SPONSOR:

Autolus

PROTOCOL NUMBER:

AUTO2-MM1

STATISTICAL ANALYSIS PLAN

Author:	[redacted]
Version:	**Final 1.0**
Date:	**21Apr2020**

1 Cover and signature pages

Sponsor:	Autolus
Protocol Number:	AUTO2-MM1
Study Title:	A Single-Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity of AUTO2, a CAR T Cell Treatment Targeting BCMA and TACI, in Patients with Relapsed or Refractory Multiple Myeloma
Document Version No	Final 1.0

We, the undersigned, confirm that we have read, understood and agree to the content of this document and hereby authorize its approval.

Name and Date are not required if electronic signatures are used. Do not resize boxes.			
Name	**Title [text box when using eSignatures]:**	**Date**	**Signature**
[redacted]	[redacted]		

Name and Date are not required if electronic signatures are used. Do not resize boxes.			
Name	**Title [text box when using eSignatures]:**	**Date**	**Signature**
[redacted]	[redacted]		

Name and Date are not required if electronic signatures are used. Do not resize boxes.			
Name	**Title [text box when using eSignatures]:**	**Date**	**Signature**
[redacted]	[redacted]		

Name and Date are not required if electronic signatures are used. Do not resize boxes.			
Name	**Title [text box when using eSignatures]:**	**Date**	**Signature**
[redacted]	[redacted]		

Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Event of special interest
ALT	Alanine Aminotransferase
APRIL	A proliferation inducing ligand
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATIMP	Advanced therapy investigational medicinal product
BCMA	B cell maturation antigen
BOR	Best overall response
BSA	Body Surface Area
CAR	Chimeric antigen receptor
CBR	Clinical benefit rate
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CR	Complete response
CRF	Case Report Form
CRS	Cytokine release syndrome
CSR	Clinical Study Report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
Cy/Flu	Cyclophosphamide and fludarabine
DLT	Dose limiting toxicity
DSUR	Development safety update report
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full analysis set
FLC	Free light chain
GCP	Good clinical practice

IA	Interim analysis
ICH	International Conference on Harmonisation
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IMWG	International Myeloma Working Group
IV	Intravenous(ly)
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MUGA	Multiple Gated Acquisition
MR	Minimal response
MRD	Minimal Residual Disease
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not evaluable
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive Disease
PDvs	Protocol deviations
PET-CT	Positron emission tomography-computerised tomography
PFS	Progression-free survival
PR	Partial response
PT	Preferred Term
QIgs	Serum quantitative immunoglobulins
qPCR	Quantitative polymerase chain reaction
QTCF	Heart rate-corrected QT interval (Fridericia's formula)
RCR	Replication competent retrovirus
RP2D	Recommended Phase II dose

RQR8	Safety switch gene containing 2 copies of the rituximab mimotope flanking the QBEnd10 epitope on a CD8 stalk
SAE	Serious adverse event
SAP	Statistical analysis plan
sCR	Stringent complete response
SD	Standard deviation
SFLC	Serum Free Light Chain
SI	International System
SOC	System Organ Class
SPEP	Serum protein electrophoresis
TACI	Transmembrane activator and calcium modulator and cyclophilin ligand interactor
TEAE	Treatment-emergent adverse event
TFL(s)	Table(s), figure(s), listing(s)
TNF	Tumour necrosis factor
TTP	Time to disease progression
UPEP	Paraprotein in Urine
VGPR	Very good partial response
WHODDE	World Health Organization drug dictionary

3 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in the analysis of study AUTO2-MM1 for Autolus in AUTO2, a CAR T cell treatment targeting BCMA and TACI, in patients with relapsed and refractory multiple myeloma.

The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to Protocol AUTO2-MM1 Version 7.0 (27 Jun 2018) and Protocol AUTO-LT1 Version 2.0 (01 Feb 2018).

4 Study Objectives

PRIMARY OBJECTIVES

The primary objectives of the study are defined on Phase I and Phase II as follows:

- Primary objective for Phase I (dose escalation):
    - To assess the safety and tolerability of AUTO2 administration;
    - To identify the recommended Phase II dose (RP2D) and maximum tolerated dose (MTD), if an MTD exists, of AUTO2.
- Primary objective for Phase II (expansion):
    - To evaluate the anti-tumour effect of AUTO2;
    - To assess the safety and tolerability of AUTO2 administration.

SECONDARY OBJECTIVES

- To evaluate the feasibility of generating the advanced therapy investigational medicinal product (ATIMP), AUTO2;
- To evaluate the clinical efficacy of AUTO2;
- Biomarker and pharmacodynamic effects of AUTO2.

[redacted]

5 Study Design

5.1 STUDY DESIGN AND POPULATION

The study population is patients with confirmed diagnosis of multiple myeloma (MM) as per the International Myeloma Working Group (IMWG) who have relapsed or become refractory after exposure to alkylator therapy or monoclonal antibody, immunomodulatory drug and proteasome inhibitor.

The study is a single-arm, open-label, Phase I/II, multi-centre study to characterize the safety and clinical activity of APRIL CAR T cells when administered to patients with relapsed or refractory MM. The study will consist of 2 parts, a Phase I (dose escalation) followed by a Phase II (dose expansion).

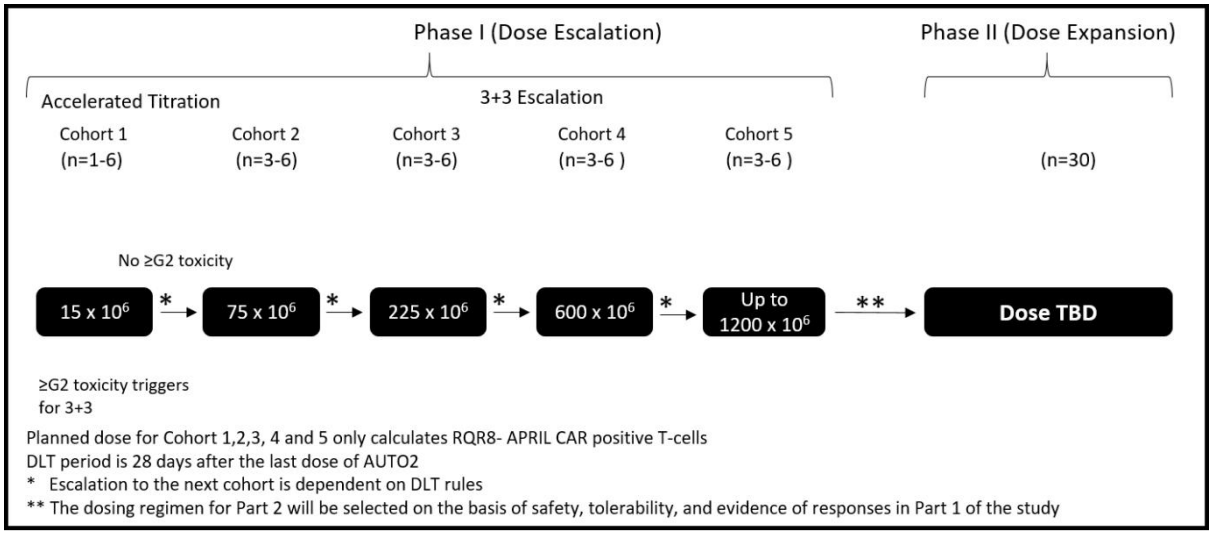
- **Phase I (Dose Escalation):** To identify the optimal dose (based on safety, tolerability and antitumour activity) of AUTO2 using an accelerated titration design (Simon et al. 1997). Up to 5 cohorts and a maximum of 42 patients with MM will be enrolled. Doses from 15 x 10^6 to up to 900 x 10^6 RQR8/APRIL CAR positive T cells will be evaluated.

