A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and Safety of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Patients

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON37972

Source
ToetsingOnline

Brief title
MK0869-208

Condition

- Gastrointestinal conditions NEC

Synonym
nausea and vommitting associated with emetogenic chemotherapy

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme Corp.

Intervention

Keyword: Anti-emetic, Chemotherapy, Nausea, Vomitting

Outcome measures

Primary outcome

Complete Response (no vomiting and no use of rescue medication) in the 120 hours following the initiation of emetogenic chemotherapy in Cycle 1 (overall phase).

Secondary outcome

- Complete Response in the 0 to 24 hours following the initiation of emetogenic chemotherapy in Cycle 1 (acute phase).

- Complete Response in the 25 to 120 hours following the initiation of emetogenic chemotherapy in Cycle 1 (delayed phase).

- No Vomiting, regardless of rescue medication use, in the 120 hours following the initiation of emetogenic chemotherapy in Cycle 1 (overall phase).

- safety and tolerability of the three-day oral aprepitant regimen in patients from 6 months to 17 years of age who are receiving emetogenic chemotherapy in Cycle 1.

Study description

Background summary

Oral aprepitant (EMEND*), MK-0869 is a potent and selective substance P (neurokinin 1 (NK1) - receptor) antagonist that is given in combination with other antiemetic agents for the prevention of chemotherapy induced nausea and vomiting (CINV). Aprepitant received marketing approval in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC), including high dose cisplatin in March 2003; and for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) in October 2005. For both HEC and MEC, the currently approved 3-day dosing regimen in adults for orally administered aprepitant is 125 mg on Day 1 followed by 80 mg on Days 2 and 3, in combination with a 5-hydroxtryptamine (5-HT) type 3 receptor antagonist (5-HT3 antagonist) and dexamethasone. Aprepitant is not yet approved for use in children.
Nausea and vomiting remains a major problem in a significant number of children undergoing chemotherapy despite the wide use of 5-HT3 antagonists (i.e., ondansetron) with or without corticosteroids for antiemetic prophylaxis. Thus, there is an ongoing need to clarify the role of new anti-emetic agents, such as aprepitant, in alleviating CINV in children receiving emetogenic chemotherapy.

A recent Phase III study (PN097) was conducted to evaluate the safety of aprepitant triple therapy in adolescents, aged 12-17 years, with confirmed solid malignancies undergoing treatment with emetogenic chemotherapy. In PN097, the aprepitant triple therapy regimen was found to be generally safe and well tolerated, with the overall adverse event profile similar to what was previously reported in adults. The pharmacokinetic data in this study suggest that the aprepitant dosing regimen approved for CINV prevention in adults should also be appropriate in adolescent patients. Moreover, the use of aprepitant triple therapy regimen showed numerically greater response rates compared to the standard regimen suggesting a treatment difference between the two study arms, although the study was not powered for efficacy.

A second pediatric study examining the pharmacokinetics, safety and exploratory efficacy of aprepitant triple therapy in pediatric patients ages birth to 17 years, is ongoing (PN134). Results from PN097, PN134, and PN148 (an ongoing aprepitant pediatric pharmacokinetic study for post-operative nausea and vomiting (PONV)) are being evaluated together in order to inform age-appropriate dose(s) for the aprepitant triple therapy regimen in children.

Study objective

The purpose of this current study is to evaluate the efficacy and safety of the 3-day oral aprepitant regimen when administered concomitantly with ondansetron, with or without dexamethasone, in pediatric patients, from 6 months to 17 years

of age, receiving emetogenic chemotherapy for a documented malignancy.

Study design

Patients will be stratified into 4 age groups as follows:
• 12 to 17 years.
• 6 years to < 12 years.
• 2 years to <6 years.
• 6 months to <2 years.

This study will evaluate a 3-day regimen of oral aprepitant in combination with the 5-HT3 antagonist ondansetron. Patients will be randomized into 1 of 2 treatment arms and will receive either the 3-day regimen of oral aprepitant, in combination with ondansetron, beginning on chemotherapy Day 1, or ondansetron alone. Intravenous (IV) dexamethasone may be administered as part of the antiemetic regimen at the discretion of the investigator.

