CONFIDENTIAL

CLINICAL TRIAL PROTOCOL

Naxitamab and Granulocyte-Macrophage Colony Stimulating Factor in Combination with Irinotecan and Temozolomide in Patients with High-Risk Neuroblastoma with Primary Refractory Disease or in First Relapse. An International, Single-Arm, Multicenter Phase 2 Trial

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Approval of Clinical Trial Protocol

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE	Angiotensin-converting enzyme
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody dependent cellular phagocytosis
AE	Adverse Event
AESI	Adverse event of special interest
allo-SCT	Allogeneic hematopoietic stem cell transplantation
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BM	Bone Marrow
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C	Cycle
CBC	Complete Blood Count
CDC	Complement-Dependent Cytotoxicity
CI	Confidence Interval
CNS	Central Nervous System
COG	Childrens Oncology Group
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
D	Day
DLT	Dose-Limiting Toxicity

DMC	Data Monitoring Committee
DoR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFS	Event-Free Survival
eGFR	estimated Glomerular Filtration Rate
EOT	End of Treatment
ES	Ewing Sarcoma
FAS	Full Analysis Set
FDA	The Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FLACC	Face, Legs, Activity, Cry, Consolability
FPFT	First Patient First Treatment
FSH	Follicle-Stimulating Hormone
FU	Follow-Up
GCP	Good Clinical Practice
GD2	Disialoganglioside
GM-CSF	Sargramostim - Granulocyte-Macrophage Colony Stimulating Factor
HACA	Human Anti-Chimeric Antibody
HITS	Naxitamab + GM-CSF + irinotecan +temozolomide
HPC	Hematopoietic Progenitor Cell
IB	Investigator's Brochure
ICF	Patient Information and Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IHC	immunohistochemistry
IL-2	Interleukin-2

IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INRC	International Neuroblastoma Response Criteria
INRG	International Neuroblastoma Risk Group
IQR	Interquartile range
IRB	Institutional Review Board
IT	Irinotecan and temozolomide
ITCC	Innovative Therapies for Children with Cancer
IU	International Unit
IV	Intravenous
kg	Kilogram(s)
L	Liter
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MeDRA	Medical Dictionary for Regulatory Activities
MD	Minimal disease
µg	Microgram
mg	Milligram
MIBG	Metaiodobenzylguanidine
min	Minute(s)
mL	Milliliter(s)
mmol	Millimol
MR	Minor Response
MRD	Minimal residual disease
MRI	Magnetic Resonance Imaging
MSK	Memorial Sloan Kettering Cancer Center
MYCN	Myelocytomatosis Viral-Related Oncogene, Neuroblastoma Derived
N	Number of subjects
NB	Neuroblastoma

NCI	National Cancer Institute
NE	Not Evaluable
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect-level
OR	Objective Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PO	Per Os (by mouth)
PPS	Per Protocol Analysis Set
PR	Partial Response
PRES	Posterior reversible encephalopathy syndrome
PRN	When necessary (pro re nata)
RT	Radiation therapy
RTqPCR	Reverse transcriptase-quantitative polymerase chain reaction
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Stable disease
SIOPEN	International Society of Paediatric Oncology Europe Neuroblastoma
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SPECT	Single-Photon Emission Computed Tomography
SpO_2	Peripheral Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event

TFST	Time to First Subsequent Therapy
UNL	Upper Normal Limit
WBC	White Blood Cells
W	Week
WHO	World Health Organization
WOCBP	Woman of child-bearing potential

2 PROTOCOL SYNOPSIS

Title	Naxitamab and Granulocyte-Macrophage Colony Stimulating Factor in Combination with Irinotecan and Temozolomide in Patients with High-Risk Neuroblastoma with Primary Refractory Disease or in First Relapse**.** An International, Single-Arm, Multicenter Phase 2 Trial
EudraCT number	2020-003068-21
Investigational New Drug (IND)	132793
Sponsor	Y-mAbs Therapeutics A/S Agern Allé 11 2970 Hoersholm Denmark
Trial ID	203
Trial design	This is an international, single-arm, multicenter phase 2 trial, in patients ≥ 12 months of age with high-risk NB with primary refractory disease or in first relapse. Patients will receive naxitamab + GM-CSF + irinotecan/temozolomide. The Follow-Up period ends 2 years after End of Treatment.
Patient population	The trial will include patients with high-risk neuroblastoma with measurable and/or evaluable disease and with either primary refractory disease or first relapse following induction and consolidation therapy.
Objectives	**Primary objective:** • To investigate the efficacy of naxitamab + GM-CSF in combination with irinotecan/temozolomide as assessed by overall response rate in patients with high-risk neuroblastoma with primary refractory disease or in first relapse **Secondary objectives:** • To further investigate the efficacy and safety of naxitamab + GM-CSF in combination with irinotecan/temozolomide in patients with high-risk neuroblastoma with primary refractory disease or in first relapse.
Endpoints	**Primary Endpoint:** Overall response rate, defined as the proportion of patients obtaining a centrally assessed complete or partial response according to the International Neuroblastoma Response Criteria at or before completion of four cycles **Key Secondary Endpoints:**

	• Overall response rate after 2 cycles defined as the proportion of patients obtaining a centrally assessed complete response or partial response according to the International Neuroblastoma Response Criteria at completion of two treatment cycles • Duration of response, defined as the time from first centrally assessed overall response (complete response or partial response according to the International Neuroblastoma Response Criteria) to progressive disease or death • Complete Response rate, defined as the proportion of patients obtaining a centrally assessed complete response according to the International Neuroblastoma Response Criteria at or before completion of four treatment cycles • Time to First Subsequent Therapy (defined as the time from initiation of treatment with investigational medicinal product until death or start of new anti-cancer treatment (prohibited as per protocol)) • Progression Free Survival defined as the time from first investigational medicinal product administration until centrally assessed Progressive Disease or death, whichever comes first • Overall survival defined as the time from first investigational medicinal product administration until death • 1- and 2-years Progression Free Survival defined as the proportion of patients alive and with no centrally assessed Progressive Disease at 1- and 2 year, respectively after first investigational medicinal product administration • 1- and 2-years overall survival defined as the proportion of patients alive at 1- and 2 years after first investigational medicinal product administration
Patient selection criteria	**Key inclusion criteria:** • Documented neuroblastoma at time of initial diagnosis defined as: o Histopathological verification of neuroblastoma or ganglioneuroblastoma nodular, or o Bone Marrow aspirate or biopsy indicative of neuroblastoma (according to International Neuroblastoma Response Criteria and high blood or

urine catecholamine metabolite levels (> 2 x upper limit of normal)

- Documented high-risk disease at time of initial diagnosis defined as:
    - MYCN-amplified any stage (according to International Neuroblastoma Risk Group) of any age or
    - MYCN-nonamplified with stage M (according to International Neuroblastoma Risk Group) and diagnosed at ≥18 months of age
- Patient should have received standard of care (SoC) frontline induction/ consolidation therapy (surgery, chemotherapy, autologous stem cell transplant, MIBG, radiotherapy, immunotherapy, or retinoids)
- Patients must have active disease despite previous aggressive multi-drug chemotherapy (≥ 2 agents, including an alkylating agent and a platinum containing compound) defined as one of the following:
    - Verified first progression during multi-drug frontline treatment or
    - Verified first episode of relapse, defined as recurrence after response to frontline treatment, or
    - Verified first designation of refractory disease, defined as persistent metastatic disease (SD or minor response by International Neuroblastoma Response Criteria and MIBG curie score ≥3) detected at conclusion of at least 4 cycles of multi-drug induction chemotherapy on or according to a high-risk NB treatment protocol
- The patients must have one of the following (locally assessed) obtained within 3 weeks prior to enrollment and at least 10 calendar days after end of any prior anti-cancer treatment:
    - Measurable tumor on CT/MRI scan that is MIBG-avid or demonstrates increased FDG uptake on PET scan
    - MIBG scan with positive uptake at a minimum of one site. This site must represent disease recurrence after completion of therapy, progressive disease on therapy, or refractory disease during induction
- Aged ≥ 12 months at enrollment

- Written informed consent from legal guardian(s) and/or child obtained in accordance with local regulations. Pediatric patients must provide assent as required by local regulations

Key Exclusion criteria:

- Any systemic anti-cancer therapy, including chemotherapy, or immunotherapy, within 3 weeks prior to enrollment
- Autologous Stem Cell Transplantation within 6 weeks prior to enrollment or ongoing toxicity due to the stem cell transplant at the discretion of the investigator
- Therapeutic ^{131}I-MIBG within 6 weeks prior to enrollment
- Radiation therapy within 4 weeks prior to enrollment at the site of any lesion that will be identified as a target lesion to measure tumor response. Lesions that have been previously radiated cannot be used as target lesions unless there is radiographic evidence of progression at the site following radiation or a biopsy done following radiation shows viable neuroblastoma. There are no time restrictions following prior radio therapy for non-target lesions or for palliative radiation to sites that will not be used for response assessment
- Prior treatment with anti-GD2 therapy if the patient experienced progressive disease while on anti-GD2 treatment
- Patients with neuroblastoma in bone marrow only
- Neuroblastoma in the CNS or leptomeningeal disease within 6 months prior to enrollment
- Performance status of < 50% as per the Lansky scale (patients less than 16 years of age) or Karnofsky scale (for patients aged 16 years or older)
- Life expectancy of less than 6 months, as judged by the Investigator
- Allogeneic hematopoietic stem cell transplantation or donor-lymphocyte-infusion (defined as any kind of active allogeneic lymphocyte suspension)
    - within 6 months of 1st dose of GM-CSF or
    - with a lymphocyte count < 0.2 x10^9/L
- Treatment with Hematopoietic Progenitor Cell boost within 2 months prior to enrollment

Methodology	The efficacy and safety of naxitamab + GM-CSF in combination with irinotecan/temozolomide will be evaluated using a single-arm trial design in patients with high-risk neuroblastoma with either primary refractory disease or in first relapse. At the discretion of the investigator patients may receive treatment for up to 70 weeks. Each patient will have a long-term follow-up for 2 years after End of Treatment.
Number of patients (planned)	Approximately 70 patients will be screened to achieve the planned 52 enrolled patients who have all received at least 1 dose of IMP.
Investigational Medicinal Product (IMP)	The following investigational medicinal products are supplied by Y-mAbs: • Irinotecan, 20 mg/mL, solution for infusion, IV infusion • Temozolomide, 5 mg, 20 mg and 100 mg, capsules, orally • The humanized immunoglobulin isotype G (IgG1) monoclonal antibody (mAb) naxitamab, 4 mg/mL, solution for infusion, IV infusion • Sargramostim (GM-CSF), 250 µg/vial, lyophilized 250 µg single use vial, subcutaneous
Trial period(s) and duration	Each patient will receive up to 70 weeks of treatment. End of Treatment will be 6 weeks after last treatment. Each patient will have a long-term follow-up up for 2 years after end-of-treatment.
Statistical considerations	Results will be presented by appropriate descriptive statistics. With the statistical analysis methodology of the primary endpoint and a drop-out rate of 20%, in mind: 52 patients are needed to, with 82% power, demonstrate that the overall response rate is statistically significantly higher than 20%. The null hypothesis that the probability of the centrally assessed response rate after 4 cycles is equal to 20% will be tested against the two-sided alternative using the two-sided exact binomial test on the 5% significance level. Secondary endpoints based on INRC responses, based on both central and local assessments, will be presented using descriptive statistics. Responses based on investigators' local assessments are used as sensitivity analyses. Duration of response, PFS and OS will be estimated using Kaplan-Meier methodology. Two-sided 95% confidence intervals will be presented. Safety data will be summarized and where relevant, presented in graphs.

3 FLOW CHART

Table 1 Schedule of time and events: screening, treatment and follow-up

Please refer to Appendix 2 for flowchart for patients who have discontinued treatment with irinotecan and temozolomide due to toxicity.

Treatment / Measurements / Evaluations	Screening	First treatment cycle														
	D -24 to -4	D -3 to 0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	Next cycles[3]	EOT[4]	Long-term FU[5]
Informed consent (13.3)	X															
Eligibility check (7.11.1, 7.11.2)	X	X														
Demographics and baseline characteristics (9.3.1)	X															
Medical and Surgical history (9.3.3)	X	X[7]														
Physical examination (9.2.1)	X	X[8]	X[8]											X[8]	X	
Height and weight (9.3.2)	X	X[8]	X[8]											X[8]		
Serum pregnancy test, if applicable (9.2.8)	X	X[9]												X	X	
Vital signs (9.2.2)	X		X	X	X	X	X			X		X		X	X	
Echocardiography (9.2.4)	X															
Pulmonary function tests and oxygen saturation[1] (9.2.5)	X															
Electrocardiogram [2] (9.2.6)	X														X	
Clinical laboratory assessments (11.1)	X	X[8]	X[8]		X		X			X			X[10]	X[8]	X	
Anti-drug antibodies (11.2)		X[8]	X[8]											X[8]	X	

Treatment / Measurements / Evaluations	Screening	First treatment cycle														
	D -24 to -4	D -3 to 0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D15	Next cycles[3]	EOT[4]	Long-term FU[5]
Bone marrow biopsy/aspirates (9.1.1, 9.1.1.1, 9.1.2)	X[6]													X[11]	X[13]	X[14]
Imaging (9.1.1, 9.1.2)	X[6]													X[12]	X[13]	X[14]
Performance test (9.3.4)	X	X[8]	X[8]											X[8]	X	
Pain assessment (9.2.7)				X		X				X		X		X		
Pre-treatment (8.4.1, 8.4.3)		X	X	X	X	X	X	X	X	X	X	X		X		
Treatment (8.1.1, 8.1.2)			X	X	X	X	X	X	X	X	X	X		X		
Drug accountability and compliance check (8.1.5)			X	X	X	X	X	X		X		X		X		
Hand out diary (8.1.5)							X							X		
Adverse events (10)	X	X	X	X	X	X	X	X		X		X	X[10]	X	X	X
Concomitant medication(s) (8.4)	X	X	X	X	X	X	X	X		X		X	X[10]	X	X	X

1 If clinically indicated, please see exclusion criteria 13.
2 Local assessment of electrocardiogram (ECG) during screening and at end of treatment (EOT). If the patient needs sedation before ECG, the ECG can be performed in connection with imaging.
3 The next cycle may be postponed up to 3 weeks in case of irinotecan and temozolomide toxicities: Please refer to Section 8.4.4.
4 EOT visit should take place 6 (up to 10) weeks after last treatment. If treatment is discontinued due to progressive disease (PD), initiation of new anti-NB treatment prohibited as per protocol, withdrawal from the trial or investigator judges it warranted due to medical reasons/non-compliance, the patient should be called for EOT visit as soon as possible and subsequently be followed for safety and new anti-cancer therapy for 6 weeks after last treatment, and herafter continue in the long-term follow-up.
5 Long-term follow-up (FU) evaluations should take place approximately every 4 months until 2 years after End of Treatment. During long-term FU, information on death, PD, serious adverse events (SAEs) ongoing at EOT, new SAEs at least possibly related to naxitamab, new onset of secondary malignancies and autoimmune diseases should be collected. Furthermore, new anti-cancer therapy should be collected as concomitant medication. (see Section 9.1).
6 Screening imaging and BM examination must be obtained at least 10 calendar days after any prior anti-cancer treatment.
7 Only applicable for D-3 to 0 in cycle 1.
8 Height, weight, physical examination, clinical laboratory assessments, anti-drug antibodies (ADA) and performance test must be performed prior to dosing in each cycle; prior to day (D)1 or at D1.
9 Serum pregnancy test must be done on D-3 prior to gabapentin administration for women of childbearing potential
10 Should only be performed at D15 during C1.
11 Bilateral aspirates and bone marrow (BM) biopsies (2+2), performed at screening and after C2, C4, C8, C13, and EOT. In addition, for patients who achieve a first CR or PR after C4 or a first CR or PR after C8 a confirmatory response assessment should be performed within 4-6 weeks after detection of the overall response. Samples for RTqPCR should be taken at Screening and after C2 and C4. See section section 9.1.2

12 Imaging schedule follows timing of BM biopsies (see #11 above). For a Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography (FDG PET/CT) scan, the patient must be in fasting state for at least 4 hours prior to the scan. If the patient is not fasting serum glucose determination must be performed prior to the administration of FDG. Please refer to the imaging acquisition guideline for more details.
13 Not to be performed at EOT if the patient discontinue treatment due to PD, provided that PD is documented by scan and/or biopsy. See section section 9.1.2
14 For patients who have not experienced PD, response assessment should be performed approximately every 4 months after EOT during long-term FU. See section section 9.1.2

4 INTRODUCTION

4.1 Medical Background

Neuroblastoma (NB) is a rare cancer but is the most common extracranial solid tumor of childhood. It has a varied prognosis, ranging from spontaneous regression to aggressive metastatic tumors with fatal outcomes despite multimodality therapy. The prognosis of NB correlates closely with numerous biological and clinical factors such as age, tumor stage and histology, genetic and chromosomal abnormalities[1]. At diagnosis, more than 50 percent of patients present with metastatic disease (stage 4), typically in the bone marrow (BM)[2-4]. BM invasion is associated with a very poor prognosis[3, 5]. Despite advances in frontline multimodality therapy, approximately 50% of patients with high-risk NB have persistence of disease or develop progressive disease (PD)[6]. After relapse, the outcome has been poor for decades, with 10-year overall survival (OS) of <15%[7]. The disappointing prognosis is supported by a meta-analysis of 3 Phase 2 trials (71 patients), conducted by Innovative Therapies for Children with Cancer (ITCC)/ International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN) European, showing a median progression free survival (PFS) for all patients, patients with primary refractory disease, and patients with relapsed disease of 6.4, 12.5, and 5.7 months, respectively. The corresponding numbers for OS were 16.1, 27.9, and 11.0 months, respectively[8]. Moreover, another meta-analysis of 35 phase 1-2 trials from Children's Oncology Group (COG) from 2002 to 2014 (383 patients) in recurrent or refractory NB revealed 1-year and 4-year PFS rates of 21% and 6%, respectively, and 1-year and 4-year OS rates of 57% and 20%, respectively[9].

Thus, there is a high unmet medical need for more efficacious treatments for patients with high-risk NB with primary refractory or relapsed disease.

4.2 Rationale for antibody therapy for High-Risk NB

The disialoganglioside GD2 is an adhesion molecule abundantly expressed in NB[10]. This genetically stable antigen is rarely lost and relatively inert on the cell membrane. Monoclonal antibodies (mAbs) that target GD2 have shown clinical efficacy in the treatment of GD2 expressing tumors. This includes metastatic cancer in well-vascularized sites of metastases, such as BM infiltrated by NB cells[10, 11]. Three anti-GD2 mAbs are currently approved for the treatment of high-risk NB. Dinutuximab (Unituxin®) and naxitamab (Danyelza®) are approved in the United States (US) for the treatment in the post-consolidation setting and of relapsed/refractory NB in the bone and/or BM, respectively[12, 13]. Dinutuximab beta (Qarziba®) is approved in the European Union (EU) for the treatment in the post-consolidation setting and of relapsed or refractory NB[14]. Dinutuximab and dinutuximab beta contain significant murine fractions and represent so called chimeric antibodies. Rapid production of human anti-chimeric antibody (HACA) can develop in patients and can delay treatment, prevent further cycles, and compromise anti-tumor effects of the mAb treatment. Furthermore, treatment with these antibodies requires long time infusions; dinutuximab is administered over 10

to 20 hours for 4 consecutive days; dinutuximab beta is administered over 8-hours for 5 days or during continuous infusion with a pump for 10 days. Treatments are typically performed or initiated in the in-patient setting. Humanization of the anti-GD2 antibody reduces or eliminates the mouse epitopes and has the potential to reduce development of such anti-drug-antibody (ADA) responses. Furthermore, a shorter infusion time may decrease the treatment burden for patients and their families. Naxitamab represent such an approach.

4.3 Naxitamab profile

4.3.1 Non-clinical data for naxitamab

Naxitamab (humanized 3F8) is a humanized anti-GD2 mAb with approximately ten-fold higher binding affinity to GD2 compared to dinutuximab and dinutuximab beta primarily due to a slower dissociation rate. Naxitamab has preferential affinity for NB tissue. In normal tissues naxitamab binding is observed in cerebellum, cerebral cortex, spinal cord, peripheral nerves, [redacted]. The effect of naxitamab is mediated through antibody-dependent cellular cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC) (see the current version of the Investigator's Brochure (IB) and any updates hereof).

