CLINICAL TRIALS RESEARCH UNIT (CTRU)
UNIVERSITY OF LEEDS

FINAL STATISTICAL ANALYSIS PLAN

CATALYST

V1.0

MAY 2019

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Amendments

None

1. Introduction

1.1 Background

Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited as abnormal, insoluble fibrils that progressively disrupt tissue structure and impair function. Systemic AL amyloidosis, which is the commonest amyloid type, is a malignant disorder occurring in a small proportion of individuals with monoclonal B cell dyscrasias and AL amyloidosis is a myeloma defining criteria according to the international working group definition of myeloma 2003 (Kyle 2003). AL amyloidosis occurs at an incidence of 3-5 cases per million population and is the cause of death of between 0.5-1 per thousand individuals in the UK. AL fibrils are derived from monoclonal immunoglobulin light chains which are unique in each patient underlying the remarkably heterogeneous clinical picture in this particular form of amyloidosis; virtually any organ or combination of organs other than the brain may be affected. Treatment in AL amyloidosis is aimed at suppression of the underlying B cell dyscrasia using chemotherapy regimens based on those used for multiple myeloma. Without therapy it is inexorably progressive and until recently the median survival was just 6-15 months. Survival for patients who achieve a less than VGPR or refractory patients is even poorer (Palladini, Dispenzieri et al. 2012).

Many studies have demonstrated a link between hematologic responses and improved organ function and survival. Stopping the production of the toxic light chain species can translate into significant benefit for most patients except those with most advanced organ involvement, while stable hematologic disease despite therapy means it is likely that the effects of the toxic light chain species will continue. Consensus criteria for hematologic and cardiac response have been recently developed and validated (Palladini, Dispenzieri et al. 2012). Advanced cardiac and extensive organ involvement limit benefits that can be derived from treatment including eligibility for autologous stem cell transplantation (ASCT) and can shorten survival despite treatment (Merlini, Seldin et al. 2011, Cordes, Dispenzieri et al. 2012). Another treatment limitation is related to the type of organ involvement predisposing patients to the adverse effects of specific drugs. In AL amyloidosis clinical trials, it has been a challenge to distinguish drug-specific side effects from disease-mediated organ dysfunction (Comenzo, Reece et al. 2012)

Carfilzomib (PR-171) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®). In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib. There is limited data on the use of carfilzomib in AL amyloidosis, we therefore propose a gradual dose escalation study. There is an ongoing study of carfilzomib in AL amyloidosis.

Proteasome inhibitors are associated with highest response rates in AL amyloidosis. Bortezomib has toxicity and limitations in AL amyloidosis. In particular, the high specificity of carfilzomib for proteosome inhibition and it's favorable toxicity profile makes it very appealing in AL amyloidosis. For instance, toxicities which commonly complicate Bortezomib use, such as autonomic and peripheral neuropathy, appear uncommon with carfilzomib. Combination of proteosome inhibitors with Immunomodulatory Drug (IMiDs) appears to be synergistic in myeloma and the phase II data using carfilzomib with lenalidomide or thalidomide appears promising. In the UK, we have extensive experience using thalidomide in the treatment of patients with AL amyloidosis. Combining carfilzomib with thalidomide offers an attractive treatment option for patients with relapsed refractory disease due to their non-overlapping toxicity profile. Low dose thalidomide is generally well tolerated by patients with AL amyloidosis but as single agent has limited efficacy. However, in combination with other agents, response rates are high as we have documented by using risk adapted CTD regime. This study is designed to improve the response rates seen with CTD protocol by using carfilzomib in combination with thalidomide and dexamethasone.

1.2 Design

This will be a single arm open label multicentre phase Ib dose escalation study with expansion phases.

Patients will receive treatment with Carfilzomib in escalating dose cohorts along with a fixed dose of Dexamethasone and Thalidomide (KTD). The dose escalation phase of the study will use a 3+3 dose escalation design. Cohorts of 3-6 participants will be treated with KTD as outlined in the Section 8. Carfilzomib doses will be increased between cohorts until the occurrence of dose limiting toxicities (DLTs) define the MTD. The Safety Review Committee will review the safety and ethics of the trial by reviewing interim data after each cohort of treatment during recruitment to the Dose Escalation Cohort. Once the MTD and/or RD has been established a maximum of 20 participants will be recruited for entry into the expansion phase of the study at the RD.

