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Study Title: Study on Safety and Efficacy of NMS-01940153E in Adult Patients With Unresectable Hepatocellular Carcinoma (HCC) Previously Treated With Systemic Therapy

Protocol Reference Number: MPSA-153-001

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Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN (SAP)

Protocol Title	Phase I/II study on safety and efficacy of NMS-01940153E in adult patients with unresectable hepatocellular carcinoma (HCC) previously treated with systemic therapy
Investigational Medicinal Product(s) Code /Name	NMS-01940153E
Development Phase	Phase I/II
Protocol Number	MPSA-153-001
Protocol Version and Date	Version 5.0, 9-Jan-2023
SAP Version Number	2.0
SAP Date	30-Jun-2023

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Statistical Analysis Plan

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AFP	Alpha-Fetoprotein
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
cfDNA	Circulating Free DNA
CI	Confidence Interval
Cmax	Maximum plasma Concentration
CR	Complete Response
CSR	Clinical Study Report
CT	Clinical Trial
CTCAE	Common Terminology Criteria for Adverse Events
CT Scan	Computerized tomography scanner
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DLTES	Dose Limiting Toxicity Evaluable Set
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
eCRF	electronic Case Report Form
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ES	Enrolled Set
FIH	First in Human
(γ) −GT	Gamma - Glutamyl Transferase
HCC	Hepatocellular Carcinoma
HR	Heart Rate
ICH	International Conference on Harmonisation
INR	International Normalized Ratio

LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
MeDRA	Medical Dictionary for Regulatory Activities
MPS1	Monopolar Spindle 1 kinase
MTD	Maximum Tolerated Dose
MRI	Magnetic Resonance Imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	Overall Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease (unless otherwise specified in the text)
PK	Pharmacokinetic
PFS	Progression Free Survival
PR	Partial Response (unless otherwise specified in the text)
QTc	Corrected Fridericia QT Interval
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Dose Recommended for further Phase II investigations
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation (unless otherwise specified in the text)
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLG	Table Listing and Graph
TKI	Tyrosine kinase Inhibitor
TTK	Tyrosine/Threonine Kinase
TS	Treated Set
ULN	Upper Limit of Normal
WBC	White Blood Cells

2. PURPOSE OF THE STATISTICAL ANALYSIS PLAN

This Statistical Analysis Plan (SAP) version 2.0, describes the planned Phase I analysis, Phase II interim and final analyses and reporting for MPSA-153-001 Clinical Trial (CT). All analyses take origin from the specifications in the statistical section of the CT Protocol version 5.0 (9-Jan-2023). Details of changes of the SAP version 2.0 respect to the first version, created based on CT Protocol version 2.0 dated 28-Jan-2021, are reported in Section 2.1.

Of note, this SAP does not cover the pharmacokinetic (PK) data analyses, described in the Protocol. These analyses are covered in a separate document written by Accelera S.r.l.

The structure and content of this SAP provide sufficient detail to guarantee compliance with the requirements identified by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials and Integrated Addendum to E9(R1) [1].

The planned analyses identified in this SAP may be included in future abstracts, presentations and manuscripts, and may also support other documents, e.g. Development Safety Update Report (DSUR). Exploratory analyses not necessarily identified in this SAP may be performed to support planned analyses. Any post-hoc or unplanned analyses not specified in this SAP will be clearly identified as such in the Clinical Study Report (CSR).

The following documents were reviewed when preparing this SAP:

- CT Protocol version 5.0 (09-Jan-2023)
- CT Specific Case report forms (CRFs) Blank version 5.3 (23-Jun-2023)
- E9 - Statistical Principles for Clinical Trials [Integrated Addendum to E9(R1)] [1]
- E6(R2) - Guidance on Good Clinical Practice [Integrated Addendum to E6(R1)] [1]
- E3 - Guidance on Structure and Content of Clinical Study Reports [1]
- Applicable NMS procedural documents

2.1. Changes to Previous Version

The following changes are made in the current version 2.0 of the SAP:

- SAP re-written using new template (version T1_02, 17-May-2023). The mock-ups of tables, listings and graphs and algorithms are provided as separated Appendix using a new template (version T2_02, 17-May-2023).
- Section 3 Study Objectives and Endpoints was modified based on updated definition of primary efficacy objective and endpoint for Phase II and inclusion of additional secondary and exploratory endpoints.