No adverse findings were observed after administration of naxitamab as a single dose of [redacted] to mice or after two cycles of three doses of [redacted], amounting to a maximum of [redacted], in a [redacted] toxicity study in nude rats. Moreover, in a [redacted] repeat-dose toxicity study in nude rats, naxitamab was well tolerated clinically when administered over 4 cycles of 3 treatment days, and up to [redacted]. Up to moderate hyperplasia accompanied by inflammatory changes [redacted] were considered adverse. Complete recovery occurred in males with partial recovery in females. In view of the severity of these stomach changes, [redacted] (see the current version of the IB and any updates hereof).

4.3.2 Clinical data for naxitamab

Two ongoing, open-label, single arm, phase 2 clinical trials (trials 12-230 and 201, interim analyses) have proven naxitamab to be efficacious (Table 2) with a manageable safety profile as single anti-cancer agent in combination with granulocyte-monocyte colony stimulating factor (GM-CSF) in patients with high-risk refractory or relapsed NB in bone and/or BM (the current version of the IB and any updates hereof). In these trials, naxitamab was administered intravenously (IV) over 30 minutes (min) on Days 1, 3 and 5 at 3.0 mg/kg/infusion (9.0 mg/kg/cycle) in combination with GM-CSF (Sargramostim) subcutaneously (sc) at 250 ug/m^2/day on Days -4 to 0 and at 500 ug/m^2/day on Days 1 to 5. Treatment cycles were repeated every 4 weeks until complete response (CR) or partial response (PR), followed by 5 additional cycles every 4 weeks. In Trial 201, in which

detailed information on infusions was captured, the vast majority (95%) of naxitamab infusions were administered in the outpatient setting. The duration of infusions was short, at a median of 37 minutes and all infusions were <2 hours[15].

Table 2 Efficacy results for interim analyses of Trials 12-230 and 201

	ORR (%)	CR (%)	PR (%)
Trial 201 (N=22)	68 [95% CI: 45 to 86]	59	9
[redacted]	[redacted]	[redacted]	[redacted]

Note. CR = complete response; ORR = overall response rate; PR = partial response. N = number of subjects. CI = confidence interval.

[redacted]

In terms of safety across Trials 12-230 and 201, naxitamab was found to be generally well tolerated with a manageable safety profile. The acute toxicities/infusion related adverse events (AEs) included mainly Common Terminology Criteria for Adverse Events (CTCAE) Grade 1-2 events. Treatment-Emergent AEs (TEAE) occurring in ≥ 50% of patients in at least one of the 2 trials included hypotension, urticaria, abdominal pain, pyrexia, tachycardia, bronchospasm, cough, flushing, nausea, vomiting, decreased appetite, diarrhoea, pain in extremity and pruritus. Across the 2 trials, TEAEs of CTCAE grade 3 or higher were reported in [redacted] to 92% of patients. TEAEs of grade 3 or higher reported in ≥10% of the patients in at least one of the trials were pain, hypotension, urticaria, bronchospasm, stridor, depressed level of consciousness and neutropenia The acute toxicities/infusion related AEs were generally managed by pre-medications (opioids, corticosteroids, antipyretics, and antihistamines) along with concomitant administration of normal saline, opioids, nebulized beta-2 agonists, and oxygen as applicable during the naxitamab infusion. [redacted], 2 events of posterior reversible encephalophathy syndrome (PRES) (CTCAE grade 3) with onset 2 and 7 days after the last dose in Cycle 1 were reported in connection with hypertension in [redacted]. No new events of PRES have been reported after the implementation of mitigations for hypertension. One (1) case of transverse myelitis (CTCAE Grade 3) has been reported in a single patient treated under single patient use [redacted]. The patient was treated with high dose methylprednisolone and recovered subsequently. The event is seen as a possible class effect with anti-GD2 antibodies.

In trials 12-230 and 201, 23.1% and 8.3%, respectively, developed ADAs. [redacted] As only 2 subjects developed ADA in 201 at the time of the interim analysis, very limited information was available regarding efficacy and safety in this subgroup.

Based on the above data, naxitamab (Danyelza®) received accelerated regulatory approval on 25Nov 2020 by the FDA in the US for the treatment in combination with

GM-CSF of patients ≥ 1 year of age with relapsed or refractory high-risk NB in the bone or BM demonstrating a PR, minor response (MR), or stable disease (SD) to prior therapy for NB.

4.3.3 Choice of chemotherapy regimen as backbone treatment

No single-agent induction chemotherapy regimen has proven superior in obtaining response in high-risk NB. Therefore, induction and consolidation regimens employ intensive multi-agent chemotherapy including platinum and alkylating agents, as well as topoisomerase-inhibitors, most often followed by surgical resection, high-dose chemotherapy with autologous cell rescue and radiation therapy (RT)[6].

When the induction chemotherapy regimen fails, an alternative approach to second line therapy is needed. No SoC currently exists for the treatment of patients with primary refractory or first relapse of high-risk NB.

Irinotecan and temozolomide (IT) are widely used as salvage chemotherapy supported by clinical trials data.

Wagner et al assessed the effect of IT treatment in a small phase 1 study including 12 evaluable heavily pretreated patients with refractory solid tumors (incl 2 patients with NB). Oral temozolomide at 100 mg/m^2/day for 5 days and IV irinotecan at either 10 mg/m^2/day (n = 6) or 15 mg/m^2/day (n = 6) was given daily for 5 days for 2 consecutive weeks. Median number of courses was 4. One patient had CR (Ewing Sarcoma (ES), dose level 1), two had PR (NB and ES at dose levels 1 and 2, respectively), and one had minor response (MR) (ES, dose level 1)[16].

A phase 2, single-arm, single center study by Kushner et al, included 36 assessable heavily pre-treated patients with high-risk stage 4 refractory (N=19) or relapsed (N=17) NB[17]. Patients received IV irinotecan 50 mg/m^2/day over 1 hour and temozolomide 150 mg/m^2/day orally at Days 1-5. The median number of cycles was 5 (range 1-15). Overall, of the 36 patients assessable for response, 12 patients (33%) had disease regressions, including three patients (8%) with CR or PR, and nine patients with objective responses (i.e., less than PR). The safety profile was associated with manageable adverse effects and no unexpected toxicities.

A phase 2, multi-center, single arm study by Bagatell et al, included patients with primary refractory (25%) or first relapsed NB[18]. IT was administered in 6 cycles of 21 days with irinotecan given IV at 10 mg/m^2/dose on Days 1-5 and 8-12 and temozolomide orally at 100 mg/m^2/dose on Days 1-5. Of the 55 evaluable patients, 28 (stratum 1) had measurable disease by cross-sectional imaging and 27 (stratum 2) had disease only assessable by BM aspirate/biopsy or metaiodobenzylguanidine (MIBG) scan. The objective response rate was 15% overall, 11% on stratum 1, and 19% on stratum 2. Furthermore, 50% on stratum 1 and 56% on stratum 2 had stable disease (SD). Two-year event-free survival (EFS) and OS rates in the overall cohort were 13% ± 9% and 30% ± 10%, respectively. IT therapy was generally well tolerated and with acceptable AEs: Less

than 6% of patients experienced > Grade 3 diarrhea. Although > Grade 3 neutropenia was observed, less than 10% of patients developed evidence of infection while neutropenic.

Finally, in the BEACON study in patients with high-risk refractory/relapsed NB, temozolomide was administered at 100mg/m^2/day orally and irinotecan at 50mg/m^2/day IV on Days 1 to 5 of a 3-week cycle, for 6 cycles or until progression (NCT02308527). With a median follow-up time of 15.4 months, irinotecan + temozolomide ± bevacizumab (N=60) vs. temozolomide ± bevacizumab (N=61) improved PFS and OS: Hazard ratios of 0.66 [95%CI 0.43-1.00] and 0.63 [95%CI 0.41-0.99], respectively[19].

Based on the above data, IT will serve as backbone chemotherapy in Trial 203.

4.3.4 Combining naxitamab with irinotecan and temozolomide

Although IT therapy may result in disease stabilization in patients with primary refractory or first relapse of NB, response rates remain relatively low with CR rates of 5-10%[17, 18]. To improve the outcome for these patients, the IT regimen could serve as a backbone on which mAb targeting GD2 is added. Although IT have known myelosuppressive adverse effects, anti-GD2 mAb therapy may be effective in this IT chemotherapy setting when combined with GM-CSF; ADCC and CDC are dependent on complement and myeloid cells such as neutrophils, which recover faster than lymphocytes[20].

In support of these considerations, a significant and early anti-tumor activity was observed in a small, randomized phase II trial by Mody et al. with dinutuximab + GM-CSF vs temsirolimus both as add-on to IT therapy in patients with primary refractory or first relapse of NB. All patients received oral temozolomide (100 mg/m^2/dose) and IV irinotecan (50 mg/m^2/dose given over 90 min) on Days 1–5. Treatments were repeated in cycles of 21 days. Median number of treatment courses were 3 [interquartile range (IQR) 2–10]) and 6 [IQR 3–17] in the temsirolimus and dinutuximab arm, respectively. Of the 17 patients randomized to IT + dinutuximab, 9 (53%, 95% CI: [29.2%, 76.7%]) had objective response (OR)(5 CR, 4 PR,). In the temsirolimus arm, 1 PR was observed (5.6%, 95% CI: [0.0%, 16.1%]). These responses appeared to be irrespective of disease status (relapsed vs. refractory disease, measurable vs. evaluable disease)[21]. A follow-up study including additional 36 patients non-randomly assigned to IT + dinutuximab + GM-CSF confirmed the favorable results. Of 53 patients overall, 22 had OR (41.5%, 95% CI: [28.2%, 54.87%]; 11 CR, 11 PR) and 22 patients had SD[22]. This IT dosing regimen has been applied as backbone therapy with median number of cycles around 4 in several other NB clinical trial settings[23-25].

Preliminary and promising results have also been obtained with naxitamab + GM-CSF in combination with irinotecan and temozolomide (human3F8, irinotecan, temozolomide, sargramostim; HITS). One study included 46 (23 enrolled on protocol and 23 on compassionate use basis) heavily prior-treated patients with high-risk NB refractory to induction chemotherapy (N=7) or prior relapse (N=39). Each cycle comprised of irinotecan 50 mg/m^2/day IV plus temozolomide 150 mg/m^2/day IV or orally (Days 1-5);

naxitamab 2.25 mg/kg/day IV over 30 minutes, Days 2, 4, 8 and 10 (total 9 mg/kg or 270 mg/m^2 per cycle) and GM-CSF 250 mg/m^2/day sc, Days 6-10. Median age at enrollment was 6.6 years and median number of prior relapses was 2. Early responses, assessed after 2 cycles, were documented in 18 (39%) patients and were complete (N = 9), partial (N = 8), and mixed (N = 1); 13 patients had SD[26]. Another study included 44 (36 evaluable and 8 non-evaluable) heavily prior-treated patients with NB treated with the same IT/naxitamab treatment regimen as above under compassionate use in the outpatient setting in Spain[27]. The median number of cycles was 5 (range 1-15). Median age at enrollment was 6 years, 16 patients had high-risk NB refractory to induction chemotherapy and 28 patients had previously ≥1 relapse (median number of prior relapses was 2). Early responses, assessed after 2 cycles, were documented in 17 (47.2%) of the 36 evaluable patients; 11 patients had CR (30.5%), and 6 patients had PR (16.7%). Ten patients had SD. One-year PFS was 37.0% (95% CI: 21.8% to 62.9%), median time to progression was 9.2 months. One-year OS was 55% (95% CI: 39.4% to 76.9%). In both studies, toxicities included myelosuppression and diarrhea as expected with IT, and pain and hypertension as expected with naxitamab. No other >Grade 2 related toxicities occurred.

In all the above studies the safety profile of the IT regimen was manageable.

Based on these data, naxitamab may have the potential to improve outcomes when used as second line therapy in combination with IT in patients with high-risk NB with primary refractory disease or first relapse. In line with the study by Mody et al., IT will be administered on Days 1 to 5 at cycles of 21 days for up to 18 cycles: irinotecan IV at 50 mg/m^2/dose/day over 90 min and temozolomide orally at 100 mg/m^2/dose.

4.3.5 Naxitamab dose selection and infusion rate

The efficacy and safety of naxitamab has been substantiated in Trials 12-230 and 201 at 3.0 mg/kg/infusion over a 30-minute infusion period on Days 1, 3 and 5 (9.0 mg/kg/cycle) every 28 days. In Trial 203, naxitamab will be administered in combination with GM-CSF in combination with IT in cycles of 21 days (see 4.3.4). To reduce the risk of naxitamab associated AEs in this treatment regimen, a slightly slower naxitamab dosing regimen per cycle will be applied at 2.25 mg/kg/day on Days 2, 4, 8 and 10 (total 9 mg/kg per cycle) as described by Mora J et al. (see Section 4.3.4)[26, 27]. Furthermore, to reduce the risk of infusion related toxicity, naxitamab will be administered over minimum 60 min for the first infusion and 30 min for subsequent infusions.

If patients discontinue IT treatment due to toxicity, the naxitamab+GM-CSF regimen can be continued: naxitamab will then be administered IV at 3.0 mg/kg/day on Days 1, 3 and 5 (9.0 mg/kg/cycle) in cycles of 28 days in accordance with the regimen applied in the naxitamab clinical development program (see Section 4.3.2) .

4.3.6 Use of GM-CSF in combination with naxitamab

During the naxitamab clinical development program, naxitamab has been administered in combination with GM-CSF (sargramostim) (see Section 4.3.2). Furthermore, naxitamab

is approved for combination treatment with GM-CSF in the US and dinutuximab (Unituxin®) is approved for use in combination with IL-2 and GM-CSF in the US[12, 13]. In the clinical setting, GM-CSF increases neutrophil production and maturation of monocytes to macrophages and can amplify the anti-NB activity of naxitamab via effects on these cells[28, 29]. Moreover, GM-CSF has been found to be well tolerated compared to other cytokines such as interleukin-2 (IL-2)[26, 27]. Based on these considerations, naxitamab will be administered in combination with GM-CSF in this trial. GM-CSF (sargramostim) will be administered at 250 ug/m^2/day sc on Days 6-10, in accordance with a dosing regimen found to be efficacious and with a manageable safety profile[11, 29, 30] and in an ongoing clinical trial at MSK (NCT03189706). If patients discontinue IT treatment due to toxicity, the naxitamab+GM-CSF regimen can be continued: GM-CSF will be administered sc at 250 ug/m^2/day on Days -4 to 0 and at 500 ug/m^2/day on Days 1 to 5 in cycles of 28 days in accordance with the regimen applied in the naxitamab clinical development program.

4.3.7 Choice of trial population

The trial will include patients with high-risk NB with measurable and/or evaluable disease and either with primary refractory disease or in first relapse following induction and consolidation therapy. Primary refractory disease or first relapse following induction therapy is associated with poor outcomes and no approved SoC exists for treatment of this patient population. Thus, there is a high unmet medical need for more efficacious treatments. The age cut-off of 12 months is applied, as most infants with disseminated disease have a favorable outcome following treatment with chemotherapy and surgery[31-33].

4.3.8 Choice of trial design

Trial 203 is an open label, uncontrolled, multicenter trial. Due to the devasting nature of refractory and relapsed high-risk NB with 10-years OS of less than 15% and the only modest effect of IT treatment alone, a single arm trial design is applied. The primary endpoint ORR is an endpoint accepted for single arm trials by regulatory authorities for efficacy evaluation of anti-cancer therapies[34, 35].

The assessment of the primary endpoint after completion of 4 cycles is considered appropriate based on published clinical trials on IT treatment and on completed trials on naxitamab[17, 18, 21, 22]. The long-term follow-up of 2-years after End of Treatment is to gain data on long-term efficacy and safety of naxitamab in combination with IT.

4.4 Benefit-risk assessment

Chemo resistant and relapsed disease are major obstacles to curing high-risk NB. Despite intensive frontline therapy, approximately 50% of patients with high-risk NB experience persistence of disease or develop PD[6]. The prognosis for patients with recurrent or refractory NB is extremely poor with 10-years OS of less than 15%[7]. Thus, more efficacious treatments for this patient population remains a large unmet medical need.

Naxitamab is a mAb targeting GD2 widely expressed on NB cells. Across Trials 12-230 and 201 in patients with high-risk refractory or relapsed NB in bone and/or BM, naxitamab in combination with GM-CSF was found to provide a statistically significant and clinically relevant ORR ranging from [redacted] to 68% and CR rates ranging from [redacted] to 59%. In these trials, naxitamab was found to be overall well tolerated with acute toxicities/infusion related AEs that could be managed by pre-medications (opioids, corticosteroids, antipyretics, and antihistamines) along with concomitant administration of normal saline, opioids, nebulized beta-2 agonists, and oxygen as applicable. In further support of a manageable safety profile, 95% of all infusions were performed in the out-patient setting with similar rates across cycles and infusions in Trial 201. Moreover, treatment of patients with naxitamab + GM-CSF in combination with IT indicated promising anti-cancer effect also with a manageable safety profile[26, 27].

Based on the above, naxitamab + GM-CSF in combination with IT has the potential to improve outcomes earlier during the high-risk NB disease course and thereby address the important unmet medical need in this patient population.

5 TRIAL OBJECTIVES

5.1 Primary Objective

To investigate the efficacy of naxitamab + GM-CSF in combination with IT as assessed by ORR in patients with high-risk NB with primary refractory disease or in first relapse.

5.2 Secondary Objective

To further investigate the efficacy and safety of naxitamab + GM-CSF in combination with IT in patients with high-risk NB with primary refractory disease or in first relapse.

6 ENDPOINTS

6.1 Primary Endpoint

ORR, defined as the proportion of patients obtaining a centrally assessed CR or PR according to the International Neuroblastoma Response Criteria (INRC) at or before completion of four cycles.

6.2 Secondary Endpoints

1. ORR after 2 cycles defined as the proportion of patients obtaining a centrally assessed CR or PR according to the INRC at completion of two treatment cycles
2. Duration of response (DoR), defined as the time from first centrally assessed OR (CR or PR according to the INRC) to PD or death
3. CR rate, defined as the proportion of patients obtaining a centrally assessed CR according to the INRC at or before completion of four treatment cycles
4. CR rate after two cycles defined as the proportion of patients obtaining a centrally assessed CR according to the INRC at completion of two treatment cycles
5. Minor response (MR) rate, defined as the proportion of patients obtaining a centrally assessed MR according to the INRC at or before completion of four treatment cycles
6. ”MR or better” rate, defined as the proportion of patients obtaining a centrally assessed CR, PR or MR according to the INRC at or before completion of four treatment cycles
7. Proportion of patients with disease in BM at enrollment who obtain centrally assessed CR in BM and convert to minimal residual disease (MRD) negative (assessed by reverse transcriptase-quantitative polymerase chain reaction (RTqPCR)) at or before completion of four cycles
8. Time to First Subsequent Therapy or death (defined as the time from initiation of treatment with investigational medicinal products (IMP) until death or start of new anti-cancer treatment (prohibited as per protocol))
9. PFS defined as the time from first IMP administration until centrally assessed PD or death, whichever comes first
10. OS defined as the time from first IMP administration until death
11. 1- and 2-years PFS defined as the proportion of patients alive and with no centrally assessed PD at 1- and 2 year, respectively after first IMP administration
12. 1- and 2-year OS defined as the proportion of patients alive at 1- and 2 years after first IMP administration
13. Safety incl. incidence of AEs and SAEs graded according to Common Terminology Criteria for AEs (CTCAE) version 5.0
14. Pain during naxitamab infusions as assessed by Wong Baker- and FLACC scales
15. Incidence of ADA (including assessment for neutralizing potential and time to first positive ADA assessment from first day of naxitamab administration)
16. Number of naxitamab infusions done in an out-patient setting defined as infusions not requiring admission to hospital due to adverse events

6.3 Exploratory Endpoints

1. Confirmed ORR after 2 cycles defined as the proportion of patients obtaining a centrally assessed confirmed CR or PR according to the INRC at completion of two treatment cycles
2. Duration of confirmed response, defined as the time from first centrally assessed confirmed OR (CR or PR according to the INRC) to PD or death
3. Confirmed CR rate, defined as the proportion of patients obtaining a centrally assessed confirmed CR according to the INRC at or before completion of four treatment cycles
4. Confirmed CR rate after two cycles defined as the proportion of patients obtaining a centrally assessed confirmed CR according to the INRC at completion of two treatment cycles
5. Primary endpoint and secondary efficacy endpoints (number 1-7, 9 and 11) based on investigators' local assessments

7 DESCRIPTION OF DESIGN AND TRIAL POPULATION

7.1 Overall Trial Design

This is an open label, single-arm, multicenter, phase 2 trial, in patients ≥ 12 months of age with high-risk NB with primary refractory disease or in first relapse. 52 patients who have all received at least 1 dose of IMP will be enrolled. Response assessment of images and BM biopsies and aspirates will undergo central review by independent external experts. An independent Data Monitoring Committee (DMC) will oversee trial safety.

