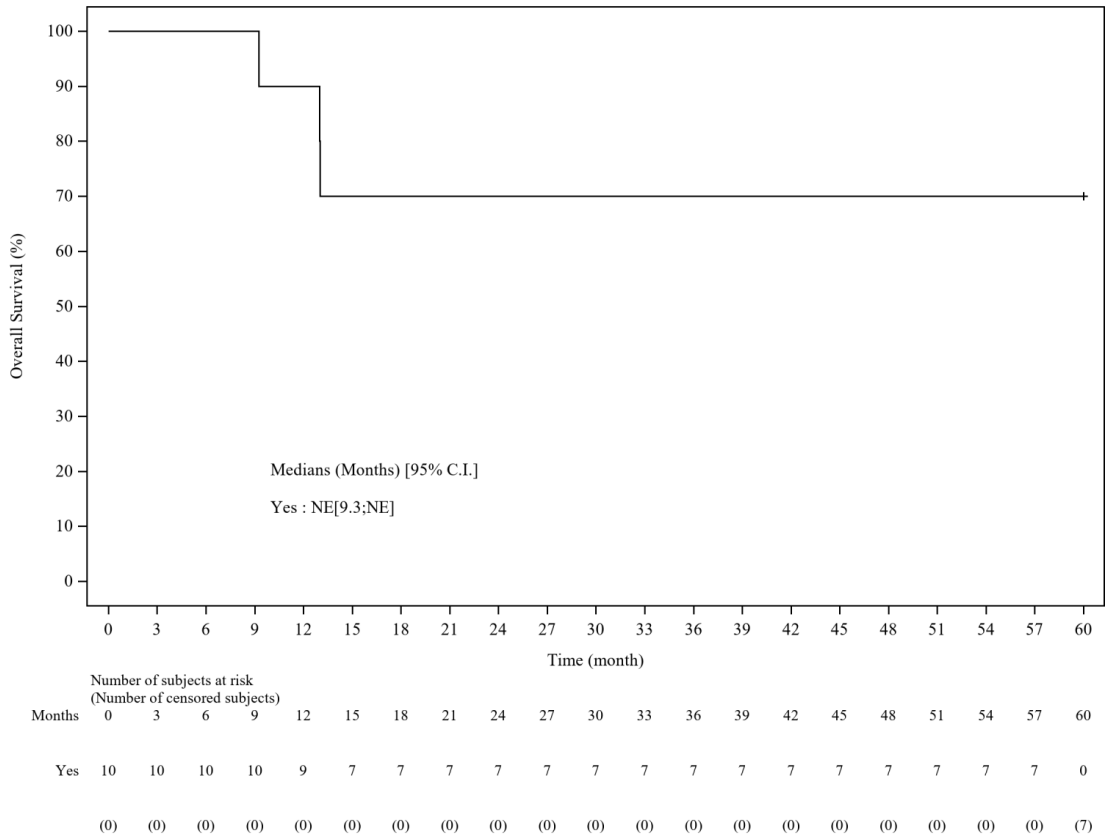
The 5-year OS of the 1347 high-risk patients enrolled in the frontline HRNBL1 trial is 43% [Ladenstein et al, 2017]. For the refractory patient population treated with TMZ in combination with irinotecan or topotecan (n=18) in BEACON-CHEMO (with or without access to consolidation), the 5-year OS is 50.00% [25.93 ;70.05] for the ITT population. This suggests that the survival of refractory patients treated within the BEACON-CHEMO study is comparable to the survival of frontline high-risk patients with adequate response to 1st line induction therapy and consolidation.

Figure 22. OS for refractory IT and TTO treated patients in the ITT population of BEACON CHEMO



For the 10 refractory patients treated with TMZ in combination with irinotecan or topotecan and who proceeded to consolidation, the 5-year OS is 70.00% [32.87 ;89.19] for the ITT population (see figure below).

Figure 23. OS for refractory IT and TTO treated patients with consolidation in the ITT population of BEACON CHEMO



Similarly, for the refractory patient population treated with TMZ in combination with irinotecan or topotecan (n=43) in the retrospective RetroTMZ study (with or without access to consolidation), the 5-year OS is 56.3% [41.1 ; 70.4], and for these who proceeded to consolidation (n=28), the 5-year OS is 73.7% [54.4 ; 86.8].

In conclusion, despite the absence of historical data to perform ad hoc IC, the consistently high rate of long-term survival of the refractory patients treated with TMZ in combination with irinotecan or topotecan in BEACON-CHEMO (as well as in RetroTMZ) supports the efficacy of the current refractory patient strategy, for which TMZ-based therapy is a key element. Patients achieving response or SD should proceed to consolidation with HDC and ASCR, as per SIOPEN recommendations.