1.3 Aims

The Catalyst (*Ca*rfil-*t*hal-Dex in *AL t*reatment) Trial aims to assess the safety and tolerability of KTD (Carfilzomib-thalidomide-dexamethasone) using the phase 1 dose escalating component to define the maximum tolerated dose (MTD) and recommended dose (RD) and the expansion cohort to further assess the safety and tolerability and to gain an understating of efficacy to allow design for further trials.

Primary:

Dose escalation

To define the MTD and RD of Carfilzomib used in combination with Thalidomide and Dexamethasone in patients with relapsed or refractory AL amyloidosis

Dose expansion

To further assess the safety and tolerability of KTD at the RD of Carfilzomib identified in the dose escalation phase

Secondary:

To make a preliminary assessment of the activity of KTD in patients with relapsed refractory AL amyloidosis

1.4 Sample size and expected accrual

In the dose escalation phase of this study, a minimum of 6 (3 at dose level 0 and 3 at dose level -1) and a maximum of 18 (6 at dose level 0 1 and 2) patients will recruited in a 3+3 design with cohorts of between 3 and 6 patients, in order to determine maximum tolerated dose and recommended dose.

At the recommended dose level identified, a further 20 patients will be recruited to further assess safety and toxicities at the RD.

The study will run in 15 UK centres. The study duration is expected to be approximately 42 months – including 6 months of set up, 24 months of recruitment, 6 months of follow-up and 6 months of analysis/write-up.

1.5 Planned analyses

During the Dose Escalation Phase, recruitment will be halted after each group of three patients have completed at least one cycle of KTD, to allow safety data to be assessed. CTRU will produce a summary of DLTs at each dose level, detailed safety listings, and recruitment figures for consideration by the Safety Review Group.

No formal analyses are planned until after the trial is closed to recruitment and the required number of patients has been recruited. Final analysis will be carried out when the required number of patients has been recruited and all patients have been followed up for at least 6 months from registration.

2. Endpoints

2.1 Primary endpoint

Dose-Limiting Toxicities (Dose escalation phase), between the time of receiving the first registered dose of Carfilzomib in cycle 1 and day 1 cycle 2, in order to establish the Maximum Tolerated Dose (MTD) and recommended dose (RD) of Carfilzomib in combination with Thalidomide and Dexamethasone.

Proportion of patients treated who experience any grade 3 or 4 CTCAE toxicity throughout all treatment cycles.

2.2 Secondary endpoints

- Clonal response rate within 3m, at 3m, within 6m and at 6m
- Amyloidotic organ response rate within 3m and 6m
- Time to amyloidotic organ response
- Number of deaths at 6 months
- Number of patients progression free at 6 months
- Maximum response
- Time to maximum response
- Number of patients withdrawing from treatment
- Number of patients experiencing dose delays, and compliance profile of KTD.
- Relative Dose intensity

2.3 Derivation of endpoints

2.3.1 Primary endpoints

Dose limiting toxicities (DLTs) will be collected from the time of receiving the first dose of Carfilzomib in cycle 1 up to the first dose of treatment administered in cycle 2. Only DLTs that are attributed to the registered dose of Carfilzomib will be included when determining the MTD. A DLT will be defined as any of the following events that are determined to be related to trial drug administration:

1. Any non-haematological toxicity ≥ Grade 3 according to NCI CTCAE Version 4.03 which fails to return to ≤Grade 1 or baseline after 7 days. Nausea, vomiting, diarrhoea and electrolyte imbalances will be considered DLTs only if they reach ≥ Grade 3 severity despite adequate supportive care measures. Similarly, fluid retention or worsening symptoms of heart failure will be considered as DLTs if they are persistent ≥Grade 3 despite increase in oral diuretics or there is an increase in dyspnoea by ≥ 2 NYHA grades within 12 hours of administration of Carfilzomib which persists for > 6 hours or needs hospital admission
2. Grade 4 neutropenia lasting > 7 days or Grade 4 neutropenia with sepsis despite adequate supportive measures.
3. Any grade 4 thrombocytopenia which fails to return to Grade 2 within 7 days without platelet support
4. Delay of >8 days within cycle 1 or delay of commencement of 2nd cycle by more than 14 days, due to significant toxicity or tolerability issue*
5. Any other event which, in the opinion of the Safety Review Committee, is considered to be clinically significant and related to treatment

The MTD is defined as the highest dose level at which no more than 1 patient experiences a DLT, from the time of receiving the first registered dose of Carfilzomib in cycle 1 up to the first dose of treatment administered in cycle 2, i.e. the dose level below that at which 2 or more patients experiences a DLT. If no more than one patient experiences a DLT at the highest dose level then this will be considered as the MTD.

Once the MTD has been established, a minimum of 6 patients will be treated at this dose level in order to establish the RD. The RD is the dose which will be used in the dose expansion phase of the study to evaluate activity.

The proportion of patients treated who experience any grade 3 or 4 CTCAE toxicity will be calculated as number of patients who experience any grade 3 or 4 CTCAE toxicity throughout their treatment cycle.

* This will not be defined as a DLT if the delay is due to one of the other specified DLT criteria.

2.3.2 Secondary endpoints

Clonal response rate (based on paraprotein and FLCs) is defined as the proportion of patients who achieve at least a PR within 3 months, at 3 months, within 6 months and at 6 months after trial registration.

Amyloidotic organ response rate is defined as the proportion of patients who achieve organ response within 3

months and within 6 months of trial registration.

Time to Amyloidotic organ response is defined as the time from the dose allocation to first achieving organ response.

The number of patients experiencing dose delays will be defined as the number of patients experiencing delays in treatment with any of the study treatments.

KTD compliance: Patients will be regarded as compliant to treatment where treatment is received as per protocol until withdrawal from treatment and have no more than 1 dose omission of Carfilzomib, 5 of Thalidomide or 1 of Dexamethasone during each cycle.

Relative Dose intensity will be calculated as the percentage ratio between the received and planned dose intensities, where dose intensity is the cumulative dose divided by the duration of treatment.

3. Analysis Sets

Statistical analysis will be descriptive for all endpoints, and will be summarised overall and by dose cohort. All safety analyses will be based upon the safety analysis set; safety data from patients not included in this analysis set will be listed separately. All efficacy analyses will be based upon the per protocol set. Patients who do meet the criteria to be included in each of analysis sets will have the reasons for emission listed. A sensitivity analysis on the efficacy endpoints may be considered if the total number of patients in each of the analysis sets differs by more than 3 patients.

3.1 Eligibility

Participants considered eligible for the study are those that fulfil all the inclusion and none of the exclusion criteria noted in the protocol. All participants in the analysis population should remain in the trial after registration unless they explicitly withdraw consent. If a participant is found to be ineligible after registration they will be included in the analysis population as appropriate unless written informed consent has not been obtained. If a participant withdraws consent from further trial treatment and / or further collection of data their samples will remain on file.

3.2 Safety analysis set

All patients that receive at least one dose of Carfilzomib and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

3.3 Per protocol set

The per protocol set will include all patients with at least one post baseline efficacy assessment who receive at least one dose of Carfilzomib and have no protocol deviations with relevant impact on efficacy.

3.4 Evaluability for determining the MTD

Determination of the MTD in the dose escalation phase of the trial will be based on those patients who have received at least one cycle KTD and will be evaluated between the time of receiving the first dose of Carfilzomib in cycle 1 and the first dose of treatment in cycle 2. The safety review committee will review each DLT and attribute the DLT to the loading dose or the registered dose; any DLT attributed to the loading dose will be excluded when determining the MTD. KTD Patients who do not receive one complete cycle due to experiencing a DLT will be included in the analysis; patients who do not receive at least one complete cycle for reasons other than toxicity, without experiencing a DLT, and who miss a dose of Carfilzomib, more than 14 doses Thalidomide or 2 doses of Dexamethasone in the first cycle, will be replaced. Evaluability will be considered by the safety review committee on an individual basis to account for attributing DLTs and missed doses to the loading or the registered dose.