7.2 Overall Trial Plan

The trial includes a screening visit to assess the patient's eligibility. Patients fulfilling the eligibility criteria will receive up to 70 weeks of treatment with naxitamab and GM-CSF in combination with IT. End of Treatment (EOT) will be 6 (up to 10) weeks after last treatment. After EOT the patient will enter a long-term FU up to 2 years. Please refer to Figure 1 in 7.2.1.

7.2.1 Treatment

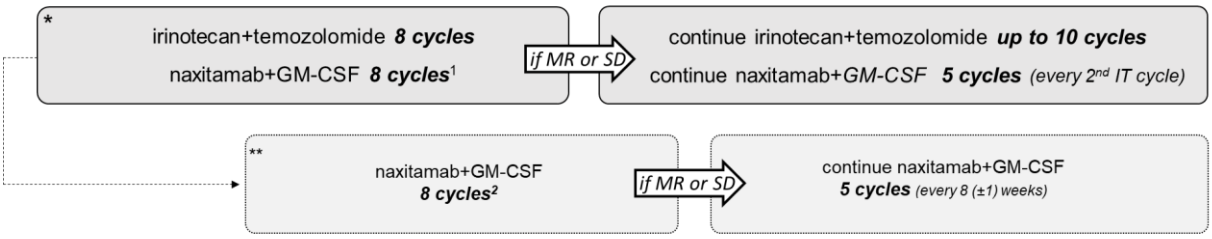
Each treatment cycle is 21 days. Patients will receive irinotecan 50 mg/m^2/day IV and temozolomide 100 mg/m^2/day orally (both on Days 1-5) in combination with naxitamab 2.25 mg/kg/day IV (Days 2, 4, 8 and 10) (total 9 mg/kg per cycle), and GM-CSF 250 ug/m^2/day sc, (Days 6-10). Patients will receive up to 18 IT cycles after enrollment. Naxitamab and GM-CSF will be given for at least 8 cycles.

Patients who discontinue IT due to unacceptable toxicity will be offered treatment with naxitamab + GM-CSF alone. The treatment will be administered in 28-days cycles with naxitamab 3.0 mg/kg/infusion at Days 1, 3 and 5 and GM-CSF 250 µg/m^2/day for 5 days from Days -4 to 0, and at 500 µg/m^2/day for 5 days from Day 1 to Day 5. The total number of naxitamab treatment cycles will be at least 8 cycles (including the cycles given in the HITS regimen.

Patients who discontinue GM-CSF due to unacceptable toxicity should continue naxitamab treatment.

Patients achieving a CR or PR (both patients receiving HITS or naxitamab + GM-CSF alone) should receive 8 naxitamab cycles or 5 additional naxitamab cycles following the objective response, whichever provides the longest treatment with naxitamab. Patients who have achieved a MR or SD at completion of the 8 cycles (both patients receiving HITS or naxitamab + GM-CSF alone) may receive naxitamab + GM-CSF consolidation treatment for 5 cycles administered at every 6 weeks (in the HITS regimen) or 8 weeks (in the naxitamab + GM-CSF alone regimen). The total number naxitamab cycles to be administered includes the treatment cycles administered in the HITS regimen.

Figure 1 Trial design



*each cycle is 21 days, ** each cycle is 28 days
[1]Patients achieving a CR or PR should receive at least 8 naxitamab cycles or 5 additional naxitamab cycles following the objective response, whichever provides the longest treatment with naxitamab
[2] Patients should receive at least 8 cycles of naxitamab + GM-CSF including the cycles in the HITS regimen

7.3 Recruitment Period

It is estimated that ~18 months will be needed to recruit the planned number of patients.

7.4 Screening/Pre-treatment Evaluation

Pre-treatment evaluations should be completed within 21 days prior to start of trial treatment on Day -3. Please refer to the screening visit in the flowchart (Section 3) Procedures (except BM biopsies/aspirates and imaging) performed by site as part of SoC within the screening period may be used for the evaluation of patient eligibility even if the evaluation is performed prior to patient information and ICF signature.

7.5 Patient Replacement

No patient replacement is allowed.

7.6 Screening Failures and Re-screening

Screen failures are defined as patients who consent to participate in the clinical trial but are not eligible according to in/exclusion criteria.

Individuals who do not meet the criteria for participation in this trial may be re-screened under the following circumstances:

- If the time elapsed since occurrence of a treatment/procedure would otherwise qualify for an exclusion criterion
- If the laboratory parameters defined in the exclusion criteria are met but are expected to improve and not meet the exclusion criteria at the discretion of the investigator.
- Age < 12 months
- Stabilization or improvement of a clinical condition that would otherwise qualify for an exclusion criterion at the discretion of the investigator

If a patient is re-screened the patient should receive a new patient identifier (ID), i.e., a patient can have multiple screening IDs, but only one treatment ID. If a patient is re-screened the parents/patient must sign a new informed consent form (ICF).

7.7 Enrollment

A patient is defined as enrolled, when the patient is confirmed eligible according to in/exclusion criteria and ready to start pre-treatment Day-3.

7.8 Follow-up

EOT assessments should take place minimum 6 weeks (up to 10 weeks) after last treatment. If treatment is discontinued due to PD, planned initiation of new anti-NB treatment prohibited as per protocol, withdrawal from the trial or investigator judges it warranted due to medical reasons/non-compliance, the patient should be called for EOT visit as soon as possible and before initiation of new anti-NB treatment. The patients should subsequently be followed for safety and new anti-cancer therapy for a total of 6 weeks after last treatment (see flowchart in Section 3 and treatment discontinuation criteria in Section 7.12).

After EOT, a long-term FU period will start. The patient will attend long-term FU visits approximately every 4 months for up to 2 years after EOT.
The investigator will perform response assessments (if the patient has not experienced PD) (see Section 3, 9.1.1, 9.1.2 and Appendix 2), report death and PD (as applicable) and collect information on SAEs ongoing at EOT visit, new SAEs at least possibly related to naxitamab treatment, secondary malignancies, and autoimmune diseases. Furthermore, new anti-cancer therapy should be collected as concomitant medication. Please refer to flowcharts in Section 3 and Appendix 2.

Trial period completion is defined as when the patient has completed the final scheduled visit (long-term FU visit 2 years after EOT).

7.9 End of Trial

End of Trial is defined as last patient's last visit or death. "Date of trial completion" is the date the patient completed the final scheduled visit.

7.10 Number of Patients

With an estimated screen failure rate of 25% approximately 70 patients will be screened to achieve the planned 52 patients.

7.11 Patient Selection

The trial will include patients with high-risk NB who have received SoC frontline chemotherapy with or without autologous stem cell transplant (ASCT) and have been designated primary refractory disease or have experienced first relapse following frontline SoC, comparable to the following protocols for frontline therapy:

- Childrens Oncology Group (COG) protocol 0532,
- COG-US protocol A3973
- GPOH based induction (as per the NB 2004)
- MSKCC N5 or N7 (MSK-US)
- Rapid Cojec (SIOPEN)

To be eligible, the patient must meet all inclusion criteria and must not violate any of the exclusion criteria. Patient eligibility must be approved by the sponsor before the patient receives IMP in the trial. This is done by completing the patient eligibility form.

7.11.1 Inclusion Criteria

1. Documented NB at time of initial diagnosis[36] defined as:
    - Histopathological verification of NB or ganglioneuroblastoma nodular, or
    - BM aspirate or biopsy indicative of NB (according to INRC)[37] and high blood or urine catecholamine metabolite levels (> 2 x upper limit of normal)
2. Documented high-risk disease at time of initial diagnosis defined as[33, 38]:
    - MYCN-amplified any stage (according to International Neuroblastoma Risk Group (INRG)) of any age or
    - MYCN-nonamplified with stage M (according to INRG) and diagnosed at ≥ 18 months of age
3. Patient should have received SoC frontline induction/consolidation therapy (surgery, chemotherapy, ASCT, MIBG, radiotherapy, immunotherapy, or retinoids)
4. Patients must have active disease despite previous aggressive multi-drug chemotherapy (≥ 2 agents, including an alkylating agent and a platinum containing compound) defined as one of the following:
    - verified first progression during multi-drug frontline treatment or
    - verified first episode of relapse, defined as recurrence after response to frontline treatment, or
    - verified first designation of refractory disease, defined as persistent metastatic disease (SD or minor response by INRC[37, 39] and MIBG curie score ≥3[39]) detected at conclusion of at least 4 cycles of multi-drug induction chemotherapy on or according to a high-risk NB treatment protocol as defined above (7.11).
5. The patients must have one of the following (locally assessed) obtained within 3 weeks prior to enrollment and at least 10 calendar days after end of any prior anti-cancer treatment:
    - Measurable tumor on CT/MRI scan that is MIBG-avid or demonstrates increased FDG uptake on PET scan
    - MIBG scan with positive uptake at a minimum of one site. This site must represent disease recurrence after completion of therapy, progressive disease on therapy, or refractory disease during induction
6. Aged ≥ 12 months at enrollment
7. Written informed consent from legal guardian(s) and/or patient obtained in accordance with local regulations. Pediatric patients must provide assent as required by local regulations

7.11.2 Exclusion Criteria

1. A diagnosis of myelodysplastic syndrome or any malignancy other than NB
2. Any systemic anti-cancer therapy, including chemotherapy, or immunotherapy, within 3 weeks prior to enrollment
3. ASCT within 6 weeks prior to enrollment or ongoing toxicity due to the stem cell transplant at the discretion of the investigator
4. Therapeutic ^{131}I-MIBG within 6 weeks prior to enrollment
5. RT within 4 weeks prior to enrollment at the site of any lesion that will be identified as a target lesion to measure tumor response. Lesions that have been previously radiated cannot be used as target lesions unless there is radiographic evidence of progression at the site following radiation or a biopsy done following radiation shows viable NB. There are no time restrictions following prior RT for non-target lesions or for palliative radiation to sites that will not be used for response assessment
6. Prior treatment with anti-GD2 therapy if the patient experienced PD while on anti-GD2 treatment
7. Receipt of second line chemotherapy after designation of primary refractory disease or first relapse or PD
8. Patients with NB in BM only
9. NB in the CNS or leptomeningeal disease within 6 months prior to enrollment
10. Performance status of < 50% as per the Lansky scale (patients less than 16 years of age) or Karnofsky scale (for patients aged 16 years or older)
11. Life expectancy of less than 6 months, as judged by the Investigator
12. Left ventricular ejection fraction < 50% by echocardiography
13. Inadequate pulmonary function defined as evidence of dyspnea at rest, exercise intolerance, and/or chronic oxygen requirement. In addition, room air pulse oximetry < 94% and/or abnormal pulmonary function tests if these assessments are clinically indicated
14. Patients with ≥ Grade 2 diarrhea
15. Treatment with long-acting myeloid growth factor within 14 days or short-acting myeloid growth factor within 7 days prior to first dose of GM-CSF
16. Treatment with immunosuppressive treatment (local steroids excluded) within 4 weeks prior to enrollment
17. Life threatening infection(s)
18. Patients with uncontrolled seizure disorders despite anticonvulsant therapy (defined as a seizure event within 3 months prior to enrollment)
19. Treatment with enzyme-inducing anticonvulsants including phenytoin, phenobarbital, or carbamazepine for at least 7 days prior to enrollment
20. Concomitant use with St John's wort

21. Allogeneic hematopoietic stem cell transplantation (allo-SCT) or donor-lymphocyte-infusion (defined as any kind of active allogeneic lymphocyte suspension)
    a. within 6 months of 1st dose of GM-CSF or
    b. with a lymphocyte count < 0.2 x10^9/L
22. Treatment with Hematopoietic Progenitor Cell (HPC) boost within 2 months prior to enrollment
23. History of allergy or known hypersensitivity to GM-CSF, yeast-derived products, or any component of GM-CSF, naxitamab, irinotecan or temozolomide
24. History of anaphylactic reactions CTCAE Grade 4 related to prior anti-GD2 antibody therapy
25. Unacceptable hematological status at screening (hematological support is allowed if administered ≥1 week before screening procedure), defined as one of the following:
    a. Hemoglobin <5.0 mmol/L (<8 g/dL)
    b. White blood cell count <1000/µL
    c. Absolute neutrophil count <750/µL
    d. Platelet count < 75,000/µL
26. Unacceptable liver function at screening, defined as one of the following:
    a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >5 times upper normal limit (UNL)
    b. Total bilirubin >1.5 x UNL
27. Unacceptable kidney function at screening, defined as:
    - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 calculated by the 2009 revised Bedside Schwartz Equation (Appendix 1)
28. Inability to comply with protocol
29. Patients with a significant intercurrent illness (any ongoing serious medical problem unrelated to cancer or its treatment) that is not covered by the detailed exclusion criteria and that is expected to interfere with the action of IMPs or to significantly increase the severity of the toxicities experienced from trial treatment
30. Females of childbearing potential (as defined in Section 9.2.8) who are pregnant, breast feeding, intend to become pregnant, or are not using adequate contraceptive methods as defined in 9.2.8 or males who are not using adequate contraceptive methods as defined in 9.2.8. Contraception must be used for 6 months after last IT treatment or 42 days after last naxitamab treatment whichever comes last for both genders

7.12 Premature Discontinuation of Treatment

General discontinuation criteria

A patient should be discontinued from treatment with all IMPs if any of the following situations occur:

1. Grade 4 anaphylaxis related to naxitamab
2. Grade 3 anaphylaxis related to naxitamab not responding to medical intervention at the discretion of the investigator
3. Grade 4 sensory neuropathy or Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks at the discretion of the investigator
4. CTCAE Grade 3 pain unresponsive to maximum supportive measures at the discretion of the investigator
5. Grade 4 bronchospasm
6. Grade 3 bronchospasm not responding to medical intervention at the discretion of the investigator
7. Posterior reversible encephalopathy syndrome (PRES)
8. The investigator judges it necessary for medical reasons/non-compliance
9. The patient receives prohibited therapy and/or procedures during the trial, see Section 8.4.8
10. Pregnancy
11. Patient/legal guardian withdraw consent to treatment
12. PD

Discontinuation criteria for IT

A patient should be discontinued from IT treatment if any of the following situations occur:

1. If the patient experiences neutropenia that causes a delay ≥ 14 days after the first dose reduction by 20% of irinotecan and the second dose reduction by 20% of temozolomide
2. If the patient experiences thrombocytopenia that causes a delay ≥ 14 days after the first dose reduction by 20% of irinotecan and the second dose reduction by 20% of temozolomide
3. If the patient does not meet the criteria to start the next cycle within 21 days after the planned subsequent cycle start date
4. Recurrence of ≥ Grade 3 diarrhea despite maximal use of anti-diarrheals, prophylactic antibiotics, and a dose reductions of irinotecan of 20%
5. Recurrence of ≥ Grade 3 regimen-related nausea and/or vomiting despite optimization of anti-emetic drugs and a dose reduction of IT by 20%
6. If ≥ Grade 3 regimen-related dehydration recurs and persists for >3 days despite a dose reduction of IT by 20%

Discontinuation criteria for GM-CSF

A patient should be discontinued from GM-CSF treatment if any of the following situations occur:

1. Injection site reactions ≥ CTCAE Grade 3
2. Allergic reactions (including anaphylactic reactions) ≥ CTCAE Grade 3

For patients discontinuing all IMP treatments due to PD or toxicity as described above, the patient should attend the EOT visit (see Section 3) and subsequent enter long-term follow-up (see Section 7.8).

7.13 Withdrawal

A patient should be withdrawn from the trial at any time if:

- Patient/legal guardian withdraw consent

If the patient withdraws from the trial, the patient should be asked to attend an EOT visit as soon as possible. Furthermore, if possible the patient should be followed for safety for 6 weeks after last dose of naxitamab for safety reasons.

8 TREATMENTS

8.1 Investigational Medicinal Products (IMPs)

For this trial, Y-mAbs will provide naxitamab, GM-CSF, irinotecan and temozolomide. All 4 products are classified as IMPs. The IMPs provided must be used solely for this trial as described in this protocol and for no other purpose. For further information on naxitamab, GM-CSF and IT refer to the IB and current summary of product characteristics (SmPCs). A summary of the IMPs is provided in Table 3.

No other medicinal products or auxiliary supplies will be provided by Y-mAbs.

Table 3 IMPs provided by Y-mAbs

IMP:	Irinotecan	Temozolomide	Sargramostim (GM-CSF)	Naxitamab
Route:	IV infusion	Orally	Sc	IV infusion
Dosing instruction:	Days 1-5 50 mg/m^2/day	Days 1-5 100 mg/m^2/day	Days 6-10[1] 250 µg/m^2/day[1]	Days 2, 4, 8 and 10[1] 2.25 mg/kg/day[1]
Pharmaceutical form:	Solution for infusion	Capsules	Lyophilized 250 µg single use vial	Solution for infusion
Unit strength	20 mg/mL	5, 20 and 100 mg	250 µg/vial	4 mg/mL

1 Please refer to Appendix 2 for dosing days and dose for treatment of patients who discontinue IT treatment

8.1.1 Administration of IMP for Each Patient

The patient must have a well-functioning intravenous catheter before initiating any treatments for IV administration; a central line is recommended. For naxitamab treatment, site should have emergency equipment readily available, and the patient should have 2 well-functioning IV accesses before any naxitamab treatment is initiated.

Please refer to the IMP manual for more details on preparation and administration of temozolomide, irinotecan, GM-CSF and naxitamab.

Before administration of IMPs, patients must meet hematologic, renal and hepatic eligibility criteria for trial entry at the start of each treatment cycle (see Section 7.11.2).

8.1.2 Treatment schedule

Please refer to Appendix 2 if the patient has discontinued IT treatment due to toxicity.

Table 4 Treatment schedule

Treatment days in cycles of 21 days	-3 to 0	1	2	3	4	5	6	7	8	9	10	11-12	13-21
Premedication (8.4.1, 8.4.3)	X	X	X	X	X	X	X	X	X	X	X	X	
Irinotecan 50 mg /m^2/day (IV) + temozolomide 100 mg/m^2/day (orally) (8.1.2.1, 8.1.2.2)		X	X	X	X	X							
Naxitamab 2.25 mg/kg/day IV (9mg/kg/cycle)[1] (8.1.2.3)[1]			X		X				X		X		
GM-CSF 250 ug/m^2/day s.c (8.1.2.4)[1]							X	X	X	X	X		

1) Patients achieving a CR or PR should receive 8 naxitamab cycles or 5 additional naxitamab cycles following the OR, whichever provides the longest treatment with naxitamab. Patients who have achieved a MR or SD at completion of the 8 cycles may receive naxitamab + GM-CSF consolidation treatment for 5 cycles administered at every 6 weeks

8.1.2.1 Temozolomide

Temozolomide will be administered orally at 100 mg/m^2/day on Days 1-5. For patients, whose body surface area (BSA) is ≥ 0.5m^2, the temozolomide dose should be rounded off to the nearest 5 mg (Appendix 3). Administration should preferable be on an empty stomach (at least 1 hour before or 2 hours after food intake) to decrease nausea and vomiting and improve absorption. For patients who are unable to swallow capsules, the capsule content may be mixed with apple sauce or apple juice or be prepared for suspension, please refer to Appendix 6 and Appendix 7. If emesis occurs within 20 min of taking a dose of temozolomide, the dose may be repeated once. If emesis occurs after 20 min, the dose should not be repeated.

8.1.2.2 Irinotecan

Irinotecan will be infused IV at 50 mg/m^2/day over 90 min on Days 1-5. Antiemetics should be administered as necessary according to local SoC. Irinotecan should be administered at least 1 hour after temozolomide has been given.

8.1.2.3 Naxitamab

On days when co-administered with GM-CSF, naxitamab infusion is started ≥ 60 min after GM-CSF.

On days when co-administered with IT (i.e., Days 2 and 4), it is recommended to start naxitamab infusion at least 1 hour after irinotecan administration to allow for preparations and administration of pre-medications.

Naxitamab should be infused IV at 2.25 mg/kg/day on Days 2, 4, 8 and 10 for a total dose of 9 mg/kg per cycle (Please refer to Appendix 2 for details on naxitamab treatment if the patient has discontinued IT treatment due to toxicity). Administration of naxitamab should be adjusted according to Section 8.4.5, if selected naxitamab adverse reactions are observed. If any events occur fulfilling a general discontinuation criterion the patient must be withdrawn from all treatments immediately and enter long-term FU, see Section 7.12.

