STATISTICAL ANALYSIS PLAN

Lokon Pharma AB

LOKON003

Protocol Title:	A Phase I/II Trial Investigating LOAd703 in Combination with Atezolizumab in Malignant Melanoma
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1 STATISTICAL ANALYSIS PLAN APPROVAL

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2 TABLE OF CONTENTS

TABLE OF TABLES

3 LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BOIN	Bayesian Optimal Interval
BOMR	Best Overall Metabolic Response
BOR	Best Overall Response
CBR	Clinical Benefit Rate
CMR	Complete Metabolic Response
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CRP	C-Reactive Protein
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
i.t.	Intratumoral
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IV	Intravenous
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MCBR	Metabolic Clinical Benefit Rate
MORR	Metabolic Overall Response Rate
MR	Mixed Response
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute

Abbreviation	Definition
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PMD	Progressive Metabolic Disease
PMR	Progressive Metabolic Response
PR	Partial Response
Q1	25th Percentile
Q3	75th Percentile
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SI	Système International
SMD	Stable Metabolic Disease
SUV	Standardized Uptake Value
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TTP	Time to Progression
VP	Virus Particles
WHODD	World Health Organization Drug Dictionary

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Lokon Pharma AB Protocol LOKON003 (A Phase I/II Trial Investigating LOAd703 in Combination with Atezolizumab in Malignant Melanoma). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

This SAP will be finalized prior to data analysis and database lock to provide full details, including templates for tables, listings, and figures, to be presented in the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

5 STUDY OBJECTIVES

5.1 Primary Study Objective

The primary objective of this study is to determine the tolerability of LOAd703 given by intratumoral (i.t.) injection(s) in combination with intravenous (IV) atezolizumab.

5.2 Secondary Study Objectives

The secondary objectives of this study are to determine the antitumor activity as well as the pharmacokinetics and biological mechanisms-of-action of LOAd703 in combination with atezolizumab.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

This trial is a multicenter, open label, single arm, dose-escalation Phase I/II trial. The study will have a Bayesian Optimal Interval (BOIN) design (Ying Yuan 2016) with a target dose limiting toxicity (DLT) rate=0.3 to determine the maximum tolerated dose (MTD) of LOAd703 against a fixed dose of atezolizumab. This design has algorithmic escalation/de-escalation rules like a traditional 3+3 design, but it also allows for specification of the DLT target rate and expanded accrual beyond N=6 with continued and consistent toxicity monitoring. This means that the assessment of DLT rate continues throughout the study, giving a well-defined safety evaluation of the entire study.

[redacted] The total number of subjects to be enrolled in the study to achieve at least 25 evaluable subjects at MTD, should not exceed 50.

[redacted]

The trial encompasses a treatment phase ending with last subject last visit (LSLV). For each subject, active participation with study visits is maximum 60 weeks where after they are followed for survival as long as the trial remains open.

After a screening period [redacted], each subject will receive a maximum of 12 LOAd703 injections (q3w) in combination with atezolizumab (q3w) after which supportive therapy with atezolizumab alone is continued until the final clinical visits (i.e., maximum 7 additional infusions).

The subjects will be scheduled for study visits until final clinical follow-up in study [redacted] If both treatments are prematurely withdrawn the final clinical follow-up visit could be scheduled earlier, [redacted].

In total, subjects will visit the clinic regularly for a maximum 60 weeks [redacted]. Thereafter only OS will be recorded [redacted] whereby information will be collected via telephone calls (US) or medical records (Sweden, US) until death or study end.

The end of the treatment stage is defined as the date of the LSLV and the end of study is defined as LSLV.

The study is initially planned to be conducted at 2 sites in US and 1 site in Sweden. The study has been conducted in 3 sites in US and 1 site in Sweden.

Before beginning the screening visit, the subject will be informed about the trial and sign informed consent whereupon the subject is enrolled in the trial. The subject will be evaluated for health status, pregnancy (if applicable) and tumor load (by appropriate radiological imaging). If the subject has been subjected to radiology examination within

three weeks prior to registration, this imaging can be reused for evaluation at the discretion of the Investigator. If all of the inclusion criteria and none of the exclusion criteria are met, the subject is registered to participate in the trial.

