A Phase I/II Combination Study of NMS-03305293 and Temozolomide in Adult Patients with Recurrent Glioblastoma

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This study has been transitioned to CTIS with ID 2023-508318-41-00 check the CTIS register for the current data. Primary Objective:• To determine the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D) of NMS-03305293 in combination…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56287

Source
ToetsingOnline

Brief title
Study of NMS-03305293+TMZ in Adult Patients with Recurrent Glioblastoma

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Diffuse Glioma, Glioblastoma

Research involving
Human

Sponsors and support

Primary sponsor: Nerviano Medical Sciences Srl, Italy
Source(s) of monetary or material Support: Nerviano Medical Sciences Srl.

Intervention

Keyword: Diffuse Gliomas, Glioblastoma, NMS-03305293, Temozolomide

Outcome measures

Primary outcome

Primary Endpoint(s):

• First cycle Dose Limiting Toxicities (DLTs) (Phase I)

• Objective Response Rate (ORR), calculated as the proportion of evaluable patients who have achieved, as best overall response (BOR), confirmed complete response (CR) or partial response (PR) through central retrospective assessment of RANO criteria (Phase II)

Secondary outcome

Secondary Endpoint(s):

• Overall safety profile of the combination of NMS-03305293 and TMZ characterized by type, frequency, severity (graded using the NCI CTCAE Version 5.0), duration of adverse events (AEs), ECGs, laboratory abnormalities and relationship of AEs to the study treatment

• Plasma pharmacokinetic profile of NMS-03305293 and possible identified metabolites (if appropriate) after oral administration

• Renal clearance and fraction of NMS-03305293 and possible identified metabolites (if appropriate) excreted in urine

Secondary efficacy endpoints:

Phase I

o Objective Tumor Response (Partial and Complete Response) (RANO criteria)

o Duration of response (DoR)

o Progression-free survival (PFS)

o Overall survival (OS)

Phase II

o Duration of response (DoR) through central retrospective assessment of

RANO criteria

o Progression-free survival (PFS) and 6-month PFS rate

o 9 and 12-month overall survival rates

o Overall survival (OS)

Exploratory Endpoints:

• Correlation of outcome measurements with MGMT promoter methylation status

determined in tumor tissue from initial or salvage surgery

Changes in corrected QT intervals from baseline versus plasma concentrations of

NMS-03305293 and possible identified metabolites, if appropriate.

Study description

Background summary

Glioblastoma is one of the most common malignant primary brain tumors in adults. Due to its aggressive and highly proliferative course, glioblastoma is defined a grade 4 tumor based on the World Health Organization (WHO) classification.

Standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (RT) with concomitant daily temozolomide (TMZ) chemotherapy, and then maintenance treatment with TMZ for 6 months according to the EORTC NCIC protocol (Stupp et al.; 2005). Despite some improvements over the years in neuro-imaging, chemotherapy, surgical and RT techniques and chemotherapy, the prognosis for these patients remains poor, with a median OS of 14.6 months, an OS rate of 27% at 2 years, and only about 10% surviving at 5 years. Glioblastoma is considered a chemo and radio-resistant tumor, in fact recurrence occurs in more than 90% of patients, mostly in the irradiation field and, even in tumors with O6-methylguanine DNA methyltransferase (MGMT) promoter methylation, the response to chemotherapy is temporary. At recurrence, there is no standard of care available. Surgery or reirradiation can be offered to patients with circumscribed recurrences. Most patients with recurrent glioblastoma who are eligible for salvage therapy are treated with a second course of alkylating agent chemotherapy, e.g. re-treatment with TMZ, especially after a long time to recurrence after initial therapy with adjuvant TMZ, or mostly lomustine (CCNU). Bevacizumab as a single agent was approved in the USA, although not in the European Union, based on prolonged progression- free survival, but no survival benefit was ever proven. Bevacizumab, where available, is commonly used in symptomatic patients at later recurrences. In the absence of effective therapies for recurrent glioblastoma, participation of subjects in clinical trials is encouraged.

In the effort to identify effective therapies for patients with glioblastoma, an attractive approach is the enhancement of the antitumor activity of irradiation or alkylating therapies (e.g. TMZ, RT) by impairing DNA repair. PARP-1 is known to have an important function in DNA repair and PARP inhibition has been considered as a novel approach to target tumors with deficiencies in DNA repair mechanisms and to enhance the DNA damaging effect of chemotherapy and ionizing radiation.