Applicant General Conclusion

It has been established that TMZ regimens treatment effect (DCR), which reflects the clinical activity, is reasonably likely to translate in true clinical benefit and that time to event data can be used to better support the patients' benefit. Despite the possible inherent bias in any indirect comparison analyses, the methodological concerns have been addressed and the IC of post-relapse OS data for patients treated with TMZ combined with irinotecan or topotecan in BEACON-CHEMO consistently showed a significant survival benefit over 4 European historical cohorts, providing further context for the patient relevance of achieving objective response or stable disease in this setting. For the refractory patients, for whom no historical cohorts exist, the high rate of OS supports the efficacy of the current refractory patient strategy.

5.2. Scientific advice group (SAG) consultation

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

Report from the SAG

Please discuss the likelihood that the patients included in the BEACON-CHEMO study would have fulfilled criteria for progressive disease per RECIST or INRC (Park et al, J Clin Oncol 2017) within 24 weeks, if no therapy had been given.

- The answer to this question remains a matter of uncertainty. However, it should be noted that most patients with relapsed/refractory disease are expected to progress relatively quickly in the absence of treatment. Progression of disease is generally rapidly symptomatic.
- However, it is difficult to give an exact estimate of the proportion of untreated relapsed or refractory high-risk patients that would have experienced progressive disease at 24 weeks. A recent meta-analysis by London 2017 showed about 75% patients had experienced disease progression within 6 months. The studies included a variety of treatments of unknown efficacy. A time-trend towards improved response over time was suggested.
- The 24-week progression-free survival observed in the BEACON-CHEMO study of about 60% appears to be higher than reported in the meta-analysis using a variety of regimens of unknown efficacy. However, it is difficult to directly compare the studies due to different patients and disease characteristics, different response evaluation methods, and variable frequency of response assessment. For instance, the different time period of the BEACON-CHEMO study versus some of the studies included in the meta-analysis, and apparent time trends in terms of outcome in the meta-analysis, may have to be considered. Accordingly, if the estimate from the meta-analysis is restricted to the study period of the BEACON-CHEMO study, taking into account the apparent time trends observed in the meta-analysis, it may be that the 24-week progression-free survival would be more comparable between the BEACON-CHEMO study and the meta-analysis. Thus, the apparent higher proportion observed in the BEACON -CHEMO study may, to an unknown extent, be due to factors other than treatment, including potential imbalances in risk factors between study populations and temporal factors.

Please discuss what are the key predictors of response to (salvage) chemotherapy, that need to be taken into account in cross-study comparisons.

- Predictors of response to salvage chemotherapy are not easy to identify.
- Known prognostic factors for overall survival that should generally be considered when making cross-study comparisons include time to first relapse (TTFR), age, MYCN status, risk classification of disease. Other possible factors to be considered are ALK status and other genetic abnormalities (ploidy, chromosomal aberrations, etc.); response at end of induction; no. of relapses; relapsed v. refractory disease; and the fact that outcomes have improved over time.
- Indirect comparisons are generally difficult when all potential confounders are not considered. In addition, unknown confounders with potential impact on study results adds to uncertainties related to cross study comparisons. Finally, bias related to differences in surveillance/assessment schedules for relapse/progression may contribute to observed

study differences.

Please describe the role of TMZ in the treatment of neuroblastoma. How do TMZ regimens compare to other salvage therapies used in clinical practice?

- Patients with relapsed or refractory disease are treated with a variety of combination treatments of unclear efficacy. TMZ is commonly used in combination in this setting and generally the first choice in patients with refractory or relapsed neuroblastoma when clinical trials are not available/relevant. This is based on historical data of variable quality as well as institutional and sometimes national recommendations. The recommendations are not based on stringent scientific criteria or extensive evidence that firmly establish the efficacy of TMZ combination therapies, or how it compares with other treatment regimens. However, the challenges of conducting studies in this rare disease setting are acknowledged. TMZ-based regimens are considered tolerable and active, based on personal experience, and treatment without need for hospitalizations in this clinical setting is of value to patients and families/caregivers. Other agents commonly used in subsequent relapse setting include cyclophosphamide/topotecan.

In the context of treating neuroblastoma, absence of disease progression may facilitate access to consolidation or immunotherapy. The SAG is asked to explain the criteria used to proceed to consolidation therapy/immunotherapy and to discuss the long-term benefit of both treatment pathways.

- The role of consolidation treatments for patients with stable disease after initial salvage therapy for relapsed/refractory high-risk neuroblastoma setting is not well-established. The long-term benefit of consolidation in this setting is uncertain. Partial response after induction therapy according to criteria used is generally required. The decision to proceed to consolidation treatment in patients that do not formally fulfil criteria for partial response or better is a case by case decisions based on clinical judgement.

Please comment on the feasibility and informativeness of the applicant's proposed post-authorisation registry study.

- Generally, patients in this setting should be offered enrolment in a clinical trial if available/relevant. However, it should be feasible to enrol 100 patients treated in the routine setting with a TMZ-based regimen in a non-interventional registry study. Collection of health-related quality of life data is recommended.