Appendix 1 (Schedule of Events) of the clinical study protocol shows the treatment schedule and timing of the study visits. Subjects will undergo 12 LOAd703 treatments (q3w) administered by i.t. injection until study [redacted]. Atezolizumab infusions (q3w) will continue during the study until progression or toxicity requires treatment discontinuation. On the day of the treatment, [redacted]

The treatments are scheduled on any of the designated study week working days. If the treatments are delayed to the next week, then they must be omitted in order to adhere to the protocol schedule.

Laboratory samples (toxicity, [redacted]

If both treatments are discontinued, a modified follow-up schedule will apply (see Appendix III of the protocol for further details).

During evaluation visits, the subject will be evaluated for health status, toxicity, and treatment effect on tumor size (radiology exam). Laboratory samples are taken for [redacted]. The final follow-up visit is scheduled at study [redacted].

If both LOAd703 and atezolizumab are discontinued (i.e., off-treatment subject), the subject should still be followed up and participate in the evaluation visits according to the Modified follow-up schedule, unless consent is withdrawn as well. Modified follow-up: subjects should complete visits [redacted] and after visit [redacted], the subjects will return for visits [redacted]

For off-treatment subjects, the final follow-up visit can be scheduled earlier but [redacted]

If another treatment is initiated due to progressive disease or other reasons, the subject will only be followed for survival (see Section 7.5.3 of the protocol: Survival Follow-Up). The final clinical follow-up visit ([redacted]) should then be scheduled to collect endpoint data ([redacted]) as close to the start of new treatment as possible.

If subjects prematurely are withdrawn from the study (i.e., survival follow-up subjects), they will be followed for a minimum [redacted] The final clinical follow-up visit should be scheduled as soon as possible to collect endpoint data prior to the subject's withdrawal, if possible. After the final evaluation visit, subjects enter survival follow-up until death or study end. The date of death will still be collected.

6.2 Schedule of Assessments

For the complete schedule of assessments, refer to Appendix I of the clinical study protocol.

6.3 Treatments

6.3.1 Treatments Administered

Within 7 days after registration, the subjects will initiate treatment. The subjects will be given up to 12 percutaneous LOAd703 i.t. injections combined with atezolizumab, both administered every 3 weeks. Two cohorts consisting of at least 3 subjects per cohort will be evaluated. The LOAd703 dose will be escalated, one dose per cohort, to evaluate the following dose levels: $1x10^{11}$ virus particles (VP) per injection (cohort 1) and $5x10^{11}$ VP per injection (cohort 2). The treatment will be administered by percutaneous i.t. injection which may be image-guided depending on the tumor location.

Atezolizumab will be administered IV using a fixed dose (1200 mg/infusion).

On the day of the treatment, [redacted]. LOAd703 dose, dose modifications and omissions will be carried out as per instructions in Sections 5.6.8 and 7.2.5 of the protocol.

Atezolizumab dose, dose modifications, and omissions will be instituted per standard guidelines and Section 7.2.5 of the protocol.

Missed LOAd703 or atezolizumab doses will not be made up in order to maintain adherence to the protocol schedule.

For the first 2 LOAd703 treatments of any trial subject, the subjects are monitored overnight. Vital signs will be noted [redacted]

[redacted]

6.3.2 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to the active dose cohort at the time of their enrollment into the study.

6.4 Safety and Efficacy Variables

The following safety and efficacy endpoints are defined for this study:

Primary:

- Safety, determined by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) v5.0.

Secondary:

- Overall response rate (ORR) evaluated by RECIST v1.1.
- Shedding determined as level of LOAd703 in [redacted]
- LOAd703 leakage to blood [redacted]
- Anti-adenovirus immunity [redacted]
- [redacted]
- [redacted]
- Immune profile as [redacted]

- [redacted]

Other:

- Changes in clinical laboratory evaluations, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status scores, physical examination results, and 12-lead electrocardiogram (ECG).
- Clinical benefit rate (CBR) evaluated by RECIST v1.1.
- CBR including mixed response (MR).
- Time to progression (TTP) and progression free survival (PFS) evaluated by RECIST v1.1.
- Overall survival (OS).
- Metabolic response [including metabolic overall response rate (MORR) and metabolic clinical benefit rate (MCBR)] assessed using European Organisation for Research and Treatment of Cancer (EORTC) criteria in a subset of subjects where positron emission tomography (PET) scans were performed.

