A Phase I/IIa Trial With BMS-986158, a Small Molecule Inhibitor of the Bromodomain and;Extra-Terminal (BET) Proteins, in Subjects with Selected Advanced Solid Tumors

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To assess the safety and tolerability and to define the dose limiting toxicities (DLT) and maximum tolerated dose (MTD) of BMS-986158 as for subjects with selected advanced solid tumors.

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46213

Source
ToetsingOnline

Brief title
Study of BET Inhibitor BMS-986158 in advanced solid tumours

Condition

- Other condition
- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
advanced solid tumours, cancer

Health condition

neoplasms, in addition to the above: small cell lung cancer, BRCA1/2 wild type ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: advanced solid tumours, BET Inhibitor

Outcome measures

Primary outcome

Primary Endpoints: Incidence of adverse events (AEs) at its worst grade,

serious adverse events (SAEs) at its

worst grade, adverse events leading to discontinuations, deaths, frequency of

laboratory test toxicity grade shifting

from baseline. Safety will be evaluated from the time that the subject signs

the informed consent and for up to

30 days after the last dose of study drug or until resolution of any adverse

event for which alternative causes could

not be identified resolve to <= Grade 1 or baseline or until the event has

stabilized, whichever is longer.

Secondary outcome

- Pharmacokinetics: Select PK parameters including Cmax, Cmin, Tmax, AUC (TAU),

AUC(0-T), will be derived from parent (BMS-986158) and metabolite plasma

concentration versus time data for all schedules. In addition parameters

specific to single dose only, if data permits, (T-HALF, AUC(INF), CLT/F, Vz/F)

or multiple dose only (Cmin, Ctau, Ctrough, DF, Swing, AI and T-HALFeff) will

be calculated derived from parent (BMS-986158) and metabolite plasma concentration versus time data. The metabolite to parent ratios (MR) will also be calculated for Cmax, AUC(0-T), AUC(INF) and AUC(TAU).

- Efficacy: Objective response rate (ORR), Duration of response (DOR), and Progression Free Survival Rate (PFSR) at select times are efficacy endpoints. ORR is defined as the total number of subjects who*s best overall response (BOR) is either a CR or PR, divided by the total number of subjects in the population of interest.
Overall survival rate at select times is an exploratory efficacy endpoint.

- ECG: Changes in QTcF (ΔQTcF) from baseline at selected times.

- Biomarkers for pharmacodynamic assessments: Summary changes from baseline in the expression of BET- regulated genes will be assessed in blood collected at multiple time points after BMS-986158 administration on the first day of dosing and then following multiple dosing schedules.

Study description

Background summary

Patients with relapsed or refractory solid tumours have a very poor prognosis. Despite advances in multimodal therapy, increases in overall survival in these patient populations have been limited. The unmet need resides in the lack of effective treatments to achieve long term survival, hence the need to test compounds that have novel mechanisms of action, such as BET inhibitors, in clinical studies.

Therapies that target the immune system to activate antitumour immune responses have become an intense area of clinical and preclinical oncology research. Several immunotherapeutic drugs have come to the market in recent years including ipilimumab, pembrolizumab and nivolumab. Optimal combination partners for these agents that will allow maximal antitumour effects will be critical to realise the full potential of both immunotherapeutics and targeted anticancer agents such as BMS-986158.
Acetylation of lysine residues is a widespread protein post-translational modification (PTM), and extensively relevant to modulation of cellular processes, including protein conformation and interaction. Histone lysine acetylation was historically proposed to be a hallmark of transcriptionally active genes. Therefore, deregulation of histone acetylation patterns often drives the abnormal expression of oncogenes resulting in proliferation and tumorigenesis. Bromodomain (BRD) proteins have been identified to regulate lysine acetylation. Their interaction with acetylated chromatin influence gene transcription.
Bromodomain and extra-terminal (BET) proteins belong to human BRD proteins family, comprised of 4 members (BRD2, BRD3, BRD4, and BRDT). BET proteins have been identified in oncogenic rearrangements, leading to highly oncogenic fusion proteins, and thus play key roles in development of several types of cancer. For example, BRD4 was found to form fully functional fusion gene with the NUT (nuclear protein in testis) gene in NUT midline carcinoma, an aggressive squamous cell carcinoma. BRD4 gene amplification and overexpression has been correlated with adverse prognosis in many solid tumours.