- **Phase II (Dose Expansion):** To further characterize the safety and assess the efficacy of AUTO2 at the recommended dose identified in Phase I, 30 patients will be treated in the dose expansion phase.

Up to 80 patients in total are expected to be enrolled into both the dose escalation and dose expansion phases of the study, and up to 72 patients in total are anticipated to receive the AUTO2 therapy.

An overview of the study design is presented in Figure 1 below.

Figure 1. Dose Escalation and Dose Expansions Phases



The total study duration is estimated to be 4.5 years from first patient enrolled to the last patient, last visit (24-month visit). The end of the study will be 24 months after the last patient has received AUTO2 infusion (or earlier if appropriate).

All patients will be enrolled into a long-term follow-up protocol (AUTO-LT1) at the End of Study visit and will be followed for safety evaluation and survival for 15 years from the first AUTO2 infusion or until death or withdrawal of consent, which ever happens first.

The long-term follow-up study will be covered by a separate protocol (AUTO-LT1). All corresponding long-term follow-up data for AUTO2-MM1 study will be reported with the relevant parent study data, as stated in relevant section in this SAP.

Patients who have received AUTO2 and have discontinued or completed the study may continue to be monitored for AUTO2 treatment-related SAEs and AEs until they enroll onto the long-term follow-up study (AUTO-LT1) and the End of Study visit will be delayed.

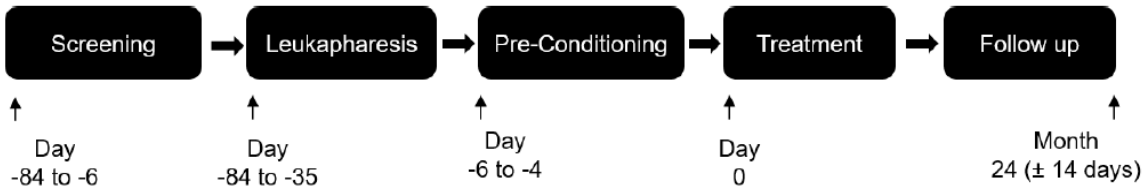
5.2 STUDY TREATMENTS AND ASSESSMENTS

The study will consist of the following 5 stages:

- **Screening**: After providing written informed consent for study participation, all patients will be screened for study eligibility. Eligible patients will proceed to leukapheresis.
- **Leukapheresis**: Eligible patients will undergo leukapheresis to facilitate manufacture of the ATIMP, AUTO2. If sufficient quantity of the cells (prescribed dose ± 20%) are produced, the patient will proceed to the Pre-Conditioning Phase.
- **Pre-Conditioning**: If sufficient AUTO2 for the prescribed dose is successfully manufactured and the patients continue to meet eligibility requirements for the study, they will proceed to receive a lymphodepleting pre-conditioning treatment with cyclophosphamide and fludarabine for 3 days, timed to end 4 days before AUTO2 infusion.
- **Treatment**: AUTO2 for the prescribed dose will be administered IV as a single infusion on Day 0. The treatment phase will extend from Day 0 (infusion day) until the end of the dose limiting toxicity (DLT) observation period (28 days post last AUTO2 infusion).
- **Follow-up**: The follow-up phase will begin after the treatment stage and end 2 years (± 14 days) after infusion with AUTO2 or at disease progression or withdrawal of consent, which ever happens first (End of Study visit).

An overview of the 5 study stages is presented in Figure 2.

Figure 2. Overview of the Stages of the Study



The schedule of assessments to be performed during the study is detailed in [redacted].

Eligible patients will receive AUTO2 IV following pre-conditioning treatment. The AUTO2 product contains both transduced (RQR8/APRIL CAR positive) and non-transduced cells. The dose is expressed as the number of RQR8/APRIL CAR positive T cells. Five dose cohorts are planned in Phase I:

- Cohort 1, Dose Level 1: 15 x 10^6 RQR8/APRIL CAR positive T cells;
- Cohort 2, Dose Level 2: 75 x 10^6 RQR8/APRIL CAR positive T cells;
- Cohort 3, Dose Level 3: 225 x 10^6 RQR8/APRIL CAR positive T cells;
- Cohort 4, Dose Level 4: 600 x 10^6 RQR8/APRIL CAR positive T cells;
- Cohort 5, Dose Level 5: 900 x 10^6 RQR8/APRIL CAR positive T cells.

Patients weighing less than 50 kg will have a 25% reduction in total dose, patients weighing more than 100 kg may receive a 25% increase in total dose.

The Safety Evaluation Committee will convene after the first and third patient as well as at the end of each cohort to decide on the next dose level, after the last cohort in the escalation phase to decide on the dose level for Phase II, and at the interim analysis stage. When a recommended Phase II dose decision is made by the Safety Evaluation Committee, the decision will need to be reviewed and endorsed by the Independent Data Monitoring Committee prior to opening Phase II. On occasion, a patient may receive re-treatment upon satisfying re-treatment criteria.

5.3 RANDOMISATION AND BLINDING

Randomisation will not be used in this study. Patients will be allocated to receive study treatment in the order in which they qualify for the study. As this is an open-label study, blinding procedures are not applicable.

5.4 SAMPLE SIZE JUSTIFICATION

Approximately 80 patients will be enrolled into the study and up to 72 patients will be treated.

- Phase I (Dose escalation): up to 42 patients in total (up to 6 patients per dose cohort and up to 12 at R2PD).
- Phase II (Dose expansion): up to 30 patients in total.

In the dose escalation phase, an accelerated titration design will be used for the first cohort, with 1 patient being recruited into the lowest dose level. However, if Grade 2 or higher toxicity is observed during the DLT observation period, the design will transition into a standard 3+3 design. All subsequent cohorts will follow a 3+3 design.

Phase II of the study will follow Simon's 2-stage optimal design. The null hypothesis that the true response rate is 10% will be tested against a 1-sided alternative. In the first stage, 10 evaluable patients will be accrued (6 weeks post treatment of 10th evaluable patient). If there are 1 or fewer responses in these 10 evaluable patients, the study will be stopped. Otherwise, 19 additional evaluable patients will be accrued for a total of 29. The null hypothesis will be rejected if 6 or more responses are observed in 29 evaluable patients. This design yields a type I error rate of 5% and power of 80% when the true response rate is 30%.

6 Statistical Considerations

6.1 PREMATURE TERMINATION OF THE STUDY DURING THE COURSE OF PHASE I

In September 2019, 12 patients have been consented to enter the study, of which 11 patients have been infused with AUTO2 in the Phase I part of the study. The remaining patient did not receive the manufactured AUTO2 and subsequently died. Although the safety profile of AUTO2 in multiple myeloma is considered tolerable, the efficacy is considered moderate when compared to other BCMA targeting products in development. Therefore, Autolus have made the decision to terminate the study.