5.3. CHMP Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group.

5.3.1. Ground #1.1: TMZ-based chemotherapy has meaningful clinical activity in the context of relapsed or refractory high-risk neuroblastoma

Natural course of the condition

Neuroblastomas are heterogenous tumours varying in terms of location, histopathologic appearance and biologic characteristics. Overall, they display a broad spectrum of clinical behaviours ranging from spontaneous regression to aggressive disease with metastatic dissemination leading to death. However, the applied indication targets refractory and actively progressing recurrent high-risk neuroblastoma narrowing the scope to a high-risk severe patient population.

High-risk relapsed or refractory neuroblastoma is a rare condition with poor prognosis, mainly affecting young children. The claimed indication contains the element of division of the patients between relapsed and refractory, which reflects different prognoses and possibilities to long-time survival and availability of follow-up treatment alternatives. To date, there are limited treatment options for patients with relapsed or refractory disease (Dubois et al. ASCO Educ Book. 2022). The dismal prognosis in neuroblastoma has been taken into account in the evaluation of the re-examination dossier.

According to the Applicant, the historical (untreated) cohorts confirm the poor natural course of disease. It is, however, important to highlight that selection bias as well as confounding factors are risks when comparing non-randomised cohort. In particular, the studies by Simon *et al* 2011 and Basta *et al* 2016 detail patients selected by not receiving active treatment after relapse. Simon *et al.* even discuss that "The decision for or against relapse chemotherapy and second ASCT depended on the advice of the physician and the wishes of the patient. The continuation of salvage therapy also depended on the response and toxicity of the first chemotherapy cycles, and this very likely led to selection of patients with favourable chemo-resistance profiles and/or high motivation for treatment (Simon *et al.* Pediatr Blood Cancer 2011)". Besides, multiple advancements in the treatment of neuroblastoma have had a positive impact on the overall prognosis in high-risk neuroblastoma in more recent years (Smith et al. Children. 2018). Due to such clinical benefit it will be difficult to determine to which extent individual components added to the overall improvement in prognosis in comparison to the more out-dated historical cohorts.

In line with the natural course of the disease, the Applicant claims that disease stabilisation as defined in the protocol (not fulfilling PD criteria after 6 cycles while not fulfilling response criteria) cannot occur spontaneously, and refers to literature to support this claim (Vassal *et al.* Eur J Cancer. 2008). The Applicant assumes that all patients would rapidly progress if not responding to therapy, but the level of evidence available to substantiate this claim is low. The study by Vassal *et al* 2008 was very small (n=37) and cannot be considered an exhaustive description of the course of disease. Besides, as described in the SAT reflection paper, time-to-event outcomes cannot be attributed to treatment, since these can occur in the absence or presence of treatment (EMA/CHMP/458061/2024). Input from the SAG was requested on the rapidness of progression in case patients are not being treated. They informed that "Most patients with relapsed/refractory disease are expected to progress relatively quickly in the absence of treatment. Progression of disease is generally rapidly symptomatic". An estimate of the proportion of untreated relapsed or refractory high-risk patients that would have experienced progressive disease at 24 weeks could not be given by the SAG and the scarcity of data on untreated patients was highlighted. The difficulties associated with cross-study comparisons was noted by the SAG.

Activity data from pivotal BEACON-CHEMO study

Considering the lack of a control-arm, the regulatory endpoint for isolating drug activity is ORR, as reductions in solid malignant tumour mass fulfilling RECIST criteria are generally not anticipated to occur without active anticancer therapy (Ghatalia et al, 2016). This is consistent with the original assessment procedure (i.e., "The primary endpoint was Best Overall Response Rate (Best ORR), which allows in principle some determination of anti-tumour activity as accepted previously in phase I/II trial.").

Results from the BEACON-CHEMO study have been thoroughly discussed during the initial assessment procedure. Briefly, best ORR (RECIST 1.1) was 15.8% (95% CI 5.5%, 37.6%, n=19) and 23.1% (95% CI 11.0, 42.1, n=26) for the ITT relapsed patients treated with TEMIRI and TOTEM respectively. For refractory patients, the ORR was 18.2% (95% CI 5.1, 47.7%, n=11) and 28.6% (95% CI 8.2%, 64.1%, n=7) for the respective treatments.