- Section 4 Study Design, specifically Overview, Subject Selection and Sample Size, was modified based on the updated Phase II design.
- Section 5.2 Planned Schedule for Interim Analyses was modified based on the updated Phase II design that includes also a safety monitoring rule.
- Section 7, was updated to add clarifications for the definition of Evaluable Set for Phase II portion based on protocol version 5.0.
- Section 8 General Specification for Statistical Analysis, was mainly updated to include secondary phase II efficacy endopoints based on mRECIST evaluation.
- Section 9.7 Efficacy Analyses and Sections 9.7.1 Primary Efficacy Endpoint and 9.7.2 Secondary Efficacy Endpoints, were updated.
- Section 9.8.5 was updated to include additional ECG parameters collected for patients enrolled in Phase II.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objective(s)

- To determine the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of NMS-01940153E administered as single agent to adult patients with unresectable hepatocellular carcinoma (HCC) previously treated with systemic therapy (Phase I).
- To assess the anti-tumor efficacy of NMS-01940153E administered as single agent to adult patients with unresectable hepatocellular carcinoma previously treated with systemic therapy (Phase II).

3.1.2. Secondary Objective(s)

- To define the safety and tolerability profile of NMS-01940153E.
- To evaluate the pharmacokinetics of NMS-01940153E and its main metabolite NMS-03593478 in plasma and, limited to Phase I, also in urine.
- To evaluate additional measures of antitumor efficacy of NMS-01940153E.

3.1.3. Exploratory Objective(s)

- To explore correlation among Alpha-Fetoprotein (AFP) levels changes with NMS-01940153E exposure and clinical outcomes.
- To explore correlation among baseline tumoral and clinical prognostic factors with clinical outcome.

- To explore the potential correlation of selected molecular alterations in circulating free DNA (cfDNA) at baseline with clinical outcome.

3.2. Endpoints

3.2.1. Primary Endpoint(s)

- Drug related Dose Limiting Toxicities (DLTs) (Phase I).
- Objective Response Rate (ORR). The ORR will be calculated as the proportion of evaluable patients who have achieved, as best overall response (BOR), confirmed complete response (CR) or partial response (PR) measured by investigator-assessed RECIST 1.1 (Phase II).

3.2.2. Secondary Endpoint(s)

- Overall safety profile of NMS-01940153E characterized by type, severity (graded using NCI CTCAE Version 5.0), duration of the adverse events (AEs) and laboratory and ECG abnormalities, and relationship of the AEs to study treatment in the first and subsequent cycles of therapy.
- Pharmacokinetic parameters of NMS-01940153E and its main metabolite NMS-03593478 in plasma and urine (urine only in Phase I).
- Objective Tumor Response (Partial and Complete Response) as measured by investigator-assessed RECIST 1.1 (Phase I).
- Objective response rate as measured by investigator-assessed mRECIST (Phase II).
- Duration of response (DoR) as measured by investigator-assessed RECIST 1.1. and investigator-assessed mRECIST.
- Progression Free Survival (PFS), including landmark analyses, as measured by investigator-assessed RECIST 1.1.
- Overall survival (OS).

3.2.3. Exploratory Endpoint(s)

- Evaluation of AFP plasma levels.
- Evaluation of tumoral and other clinical prognostic features at baseline.
- Assessment of selected molecular alterations in circulating free DNA (cfDNA) at baseline.

4. STUDY DESIGN

4.1. Overview

This is a Phase I/II, open-label, non-randomized, multicenter study to explore safety, tolerability and antitumor activity of NMS-01940153E as single agent in adult patients with unresectable HCC previously treated with systemic therapy.

An independent Data Safety Monitoring Board (DSMB) will provide study oversight through periodic safety evaluations and make recommendations on study progress in the transition from Phase I to Phase II and at the planned interim analysis for the futility of Phase II.

The Phase I portion is designed as a dose-escalation study in sequential cohorts of patients aimed to obtain the MTD that is defined based on the DLTs observed in the first cycle of treatment.

The safety profile of NMS-01940153E administered IV on days 1, 8, 15 every 4 weeks has been characterized in the FIH, dose escalation study, conducted in adult patients with advanced/metastatic solid tumors up to the dose of 135 mg/m2/week. This dose was not defined as MTD in study 2014-002023-10 (EudraCT), since only one patient experienced DLT (Grade 3 fatigue) out of 6 evaluable patients.