Two early BET inhibitors, called JQ1 and I-BET, demonstrated therapeutic effects in multiple tumour models of hematologic malignancies including multiple myeloma (MM), as well as in solid tumours. The therapeutic activity of BET inhibitors in hematologic malignancies correlates with transcriptional suppression of key proto-oncogenes, including MYC and BCL2. c-MYC is the most frequently amplified oncogene and is deregulated in 40% to 70% of all cancers; in particular, amplification or over-expression of MYC is frequently observed in lung cancer, ovarian cancer and breast cancer
Efforts to inhibit MYC have not been successful to date. Due to their mechanism of action, BET inhibitors have the potential to effectively target the MYC oncogene mediated tumour development.
Examination of BRD4 interaction with genes whose transcription is highly sensitive to BET inhibitor JQ1, led to the observation that BRD4 (and potentially other BET family members) localises to the promoter regions of many oncogenes. Additionally, BRD4 is enriched in enhancer regions, leading to high expression levels of many growth promoting genes, in addition to MYC oncogene. In particular, the level of BRD4 presence in the so called super-enhancer regions has been found to be remarkable. Super-enhancers are considerably larger than typical gene enhancer regions and are densely populated by transcription factors, leading to strong activation of gene transcription. Super-enhancers are present in the many key oncogenes. As BRD4 is particularly enriched in these critical control regions, it is suggested that inhibition of

the bromodomain activity of BRD4 will lead to transcriptional repression of these key oncogenes. The close relationship between super-enhancers and BRD4 may explain why cancer cells are specifically sensitive to BRD4 inhibition, despite ubiquitous BRD4 expression in a wide range of cells. Because tumour cells are frequently highly reliant on high oncogene expression for survival, selective disruption of super-enhancers by a BET inhibitor may represent an effective strategy for the treatment of multiple tumour types with an acceptable safety profile.

BMS-986158 has been tested against a wide-array of cancer cell lines in vitro and has demonstrated potent cytotoxicity against multiple haematologic and solid tumours. Many of the most sensitive cancer types are driven by c-MYC including multiple myeloma (MM), acute myeloid leukemia (AML) and small cell lung carcinoma (SCLC). In particular, BMS-986158 demonstrated potent and selective cytotoxic activity in multiple SCLC cell lines.
BMS-986158 was evaluated in vivo in a panel of patient-derived xenografts (PDX) in mice. In an ovarian cancer PDX model that was determined to have amplification of the BRD4 gene, tumour regression was observed during the BMS-986158 dosing period suggesting that tumours with BRD4 amplification may be particularly sensitive to BET inhibition. Analyses of the human cancer genome atlas (TCGA) data show that approximately 27% of ovarian tumours of serous histology, that are BRCA 1/2 wildtype, also have BRD4 amplification. Moreover, therapeutic effects of BET inhibitors were also observed in xenograft models of breast cancer.
In the pivotal 1-month oral toxicity studies, the highest non-severely toxic dose (HNSTD) in dogs was 0.15 mg/kg. The dog was considered the most appropriate species for calculation of the maximum recommended starting dose (MRSD) in human trials because a non-tolerated dose was attained in dog (i.e. the more sensitive species) but not rat. The starting dose of 0.75 mg/day was selected based upon the human equivalent dose (HED; scaled by body-surface area) of the HNSTD in dogs. Projections of the human minimum efficacious dose are 4 to 11 mg/day. For further details please refer to Protocol section 1.4 and Investigator Brochure.
The nonclinical toxicity profile of BMS-986158 has been well characterised and it supports first-in-human dosing in cancer patients, currently ongoing in the Escalation part of the study. As mentioned previously, patients in the Netherlands will only participate to the subsequent cohort Expansion part of the study.

Study objective

To assess the safety and tolerability and to define the dose limiting toxicities (DLT) and maximum tolerated dose (MTD) of BMS-986158 as for subjects with selected advanced solid tumors.