Considering the overall experience from the treatment of solid tumours, as well as regulatory precedent, the objective response rate (ORR) indicating the activity of temozolomide in the used regimens as reported in the BEACON-CHEMO study is modest. Overall, the observed ORR is around 20% and the lower bound of the confidence interval is 12.5% for the pooled combination regimens (i.e., the worst-case scenario) which indicate a not very active drug. Moreover, the point estimate is uncertain as reflected by the large CIs. In addition, the very small sample size of the cohort studied makes selection bias more likely when comparing with external controls. Besides, the BEACON study was primarily not designed to investigate the activity of TMZ. BEACON is an open label multi-regiment study with several treatment arms, which for the purpose of this assessment can be interpreted as a SAT based on the treatment arms TMZ+topotecan (TOTEM n=30) and TMZ+irinotecan (TEMIRI n=33) In line with the SAT reflection paper (EMA/CHMP/458061/2024), a SAT is expected to have an "a priori definition of a clear success criterion" based on external evidence. For the BEACON study, this would mean a pre-defined threshold defining meaningful activity of TMZ.

It is acknowledged that temozolomide-containing regimens are widely used to treat patients with relapsed/refractory (R/R) neuroblastoma, albeit there are also other treatment options investigated in R/R neuroblastoma (e.g., topotecan + vincristine + doxorubicin is another treatment option (Mueller et al. MAbs. 2018)). NCCN guideline recommends patients to proceed to chemoimmunotherapy, although specific treatment choices are not provided (Bagatell et al. J Natl Compr Canc Netw. 2024). The high-risk neuroblastoma study 2 includes as intervention 4 courses TEMIRI/dinutuximab beta (DB) in case of insufficient response to induction (High-Risk Neuroblastoma Study 2 protocol).

This was further confirmed by SAG that, describing the role of TMZ in the treatment of neuroblastoma, informed that "Patients with relapsed or refractory disease are treated with a variety of combination treatments of unclear efficacy. TMZ is commonly used in combination in this setting and generally the first choice in patients with refractory or relapsed neuroblastoma when clinical trials are not available/relevant. This is based on historical data of variable quality as well as institutional and sometimes national recommendations. The recommendations are not based on stringent scientific criteria or extensive evidence that firmly establish the efficacy of TMZ combination therapies, or how it compares with other treatment regimens. However, the challenges of conducting studies in this rare disease setting are acknowledged. TMZ-based regimens are considered tolerable and active, based on personal experience, and treatment without need for hospitalizations in this clinical setting is of value to patients and families/caregivers. Other agents commonly used in subsequent relapse setting include cyclophosphamide/topotecan"

The duration of response in each subgroup from BEACON-CHEMO study is noted, but this effect cannot be solely attributed to the study treatment due to potential follow-up therapies, as also made clear by the Applicant.

The Applicant argues that disease control rate (DCR) is an important endpoint in this disease setting, however this is challenged: according to Mittal *et al.* 2024 disease control rate is a misleading surrogate endpoint, as it is "based on the false premise that anything short of PD is a therapeutic benefit." (Mittal *et al.* EClinicalMedicine. 2024). The problem with DCR pertains to the stable disease part of the endpoint; in the BEACON-CHEMO study, SD was defined as patients not fulfilling response criteria and also not fulfilling criteria for progressive disease throughout 6 cycles of treatment. Stable disease is a mixture of the natural course of disease and treatment. Hence, DCR cannot be considered an isolated drug effect.

Overall, it is agreed that spontaneous regressions are unlikely in the target population. It is therefore agreed that TMZ-containing chemotherapy show some moderate activity in R/R neuroblastoma. However, for neuroblastoma, DCR does not isolate treatment effects in a SAT and results by themselves do not mirror clinical benefit (see further discussion below in ground #1.2). Furthermore,

the recommendations to use TMZ-containing chemotherapy are not based on stringent scientific criteria or extensive evidence that firmly establish the efficacy of TMZ combination therapies, or how it compares with other treatment regimens. In that regard, TMZ-containing chemotherapy is not the only active chemotherapy regimen investigated in R/R neuroblastoma.

In conclusion, the argumentation provided by the applicant for this ground for re-examination does not solve this ground for refusal.

5.3.2. Ground #1.2: TMZ-based chemotherapy clinical activity translates into quantifiable patient benefit

The Applicant attempts to demonstrate that DCR translates into clinical benefit. While this is appreciated, there remains a high level of uncertainty. In particular, there is only a sparse amount of evidence available to support the position of the Applicant.

Supportive evidence of clinical benefit: access to consolidation

In theory, adequate response to salvage/second-line chemotherapy will allow patients with refractory disease to proceed to the consolidation phase. However, it is not evident that all patients entering the consolidation phase will automatically derive long-term benefit from treatment. Moreover, the link between DCR and access to follow-up therapy is hampered by the lack of control arm and inability to fully isolate the treatment effect. Importantly , the SAG informed that the long-term benefit of consolidation therapy in patients with stable disease is uncertain. Generally, a partial response is required to proceed to consolidation.

In conclusion salvage/second-line chemotherapy can allow access to complementary therapy, however, DCR does not isolate a treatment effect in a SAT. Moreover, the extent to which SD as defined in the protocol confers clinical benefit is unclear.