[redacted]

6.4.1 Description of Safety Variables

6.4.1.1 Dose Limiting Toxicities

As LOAd703 will be dose escalated, the subjects will be monitored for dose limiting toxicity (DLT). DLT is defined as any grade 3 or higher toxicity according to the NCI CTCAE version 5.0 that is attributed (definitely, possibly, or probably) to LOAd703. A DLT attributed to LOAd703 will lead to dose reduction.

[redacted] Subjects 2 and 3 should start treatment at least 24 hours apart.

All 3 subjects in the cohort must have been evaluated for DLT before decision on dose escalation is taken for the next cohort.

[redacted].

Toxicity attributed to atezolizumab will not be assessed as DLTs in the study but can still lead to dose modifications.

If a subject experiences an AE grade 3 or higher that can be attributed to the LOAd703 injection procedure (i.e., a bacterial infection, injection site pain, etc.), to disease, or another unrelated cause, it is not a DLT. Serious AEs (SAEs) due to injection procedure can lead to a change of injection procedure (such as change of lesion) instead of treatment discontinuation, depending on the type of AE and the risk of recurrence of the AE.

[redacted]

6.4.1.2 Adverse Events

An AE is any untoward medical occurrence that does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable, unintended clinical sign, symptom, disease or clinically relevant change in laboratory variables or clinical tests temporally associated with the use of an investigational product, whether or not considered related to the investigation product, that requires clinical intervention or further investigation (beyond ordering a repeat/confirmatory test). Injury or accidents, medical conditions for operations that are not preplanned, or deterioration of the concurrent illness are also considered as AEs.

AEs are graded in the study according to NCI CTCAE version 5.0. All AEs (except for grade 1 and 2 laboratory abnormalities that do not require an intervention) are to be recorded on the AE page in the electronic case report form (eCRF).

During [redacted], the Investigator will note the occurrence and nature of each subject's existing medical condition(s). Occurrence and nature of AEs (including laboratory events) directly observed by the study personnel or spontaneously reported by the subject during the study will be reported. Each subject will be asked about AEs at each visit after the first dose of the investigational products LOAd703 and/or atezolizumab.

The general AE reporting period for this trial begins upon receiving the first LOAd703 and/or atezolizumab treatment and continues until final clinical follow-up visit at [redacted].

If both study treatments are prematurely withdrawn, AEs should be recorded [redacted]

If subjects are prematurely withdrawn from the study and enter survival follow-up (i.e., survival follow-up subjects), they will be followed for a minimum [redacted]

If a subject experiences an AE after signing the informed consent, but before treatment is started, the event will be recorded as an existing medical condition unless the Investigator believes that the event may have causal relationship to a study-specific procedure described in the protocol. If LOAd703 and/or atezolizumab have been administrated when an AE occurs, its relationship to the study drugs will be judged by the Investigator.

6.4.1.3 Clinical Laboratory Parameters

Blood sampling should be done at [redacted]

If treatments are discontinued, sampling should still be collected at all scheduled visits up to [redacted]

The following parameters will be analyzed:

Serum chemistry: [redacted]

Hematology: [redacted]

In addition, [redacted]

Blood samples are collected prior to the initiation of pre-medications or treatments according to local hospital routines and sent to the local laboratory for analyses.

6.4.1.4 Vital Signs

At [redacted] blood pressure and pulse will be recorded.

Following LOAd703 treatments: [redacted]

Following atezolizumab treatments: [redacted]

[redacted]

6.4.1.5 ECOG Performance Status

ECOG performance status grade will be recorded at [redacted] If treatments are discontinued, ECOG score will still be evaluated at all scheduled visits up to [redacted]

6.4.1.6 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed after 5 minutes rest at [redacted] and the results will be judged clinically normal or abnormal by the Investigator. Any abnormality will be explained in the eCRF.

6.4.1.7 Physical Examination

A physical examination will be performed at [redacted]. The physical assessment includes, but is not limited to, assessment of head/neck, chest/lungs, skin, abdomen, lymph nodes and the cardiovascular system. Other assessments should be added as applicable. The outcome

will be recorded as "normal" or "abnormal". Abnormal findings will be assessed as "clinically significant" or "not clinically significant".