As a result, an abbreviated clinical study report (CSR) will be written to summarize the primary and secondary objectives defined for Phase I. [redacted]

The status of the study at the time of the decision to prematurely stop it is summarized in the below table.

Cohort number	Number of treated patients	Last attended visit in AUTO2-MM1 study	Patients status
1	1	Month 24	1 patient completer
2	3	Month 5 (1 patient) Month 6 (1 patient) Month 8 (1 patient)	3 patients discontinued
3	3	Month 3 (1 patient) Month 4 (1 patient) Month 6 (1 patient)	3 patients discontinued
4	3	Month 2 (1 patient) Month 4 (1 patient) Month 8 (1 patient)	3 patients discontinued
5	1	Month 3	1 patient discontinued
All	11	Month 24 (1 patient) Month 8 or earlier (10 patients)	1 patient completer 10 patients discontinued

6.2 MISSING DATA HANDLING

No other imputation for missing data will be carried out other than to complete partial dates using standard imputation techniques as described below.

For the time to event variables censoring rules will apply as defined in section 8.9, so there should be no missing data.

6.3 PARTIAL DATE IMPUTATION

The following rules should be used when modifying partial or missing dates for reporting purposes such as defining on treatment flags.

A permanent new date variable should be created if there is a requirement to be used in determining flags, sort orders and other derived variables needed for a table, listing or figure. Imputed date variable names will be defined in the derived dataset specifications.

Original (raw) date variables must not be overwritten. Imputed dates will not be displayed in the listings.

General rules

Adverse Events or Prior/Concomitant Medications or Prior Cancer Therapies / Bridging Therapies

Adverse events (AE), prior/concomitant medications and prior cancer therapies/bridging therapies are considered to have started at the earliest possible date and end at the latest possible date.

In case of partial start dates with missing day:

- Any partial start date in the same month as the AUTO2 infusion would be imputed at the date of the AUTO2 infusion.
- Any partial start date in the month before AUTO2 infusion and in the same month as pre-conditioning treatment would be imputed at the date of earliest pre-conditioning treatment date during that month.
- Any partial start date after the month of AUTO2 infusion would be imputed at the first day of the month.
- Any partial start date before the month of first AUTO2 infusion and before the month of first pre-conditioning treatment would be imputed at the last day of the month.

In case of partial start dates with missing day and missing month:

- Any partial start date during the year of AUTO2 infusion would be imputed at the date of the AUTO2 infusion.
- Any partial start date before the year of first AUTO2 infusion and during the year of pre-conditioning treatment would be imputed at the date of earliest pre-conditioning treatment date during that year.
- For any AE or concomitant medication starting after the year of first AUTO2 infusion, the start date would be imputed at 01 January of that year.
- For any AE or concomitant medication started before the year of first AUTO2 infusion and before the year of first pre-conditioning treatment, the start date would be imputed as the 31 December of that year.

In case of partial end dates with missing day:

- Partial end dates would be imputed at the last day of the month or at the date of study discontinuation, whichever occurs first.

In case of partial end dates with missing day and month:

- Partial end dates would be imputed at the last day of December (i.e. 31st December) or at the date of study discontinuation, whichever occurs first.

Some examples are given below (YYYY-MM-DD).

In most cases, start dates are imputed as first day of the month or first of January.

Data Type	Start Date	Imputed Start Date	First pre-condition treatment date	Last pre-condition treatment date	First AUTO2 infusion date	End Date	Imputed End Date
Adverse Event, Prior/Concomitant Meds	2017-02	2017-02-01	2016-12-11	2016-12-13	2016-12-17	2017-02	2017-02-29
Adverse Event, Prior/Concomitant Meds	2017-02	2017-02-03	2017-01-27	2017-01-29	2017-02-03	2017-02	2017-02-29
Adverse Event, Prior/Concomitant Meds	2017-02	2017-02-11	2017-02-11	2017-02-13	2017-02-18	2017-02	2017-02-29
Adverse Event, Prior/Concomitant Meds	2017-02	2017-02-03	2017-01-27	2017-01-29	2017-02-03	2017-03	2017-03-31

Data Type	Start Date	Imputed Start Date	First pre-condition treatment date	Last pre-condition treatment date	First AUTO2 infusion date	End Date	Imputed End Date
Adverse Event, Prior/Concomitant Meds	2017	2017-01-27	2017-01-27	2017-01-29	2017-02-03	2017	2017-03-16 £
Adverse Event, Prior/Concomitant Meds	2017-03	2017-03-01	2017-01-27	2017-01-29	2017-02-03	2017-03	2017-03-31
Adverse Event, Prior/Concomitant Meds	2017-01	2017-01-27	2017-01-27	2017-01-29	2017-02-03		2017-03-01 *
Adverse Event, Prior/Concomitant Meds	2017-01	2017-01-31	2017-02-27	2017-02-29	2017-03-03	2017-01	2017-01-31

£ Patient discontinued on 2017-03-16; * Patient discontinued on 2017-03-01.

Partial dates for initial diagnosis or most recent relapse/confirmation of disease will be imputed as the 15th of the month if the month is present, or the 1st of July if only the year is present.

Partial dates are not expected for response assessment data and death. However, should partial dates be present on treatment disease assessments, the dates would be imputed as the first day of the month if the month is present or the latest between first of January and date of initial AUTO2 infusion if only the year is present. In case of partial date for death, the date would be imputed as the day after the last visit/assessment date when the patient was known alive.

6.4 VISIT WINDOWING

Visit windowing will be considered only for pharmacodynamic assessments. The halfway point corresponding to the visits will be considered in relation to date of first AUTO2 infusion. One month is defined as 30.4375 days. Response assessments are planned to be conducted at end of DLT period, Month 2, Month 3, Month 4, Month 5, Month 6, Month 8, Month 10, Month 12, Month 15, Month 18 and Month 24. The following windowing rules will be taken into account to establish the visit corresponding to each response assessment:

- End of DLT period: any pharmacodynamic assessment performed between 28 to 45 days after the first dose of AUTO2;
- Month 2: any pharmacodynamic assessment performed between 1.5 to 2.5 months (e.g. 46 to 76 days) after the first dose of AUTO2;
- Month 3: any pharmacodynamic assessment performed between 2.5 to 3.5 months (e.g. 77 to 106 days) after the first dose of AUTO2;

- Month 4: any pharmacodynamic assessment performed between 3.5 to 4.5 months (e.g. 107 to 137 days) after the first dose of AUTO2;
- Month 5: any pharmacodynamic assessment performed between 4.5 to 5.5 months (e.g. 138 to 167 days) after the first dose of AUTO2;
- Month 6: any pharmacodynamic assessment performed between 5.5 to 7 months (e.g. 168 to 213 days) after the first dose of AUTO2;
- Month 8: any pharmacodynamic assessment performed between 7 to 9 months (e.g. 214 to 273 days) after the first dose of AUTO2;
- Month 10: any pharmacodynamic assessment performed between 9 to 11 months (e.g. 274 to 334 days) after the first dose of AUTO2;
- Month 12: any pharmacodynamic assessment performed between 11 to 13.5 months (e.g. 335 to 410 days) after the first dose of AUTO2.
- Month 15: any pharmacodynamic assessment performed between 13.5 to 16.5 months (e.g. 411 to 502 days) after the first dose of AUTO2.
- Month 18: any pharmacodynamic assessment performed between 16.5 to 20 months (e.g. 503 to 608 days) after the first dose of AUTO2.
- Month 24: any pharmacodynamic assessment performed between 20 to 24.5 months (e.g. 609 to 746 days) after the first dose of AUTO2.