5.3.3. Ground #1.3: Impact of TMZ on time-dependent endpoints provides supportive evidence of the patients' clinical benefit

Contextualisation of the results from uncontrolled studies is key, as has been highlighted in the "anticancer guideline" (EMA/CHMP/205/95 Rev.6). It is appreciated that the Applicant generated external controls for the BEACON-CHEMO study. However, as already described above, selection bias seems likely, considering that patients who do not receive treatment are not expected to be similar to those who do receive treatment; this concern is most relevant for the Basta and Simon cohort as described and discussed above. A further comparison is available with MAIC-adjusted data from the cohort of relapsed patients reported by Garavanta 2009, who were treated with non TMZ-containing chemo regimens. Notably, these patients were recruited between 1992-2004, whereas patients in the BEACON-CHEMO study were recruited between 2013-2019. London et al 2017 describes secular trends in outcome within the relevant timeframe.

To justify the validity of a comparison with external controls, it must be assumed that any differences between cohorts not due to the treatment given, can be controlled by adjusting based on measured confounders. The use of external controls suffers from several limitations including limited information for establishing similarities in patient populations with regard to prognosis and the presence of effect modifiers. Notably, important background characteristics are also missing from the BEACON-CHEMO study including histology characteristics, grade of tumour differentiation, 11q aberration status and tumour cell ploidy, increasing the difficulty to predict the expected disease course without treatment of the patients in BEACON-CHEMO. The SAG also stated that "Indirect comparisons are generally difficult when all potential confounders are not considered. In addition, unknown confounders with potential

impact on study results adds to uncertainties related to cross study comparisons. Finally, bias related to differences in surveillance/assessment schedules for relapse/progression may contribute to observed study differences".

Importantly, whereas randomisation produces a common time 0 between treatment arms, in calibrating time-dependent outcomes, no such time can be identified comparing patients that are refractory to prior therapy or who have relapsed, without a randomisation event. This hampers the interpretation of time-to-event endpoints.

As for the RetroTMZ cohort, several limitations have earlier been discussed including lack of standardised and formal evaluation, continued response of previous treatments, and more diverse population compared to BEACON-CHEMO including many refractory patients not recorded for previous treatment. ORR calculated for the ITT population was 23% after 2 cycles and best ORR was 37.2% in the overall population i.e. patients categorised as either relapsed or refractory. It should also be noted that patients who received TMZ as monotherapy were included. Some support for activity of TMZ in neuroblastoma can be gained but considering the limitations and less stringently selected patient population, quantification of this activity is uncertain. Also, this study does not isolate the effect of temozolomide on time-dependent endpoints. The results from RetroTMZ in supporting claims of efficacy for a market authorisation is at best supportive.

Overall, the indirect comparisons are less reliable and results should be interpreted with caution, as already discussed during the initial assessment procedure. This position remains unchanged after the re-examination.

In conclusion the indirect comparisons do not add much to the overall benefit-risk assessment, due to their inherent limitations.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

The applicant applied for the following indication:

"*Kizfizo in combination with irinotecan or topotecan is indicated for the treatment of paediatric patients aged 12 months and above with:*

- refractory high-risk neuroblastoma as second line chemotherapy after insufficient response to induction chemotherapy, to proceed to consolidation,

- actively progressing recurrent high-risk neuroblastoma after at least partial response to induction chemotherapy followed by myeloablative therapy and stem cell transplantation.

6.1.2. Available therapies and unmet medical need

Therapy for neuroblastoma is stage and risk stratified. The therapeutic modalities include surgery, chemotherapy, radiotherapy and biotherapy; observation-only is undertaken in a few very low-risk patients.

The management of neuroblastoma takes into consideration the risk stratification-based therapeutic modalities in accordance with the 2009 International Neuroblastoma Risk Group (INRG) Consensus Pre-treatment Classification Scheme. Treatment is based on 4 defined risk groups (very low risk, low risk, intermediate risk and high risk).

Up to 30% of the high-risk neuroblastoma patients are refractory to induction chemotherapy, therefore requiring further chemotherapy. Furthermore, half of the high-risk patients that initially respond to chemotherapy experience relapse within 3 years with a dismal prognosis.

High-risk patients treated according to the current SIOPEN HR-NBL2 protocol and who achieve insufficient response (PR<50% or SIOPEN score >3) after induction chemotherapy (i.e., refractory patients) receive 3 courses of TEMIRI as second line chemotherapy according to the HR-NBL2 amendment.

There are no uniform guidelines to direct the therapy of patients with recurrent neuroblastoma. Historically, recurrent neuroblastoma has been treated with a combination of chemotherapy and radiotherapy for the purposes of palliation only. In more recent times, treatment has evolved comprising salvage chemotherapy, radiotherapy and surgery, and 131I-MIBG therapy, and dinutuximab with interleukin-2 (IL-2) (De Sio et al, 2006; Rubic et al, 2006; Wagner et al, 2004; Kushner et al, 2006; Wagner et al, 2009; Bagatell et al, 2011; Rubie et al, 2010, Di Giannatale et al, 2014; Simon et al, 2007).