<u>At Cycle 1 Day 2 (C1D2):</u>

Naxitamab should be infused over approximately 60 min.

All subsequent naxitamab infusions:
Naxitamab should be infused over approximately 30 min.

Special circumstances
The infusion may be given over approximately 60 min. at Day 2 of any cycle at the investigator's discretion if:

- The patient during C1D2 experienced naxitamab related hypotension:
  - Grade 4 **or**
  - Grade 3 not adequately responding to intervention
- At the investigator's discretion due to severe infusion related adverse drug reactions not adequately responding to interventions

The 60/30 min infusion time is a minimum infusion time. If infusion pause or infusion rate reduction is required due to infusion related AE (see Section 8.4.5) the infusion time will become longer.

Naxitamab treatment in an out-patient setting is defined as a naxitamab infusion performed in the ambulatory setting.

In-patient treatment (i.e. requiring hospitalization) includes both short term admissions and admissions requiring overnight stay.

8.1.2.4 GM-CSF

GM-CSF will be administered sc at 250 µg/m^2/day on Day 6 to Day 10. (Please refer to Appendix 2 for details on GM-CSF treatment if the patient has discontinued IT treatment due to toxicity). The first dose of GM-CSF should be administered at the trial site. GM-CSF and auxiliary supplies will be provided to the patient/parents for administration at home after the patient/parents has received appropriate training on how to administer the drug. Thorough instructions should be given orally and in writing including instructions on how to store and administer the reconstituted GM-CSF at home. The patient/parents will be asked to fill in records of administration (patient diary). Auxiliary supplies include e.g., syringe, needles, sharps disposal container, gloves, alcohol wipes.

GM-CSF must not be administered simultaneously with, within 24 hours preceding or 24 hours following receipt of chemotherapy or radiotherapy.

8.1.3 Treatment delays and missed dosing

Minor adjustment of the treatment schedule due to medical circumstances (e.g., infection) at the discretion of the investigator or non-medical circumstances (e.g., public holidays) is allowed.

It is allowed to postpone the start of a new cycle due to IT toxicity for up to 21 days after the planned subsequent cycle start date (i.e., < 3-weeks delay in start of next cycle) (please see treatment discontinuation criteria Section 7.12).

If a naxitamab dose is missed, administer the missed dose on Day 12. In that case, treatment with GM-CSF at 250 µg/m^2/day should be continued until Day 12 (i.e., treatment from Day 6 to Day 12). Please refer to Appendix 2 if the patient has discontinued IT treatment due to toxicity.

8.1.4 Treatment after Discontinuation of IMP

If the patient prematurely discontinues all IMPs and after End of Trial, any treatment deemed safe and justified by the Investigator can be administered according to clinical practice and at the discretion of the Investigator.

8.1.5 Drug Accountability and Compliance Check

Each trial site will be supplied with sufficient IMPs for the trial on an ongoing basis. IMPs will be distributed to the trial sites according to enrollment.

Drug accountability must be documented by the trial staff on the dedicated forms. The investigator or designee is responsible for drug accountability and record maintenance (i.e., receipt, accountability, and final disposition records). The patient/parents will be provided with a diary to record the administration of GM-CSF at home. The patient/parents should bring these records to the hospital visits together with all used, partly used and unused GM-CSF, as instructed by the investigator. All returned, expired, or damaged IMP must be stored separately from non-allocated trial products. Non-allocated IMP including expired or damaged IMP must be accounted as un-used, at the latest at closure of the trial site. For more information on accountability procedures, please refer to IMP manual.

Clinical personnel at the site will record in the source notes the timing (i.e., date and time) and the way of administration of all administrations of irinotecan, temozolomide and naxitamab, including changes to infusion rate and dose reductions. Furthermore, the clinical personnel will assess the GM-CSF treatment compliance by reviewing the patient diaries. Any reasons for non-compliance should be documented in the hospital records and be discussed with the patient/parent(s) as applicable.

8.1.6 Packaging and Labelling

Packaging and labelling of naxitamab, GM-CSF and IT will be outsourced to a clinical packaging contract manufacturing organization. All products are labelled according to Annex 13, EudraLex, volume 4 and local requirements. Each unit of product are uniquely numbered. Further detailed information on labelling and packaging is described in the IMP manual.

8.1.7 Storage and Handling

The IMPs provided by Y-mAbs must be stored according to the IMP label in a secure location with controlled access separately from normal clinical stock. The storage conditions must be monitored for adherence to label claims. Temperature monitoring data must be reviewed by the Clinical Research Associate (CRA) during monitoring visits. Any deviations in storage temperature must be reported immediately and the IMP must not be used until acceptance is received. Monitoring must be done using a calibrated, stationary, and continuously recording system. As a minimum a calibrated min/max thermometer is required. Further detailed information on storage and handling of the IMP is described in the IMP Manual.

8.2 Medication Errors, Misuse and Abuse

Medication errors, misuse and abuse must be reported in the medication error eCRF

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the IMPs may include:

- Administration of wrong drug
- Wrong route of administration, such as intramuscular (IM) instead of IV
- Accidental administration of a lower or higher dose than intended. An overdose is defined as a patient receiving a dose of the IMP exceeding 10% as compared to the protocol-specified dose. An underdose is defined as a patient receiving a dose of the IMP less than 10% as compared to the protocol-specified dose.
- Misuse: Inappropriately use of a medicinal product outside the terms of the protocol
- Abuse: Intentional excessive use of the IMP which is accompanied by harmful physical or psychological effects *(e.g., suicide attempt)*

If a medication error results in an AE, the AE must also be reported in the electronic case report form (eCRF). If the event qualifies as a SAE it must be reported using the paper Clinical AE Report form in addition to the AE form in the eCRF (see also Section 10 for reporting of AEs).

8.3 Technical complaint

A technical complaint is any written or oral communication that states any dissatisfaction regarding the IMP characteristics and alleges a product defect. A technical complaint can be related to e.g., the product appearance (discoloration, presence of particles or sediments), product container (damaged or missing seal), product label (damaged, missing, misleading), or consignment (wrong amount of vials in the package). A complaint should also be initiated if the product is suspected to be falsified.

Complaints should be immediately (within 24 hours) reported to Y-mAbs Quality Assurance.

Please refer to the IMP manual for information regarding reporting of a technical complaint.

8.4 Concomitant Therapy

A concomitant medication is any medication other than the IMPs. All concomitant medications (including over the counter) that the patient is receiving at the time of screening or receives during the trial must be entered in the eCRF with the following information:

- Generic name (preferred) or trade name
- Start date
- Stop date of administration or ongoing at trial termination
- Time of administration if administered as naxitamab pre-medication (see Section 8.4.1)
- Indication/ reason for use

- Dose
- Frequency
- Outcome (for anti-cancer treatments during long-term FU).

Any changes to concomitant during the trial should be recorded in the eCRF. If a change is due to an AE/SAE, then the AE/SAE must be recorded according to Section 10. During long-term FU, only new anti-cancer therapy should be collected.

8.4.1 Pre-medications Prior to Naxitamab Infusions

Pre-medication is needed to mitigate expected AEs with naxitamab. These include pain, infusion-related reactions, hypotension, allergic reactions, nausea/vomiting and potentially anxiety.

Infusion with naxitamab is associated with pain that may be severe. The pain may involve the abdomen, lower back, chest, legs and arms. The duration may vary but, for most patients, the pain lasts for a couple of hours, and tends to be worst during the naxitamab infusion, subsiding approximately 15 min after end of infusion . Due to the pain, patients may "hold their breath". A marked variation in the naxitamab-associated pain may be observed from infusion to infusion, and hence the recommended opiod dosages below are applicable only to the first infusion. Opiod pre-medications for mitigation of pain during subsequent infusions of naxitamab and pain medications after completion of the naxitamab infusion should be adjusted at the discretion of the investigator.

All medications (including opioid usage) should be captured on the concomitant medication eCRF.

At home

To reduce the risk of pain, gabapentin should be administered from Day -3 to Day 12 of each cycle according to local SoC (e.g., dose of 5 to 10 mg/kg with a max dose of 600 mg).
It is recommended to titrate to the final effective dose during the first 3 days of treatment: Day -3: Once daily; Day -2: Twice daily; Day -1 and until Day 10: 3 daily doses (please refer to Appendix 2 if the patient has discontinued IT treatment due to toxicity).
After completion of the naxitamab treatment (i.e. Day 10), it is recommended to tapper off the gabapentin treatment: Day 11: Twice daily; Day 12: Once daily. If nerve pain lingers, the patient may continue gabapentin on twice daily dosing for up to a week post naxitamab treatment before further weaning.

At hospital

- Saline solution 0.9% (to reduce risk of severe hypotension)
  - Patients should be preloaded with saline 0.9% infusion 10mL/kg over 1 hour just prior to the start of all naxitamab infusions
- Opioids
  Per os (PO) opioids are preferred over IV to diminish IV related side effect such as hypotension, respiratory depression, and/or decreased responsiveness
  - Oxycodone 0.1 – 0.2 mg/kg with a max dose of 5 mg PO (45 – 60 min before naxitamab infusion) **or** equivalent dose of PO opioids **or**

- In cases where PO administration is not feasible (15 min before naxitamab infusion):
  - Hydromorphone 0.00375 – 0.015 mg/kg IV administration over 2 - 10 min

  or
  - Morphine Sulfate/ Morphine Sodium Chloride 0.025-0.1 mg/kg given IV over 2-10 min

- Corticosteroids (30 min – 2 h prior to naxitamab infusion)
  - All patients at the first infusion in the first cycle must receive:
    - IV methylprednisolone 2 mg/kg with a max dose of 80 mg **or** equivalent corticosteroid dose
  - The same corticosteroid premedication should be given in the following circumstances:
    - At the first infusion in the following cycle if the patients had a CTCAE Grade 3 bronchospasm/anaphylaxis at the last cycle's first infusion
    - At the following infusion if the patient had a Grade 3 bronchospasm/anaphylaxis at the last infusion
    - When infusion related reactions are not sufficiently controlled by the other premedications at the investigator´s discretion.
- Antipyretics (30 min before naxitamab infusion)
  - Paracetamol (acetaminophen) 10 mg/kg to maximum 15 mg/kg (max 750 mg total dose) PO or IV
- Antihistamine (30 min before naxitamab infusion)
  - Hydroxyzine 0.5 – 1 mg/kg (max 50 mg) PO/IV, **or**
  - Diphenhydramine 0.5 – 1 mg/kg (max 50 mg) IV **or**
  - Cetirizine <20 kg: 2.5 mg; >20 kg: 5 mg; If > 12y AND > 30 kg: 10 mg PO **or**
  - Loratadine 5 mg for patients 2 – 5 years of age; 10 mg for patient > 5 years of age PO **or**
  - Equivalent according to local SoC
- H_2 antagonist according to local SoC
- Antiemetics (30 min before naxitamab infusion)
  - Ondansetron 5 mg/m^2 **or**
  - Equivalent according to local SoC

  If a patient receives antiemetics prior to IT treatment on Days 2 and 4, additional administration of antiemetics prior to naxitamab infusion will be at the discretion of the investigator
- Anxiolytics, if applicable
  - Lorazepam 0.01 – 0.02 mg/kg (max 1mg) IV pro re nata (PRN) **or**
  - Equivalent according to local SoC

In case of inadequate pain control or hypersensitivity to the above-mentioned pain medications, an alternative strategy to mitigate treatment-induced pain can be introduced at the discretion of the investigator. Ketamine can be a useful alternative to mitigate naxitamab-induced pain[40]. In case of inadequate pain control with opioids, ketamine can be used according to local SoC.

8.4.2 Supportive therapy to be readily available during naxitamab

The following supportive therapies should be readily available at the bedside as pre-prepared treatments when the naxitamab infusion is initiated

- For use at the onset of pain (pre-charged syringes):
  - Hydromorphone 0.00375 – 0.015 mg/kg given IV over 1 – 5 min, **or**
  - Morphine sulfate/ Morphine Sodium Chloride 0.025 – 0.1 mg/kg given IV over 1 –5 min.
  - Opiate doses may be repeated every 5 min for a total of 4 doses. The low, but frequent intermittent doses are preferred to mitigate the risk of opioid associated hypotention.
  - Additional doses may be ordered and given PRN at the discretion of the treating physician
- PRN:
  - Lorazepam 0.01-0.02 mg/kg PO or IV (max 1 mg) or equivalent according to local SoC
  - H1 receptor blocker according to local SoC (e.g., dexclorfeniramine at 0.15 mg/kg IV (max 5 mg) or diphenhydramine for IV administration)
  - NSAID according to local SoC
  - Methylprednisolone 2 mg/kg IV with a max dose of 80 mg (in case corticosteroid was not given as pre-medication) **or** equivalent corticosteroid dose. If corticosteroid was administered as pre-medication, a dose reduction should be considered at the investigator's discretion
  - Adrenalin (epinephrine) 0.01 mg/kg IV or IM (max 0.5 mg)
  - Selective beta2-adrenergic receptor agonist nebulized administered PRN according to local SoC (e.g., salbutamol < 20 kg: 2.5 mg; >20 kg: 5 mg) for bronchospasm
  - Epinephrine for inhalation PRN for stridor
  - Naloxone IV 1 mcg/kg/doses (to be repeated every 2-3 min until response) for management of potential acute cases of respiratory depression:
  - Saline 0.9% for bolus infusion: 10-20 mL/kg IV according to Section 8.4.5.2
  - Cold and hot pads to be applied locally in any body area ad libitum as part of pain management
  - Oxygen (oxygen mask and humidified oxygen inhalation equipment must be available)

8.4.3 Pre-medication prior to administration of irinotecan

Prevention and management of irinotecan associated diarrhea

Irinotecan associated early and late diarrhea and the risk hereof should be handled according to local SoC. This includes but is not limited to:

- Advise on diet (e.g., to eliminate substances that may contribute to diarrhea)
- Instructions on the use of loperamide
- Instructions on how to prevent diarrhea-induced dehydration
- Instructions on what situations the patient/parent should contact the investigator
- Cephalosporin

- For prevention of irinotecan-associated diarrhea, it is recommended to administer cephalosporin according to SoC (e.g., cefixime 8 mg/kg/day PO once daily or cefpodoxime 10mg/kg/day PO divided into 2 daily doses, maximum dose 400mg/day). Treatment should be started 2 days prior to the first dose of irinotecan and continued until 3 days after the last dose of irinotecan (i.e., a total of 10 days in each cycle)

Pneumocystis prophylaxis

- Patients should receive pneumocystis prophylaxis according to local SoC while on IT treatment

8.4.4 Management of selected IT adverse reactions

8.4.4.1 Management of hematologic toxicities

Patients who experienced hematologic toxicity should receive dose-reduction of IT treatment as described in the following sections at the discretion of the investigator.

Dose-limiting neutropenia

Patients who experience neutropenia (absolute count <750/µL) that causes a delay of ≥ 14 days between treatment cycles in the absence of other toxicity requiring dose modification, should have the temozolomide dose reduced by 20% for subsequent cycles (i.e., 80 mg/m^2/day see dose reduction nomogram in Appendix 4). If despite this 20% dose reduction neutropenia (absolute count <750/µL) recurs, causing a delay of ≥ 14 days between treatment cycles, reduce the irinotecan dose by 20% (i.e., irinotecan dose 40.0 mg/m^2/day) and temozolomide dose by additional 20% (i.e., 60 mg/m^2/day see dose reduction nomogram in Appendix 5) for subsequent cycles. For neutropenia requiring discontinuation of IT (please refer to Section 7.12).

Dose-limiting thrombocytopenia

For patients who experience thrombocytopenia (<75,000/µL) that causes a delay of ≥ 14 days between treatment cycles with or without other hematologic toxicities, the dose of temozolomide should be reduced by 20% for subsequent cycles (i.e., 80 mg/m^2/day see dose reduction nomogram in Appendix 4). If despite this 20% dose reduction, thrombocytopenia (<75,000/µL) recurs causing a delay of ≥ 14 days between treatment cycles, reduce the irinotecan dose by 20% (i.e., irinotecan dose 40.0 mg/m^2/day) and temozolomide dose by additional 20% (i.e., 60 mg/m^2/day see dose reduction nomogram in Appendix 5) for subsequent cycles. For thrombocytopenia requiring discontinuation of IT (please refer to Section 7.12).

Delayed recovery of platelets, neutrophils, hepatic and/or renal laboratory parameters

Patients who do not meet laboratory criteria to start the next treatment cycle (see eligibility criteria Section 7.11.2) within 21 days after the planned subsequent cycle start date (i.e., there is a ≥ 3-week delay in start of next cycle) must be discontinued from IT.

8.4.4.2 Management of non-hematologic toxicities

Patients who have experienced non-hematologic toxicity should receive dose-reduction of IT treatment as described in the following sections at the discretion of the investigator.

Dose modification for diarrhea

See Section 8.4.3 for patient/family instructions for supportive care measures for patients who develop therapy-associated diarrhea.

- If ≥ CTCAE Grade 3 therapy-associated diarrhea is experienced by a patient despite maximal use of anti-diarrheal medications and appropriate use of prophylactic antibiotics, the dose of irinotecan should be reduced by 20% for subsequent cycles (i.e., irinotecan dose 40.0 mg/m^2/day)

- For treatment related diarrhea requiring discontinuation of IT (please refer to Section 7.12)

An IT cycle should not be initiated until treatment-related diarrhea is recovered to ≤ CTCAE grade 1.

Dose modifications for nausea and vomiting

- For patients with ≥ CTCAE Grade 3 regimen-related nausea and/or vomiting adjustments in the anti-emetic regimen should be made during the next cycle of therapy

- If ≥ CTCAE Grade 3 regimen-related nausea and/or vomiting recurs despite optimized anti-emetic usage, doses of IT should be reduced by 20% for subsequent cycles (ie, irinotecan dose 40 mg/m^2/day; for temozolomide see dose reduction nomogram in Appendix 4)

- For ≥ CTCAE Grade 3 regimen related nausea and/or vomiting requiring discontinuation of IT (please refer to Section 7.12)

Dose modifications for dehydration

- If dehydration is related to diarrhea or nausea/vomiting, the guidance in the preceding section should be followed

- If regimen-related ≥ CTCAE Grade 3 dehydration persists for > 3 days in the absence of significant diarrhea or nausea/vomiting, doses of IT should be reduced by 20% for subsequent cycles (i.e., irinotecan dose 40 mg/m^2/day; for temozolomide see dose reduction nomogram in Appendix 4)

- For recurrent ≥ CTCAE Grade 3 regimen-related dehydration requiring discontinuation of IT, please refer to Section 7.12)

8.4.5 Management of selected naxitamab adverse reactions

8.4.5.1 Management of bronchospasm and hypoxia

Bronchospasm Grade 2

- Reduce naxitamab infusion rate to approximately 50% of previous infusion rate
- Give nebulized beta2-adrenegic receptor agonist
- If the patient stabilizes and recovers (i.e., bronchospasm CTCAE Grade ≤ 1), the infusion rate can be increased to previous rate based on clinical judgement

Bronchospasm with hypoxia CTCAE ≥ 3

- Pause naxitamab infusion
- Give nebulized beta2-adrenergic receptor agonist
- If the response is not satisfactory treat according to local SoC
    - Consider epinephrine inhalation
    - Consider additional IV antihistamine
    - Consider IV corticosteroids
- If the patient stabilizes and recovers from hypoxia (meaning bronchospasm CTCAE Grade ≤ 2), resume infusion at approximately 50% of previous infusion rate. If the patient continues to be stabilized, infusion rate can gradually be increased to infusion rate prior to the event based on clinical judgement
- Please refer to Section 7.12 for treatment discontinuation criteria

8.4.5.2 Management of hypotension

Hypotension Grade 2

- Administer 0.9% saline bolus 10-20 mL/kg IV over 5-15 min

Hypotension Grade 3 without other signs or symptoms

- Decrease naxitamab infusion rate to approximately 50%
- Administer IV 0.9% saline bolus 10-20 mL/kg over 5-15 min. Monitor blood pressure (BP) closely (at least after completion of the bolus and again 15 min later)
    - If the patient remains hypotensive, repeat bolus as described above (maximum a total of 60 mL/kg) and consider additional treatments as described below
    - If the patient stabilizes, consider increasing to the infusion rate prior to the event

Hypotension Grade 3 with other signs or symptoms such as bradycardia, hypoxia, not adequately responding to treatment or Grade 4 hypotension

- Pause naxitamab infusion
- Initiate aggressive fluid resuscitation according to local standard of care (e.g., American College of Critical Care Medicine (ACCC)[41]
- Monitor vital signs closely
- If the patient remains hypotensive, repeat IV 0.9% saline bolus as described above
    - If resolution to CTCAE ≤ Grade 2: resume naxitamab infusion at approximately 50% of the previous infusion rate. If the patient has stabilized and the naxitamab infusion is well tolerated increase to the infusion rate prior to the event at the discretion of the investigator