Once the MTD is identified and the safety profile of NMS-01940153E has been reviewed by the Investigators, the Sponsor and the independent DSMB and is considered adequate based on the entire Phase I data available, the Phase II portion of the study will start.

The Phase II portion is designed as a two-stage study with an interim analysis for futility and stopping criteria for unacceptable toxicity to assess the antitumor activity of NMS-01940153E in adult patients with unresectable HCC previously treated with systemic therapy measured as objective response rate. In the Phase II portion, patients will receive the RP2D defined in the Phase I portion of the study as starting dose. Patients will be enrolled in continuous, and continuously evaluated for endpoints, with a futility analysis and stopping criteria for unacceptable toxicity performed as described in Section 5.2. The enrollment will be stopped in the event of futility as described in Section 5.2, with no more than 20 subjects treated overall until non-futility can be declared, if appropriate. In any case, the Sponsor may stop or pause enrollments any time during the study based on safety, efficacy or strategic reasons.

4.2. Subject Selection

This is a Phase I/II study in adult patients (>=18 years) with unresectable HCC, disease relapsed or refractory to the standard of care treatment not exceeding 3 lines of prior systemic treatment. For the Phase I portion subjects intolerant to previous treatment with tyrosine kinase inhibitors (TKIs) are eligible.

For the Phase II portion subjects must have disease relapsed or refractory to the standard of care treatment including an immunocheckpoint inhibitor as first line and at least a TKI, with no more than 3 prior lines of systemic therapies.

4.3. Sample Size

An overall sample size of approximately 55 patients may be anticipated considering both phases of the study.

For the Phase I, approximately 12-15 treated patients may be expected. Since the trial design foresees that sequential dose-escalation steps are applied to cohorts of 3 to 6 patients up to the identification of the MTD, the number of patients who will be enrolled and treated may vary, depending upon the toxicity observed that will influence cohort size and number of dose levels tested.

For the Phase II, the investigator-assessed objective response rate by RECIST 1.1. [2] will be the primary outcome measure.The sample size is based on precision considerations for the estimate of the primary efficacy endpoint. A single-group design will be used to obtain a one-sided 95% lower-limit confidence interval for a single proportion. The sample proportion is assumed to be 0.3. To produce a confidence interval with a distance from the sample proportion to the lower limit of no more than 0.12, 38 patients will be needed. A lower bound of 18% for ORR by RECIST would be meaningful relative to second line therapies in HCC. The emergence of atezolizumab with bevacizumab in first line has obscured true current second line outcomes with regorafenib, lenvatinib or sorafenib but it is logical to assume second line ORR would be no better relative to the pre-atezolizumab/bevacizumab era in which sorafenib was the first line standard. Prior to the atezolizumab/bevacizumab era, regorafenib in second line showed ORR of 11% by RECIST1.1 [3] and cabozantinib 4% [4], nivolumab 15% [5], pembrolizumab 18% [6] and apatinib 10.7% [7]. Therefore, in the third line setting following failure of atezolizumab/bevacizumab in first line followed by TKI in second line, and where current third line standards are not yet defined, it is reasonable to expect historical ORR no higher than 18%. Accounting for a 10% proportion of non-evaluable patients and if the stopping rule for futility is not met, up to 43 patients could be required for completing the trial, as reported in detail in Section 5.2; however, the Phase II part of the study will not enroll beyond 40 subjects unless discussed and agreed with FDA or relevant health authority, based on emerging response rates.

4.4. Treatment Allocation (and Blinding)

Not applicable

5. OVERVIEW OF PLANNED ANALYSES

5.1. Independent Data Monitoring Committee (IDMC) / Independent Data Safety Monitoring Board (DSMB)

An independent DSMB will provide study oversight through periodic safety evaluations and make recommendations on study progress in the transition from Phase I to Phase II and at the planned interim analysis for the futility of Phase II.

During the Phase I part, teleconferences will be held at the end of each cohort between the Investigators and the Sponsor to review all relevant safety and PK data and take decision on the dose escalation to be applied to the next cohort of patients. Once the MTD is identified, and the safety profile of NMS-01940153E has been reviewed by the Investigators, the Sponsor and the independent DSMB and is considered adequate based on the Phase I data available, the RP2D will be defined and the Phase II portion of the study will start.