Second line chemotherapies with mild to modest toxicities that have not been included in frontline treatment are often considered for salvage. For the majority of patients with relapsed HR-NBL, initial treatment will comprise reinduction chemotherapy typically based around combinations of topotecan or irinotecan, with temozolomide or cyclophosphamide (Morgenstern et al, 2021).

Off-label use of TMZ in patients with neuroblastoma is currently based on oral TMZ-containing drug products, which are commercially available in the form of hard capsules.

Long-term survival after relapse of high-risk neuroblastoma is uncommon and although therapy may be able to prolong survival, careful consideration needs to be given to the individual needs of patients, balancing toxicity and burden of therapy with likelihood of benefit.

6.1.3. Main clinical studies

The pivotal trial supporting this application is BEACON-CHEMO; a sub-study of the BEACON Phase II randomised, open label, multinational study investigating the activity of several TMZ regimens in paediatric relapsed or refractory neuroblastoma patients (n=80); and ORP-TMZ-4 study (Retro TMZ), an international, multicentre retrospective study evaluating the use of TMZ in paediatric refractory or relapsed neuroblastoma (N=196).

The primary endpoint of the BEACON-CHEMO study was best Overall Response Rate (ORR), which was defined as Complete Response or Partial Response at any time during the first 6 cycles of trial treatment. RECIST 1.1 and INRS criteria were used to evaluate response in patients with measurable tumours. Stable disease (SD) was defined as lack of response but not meeting criteria for progressive disease during up to 6 cycles of treatment. Secondary endpoints included ORR at 2 cycles, PFS, EFS, OS and duration of response.

The primary endpoint of RetroTMZ study was to describe the population treated with TMZ and evaluate the time taken from start of first TMZ to first progression (time-to-progression [TTP]). Secondary endpoints included response rates (best response and response at 2 cycles), PSF and OS.

6.2. Favourable effects

In the BEACON-CHEMO study (ITT population), for the irinotecan + temozolomide (IT)/TEMIRI and temozolomide + topotecan (TTo)/TOTEM arms together, the ORR according to best response was 20.6% (95% CI: 12.5 - 32.2).

- IT group: 16.7% (95% CI: 7.3 - 33.6).
- TTo group: 24.2% (95% CI: 12.8 - 41.0).

For the IT and TTo arms together, the median DoR was 11.7 months (95% CI: 6.4 - 37.3).

For the IT and TTo arms together, DCR at best response was 63.5% (95%CI: 51.1 - 74.3)

- IT group: 63.3% (95% CI: 45.5 - 78.1); 60.0% (95% CI: 42.3 - 75.4) at the end of treatment.
- TTo group: 63.6% (95%CI: 46.6 - 77.8); 39.4% (95% CI: 24.7 - 56.3) at the end of treatment.

Access to complementary therapy:

- 12 out of 18 patients with refractory disease had response or SD and 10 patients received consolidation therapy (the remaining two entered a different clinical trial)
- 28 out of 45 patients with relapsed disease had response or SD and 12 patients received dinutuximab beta (Qarziba) as a follow-up therapy.

6.3. Uncertainties and limitations about favourable effects

Design techniques to avoid/minimise bias, such as randomisation and blinding, were not implemented in the BEACON-CHEMO trial.

The results from BEACON-CHEMO are based on only 45 relapsed patients and only 18 refractory patients. Hence, the activity estimation is fraught with uncertainty.

Stable disease, as part of DCR, cannot be entirely attributed to treatment. DCR is not a validated endpoint in R/R neuroblastoma.

In general, time-to-event endpoints do not isolate drug effects in the absence of a control arm.

Access to complementary therapy might not be clearly attributable to TMZ alone.

There is a sparse amount of historical data on the natural course of disease and the treatment landscape has changed over time. However, the very small dataset complicates – even further - cross study comparisons, due to patient selection. Cross study comparisons suffer from lack of pre-specification, different selection criteria, incomplete documentation of potential confounders, the inability to reliably establish a common time 0 in the absence of a randomisation event, possibly different handling of missing data, possibly inconsistent evaluation of outcomes, as well as the possible impact of different supportive care and overall secular trends in outcomes.

6.4. Unfavourable effects

As shown by results from the BEACON-CHEMO study, the safety profile of the temozolomide therapy in the targeted population was comparable to the known safety profile of temozolomide in approved indications. In the TEMIRI group, diarrhoea and vomiting were the most frequent AEs (64.3% and 53.6%,

respectively). Thrombocytopenia and Neutropenia had the highest incidences in the TOTEM group (69.2% and 53.8%, respectively).

The main cause of death was the disease itself. As expected, more patients in the refractory population (approx. 50%) were still alive at their last follow-up whereas 87% of the relapsed patients had died.