Gliomas are highly infiltrative with tumor cells extending beyond regions of contrast enhancement in essentially all tumors; thus, brain distribution of drugs used to treat glioblastoma is critically important to target all tumor cells within the brain. Poor penetration of the blood brain barrier (BBB) undermines the efficacy of many pharmaceutical agents in CNS tumors, including PARPi, tested for the treatment of glioblastoma.

Several studies have been launched to assess the safety and efficacy of various PARPi in patients with glioblastoma, but no proven benefit has been demonstrated yet possibly due to low brain penetration and/or low potency (veliparib) or to the increased hematological toxicity likely linked to the low

selectivity on PARP-1 and to the ability of trapping the PARP proteins on DNA, thus interfering with DNA replication and ultimately causing cell death of highly proliferating cells (olaparib, niraparib, rucaparib and talazoparib).

NMS-03305293 is a member of the isoindolinone chemical class and is a potent inhibitor of PARP-1 (KD=2.72 nM). NMS-03305293 has high selectivity for PARP-1 vs the other enzymes of the PARP family, including PARP-2 (KD=691 nM). The compound exhibited potent anti-proliferative activity against BRCA mutated or homologous recombination deficient (HRD) tumor cell lines, with IC50 in the low nanomolar range.
Specificity was confirmed using a panel of DNA repair proficient cell lines, against which the compound was essentially inactive.

When NMS-03305293 was combined with TMZ in glioblastoma models, either sensitive or resistant to TMZ treatment, good tolerability and more than additive antitumor activity were observed.

NMS-03305293 was tested in combination with TMZ against three glioblastoma models: T98-G, BT-308 and intracranially implanted U-87 MG showing remarkable and reproducible activity and ability to restore sensitivity to TMZ in resitant models.

Pivotal GLP toxicity studies were conducted in rats and dogs with NMS-03305293 administered orally for 4 weeks followed by a 2- or 4- week recovery period, respectively. Noteworthy findings in these pivotal GLP repeated dose toxicity studies included effects on the hemolymphopoietic system in rats and dogs, CNS-related clinical signs and changes in the brain in dogs, and effects on testes and liver in rats. Effects on the hemolymphopoietic system included slight to moderate dose-related hematological changes and alterations in bone marrow and thymus with a complete recovery of bone marrow and thymus changes at the end of the recovery period. CNS clinical signs, characterized by aggressiveness, fear reaction, hunched posture, abnormal posture/gait, and tremors were observed soon after dosing in dogs from the intermediate dose (20 mg/kg/day) and convulsions were observed in two females treated at the highest dose tested (30 mg/kg/day). These signs generally started 15-30 minutes post-dose and resolved within about one hour after onset. CNS effects were associated with minimal to slight inflammatory infiltrates in the meninges and no specific neuronal cell degeneration was detected. A complete recovery of brain changes occurred after 4 weeks of drug withdrawal. Germ cell depletion in the testes and liver findings not associated with any serum chemistry abnormality were detected in rats from 25 mg/kg/day with partial recovery at the end of the 2-week observation period.

In the GLP 4-week studies in rats and dogs, the terminal half-life of the compound was short (6-11 hours in rats and 6-7 hours in dogs). No accumulation in dogs or weak accumulation in rats was observed in the GLP 4- week studies. Overall, no deviation from dose proportionality and time linearity was seen in

the PK studies.

NMS-03305293 has been proven to distribute extensively into brain tissue of mice, rats and dogs. Two studies performed in mice and rats demonstrated that brain concentrations of NMS-03305293 were four to twenty times higher than those in plasma after a single oral administration at the dose of 10 mg/kg and concentrations declined in parallel. In an additional study conducted in dogs, treated with NMS-03305293 given orally at the daily dose of 20 mg/kg for seven days, NMS-03305293 was detectable up to 48 hours post-dosing in the brain and the systemic exposure in brain was about 6-fold higher than in plasma.

A Phase I, dose-escalation study with NMS-03305293 (PARPA-293-001) administered as single agent daily for 21 or 28 consecutive days in 4 week-cycles is ongoing in patients with selected solid tumors (cancer of the ovary, breast, prostate and pancreas). The starting dose in this study was 20 mg/day. The PARPA-293-001 study is closely monitored and safety results from completed cohorts are made available to inform investigators participating to the PARPA-293-002 study.