No other programmatic windowing of visits will be considered for safety data. Post-baseline data will be presented according to the visit at which it was collected on the eCRF or as described in this SAP.

6.5 BASELINE

Baseline is defined as the last non-missing value/result where assessment date is less than or equal to the date of first pre-conditioning treatment, unless otherwise specified for individual assessments or below. Baseline will be determined based on all assessments, including additional assessments.

Change from baseline is defined as the difference between the post-baseline assessment value and the baseline value.

6.6 REPORTING GUIDELINES

The following guidelines will be followed:

- **Page Orientation:** Landscape.
- **Post-text listings**: will be generated in .lst and converted to rtf and converted to PDF.
- **Post-text tables**: will be generated using ODS rtf and converted to PDF.
- **Post-text figures**: will be generated directly in .rtf and converted to PDF.

- **Font**:
  - Listings will use Courier New font with minimum of 8-point font size.
  - Tables will use Arial font with a font size of 9.
  - Figures will use Times New Roman font with a font size of 10.
- **Margins**: Left: 3.8 cm, Right: 2 cm, Top: 3 cm, Bottom 2 cm on A4 paper.
- **Columns header** will be left aligned.
- **Treatment labels for Phase I** will be the following and displayed in the following order, unless otherwise stated:
  - 15x10^6
  - 75x10^6
  - 225x10^6
  - 600x10^6
  - 900x10^6
  - Phase I screening only
  - Phase I pre-conditioning only

  In addition, the label 'Overall' will be defined to display the data/results for all subjects combined of an analysis set.
- **Visit labels**: the visit labels displayed in Table 2 will be used as required.

Table 2: Visit Labels

Study Stage	CRF Visit	Tables, Figures and Listings Label
Screening and Leukapheresis	Screen 1	SCR1
	Leukapheresis	Leukapheresis
	Screen 2	SCR2
Re-Treatment Screening and Leukapheresis	Re treat Leukapherisis	Re-TRT Leukapheresis
	Re treat Screen 2	Re-TRT SCR2
Pre-conditioning	Pre-conditioning Day -6	PRE-COND Day -6
	Pre-conditioning Day -5	PRE-COND Day -5
	Pre-conditioning Day -4	PRE-COND Day -4
Treatment phase	Treatment - 1st dose: Day 0	TRT Day 0
	Single Dose: Day 1	Single Dose: Day 1
	Single Dose: Day 3	Single Dose: Day 3
	Single Dose: Day 5	Single Dose: Day 5
	Single Dose: Day 7	Single Dose: Day 7

Study Stage	CRF Visit	Tables, Figures and Listings Label
	Single Dose: Day 9	Single Dose: Day 9
	Prolonged Hospitalization	Prolonged Hospitalization
	Single Dose: 1 week after discharge	Single Dose: 1w
	Single Dose: 2 weeks after discharge	Single Dose: 2w
	Single Dose: 3 weeks after discharge	Single Dose: 3w
	Single Dose: End of DLT period	Single Dose: End DLT
	Treatment – 2nd dose	Second Dose
Re-Treatment Pre-conditioning phase	Re treat Pre-conditioning Day -6	Re-TRT PRE-COND Day -6
	Re treat Pre-conditioning Day -5	Re-TRT PRE-COND Day -5
	Re treat Pre-conditioning Day -4	Re-TRT PRE-COND Day -4
Re-Treatment phase*	Re treat - 1st dose: Day 0	Re-TRT Day 0
	Re treat Single Dose: Day xx	Re-TRT Single Dose: Day xx
	Re treat Single Dose: 1 week after discharge	Re-TRT Single Dose: 1w
	Re treat Single Dose: 2 weeks after discharge	Re-TRT Single Dose: 2w
	Re treat Single Dose: 3 weeks after discharge	Re-TRT Single Dose: 3w
	Re treat Single Dose: End of DLT period	Re-TRT Single Dose: End DLT
Follow-up phase	Follow-up Phase: Month 2	FU (M2)
	Follow-up Phase: Month 3	FU (M3)
	Follow-up Phase: Month 4	FU (M4)
	Follow-up Phase: Month 5	FU (M5)
	Follow-up Phase: Month 6	FU (M6)
	Follow-up Phase: Month 8	FU (M8)
	Follow-up phase: Month 10	FU (M10)
	Follow-up phase: Month 12	FU (M12)
	Follow-up phase: Month 15	FU (M15)
	Follow-up phase: Month 18	FU (M18)
	Follow-up phase: Month 24	FU (M24)
	Early Withdrawal	Early Withdrawal
	End of Study	EoS
*Days corresponding to the visits during the Re-Treatment phase are same as the days corresponding to the visits during the Treatment phase.		

- **Unscheduled visit / repeat assessments**: Data obtained at unscheduled or repeat assessments will be included in time to event analyses, baseline determination and best overall response summaries based on windowed visits. For safety data during the DLT period, the 'worst' observed value (including unscheduled or repeat assessments) will be summarized. All other data from unscheduled or repeat assessment will not be included in summaries but only be presented in data listings, if not otherwise specified.
- Data collected during re-treatment will only be listed, if not otherwise specified. An exception is for adverse events, where all adverse events will be included in summaries under the **planned** dose for the treatment period. Therefore, if a patient is re-treated under a higher dose of AUTO2, then AEs beginning after re-treatment with the higher dose will be summarized under that dose level, and all AEs up until the re-treatment summarized under the initial dose level.
- **N:** The number of patients in the specified population and cohort.
- **Treatment presentation:** The summaries for Phase I will be presented by cohort and overall.
  In some cases, also a screening only column (including patients that discontinued or withdrawn before the pre-conditioning treatment) and pre-conditioning only column (including patients that discontinued or withdrawn between pre-conditioning treatment and start of AUTO2 infusion) will be considered for phase I summaries.
- **Continuous data** will be summarized using number of patients (n), mean, standard deviation (SD), median, minimum value, maximum value and number of missing data (if there are any).
- **Categorical data** will be summarized using n and percentage based on number of non-missing data.
    - All categories will be presented, even if no patients are counted in a particular category.
    - In case 1 or more patients have missing data for the summary, the number of missing data will be presented as a separate category, labelled accordingly as 'Missing', if not otherwise stated.
    - Counts of zero in any category will be presented without percentage.
    - All summaries percentages will be calculated using the number of patients with an assessment, unless otherwise stated.
    - For AEs, medical history, prior and concomitant medications the counts are based on single counts of patients with multiple events/treatments under same category, while the percentages are calculated using N.