Two clinical experts in the field of hepatology or onco-hepatology and a statistician, who are not involved in the study and have no conflict of interest with respect to study results, will compose the independent DSMB.

Tasks of the independent DSMB will be:

- To provide a recommendation on study progress in the transition from Phase I to Phase II and at the planned interim analysis for the futility of Phase II, based on risk-benefit evaluation;
- To periodically review adverse events, serious adverse events and all other safety and pharmacokinetic data collected during the study;
- To suggest other toxicities to be recorded/monitored in the group of patients who will be enrolled after the independent DSMB safety evaluation.

5.2. Planned Schedule of Interim Analyses

In the Phase II part of the study an interim evaluation for futility will be undertaken as soon as the first 10 evaluable patients will be enrolled and the data for primary efficacy endpoint analysis will be available including observations through at least 3 months with at least 1 on treatment tumor assessment by RECIST 1.1 [2]. If less than 1 responder i.e., patients who achieved CR or PR as best overall response, are observed, the study will be terminated for futility. This futility decision must be taken before 20 subjects total are enrolled otherwise enrollment will pause at 20 subjects until non-futility can be declared (if applicable). If at least 1 unconfirmed or confirmed responder is observed and there are no safety limitations, patients' enrollment will continue and proceed up to an overall enrollment of 38 evaluable patients or 40 total patients. For the safety monitoring, if two

or more patients on study experience Grade 4 adverse events the study will be put on hold to evaluate whether to continue or if additional risk mitigation is warranted.The independent DSMB will review the interim results and provide a recommendation on the study progress.

5.3. Final Analyses and Reporting

All final planned analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the last visit scheduled, including follow-up and the clinical database has been cleaned and locked.

The mock-ups tables, listings and graphs for reporting purpose of CT MPSA-153-001 are reported in the separate appendix “Tables, Listings and Graphs Mock-ups and Algorithms”.

6. CHANGES IN THE PLANNED ANALYSIS

Not applicable

7. ANALYSIS POPULATIONS

Phase I Dose Escalation

Enrolled Set (ES): this population will include all patients who are enrolled in Phase I part, regardless of whether patients receive study treatment or not. This population will be evaluated in the analysis of patients’ disposition.

Treated Set (TS): this set will include all enrolled patients who take at least one dose of NMS-01940153E. This population will be evaluated in the analysis of patients’ disposition, baseline characteristics, treatment exposure, safety and efficacy.

Dose-Limiting Toxicity Evaluable Set (DLTES): this set will include all patients who receive in the first cycle at least 66% of study drug, unless the reason for non-compliance is drug-related toxicity, and undergo a DLT assessment within the DLT window. Patients not fulfilling one or more of aforementioned criteria will not be considered evaluable for MTD determination and will be substituted.

Phase II Part

Enrolled Set (ES): this population will include all patients enrolled in Phase II, regardless of whether patients receive study treatment or not. This population will be evaluated in the analysis of patients’ disposition.

Treated Set (TS): this set will include all enrolled patients who actually receive at least one dose of NMS 01940153E. This population will be evaluated in the analysis of patients’ disposition, baseline characteristics, treatment exposure and safety.

Evaluable Set (ES): this is the patient population for the primary efficacy analysis. This set will include patients of the TS who have measurable disease at baseline assessed according to RECIST 1.1 and at least one tumor evaluation on treatment, unless they die before the first tumor on-treatment assessment (i.e. if the patients died within 61 days from the start of the treatment considering that the first on treatment tumor assessment is forseen at the end of cycle 2 with a time window of -2/+5 days), in which case they will be considered treatment failure. Moreover, subjects must have disease relapsed or refractory to the standard of care treatment including an immunocheckpoint inhibitor as first line and at least a tyrosine kinase inhibitor, not exceeding 3 lines of prior systemic treatment. Patients who received the RP2D defined in phase I portion as starting dose and from cycle 2 a dose increment of 25% (as per protocol version 4.0 dated 30-Jun-2022) were considered not evaluable for efficacy analysis (intra-patient dose escalation no more applicable as per protocol version 5.0). In detail, the evaluable population for primary efficacy endpoint will consist of a subset of the evaluable population up to the total number of subjects pre-determined by the interim for futility and final analyses. This means that, if the number of evaluable subjects exceeds the planned total number of subjects at either stage, the exceeding subjects will not be considered for primary efficacy analysis. Subjects will be counted into the primary evaluable population, consecutively, based on the date of first NMS-01940153E administration.