6.4.2 Description of Efficacy Variables

The tumor response will be evaluated using an appropriate imaging technique, depending on the localization of the tumor. Tumor regression or progression will be evaluated according to RECIST v1.1 criteria (Eisenhauer 2009). Further details are contained with the study protocol.

Due to the potential immunostimulatory capacity of the study treatments, it is possible that the induced immune stimulation may induce an inflammatory swelling of the tumor that initially may be mistaken for progression. Therefore, progressive disease (PD) during study participation leading to discontinuation of repeated treatment needs to be confirmed by radiological imaging at a later time point (within 4-12 weeks) and/or by a biopsy and/or tumor serum marker to confirm tumor progression.

Separate from the RECIST assessment, at each visit, subjects will also be assessed (by the Investigator) for MR, defined as one or more lesions fulfilling the criteria for PR and other(s) for PD.

In addition to computed tomography (CT)/magnetic resonance imaging (MRI) imaging, PET may be performed as a part of the tumor assessment (at the discretion of the Investigator). If PET is used, the measures are documented according to the EORTC assessment (Aide 2019):

- Complete metabolic response (CMR)
- Partial metabolic response (PMR)
- Stable metabolic disease (SMD)
- Progressive metabolic disease (PMD)
- Not evaluable (NE)

Metabolic response is defined as a $\geq$ 15% decrease in maximum standardized uptake value (SUV_{max}) and metabolic progression as a $\geq$ 25% increase in SUV_{max}.

6.4.2.1 Primary Efficacy Variable

There is no primary efficacy endpoint in this study.

6.4.2.2 Secondary Efficacy Variable

The secondary efficacy endpoint is:

- ORR defined as the proportion of subjects with a best overall response (BOR) of CR or PR (according to RECIST v1.1).

BOR is defined as the best response achieved by a subject over the whole study.

An additional BOR variable will also be derived which includes a category of MR. If a subject has PD according to RECIST v1.1 but the investigator has assessed the subject as having mixed response, then the response at that visit will be classified as MR. In this additional BOR derivation, MR is classed as a better response than PD.

[redacted]

[redacted]

6.4.2.3 Other Efficacy Variables

Other efficacy endpoints are:

- CBR according to RECIST v1.1, defined as the proportion of subjects with a BOR of CR, PR, or stable disease (SD).
- CBR according to the BOR definition which includes MR, defined as the proportion of subjects with a BOR of MR or better (i.e., CR, PR, SD, or MR).
- Time to progression defined as the time from first dose of study treatment until progression according to RECIST v1.1. Subjects without progression are censored at the date of the last evaluable tumor assessment. If a subject does not have any evaluable post-dose tumor assessments, they will be censored at the date of first dose plus 1 day.
- Progression free survival defined as the time from first dose of study treatment until progression according to RECIST v1.1 or death (whichever occurs first). Subjects without progression/death are right censored at the date of the last evaluable tumor assessment. If a subject does not have any evaluable post-dose tumor assessments, they will be censored at the date of first dose plus 1 day.
- Overall survival defined as the time from first dose of study treatment until death. Subjects without death are right censored at the date of last contact.

[redacted]

6.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

7 STATISTICAL METHODS

7.1 General Methodology

Data will be analyzed by Precision for Medicine biostatistics personnel. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

7.1.1 Reporting Conventions

Baseline and safety tables will be summarized by dose group ($1x10^{11}$ VP LOAd703; $5x10^{11}$ VP LOAd703). Tables summarizing demographics and other baseline

characteristics will also include a column for all subjects combined (Total). Except where stated, efficacy tables and figures will be summarized for efficacy evaluable subjects by dose. In general, all data collected, and any derived data will be presented in subject data listings for all enrolled subjects. Listings will be ordered by dose group, subject number and assessment or event date. The dose group presented in listings will be based on the planned assignment, unless otherwise noted.

In general, [redacted]

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the eCRF or as provided within an external file) and are outlined as follows:

- [redacted]
- [redacted]
- [redacted]

Other statistics [redacted] will be presented using the same general rules outlined above or assessed for the most appropriate presentation based on the underlying data.