- **Precision of summary statistics:**
  - Integer – Sample size (n, N) and number of missing data (if displayed);
  - One additional decimal place than reported/collected – mean, median, other percentile, confidence interval;
  - Two additional decimal places than reported/collected – standard deviation;
  - Same number of decimal places as reported/collected – minimum, maximum;
  - Percentages – one decimal place.
- **Study day, as displayed in TFLs:** Will be calculated with reference to first AUTO2 infusion date as Day 0 for consistency with the protocol. This will be derived as: (assessment date – date of first AUTO2 infusion). This will be the study day as presented in the TFLs.
- **Study day, for inclusion in CDISC compliant datasets:** Will be calculated with reference to first AUTO2 infusion date as Day 1. It will be included in CDISC compliant datasets only and will not be displayed in TFLs. This will be calculated as (assessment date – date of first AUTO2 infusion) + 1 if it's on or after first date of AUTO2 infusion, or (assessment date – date of first AUTO2 infusion) if it is prior to AUTO2 infusion.
- **DLT period:** 28 days after AUTO2 dose.
- Data will be presented in listings by study phase and cohort. The order will be subject ID, visit, assessment date/time and assessment type/parameters (in order collected on e-CRF, unless otherwise specified). In case of clinical laboratory results, the listings will be presented in order of study phase and cohort, subject ID, parameter, assessment date/time, visit.
- Dates will be presented in format YYYY-MM-DD.
- The SAS system version 9.4 (or higher), will be used for all analysis, unless otherwise specified.
- Version 4.03 of the NCI-CTC grading criteria (CTCAE v4.03) will be used for relevant tables. The version will be documented in the footnote of the corresponding TFLs.
- Latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used for relevant tables. The version will be documented in the footnote of the corresponding TFLs.
- Latest version of the WHODDE WITH HERBALS (WHOHD-B3) dictionary will be used for prior and concomitant medication coding. The version will be documented in the footnote of the corresponding TFLs.

- File naming: Each TFL output file will be named with a t, l or f to denote the output type and then according to its table numbering, domain and analysis set in the following way: Table 14.1-2.1.2 will be t14_1_2_1_2_DM, Listing 16.2.7-1.1 will be l16_2_7_1_1_AE, and Figure 14.3-1.2 will be f14_3_1_2_PD.
- In the event of a data cut-off, the rules as defined in Appendix D will be considered in order to determine which data will be included in the analysis.

7 Analysis Sets

7.1 ANALYSIS SETS

Full analysis set (FAS)

The full analysis set will consist of all patients enrolled into the study, regardless of whether or not they receive pre-conditioning therapy of cyclophosphamide and fludarabine or receive AUTO2 therapy.

Safety analysis set for the study treatment

All patients who receive at least 1 dose (complete or partial dose) of AUTO2 therapy will be included in the safety analysis set for the study treatment.

Infused set

All patients who receive at least 1 dose (complete or partial dose) of AUTO2 therapy will be included in the infused set.

7.2 PROTOCOL DEVIATIONS

The full list of types of protocol deviations (PDvs) and their relation to the analysis sets, along with the method of identification of each protocol deviation, are detailed in the protocol deviation criteria form which is separate to this SAP. This will be used as a basis for identifying patients with protocol deviations throughout the study.

Protocol deviations noted during the trial will be tracked throughout the study by Autolus. The PDvs will be read into SAS® prior to reporting.

Prior to database lock, PDs will be reviewed and agreement of the final analysis populations made.

Important protocol deviations will be summarized by deviation category for phase I.
A listing of all reported protocol deviations (with both major and minor importance) by patient will also be provided along with the deviation verbatim term and deviation date.

8 Methods of Analyses and Presentations

8.1 SUBJECT DISPOSITION

For phase I, the subject disposition summary will be presented overall on the FAS. Overall will include all patients enrolled into the study.
The subject disposition summary will display the number and percentage of patients belonging to each of the following categories (if there is at least one patient counted in the category):

- Patients screened in the study;
- Reasons for discontinuation for the patients discontinued before leukapheresis;
- Patients leukapheresed;
- Reasons for discontinuation for the patients discontinued between leukapheresis and pre-conditioning;
- Patients started pre-conditioning;
- Reasons for discontinuation for the patients discontinued before AUTO2 infusion;
- Patients AUTO2 infused;
- Patients completed study;
- Reasons for discontinuation for the patients discontinued after AUTO2 infusion;

Information on analysis populations, study completion and reasons for discontinuation will also be displayed in a listing.

For phase I, the number and percentages of patients in each analysis set defined in Section 7 will be presented by cohort and overall as well as for the patients who had screening only and pre-conditioning only.

8.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

For phase I, the following demographic and baseline characteristics will be summarized by cohort and overall on the Infused set:

- Age;
- Age group (<65 years, ≥65 years)
- Gender;
- Race;
- Ethnicity;
- Weight;
- ECOG performance at study entry

Height and Body Surface Area (BSA) will be listed only.

For phase I, the following multiple myeloma disease characteristics will be separately summarized by cohort and overall on the Infused set:

- Stage at initial diagnosis;
- Refractory;
- Stage at presentation;
- Histological confirmation of disease diagnosis;
- Cytogenetic markers;
- Time between initial diagnosis and informed consent, derived as number of months between the initial diagnosis date to informed consent date:
  (date of informed consent – date of initial diagnosis)/30.4375;
- Time between most recent relapse/confirmation of disease and informed consent, derived as number of months between the most recent relapse/confirmation of disease date to informed consent date:
  (date of informed consent – date of most recent relapse/confirmation of disease)/30.4375.

In addition, listings of the above data will be produced.

8.3 PRIOR MULTIPLE MYELOMA TREATMENTS

For phase I, a summary table of prior multiple myeloma treatments (therapies and procedures) will be produced by cohort and overall on the Infused set.

The counts presented in the summaries will be based on single counts of patients with multiple prior therapies/procedures under the same preferred term and Anatomical Therapeutic Chemical (ATC) level 4 grouping.

All therapies will be counted for the number of lines of therapy of each individual patient.

A similar summary will be produced separately for refractory patients only.

Listings of all prior multiple myeloma treatments, including the line of therapy with prior stem cell transplant, will be produced.

8.4 MEDICAL HISTORY

Medical histories and concomitant diseases will be coded using MedDRA.

Listing of medical history data will be produced.

A separate listing presenting surgical and medical procedures will also be provided.
In addition, a listing of new medical history events since enrolment that are related to multiple myeloma will be presented.

8.5 PRIOR AND CONCOMITANT MEDICATIONS

Medications other than the study treatment (including leukapheresis related medications, pre-conditioning related medications and AUTO2 related medications) will be coded using the WHODDE WITH HERBALS (WHOHD-B3) dictionary. Medications will be defined as follows:

- Prior Medication: Any medication whose medication end date is before the first AUTO2 infusion date.
- Concomitant Medication: Any medication whose medication start or end date is either the same as or after the first AUTO2 infusion date.

Any medication with a missing medication end date will be assumed to be concomitant medication. Ongoing medications will also be considered as concomitant medications.

A listing of prior and concomitant medications will be presented.
A separate listing presenting concomitant immunoglobulin therapy will also be provided.

8.6 BRIDGING THERAPIES

Patients may receive bridging therapy while the product is being manufactured. These therapies should also have an adequate washout as indicated in exclusion criterion 22.