In conclusion, PARP inhibitors are hypothesized to enhance the efficacy of alkylating therapies such as TMZ by impairing DNA repair. The results of the preclinical studies demonstrate that the combination of NMS- 03305293 with TMZ is effective both in TMZ-sensitive and TMZ-resistant models with good tolerability. In addition, the toxicology studies conducted with NMS-03305293 as single agent demonstrate an adequate safety profile and safety margin to support the proposed clinical trial in combination with TMZ. NMS-03305293, due to its PARP-1 selectivity and lack of trapping activity, is expected to be well tolerated in combination with myelotoxic agents. In addition,

Study objective

This study has been transitioned to CTIS with ID 2023-508318-41-00 check the CTIS register for the current data.

Primary Objective:
• To determine the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D) of NMS-03305293 in combination with temozolomide (TMZ) in patients with diffuse gliomas at first relapse (Phase I)
• To assess the antitumor efficacy of the combination of NMS-03305293 and TMZ in patients with Isocitrate dehydrogenase (IDH) wild type glioblastoma (Phase II) at first relapse

Secondary Objectives:
• To characterize the safety profile of NMS-03305293 in combination with TMZ
• To evaluate the pharmacokinetics of NMS-03305293 in combination with TMZ
• To evaluate additional measures of antitumor efficacy of NMS-03305293 in combination with TMZ

Exploratory Objectives:
• To explore the role of MGMT promoter methylation status for antitumor efficacy of the combination
• To explore the relationship between NMS-03305293 and possible identified metabolites (if appropriate) plasma concentrations and relevant ECG parameters

Study design

This is a multicenter, Phase I/II study on the safety and efficacy of the combination of NMS-03305293 and temozolomide (TMZ) in adult patients with diffuse gliomas (Phase I) and glioblastoma (Phase II) at the first relapse.

The Phase I portion of the study is designed as a single-arm, dose-escalation study aimed at defining the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D) of NMS-03305293 in combination with TMZ and the safety profile and tolerability of the combination therapy in patients with diffuse gliomas.

The dose escalation part is designed with a conventional scheme of sequential cohorts of 3 to 6 patients allocated to progressively higher dose levels of NMS-03305293 in combination with a fixed dose of TMZ (150 mg/m2), based on the occurrence of first-cycle DLTs up to the MTD.

All patients enrolled before the finalization of protocol v.2 received TMZ and NMS-03305293 administered orally once daily (TMZ days 1-5; NMS-03305293 days 1-7) in repeated 4-week cycles. Based on NMS- 03305293 safety and preliminary PK data in humans obtained in this study and in the ongoing first in human (FIH) study (PARPA-293-001), the administration of NMS-03305293 may be explored also as twice daily dosing (BID), starting either at the total daily dose <= 33% increase of the highest QD dose level deemed safe, or at an intermediate total daily dose between the previous QD dose level that has been deemed safe and the QD dose level with unacceptable toxicity (if applicable), or a lower dose as determined by the Sponsor and Investigators.

Through a protocol amendment, the Sponsor has the option to explore additional schedules (e.g. TMZ days 1-5; NMS-03305293 days 1-12 in repeated 4-week cycles) based on emerging data, starting at the same total daily dose or a lower dose already explored and deemed safe as determined by the Sponsor and Investigators.

After the completion of each cohort, available safety and PK data will be reviewed and the next dose level will be decided jointly by the Investigators and the Sponsor. During the dose escalation phase, few additional patients (up to 3-6) may be enrolled in one or more dose levels, completed and declared safe (i.e. 0 DLT out of 3 or <=1 out of 6 patients), to further explore the safety profile of NMS-03305293 in combination with TMZ before the Phase II starts. Such patients will not be evaluated by DLT criteria. Patients must fulfill the eligibility criteria and the schedule of the events for the Phase I.

Once the safety has been reviewed by the Investigators and the Sponsor and is considered adequate based on the entire Phase I data available, the RP2D of NMS-03305293 in combination with TMZ at 150 mg/m2 will be defined. At this point, the Phase II part of the study will start. The Phase II portion is designed as an exploratory study with an interim analysis for futility to assess the antitumor activity of the study treatment measured as objective response rate by central retrospective assessment in adult patients with IDH wild type recurrent glioblastoma at first relapse after initial standard therapy including up to 6 cycles of temozolomide and provided that patients completed standard of care concurrent temozolomide and the radiation therapy.