8. GENERAL SPECIFICATIONS FOR STATISTICAL ANALYSES

This section provides a general overview of the methods to analyze the study data. Specific analyses will be reported in the appropriate section 9.

Continuous (quantitative) variables will be summarized using descriptive statistics including number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Selected continuous variables will also be described in classes (e.g. age, QTc, etc.)

Frequency and percentage will be provided for categorical variables and generated for parameter estimates of interest. In general, the denominator for the percentage calculation will be based upon the number of treated patients, unless otherwise indicated, by dose level and overall in the study population.

For the efficacy analyisis, the percentage of the ORR, according to the RECIST 1.1 [2] or mRECIST [8], will be reported both as a point estimate and by means of 95% CIs .

The survival curve and the quartiles (25th percentile, median, 75th percentile) will be estimated for the time-to-event endpoints (i.e. DoR, PFS and OS) using the Kaplan-Meier method [9] and will be reported along with the corresponding 95% Confidence Intervals (CIs). Reverse Kaplan-Meier method [10] will be used to estimate the median length of follow-up for PFS and OS.

8.1. Handling Missing Data

Specific information for imputing missing data, where appropriate, will be documented in the separate appendix TLGs Mock-ups and Algorithms. Except for time related endpoints, missing observations will not be imputed, unless otherwise noted.

8.2. Analysis Conventions

All collected data will be presented in listings. Data not subject to analyses according to this plan will not appear in any tables or graphics but will be included only in the data listings.

Partial dates in principle will not be imputed except for date of birth. Only year of birth will be collected in the database and to estimate patient's age, December 31st will be used to replace the missing month and day, respectively.

Censoring rules for time-to-event endpoints are reported in the appendix TLGs Mock-ups and Algorithms, provided as a separate document.

Study day will be calculated in reference to the date of first study treatment dose. For assessments conducted on or after the first dose, study day is calculated as (assessment date – first dose date +1). For assessments conducted before the first dose, study day is calculated as (assessment date – first dose date). The study day will be displayed in all relevant data listings.

The baseline visit will correspond to the last assessment with non-missing result performed before initial study drug administration, unless otherwise indicated in the appendix TLGs Mock-ups and Algorithms.

All analysis conventions are detailed in the separate appendix TLGs Mock-ups and Algorithms.

8.3. Analysis Software

Data processing, data listings, tabulation of descriptive statistics, calculation of inferential statistics and graphical representations will be performed using SAS® Software (release 9.4 or higher) for Windows, unless otherwise specified.

9. STATISTICAL ANALYSES

9.1. Patient Disposition

Patients' disposition and reasons for ending the treatment and the study will be presented in frequency distribution tables and individual data listings by study phase and dose level. The patients not meeting the eligibility criteria, and who are considered protocol violators will be identified and described by individual data listing by study phase. Reasons for stopping treatment will be summarized as frequency distribution in the treated patient population. Untreated patients will be identified and described separately.

9.2. Protocol Deviations

Protocol deviations will be classified as critical, major or minor based on MPSA-153-001 Protocol Deviations classification document. The patients not meeting the eligibility criteria, and who are considered protocol violators as well as patients excluded from efficacy analysis, will be identified and described by individual data listings.

Protocol deviations that will exclude patients from analysis populations are defined in section 7.

9.3. Demographics and Other Baseline Characteristics

Demographic information, disease history, medical history, prior antitumor therapies/ procedures for enrolled patients, will be provided as listings.

Descriptive statistics for demographic data will be generated for both enrolled and treated patients by study phase. Other baseline characteristics such as history of current and other tumors, relevant medical history, previous antitumor treatments and procedures, and vital signs will be generated across all treated patients by study phase.

The baseline assessment corresponds to the last non-missing analysis performed before initial study drug administration, unless otherwise indicated in in the appendix TLGs Mock-ups and Algorithms.

Frequency distributions will be presented for the categorical/categorized variables (e.g. sex, ECOG PS and race). Summary statistics including mean, standard deviation, median, minimum, maximum and the number of assessed patients will be calculated, as appropriate, for the quantitative variables (e.g. age, weight, systolic and diastolic blood pressure).

The continuous data, such as age, will also be described in classes.

9.4. Previous or Concomitant Medications/ Procedures

Previous or concomitant medications/procedures will be descriptively analyzed in the treated patient population by dose level and by Study Phase, and reported in data listings. Previous or concomitant medications will be coded by World Health Organization Drug (WHODrug) Global B3 dictionary [11]. The frequency and percentage of all previous or concomitant medications will be summarized by preferred term. Patients will only be counted once within preferred term. Previous or concomitant procedures/radiotherapy will be coded by Medical Dictionary for Regulatory Activities (MedDRA) and the number and percentage of subjects with previous or concomitant procedures/radiotherapy will be summarized by MedDRA preferred term [12].

9.5. New Anticancer Therapies / Procedures

No other approved or investigational anticancer treatment will be permitted during the study treatment period, including chemotherapy, immunotherapy, biological response modifiers, and hormones.

New antitumor systemic therapies, new radiotherapies and new procedures after discontinuation of study treatment will be provided respectively in a data listing.

9.6. Treatment Exposure and Compliance

For each study phase, the treatment exposure and the compliance with study treatment will be descriptively analyzed in the treated patient population. Descriptive statistics (e.g. min, max, mean, standard deviation, and median value) will be calculated on a per-patient basis for the following variables: the number of cycles administered, the overall duration of treatment, the actual and total doses administered, and the absolute and relative dose intensity. Frequency distributions of patients and/or cycles will be used to describe dose modifications such as dose delayed, dose increased, dose omitted, infusion slowed, infusion interrupted and cycle delayed or in advance, as well as the reasons for deviation from the planned therapy. Individual data will be presented in listings as reported in the relevant CRF sections.

9.7. Efficacy Analyses

The efficacy of NMS-01940153E will be assessed on the treated set for Phase I and evaluable set for Phase II, respectively, as defined in Section 7. For Phase II, only if deemed of interest and only as supportive analysis, efficacy could be also evaluated on the treated population.

Event dates, censoring definitions for time-to-event efficacy endpoints and other specific definitions are provided in the separate appendix TLGs Mock-ups and Algorithms.

9.7.1. Primary Efficacy Endpoint(s)

For Phase II part, the primary efficacy endpoint ORR will be evaluated as the proportion of patients who have achieved as best overall response, CR or PR as defined by investigator assessed RECIST 1.1. In addition to the point estimate, binomial exact 95% confidence intervals will be provided.

The decision rules for interim analysis for futility are specified in Section 5.2.

9.7.2. Secondary Efficacy Endpoint(s)

For the Phase I part, the objective tumor response (Partial and Complete response) will be reported in patients' data listings.

ORR will be also calculated for Phase II part only, as the percentage of evaluable patients with best response equal to complete response (CR) or partial response (PR) as defined by investigator-assessed mRECIST. Binomial exact 95% confidence intervals will be also provided.

Time-to-event endpoints (i.e. DoR, PFS and OS): they will be carried out on treated set for Phase I and evaluable set for Phase II, respectively. The individual calculated times will be presented in patients' data listings together with the identification of censored vs. failure status. Time-to-event endpoints will be also summarized using Kaplan Meier (KM) curves and further characterized in terms of median, 6-month, 9-month and 12-month estimates with the corresponding 95% confidence intervals, for Phase II part only.

Reverse Kaplan-Meier method [9] will be used to estimate length of follow-up for DoR, PFS and OS by reversing censored and event observations, if applicable.

9.8. Safety Analyses

Unless otherwise indicated, all safety analyses will be performed on the treated patient population by study phase and dose level. All collected safety data (adverse events, laboratory assessments, vital signs, ECG parameters, concomitant medications etc.), will be presented in individual patients' data listings.

9.8.1. Treatment Emergent Adverse Events

Adverse events (AEs) will be coded by Medical Dictionary for Regulatory Activities (MedDRA) and their severity will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) [13]. The analysis will focus on the events emerged during treatment and on those worsened on treatment in comparison to the baseline condition (TEAE, treatment emergent adverse events). For each dose level and overall, the incidence of AEs will be grouped by System Organ Class (SOC) and preferred term or by preferred term only. Each patient will be counted once according to the worst grade reported throughout the whole treatment period for each SOC and/or for each preferred term.