If needed, new anti-cancer medications or new anti-cancer radiotherapy since enrolment can be administered between screening and pre-conditioning therapy.

A summary of bridging therapies (therapies between informed consent up to AUTO2 dosing) will be produced on the Infused set.

The new anti-cancer medications and new anti-cancer radiotherapies details will be presented in separate listings.

8.7 IMMUNOGLOBULIN THERAPIES

If needed, intravenous immunoglobulin therapy (IVIG) can also be administered to the patients. Immunoglobulin administration details will be presented in a listing.

8.8 LEUKAPHERESIS

A listing of leukapheresis details will be presented.

Leukapheresis-related medications will be presented with the prior and concomitant medications.
All the reasons why patients did not continue in the next study phase (pre-conditioning) will be summarized in the disposition table.

8.9 STUDY TREATMENT

Pre-Conditioning: Fludarabine and Cyclophosphamide

All the reasons why leukapheresed patients did not receive pre-conditioning will be summarised in the disposition table.

A listing of pre-conditioning treatment administration with Fludarabine and Cyclophosphamide will be presented. Pre-conditioning related medications will also be listed.

Exposure to pre-conditioning treatment (Fludarabine and Cyclophosphamide) is assessed through cumulative dose (in mg and mg/m^2) which will be summarized. For the calculation of the cumulative dose (in mg/m^2), the cumulative actual dose (in mg) will be divided by the patient's BSA as collected at Day -6 visit (or at Screen 1 visit if the patient's BSA was not collected at Day -6 visit).

The planned number of Fludarabine and Cyclophosphamide administrations is 3.
The actual number of administrations for each drug, as well as any delays in administrations and any dose reductions with the associated reasons, will be summarized.
For the two subjects re-treated in the study, the data collected for the pre-conditioning Fludarabine and Cyclophosphamide treatments prior to the re-treatment dose will **not** be summarized in tables, and only listed as appropriate.

If the actual dose is lower than the planned dose then it will not be counted as a dose reduction if the dose administration was noted as per protocol as assessed by the investigator.

8.10 STUDY DRUG EXPOSURE AND COMPLIANCE

The number (percentage) of subjects who have had pre-conditioning but not AUTO2, and the reason for not receiving AUTO2, will be summarized in the disposition table.

Days from leukapheresis to first AUTO2 infusion will be calculated as [(Date of first AUTO2 treatment – Date of last leukapheresis) + 1] and summarized.

The following durations will be calculated for each infused bag and summarized:

- Thawing duration calculated in minutes from the start time of thaw to the start time of infusion;
- Infusion duration calculated in minutes from the start time of infusion to the end time of the infusion.

The above-mentioned durations will be calculated for each bag in the event that multiple bags have been administered to a patient. The corresponding durations for each bag will be summarized.

For AUTO2 infusion exposure summary statistics will be presented for the following:

- Number of cells administered to the patient;
- Percentage of patients receiving planned dose, which is defined by an amount of 80-120% of percentages of cells administered from the planned dose. All patients that received less the 80% of cells administered from the planned dose will be considered as not received the planned dose.

The number of days between the last pre-conditioning treatment and the first AUTO2 treatment will be summarized. The number of patients with delay in starting AUTO2 and the reason for delay will be summarized.

Re-treatment will not be considered for the above calculations (thawing duration, infusion duration, number of cells manufactured, percentages of the manufactured dose from the planned dose, number of cells administered, percentages of cells administered from total planned dose).

In addition, the number and corresponding percentages of patients that had a single dose, split dose and re-treatment will be presented.

For phase I, summaries will be presented by cohort on the safety analysis set for study treatment.

Details of AUTO2 infusion administration and treatment exposure will be listed.

AUTO2-related medications will be listed and summarized.

All re-treated patients will be presented in a listing. The listing will include information regarding the dates when AUTO2 infusion was administered, during main treatment and also re-treatment.

8.11 FOLLOW-UP TIMES

Follow-up time will be calculated for each patient using the following formula:

> Follow-up time (months) = [(Date of last follow-up visit when patient was known alive (or date of death (if applicable)) – Date of first AUTO2 treatment) + 1]/ 30.4375 days

In case of a long-term follow-up patient, follow-up visits dates from the long-term follow-up study will be used for the above calculation.

For phase I, follow-up times will be summarized on the safety analysis set for study treatment.

8.12 EFFICACY DATA ENDPOINTS AND ANALYSES

Tumour response will be assessed using the following IMWG uniform response criteria for MM guidelines:

- 2011 IMWG guideline, as presented in Appendix B1 for all response assessments done before v.4.0 of the protocol.
- 2016 IMWG guideline, as presented in Appendix B2 for all response assessments done from v.4.0 of the protocol onwards.

The investigators assessment of tumor response will be considered for all efficacy analyses. Disease evaluation will be performed to assess disease status at the end of DLT period, at Month 2, Month 3, Month 4, Month 5, Month 6, Month 8, Month 10, Month 12, Month 15, Month 18 and Month 24 (end of study), until disease progression. All post-baseline response assessments will be considered for the analyses (unless otherwise stated).

A listing will be provided detailing the disease assessment IMWG response for each patient at each visit. As part of the disease assessments, soft tissue plasmacytomas evaluation will be also presented in the same listing.

The following myeloma protein measurements in serum and urine will also be listed:

- Serum quantitative immunoglobulins (QIgs): IgG, IgA, IgM;
- Serum M-protein quantitation by serum protein electrophoresis (SPEP) measured through paraprotein quantity at screening visit, Day 0 and then at every visit (with a minimum of 4 weeks between 2 consecutive measurements);
- Serum immunofixation at Screening and thereafter when a CR is suspected;
- Serum free light chain (SFLC) assay (both kappa and lambda), performed at screening and repeated at every visit (with a minimum of 4 weeks between 2 consecutive measurements) for patients who are serum free light chain positive i.e. light chain positive MM or when CR is suspected or maintained;
- Paraprotein in urine (UPEP) measured through light chain Quantity.

β2-microglobulin will be listed.

Bone marrow aspirate results and biopsy findings will also be listed.

8.12.1 Subgroup Analysis

Not applicable.

8.13 PHARMACOKINETIC ENDPOINTS AND ANALYSES

Not applicable.

8.14 CAR-T CELLULAR KINETICS

Blood-based CAR-T cellular kinetics markers will be evaluated for infused patients.

The qPCR assays in whole blood (expressed in /ug DNA) in will be presented in a listing.
Post-infusion kinetics of CAR T-cells in the blood (qPCR) will be presented using profile plot.

8.15 QUALITY OF LIFE OR PHARMACOECONOMIC ENDPOINTS AND ANALYSES

Not applicable.

8.16 SAFETY DATA ENDPOINTS AND ANALYSES

8.16.1 Adverse Events (AEs)

Adverse events will be coded using the MedDRA coding system. The version of the dictionary will be provided in the adverse events TFLs footnotes.

Treatment-emergent adverse event for study treatment (TEAE1) is defined as any AE that occurs during or after administration of AUTO2 up to 60 days after each AUTO2 infusion, any event that is considered drug-related (to AUTO2 treatment) regardless of the start date of the event, or any event that is present at baseline and continues after the first dose of AUTO2 but worsens in intensity.