- If the patient remains hypotensive, consider additional treatments as described below

- If the patient is NOT warm and well-perfused **or** do not respond satisfactorily to IV 0.9% saline bolus treatments **or** does respond to IV 0.9% saline bolus but only temporarily, the following should be considered:
  - Give naloxone if the patient is difficult to arouse
  - If naloxone has no effect or based on clinical judgement, consider administration of an inotrope/pressor according to local SoC (e.g., epinephrine IV/intramuscular (IM))
    - If desired effect is achieved and the hypotension is CTCAE ≤ Grade 2, consider resuming naxitamab infusion at 50% of the previous infusion rate. If hypotension CTCAE Grade 3 occurs again consider halting naxitamab infusion
    - If the patient continues to be hypotensive and difficult to arouse, stop the current naxitamab infusion permanently and initiate appropriate treatment and observations at the discretion of the investigator (e.g., hospitalization in the intensive care unit)
- Next naxitamab infusion is to be initiated at 50% of the initial infusion rate prior to the event at the discretion of the investigator. Adjustment of the premedication's should be considered

8.4.5.3 Management of hypertension

- Treat all possible causes including pain, urinary retention, allergic reaction, anxiety, and agitation
- Treat hypertension according to local SoC

If hypertension persists at the 90th percentile or higher of BP for age, height, and sex according to National Institutes of Health (NIH)[42] guideline

- Before naxitamab infusion: The investigator should be informed.
- During naxitamab infusion: Follow the patient closely with additional BP measurements
- After naxitamab infusion: The patient should be followed closely with additional BP measurements and physical examination:
  - During the naxitamab treatment cycle: Additional BP measurements between treatment days i.e., on Days 3, 5, 7 and 9 (on Days 2 and 4 for patients treated with naxitamab+GM-CSF alone (see Appendix 2)
  - After the last dose of naxitamab in a cycle, i.e., on Day 10 (on Day 5 for patients treated with naxitamab + GM-CSF alone, see Appendix 2):
    - additional BP measurements the following 3 days on Days 11, 12 and 13 (on Days 6, 7 and 8 for patients treated with naxitamab + GM-CSF alone, see Appendix 2)
    - physical examination on Day 13 (Day 8 for patients treated with naxitamab + GM-CSF alone, see Appendix 2)

If hypertension persists at the 99th percentile or higher of BP for age, height, and sex according to NIH[42] guideline

- Before naxitamab infusion:

- The BP should be treated before infusion can be initiated (see below for details on hypertension algorithm)

- During naxitamab infusion:
  - Treat any pain, anxiety, and/or fluid retention as applicable follow the patient closely with additional BP measurements
  - Consider medical interventions at the discretion of the investigator
- After naxitamab infusion:
  - Start therapy for acute hypertension according to local SoC (e.g., a calcium channel blocker as needed)
  - Admit to inpatient services for monitoring
  - If the patient does respond to anti-hypertensive therapy, an angiotensin-converting enzyme (ACE) inhibitor (e.g., enalapril at starting dose 0.08 mg/kg/dose once daily; max dose 5mg daily) or a calcium antagonist (e.g., amlodipine according to local SoC) may be prescribed prior to future cycles of naxitamab at the discretion of the investigator
  - If the patient has a history of hypertension with naxitamab requiring antihypertensive treatment (e.g., enalapril/amlodipine) on treatment days, consider holding the antihypertensive therapy on Day 2 to avoid potential hypotension
  - If the patient does not respond to anti-hypertensive therapy, consider permanent discontinuation from naxitamab treatment

Posterior reversible encephalopathy syndrome (PRES)
In case of increased risk of PRES (including high BP, headache, seizures, altered consciousness and visual disturbance):

- Admit patient for observation and consider anti-hypertensive therapy
- When BPs are stable < 99th percentile for height according to NIH[42] the patient can be discharged but should return the next day for follow-up and further treatment of hypertension at the discretion of the investigator
- Please also refer to Section 7.12 for treatment discontinuation criteria

8.4.5.4 Management of infusion-related reactions ≥ CTCAE Grade 2, other than hypoxia, bronchospasm, hypotension, and hypertension

- Pause naxitamab infusion
- If resolution to CTCAE Grade ≤ 1:
  - Resume naxitamab infusion at 50% of the previous infusion rate and monitor closely at bedside
  - When signs and symptoms resolve, gradually increase infusion rate up to the rate before the event at the investigator´s discretion
  - If reaction occurs again, reduce naxitamab to the tolerated infusion rate throughout the remaining time of the infusion
  - At the next naxitamab infusion, the infusion rate should be initiated at the reduced rate. If well tolerated the infusion rate can be gradually increased at the investigator's clinical judgement
- If no resolution of the reaction:

- Consider appropriate treatment at the discretion of the investigator (see Section 8.4)
- If resolution to ≤ CTCAE Grade 1, consider resuming naxitamab infusion at 50% of the previous infusion rate as described above
- If no resolution, consider additional treatments and observations, and whether to stop current infusion at the investigator's clinical judgement.

- Please refer to Section 7.12 for discontinuation criteria

8.4.6 Management of GM-CSF (sargramostim) Adverse Reactions

- Hold GM-CSF if total white blood cell (WBC) count is > 50 x10^9/L and/or absolute neutrophil count (ANC) > 20 x10^9/L; resume at 50% dose when the WBC count and/or ANC is < 20 x10^9/L. Administer full dose with subsequent cycles and modify again if the WBC count exceeds 50 x10^9/L and/or ANC exceeds 20 x10^9/L

- Localized skin reactions to GM-CSF are common, and GM-CSF can be continued when reactions are mild. Rotation of sites of injections is recommended when skin reactions occur. Consider use of antihistamines. If ≥ CTCAE Grade 3 injection site reactions occur, stop GM-CSF for the current cycle and discontinue GM-CSF for subsequent cycles of therapy

- Serious allergic reactions (including anaphylactic reactions) have been reported with GM-CSF. If ≥ CTCAE Grade 3 allergic reaction occurs discontinue GM-CSF

8.4.7 Therapy and Procedures Allowed During Trial

Any treatment needed for patient wellbeing (including supportive care) that will not interfere with IMP administration may be given at the discretion of the Investigator.

Radiotherapy:
Radiotherapy may be administered for local control of primary site in patients who have achieved a response at metastatic sites but with residual primary tumor after 8 cycles. Furthermore, radiotherapy to localized painful lesions is allowed, provided at least one measurable/MIBG evaluable lesion is not irradiated.

Lesions irradiated during protocol therapy cannot be used to assess tumor response. Patients should be evaluated prior to radiotherapy with appropriate tumor imaging.

For discontinuation criteria due to PD, see Section 7.12.

Surgery:
Surgery to primary site is allowed for patients who have achieved a response at metastatic sites but with residual primary tumor after 8 cycles. If a patient is to undergo surgery due to residual primary tumor, a pause in treatment with IMPs will be allowed. This should be as short as possible with a delay of next cycle of maximum 3 weeks.

8.4.8 Prohibited Therapy/Procedures During the Trial

The following are prohibited during the trial:

- Systemic anti-cancer treatment, other than naxitamab and IT.
- St John's wort
- CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital, carbamazepine
- Aprepitant as an anti-emetic
- Radiotherapy to metastatic site(s) other than mentioned in Section 8.4.7
- Surgery to metastatis site(s) other than mentioned in Section 8.4.7
- Any live-attenuated vaccines
- IV Immunoglobulin
- Any IMP not defined in this protocol

Except for IV methylprednisolone or equivalent corticosteroid for pre-medication prior to naxitamab infusion (see Section 8.4.1), pharmacologic doses of systemic corticosteroids should be used ONLY for life-threatening conditions (i.e., life-threatening allergic reactions or anaphylaxis such as bronchospasm or stridor) unresponsive to other measures. The use of dexamethasone as an anti-emetic is not permitted. Corticosteroid therapy can be used as a premedication for transfusion in patients known to have a history of transfusion reactions or for treatment of an unexpected transfusion reaction (hydrocortisone 2 mg/kg or less or an equivalent dose of an alternative corticosteroid).

The use of corticosteroid during protocol therapy beyond pre-medication (as mentioned above) must be clear from the indication in the eCRF.

9 PROCEDURES AND ASSESSMENTS

9.1 Efficacy Assessments

9.1.1 Response Assessments

The primary endpoint is ORR. This will be based on BM biopsies and aspirates (histology, cytology) and imaging and assessed according to INRC[37] (see Table 5, Table 6, Table 7 and Table 8). The imaging should be done either as:

- CT/MRI and ^{123}I-MIBG + single-photon emission computed tomography (SPECT)/CT **or**
- CT/MRI and ^{123}I-MIBG whole body planar scan if no hybrid gamma camera is available **or**
- CT/MRI and FDG-PET/CT if MIBG-nonavid tumor

The same imaging modality should preferably be used throughout the trial (please refer to the imaging acquisition guideline).

BM examinations should comprise bilateral BM trephine biopsies and BM aspirates (i.e., 2+2 samples) as per INRC[43] (please refer to laboratory manual).

BM trephine biopsies should be evaluated by histology and immunohistochemistry (IHC). Two highly specific target antigens should be used for IHC, such as synaptophysin, tyrosine hydroxylase, chromogranin A, or paired-like homeobox 2b (PHOX2B). The target antigens used for IHC should remain the same throughout the trial. BM aspirates should be evaluated by cytology and MRD (please see Section 9.1.1.1). If volume of aspirates is not sufficient, BM response assessment should be prioritized over MRD assessment by RTqPCR.

Images and BM biopsies/aspirates (excluding results from RTqPCR, see Section 9.1.1.1) will be assessed locally at site but will also be reviewed centrally by independent external experts. The local response assessment will be used throughout the trial for the decision to continue or discontinue IMPs. Imaging and BM biopsies/aspirates must be done within 7 days (+ 3 days) of the same response assessment (except at screening).The centralized review will be done retrospectively.

Table 5 Primary (soft tissue) Tumor response

Response	**Anatomic + MIBG (FDG-PET†) Imaging**
CR	< 10 mm residual soft tissue at primary site AND Complete resolution of MIBG or FDG-PET uptake (for MIBG-nonavid tumors) at primary site
PR	≥ 30% decrease in longest diameter of primary site AND MIBG or FDG-PET uptake at primary site stable, improved, or resolved
PD	> 20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND Minimum absolute increase of 5 mm in longest dimension‡
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site
Abbreviations:	CR, complete response CT, computed tomography FDG, [18F] fluorodeoxyglucose MIBG, metaiodobenzylguanidine PD, progressive disease PET, positron emission tomography PR, partial response

Response	Anatomic + MIBG (FDG-PET†) Imaging
	SD, stable disease

*Not for use in assessment of metastatic sites.
†Used for MIBG-nonavid tumors.
‡Mass that does not meet PD measurement criteria but has fluctuating MIBG avidity will not be considered PD.

Table 6 Tumor response at metastatic soft tissue and bone sites

Response	Anatomic + MIBG (FDG-PET*) Imaging
CR	Resolution of all sites of disease, defined as: • Nonprimary target and nontarget lesions measure < 10 mm AND • Lymph nodes identified as target lesions decrease to a short axis< 10 mm AND • MIBG uptake or FDG-PET uptake (for MIBG-nonavid tumors) of nonprimary lesions resolves completely
PR	• ≥ 30% decrease in sum of diameters† of nonprimary target lesions compared with baseline AND all of the following: • Nontarget lesions may be stable or smaller in size AND • No new lesions AND • ≥50% reduction in MIBG absolute bone score (relative MIBG bone score ≥0.1 to ≤0.5) OR ≥50% reduction in number of FDG-PET–avid bone lesions§
PD	Any of the following: • Any new soft tissue lesion detected by CT/MRI that is also MIBG avid or FDG-PET avid • Any new soft tissue lesion seen on anatomic imaging that is biopsied and confirmed to be NB or ganglioneuroblastoma • Any new bone site that is MIBG avid • A new bone site that is FDG-PET avid (for MIBG-nonavid tumors) AND has CT/MRI findings consistent with tumor OR has been confirmed histologically to be NB or ganglioneuroblastoma • >20% increase in longest diameter taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) AND minimum absolute increase of 5mm in sum of diameters of target soft tissue lesions • Relative MIBG score ≥1.2§
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD of nonprimary lesions
Abbreviations:	CR, complete response CT, computed tomography FDG, [18F] fluorodeoxyglucose MIBG, metaiodobenzylguanidine MRI, magnetic resonance imaging PD, progressive disease PET, positron emission tomography PR, partial response SD, stable disease

* Used for MIBG-nonavid tumors
†Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (ie, cervical, axillary nodes) added to the sum of the longest diameters of non–lymph node soft tissue metastases. Masses of conglomerate nondiscrete lymph nodes will be measured using longest diameter.
§ Relative MIBG score (based on Curie) is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at baseline before therapeutic interventions
‡For patients with soft tissue metastatic disease, resolution of MIBG and/or FDG-PET uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

Table 7 BM metastasis response

Response	Cytology/Histology
CR	BM with no tumor infiltration on reassessment, independent of baseline tumor involvement
PD	Any of the following: -BM without tumor infiltration that becomes > 5% tumor infiltration on reassessment **or**

	-BM with tumor infiltration that increases by > twofold and has >20% tumor infiltration on reassessment
MD	Any of the following: -BM with ≤5% tumor infiltration and remains >0 to ≤5% tumor infiltration on reassessment **or** -BM with no tumor infiltration that has ≤5% tumor infiltration on reassessment **or** -BM with >20% tumor infiltration that has >0 to ≤5% tumor infiltration on reassessment
SD	BM with tumor infiltration that remains positive with >5% tumor infiltration on reassessment but does not meet CR, MD, or PD criteria
NOTE. In the case of discrepant results between aspirations or core biopsies from two or more sites taken at the same time, the highest infiltration result should be reported using the criteria in this table	
Abbreviations: BM, bone marrow; CR, complete response; MD, minimal disease; PD, progressive disease; SD, stable disease	

Overall response

Overall response will be defined by combining response of the individual components (i.e., primary (soft tissue) tumor, metastatic soft tissue, bone sites, and BM metastasis).

Table 8 Determination of overall response

Response	Criterion
CR	All components meet criteria for CR
PR	PR in at least one component and all other components are either CR, MD* (BM), PR (bone), or NI†; no component with PD
MR	PR or CR in at least one component but at least one other component with SD; no component with PD
SD	SD in one component with no better than SD or NI† in any other component; no component with PD
PD	Any component with PD
Abbreviations: BM, bone marrow; CR, complete response; MD, minimal disease; MR, minor response; NI, not involved; PD, progressive disease; PR, partial response; SD, stable disease (a minimum duration of 6 weeks is required[#])[44]	
* For BM assessment only. † Site not involved at trial entry and remains uninvolved. # Time window of – 5 days is acceptable	

9.1.1.1 Response assessment of BM MRD[43]:

BM aspirate samples for RTqPCR should be taken at baseline, after C2 and after C4. RTq-PCR analyses will be performed centrally.

The results of RTqPCR will reported as the cycle threshold (Ct) value in which the expression of the NB mRNA for tyrosine hydroxylase and PHOX2B is normalized to the internal control (the reference housekeeping gene; β2-microglobulin)[43]. The lower Ct for reporting RTqPCR for the neuroblastoma mRNAs is a Ct value of 40. A tumor negative BM has a Ct value ≥ 40 for all of the neuroblastoma mRNAs examined, when amplification of the reference housekeeping gene generates a Ct value of <25. Further details on BM sampling for RTqPCR analysis will be provided in the laboratory manual.

9.1.2 Timing of response assessment

For timing of response assessment for patients who have discontinued IT treatment due to toxicity, please refer to Appendix 2.
The response assessments will be performed after C2, C4, C8, C13, and EOT. All response assessments (except EOT) should be performed before D1 of next cycle.
In addition, for patients who achieve:

- a first CR or PR after C4 *OR*
- a first CR or PR after C8

a confirmatory response assessment should be performed within 4-6 weeks after detection of the overall response.

If the patient discontinue treatment due to PD, response assessment at EOT is not required provided that PD is documented by scan and/or biopsy.

For patients who have not experienced PD or started new anti-cancer treatment, response assessment should be performed at approximately every 4 months after EOT during long-term FU (see Section 3).

9.2 Safety Assessment

9.2.1 Physical Examination

The physical examination should include an assessment of general appearance and a review of systems (dermatologic, head, eyes (incl examination for mydriasis, signs/symptoms of blurred/altered vision), ears, nose, mouth/throat/neck, thyroid, lymph nodes, and respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic systems). A physical examination should be performed at screening, prior to first treatment with IMP in each cycle, at EOT and otherwise as clinically indicated.

9.2.2 Vital Signs

Vital sign measurements must include heart rate, respiratory rate, body temperature and BP. Additionally, peripheral oxygen saturation (SpO_2) must be measured when clinically indicated. Temperature must be measured by using the same method (e.g., ear thermometer) each time. Vital signs must be assessed at screening and in connection with each treatment cycle as outlined below:

On Days 1, 3 and 5 prior to administration of temozolomide.

On naxitamab in fusion days (Days 2, 4, 8 and 10)

- Prior to administration of temozolomide (Days 2 and 4)
- Prior to pre-medication (e.g.,hydromorphone or morphine)
- Prior to start of naxitamab infusion
- ~15 min after start of naxitamab infusion
- ~30 min after start of naxitamab infusion
- Prior to each hydromorphone or morphine IV therapy as feasible (no temperature)
- At completion of naxitamab infusion including flush (no temperature)

- ~15 min after completion of the flush (no temperature)
- Every hour while patient is recovering in the outpatient clinic

Furthermore, vital signs must be assessed at EOT and as clinically indicated. The latter includes when a vital sign parameter is part of an AE on an infusion day.

Please refer to Appendix 2 for patients who have discontinued IT treatment due to toxicity.

9.2.3 Naxitamab Discharge Criteria

Vital signs should be stable and satisfactory at the discretion of the investigator
A minimum of 2 hours after completion of naxitamab treatment, **or** 2 hours after the last dose of any IV opioid must have elapsed.

9.2.4 Echocardiography

An echocardiography should be performed at screening (refer to Section 3). The investigator should make an overall interpretation and assess for trial eligibility.

9.2.5 Pulmonary Function Test and Oxygen Saturation

A pulmonary function test and oxygen saturation should be performed at screening, if clinically indicated. The investigator should make an overall interpretation of the pulmonary function test(s) and oxygen saturation and assess for trial eligibility.

9.2.6 ECG

12-lead ECG should be obtained as outlined in the flow chart (see Section 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

ECG is a local assessment at screening, and at EOT. If the patient needs sedation before ECG, the ECG can be performed in connection with imaging. The investigator should make an overall interpretation of the ECG and at screening assess for trial eligibility.

9.2.7 Pain Assessment

Pain scores should be assessed for all naxitamab infusions and at the following time points:

- Prior to start of naxitamab
- Worst pain during infusion; to be assessed at the end of infusion
- ~ 15 min after end of infusion
- ~ 30 min after end of infusion
- Prior to discharge

The same scale must be used during all naxitamab infusions, also if the patient turns 6 years during the trial. The Face, Legs, Arms, Cry, Consolability (FLACC) scale for patients ≤ 5 years old at screening and Wong-Baker FACES® pain scale for patients 6 years or older at screening.
If patients of at least 6 years of age cannot comply with the Wrong-Baker faces pain scale it is permitted to use the FLACC scale at the investigators discretion as long as it is used consistently throughout all naxitamab infusions. Please refer to Appendix 8 and Appendix 9.

9.2.8 Non-child-bearing Potential/Pregnancy Test

Pregnancy testing and contraceptive requirements do not apply for female patients of non-child-bearing potential. Non-child-bearing potential in female patients will be confirmed by one of the following:

- Females who have not reached menarche or
- Females who have not had menses within the past 12 months and have a follicle-stimulating hormone (FSH) ≥40 IU/L or
- Females who have not had menses within the past 24 consecutive months if a FSH measurement is not available or
- Females who have undergone surgical sterilization (e.g., hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy).

Pregnancy and contraceptive requirements for female patients of child-bearing potential

Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test at screening and are excluded from the trial if they do not agree to use highly effective contraception for a period of 6 months after the last treatment with IT or 42 days after last treatment with naxitamab whichever comes last. Highly effective contraceptive methods can achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner[1]
- sexual abstinence[2]

[1] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the female patient and that the vasectomised partner has received medical assessment of the surgical success.