The main focus of this study will be on a single cycle of aprepitant (Cycle 1). Patients will have an opportunity to receive open-label aprepitant in subsequent cycles (Optional Cycles 2-6), if they elect to participate.

Intervention

GROUP 1
Patients 12 to 17 years of age:
Day 1: aprepitant 125 mg capsule PO + ondansetron
Days 2-3: aprepitant 80 mg capsule PO

Patients 6 months to <12 years of age
Day 1: aprepitant PFS: 3.0 mg/kg (up to 125 mg) + ondansetron
Days 2-3: aprepitant PFS: 2.0 mg/kg (up to 80 mg)

GROUP 2 (Control)
Patients 12 to 17 years of age:
Day 1: matching placebo for aprepitant 125 mg capsule PO + ondansetron
Days 2-3: matching placebo for aprepitant 80 mg capsule PO

Patients 6 months to <12 years of age
Day 1: matching placebo PFS: 3.0 mg/kg (up to 125 mg) + ondansetron
Days 2-3: matching placebo PFS: 2.0 mg/kg (up to 80 mg)

Intravenous dexamethasone may be administered as part of the anti-emetic regimen at the discretion of the investigator. If dexamethasone is administered as part of the anti-emetic regimen for patients receiving aprepitant, dexamethasone should be administered at 50% of the established dose

in children. No dose adjustment will be made for patients allocated to receive placebo for aprepitant; to maintain blinding, dexamethasone will be prepared in a blinded manner by an unblinded study pharmacist/designee. This recommendation may be modified, as needed, based on an ongoing pediatric pharmacokinetic study examining the interaction of dexamethasone and aprepitant in pediatric patients.

Study burden and risks

Risks: adverse reactions of aprepitant and ondansetron.

Burdens:
- Physical examination at screening/baseline.
- 3x ECG (cycle 1)
- Laboratory Safety test 3x in cycle 1 and 2x per cycle in de optional cycle 2-6
- 1x Laboratory Safety test at Study Discontinuation
- 3 daily administration of aprepitant or placebo administered concomitantly with ondansetron
- daily completion of patient diary by the patients or their parent for 6 consecutive days

Contacts

Public
Merck Sharp & Dohme (MSD)

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Male or female, 6 months to 17 years of age.
2. Patient is scheduled to receive chemotherapeutic agent(s) associated with moderate, high risk or very high risk of emetogenicity for a documented malignancy, or a chemotherapy regimen not previously tolerated due to vomiting.
3. Patient with documented malignancy at either original diagnosis or relapse;
4. Patient is expected to receive ondansetron as part of their antiemetic regimen.
5. Patient aged >10 years has a Karnofsky score >= 60; patient aged <= 10 years has a Lansky Play Performance score >= 60 .

Exclusion criteria

1. Patient is scheduled to receive stem cell rescue therapy in conjunction with study related course(s) of emetogenic chemotherapy.;2. Patient has a symptomatic primary or metastatic CNS malignancy causing nausea and/or vomiting. Patient who is asymptomatic is allowed to participate.;3. Patient has abnormal laboratory values as follows :
a. Bone Marrow Function
- Peripheral absolute neutrophil count (ANC) <1000/mm3
- Platelet count <100,000/ mm3
b. Liver Function
- AST>5.0 x upper limit of normal (ULN) for age
- ALT>5.0 x upper limit of normal (ULN) for age
- Bilirubin > 1.5 x upper limit of normal (ULN) for age
c. Renal function
- A serum creatinine > 1.5 x upper limit of normal (ULN) for age;4. Patient has been started on systemic corticosteroid therapy within 72 hours prior to study drug administration or is planned to receive a corticosteroid as part of the chemotherapy regimen.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-11-2011
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Emend
Generic name:	aprepitant
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Zofran
Generic name:	ondansetron
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	05-07-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	11-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-05-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2011-000651-16-NL
CCMO	NL36840.078.11
Other	Nog niet bekend