No formal statistical analysis will be performed to compare dose groups. Results will be presented with descriptive statistics will be tabulated by dose group and reviewed to evaluate all study endpoints.

7.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF.

Data collected at unscheduled visits will not be included in by-visit summaries but will be considered when endpoint derivations potentially include multiple visits (e.g.,

determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in subject listings.

7.1.3 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose of study drug, if the assessment/event date is prior to the date of first dose; and
- The assessment/event date minus the date of first dose of study drug, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
  - Later date – earlier date + 1, if the earlier date is on or after the date of first dose of study drug; or
  - Later date – earlier date, if the earlier date is prior to the date of first dose of study drug.
- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12);
- **Change from Baseline:** Change from baseline will be calculated as the post-baseline value minus the baseline value;
- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

7.2 Analysis Populations

The analysis populations are defined as follows:

- Safety Population: [redacted]
- Efficacy Evaluable Population: [redacted]

Data summaries to be presented on both the Safety Population and the Efficacy Evaluable Population will only be produced on both analysis sets if there is a difference in the population groups.

Although not formal analysis populations, the following subgroups of subjects are also relevant:

- [redacted]
- [redacted]
- [redacted]

7.3 Study Subjects

7.3.1 Disposition of Subjects

Subject disposition will be summarized for all enrolled subjects by dose group and over all subjects combined (total). Summaries will include the number and percentage of subjects in each analysis population, completing treatment, discontinuing treatment early by the primary reason for discontinuation, with Coronavirus Disease 2019 (COVID-19) as part of the reason for discontinuation of treatment, completing the study, discontinuing the study early by the primary reason for discontinuation and with COVID-19 as part of the reason for discontinuation of study. A by-subject listing will also be provided.

[redacted]

7.3.2 Protocol Deviations

When all subjects have been completed, all data have been entered into the eCRF database, all coding is done and approved, and all queries are solved, the Database Closure procedures will begin. Decisions will be made on how to classify subjects into analysis populations, and how to handle protocol violations and deviating or missing data. All decisions will be dated and documented in a Database Closure document.

All protocol deviations will be listed, and major protocol deviations will be summarized by site (and for all sites combined), protocol deviation category, subcategory, and dose group and over all subjects combined (total).

7.3.3 Compliance with Study Schedule

A listing showing compliance with the study schedule (i.e., including all visits that were performed or missed for each subject) will be provided.

7.4 Demographic and Other Baseline Characteristics

Demographic variables including age, sex, ethnicity, country, and race will be summarized by dose group and over all subjects combined (total) for the Safety and Efficacy Evaluable Populations and will be presented in a by-subject listing.

Age will be summarized using descriptive statistics. Sex, ethnicity, country, and race will be summarized with the number and percentage of subjects in each parameter category.

Baseline and disease characteristics including time from initial diagnosis (months), disease stage (at initial diagnosis and study entry), positive tumor-specific genetic markers*, height, weight, body mass index (BMI), pregnancy test results and smoking status at Screening will be summarized for the Safety and Efficacy Evaluable Populations by dose group and over all subjects combined (total) and will be presented in by-subject listings.

BMI will be derived by the electronic data capture system as: weight (kg) / [height (cm) / 100]^2.

Time from initial diagnosis (months) will be calculated as (Date of Informed Consent – Date of Initial Diagnosis + 1) / (365.25 / 12). Partial diagnosis dates will be imputed as per Section 7.6.5.2.

[redacted]

Height, weight, and BMI at baseline and time from initial diagnosis will be summarized using descriptive statistics. Disease stage at initial diagnosis, disease stage at study entry, positive tumor-specific genetic markers, pregnancy test results and smoking status at Screening will be summarized by the number and percentage of subjects with each response.

Frequency counts and percentages to summarize subjects reporting relevant medical history by Medical Dictionary for Regulatory Activities (MedDRA, version 23.0) system organ class and preferred term will be presented for the Safety Population by dose group and over all subjects combined (total).