AEs will be summarized by descending frequency of SOC and preferred term, or preferred term only, depending of the analysis reported, unless otherwise specified. In addition, serious AEs, AEs with severity grade 3-5, AEs leading to treatment withdrawal, AEs leading to treatment reduction, omission, delay, infusion interrupted, infusion rate slowed, and AEs related to study treatment, will be analysed separately. A summary table of number and percentage of each possible AE categories (e.g. all AE, related AEs, serious, serious related etc.) will be also provided.

The analysis of number of occurrences of non-serious AEs, serious AEs, serious related to NMS-01940153E AEs and serious AEs leading to death by SOC and preferred term will be performed

only for regulatory purpose since these data have to be recorded in EudraCT/Clingov databases at end of the trial. This analysis will be only reported as appendix in the CSR.

9.8.2. Dose Limiting Toxicities

A DLT will be defined as any of the adverse events described in MPSA-153-001 Clinical Protocol Section 5.2.1 occurring in Cycle 1, during Phase I dose escalation, for which the relationship to NMS-01940153E cannot be definitely excluded. Toxicities are to be graded according to the NCI CTCAE version 5.0 [13]. In particular:

Hematological Toxicity

- Neutropenia Grade 4 lasting >7 days or Grade 4 of any duration associated with Grade ≥2 infection
- Febrile neutropenia ANC <1000/mm3 and a single temperature of >38.3 degrees C or a sustained temperature of ≥38 degrees C for more than one hour.
- Thrombocytopenia Grade 3 associated with any grade bleeding or Grade 4
- Anaemia Grade ≥4

Non-Hematological Toxicity

- Nausea, vomiting or diarrhea Grade ≥3 despite optimal treatment
- Signs of potential severe drug-induced liver injury as assessed according to Hy's law: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 ULN and total bilirubin >2 ULN in the absence of cholestasis (alkaline phosphatase [ALP] <2 ULN) and no other reason can be identified.
- Any other non-hematological toxicities: Grade ≥ 3 toxicities unless clear alternate etiology is documented by the investigator and except:
    - asymptomatic Grade 3 electrolyte changes that can be successfully supplemented (e.g., hypokalemia) and resolve/recover to baseline within 72 hours
    - Grade 3 fatigue that improves to ≤ Grade 2 in no more than 5 days
    - alopecia

Other significant toxicity

- Failure to complete the first cycle of treatment with at least 66% of the planned total dose due to toxicity possibly related to the study medication
- Failure to start Cycle 2 for more than 1 week (day 36 or later) due to persistent Grade ≥ 2 toxicities possibly related to the study medication, excluding fatigue
- Any toxicity that is possibly related to the study medication and requires the withdrawal of the patient from the study during the DLT observation period

- Any on-study death not clearly due to underlying disease or extraneous causes

For the Phase I part only, first cycle DLT analysis will be performed on the dose-limiting toxicity evaluable set. For each dose level, patients who experienced a DLT during the first cycle of treatment and type of DLT experienced, will be reported in a data listing.

9.8.3. Deaths

Frequency of deaths will be presented by study phase and dose level and relationship to the study treatment and according to the time since treatment discontinuation

Date of death, primary reason for death and relation to study treatment will be provided in a data listing together with selected dosing information (dose level, date of first / last dose administration, number of cycles received of study treatment, time from last dose administered). Primary reason for death and time in days of occurrence of death since last dose of study treatment administered, will be tabulated.

9.8.4. Clinical Laboratory Evaluations

Quantitative laboratory variables (hematology, blood chemistry, coagulation) will be summarized using mean, standard deviation, minimum, maximum and median, by study phase and dose level at each visit. At each cycle, the same descriptive statistics of within-subject changes from baseline measurements will be also presented.

The following laboratory data will be graded from Grade 1 up to Grade 4 according to the NCI CTCAE scale (version 5.0): hemoglobin (except Grade 4 for anemia), platelets, white blood cells (except Grade 4 for leukocytosis), neutrophils, lymphocytes, glucose (graded only for glucose decrease; i.e. hypoglycemia), sodium (graded only for sodium increase; i.e. hypernatremia), potassium (graded only for potassium increase; i.e. hyperkalemia), total calcium after correction with albumin, magnesium, creatinine, albumin (except Grade 4), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-GT (GGT), total bilirubin and lactate dehydrogenase (LDH) (only Grade 1 possible). For lab tests reported in the NCI CTCAE scale for which the grading system is based mainly on clinical assessments, the grade will not be calculated. For example, this applies to eosinophils, glucose (hyperglycemia), phosphorus (both hyperphosphatemia and hyperphosphatemia), sodium (hyponatremia), potassium (hypokalemia) and INR.

