(BRAMble) Brukinsa Real-world Analysis in Marginal Zone Lymphoma

Site Initiation Visit

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Trial Management

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SCTU – Southampton Clinical Trials Unit	UK Coordinator, responsible for managing the regulatory set up for UK sites and communication link	
Sponsor	The University of Manchester	
Funder	BeOne (formerly BeiGene)	

Introduction (Protocol section 2)

- The Marginal zone lymphomas (MZL) broadly comprise extranodal, splenic and nodal subtypes and represent the second most common form of indolent non-Hodgkin lymphomas.

- Zanubrutinib was NICE approved for treatment of patients with relapsed/refractory MZL based on results from the MAGNOLIA study.

- Prior to NICE approval, Zanubrutinib was available to patients in the UK between January 2022 and July 2024 on a pre-reimbursement access programme; approximately 160 patients were treated.

- BRAMble is a UK lymphoma research group multicentre, non interventional retrospective observational study aimed at collecting clinical outcome data for patients with relapsed or refractory MZL who were treated with Zanubrutinib within the programme in the UK.

- This is a pseudonymised, non-consent study in which patients who received at least one dose of Zanubrutinib are eligible to take part. BeOne has contacted sites with at least one registered patient on the scheme for permission to be contacted by the SCTU trial team.

Study Design (Protocol Section 5)

- **Participants**

Adults with MZL treated with Zanubrutinib via the pre-reimbursement access programme (PRAP) between January 2022-July 2024 (approximately 160 patients are eligible).

- **Study Design**
  - This is a multicentre, retrospective, real-world observational study in patients with relapsed or refractory MZL treated with Zanubrutinib on the PRAP. Data will be collected at sites and uploaded to Medidata RAVE.
  - Data will be collected from initial diagnosis until death or last follow up at the time of data lock.
  - Limited data will also be collected on prior therapy for MZL, including systemic therapies and response rates. Details of Zanubrutinib treatment will be collected, as well as efficacy and safety data.
  - No patient intervention is planned, and data collection is expected to take 12 months.

- **End of Study**

End of Study is defined as the date of completion of data analysis and publication.

Inclusion Criteria (Protocol section 6)

1. Histologically confirmed MZL

2. Relapsed/refractory disease after at least one line of CD20 directed systemic therapy.

3. Patient treated with Zanubrutinib on the BeOne PRAP according to the inclusion criteria listed in full on page 7 of the protocol, including:

   - ECOG PS = 0-2
   - Patient aged ≥ 18 years.
   - Patient's disease is serious or life threatening.
   - All other alternative therapies have been exhausted.

Exclusion Criteria (Protocol section 6)

1. A significant proportion of MZL treatment data is unavailable for collection.

2. Excluded from the BeOne Zanubrutinib PRAP due to one or more of the following criteria listed in full on page 7 of the protocol.
   - The patient is actively participating in a clinical trial.
   - If female, the patient is pregnant or breast feeding.
   - Patient has clinically significant cardiovascular disease.
   - Patient has history of bleeding disorder, stroke or intracranial haemorrhage within the last 180 days.

Outcome Measures (Protocol Section 7)

Primary	Secondary
- **Progression Free Survival** (PFS) defined as time in months from first dose of Zanubrutinib to disease progression or death from any cause. Patients who do not progress or die will be censored at their date of last clinical follow up.	- Best overall and **complete response** rates. - **PET assessed overall and complete response rates**. - **Duration of response** – time from first PR or CR to disease progression or death from any cause. - **Duration of complete response** – time from first CR to disease progression or death from any cause. - **Time to next treatment** – time from start of - Zanubrutinib to start of any new anti lymphoma therapy. - **Overall survival –** time in months from first dose of Zanubrutinib to death from any cause. - Rate of **grade 3-5 adverse events**. - Rate of **grade 1-5 adverse events of special interest**. - **Zanubrutinib treatment delivery** including duration and frequency of Zanubrutinib, dose delays and reductions/reason for discontinuation.

Data Collection and Source Data

(Protocol Section 8)

- SCTU are responsible for data management and pseudonymised data will be entered onto iMedidata RAVE.
- The participant data is pseudonymised by assigning each participant a unique identifier code which is used to identify the participant during the study and for any participant specific clarification between SCTU and site.
- Sites will store personal data and the identifier for 15 years, to allow scope for updated analysis
- Trained personnel with specific roles assigned will be granted access to the eCRFs and completion guidelines will be provided to help with data entry.
- The database will automatically flag any missing data or mistakes/data queries and the study statistician will also perform checks looking for any inconsistencies and general checks. The data coordinator/manager will flag these to sites for completion.
- There will be no source data verification for this study.

Case Report Forms and Website

Case Report Forms:

- Can be accessed on the trial specific RAVE database https://login.imedidata.com/login.
- New users will have to complete training before they can access the database.
- Sites can be sent the "Forms and Layouts" and eCRF guidelines documents on request to familiarise themselves in advance of site opening.
- Updates will be notified in a timely manner to sites and added to the database.

Website:

- All current versions of approved documents will be available on SCTU website (password protected) : www.ctu.soton.ac.uk
- Website instructions and passwords will be emailed to sites once initiation has taken place.
- Any amendments to study documents will be notified to sites by email and uploaded to the CTU website once approval has been received from the relevant regulatory authority

AE Reporting Requirements (Protocol Section 8)

Adverse events (AE) to document:

- AEs experienced by the patient from the start of Zanubrutinib up to 30 days after the last administration of grades 3-5 should be recorded.
- As this is retrospective data collection SCTU will not notify REC/MHRA of any SUSARs and will not submit a Development Safety Update Report.

Adverse events of special interest (AESI) to document (per protocol):

- AESI of any grade experienced by the patient from the start of Zanubrutinib up to 30 days after the last administration should be recorded and submitted to SCTU.
- AESIs include:
- Neutropenia – including the terms “neutropenia” and “neutrophil count decreased.”
- Infections
- Bleeding – including major haemorrhage defined as any serious or grade ≥3 bleed at any site, or central nervous system bleed of any grade.
- Atrial fibrillation/flutter
- Ventricular arrhythmia (e.g. ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia and ventricular fibrillation)
- Hypertension
- Second primary malignancies including skin cancer
- Grade to be assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.
- Any questions to an event being an AESI should be referred to the SCTU.

Monitoring (Protocol section 10)

Central monitoring

- eCRFs will be completed on the RAVE database.
  - Data queries will either be automatically generated within the eCRF or manually raised by the study team. Any suspect data will be returned to site in the form of data queries.
  - Queries and responses are recorded within the database audit trail.
  - There will not be any planned on-site monitoring visits.

Audits and Quality Assurance

- The study may be participant to inspection and audit by University of Manchester (as Sponsor), SCTU (as Sponsor's delegate) and other regulatory bodies to ensure adherence to GCP and research governance framework.
- The day to day management of the trial will be co-ordinated through the SCTU and oversight maintained by the Trial Management Group (TMG).
- The TMG is responsible for overseeing progress of the study including the clinical and practical aspects. The chair of the TMG will be the CI of the trial and the TMG charter will define the membership, roles, responsibilities of the TMG, including the timings and frequency of the meetings.

Publication Policy

- The results of the study will be published in peer review journal and presented at relevant conferences.
- Results will also be disseminated through patient lymphoma organisations and charities.
- Investigators will be acknowledged on all presentations and publications arising from the study.
- Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications.
- In order to meet ethical obligations, anonymous data will be available for request from three months after publication of an article.
- Researchers interested in the data will be asked to complete the Request for Data Sharing form and to provide a brief research proposal on how they wish to use the data.

Investigator Site File Responsibilities

- SCTU will supply an investigator site file (ISF) prior to site initiation.
- Indexes and study documentation for these files will be provided by the SCTU as part of site set-up.
- Site responsibility to:
  - Maintain and store in secure location
  - File documents in the correct sections of the ISF
  - All study logs must be maintained on a regular basis for monitoring purposes.

Study Conduct

- Study will comply with the principles of Good Clinical Practice.

- The PI's GCP and CV must be sent to us ahead of site opening:
  - Current – within 3 years, certificate provided to us.
  - Must be updated if due to expire during the term of the trial.

- Conducted in compliance with the protocol, the current data protection regulations and all other applicable regulatory requirements.

<u>Staff Responsibilities:</u>

Principal Investigator - will have overall responsibility for conduct of study at site, appropriate delegation of duties and compliance.

Research Team (Sub-Investigator, Research Nurse, Data Manager etc) conduct tasks per delegation log.

Any Questions?