Study design

Study Phase: Phase I/IIa
Part 1A (monotherapy, ovarian, triple negative breast [TNBC] and small cell lung cancer [SCLC]), dose
escalation with Arms A, B, and C enrolling at different dosing schedules (See Figure 3.1-1). Arm A will enroll
first. Each subject in Arm A, B and C will be administered a single dose of BMS-986158 on Cycle 1 Day 1 and no
additional doses will be administered until Cycle 2 Day 1. For subjects in Arm A on Cycle 2 Day 1, which must be
within 7 days of the Cycle 1 Day 1 dose administration, and on each subsequent cycle, subjects will receive once
daily dosing for 5 consecutive days of each week, followed by a 2-day rest period, on a 28-day cycle. For subjects in
Arm B on Cycle 2 Day 1, which must be within approximately 7 days of the Cycle 1 Day 1 dose administration, and
on each subsequent cycle, subjects will receive once daily dosing for 14 consecutive days, followed by a 7-day rest
period, on a 21-day cycle. For subjects in Arm C on Cycle 2 Day 1, which must be within approximately 7 days of
the Cycle 1 Day 1 dose administration, and on each subsequent cycle, subjects will receive once daily dosing for 7
consecutive days, followed by a 14-day rest period, on a 21-day cycle. Depending on the accumulated safety and
pharmacokinetics (PK) of Treatment Arm A in Part 1A, at the Sponsor*s discretion, a decision will be made to
select, initially, either Treatment Arm B or C for enrollment. The starting dose levels of Arms B or C will depend
on the safety and tolerability of the dose levels in Arm A, but will be no greater than the maximum dose tolerated in
Arm A. Subjects may continue to receive treatment until disease progression, unacceptable adverse events (AEs) or
withdrawal of consent, or as defined in Section 3.5.
Part 2A (monotherapy) expansion. Cohort expansions will be carried out at the doses selected from dose
escalation, and may represent the maximum tolerated dose (MTD), maximum administered dose, or an alternative
dose selected from dose escalation.
Part 1 consists of the dose escalation phase with BMS-986158 administered as monotherapy (Part 1A). To
minimize risks to subjects from unanticipated acute toxicities, a waiting period of at least 5 days will occur between
dose administrations for the first, second, and third subjects. This waiting period is mandatory only in the first
Cohort of Treatment Arm A of Part 1A.
Part 2 consists of cohort expansions in solid tumors (monotherapy). Treatment in Part 2 will be initiated when the
MTD (or maximum administered dose level if no MTD is determined) and dose

schedule for Part 1 has been
determined. The doses selected for Part 2 will not exceed the Part 1A MTD or maximum administered dose level.

Intervention

Study Drug: includes Investigational [Medicinal] Products (IP/IMP) as listed:
BMS-986158 is formulated as a hard gelatin capsule partially filled with a white to off-white waxy, semi-solid to
solid dispersion to be administered by oral route.
Study Drug for BMS-986158
Medication Potency:
BMS- 986158 0.25 mg and 2 mg

Study burden and risks

The potential side effects and risks of BMS-986158 are based on what we have learned from studies in animals and in limited human trials with compounds similar to BMS-986158.

Based on what we have learned from ongoing small clinical studies with similar compounds (<100 patients total) and from animal studies with BMS-986158 the following side effects and risks may be experienced.

• Common (>20%): nausea, vomiting, diarrhea, low platelet counts
• Less common (<20%): low red blood cell counts, low white blood cell counts, high sugar levels, low amounts of some blood clotting proteins, sores in mouth, stomach pain/sores
• Rare, but may be serious: bleeding from the stool, low sperm counts, sensitivity to the sun, increased susceptibility to infections

In particular, the following will be closely monitored during the study:

o Stomach and intestines: patients will be instructed to report to the study team any changes in stool frequency or consistency and also any abdominal symptoms such as pain or nausea. Diarrhoea can cause dehydration, and in severe cases, can lead to kidney impairment (decreased kidney function). Patients will be provided with medication and instructions how to treat diarrhoea.
o Blood sugar levels (metabolism). Because of potential changes in the blood sugar levels, patients will be asked to fast (not eat or drink for at least 8 hours) before their blood samples are drawn and study medication taken on cycle 1 day 1 and cycle 3 day 1 and on additional days if clinically indicated.
o Immune system: blood cell counts and in particular white blood cell counts will be evaluated frequently throughout the study. Patients will also be examined for signs of infection (such as fever, aches, and chills).