Laboratory abnormalities will be summarized in frequency distribution tables by study phase, dose level and treatment period (i.e. treatment Cycle 1, Cycle >1 and the whole treatment period).

For each parameter graded according to NCI CTCAE scale, patients will be classified based on the maximal severity grade observed during the analyzed time-window. Changes of severity grade

vs. baseline will be evaluated by shift tables. Selected laboratory parameters will be further explored by analyzing the nadir/zenith values, the time to nadir/zenith and the time to recovery after nadir/zenith, as clinically appropriate.

For the laboratory data not graded by the NCI CTCAE scale, a cross tabulation of on treatment worst finding versus baseline finding will be presented reporting the number of patients with values within or out of the normal range (i.e. hypo and/or hyper depending of the lab test considered), during the analyzed time-window. This analysis will be performed for the following lab tests: erythrocytes, monocytes, eosinophils, basophils, glucose (only for hyperglicemia), phosphorus, sodium (only for hyponatremia), potassium (only for hypokalemia), urea, blood urea nitrogen (BUN), total protein, unconjugated bilirubin.

Laboratory results (hematology, blood chemistry, coagulation) will be listed for all treated patients by study phase, assigned schedule and dose level at each visit. All other parameters collected on the eCRF, i.e. urinalysis and pregnancy tests, will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

9.8.5. Other Safety Evaluations (e.g. Vital signs, ECG, ECOG PS, etc.)

All vital sign parameters (i.e. systolic blood pressure, diastolic blood pressure and pulse), weight and BSA will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) of actual values and changes from baseline for each cycle with a minimum number of patients with at least one valid assessment. The maximum on-treatment change from baseline will be calculated and categorized by systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements. Additionally, the worst assessment on treatment versus baseline, defined in terms of classes (i.e. normal BP: SBP < 140 mmHg and DBP < 90 mmHg; abnormal BP: SBP≥140 mmHg and/or DBP ≥ 90 mmHg), will be summarized by shift table. The ECOG PS shift from baseline to highest score during the on-treatment period will be also summarized.

Descriptive summaries of actual values and changes from baseline will be presented, for both Phase I and Phase II, for corrected Fridericia QT interval (QTc). The following additional ECG parameters collected in triplicate for patients enrolled in Phase II, will be also analyzed: synus rhythm, heart rate (HR), RR interval, PR interval, QRS interval, QT interval. The maximum on-treatment change from baseline will be calculated and categorized by QTFc (for both Phase I and Phase II), HR, RR, PR and QRS (only for Phase II) measurements. Absolute frequency and percentage of treated patients with at least one clinically significant ECG abnormality during the treatment period will be summarized by category of ECG abnormalities.

Additionally, for all ECG parameters, the worst assessment on treatment versus baseline, defined in terms of classes, will be summarized by shift table. Frequency and percentage of treated patients with at least one clinically significant ECG abnormality during the treatment period will be summarized by category of ECG abnormalities.

Vital signs data, weight, BSA, ECOG PS and ECG data (both quantitative and qualitative) will be also presented in data listings.

9.9. Exploratory Analyses

Exploratory analysis on the relationship between AFP levels and treatment efficacy variables in patients treated with NMS-01940153E will be performed if sufficient data are collected.

Graphical display of AFP levels during the study will be used to support data interpretation.

Exploratory analyses on biomarkers/molecular alteration in blood and tumor at baseline will be conducted based on the completeness of data collected.

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11. APPENDICES

The appendix “TLGs Mock-ups and Algorithms” is provided as a separate document.

12. APPROVAL AND SIGNATURES

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13. VERSION HISTORY

Version N°.	Effective Date	Changes from the Previous Version
1.0	22-Oct-2021	Initial Version (related to Protocol version 2.0 and eCRF Unique, Blank and Design Specifications version 2.0)
2.0	30-Jun-2023	See Section 2.1

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