There was no obvious age effect and the subgroup analysis in children aged < 3 years and ≥ 3 years did not identify any safety signal in any age category. Cycle delays were seen in about 30% of the patients, dose reductions in 15%.

6.5. Uncertainties and limitations about unfavourable effects

The number of patients exposed to temozolomide in the target population (in the context of the BEACON-CHEMO study and the published studies) is substantial. However, the populations of the subgroups (age, disease indication, dose regimens) are quite small; thus subgroup results should be interpreted with caution.

6.6. Effects table

Table 67. Effects Table for Kizfizo in R/R neuroblastoma.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	CR or PR at any time during the first 6 cycles of treatment	Percentage	20.6% (95%CI: 12.5-32.2)	n.a.	Uncertainties: ORR is a surrogate endpoint; not a direct measure of clinical benefit. Lower bound of the CI was 12.5% only. Strengths Consistent with results from meta-analysis.	
mDoR	Time (in months) from the date of the first initial occurrence of a CR or PR to the PFS event or censoring date.	months	11.7 months (95% CI: 6.4 - 37.3)	n.a.	Uncertainties: May have been influenced by follow-up therapies Time-to-event endpoints are difficult to interpret without a control arm.	
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Main AEs by PT for TEMIRI	Vomiting		53.6 %	n.a.	Uncertainties: An overview of the treatment related AEs is missing Small subgroups	
	Diarrhoea		64.3 %	n.a.		
	Neutropenia		42.9%	n.a.		
	Thrombocytopenia		35.7 %	n.a.		
Main AEs by PT for TOTEM	Vomiting		53.8 %	n.a.	Uncertainties: An overview of the treatment related AEs is missing Small subgroups	
	Diarrhoea		23.1 %	n.a.		
	Neutropenia		53.8 %	n.a.		
	Thrombocytopenia		69.2 %	n.a.		

Abbreviations: ORR: objective response rate; CR: complete response; PR: Partial response; mDoR: median duration of response; PFS: progression free survival; AEs: adverse events; PT: preferred term
Notes:

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

The applicant seeks approval for the treatment of relapsed or refractory neuroblastoma in combination with a topoisomerase inhibitor (irinotecan or topotecan). The reference product for this hybrid application is currently used off-label for the treatment of neuroblastoma.

The development of a new formulation of temozolomide is considered an advantage, as the administration of hard capsules – the pharmaceutical form of the reference product (Temodal) – is not recommended for paediatric patients (e.g., birth to 6 years) and caregivers therefore open the capsules and mix the content with soft food or drink for administration.

Bioequivalence of Kizfizo with Temodal capsules has been shown. In addition, the Pop-PK model based on the TEMOkids study has been used to extrapolate PK parameters to the children from 1-3 years of age for temozolomide up to doses of no higher than 150 mg/m2 which covers the posology applied for temozolomide in combination with irinotecan or topotecan.

Relapsed as well as refractory neuroblastoma have a poor prognosis and only a few treatment options are available. If not treated, it has been reported that the majority of patients will rapidly progress. However historical evidence on the natural course of disease is sparse, which makes it difficult to contextualise results from uncontrolled clinical trials. Moreover, the treatment landscape of neuroblastoma has changed over the years; older references might therefore be outdated and secular trends in outcomes have been noted.

The pivotal trial supporting this application is the BEACON-CHEMO study. Results indicate that TMZ-containing regimens are active in R/R neuroblastoma and TMZ-containing regimens may be first choice in R/R neuroblastoma in clinical practice considering the large off label use.

There are, however, several uncertainties about the favourable effects. As already discussed during the initial assessment of the procedure leading to a negative opinion (see assessment report above), the response rate of TMZ-containing chemotherapy is modest; the lower bound of the 95% confidence interval is 12.5%. This level of activity is not usually considered sufficient to infer that an anticancer treatment will provide clinical benefit, based on trials without a relevant control arm.

As the majority of patients are expected to rapidly progress if not being treated, stable disease could be of interest as part of the DCR endpoint. However, it is not evident to what extent SD can be attributed to therapy, and to what extent a modest delay in progression may translate into longer term benefit. The SAG highlighted that the use of TMZ-based regiments "is based on historical data of variable quality as well as institutional and sometimes national recommendations. The recommendations are not based on stringent scientific criteria or extensive evidence that firmly establish the efficacy of TMZ combination therapies, or how it compares with other treatment regimens".

It is expected that an undefined subset of patients that receive follow-up therapy will derive long-term benefit from this. However, as discussed by the SAG, the long-term benefit of consolidation in patients without prior treatment response is uncertain. This adds to the overall uncertainty.

The externally provided data are currently seen as of limited value in this case, considering the above-mentioned limitations comparing literature and registry data vs the pivotal study.

Overall, the efficacy and clinical benefit of TMZ in the proposed indication have not been sufficiently demonstrated.