o Bone marrow: blood cell counts will be evaluated frequently throughout the study and patients will also be examined for signs of anaemia, fatigue and bleeding.
o Proteins that regulate blood clotting (coagulation). Patients* blood will be tested for any abnormalities concerning these proteins during Cycle 1 and beyond, if clinically indicated.
o Reproductive organs: shrinkage in size and other changes to the reproductive organs have been observed in male animals treated with multiple doses of BMS-986158. If appropriate, the Investigator will discuss the potential risks to patients* reproductive organs and the option of sperm and egg banking.
o Skin: BMS-986158 may make one*s skin more sensitive to sunlight. Patients will be instructed to wear sunscreen and protective clothing when outside.

The risks will be further minimised by using of pre-medications (as permitted), frequently monitoring the safety of the participants during and after treatment, and providing a list of prohibited medications to the subjects, and their GPs to prevent possible drug to drug interactions.

Risks for men/women of childbearing potential (known and unknown) will be minimised through regular pregnancy testing, and by informing female subjects that they must use contraception during the study and for 30 days following treatment with BMS-986158 and that they must not breastfeed while receiving BMS-986158 and up to 30 days from the last dose of BMS-986158. Male subjects with female partners of childbearing potential must also use contraception during the study and for 90 days after treatment with BMS-986158.

Other side effects
Blood draws or use of an IV catheter may cause infection, bruising, redness, discomfort, or bleeding at the needle puncture site.

In rare cases, patients have allergic reactions (itching or rash) to the dyes used in different types of imaging assessments. If severe, patients may have difficulty breathing and dangerous lowering of blood pressure. If subjects are aware of an allergy to a contrast dye, or to iodine or shellfish, they will be advised to notify their study doctor and radiologist.

For subjects who undergo a tumour tissue biopsy, a fine needle aspiration or core biopsy may cause pain, swelling or bruising at the insertion site. A surgical biopsy may cause pain or bruising at the incision site, a possible reaction to the anaesthesia or numbing agents, irritation from stitches or staples, and the possibility of infection. For biopsies, risk will be minimised by controlling the pain using medication, if necessary. If the biopsy is CT guided this will involve exposure to ionising radiation. These tests and procedures will be conducted by trained medical professionals.
CT, MUGA and bone scans are also associated with exposure to ionising radiation. Please refer to Part B section 3 for further details.

Risks from taking prohibited medications will be minimised, as the study team will frequently review all concomitant medication being taken by subjects.

Subjects will be required to attend the research unit on a regular basis whilst they are on the study, thus involving an increase in travel. Reasonable travel expenses will be reimbursed. Subjects may have to alter any pre-existing plans/appointments to fit in with the required visits, as laid out in the protocol. These visits are necessary to monitor the subjects* safety and well-being.

As a subject in this study, risks may be associated with loss of patient confidentiality if identifiable genetic or health information were disclosed to unauthorised persons. There is possible discrimination by employers or insurance providers, if this information were to be disclosed. Bristol-Myers Squibb (study sponsor) believes that the risks of such improper disclosure are very small because they have adopted strict privacy and confidentiality procedures.

Occasionally during the course of a study, subjects may be found to have a previously undiagnosed medical condition. In this situation, their study doctor will take the necessary steps to ensure they receive appropriate treatment.