The maximum severity of TEAEs will be determined by using the NCI CTCAE toxicity grading.
The CTCAE version will be provided in the footnotes of the relevant adverse events TFLs.

AEs that are considered related to Cyclophosphamide, Fludarabine and/or AUTO2 treatment (possibly, probably, or definitely related) will be collected accordingly on the eCRF.

Any AE that is present at baseline but worsens in intensity after the first dose of study treatment should be entered into the eCRF as different AE record with the differing grade recorded.

The number and percentage of patients will be summarized by System Organ Class (SOC) and Preferred Term (PT). Patients will be counted only once within each SOC and PT by dose level. Patients who are re-treated will have their AEs following re-treatment summarized as described in Section 6.6. SOCs will be presented in alphabetical order, while PTs will be presented in alphabetical order within each SOC. The following summaries will be presented:

- All TEAEs from start of AUTO2 treatment
- TEAEs related to AUTO2 treatment
- Serious TEAEs
- DLT TEAEs
- TEAEs of special interest (CRS TEAEs and neurotoxicity TEAEs as described in Section 8.16.2)

Summaries of TEAEs, CRS TEAEs and neurotoxicity TEAEs by SOC, PT, and maximum severity will be produced. Patients will be counted only once within each SOC, PT, severity grade and dose level.

For phase I, all summaries will be presented by cohort and overall on the safety analysis set for the study treatment.

All information on AEs will be listed.

Separate listings of TEAEs, SAEs, and DLT AEs will be provided.

In addition, the activation of safety switch details will be presented in a listing.

For patients that were re-treated, separate listings of AEs and DLT AEs will also be produced.

8.16.2 AEs of special interest (AESIs)

The following are defined as AEs of special interest (AESIs):

- CRS AEs
- Neurotoxicity AEs (including depressed level of consciousness, dysphagia, ataxia, seizures, and cerebral oedema)

8.16.2.1 CRS AEs

Summaries similar to those for TEAEs by SOC, PT and maximum severity will also be presented for CRS TEAEs considering the associated maximum CRS severity (as determined by the CRS grading).

8.16.2.2 Neurotoxicity AEs

Summaries similar to those for TEAEs by SOC, PT and maximum severity will also be presented for neurotoxicity TEAEs.

8.16.3 Clinical Laboratory Evaluations

Laboratory results will be presented in separate listings for all haematology, coagulation and biochemistry (including ferritin and C reactive protein) parameters.

In addition, infectious disease screen results will be presented in a listing.

A listing displaying the pregnancy test results will also be presented.

8.16.4 12-lead Electrocardiogram (ECG)

ECG assessments will be performed during Screening 1, on Day 0 of the treatment phase with AUTO2 infusion and at the end of the DLT period.

The heart rate, PR, RR, QRS duration, QT intervals, and corrected QTc intervals will be collected.

All ECG assessment measurements will be listed.

8.16.5 Echocardiogram (ECHO) or Multiple Gated Acquisition (MUGA)

Echocardiogram (ECHO) is the preferred method to assess cardiac ejection fraction and cardiac valve abnormalities (to note, Multiple Gated Acquisition (MUGA) is an acceptable alternative). Assessments will be performed at Screening and will include an evaluation for left ventricular ejection fraction (LVEF). Additional ECHO/MUGA assessments may be performed as clinically indicated.

All LVEF results from ECHO or MUGA assessments will be listed.

8.16.6 Vital Signs

Temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate will be recorded while the patient is in a seated position. On Day 0 of any treatment phase, vital signs will be recorded immediately prior to AUTO2 infusion and every 15 min (± 5 min) for the 1st hour and every 30 minutes (± 10 min) for the next 3 hours post AUTO2 infusion.

All vital signs measurements will be listed.

8.16.7 Physical Examination

A complete physical examination will be conducted at screening. In addition, physical examination will be conducted at subsequent visits during treatment and follow-up phases.
Any detected abnormalities will be recorded as adverse events and will be summarized and listed as described in section 8.13.1.
No separate listing of physical examination data will be produced.

8.16.8 ECOG Performance Status

ECOG performance status will be assessed at screening, during pre-conditioning phase, at the end of DLT period, during follow-up phase at months 2, 3, 4, 5, 6, 8, 10, 12, 15, 18 and 24 and at end of study.

All ECOG performance assessments will be listed.

8.16.9 Death information

For phase I, the number and percentage of deaths and the primary reason for death will be presented by cohort and overall on the safety analysis set for the study treatment.

All patients who died and their reason for death will also be listed.
Any death having occurred in the long-term follow-up study will be included in the summary and listing.

Separately, a listing will be produced to present survival status of patients based on corresponding data collected during both the AUTO2-MM1 study and the AUTO-LT1 long-term follow-up study displaying the most recent survival status only.

9 Interim Analyses

Given the premature termination of the study, the interim analyses initially planned for phases I and II will not be performed.

10 Development safety update report

A development safety update report (DSUR) will include safety data. DSUR is intended to serve as an annual report to regulatory authorities at the DSUR anniversary of the study. DSUR anniversary is the date of first authorization anywhere in the world. DSUR shells will be created in a separate document.

11 Changes to Planned Analyses

The following are changes to the planned analyses from that stated in the protocol Version 7.0 (27 Jun 2018):

- Given the premature termination of the study, the following decisions have been made:

  - Only the primary objectives defined for Phase I and the secondary study objectives (see Section 4) will be taken into consideration for the final analysis.

  - Only listings will be produced for efficacy endpoints/data.
  - The interim analyses initially planned for phases I and II will not be performed.
- The Efficacy analysis set defined in the protocol has been renamed Infused set.

12 Document History

Date	Version	Modified by	Brief details of changes made to template
21APR2020	1.0	[redacted]	Initial final version of SAP

13 References

[1] Simon, R., B. Freidlin, et al. (1997). "Accelerated titration designs for phase I clinical trials in oncology." J Natl Cancer Inst 89(15): 1138-1147.

[2] (CTCAE v4)
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

14.2 APPENDIX B1 – International Myeloma Working Group (IMWG 2011) response criteria for multiple myeloma for documenting disease response (pre v4.0 protocol)

Response	IMWG
Stringent clinical response	Complete response as defined below plus normal free light chain (FLC) ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence [a].
Complete response (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow [b].
Very good partial response (VGPR)	Serum and urine monocloncal protein (M-protein) detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 hours.
Partial response	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥ 90% or to < 200 mg/24 hours. If the serum and urine M-protein are unmeasurable [c] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%. In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal Response	≥25 but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50 to 89%. If present, a 25 to 49% reduction in the size of soft tissue plasmacytomas is also required.
No change/Stable disease	Not meeting criteria for CR, VGPR, partial response, or progressive disease.
Progressive disease[d]	Increase of ≥ 25% from lowest response value in any 1 or more of the following: Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL) [d] Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 hours) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL.