[2] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

If a patient is assessed to be of child-bearing potential, either at screening or become so during the course of the trial, a serum pregnancy test must be performed prior to each treatment cycle and at EOT.

Contraceptive requirements for male patients

Male patients must use contraception (condom) for a period of 6 months after last treatment with IT or 42 days after last treatment with naxitamab whichever comes last. Male partners for female patients are advised to use condom while the female partner is being treated with IT and for 2 weeks after last treatment.

9.2.9 Clinical Laboratory Assessments

All protocol clinical laboratory assessments, as defined in Section 11.1, must be conducted in accordance with the flowchart and the laboratory manual.

9.3 Other Assessments

9.3.1 Demographics and Other Baseline Characteristics

Information on the patient's demographics will be collected during screening in the eCRF.

The following demographic information will be entered:

- Age or date of birth if allowed by local legislation
- Gender
- Ethnic origin if allowed by local legislation
- Race if allowed by local legislation
- Current average alcohol consumption per week, if applicable
- Smoking status, if applicable

9.3.2 Height and Body Weight

Height (without shoes) must be measured at screening and before each cycle and entered in the eCRF (centimeter or inches, one decimal). Body weight (without overcoat and shoes) will be measured at screening and before the first administration of IMP in each cycle and entered in the eCRF (kilogram (kg) or pounds, one decimal). The BSA should be calculated using the Mosteller formula before each treatment cycle for calculation of the IMP doses.

9.3.3 Medical and Surgical History

Information on the patient's medical history, past and all current diseases (including surgical procedures) and general health, will be collected if available during screening and includes, but is not limited to:

- General medical history
- Information on NB diagnosis including tumor characteristics, prior treatment for NB and response to prior treatment, DoR, site(s) of relapse, date of relapse as applicable

A concomitant illness is any illness, other than the disease being investigated, which is present at trial start or found as a result of the screening procedure.

The information collected for medical history and concomitant illnesses includes:

- Diagnosis
- Date of onset
- Date of resolution

Any clinically significant worsening of a concomitant illness that occurs after a patient provided consent must be reported as an AE (Section 10.5).

9.3.4 Performance Test

A performance test will be performed at screening, prior to each cycle and EOT. The scales to be used are Lansky for children < 16 years of age and Karnovsky for adolescents and adults ≥ 16 years of age. Please refer to Appendix 10. The same scale must be used during the trial, also if the patient turns 16 years during the trial.

9.3.5 Unscheduled Visits

If any assessments need re-evaluation, an additional response assessment is needed, or follow up on an (S)AE is required, the patient can be called for an unscheduled visit at the discretion of the Investigator. Data obtained during unscheduled visits pertaining to the clinical trial will be collected as unscheduled visits in the eCRF.

10 ADVERSE EVENTS

10.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product which does not necessarily have a causal relationship with the treatment.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A laboratory abnormality which is clinically significant, i.e., an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes interventional treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

Pre-existing condition, (i.e., a disorder present before the AE reporting period started and noted on the medical history/physical examination form) should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. A medical condition for which an unscheduled procedure was performed should, however, be reported if it meets the definition of an AE. For example, an acute appendicitis should be reported as the AE and not the appendectomy.

10.2 Definition of Serious Adverse Events

Each AE is to be classified by the Investigator as either serious or non-serious. This classification of the seriousness of the AE determines the reporting procedures to be followed. An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Is fatal or life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization[2]
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Medically important event[3]

[1]: The term "life-threatening" in the definition of "serious" refers to an event in which the patient, in view of either the Investigator or Sponsor, was at risk of death at the time of the event; it does not refer to an event, that hypothetically might have caused death if it was more severe. Death alone is not considered an AE; it is an outcome of an AE.

Reports of death should be accompanied by the corresponding AE term for the event that led to death. However, sudden death or death due to unexplainable cause should be reported as an SAE, while follow-up is pursued to determine the cause.

[2]: Hospitalization is defined as admission to a hospital/inpatient (irrespective of the duration of physical stay) or is not admitted to a hospital/not an inpatient but stays at the hospital for treatment or observation for more than 24 hours. Events leading to hospitalizations for the following reasons should not be reported as SAEs:

- Trial-related purposes, not associated with any deterioration in condition
- Social reasons in the absence of any deterioration in the patient's general condition
- Elective surgery or other scheduled hospitalization periods that were planned before the patient was included in this trial.

[3]: Medical and scientific judgment must be exercised in deciding whether an AE is believed to be "medically important". Medically important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

10.3 Definition of Non-Serious Adverse Events

A non-serious AE is any AE which does not fulfil the definition of an SAE.

10.4 Definition of Predefined Adverse Events of Special Interest

The following AEs (serious and non-serious) are selected as AEs of Special Interest (AESIs):

- Hypertension:
  - Requiring antihypertensive therapy or
  - Which persists at the 90th percentile or higher for age, height and sex and requires additional monitoring after naxitamab infusion according to Section 8.4.5.3
- Hypotension CTCAE Grade 3
- AEs leading to incomplete dosing of naxitamab during a cycle (i.e., the total planned dose of naxitamab was not given in a cycle)

10.5 Adverse Event Reporting

10.5.1 Non-Serious Events

Non-serious AEs should be reported from the day of first IMP administration until 42 days after the last IMP administration. Non-serious AEs occurring between signing the ICF and the first IMP administration must be recorded as medical history.

10.5.2 Serious Adverse Events

Serious AEs should be reported from signing the ICF until 42 days after the last IMP administration.

10.5.3 Adverse Events during Follow-up

From 42 days after the last IMP dose and until the end of the trial, only SAEs at least possibly related to naxitamab, new onset of secondary malignancies and autoimmune diseases (irrespective of seriousness) regardless of causality should be reported (within 24 hours of knowledge).

10.5.4 Adverse Events with Onset after End of Trial

If the Investigator becomes aware of an SAE after End of Trial with a suspected causal relationship to the IMPs, it should immediately be reported to Sponsor (see contact details in Section 10.7.1)

10.5.5 Recording of Adverse Events

All events meeting the definition of an AE must be collected and reported in the eCRF. SAEs, and AESIs (whether serious or non-serious) should be reported both in the eCRF and on the Clinical AE Report form.

During each contact with the trial site staff, the patient must be asked about AEs, for example by asking: “Have you experienced any problems since the last contact?” All AEs, observed by the Investigator or patient, must be reported by the Investigator.

10.5.6 Diagnosis of Adverse Events

The Investigator should report the diagnosis, if available. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs using separate AE forms. If a diagnosis becomes available, the signs and/or symptoms reported should be replaced by the diagnosis.

10.5.7 Onset Date and Time

Start date for an (S)AE is the date of occurrence of the first symptom. The time should be entered if

- the event starts on an IMP dosing day *or* the day after a naxitamab dosing day
- if the duration of the event is less than 24 hours.

10.5.8 End Date and Time

The end date should be filled in if the outcome of an AE is fatal, recovered/resolved or recovered/resolved with sequelae. The end time should be entered for all AEs for which start time should be entered (see section 10.5.7), and/or if the duration of the event is less than 24 hours or if deemed relevant.

10.5.9 Severity

The Investigator will use the CTCAE version 5.0 to describe the severity of the AE. If the severity changes over the course of the event, the grade assigned by the Investigator should be the most severe, that occurred during the AE period.

10.5.10 Outcome

Investigator must judge outcome of the AE by the following terms:

- Recovered
- Recovered with sequelae (description of the sequelae should be provided)
- Not recovered
- Fatal

- Unknown*

*Should only be used if patient is lost to follow-up.

10.5.11 Relationship to Investigational Medicinal Product

The Investigator must assess whether the event is related to the IMPs. A suspected adverse drug reaction is defined as one in which there is a reasonable possibility that one of the IMPs caused the AE. Relatedness must be assessed and reported from the first time the AE is being reported. When assessing the causal relationship of an AE to the IMPs, the following should be taken into consideration:

Not related (unlikely)

The AE is not related to any of the IMPs, which means the AE:

- Does not follow a reasonable temporal sequence from IMP administration
- Is readily explained by the patient's clinical state or by other modes of therapy administered to the patient
- Is clearly not related to the IMP

Possibly Related

The AE follows a reasonable temporal sequence from IMP administration but could have been produced by the patient's clinical state, medical history, or the trial procedures/conditions.

Alternative etiology should be provided for all AEs assessed as possibly related to IMPs.

Probably Related

The AE is probably related to one or more of the IMPs, which means the AE:

- Follows a reasonable temporal sequence from IMP administration
- Abates spontaneously upon discontinuation of the relevant IMP(s) (de-challenge) without any curative treatment
- Is confirmed by reappearance of the same reaction on repeat exposure (re-challenge) (if applicable)
- Cannot be reasonably explained by the known characteristics of the patient's clinical state or medical history

10.5.12 Action Taken with Investigational Medicinal Product

The action taken with the IMPs should be noted as:

- Dose decreased
- Dose administration rate decreased
- Drug interrupted
- Drug postponed

- Drug discontinued
- None
- Not Applicable**
- Unknown.

**: should be used if the AE occurs before first treatment or after end of treatment.

10.6 Events Requiring Immediate Reporting

The following events require reporting within 24 hours of knowledge (for details see Section 10.5):

- SAE
- AESI
- Pregnancy

10.6.1 Pregnancy

Any pregnancy, including partner pregnancy, that occurs during trial participation must be reported to Sponsor within 24 hours of knowledge using the pregnancy form. Pregnant trial patients must be discontinued from IMP treatment immediately (see Section 7.12). The pregnancy must be followed up to determine outcome and status of mother and child. The child must be followed at least to the age of one month. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

10.7 Timelines for Initial Reporting of AEs

SAEs/AESIs

- The paper Clinical AE Report form must be reported from site to Sponsor within 24 hours of the Investigator's first knowledge of the event. The paper Clinical AE Report form is to be sent to the designated drug safety provider (see Section 10.7.1). New follow-up information available at site must be reported within 24 hours of knowledge

All AEs

- The eCRF AE form should be updated in accordance with agreed data entry timelines (see Section 15.2.2).

Please follow the eCRF completion instructions for reporting of AEs.

10.7.1 Contact details for reporting:

Completed paper Clinical AE Report forms and paper pregnancy forms must immediately be reported to:

safetymailbox@ymabs.com

10.8 Follow-up on Adverse Events

SAE/AESIs:

- New follow-up information available at site must be reported within 24 hours of knowledge.
- Follow-up information requested from Sponsor must be replied to within three working days. The eCRF AE form should be updated in accordance to agreed data entry timelines (see Section 15.2.2).
- If an ongoing SAE/AESI changes in intensity, relationship to IMP or as new information becomes available for the event, the paper Clinical AE Report Form should be completed and sent to the designated drug safety provider within 24 hours of the change in assessment (see Section 10.6).
- Grade 3 or higher non-serious AEs that are considered treatment related and all SAEs (including AESIs) should be followed on a regular basis, according to the Investigator's clinical judgment, until the event has been resolved or until the Investigator can assess it as chronic or stable. This includes follow-up after EOT

Non-SAEs

Non-serious AEs should be followed until they are either resolved, returned to baseline, or until 42 days after last dose of IMPs, whichever comes first

10.9 Reporting of SUSARs

Sponsor will ensure that all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) is reported to regulatory authorities in accordance with regulatory requirements.

The Contract Research Organization (CRO) appointed by Sponsor will notify Investigators of SUSARs in accordance with local requirements. Furthermore, Investigators will be informed of any trial-related SAEs that may warrant a change in any trial procedure. The CRO appointed by Sponsor will inform the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of SUSARs in accordance with local requirement, unless locally this is an obligation of the Investigator.

The Sponsor assessment of expectedness for naxitamab will be performed according to the current version of the IB. For IT and GM-CSF the applicable reference documents will be used.

10.10 Communication of Significant Safety Issues

In the event of any significant safety related issues, the Sponsor will decide upon immediate action to be taken including prompt notification of the DMC and will communicate to regulatory authorities, Investigators, IECs/IRB, and patients as needed within regulatory timelines.

10.11 Data Monitoring Committee

The DMC is an external committee composed of members whose expertise covers relevant specialties. The DMC is established to review and evaluate accumulated data from the trial with an interval between meetings of approximately 3 months and ad hoc. The DMC is established to assure patient safety and to evaluate benefit-risk balance during conduct of the trial. The DMC will provide recommendations on trial continuation, modification, or termination. Responsibilities, procedures, and workflow of the DMC are specified in the DMC charter.

Recommendation from the DMC will be discussed by the Sponsors Safety Committee. The outcome will be communicated to the regulatory authorities/IRBs/IECs/investigators if there are a significant change to trial conduct e.g., urgent safety measure, amendment to trial protocol and/or ICF.

11 LABORATORIES

11.1 Clinical Laboratory Assessments

The laboratory samples specified in Table 9 will be measured by a local laboratory. Laboratory tests should be performed as described in Table 9 and as clinically indicated. Please refer Appendix 2 if the patient has discontinued IT treatment due to toxicity.

Table 9 Protocol required laboratory assessments

Timing of Laboratory assessments	Parameters
Screening Cycle 1*: Prior to dosing D1, D5, and D8. In addition on D15 Subsequent cycles*: Prior to dosing D1, D5 and D8 EOT *D10 all cycles: If modified naxitamab dosing due to missed dose (ie naxitamab to be administered on Day 12 and GM-CSF continued until Day 12)	Hematology • Hemoglobin • Hematocrit • White blood cells (WBC) Lymphocytes (absolute and %) • Neutrophils (absolute and %) • Eosinophils (absolute and %) • Basophils (absolute and %) • Monocytes (absolute and %) • Platelet count
Screening Cycle 1: prior to dosing D1, D3, D5, D8 and D15 Subsequent cycles: prior to each cycle and D8 EOT	Liver and kidney function blood tests • ALT • AST • Alkaline phosphatase • Total bilirubin • Lactate dehydrogenase (LDH) • Blood urea nitrogen (BUN) • Creatinine • eGRF • Albumin **(only prior to each cycle)**
Screening Cycle 1:prior to dosing D1, D3, D5, and D8 Subsequent cycles: prior to each cycle EOT	Serum electrolytes • Sodium • Potassium • PO^{4} • Mg^{++}
Prior to each cycle	Urine analysis (dipstick) • Protein • Glucose • Leucocytes
Screening Prior to each cycle EOT	Pregnancy test, if applicable • Serum pregnancy test for WOCBP see 9.2.8 for further information

The WBC and differential counts should be repeated on sequential days during all treatment cycles if ANC is > 20 x10^9/L or WBC > 50 x10^9/L on the day prior to GM-CSF treatment.

11.2 Immunogenicity

Samples for assessment of anti-drug antibodies (ADA) should be sent to a special laboratory for analysis. Please refer to the laboratory manual for more information.

Table 10 ADA samples

ADA assessment: Prior to dosing in each cycle EOT	• Anti-naxitamab antibodies*

*Analyses will be performed in batches. Therefore, results will not be available during the trial

12 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1 General Overview

The data will be summarized in tables, as appropriate, showing the number of patients with non-missing data (n), mean, standard deviation, median, minimum, and maximum for continuous data and showing counts and percentage for categorical data. Data will also be listed as deemed appropriate.

12.2 Sample Size

With the statistical methodology for the primary endpoint (Section 12.4.1) in mind, 52 patients are needed to, with 82% power, demonstrate that the response rate is statistically significantly higher than 20%. This sample size incorporates a drop-out (here: patients either not having evaluable disease at baseline based on central review vs. local assessment, or treated patient dropping out of the trial before the first post-baseline assessment) rate of 20%, based on results from the ongoing 201 trial.

Table 11 Sample sizes, assumptions and power

Null response rate	Response rate	Unadjusted number of patients	Drop-out (20%) adjusted number of patients	Statistical Power
40%	20%	41	52	82%
40%	20%	56	70	91%
40%	25%	78	98	80%
40%	25%	102	128	90%

12.3 Populations of Interest

- Full Analysis Set

  The full analysis set (FAS) will include all patients enrolled in the trial who had evaluable disease as per central review and received at least one dose of IMP.

- Per Protocol Analysis Set (PPS)

  The PPS will include all FAS patients who have no major protocol violations with impact on the primary endpoint. Additional patients with other protocol violations may be uniformly excluded on the basis of data review. The precise reasons for excluding patients from the PPS will be fully defined and documented before data lock.

- Safety Analysis Set (SAF)

  The SAF will include all enrolled patients who receive at least one dose of IMP.

12.4 Efficacy Analysis

Patients will be evaluated for response according to the INRC[37] and assigned one of the following response categories: CR, PR, MR, SD, PD or NE (Not Evaluable). In the calculations of any response rates, NE patients will be included in the denominator: not evaluable patients count as non-responders.

Overall response and DoR will be evaluated both centrally, and locally by the investigators: the central evaluation is the primary and the local evaluations are used as sensitivity analysis.

12.4.1 Primary endpoint: ORR at or before completion of four cycles

The null hypothesis: $H_0: p_{OR} = 20\%$ will be tested, using the two-sided exact binomial test, against the alternative $H_{alt}: p_{OR} \neq 20\%$ on the overall 5% significance level, where p_{OR} denotes the ORR at or before completion of four cycles. This 20% threshold is based on the results from the phase 2 study by Bagatell et al.[18] in patients with primary refractory or first relapsed NB, where the ORRs to IT treatment ranged from 11% to 19%[18] (see Section 4.3.3).

The ORR and rates of the response categories will be summarized in tables for the FAS and PPS. The rates will be presented with their corresponding exact binomial two-sided 95% confidence intervals.

The results will be presented for both central and local evaluation; the former is the basis for the primary endpoint and the latter is an exploratory endpoint.

OR information for individual patients will be presented in listings.

12.4.2 ORR after 2 cycles, CR rate after 2 and 4 cycles, MR rate and "MR or better" rate

The ORR after 2 cycles, CR rate at or before completion of four cycles, CR rate after 2 cycles, MR rate at or before completion of four cycles as well as the "MR or better" rate at or before completion of four cycles will be calculated and presented in the same way as the primary endpoint, see Section 12.4.1 above.

12.4.3 Duration of response

The DoR, in patients with OR, will be estimated and summarized using Kaplan-Meier methodology. If no progression or death event is observed, DoR will be censored at the time of the last response assessment. The DoR will be censored if:

- more than one assessment visit in a row is missed, or
- an anti-cancer therapy other than naxitmab and IT is administered (ignoring allowed therapies and procedures such as radiotherapy or surgery of the primary site, cf. Section 8.4.7 for details).

The distribution of the DoR will be summarized by estimates and two-sided 95% confidence intervals of the first, second and third quartiles. The number of patients with events and the number of censored patients will be presented. The reasons for censorings will be summarized.

Summary tables will be presented for the FAS and PPS. The DoR will be presented in patient data listings including the onset of response date, observed event date, censoring flag, censoring date and censoring reason. The results will be presented for both central and local evaluation. The latter will be considered exploratory.

12.4.4 Rate of patients who obtain CR in BM and convert to MRD negative

The proportion of patients with disease in BM at enrollment who obtain CR in BM and convert to MRD negative at or before completion of four cycles will be analyzed and

presented in the same way the primary endpoint for the sub-population of patients who are BM MRD positive at baseline, for the FAS and PPS.

12.4.5 Time to First Subsequent Therapy

Time to First Subsequent Therapy (TFST) will be estimated and summarized using Kaplan-Meier methodology. If no new subsequent anti-cancer treatment is observed, the TFST will be censored at the last visit in the trial. The TFST-results will be presented in the same way as for DoR.

12.4.6 PFS and OS

PFS will be censored in the same way as DoR. If no death event is observed, OS will be censored at the date of the last assessment. PFS and OS will be estimated using Kaplan-Meier methods and presented in same way as DoR. In addition, the Kaplan-Meier estimates of the proportions, together with the corresponding CIs, of patients without progression or death (PFS) and alive (OS) at 1 and 2 years will be presented for the two endpoints respectively. The PFS results will be presented for both central and local evaluation. The latter will be considered exploratory.

12.4.7 Exploratory Endpoints

The analyses of the exploratory endpoint will be described in the SAP.

12.5 Safety Analysis

The SAF will be used for the safety analyses. The overall observation period will be divided into 3 parts:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of IMP
2. on-treatment period: from day of first dose of IMP to 42 days after last dose of IMP
3. post-treatment period: starting at day 43 after last dose of IMP.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Additional analyses and presentations will be included in the SAP.

12.5.1 Adverse events

AE data will be presented descriptively in summary tables and listings. AEs will be regarded as Treatment-Emergent AEs (TEAEs) if they occur after start of first IMP administration.