If during the course of this study, new information becomes available about BMS-986158, it will be discussed with patients and they will be asked if they would like to continue in the study. As a consequence of this new information, and to ensure patient safety, it may be necessary to make modifications to the study design which could include changing the timing of dosing, changing the number of tests being performed or perhaps even stopping the study. In any event, the subject and investigator will be fully informed and the subject will be given every opportunity to consider their continued participation in the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed Written Informed Consent
a) The subject must sign the informed consent form prior to the performance of any study related procedures that are not considered part of standard of care.
2. Target Population
a) Subjects must have a confirmed histologic/cytologic diagnosis of one of the following preferred malignancies for participation in the study and meet the other criteria listed (a specific exception for disease diagnosis criteria is noted in inclusion criteria k)
i) Ovarian cancer
(1) Histological or cytological documented epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer.
(2) Received at least one prior Platinum Based Therapy (PBT) regimen.
(3) Have platinum-resistant/refractory disease, be intolerant of platinum-containing compounds, and/or have hypersensitivity to platinum-containing compounds.
(4) For Part 2A Expansion only: All subjects must have serous histology and have germline wild-type BRCA1 and BRCA2
ii) Triple negative breast cancer (TNBC)
(1) Women with histological or cytological confirmed triple negative breast carcinoma as defined by ASCO/CAP guidelines.
(2) Had progression or refractory disease during or after at least 1 chemotherapy regimen for the treatment of metastatic or locally advanced disease.
iii) Small cell lung cancer (SCLC)
;(1) Histologically or cytologically documented SCLC, limited or extensive stage disease.
(2) Received at least one prior Platinum Based Therapy (PBT) regimen.;b) Subjects with controlled, treated brain metastasis fulfilling all the following criteria may be screened: no radiographic progression for at least 2 weeks following radiation and/or surgical treatment,

off steroids for at least 2 weeks, without new or progressing neurological signs or symptoms.
c) All subjects must have at least one measurable lesion at baseline by CT or MRI as per RECIST v1.1
d) All subjects must have archival tumor tissue identified and available for correlative biomarker studies (if slides are provided, a minimum of 10 (ten) unstained slides with at least 5 micron thick tissue sections are required) unless a fresh biopsy is provided. All subjects not providing a fresh biopsy must consent to provide tumor blocks or slides to the sponsor and the availability of the tissue must be confirmed prior to subjects receiving study medication. If an archived tumor specimen is unavailable or unsuitable for correlative biomarker studies, subjects may consent to a pre-treatment fresh tumor biopsy to be eligible for this study if it can be performed at minimal acceptable clinical risk as judged by the Investigator and if it does not include a target lesion or lesion in an area treated with prior radiation therapy. For the first 25 ovarian subjects enrolled in dose expansion Part 2A, both a pre- treatment and on-treatment fresh biopsy must be provided.
e) Subjects must have a life expectancy of at least 3 months.
f) Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 5)
g) Subjects who have undergone any major surgery within 4 weeks of study drug administration are excluded. Subjects must have recovered from the effects of major surgery at least 14 days before the first dose of the study drug.
h) Prophylactic anticoagulation for venous access devices with low-dose heparin or similar (e.g. heparin catheter flush) will be permitted.
i) For antiplatelet agents, prophylactic doses are permitted (e.g. aspirin < 300 mg daily, clopidogrel < 75 mg daily)
j) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been treated). If re-enrolled, the subject must be re-consented.
k) Subjects with solid tumor types that are not included in the preferred target population may also be enrolled after a minimum of 2 subjects with the preferred tumor types have been enrolled at a single dose level during escalation, after discussion with the Sponsor/Study Director. These subjects must have progressed on or had refractory disease to at least one prior anti-cancer regimen, not be eligible for additional effective ;standard of care therapy for their disease, and must have the possibility of being positively impacted by the treatment offered in this study.
3. Previous Treatment
a) Prior anti-cancer treatments such as chemotherapy, radiotherapy, biological, immunotherapy or investigational agents [therapeutic or diagnostic] are permitted.
i) For cytotoxic agents, at least 4 weeks must have elapsed from last dose of prior cytotoxic anti-cancer therapy and the initiation of study drug administration.
ii) ii) For non-cytotoxic agents, at least 4 weeks or 5 half-lives (whichever is shorter) must have elapsed from the last dose of prior non-cytotoxic anti-cancer therapy and the initiation of study drug administration. If 5 half-lives is shorter than 4 weeks, agreement with Sponsor/Medical Monitor is mandatory.
b) All acute toxicities, from any prior therapy (radiotherapy, chemotherapy, or surgical procedures) must have resolved to Grade <= 1, NCI CTCAE, version 4.03 or to baseline if irreversible.
c) Concomitant therapy with bisphosphonates is acceptable as per American Society of

Clinical Oncology (ASCO) guidelines. Doses of bisphosphonates must be stable for at least 30 days prior to treatment initiation, as per ASCO guidelines.;4. Age and Reproductive Status
a) Males and Females, ages 18 years of age or greater
b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) during screening and within 24 hours prior to the start of study drug.
c) Women must not be breastfeeding
d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) BMS-986158 plus 30 days (duration of ovulatory cycle) for a total of 30 days post-treatment completion. Hormonal contraception may be used for other indications (eg. menstrual bleedings) provided it is not the primary method of contraception.
e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) BMS-986158 plus 90 days (duration of sperm turnover) for a total of 90 days post- treatment completion.
f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still undergo pregnancy testing.

