Effect of Esomeprazole on the Pharmacokinetics of BMS-275183 in Patients with Advanced Malignancies

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Primary Objective: To assess the effect of esomeprazole on the pharmacokinetics of BMS-275183. Secondary Objectives: To evaluate the safety and efficay of BMS-275183 co-administered with esomeprazole.

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON29734

Source
ToetsingOnline

Brief title
CA165-030

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced malignancies

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Advanced, Cancer, Drug, Interaction

Outcome measures

Primary outcome

Pharmacokinetic Measures: Pharmacokinetic parameters (Cmax, Tmax, AUC(INF), and T HALF) will be derived from plasma concentration versus time data.

Secondary outcome

Safety Outcome Measures: Toxicity will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (published June 10, 2003). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests throughout the conduct of the study.

Tumor Response Outcome Measures: Tumor response will be obtained from all patients with measurable lesions, using the RECIST criteria. The assessments will be made every two cycles (after Cycle 2, 4, 6, etc.) or more frequently if indicated. Furthermore, a response is considered confirmed if it is noted on two examinations at least four weeks apart.

Pharmacogenetics Measures: Single nucleotide polymorphisms (SNPs) in drug efflux transporters ABCB1 and ABCC2 will be identified.

Study description

Background summary

Co-administration of benzimidazoles with BMS-275183 may increase the systemic exposure and variability of BMS-275183 and lead to increased toxicity. There

have been five drug-related deaths in the BMS-275183 program and all patients were receiving concomitant benzimidazoles.
This study will assess the effect of the benzimidazole esomeprazole on the single dose pharmacokinetics of BMS-275183 when given together, 24 hours apart, and 12 hours apart. The information from this study may be used to guide the spacing of dosing of BMS-275183 and benzimidazoles, when BMS-275183 is administered on twice weekly and continuous daily schedules.

Study objective

Primary Objective: To assess the effect of esomeprazole on the pharmacokinetics of BMS-275183. Secondary Objectives: To evaluate the safety and efficay of BMS-275183 co-administered with esomeprazole.

Study design

This is a Phase I, open-label, randomized study with 3 treatment groups.
Patients randomized to Treatment 1 will receive BMS-275183 alone during Week 1 and BMS-275183 in combination with esomeprazole during Week 2. Patients will be administered BMS-275183 50 mg/m2 orally on the mornings of Days 1 and 8; patients will receive a morning daily oral dose of esomeprazole 40 mg on Days 5, 6, 7, 8, 9, 10, and 11. On Day 8, esomeprazole will be administered approximately 30 minutes prior to BMS-275183 administration.
Patients randomized to Treatment 2 will receive BMS-275183 alone during Week 1 and BMS-275183 and esomeprazole during Week 2, but the two drugs will not be administered on the same day, as the esomeprazole dose on Day 8 will be omitted. Patients will be administered BMS-275183 50 mg/m2 orally on the mornings of Days 1 and 8; patients will receive a morning daily oral dose of esomeprazole 40 mg on Days 5, 6, 7, 9, 10, and 11.
Patients randomized to Treatment 3 will receive BMS-275183 alone during Week 1 and BMS-275183 and esomeprazole during Week 2, where the two drugs will be administered approximately 12 hours apart. Patients will be administered BMS-275183 50 mg/m2 orally on the mornings of Days 1 and 8; patients will be administered an evening daily oral dose of esomeprazole 40 mg on Days 4, 5, 6, 7, 8, 9, and 10. Approximately 12 hours should elapse between the BMS-275183 dose and the esomeprazole dose on Day 8.

All patients will subsequently receive BMS-275183 100 mg/m2 orally on a continuous twice weekly schedule beginning on Day 15 and will continue on treatment until patient no longer benefits from the treatment.

Blood samples for Pharmacokinetics of BMS-275183 will be collected over 72 hours on Cycle 1, Days 1, 8, and 15.

Safety will be assessed from the first dose through at least 30 days after the last dose until resolution of drug-related toxicity, or when toxicity is deemed

irreversible, whichever is longer.

Study burden and risks

Patients will undergo intensive pharmacokinetic analyses during the first cycle (day 1,8,15 for 8 hr/day, and 1-2 hr/day during 10 additional days). Thereafter visits are scheduled twice weekly. Anticipated risks are related to the experimental study medication and listed in the patient information sheet.