7.5 Measurements of Study Drug Compliance

LOAd703 is given up to 12 times every 3 weeks during the study, while atezolizumab is given continuously every 3 weeks during the study if judged beneficial and safe for the subject by Investigator. The study treatment (LOAD703 and/or atezolizumab) can be omitted, but missed doses will not be made up. Compliance to the study treatment regimen will be determined, separately for LOAd703 and atezolizumab, as the number of doses received divided by the expected number of doses while subject was on-study, multiplied by 100. [redacted]

Study drug compliance will be summarized using descriptive statistics, by dose group, based on the Safety Population. [redacted]

7.6 Efficacy Evaluation

7.6.1 Datasets Analyzed

All efficacy summaries will be based on the Efficacy Evaluable Population per dose group. A data listing of subjects excluded from the Efficacy Evaluable Population, to include the reason for exclusion, will be presented. Efficacy summaries (and corresponding figures) will include all subjects per dose group.

The subjects excluded from each analysis set are described in the Analysis Set Specification.

7.6.2 Primary Efficacy Endpoint Analysis Methods

There is no primary efficacy endpoint in this study.

7.6.3 Secondary Endpoint Analysis Methods

[redacted]

[redacted]

A summary of BOR, ORR and CBR based on the derivation of BOR which includes MR will also be produced. In addition to columns for each dose, an additional column including all subjects (irrespective of dose received) will be included.

[redacted]

7.6.4 Other Efficacy Endpoint Analysis Methods

Time to event variables (TTP, PFS and OS) will be summarized as follows:

The number and percentage of subjects with an event and being censored will be presented. Kaplan-Meier product-limit estimates for the 25th percentile, median and 75th percentile will be presented with 95% CIs. The range of values (both including and excluding censored values) will also be presented. The estimated survival distribution function and the number of subjects at risk at 3-month intervals (i.e., 3, 6, 9, months etc) for TTP/PFS or 4-month intervals (i.e., 4, 8, 12, months etc) for OS will be presented.

Kaplan-Meier plots will also be produced.

[redacted]

- [redacted]

- [redacted]

[redacted]

7.6.5 *Statistical/Analytical Issues*

7.6.5.1 Adjustments for Covariates

There are no planned applications of covariate adjustments; all statistical results are descriptive in nature.

7.6.5.2 Handling of Dropouts or Missing Data

For the purpose of calculating time since initial melanoma diagnosis, partial diagnosis dates will be imputed as follows:

- Missing day only will be imputed with the 1st of the month;
- Missing day and month will be imputed with 1st January.

No imputation will be done if the diagnosis date is completely missing.

If the imputed date is after the date of informed consent, the date of informed consent will be used instead (i.e., a time since diagnosis will be computed as 1 day).

The analysis of TTP and PFS will censor subjects without events at the date of the last evaluable tumor assessment. If a subject does not have any evaluable post-dose tumor assessments, they will be censored at the date of first dose plus 1 day. The analysis of OS will censor subjects without events at the date of last contact.

7.6.5.3 Interim Analyses and Data Monitoring

There are no interim analyses planned, nor is there a plan to establish a data monitoring committee for this study. The decision to escalate dose will be taken by the Sponsor after a safety meeting including the Sponsor, Clinical Research Organization, Clinical Project

Manager (for taking notes only), Medical Advisor and at least 2 of the site Principal Investigators as a minimum.

7.6.5.4 Multicenter Studies

This is a multicenter study, with approximately 3 sites expected to participate. Efficacy data collected from all study sites will be pooled for data analysis. The effect of study site on the efficacy analysis results is not planned to be explored.

7.6.5.5 Multiple Comparisons/Multiplicity

There will be no adjustments for multiple comparisons in the efficacy analysis for this study. Results are descriptive in nature and there will be no formal comparisons made among dose groups.

7.6.5.6 Use of an "Efficacy Subset" of Subjects

No efficacy subset will be used.

7.6.5.7 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

7.6.5.8 Examination of Subgroups

ORR will be summarized by the below subgroups:

[redacted]

7.7 Safety Evaluation

Safety analysis will be carried out for the Safety Population, [redacted]. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. For safety analysis presented by study visit, the baseline value will be defined as the last value reported prior to first study drug administration.