Temozolomide has a well-described safety profile. As reported in the SmPC of Temodal, the most common adverse reactions reported in clinical trials were nausea, vomiting, constipation, anorexia, headache, fatigue, convulsions, and rash. Haematologic toxicity is dose-limiting for temozolomide (Temodal EPAR), and such adverse reactions are reported commonly (Temodal SmPC). The safety data in the submitted dossier is derived from a small and diverse patient population but is consistent with the known safety profile of temozolomide as well as of its topoisomerase combination partners, including haematological and gastrointestinal adverse effects.

6.7.2. Balance of benefits and risks

While temozolomide containing regimens exhibit some activity in the claimed target disease, this is considered limited and therefore its clinical benefit has not been established. The safety profile would be acceptable in the treatment niche, however, in the absence of a sufficient demonstration of efficacy, B/R has not been shown to be positive in the claimed indications.

6.7.3. Additional considerations on the benefit-risk balance

6.7.3.1. Third party interventions

Third party intervention was received from several countries in the form of a letter signed by patient representatives/organisations, paediatric oncologists, learned societies. The intervention expresses

concern regarding the negative opinion of the CHMP received on 14th November 2024. In particular, it was highlighted the need for an age-appropriate formulation.

The intervention emphasised the role of TMZ in clinical practice claiming that "Over more than 20 years, temozolomide has undergone extensive evaluation and is a cornerstone in the standard treatment of children with refractory or relapsed high-risk neuroblastoma across Europe, the US and beyond". The use of TMZ in clinical practice is acknowledged by the CHMP and has been duly considered in the assessment. In addition, the SAG informed that the use of TMZ "is based on historical data of variable quality as well as institutional and sometimes national recommendations. The recommendations are not based on stringent scientific criteria or extensive evidence that firmly establish the efficacy of TMZ combination therapies, or how it compares with other treatment regimens".

In the letter received from third party interveners it was also stated that "the Agency applied regulatory methodology used for new active substances, expecting a high response rate to propose a marketing authorisation on the basis of single arm data, when comparative data are not available, seemingly disregarding the clinical context and unmet needs of children with life-threatening malignancies". It is important to highlight that the CHMP applied the appropriate regulatory methodology for an application for a new indication, which is independent of the new/known status of the active substance.

In conclusion, the CHMP has taken into account the clinical context and applied the necessary regulatory methodology for the received application.

6.7.3.2. Exceptional circumstances

The Applicant is requesting approval under exceptional circumstances, as it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, for objective and verifiable reasons, as set out in Part II(6) of Annex I to Directive 2001/83/EC, because:

"it would be contrary to generally accepted principles of medical ethics to collect such information, considering that providing data from a controlled (non-temozolomide-treated) arm would require to depart from the best practice of standard of care for patients suffering from the condition, relapsed or refractory high-risk neuroblastoma, which is an ultra-rare condition, who affect very vulnerable young children".

A marketing authorisation application under Exceptional Circumstances would be considered appropriate, as comprehensive data is not expected to be provided due to feasibility considerations preventing the conduct of an informatively sized randomised trial.

However, for applications under exceptional circumstances, the benefit-risk balance needs to be positive. This cannot be established as the Applicant has not been able to convincingly demonstrate that the small clinical activity observed in the pivotal study will translate into clinical benefit to support the marketing authorisation application for Kizfizo; thus, the request for approval under exceptional circumstances is not further discussed.

6.8. Conclusions

The overall benefit/risk balance of Kizfizo is negative and the grounds for refusal are maintained.

7. Recommendations following re-examination

Based on the arguments of the applicant, all the supporting data on quality, safety and efficacy, together with the ground for re-examination, as well as the outcome of the consultation with the oncology scientific advisory group and the Oral Explanation, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that:

Based on the CHMP review of data for Kizfizo indicated in combination with irinotecan or topotecan for the treatment of patients aged 12 months and above with:

- refractory high-risk neuroblastoma as second line chemotherapy after insufficient response to induction chemotherapy, to proceed to consolidation,
- actively progressing recurrent high-risk neuroblastoma after at least partial response to induction chemotherapy followed by myeloablative therapy and stem cell transplantation. (see section 5.1 for the definition of high-risk neuroblastoma).

and having considered all the available evidence, the CHMP considers that pursuant to Article 12 of Regulation (EC) No 726/2004, the efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated and therefore recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

> *Efficacy results from the BEACON-CHEMO study (phase II uncontrolled study) and the Retro TMZ study (observational retrospective study) show limited clinical activity of temozolomide in combination with irinotecan or topotecan in relapsed / refractory high-risk neuroblastoma patients. The Applicant has not been able to convincingly demonstrate that this level of activity will translate into clinical benefit. Furthermore, time-dependent endpoints in the BEACON-CHEMO study do not isolate drug effects in absence of a control arm.*

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 outlined in the list of outstanding issues cannot be agreed at this stage.