An infusion/administration related TEAE is an AE that occurs on a day of IMP administration (after start of IMP administration) and is considered related to the IMP treatment.

An infusion related hypersensitivity TEAE is an AE that match a selected list of hypersensitivity terms based on reported preferred terms (including the MedDRA SMQ narrow scopes of anaphylactic reaction, angioedema, hypersensitivity and severe cutaneous reaction), that occurs on a day of naxitamab infusion (after the infusion start) or the day after a naxitamab infusion irrespectively of relatedness to naxitamab.

AEs with onset during the pre- and post-treatment period will be listed. AEs with onset during the on-treatment period will be summarized as follows: summaries of AEs will be presented for all TEAEs, IMP-related TEAEs, CTCAE Grade 3 or higher TEAEs, IMP-related CTCAE Grade 3 or higher TEAEs, infusion/administration-related TEAEs, infusion related hypersensitivity TEAEs, SAEs, IMP-related SAEs, CTCAE Grade 3 or higher SAEs, IMP-related CTCAE Grade 3 or higher SAEs, TEAEs leading to treatment discontinuation, AEs leading to death.

12.5.2 Safety laboratory data

Descriptive statistics will be presented for baseline values, absolute values, and changes from baseline in safety laboratory parameters. Laboratory data will be summarized in tables and presented in figures by type of laboratory test.

12.5.3 Vital signs

Changes from baseline in vital signs will be presented in summary tables.

12.6 Pain assessments during naxitamab infusions

Pain scores will be presented in summaries and listings.

12.7 Analysis of ADA Formation

ADA data will be presented in summary tables and listings. For subjects who develop ADA during the trial, time to first positive ADA assessment from first day of naxitamab administration will be presented in a figure.

12.8 Hospitalization days

The number of hospitalization days will be presented in summary tables and listings.

12.9 Naxitamab infusions in out-patient setting

The number of naxitamab infusions in out-patient setting will be presented in summary tables and listings.

12.10 Interim Analysis

Ad-hoc interim analyses may be performed in relation to health authority interactions.

12.10.1 Multiplicity adjustments

No multiplicity adjustments will be made.

12.11 Subgroup Analyses

The primary endpoint will be analyzed and presented for the following subgroups:

- primary refractory vs. first relapse vs first PD during frontline therapy
- soft tissue lesions present at baseline (yes / no)
- tumor MYCN amplification status (yes / no)
- prior exposure to anti-GD2 antibody therapy (yes / no)
- ADA status (negative at all times / positive at any time)
- disease compartment (bone, BM, bone and BM combined (*i.e.,* OR excl. soft tissue lesions) as well soft tissue)
- geographical region

- site
- age group (0 - <2, 2 - <6, 6 - <12, 12 - <18 and >=18 years)
- body weight group (<20 kg; 20-<50 kg; >=50 kg)
- sex (male/female)
- race

Overviews of AEs will be presented for the following subgroups:

- primary refractory vs. first relapse vs first PD during frontline therapy
- ADA status (negative at all times / positive at any time)
- geographical region
- age group (0 - <2, 2 - <6, 6 - <12, 12 - <18 and >=18 years)
- body weight group (<20 kg; 20-<50 kg; >=50 kg)
- sex (male/female)
- race

12.12 Handling of Missing Data

Handling of patients not evaluable for the efficacy endpoints is described in Section 12.4.1. Handling of AEs with unknown onset dates is described in Section 12.5 and handling of AEs with onset outside reporting periods is described in Section 12.5.1.

12.13 Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will in further detail describe the analyses presented above.

Handling and presentation of data such as prior cancer therapies, demographics, baseline disease status, trial drug exposure, other trial assessments and protocol deviations (incl. COVID-related ones) will be described in the SAP. In addition, analyses of the proportion of patients who discontinue IT due to unacceptable toxicity and subsequently receive naxitamab + GM-CSF alone, and the time to such a discontinuation, will be described in the SAP.

12.14 Reporting of trial results

The results from this trial will be presented in a Clinical Study Report (CSR).

13 ETHICS

13.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This protocol and any accompanying material to be provided to the patient (such as patient information sheets and/or descriptions of the trial used to obtain informed consent) will be submitted by the Investigator to an IRB/IEC. Approval from the IRB/IEC must be obtained before starting the trial and should be documented in a letter to the Investigator.

It is the responsibility of the Investigator or his/her representative to obtain approval from the IRB/IEC before enrolment of any patient into the trial for the trial protocol/protocol amendments, advertisements, the patient information and the Informed Consent, including any written material to be given to the patient.

13.2 Ethical Conduct of the Trial

The trial will be conducted in accordance with the protocol, applicable regulatory requirements, ICH Good Clinical Practice[45] (GCP and the ethical principles of the Declaration of Helsink[46] as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and sub-sequent versions.

The trial will be conducted according to Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population[47] (recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to GCP in the conduct of clinical trials on medicinal products for human use).

13.3 Patient Information and Informed Consent

The Investigator or his/her designee must obtain the written informed consent from each patient, and/or the patients acceptable authorized representative, before any trial related procedures are performed as applicable to local regulations. The written patient information must not be changed without prior discussion with the Sponsor and approval by the IRB/IEC. Patient and legal representative (e.g., parent(s) or guardian(s)) must receive full trial information, both verbally and written, before consent is given. A child or adolescent patient will be informed and included in the conversations with the parents, to the extent that he/she can understand given his/her age. A patient information sheet will be prepared addressing legal representative(s) and a version especially addressing the adolescent population will also be prepared, if applicable according to local regulations.

The patient information will contain full and adequate verbal and written information regarding the objective and procedures of the trial and the possible benefits and risks involved. This will include any information of possible transfer of biological materials, imaging and other needed for central analysis. Regardless of legal representative(s) written consent, the participation shall not take place if the patient objects. Objection can also be non-verbal and expressed by the child's attitude, body language or resistance. Informed Consent (parents), and if applicable informed assent (child/adolescent), must be signed in accordance with local regulations.

If applicable to local regulations: if the child turns 18 during his/her participation in the trial, a written consent must be obtained from him/her before the trial can continue.

Before signing the ICF, the patient/parents must be given sufficient time to consider the possible participation. Further, each patient must be informed about their right to with-draw from the trial at any time. Parents and patients will also be informed that research participation is voluntary but if they withdraw from the trial, their data will still be used. When the informed consent form has been signed, the patient/parent(s) receives a copy of the signed form and the original is retained in the Investigator site file. A second copy may be kept in the patient's medical notes. The informed consent forms must be signed and dated both by the signee and by the person providing the information to the patient/parents. It is recommended to notify the patient's family doctor of the patient's consent to participate in the trial.

13.4 Confidentiality

The Investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties according to local requirements. The Investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the trial.

The Investigator agrees that the IMPs and all information received from Sponsor including but not limited to the IB, this protocol, data, eCRFs, and other trial information, remain the sole and exclusive property of Sponsor during the conduct of the trial and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the trial or as required by law) without prior written consent from Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the trial site to any third party or otherwise into the public domain.

14 MONITORING AND QUALITY ASSURANCE

14.1 Compliance with Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, Washington, Seoul, and South Africa)[46], International Council on Harmonisation (ICH) guidelines[45], or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the trial patient.

14.2 Protocol Compliance

The Investigator is responsible for ensuring the trial is conducted in accordance with the procedures and evaluations described in this protocol. Deviations from the protocol should not occur. If deviations do occur, the Investigator must inform the CRA for discussion and decision on required action(s). Deviations should be documented in writing including an explanation. Documentation of deviations will be filed in the Investigator's site file and a copy in the Sponsor's file. Depending on the nature of the deviation, this may be reported to the appropriate regulatory authority.

14.2.1 COVID related protocol deviations

Protocol deviations related to the COVID pandemic should be documented in the source data and in the eCRF.

14.3 Changes to the Protocol

Protocol modifications, except those intended to reduce immediate risk to trial patients, may only be made by Sponsor. Protocol modifications will follow local requirements for submission to the competent authorities and IRB/IECs. Approval must be obtained before changes can be implemented.

14.3.1 Training of Personnel

Training of personnel will be conducted during the site initiation visit. If change of personnel occurs, it is the responsibility of the Principal Investigator (PI) to train new personnel and it should be documented by e.g., completion of training log form. If the protocol or any trial specific procedures are updated, it is the responsibility of the CRA and PI to ensure documented training of all personnel.

Prior to the first dosing with naxitamab, sites with no earlier experience with naxitamab treatment must have watched a video with personnel from sites with naxitamab experience.

Before administration of naxitamab, the personal should be trained in resuscitation and treatment of severe hypotension according to local standard[41].

14.4 Monitoring

In accordance with the principles of ICH GCP and the Sponsor or its designee's SOPs, monitoring of the trial will be arranged. During the trial, the CRA will have regular contacts with the trial site, including visits to ensure that the trial is conducted and documented properly in compliance with the protocol, ICH GCP, and applicable local regulations. The

extent of monitoring will be based on a risk assessment and will be described in a monitoring plan.

The CRA will ensure that accountability of IMPs is performed and will review source documents for verification of consistency with the data entered in the eCRFs (source data verification). The CRA will also provide information and support to the investigational sites.

The Investigator should provide a curriculum vitae or equivalent documentation of suitability to be responsible for the trial including valid GCP training (i.e., within the previous two (2) years), a copy of current licensure, and should sign a financial disclosure on conflict of interests. All Investigators and other responsible personnel should be listed together with their function in the trial on the signature and delegation list to be filed in the Investigator site file.

During these contacts, the monitoring activities will include:

- Drug accountability
- AE identification/review
- Checking and assessing the progress of the trial
- Reviewing trial data collected to date for completeness and accuracy
- Conducting source document verification by reviewing each patient's eCRF against source documents (e.g., medical records, ICF, laboratory result reports, raw data collection forms)
- Identifying any issues and addressing resolutions

These activities will be done in order to verify that the:

- Data are attributable, legible, contemporaneous, original and accurate
- Safety and rights of the patients are being protected
- Trial is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements

The Investigator will allow the CRA direct access to all relevant documents and allocate ample time and the time of the personnel to the CRA to discuss findings and any relevant issues.

In addition to contacts during the trial, the CRA will contact the site prior to the start of the trial to discuss the protocol and data collection procedures with the site personnel.

14.4.1 Monitoring of Pharmacies

If a pharmacy is needed to be involved at the site, then monitoring of the records kept here will be described in the Monitoring Plan.

14.5 Source Data Verification

14.5.1 Source Data

All digital or paper hospital records regarding the treatment of the patient included in the trial are considered source data. The following minimum amount of information should be reported in the hospital records:

- Clinical trial identification
- Patient identification
- Date when patient information was given and when signed Informed Consent was obtained
- Diagnosis
- Fulfilment of inclusion criteria
- Specification of treatment with IMP
- Specification of visit dates, concomitant medications, and any (S)AEs
- Specification of the patient's cessation in the trial (e.g., premature withdrawal)
- Specification of the patient's outcome in the trial

14.5.2 Direct Access to Source Data/Documents

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, review and regulatory inspection(s), access to source data/hospital records. The CRA verifies that each patient has consented in writing to direct access to the original source data/hospital records by the use of written patient information and signed informed consent.

14.5.3 Access to Information for Monitoring

In accordance with ICH GCP guidelines, the CRA must have direct access to the Investigator's source documentation in order to verify the data entered in the eCRFs for consistency. The CRA is responsible for routine review of the eCRFs at regular intervals throughout the trial to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered into the eCRF. The CRA should have access to any patient records needed to verify the entries on the eCRFs. The Investigator agrees to cooperate with the CRA to ensure that any problems detected in the course of these monitoring visits are resolved.

14.5.4 Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Sponsor may conduct inspections or audits of the clinical trial. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the CRA immediately. The Investigator agrees to provide to representatives of a regulatory agency or Sponsor access to source documentation, facilities, and personnel for the effective conduct of any inspection or audit.

14.5.5 Quality Assurance

At its discretion, the Sponsor (or designee) may conduct a quality assurance audit of this trial. Auditing procedures of the Sponsor (or designee) will be followed in order to comply with GCP guidelines and ensure acceptability of the trial data for registration purposes. If such an audit occurs, the Investigator will give the auditor direct access to all source documents, will provide a guided tour of the facilities and will allocate ample time and the time of the personnel to the auditor as may be required to have interviews and discuss findings and potential issues.

15 DATA HANDLING AND RECORD KEEPING

15.1 Electronic Case Report Forms

For each patient screened, an eCRF must be completed and signed by the Investigator. This also applies to records for those patients who fail to complete the trial. If a patient withdraws from the trial, the reason must be noted in the eCRF. If a patient is withdrawn from the trial because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome. For screening failure patients, the date of informed consent, reason for failure, demographic data and any SAE must be captured in the eCRF.

15.2 eCRF

An eCRF will be established to collect data in a validated and effective way and in compliance with ICH guidelines including audit trail and a query module. The patient's identity must always remain confidential. All information in the eCRFs should be in English.

The completed eCRF data should not be made available in any form to third parties (except for authorized representatives of appropriate regulatory authorities) without written permission from the Sponsor.

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data entered in the eCRFs.

15.2.1 Corrections to Data

Corrections to the eCRF data can be made by the Investigator or the Investigator's delegated staff. The eCRF will contain an audit trail capturing as a minimum: the original and corrected/changed data, identification of the person correcting/changing the data, date and time of the correction/change and reason for the correction.

If corrections are made by the Investigator's delegated staff after the date the Investigator has signed the eCRF, the Investigator must re-sign the eCRF.

15.2.2 Data Entry Timelines

The Investigator must ensure that data is entered in the eCRF as soon as possible after the trial visit and no later than five (5) working days after the trial visit. Timeliness of data entries are monitored in the eCRF system. Data entry later than five (5) days after the trial visit does not qualify as protocol non-compliance (Section 14.2) and does not need to be documented by the Investigator; however, the CRA will address lateness during monitoring visits.

15.3 Trial Documents at Site and Record Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. These documents should be classified into at least the following two categories: (1) Investigator's site file, and (2) patient clinical source documents. The Investigator's site file will contain the protocol/amendments, and IRB/IEC approval with correspondence, informed consent, drug records, personnel curriculum vitae and authorization forms, and other appropriate documents and correspondence. The Investigator is required to complete a source data list,

defining where the specific source data can be found (patient record/trial specific patient record).

During the trial, the Investigator will have full access to the eCRF. After the trial is completed, the Investigator will receive a copy of the eCRF on CD-ROM or other appropriate electronic storage device.

All clinical trial documents must be retained by the Investigator until at least 25 years after the clinical trial. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with Sponsor. The Investigator must notify Sponsor before destroying any clinical trial records. Should the Investigator wish to assign the trial records to another party or move them to another location, Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the trial site for any or all of the documents, special arrangements must be made between the Investigator and Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit.

When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples (for ADA assessment, and BM assessments (histology, immunohistochemistry, smears of BM and BM aspirates for RTqPCR) will be discarded after the analysis has been completed and no later than at the finalization of the full clinical trial report. If requested by the local sites, the BM material may be returned before End of Trial. The pathology vendor will store the BM material electronically for up to 20 years after End of Trial.

15.4 Data Management

All data, except laboratory data, will be collected using an eCRF compliant with 21 CFR Part 11 regulation. Laboratory data centrally collected will be transferred to data management facility for inclusion in the clinical database. Data management will be performed in accordance with applicable standards and data cleaning procedures. Only authorized access to the eCRF will be possible using encrypted username and password. Roles in the system are given according to functions. All tasks performed in the eCRF are logged in an audit trail. The eCRF will contain validation checks to maintain an ongoing quality check of data entered. The Investigator will approve the data using an electronic signature and thereby confirm the accuracy of the data entry. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Concomitant medication will be coded using the World Health Organization (WHO) Drug dictionary.

16 PREMATURE TERMINATION OF THE TRIAL

The Sponsor reserves the right to close a trial site or terminate the trial at any time for the reasons below at the sole discretion of the Sponsor. If the trial is suspended or terminated, the investigator must inform the patients promptly and ensure that adequate considerations is given to the protection of the patient's interest. The Sponsor must promptly inform the regulatory authorities and provide a detailed explanation of the termination. Furthermore, the investigator or Sponsor will inform IECs/IRBs.

Trial sites will be closed upon completion. A trial site is considered closed when it has been verified that all required documents are filed as required, that the IMP have been destroyed and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is a reasonable cause and sufficient notice in advance of the intended termination.

16.1 Criteria for Halting Patient Enrolment

Enrolment will be halted temporarily until DMC feedback on continuation of the trial has been received if one of the following criteria is met:

- If an event, alone or in combination with other safety information, is judged by either Sponsor or DMC chairman to warrant an acute DMC meeting One or more patients experience unexpected, IMP related sudden death during the treatment period

If the above-mentioned criteria are met, the DMC will review the safety results and determine how to proceed as described in Section 10.11.

Patients already included at the time of clinical trial halt, will continue in the clinical trial but further dosing will be postponed until a decision has been reached by the DMC.

16.2 Criteria for Termination of the Trial

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of patients. After such a decision, all delivered unused IMP and other trial-related materials must be collected without delay and all eCRFs must be completed as far as possible.

The trial could be prematurely discontinued in the following situations (examples):

- New findings about the IMPs that is considered significantly to worsen the benefit/risk ratio
- Compliance with the trial protocol proves difficult
- Recruitment of eligible patients is far too low or slow
- Level of Investigator, Sponsor or patient compliance becomes unacceptable
- Critical changes are observed in Sponsor or trial site personnel, administrative or scientific standards
- The DMC recommends discontinuation

17 REPORTING AND COMMUNICATION OF RESULTS

17.1 Publication

The data collected in this trial are the property of the Sponsor. Sponsor commits to communicate and make available for public disclosure, the results of the clinical trial regardless of outcome, in accordance with applicable regulatory requirements. Public disclosure implies publication in scientific journals, abstract submission for scientific meetings and other types of disclosure (e.g., via ClinicalTrials.gov). Co-authorship from Investigators will be in accordance with International Committee of Medical Journal Editors (ICMJE) rules:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A predefined publication committee will follow the entire process; decide on publication, manuscript authorship for the entire clinical trial and authorship of potential additional manuscripts based on sub-studies. All manuscripts relating to sub-studies will state that they are sub-studies and cite the main publication. The publication committee will also decide on which journal(s) to submit to. Positive, negative as well as inconclusive results will be published e.g., at www.clinicaltrials.gov or www.clinicaltrialsregister.eu.

17.2 Use of Information

Sponsor will make one main publication from the clinical trial and all other publications should come afterwards and refer to the main clinical trial publication.

All information not previously published concerning the IMPs, including patent applications, manufacturing processes, basic scientific data, clinical trial data and results, etc., is considered confidential and remains the sole property of the Sponsor. The Investigator agrees to use this information only in connection with this trial and will not use it for other purposes without written permission from the Sponsor.

No such communication, presentation, or publication will include Sponsor's confidential information. All presentation and publications will be governed by the publication committee. Proposed publication(s) or presentation(s) along with the respective scientific journal or presentation forum should be provided to the Sponsor at least 30 days prior to submission of the publication or presentation. Publication authors will comply with Sponsor's request to delete references to its confidential information (other than the trial results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

18 INSURANCE

Insurance and liability will be in accordance with applicable local laws and regulations and GCP.

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20 APPENDICES

Appendix 1 Creatine-based 2009 revised Bedside Schwartz Equation

eGRF = 0.413 x (height/Scr)[48]

Height is expressed in centimeters

Abbreviations/Units:

- eGRF = mL/min/1.73 m^2
- Scr (Standardized serum creatinine) = mg/dL

Appendix 2 Flowchart and assessment for patients who discontinues IT treatment due to toxicity

This appendix describes the Treatment/Measurements/Evaluations relevant for patients who has discontinued treatment with IT due to toxicity. The below flowchart replaces the one in Section 3, if the patient moves from treatment with HITS to treatment with naxitamab + GM-GSF alone.