3.5 Dose Cohorts

The RD cohort will include all patients who are registered to receive and receive at least one dose of Carfilzomib at the RD. This cohort will include patients from the dose escalation and dose expansion phases

of the study. All patients who do not fulfil these criteria will be included in the non-RD cohort.

4. Data Handling

4.1 Data monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. The CTRU will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU. Source data verification will involve direct access to participant notes at the participating hospital sites and the collection of copies of consent forms and other relevant investigation reports. A Trial Monitoring Plan will be developed and a Meeting Group Monitoring Schedule including primary endpoint and safety data will be defined and agreed by the Trial Management Group (TMG) if necessary.

The Safety Review Committee will be acting as the data monitoring ethics committee and will review safety and ethics of the trial as described in the protocol.

The following will also be examined continuously during the course of the trial:

- Accrual
- Data quality
- Consent
- DLTs/SAEs/SUSARs
- Withdrawal from the trial
- Pregnancy
- Protocol deviations

4.2 Data validation

The Data Manager will carry out initial validation of the forms in accordance with the guidelines developed for the study. This will ensure that data is complete, consistent and up-to-date. Reasons should be obtained when data is unobtainable.

The database will also validate most dates and data in line with the pre-programmed validation rules in real time, as data is entered. Periodic batch validation will also be carried out to detect any data queries that may be missed if CRFs are entered in an order that does not allow the real time validation checks to work.

Key data items required are those for the primary endpoints and for withdrawal information. All key data items will be checked manually by the data managers (or their delegate) at the time of final analysis. Key data items include:

- Date of randomisation/registration
- Registered dose level
- Cycle number
- Drug compliance in first cycle to confirm evaluability for determining the MTD and analysis sets
- SAE/AE data

Additionally, data regarding withdrawal of consent is also classed as key data:

- Withdrawal of consent and date

In addition the statistician will validate the data to be used in the analysis in the following steps:

- The data will be read into permanent SAS data sets using the SAS data views procedure; the names and contents of the datasets can be found on the final database specification reports in the database documentation folder.

SAS will also be used to further validate the data and identify any missing or inconsistent data. Checks to be performed include:

- Eligibility checks (if not data management validations)
- Sequential dates (if not data management validations)
- Checks for unusual and outlying data (if not database validations)
- Checks for missing data (are there items of data which are systematically missing/do specific variables

have a large amount of missing data etc) (if not database validations)
- Checks for inconsistencies in safety data
- Other checks as deemed appropriate

Any inconsistent data will be noted and an e-mail sent to the data manager responsible for the study (or their delegate). A copy of this e-mail will be kept in the statistician's trial file. All queries will be resolved, if possible in time for final analysis and the outcome documented.

5. Data Analysis

5.1 General calculations

Unless otherwise stated, percentages will be calculated using the total number of patients in the appropriate population as the denominator (i.e. including all patients with missing data for that variable). All analyses will be carried out using SAS unless stated otherwise.

All percentages and means will be rounded to 1 decimal place and standard deviations to 2 decimal places. Values that are below the limit of detection and therefore non-quantifiable will be summarised using the limit of quantification value. For listings, if required, the non-quantifiable value would be reported as an inequality.

Summaries are divided into those participants treated at the recommended dose either during the dose escalation phase (prior to the identification of the recommended dose) or during the dose expansion phase (RD population), and all other participants treated during the dose escalation phase at dose levels other than the recommended dose (Non-RD population). The non-RD population will be split by dose level.

5.2 Analysis

As defined in Section 3, data will be summarised using descriptive summary statistics only and no formal statistical testing will be carried out on any of the study endpoints.

5.3.1 Baseline characteristics

Baseline characteristics will be tabulated for all registered eligible patients using summary statistics overall and by dose.