Exclusion criteria

1. Medical History and Concurrent Diseases
a) Evidence of uncontrolled, active infection, requiring parenteral anti-bacterial, anti-viral or anti-fungal therapy < 7 days prior to administration of study medication
b) Current or recent (within 3 months of study drug administration) gastrointestinal disease such as chronic or intermittent diarrhea, or disorders that increase the risk of diarrhea, such as inflammatory bowel disease. Non-chronic conditions (e.g. infectious diarrhea) that are completely resolved for at least 2 weeks prior to starting study treatment are not exclusionary
c) Subjects with concomitant second malignancies (except adequately treated non-melanomatous skin cancers or in situ bladder, breast or cervical cancers) are excluded unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required or anticipated to be required during the study period
d) Conditions requiring chronic systemic glucocorticoid use, such as autoimmune disease or severe asthma
e) History of medically significant thromboembolic events or bleeding diathesis within the past 6 months, such as cerebrovascular accident (including transient ischemic attacks), pulmonary embolism, pulmonary hemorrhage > 2 teaspoonfuls/24hrs or repeated pulmonary hemorrhage, gastrointestinal hemorrhage requiring transfusion or procedural intervention
f) Uncontrolled or significant cardiovascular disease including:
i) Congestive heart failure NYHA (New York Heart Association) Class 3 or greater within 3 months (Appendix 6).
;ii) History of congenital long QT syndrome or clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation or Torsade de Pointes). Controlled atrial fibrillation is not an exclusion criterion.
iii) Active coronary artery disease, unstable or newly diagnosed angina or myocardial

infarction in the past 6 months.
g) Inability to tolerate oral medication.
h) HIV-related disease or known positivity for human immunodeficiency virus (HIV).
i) Past or active hepatitis B or C infection.
j) Any other sound medical, psychiatric and/or social reason as determined by the investigator.
k) Use of strong inhibitors of CYP3A4 or P-gp within 1 week or 5 half-lives (whichever is longer) or strong inducers of CYP3A4 or P-gp within 2 weeks or 5 half-lives (whichever is longer). See Appendix 3;2. Physical and Laboratory Test Findings
a) Inadequate bone marrow function defined as:
i) Absolute neutrophil count (ANC) < 1,500 cells/mm3;
ii) Platelet count < 100,000 cells/mm3;
iii) Hemoglobin < 8 g/dL
b) Abnormal blood coagulation parameters:
i) PT such that international normalized ratio (INR) is > 1.5x ULN (or > 2.5 x baseline, if a subject is on a stable dose of therapeutic warfarin) or a PTT > 1.2x upper limit of normal (ULN).
c) Inadequate hepatic function defined as:
i) Aspartate aminotransferase (AST) > 3x ULN
ii) Alanine aminotransferase (ALT) > 3x ULN
iii) Total bilirubin > 1.5 x ULN (except known Gilbert*s syndrome, direct bilirubin > 1.5x ULN);
d) Inadequate renal function defined as:
i) Creatinine clearance (CrCl) <= 50 mL/minute (either measured or calculated using a standard formula such as Cockcroft and Gault) within 14 days prior to randomization
e) Any of the following on 12-lead electrocardiogram (ECG) prior to study drug administration, confirmed by repeat.
i) QRS >= 120 msec, except right bundle branch block
ii) QTcF > 450 msec
;3. Not applicable per Protocol Amendment 05.
4. Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4
d) Women who are pregnant.
Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2016
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BET-Inhibitor
Generic name:	N/A

Ethics review

Approved WMO Date:	25-07-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	07-10-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	21-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	06-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-000324-29-NL
CCMO	NL58045.056.16