Table 12 Schedule of time and events: screening, treatment and follow-up for patients in treatment with naxitamab + GM-CSF alone

Treatment/Measurements/ Evaluation	Cycle 1 for patients in treatment with naxitamab and GM-CSF alone									
	D -4 to 0	D1	D2	D3	D4	D5	D6 +7	Next cycles	EOT[2]	Long -term FU[3]
Physical examination (9.2.1)	X	X						X	X	
Height and weight (9.3.2)	X							X		
Serum pregnancy test, if applicable (9.2.8)	X[5]							X	X	
Vital signs (Appendix 2)		X		X		X		X	X	
Electrocardiogram[1] (9.2.6)									X	
Clinical laboratory assessments (Appendix 2)	X	X		X		X		X	X	
Anti-drug antibodies (ADA) (11.2)	X							X	X	
Bone marrow biopsy/apirates (9.1.1, 9.1.1.1, 9.1.2)								X[6]	X[4]	X[8]
Imaging (9.1.1, 9.1.1.1, 9.1.2)								X[7]	X[4]	X[8]
Performance test (9.3.4)	X							X	X	
Pain assessment (9.2.7)		X		X		X		X		
Pre-treatment (8.4.1, Appendix 2)	X	X	X	X	X	X	X	X		
Treatment (8.1.1, Appendix 2)	X	X	X	X	X	X		X		
Drug accountability and compliance check (8.1.5)		X		X		X		X		
Hand out diary (8.1.5)	X							X		
Adverse events (10)	X	X		X		X		X	X	X
Concomitant medication(s) (8.4)	X	X		X		X		X	X	X

1 If the patient needs sedation before ECG, the ECG can be performed in connection with imaging.
2 EOT visit should take place 6 (up to 10) weeks after last treatment. If treatment is discontinued due to PD, planned initiation of new anti-NB treatment prohibited as per protoocol, withdrawal from the trial or investigator judges it warranted due to medical reasons/non-compliance, the patient should be called for EOT visit as soon as possible and subsequently be followed for safety and new anti-cancer therapy for 6 weeks after last treatment.
3 Long-term FU evaluations should take place approximately every 4 months until 2 years after EOT. During long-term FU, information on death, PD, SAEs ongoing at EOT visit, new SAEs at least possibly related to naxitamab, autoimmune

diseases and new onset of secondary malignancies should be collected. Furthermore, new anti-cancer therapy should be collected as concomitant medication.
4 Not to be performed at EOT if the patient discontinues treatment due to PD, provided that PD is documented by scan and/or biopsy (see Section 9.1.2).
5 Should be performed on D-4 prior to GM-CSF administration
6 Bilateral aspirates and biopsies (2+2): After C2, C4 C8 and EOT (**Cycles in the HITS regimen included**) (see Section 9.1.2).

- For patients with CR or PR after 8 cycles: Assessments will furthermore be performed after C11
- For patients with MR or SD after 8 cycles: Assessments will furthermore be performed after C10, C12
- Samples for RTqPCR should be taken after C2 and C4

All response assessments (except EOT) should be performed before D1 of next cycle.
In addition, for patients who achieve:

- a first CR or PR after C4 OR
- a first CR or PR after C8

a confirmatory response assessment should be performed within 4-6 weeks after detection of the overall response.
7 Imaging schedule follows timing of BM biopsies (see #6 above). For a FDG PET scan, the patient must be in fasting state for at least 4 hrs prior to the scan. If the patient is not fasting serum glucose determination must be performed prior to the administration of FDG (PET scan only). Please refer to the imaging charter for more details.
8 For patients who have not experienced PD, response assessment should be performed at approximately every 4 months after EOT during long-term FU (see Section 9.1.2).

Pre-medication:

Gabapentin should be administered from Day -4 to Day 7 of each cycle according to local SoC (e.g. dose of 5 to 10 mg/kg with a max dose of 600 mg). It is recommended to titrate to the final effective dose during the first 3 days of treatment:

- Day -4: once daily
- Day -3: twice daily
- Day -2 and onwards until Day 7: 3 times daily

Treatment

The treatment regimen/cycles are different for patients who are treated with naxitamab + GM-CSF alone compared to patients who are treated with HITS. Please see below:

Each treatment cycle is 28 days.

GM-CSF:
GM-CSF should be administered sc at 250 µg/m^2 per day from Day -4 to Day 0 and 500 µg/m^2 per day at Day 1 to Day 5. The patient/parents will be asked to fill in records of administration (patient diary).

If any events occur fulfilling a GM-CSF discontinuation criterion the patient must discontinue GM-CSF but will be allowed to continue naxitamab treatment, see Section 7.12

Naxitamab:
On days when co-administered with GM-CSF, naxitamab infusion is started ≥ 60 min after GM-CSF.

Naxitamab should be infused IV at 3 mg/kg/day on Days 1, 3, and 5 for a total dose of 9 mg/kg per cycle. Administration of naxitamab should be adjusted according to Section 8.4.5 if selected naxitamab adverse reactions are observed. If any events occur fulfilling a general

discontinuation criterion the patient must be withdrawn from naxitamab and GM-CSF treatment immediately and enter long-term follow-up, see Section 7.12.

Naxitamab should be infused over approx. 30 min.

Special circumstances:
The infusion may be given over approximately 60 min. at Day 1 of any cycle at the investigator's discretion if:

- The patient during the C1D2 infusion (HITS regimen) experienced naxitamab related hypotension:
  - CTCAE Grade 4 **or**
  - Grade 3 not adequately responding
- At the investigators discretion due to severe infusion related adverse drug reactions not adequately responding to interventions

The 60/30 min infusion time is a minimum infusion time. If infusion pause or infusion rate reduction is required due to infusion related AE (see Section 8.4.5) the infusion time will become longer.

Table 13 Treatment with naxitamab + GM-CSF alone

Treatment days in cycles of 28 days	-4 to 0	1	2	3	4	5	6+7	11-28
Premedication (analgesics and/or antihistamines) (8.4.1)	X	X	X	X	X	X	X	
GM-CSF 250 ug/m^2/day s.c (8.4.6)[1]	X							
GM-CSF 500 ug/m^2/day s.c (8.4.6)[1]		X	X	X	X	X		
Naxitamab 3 mg/kg/day IV (9mg/kg/cycle)[1] (8.1.2.3)[1]		X		X		X		

1 Patients achieving a CR or PR should receive 8 naxitamab cycles or 5 additional naxitamab cycles following the OR, whichever provides the longest treatment with naxitamab. Patients who have achieved a MR or SD at completion of the 8 cycles may receive naxitamab + GM-CSF consolidation treatment for 5 cycles administered at every 8 weeks. The total number naxitamab cycles to be administered includes the treatment cycles administered in the HITS regimen

Missed dosing
If a naxitamab dose is missed, administer the missed dose the following week, but the 3 infusions of naxitamab must be administered within a period of maximum 10 days. If a patient is treated on a modified schedule, the GM-CSF dosage will be the same as the standard on days -4 to 0, but GM-CSF will be administered at 500 µg/m2/day on the day of the first infusion of naxitamab, on the day before and on the day of the second infusion of naxitamab, and on the day before and on the day of the third infusion of naxitamab. The modified schedule ensures that the same total dosage of GM-CSF is administered in the standard and in the modified schedules.

Laboratory assessments:
Laboratory tests should be performed as described in the table below and as clinically indicated.

Table 14 Protocol required laboratory assessments for patient treated with naxitamab + GM-CSF alone

Timing of Laboratory assessments	Parameters
All cycles*: Prior to dosing D-4, D1, D3, D5 EOT * If modified naxitamab dosing due to missed dose (ie naxitamab missed dose to be administered within the first 10 days of a cycle) check hematology parameters on day of last naxitamab administration in the cycle prior to administration of GM-CSF	Hematology • Hemoglobin • Hematocrit • White blood cells (WBC) • Lymphocytes (absolute) • Neutrophils (absolute) • Eosinophils (absolute) • Basophils (absolute) • Monocytes (absolute) • Platelet count
All cycles: prior to dosing D1, D3, D5 EOT	Liver and kidney function blood tests • ALT • AST • Alkaline phosphatase • Total bilirubin • LDH • BUN • Creatinine • Albumin **(only prior to each cycle)**
All cycles: prior to dosing D1, D3, D5 EOT	Serum electrolytes • Sodium • Potassium
Prior to each cycle	Urine analysis (dipstick) • Protein • Glucose • Leucocytes
Prior to each cycle EOT	Pregnancy test, if applicable Serum pregnancy test for WOCBP see 9.2.8 for further information
ADA Prior dosing in each cycle EOT	• Anti-naxitamab antibodies • Naxitamab AB (neutralizing effect)

The complete blood count (CBC) and differential counts should be repeated on sequential days during all treatment cycles if ANC is > 20 x10^9/L or WBC > 50 x10^9/L on the previous day.

Vital signs

- Prior to pre-medication (e.g., hydromorphone or morphine)
- Prior to start of naxitamab infusion

- ~15 min after start of naxitamab infusion
- ~30 min after start of naxitamab infusion
- Prior to each hydromorphone or morphine IV therapy as possible/feasible (no temperature)
- At completion of naxitamab infusion including flush (no temperature)
- ~15 min after completion of the flush (no temperature)
- Every hour while patient is recovering in the outpatient clinic

Please refer to Section 9.2.7 for pain assessments and Section 9.2.3 for naxitamab discharge criteria. Furthermore, vital signs should be measured at EOT and as clinical indicated.

Appendix 3 Temozolomide dosing (100mg/m^2/day) Nomogram

Temozolomide is dosed based on BSA. The dose should be rounded off to the nearest 5 mg (round 2.5 mg down). For patients with BSA <0.5 m^2, dosing is based on body weight (kg).

For patients with a BSA < 0.5 m^2: Use **3.3 mg/kg.**

Examples:
Patient has a BSA of 0.3 m^2 and weighs 5 kg. Patient administered dose = 5 kg x 3.3 mg/kg = 16.5 mg

Patient has a BSA of 0.66 m^2. Calculated dose is 0.66 m^2 x 100 mg/m^2 = 66 mg/day; Administered dose = 65 mg temozolomide/day.

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
< 0.50	3.3 mg/kg	3.3 mg/kg
0.50-0.52	50-52	50
0.53-0.57	53-57	55
0.58-0.62	58-62	60
0.63-0.67	63-67	65
0.68-0.72	68-72	70
0.73-0.77	73-77	75
0.78-0.82	78-82	80
0.83-0.87	83-87	85
0.88-0.92	88-92	90
0.93-0.97	93-97	95
0.98-1.0	98-100	100
1.01-1.05	100-105	105
1.06-1.14	105-114	110
1.15-1.24	115-124	120
1.25-1.34	125-134	130
1.35-1.44	135-144	140
1.45-1.54	145-154	150
1.55-1.64	155-164	160
1.65-1.74	165-174	170
1.75-1.84	175-184	180
1.85-1.94	185-194	190
1.95-2.00	195-200	200
> 2.0	> 200	200

Appendix 4 Nomogram for Reduced Dosing (80 mg/m^2/day) of Temozolomide

Temozolomide is dosed based on BSA for patients whose BSA is at least 0.5 m^2. For these patients, doses are rounded to the nearest 5 mg. For patients with BSA <0.5 m^2, dosing is based on body weight (kg). If unacceptable temozolomide associated specific toxicities occur (see Section 8.4.4), a 20% dose reduction should be applied (80mg/m^2/day). If the toxicity recurs despite the dose reduction a second 20% dose reduction (60 mg/m^2/day) may be applied (see Appendix 5)

For patients with a BSA < 0.5 m^2: Use **2.6 mg/kg.**

Examples:

- For a patient with a BSA of 0.3 m2 and weighs 5 kg, the calculated dose is 5 kg x 2.6 mg/kg = 13.0 mg
- For a patient with a BSA of 0.66 m^2, the calculated dose = 52.8 mg/dose; administered dose = 55 mg temozolomide/dose.

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.2-0.49	2.6 mg/kg	2.6 mg/kg
0.50 - 0.53	40 - 42	40
0.54 - 0.59	43 - 47	45
0.60 -0.65	48 - 52	50
0.66-0.71	53 -57	55
0.72-0.78	58 - 62	60
0.79-0.84	63 - 67	65
0.85-0.90	68 - 72	70
0.91-0.96	73 - 77	75
0.97-1.03	78 - 82	80
1,04-1.09	83 - 87	85
1.10-1.15	88 - 92	90
1.16-1.21	93 - 97	95
1.22-1.28	98 - 102	100
1.29-1.34	103 -107	105
1.35-1.40	108 - 112	110
1.41-1.46	113 - 117	115
1.47-1.53	118 - 122	120
1.54-1.59	123 - 127	125
1.60-1.65	128 - 132	130
1.66-1.71	133 - 137	135
1.72-1.78	138 - 142	140
1.79-1.84	143 - 147	145
1.85-1.90	148 - 152	150
1.91-1.96	153 - 157	155
>1.96	>157	160

Appendix 5 Nomogram for Reduced Dosing (60 mg/m^2/day) of Temozolomide

Temozolomide is dosed based on BSA for patients whose BSA is at least 0.5 m^2. For these patients, doses are rounded to the nearest 5 mg. For patients with BSA <0.5 m^2, dosing is based on body weight (kg). If unacceptable temozolomide associated specific toxicities recur despite the first dose reduction by 20% (see Section 8.4.4), a second 20% dose reduction (60 mg/m^2/day) should be applied.

For patients with a BSA < 0.5 m^2: Use **2.0 mg/kg.**

Examples:

- For a patient with a BSA of 0.3 m^2 and weighs 5 kg, the calculated dose is 5 kg x 2.0 mg/kg = 10.0 mg
- For a patient with a BSA of 0.66 m^2, the calculated dose = 39.6 mg/dose; administered dose = 40 mg temozolomide/dose.

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.2-0.49	2.0 mg/kg	2.0 mg/kg
0.50 - 0.54	30 - 32	30
0.55 - 0.62	33 - 37	35
0.63 -0.70	38 - 42	40
0.71-0.79	43 - 47	45
0.80-0.87	48 - 52	50
0.88-0.95	53 -57	55
0.96-1.04	58 - 62	60
1.05-1.12	63 - 67	65
1.13-1.20	68 - 72	70
1,21-1.29	73 - 77	75
1.30-1.37	78 - 82	80
1.38-1.45	83 - 87	85
1.46-1.54	88 - 92	90
1.55-1.62	93 - 97	95
1.63-1.70	98 - 102	100
1.71-1.79	103 -107	105
1.80-1.87	108 - 112	110
1.88-1.95	113 - 117	115
>1.95	>117	120

Appendix 6 Temozolomide 10 mg/mL suspension

Preparation of oral suspension of Temozolomide[49]:

Recipe for 100 mL	
Temozolomide (from 10 Temodar 100 mg capsules)	1,000 mg
Povidone K-30	500 mg
Anhydrous citric acid	25 mg
Purified water	1,5 mL
Ora-Plus	50 mL
Ora-Sweet or Ora-Sweet SF qs	100 mL

Note: It is necessary to wear suitable protective garb and to perform this procedure in a fume hood. The suspension must be administered at the trial site.

1. Empty the contents of 10 temozolomide 100 – mg capsules in a glass mortar of sufficient size
2. Weigh 500 mg of povidone K-30 powder and add to the mortar
3. Triturate to assure thorough mixing and that the mixture is reduced to a fine powder
4. Dissolve 25 mg of anhydrous citric acid and purified water
5. Add the mixture of anhydrous citric acid and purified water to the mortar to wet the powder
6. Mix thoroughly to form a uniform paste
7. Add a small amount of Ora-Plus suspension vehicle to the triturated paste with thorough mixing to ensure a uniform mixture
8. Add the balance of the Ora-Plus suspension vehicle with thorough mixing to ensure a uniform mixture
9. Transfer the resulting mixture to a glass graduated cylinder
10. Rinse the mortar and pestle with small aliquots of the appropriate syrup (Ora-Sweet or Ora-Sweet SF); repeat the rinsing three times
11. Add an additional quantity of the appropriate syrup vehicle to the bottle to bring the final volume to 100 mL and shake the resulting suspension well
12. Package in amber plastic prescription bottles and label the containers with “Shake well” and “Refrigerate” and the expiry date which is 60 days after preparation

Appendix 7 Recommendations for administration of Temozolomide

(Patients who are unable to swallow capsules and cannot obtain a suspension)

If the patient is unable to swallow capsules, the below instructions or the one in Appendix 5 must be followed for safe administration of temozolomide.

It is necessary to wear suitable protective garb and to perform this procedure in a fume hood.

- Temozolomide can be mixed in apple sauce or apple juice
- Place the apple sauce or apple juice in a disposable container
- Open each capsule required for the daily dose and place the powder in a medicine cup
- Add the whole contents of the medicine cup to either apple sauce or apple juice. The medicine will not dissolve completely if mixing in apple juice so have extra apple juice on hand so you can add it to any remaining powder in the bottom of the cup
- If you need to have additional juice or apple sauce remove your gloves before touching the main container then place new gloves on before adding the additional juice or apple sauce to the medicine. (You do not want to contaminate the main container with any powder that may be on your gloves.)
- Anything that comes into contact with the medicine must be disposable, such as the spoon used for mixing or eating the apple sauce

Appendix 8 Wong-Baker FACES® Pain Rating Scale

Instructions

Prior to the naxitamab infusion, the Wong Baker FACES® Pain Rating Scale should be presented and explained to the patient, by informing the patient that each face on the scale represents a person who has no pain, some pain or a lot of pain. The staff who will be asking the patient to rate his/her pain should explain that:

- Face 0 does not hurt at all.
- Face 2 hurts just a little bit.
- Face 4 hurts a little bit more.
- Face 6 hurts even more.
- Face 8 hurts a whole lot.
- Face 10 hurts as much as you can imagine, although you don´t have to be crying to have this worst pain.

The rating should be done by asking the patient to choose the face that best depicts the pain they are experiencing.

For details of pain assessment please see Section 9.2.7.

Appendix 9 FLACC Behavioral Scale

FLACC Behavioral Scale

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort

Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.

FLACC Behavioral Pain Scale

Patients who are awake: Observe for at least 1-2 min. Observe legs and body uncovered. Reposition patient or observe activity, assess body for tenseness and tone. Initiate consoling interventions if needed

Patients who are asleep: Observe for at least 2 min or longer. Observe body and legs uncovered. If possible, reposition the patient. Touch the body and assess for tenseness and tone.

Face

Score 0 point if patient has a relaxed face, eye contact and interest in surroundings

Score 1 point if patient has a worried look to face, with eyebrows lowered, eyes, partially closed, cheeks raised, mouth pursed

Score 2 points if patient has deep furrows in the forehead, with closed eyes, open mouth and deep lines around nose/lips

Legs

Score 0 points if patient has usual tone and motion to limbs (legs and arms)

Score 1 point if patient has increase tone, rigidity, tense, intermittent flexion/extension of limbs

Score 2 points if patient has hyper tonicity, legs pulled tight, exaggerated flexion/extension of limbs, tremors

Activity
Score 0 points if patient moves easily and freely, normal activity/restrictions
Score 1 point if patient shifts positions, hesitant to move, guarding, tense torso, pressure on body part
Score 2 points if patient is in fixed position, rocking, side-to-side head movement, rubbing body part

Cry
Score 0 points if patient has no cry/moan awake or asleep
Score 1 point if patient has occasional moans, cries, whimpers, sighs
Score 2 points if patient has frequent/continuous moans, cries, grunts

Consolability
Score 0 points if patient is calm and does not require consoling
Score 1 point if patient responds to comfort by touch or talk in - 1 min
Score 2 points if patient require constant consoling or is unconsoled after an extended time
Whenever feasible, behavioral measurement of pain should be used in conjunction with self-report. When self-report is not possible, interpretation of pain behaviors and decision-making regarding treatment of pain requires careful consideration of the context in which the pain behaviors were observed.
Each category is scored on the 0-2 scale which results in a total score of 0-10Assessment of Behavioral Score:
0 = Relaxed and comfortable
1-3 = Mild discomfort
4-6 = Moderate pain
7-10 = Severe discomfort/pain

Appendix 10 Performance tests

Lansky Scale (recipient age < 16 years)		**Karnofsky Scale (recipient age ≥ 16 Years)**	
Able to carry on normal activity; no special care is needed		Able to carry on normal activity; no special care is needed	
100	Fully active	100	Normal, no complaints, no evidence of disease
90	Minor restriction in physically strenuous play	90	Able to carry on normal activity
80	Restricted in strenuous play, tires more easily, otherwise active	80	Normal activity with effort
Mild to moderate restrictions		Unable to work, able to live at home cares for most personal needs, a varying amount of assistance needed	
70	Both greater restrictions of, and less time spent in active play	70	Cares for self, unable to carry on normal activity or to do active work
60	Ambulatory up to 50% of time, limited active play with assistance/supervision	60	Requires occasional assistance but is able to care for most needs
50	Considerable assistance required for any active play, fully able to engage in quiet play	50	Requires considerable assistance and frequent medical care
Moderate to severe restrictions		Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly	
40	Able to initiate quiet activities	40	Disabled, requires special care and assistance
30	Needs considerable assistance for quiet activity	30	Severely disabled, hospitalization indicated, although death not imminent
20	Limited to very passive activity initiated by others (e.g., TV)	20	Very sick, hospitalization necessary
10	Completely disabled, not even passive play	10	Moribund, fatal process progressing rapidly

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