Intervention

Treatment:

Dosing schedule
All patients will receive oral treatment with NMS-03305293 administered once (QD) or twice (BID) daily on Days 1 to 7 and with TMZ administered daily on Days 1 to 5 in repeated 4-week cycles.
Additional schedules may be explored (e.g. TMZ days 1-5; NMS-03305293 days 1-12 in repeated 4-week cycles) through a protocol amendment.

NMS-03305293
NMS-03305293 is formulated as 10 and 50 mg capsules and administered as out-patient treatment.
For specific formulation and storage instructions, please refer to the product Investigator*s Brochure and the Investigational Medicinal Product Study Manual, respectively.
The proposed starting dose of NMS-03305293 was 20 mg/day flat dose (<15 mg/m2/day).
The starting dose corresponds to 1/10 the dose in mg/m2 that in rats produced testicular toxicity in all males (25 mg/kg/day = 150 mg/m2/day) and is the same used for the ongoing study PARPA-293-001, in which NMS- 03305293 was administered as single agent, daily for 21 consecutive days in 4-week repeated cycles. No DLTs and good tolerability were observed at this dose level in PARPA-293-001 study.

Temozolomide
TMZ is supplied as oral capsules and administered as out-patient treatment. The proposed dose of TMZ is 150 mg/m2 per day.

Duration of treatment
All patients may continue study treatment until disease progression, unacceptable toxicity, investigator decision, withdrawal of consent by the patient or other discontinuation criteria described in the protocol are met.

Phase I Dose Escalation

NMS-03305293 has been administered in sequential cohorts of patients at the following dose levels: 20 mg/day, 40 mg/day, 60 mg/day and 80 mg/day.

Based on NMS-03305293 safety and preliminary PK data in humans obtained in this study and in the ongoing first-in-human (FIH) study PARPA-293-001, the administration of NMS-03305293 may be explored also as twice daily dosing (BID), starting either at the total daily dose <= 33% increase of the highest QD dose level deemed safe, or at an intermediate total daily dose between the previous QD dose level that has been deemed safe and the QD dose level with unacceptable toxicity (if applicable), or a lower dose as determined by the Sponsor and Investigators. The dose escalation will proceed with <=33% increments of the total daily dose in QD and/or BID dosing (rounded to the lower or higher 10 mg strength capsules available) until the MTD and/or a lower dose above the expected efficacious threshold are reached. At each dose level, a minimum of 3 patients will be included.

If 0/3 patients experience first cycle DLT, the next cohort will start one dose level higher.
If 1/3 patients experience first cycle DLT, up to three more patients will receive the study medication at the same dose level; if 1/6 experiences first cycle DLT the next cohort will start one dose level higher.

If >=2/3 or >=2/6 patients experience DLTs in the first cycle of treatment, the MTD is considered to have been exceeded. At this point, the Sponsor and Investigators may request to evaluate three more patients at the previous dose level (if only 3 patients were treated at that prior dose), or to explore an intermediate dose level (not yet tested), in order to more precisely define the MTD. Evaluation of safety profile and exposure in patients treated in the study will guide the selection of the intermediate dose level.

During the dose escalation phase, in order to optimize the dose to be selected for further clinical development, few additional patients (up to 3-6) may be enrolled in one or more dose levels, completed and declared safe (i.e. 0 DLT out of 3 or <=1 out of 6 patient) to further explore the safety profile of NMS-03305293 in combination with TMZ before the Phase II starts. Such patients will not be evaluated by DLT criteria. Patients must fulfill the eligibility criteria and the schedule of the events for the Phase I.

The dose level will be assigned by the Sponsor at the time of patient registration.

Only one dose level will be open for enrollment at any time in each dosing schedule. Upon the implementation of protocol v 2.0, three patients for each dose level can enter simultaneously.IIn case a cohort needs to be expanded to more than 3 patients, the additional patients can be enrolled simultaneously, after the first three patients have completed the DLT period.