7.7.1 Extent of Exposure

Extent of exposure to study treatment (LOAd703 and atezolizumab separately) will be summarized for the Safety Population by dose group. The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. Duration of exposure and total number of doses received will be summarized using descriptive statistics. Total dose received (in 10^{11} VP

for LOAd703 and in mg for atezolizumab) will also be summarized. [redacted] The number and percentage of subjects who had any dose change (either an allowed reduction as per protocol or an unexpected change) will be presented for each drug separately. The number of missed doses will be summarized for both drugs and the number of additional/unplanned doses will be summarized for atezolizumab. A dose is considered missed only if it is followed by a subsequent dose, i.e., doses not administered following permanent discontinuation of a study drug are not considered missed. An additional/unplanned atezolizumab dose is defined as a dose received at [redacted].

Study drug administration information will be presented in listings (including any missed doses with reasons for doses being missed).

7.7.2 Dose Limiting Toxicities

The number of DLT evaluable subjects ([redacted]) and the total number of DLTs will be presented by dose group. The number and percentage of subjects who experienced at least one DLT and at least one DLT of each severity (grade 3 to 5) will also be presented. Percentages will be based on the number of DLT evaluable subjects. Following the BOIN principle, isotonic regression using pooled-adjacent-violators algorithm will be utilized to obtain toxicity probability estimates for each dose group and the dose which has the toxicity probability estimate closed to the target DLT rate (0.3) will be defined as the MTD for the study.

7.7.3 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized by dose group. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms, preferred terms and system organ classes using MedDRA, version 23.0.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Number of TEAEs, number and percentage of subjects with at least one TEAE and number and percentage of subjects with TEAEs by MedDRA system organ class and preferred term;

- Number of treatment-emergent SAEs (TESAEs), number and percentage of subjects with at least one TESAE and number and percentage of subjects with TESAEs by MedDRA system organ class and preferred term;

- Number of treatment-related TEAEs, number and percentage of subjects with at least one related TEAE and number and percentage of subjects with related TEAEs by MedDRA system organ class and preferred term. Summary will be presented for TEAEs related to LOAd703, TEAEs related to atezolizumab and TEAEs related to either drug;

- Summary by relationship (related to LOAd703, related to atezolizumab, related to LOAd703 and/or atezolizumab and not related to LOAd703 or atezolizumab) and CTCAE grade including: Number of TEAEs, number and percentage of subjects with at least one TEAE and number and percentage of subjects with TEAEs by MedDRA system organ class and preferred term. Events in each relationship category will be counted only once using the highest CTCAE grade.

At each level of summarization (e.g., any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once.

Related events include those reported with a causality to LOAd703 and/or atezolizumab of "Possible", "Probable" or "Definite"; events considered not related are those reported as "Unlikely" or "Unrelated".

Adverse event data (including any AEs starting before first study drug) will be presented in data listings by subject, dose group, and event. Serious AEs and AEs leading to withdrawal, interruption, or dose reduction of the study drug will be presented in separate data listings. Lowest level terms will be listed in addition to preferred terms.

7.7.4 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post treatment follow-up period, will be listed by subject, to include the primary cause of death. Serious AEs and other significant AEs, including those that led to withdrawal, interruption, or dose reduction of the study drug, will be provided in separate subject data listings.

7.7.5 Clinical Laboratory Evaluation

All descriptive summaries of laboratory results will be based on data analyzed by local laboratories and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included in by-subject data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by subject, laboratory test, and unit. In

addition, normal ranges provided by each local laboratory will be presented in a separate listing.

Clinical laboratory measurements, including serum chemistry ([redacted]) and hematology, will be summarized by dose group. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

Values reported as greater than or less than some quantifiable limit (e.g., "< 1.0") will be summarized with the sign suppressed in summary tables and figures, using the numeric value reported. Data will display on subject listings to include the sign.

Where applicable, hematology and chemistry results for select parameters will be assigned a toxicity grade based on NCI CTCAE version 5.0. If the quantitative criteria for grading are equivalent for two grades and the differentiation is described by clinical interventions, the clinical intervention component will not be considered and the highest CTCAE grade will be assigned. Similarly, death related to AE (i.e., grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Laboratory parameters that include multiple sets of criteria for each direction ([redacted]) will be summarized separately to reflect each set of criteria.

Five-by-five contingency tables will be presented for lab tests where toxicity grading can be applied, to summarize the shift from the baseline grade to the worst post-baseline grade. Grades will be presented as none (grade 0; i.e., measurements did not meet any CTCAE criteria for grades 1 through 4), mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4). Summary results will include the count and percentage of subjects within each shift category.