Response	IMWG
	Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%[e] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas. Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.
Relapse	Clinical relapse requires 1 or more of: Direct indicators of increasing disease and/or end organ dysfunction (Calcium elevation, Renal insufficiency, Anaemia and Bone abnormalities). It is not used in calculation of time to progression or progression-free survival] but is listed here as something that can be reported optionally or for use in clinical practice. Development of new soft tissue plasmacytomas or bone lesions. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. Hypercalcaemia (> 11.5 mg/dL) [2.65 mmol/L] Decrease in haemoglobin of ≥ 2 g/dL [1.25 mmol/L] Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]
Relapse from CR [c] (To be used only if the end point studied is disease free survival) [f]	Any 1 or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis. Development of ≥ 5% plasma cells in the bone marrow [e]. Appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion, or hypercalcaemia).

CR=complete response; FLC=free light chain; M-protein=monoclonal protein; PR=partial response; VGPR=very good partial response.
Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. Very good partial response in such patients is defined as a >90% decrease in the difference between involved and uninvolved FLC levels.

[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.
[b] Confirmation with repeat bone marrow biopsy not needed.
[c] All relapse categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free

survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.
[d] For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.
[e] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.
[f] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

14.3 APPENDIX B2 – International Myeloma Working Group (IMWG 2016) response criteria for multiple myeloma for documenting disease response (from v4.0 protocol onwards)

Response Category*	**IMWG Criteria**
Stringent clinical response	Complete response as defined below plus normal free light chain (FLC) ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence [a].
Complete response (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas[b] and <5% plasma cells in bone marrow [c].
Very good partial response (VGPR)	Serum and urine monoclonal protein (M-protein) detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 hours.
Partial response	≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 hours. If the serum and urine M-protein are unmeasurable a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas (SPD) is also required..[b]
Minimal Response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50 to 89%. If present, a 25% to 49% reduction in the size of soft tissue plasmacytomas is also required.[b]
No change/Stable disease	Not meeting criteria for CR, VGPR, partial response, minimal response or progressive disease.
Progressive disease[d,e]	Increase of ≥25% from lowest response value in any 1 or more of the following: Serum M-component and/or (the absolute increase must be ≥0.5 g/dL) Serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M- component is ≥5 g/dL Urine M-component and/or (the absolute increase must be ≥200 mg/24 hours)

Response Category*	IMWG Criteria
	Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL. Bone marrow plasma cell percentage; the absolute percentage must be ≥10%[f] Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis [b] ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease.
Clinical Relapse	Clinical relapse requires 1 or more of: Direct indicators of increasing disease and/or end organ dysfunction (Calcium elevation, Renal insufficiency, Anaemia and Bone abnormalities). It is not used in calculation of time to progression or progression-free survival] but is listed here as something that can be reported optionally or for use in clinical practice. Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression). Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the SPD of the measurable lesion. Hypercalcaemia (>11 mg/dL); Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from CR [d] (To be used only if the end point studied is disease free survival) [g]	Any 1 or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis. Development of ≥5% plasma cells in the bone marrow [f] Appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion, or hypercalcaemia).

CR=complete response; FLC=free light chain; M-protein=monoclonal protein; PR=partial response; SPD=sum of the products of the maximal perpendicular diameters; VGPR=very good partial response.
*All response categories require two consecutive assessments made any time before starting any new therapy
Note: A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. Very good partial response in such patients is defined as a >90% decrease in the difference between involved and uninvolved FLC levels.

[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is

kappa/lambda of >4:1 or <1:2.

[b] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler

[c] Confirmation with repeat bone marrow biopsy not needed.

[d] All relapse categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of clinical relapse, relapse from CR and relapse from MRD are not to be used in calculation of time to progression or progression-free survival.

[e] In the case where a value is felt to be a spurious result per physician discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.

[f] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

[g] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

14.4 APPENDIX C – Clinical Laboratory Tests Performed by Local Laboratory

Assessment	Description
Haematology	Haemoglobin, red blood cell count, platelet count, white blood cell count with differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils).
Coagulation	Prothrombin time, international normalised ratio, activated PTT, fibrinogen.
Biochemistry	Sodium, phosphate, potassium, ALT, AST, creatinine, CPK, lactate dehydrogenase, total bilirubin, calcium, total protein, albumin, glomerular filtration rate and creatinine clearance performed only at screening.
CRP and Ferritin	Ferritin and C-reactive protein.
Pregnancy test	Serum (β-human chorionic gonadotropin) or urine pregnancy testing for women of childbearing potential.
Serology (at screening only)	• Human immunodeficiency virus antibody. • Hepatitis B core antibody: if positive, further testing (deoxyribonucleic acid by PCR) to rule out active disease or chronic carrier. Must be confirmed negative prior to screening. • Hepatitis C virus antibody: if positive for hepatitis C virus, further testing (by RNA PCR) should be performed to rule out active infection. • Anti-human T-lymphotropic virus-1. • Anti-human T-lymphotropic virus-2. • Syphilis Serology.

AST=aspartate aminotransferase; ALT=alanine aminotransferase; CPK=creatine phosphokinase; PCR=polymerase chain reaction; PTT=partial thromboplastin time; RNA=ribonucleic acid.

14.5 APPENDIX D – Cut-off rules

The appendix is to document the rules that will be considered a data cut-off for an interim analysis or a publication purposes analysis. The date of the data cut-off will be referred as *dtcut* in the following.

Data entry continued after *dtcut*, and therefore data occurring after this date needs to be removed from the data included in the SDTM/ADaM datasets used to produce the TFLs.

This appendix documents the process followed to remove data from the SDTM datasets with a date after *dtcut*. The following will be performed, QC'd and the changes reviewed:

- All patients who are screened after *dtcut* will be removed from all datasets.
- All visits or assessments occurring after *dtcut* to be removed.
    - If a visit occurs after *dtcut*, but some assessments are performed prior to that date, then those assessments will be included and only partial information may be present for that visit.
- Any AEs or concomitant medications starting after *dtcut* to be removed.
- Any AEs or concomitant medications starting on or before *dtcut* but marked as ongoing will stay as is.
- Any AEs or concomitant medications starting on or before *dtcut* but marked ending/completing after *dtcut* will be presented as per available data.
- Any deaths with a date of death after *dtcut* will be removed.
- Partial dates:
    - For any partial date of with same month as the *dtcut,* the data will be included in the data cut-off.
    - For any partial date with same year as the *dtcut*, the data will be included in the data cut-off.
- Dosing records –
    - If dose administration date is after *dtcut* then remove the whole record
    - If the dose administration date is before or on *dtcut* then no change is needed

The original data will remain as is in the RAW datasets, and a modified set of SDTM datasets will be created, with the data removed or records modified as described above. The modified SDTM datasets will be used to create the ADaM datasets, and these ADaM datasets subsequently used

to create the TFLs. The individual variables to be modified in the modified version of the SDTM datasets will be documented in the SDTM mapping specifications.

14.6 Tables, Figures and Listing shells

A separate document was considered to cover the tables, figures and listings shells.

Signature Page

Signer Full Name	Meaning of Signature	Date and Time
[redacted]	Statistics Approval	23 Apr 2020 08:39:05 UTC
[redacted]	Statistics Approval	23 Apr 2020 11:11:36 UTC
[redacted]	Clinical Development Approval	23 Apr 2020 12:56:32 UTC
[redacted]	Clinical Development Approval	27 Apr 2020 16:24:15 UTC