All patients must be observed for one cycle before subsequent patients are enrolled at the next higher dose level. If a patient fails to receive at least 75% of both NMS-03305293 and TMZ during the first cycle of treatment, for reasons other than treatment-related toxicities or is not assessed for DLTs, an additional patient must be enrolled at the same dose level. A patient may also be replaced if, under particular circumstances (e.g. due to noncompliance), the assessment of DLTs is not possible as judged jointly by the Investigators and the Sponsor.

After the completion of each cohort, available safety and PK data will be reviewed and the next dose level will be decided jointly by the Investigators and the Sponsor.

Definition of DLT(s): DLT will be defined as any of the following adverse events occurring in cycle 1 for which the relationship with the combination therapy cannot be definitely excluded (see protocol).

The DLT observation window is defined as the time interval between the date of the first dose administration in Cycle 1 and the date of the first dose administration in Cycle 2 which is expected to be 28 days, or up to 42 days in case of dose delay due to drug related toxicity. For patients who do not receive Cycle 2 treatment, 42 days will be the maximum time interval considered for the evaluation of DLT unless no drug-related toxicities are observed, or recovery of toxicities or start of a new anticancer therapy occurs earlier.

Definition of MTD:
The MTD is defined as the highest dose level associated with the cohort at which < 33% of patients experience a first cycle DLT.
The cohort of diffuse glioma patients with the dose of NMS-03305293 identified as the MTD in combination with TMZ at 150 mg/m2 in the dose escalation and/or a lower dose above the expected efficacious threshold in QD and/or BID dosing schedule may be expanded.

Definition of RP2D:
The Recommended Phase 2 Dose (RP2D) is a dose above the expected efficacious threshold confirmed to be well tolerated in repeated cycles with the highest benefit/risk ratio based on available data. The RP2D will be determined at a dose below or equal to the MTD, if characterized, upon review of all study data by the Sponsor and Investigators.

Study burden and risks

NMS-03305293 is at an early stage of development with very limited safety data and no efficacy results in humans available so far. Based on preclinical models NMS-03305293 has demonstrated antitumor activity in glioblastoma along with good tolerability. The first-in-human PARPA-293-001 study exploring the safety and tolerability of NMS-03305293 administered as single agent daily for 21 or

28 consecutive days in 4 week-cycles is ongoing in patients with selected solid tumors (cancer of the ovary, breast, prostate and pancreas). As of 31st of January 2023, the dose escalation part of the study is ongoing and the current dose level tested is 200mg/day.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

Phase I
1. Histologically confirmed diagnosis of an intracranial diffuse glioma (i.e. diffuse astrocytoma, oligodendroglioma or glioblastoma).

2. Patients at first relapse after chemotherapy including temozolomide as long as no more than 12 cycles of temozolomide were administered.
3. Patients may have been operated for recurrence. If operated:
• residual and measurable disease after surgery is not required but pathology must have confirmed tumor recurrence.
• a post-surgery MRI should be available within 48 hours following surgery.
• surgery completed at least 2 weeks before enrolment and patient clinical status should not be worsened respect to pre-surgery condition

Phase II
1. Histologically confirmed diagnosis of Glioblastoma, IDH wildtype as per WHO 2021 classification, including IDH-wildtype diffuse and astrocytic glioma in adults, if there is microvascular proliferation or necrosis or TERT promoter mutation or EGFR gene amplification or +7/*10 chromosome copy number changes, or c-IMPACT-NOW 3 definition including diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO Grade 4. IDH1 status must be assessed locally by immunohistochemistry (IHC). If IHC is performed and is negative, and patient is <55 years old, sequencing or a PCR-based validated test must be performed to exclude other IDH1 or IDH2 most frequent mutations.
2. Patients at first relapse after initial standard therapy including temozolomide as long as no more than 6 cycles of temozolomide were administered and provided that patient completed standard of care concurrent temozolomide and the radiation therapy
3. Patients may have been operated for recurrence. If operated:
• residual and measurable disease after surgery is required
• a post-surgery MRI should be available within 48 hours following surgery.
• surgery completed at least 2 weeks before enrolment and patient clinical status should not be worsened respect to pre-surgey condition.

For Phase I and Phase II
4. For non-operated patients, with measurable disease in Phase I and for all patients in Phase II, recurrent disease must be defined by at least one bidimensionally measurable contrast-enhancing lesion with clearly defined margins with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart, based on MRI scan done within two weeks prior to enrolment.
5. Patients on steroids should have stable or decreasing dose of steroids for 7 days prior to the baseline MRI scan.
6. Life expectancy of at least 3 months.
7. Able to undergo brain MRI scans with IV gadolinium.
8. No evidence of symptomatic and acute intratumoral hemorrhage on MRI. Patients with MRI demonstrating old hemorrhage or subacute blood after a neurosurgical procedure (biopsy or resection) are eligible.
9. Sufficient tissue representative of the disease available for central MGMT promoter methylation status (Phase I and II) and IDH status evaluation (Phase I).
10. Male or female patients with age >=18 years.
11. ECOG performance status <=2.

12. Signed and dated IEC or IRB-approved Informed Consent.
13. Resolution of all acute toxic effects (excluding alopecia) of any prior anticancer therapy to NCI CTCAE (Version 5.0) Grade <=1 or to the baseline laboratory values as defined in Inclusion Criterion Number 14.
14. Baseline laboratory values fulfilling defined requirements: as stated in the protocol
15. Patients must use effective contraception or abstinence. Female patients of childbearing potential must agree to use effective contraception or abstinence during the period of therapy and in the following 6 months after discontinuation of study treatment. Being NMS-03305293 a potential CYP3A perpetrator, hormonal contraception may lose efficacy while on treatment with NMS-03305293, therefore this should be taken into account. Male patients must be surgically sterile or must agree to use effective contraception or abstinence during the period of therapy and in the following 6 months after discontinuation of study treatment.
16. Ability to swallow capsules intact (without chewing, crushing, or opening).
17. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study indications or procedures.

Exclusion criteria

Patient Exclusion Criteria
The presence of any of the following will exclude a patient from study enrollment:
1. Current enrollment in another interventional clinical trial.
2. Current treatment with other anticancer agents, or treatment at recurrence with carmustine wafer implants and proteasome inhibitors.
3. Previous treatment with PCV (procarbazine, lomustine and vincristine) or any of its components, carmustine wafer implants, or bevacizumab.
4. Previous treatment with PARP inhibitors.
5. Major surgery, other than surgery for recurrent diffuse glioma, within 4 weeks prior to treatment.
6. Standard radiotherapy within the three months (12 weeks) prior to the diagnosis of progression unless the progression is clearly outside the radiation field (eg, beyond the high-dose region or 80% isodose line) or unless the recurrence is histologically proven.
7. Prior radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy, unless the recurrence is histologically proven.
8. Use of full-dose anticoagulants unless the INR or aPTT is within therapeutic limits (according to the medical standard in the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks before enrollment.
9. Treatment with concomitant medications known to be sensitive substrates of CYP2D6 and CYP2C19 that cannot be replaced with another treatment.
10. Treatment with enzyme-inducing anti-epileptic drugs (EIAED). Patients may

be on non-EIAED or not be taking any anti-epileptic drugs. Patients previously on EIAED must be fully switched to non- EIAED at least 2 weeks prior to enrolment.
11. Pregnant or breast-feeding women.
12. Known hypersensitivity to any component of NMS-03305293 or TMZ drug formulations.
13. Known active infections (bacterial, fungal, viral including HIV positivity) requiring systemic treatment.
14. Patients with QTc interval >=460 milliseconds for women, >=450 milliseconds for men or with risk factors for torsade de pointes (e.g., uncontrolled heart failure, uncontrolled hypokalemia, history of prolonged QTc interval or family history of long QT syndrome). For patients receiving treatment with concomitant medications known to prolong the QTc interval, replacement with another treatment prior to enrollment is mandatory.
15. Active gastrointestinal disease (e.g., documented gastrointestinal ulcer, Crohn*s disease, ulcerative colitis, or short gut syndrome) or other syndromes that would impact on drug absorption.
16. Any of the following in the past 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, active bleeding disorder.
17. Prior invasive malignancy (except for non melanoma skin cancer, carcinoma in situ or localized cancer) unless the patient has been disease-free and off therapy for that disease for >= 3 years.
18. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study or could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-03-2022
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not applicable
Generic name:	Not applicable
Product type:	Medicine
Brand name:	Temozolomide
Generic name:	Temozolomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-04-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-11-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2022

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-508318-41-00
EudraCT	EUCTR2020-003417-35-NL
ClinicalTrials.gov	NCT04910022
CCMO	NL76833.078.21