7.7.6 Vital Signs, Physical Examination Findings, and Other Observations Related to Safety

7.7.6.1 Vital Signs

Vital sign parameter measurements will be summarized by dose group. Descriptive statistics will be presented for results and change from [redacted]. Measurements taken relative to the LOAd703 injection will be tabulated separately to those taken relative to the atezolizumab infusion. [redacted] data will be listed only (unless [redacted]).

7.7.6.2 ECOG Performance Status

ECOG performance status will be summarized by dose group. Descriptive statistics will be presented for observed values and changes from [redacted] at each visit where ECOG performance status was scheduled to be collected. The number and percentage of subjects with each score at each visit will also be presented by dose group.

7.7.6.3 12-Lead Electrocardiogram

Results of the 12-lead ECG will be presented in subject data listings by subject, study visit, and parameter. The overall assessment by the investigator will also be listed.

7.7.6.4 Physical Examination

Results of the physical examination will be presented in subject data listings by subject, study visit, and body system.

7.7.6.5 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHODD), September 1st 2019 version. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Prior and concomitant medications will be summarized separately, and the study phase of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first dose of study drug. A concomitant medication- is defined as any medication administered on or after the date of the first dose of study drug. A medication may be defined as both prior and concomitant. If it cannot be determined whether a medication was received prior to the start of study drug dosing due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the start of study drug dosing, it will be considered concomitant.

For both prior and concomitant medications summaries, the number and percentage of subjects receiving any medication will be summarized by dose group, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Prior medications will also be summarized over all subjects combined (total). Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. The study phase during which each medication was received (e.g., prior, concomitant, or both) will be presented on the listing of prior and concomitant medications.

7.7.6.6 Concomitant Medical or Surgical Procedures

Concomitant procedures will be listed only.

7.8 Determination of Sample Size

7.8.1 Safety

[redacted]

The study will be conducted using a BOIN design with a target DLT rate of 0.3. This design has algorithmic escalation/de-escalation rules like a traditional 3+3 design but allows for specification of the target DLT rate and expanded accrual beyond N=6 with continued consistent toxicity monitoring (i.e., the assessment of DLT rate continues throughout the study which gives a well-defined safety evaluation of Phase I/II studies).

Two LOAd703 dose levels will be tested together with a fixed dose of atezolizumab. The BOIN design allows for enrollment of 3 subjects in a cohort and the number of subjects with DLT determines whether additional subjects are treated with the current dose or if the dose is decreased or increased. In general, the dose will be escalated if the observed toxicity rate at the current dose is ≤ 0.2365, and the dose will be de-escalated if the observed toxicity rate at the current dose is ≥ 0.3585. If the observed toxicity rate is between 0.2365 and 0.3585, 3 additional subjects will be treated at the current dose. For cohorts of size 3, the decision boundaries are shown below. Additional cohorts will be added in the unlikely event that more than N=25 participants at a single dose level are needed.

Number of Subjects Treated in a Defined Cohort	3	6	9	12	15	18	21	24	25
Escalate dose if number of DLT ≤	0	1	2	2	3	4	4	5	5
Treat additional 3 subjects at current dose if number of DLT=	1	2	3	3, 4	4, 5	5, 6	5-7	6-8	6-8
De-escalate dose if number of DLT≥*	2	3	4	5	6	7	8	9	9
Eliminate** dose level and all higher doses from further use if number of DLT≥	3	4	5	7	8	9	10	11	12

* At the lowest dose level, if the recommendation is to de-escalate and the dose level has not been eliminated from consideration, 3 additional subjects can be accrued at the same dose level; otherwise, the trial will be stopped.
** Note that if the DLT level reaches the elimination limit, this dose level is abandoned from the study independently of DLT events at lower dose levels.

7.8.2 Efficacy

[redacted]

7.9 Changes in the Conduct of the Study or Planned Analyses

[redacted]

Section 10.3 of the protocol describes summaries of urinalysis [redacted]

There were no other changes to the study conduct or planned analyses identified within the development of this SAP, relative to the descriptions provided within the clinical study protocol.

8 REFERENCE LIST

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