5.3.2 Primary endpoints

The number of patients experiencing DLTs within the first cycle of KTD will be presented, with descriptive summaries of the specific DLTs observed. Summaries will be presented for each dose level. This data will be presented for patients registered to the dose escalation phase of the study only.

Further summaries of longer-term tolerability will also be presented for patients registered to the dose escalation phase to include the maximum toxicity grade experienced within the first three cycles of treatment, overall and by cycle. Individual listings of the toxicities, grade and cycle of all toxicities experienced within the first three cycles will be presented.

The number of patients experiencing any grade 3 or 4 CTCAE toxicity within all cycles of treatment will be summarised. This will be presented overall and by dose cohort, across all cycles as well as by each cycle.

5.3.2 Secondary endpoints

Safety and toxicity profiles for each cycle and cohort: data will be summarised descriptively, including the proportion of patients experiencing at least one SAE, the number of SAEs experienced per participant, and the number of SAEs experienced according to seriousness criteria, causality, and body system. Toxicity will be summarised according to CTCAE grades and will be summarised as the maximum grade toxicity experienced within each cycle, and overall.

The proportion of patients achieving at least a PR (clonal response) within 3m, at 3m, within 6m and at 6m and the proportion of patients achieving an amyloidotic organ response within 3m and 6m will be presented in tabulated form. Corresponding 90% and 95% confidence intervals will also be presented. Responses at 3 and 6 months will be broken down by response achieved, and by organ (for organ response).

Time to amyloidotic organ response and time to maximum response will be calculated using the Kaplan Meier method. Median time to amyloidotic organ response and median time to maximum response will be presented, with corresponding 95% confidence intervals.

The proportion and number of patients alive at 6 months and patients progression free at 6 months will be presented with corresponding 90% and 95% confidence intervals. If appropriate, Kaplan Meier curves for progression free survival may be explored.

Each patient will be assessed for their maximum clonal response; the number and proportion of participants in each response category within 6 cycles of treatment will be presented with corresponding 95% confidence intervals. Patients who do not achieve a maximum response will be summarised as, “no maximum response”.

Feasibility of delivering treatment according to protocol schedule will be summarised descriptively to include the number of patients requiring dose delays and/or reductions, the number of patients withdrawing from treatment, and reasons for dose delays / reductions and withdrawals. Time on treatment and reasons for stopping treatment will also be presented. The number of doses missed will be summarised overall and by cycle.

6. Reporting and Dissemination of the Results

Final analysis will be carried out after the last participant’s last data item.

After the analysis is complete, the results will be presented to the project team who will discuss them and decide if any further analysis or investigation is required. After this, members of the project team will write up the results with a view to submitting a manuscript to a peer-reviewed scientific journal. The results will also be submitted as abstracts to appropriate conferences for either poster or oral presentation. All abstracts and manuscripts must be reviewed by each member of the project team and an external referee if appropriate, before submission.

7. References

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Palladini, G., A. Dispenzieri, M. A. Gertz, S. Kumar, A. Wechalekar, P. N. Hawkins, S. Schonland, U. Hegenbart, R. Comenzo, E. Kastritis, M. A. Dimopoulos, A. Jaccard, C. Klersy and G. Merlini (2012). "New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes." J Clin Oncol 30(36): 4541-4549.

Approval of Analysis Plan

Clinical Trials Research Unit (CTRU)

The following Final analysis plan V1.0, May 2019, for the Catalyst study has been approved by the following personnel. Protocol version at time of writing is 3.0. Any signed amendments to the plan will be filed with this document.

Trial Statistician (Alexandra Pitchford): _____

Date: _____

Supervising statistician (Andrew Hall): _____

Date: _____

Scientific lead (Sarah Brown): _____

Date: _____

Senior Trial Co-ordinator (Jamie Oughton):_____

Date: _____

CTRU Delivery lead (Louise Flanagan): _____

Date: _____

Chief Investigator (Ashutosh Wechalekar): _____

Date: _____

Additional information:

