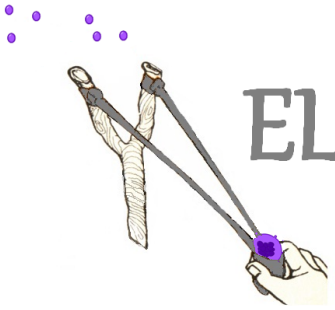

A Phase Ib Study of **El**trombopag and **A**zacitidine in Patients with High Risk Myelodyspla**stic** Syndromes and Related Disorders

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Trial Design

A 3+3 cohort trial design to evaluate the Maximum Tolerated Dose (MTD) and Optimal Biological Dose (OBD) of eltrombopag in combination with azacitidine in patients with high risk Myelodysplastic Syndromes (MDS) and related disorders.

Objectives

1. To evaluate the safety and tolerability of the oral thrombopoietin receptor agonist eltrombopag in combination with azacitidine in patients with advanced MDS and establish the Maximum Tolerated Dose (MTD) and Optimum Biological Dose (OBD).
2. To investigate the effect of eltrombopag with azacitidine on the fate of MDS/AML stem cell progenitors from patients so treated. The feasibility of Leukaemic Stem Cell (LSC) tracking as a marker of response and predictor of treatment failure in future Phase II/III studies will be explored

Outcomes

Primary Outcome

Safety and tolerability (including establishing the Maximum Tolerated Dose) of eltrombopag in combination with azacitidine when administered to patients with MDS who are suitable for azacitidine treatment.

Secondary Outcomes

- To establish the Optimal Biological dose (OBD) of eltrombopag in combination with azacitidine where this is not limited by MTD.
- To evaluate the effect of eltrombopag on platelet counts
- To evaluate the effect of eltrombopag on the need for platelet transfusions
- To evaluate the effect of eltrombopag on azacitidine treatment delays and dose reductions
- To evaluate the effect of eltrombopag on bleeding complications
- To evaluate evidence for a dose response effect of eltrombopag on bone marrow blast percentage
- To evaluate the activity of eltrombopag plus azacitidine per modified IWG 2006 haematological improvement criteria for MDS for MDS (Appendix 1 [1])
- To evaluate the activity of eltrombopag plus azacitidine per modified IWG 2006 response criteria for MDS (Appendix 8 [1])
- To evaluate the dosage effect of eltrombopag on stem/progenitor subset numbers and fate

Trial Duration

A maximum of 27 patients will be recruited to the dose finding component of the study and an additional 10 at the MTD over 12 months. Patients will be recruited from the 13 Trials Acceleration Programme (TAP) centres plus further non-TAP centres as required.

Patients will receive 1 week of eltrombopag alone followed by 2 cycles (typically 8 weeks) of treatment with azacitidine plus eltrombopag. After completing 2 cycles of combination treatment, patients will receive a third cycle of azacitidine alone (typically 4 weeks).

Patients judged as responding to eltrombopag by the treating clinician may continue eltrombopag for up to a further three cycles of azacitidine (cycles 4-6, typically 12 weeks). Follow-up will continue until

4 weeks after discontinuation of eltrombopag or the end of 6 cycles of treatment with azacitidine, whichever is later. The maximum duration the patient will be on the study is 29 weeks (if there are no delays to the azacitidine cycles). There is no long term follow-up other than collection of a bone marrow sample on disease progression if the patient is enrolled onto the MDSBio study.

Main Inclusion and Exclusion Criteria

Inclusion Criteria

- Age ≥16 years of age
- Platelet count at baseline <150 x 10^9/L
- Myelodysplastic Syndromes (MDS) classified as Intermediate 2-risk or high risk according to the International Prognostic Scoring System (IPSS) at registration OR
- Chronic Myelomonocytic Leukaemia (CMML) with 10-29% bone marrow blasts without proliferation (peripheral white blood cell count <13 x 10^9/l) OR
- Acute Myeloid Leukaemia (AML) with 20-30% bone marrow blasts
- Subjects must have a minimum of two platelet and haemoglobin counts available from a period of up to 8 weeks prior to registration, as well as a record of any platelet transfusions conducted during that period.
- A baseline bone marrow examination to evaluate blast percentage, karyotype and assessment of fibrosis within 8 weeks prior to registration
- A baseline bone marrow examination to evaluate blast percentage, karyotype and assessment of fibrotic change within 8 weeks of registration
- ALT/AST < 3 x upper limit of normal
- ECOG ≤ 2
- Valid informed consent

Exclusion Criteria

- AML with >30% blasts
- Patients who have received allogeneic bone marrow transplant
- Known HIV positive
- Known liver cirrhosis
- Uncontrolled infection (grade 4 CTCAE v4)
- Previous exposure to azacitidine
- Previous exposure to thrombomimetic agents
- Use of prior investigational agents within 4 weeks
- Other severe, concurrent diseases or mental disorders that in the opinion of the investigator make the patients unsuitable for the trial
- Concurrent active or previous malignancy within the last 3 years – except controlled, localised prostate cancer on hormone therapy or non-melanoma skin malignancy or cervical carcinoma *in situ* or completely resected colonic polyps carcinoma *in situ*
- Grade 4 bone marrow fibrosis according to the European consensus[3]
- Clinical evidence of splenomegaly
- Known hypersensitivity to study drugs or any of their excipients
- Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to study entry)
- Females of childbearing potential (i.e. not post-menopausal or surgically sterilised) who are not willing to use adequate methods of contraception to prevent pregnancy or abstain from heterosexual activity for the duration of the trial and for at least 3 months following treatment discontinuation.
- Male patients who are not willing to use an adequate method of contraception for the duration of the trial treatment if engaged in sexual activity with a female of childbearing potential and for at least 3 months following treatment discontinuation

- Patients of east Asian ancestry*

* Patients will be excluded if either parent is East Asian (such as Chinese, Japanese, Taiwanese or Korean). In previous studies, the pharmacokinetics of eltrombopag in patients of East Asian ancestry differs significantly from the non-East Asian patients. The SPC for eltrombopag recommends patients receive 50% of the recommended dose. As this is a dose finding study, inclusion of these patients may impair an accurate finding of MTD and OBD that could be applied to the UK population.

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