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

2) a). Histologically or cytologically confirmed diagnosis of non-hematological malignancy that has progressed on standard therapy or for whom no standard therapy is known.
b) Measurable or non-measurable disease (defined in Section 3.3.3.2).
c) At least 4 weeks must have elapsed from the last dose of chemotherapy, including monoclonal antibodies that have half-lives of around 2 weeks (e.g., Erbitux*, Herceptin*, Avastin*) and taxanes prior to beginning protocol therapy. At least 6 weeks must have elapsed from the last dose of nitrosoureas, mitomycin C, and liposomal doxorubicin prior to beginning protocol therapy. At least 2 weeks must have elapsed from the last dose of oral targeted anti-cancer agents (e.g., Iressa*, Tarceva*, Gleevec*) before study drug administration. Patients must have recovered to baseline or Grade 1 from the toxicities resulting from previous therapies.
d) Adequate recovery from recent surgery and radiation therapy. At least 1 week must have elapsed from the time of a minor surgery, and at least 3 weeks for major surgery or radiation therapy.
e) ECOG performance status 0-1 (Appendix 1).
f) Life expectancy at least 3 months.
g) Patient must be available for follow-up.
h) Patients must have received no more than 3 prior chemotherapy regimens, which are considered myelotoxic, given in the advanced/metastatic setting. Additional prior chemotherapy given in the adjuvant or neo-adjuvant setting is allowed.;3) Physical and Laboratory Findings
a) Adequate hematologic function with absolute neutrophil counts >= 1,500/mm3, and platelets >= 100,000/mm3.
b) Adequate hepatic function with serum total bilirubin <= 1.5 times the upper institutional limits of normal and ALT <= 2.5 times the upper institutional limits of normal.
c) Adequate renal function with serum creatinine <= 1.5 times the upper institutional limits of normal.;Age and Sex
a) Men and women, ages 18 and greater.
Women of childbearing potential (WOCBP) must be using an adequate method of contraception (female condum, cervical cap, spermicidal jelly or IUD) to avoid pregnancy throughout the study and for up to 4 weeks after the study in such a manner that the risk of pregnancy is minimized. A barrier method of contraception is required for both males and females while participating in this study.
WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea >= 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35mIU/mL]. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.
WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study medication.

Exclusion criteria

1)a) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 4 weeks after the study.
b) WOCBP using a prohibited contraceptive method.
c) Women who are pregnant or breastfeeding.
d) Women with a positive pregnancy test on enrollment or prior to study drug administration.
e) Sexually active fertile men who are unwilling or unable to use a barrier contraception (e.g., condom) or whose partners are WOCBP not using an adequate method of birth control from the time of enrollment and for 3 months after participation in the study.;2) Medical History and Concurrent Diseases
a) Prior radiotherapy that involved >= 30% of the bone marrow containing skeleton. A recovery period of at least 3 weeks (at least 4 weeks if given to the brain) after completion of radiotherapy is required prior to enrollment (Appendix 2).
b) Uncontrolled or significant pulmonary or cardiovascular disease, including a recent (<= 6 months) myocardial infarction, any significant degree of congestive heart failure with or without medical treatment, any history of clinically significant atrial or ventricular arrhythmias, any history of second or third degree heart block, any history of prolonged QTc interval.
c) CTCAE Grade 2 or greater neuropathy (motor or sensory) currently, or a prior history of Grade 3 neuropathy.
d) A serious uncontrolled medical disorder or active infection which would impair the ability of the patient to receive protocol therapy or whose control may be jeopardized by the complications of this therapy.
e) Known history of HIV.
f) Active brain metastases including evidence of cerebral edema by CT scan or MRI, or progression from prior imaging study, any requirements for steroids or clinical symptoms of/from brain metastases.
g) Superior vena cava syndrome or tumor obstruction (or near obstruction) of a vital structure.
h) QTc interval > 450 msec on ECG.
i) Any psychiatric or other disorders such as dementia that would prohibit the patient from understanding or rendering informed consent or from fully complying with protocol treatment and follow-up.
j) Inability to swallow capsules.
k) Patients with a known history of gastrointestinal disease (such as partial esophageal, gastric, small, or large bowel obstruction), surgery or malabsorption that could potentially impact the absorption of the study drug; patients requiring the use of a feeding tube.
l) Inability to be venipunctured and/or tolerate venous access.
m) Any other sound medical, psychiatric, and/or social reason as determined by the Investigator.;3) Prohibited Therapies and/or Medications
a) Prior exposure to BMS-275183.
b) Other concurrent chemotherapy, hormonal therapy, immunotherapy regimens or radiotherapy, standard or investigational (Patients may continue to receive hormonal replacement therapy. Patients with prostate cancer receiving LHRH agonist treatment will be permitted to continue treatment with LHRH agonists while on therapy).

c) Use of any of the restricted list of products known to inhibit drug metabolism or drug transport within 5 days prior to enrollment (Appendix 3).
d) Use of any of the restricted list of products known to stimulate drug metabolism or drug transport within 2 weeks prior to enrollment (Appendix 3).
e) Use of any of the restricted list of products to have a risk of Torsades de Pointes within 5 days prior to enrollment (Appendix 4).
f) Use of benzimidazoles (i.e., omeprazole, esomeprazole, lansoprazole, pantoprazole) or metoclopramide within 5 days prior to enrollment and after Cycle 1, Day 15 (Appendix 3).
g) Use of metoclopramide within 5 days prior to enrollment.
h) Use of an oral, injectable, or implantable hormonal contraceptive agent within 3 months of enrollment.;4) Other Exclusion Criteria
a) Prisoners or patients who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled into this study.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-11-2006
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Nexium
Generic name:	esomeprazole
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-10-2006
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-12-2006
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-04-2007
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2006-000005-38-NL
ClinicalTrials.gov	NCT00332748
CCMO	NL13481.031.06