A phase III, randomized, placebo-controlled clinical trial to study the efficacy and safety of MK-0517/fosaprepitant and ondansetron versus ondansetron for the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric subjects receiving emetogenic chemotherapy

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

Summary

ID

NL-OMON42702

Source
ToetsingOnline

Brief title
MK0517-044

Condition

- Gastrointestinal conditions NEC

Synonym
nausea and vommitting associated with 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

The single IV dose of fosaprepitant in combination with ondansetron with or without dexamethasone (hereafter referred to as the fosaprepitant regimen) provides superior control of CINV compared to ondansetron alone with or without dexamethasone (hereafter referred to as the control regimen) as measured by the proportion of subjects with Complete Response (no vomiting, no retching, and no use of rescue medication) in the delayed phase (>24 to 120 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

Secondary outcome

- The fosaprepitant regimen is superior to the control regimen as measured by the proportion of subjects with Complete Response in the acute phase (0 to 24 hours) following the initiation of emetogenic chemotherapy in Cycle 1.
- The fosaprepitant regimen is superior to the control regimen as measured by the proportion of subjects with Complete Response in the overall phase (0 to 120 hours) following the initiation of emetogenic chemotherapy in Cycle 1.

- The fosaprepitant regimen is superior to the control regimen as measured by

the proportion of subjects with No Vomiting, regardless of rescue medication

use, in the overall phase (0 to 120 hours) following the initiation of

emetogenic chemotherapy in Cycle 1.

Study description

Background summary

For children undergoing chemotherapy, the current Multinational Association of Supportive Care in Cancer (MASCC), European Society for Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO) guidelines recommend the use of 5-HT3 antagonists,
such as ondansetron, and corticosteroids to alleviate nausea and vomiting associated with emetogenic chemotherapy. However, despite the widespread use of these agents, nausea and vomiting continue to occur and remain a major source of distress for children
undergoing emetogenic chemotherapy . Thus, there is an ongoing need to evaluate the role of new anti-emetic agents such as fosaprepitant for pediatric CINV.

Study objective

The objective of the study is to evaluate the efficacy and safety of a single dose of fosaprepitant when administered concomitantly with ondansetron, with or without dexamethasone, in subjects birth to 17 years of age receiving emetogenic chemotherapy for a documented malignancy.

Study design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind trial to evaluate the efficacy and safety of fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV). Subjects must be scheduled to receive chemotherapeutic
agent(s) associated with moderate or high risk of emetogenicity, or chemotherapy agent(s) not previously tolerated due to vomiting. This study is to be conducted in conformance with Good Clinical Practices. This study will endeavor to enroll an approximately even distribution of subjects into the following four age groups, but final enrollment in age groups may differ:
- Birth to <2 years,
- 2 to <6 years,
- 6 to <12 years,

- 12 to 17 years.

Remark: Subjects <12 years of age will NOT be permitted to participate in the current study until Pharmacokinetic/Pharmacodynamic (PK/PD) and safety data from an ongoing PK/PD and safety study (MK-0517 Protocol 029) can be evaluated to confirm the planned dose adjustments for subjects <12 years of age. Enrollment of subjects <12 years of age will begin once the study sites are notified of the final dosing instructions
via a written letter from the SPONSOR. The age categories may be adjusted if PK/PD data from the ongoing Protocol 029 do not support opening enrollment for one or more age group(s).

Randomization will be stratified by age, planned use of High Risk emetogenic chemotherapy agent in Cycle 1 and planned use of dexamethasone as an antiemetic in Cycle 1. The main objectives of this study will be assessed during a single chemotherapy cycle (Cycle
1), where study medication will be administered in a double-blind manner. Upon completion of Cycle 1, eligible subjects may be invited to participate in an open-label fosaprepitant treatment period for up to 5 more cycles of chemotherapy. Participation in open-label Cycles
2 to 6 is optional. All subjects will be allowed a maximum of 6 months from the end of Cycle 1 to complete Cycles 2 to 6.
In Cycle 1, subjects may be screened up to 28 days prior to randomization. Eligible subjects will then enter the double-blind treatment period and will be required to complete a Patient Diary for the 120 hours following the start of emetogenic chemotherapy administration.
Subjects will be followed for 14 days after treatment with fosaprepitant or placebo to fosaprepitant. Subjects will have 4 clinic visits and phone/direct contact will be made on Days 2-5 of Cycle 1. For cycle 1 is the screening visit extra and the visit on day 6-9. The follow up visit is only extra on day 15 to 20 in case no chemotherapy is administered.

Subjects will be re-evaluated before entering optional Cycles 2 to 6 to determine if entry criteria have been met. Subjects will be followed for 14 days after his/her treatment with fosaprepitant in the last study cycle. There are 2 clinic visits during each optional cycle. For cycle 2-6 is the follow up visit on day 15-20 extra in case no chemotherapy is administered.

Intervention

Cyclus 1
GROUP 1
Day 1: fosaprepitant +ondansetron
GROUP 2
Day 1: placebo for fosaprepitant + ondansetron

Cyclus 2 (optional)

Day 1: fosaprepitant +ondansetron

Intravenous dexamethasone may be administered as part of the anti-emetic regimen at the discretion of the investigator. For subjects receiving fosaprepitant, the dose of dexamethasone should be reduced to 50% of the prescribed dose when administered within 48 hours following administration of fosaprepitant. No dose adjustment will be made for subjects receiving placebo for fosaprepitant.

Study burden and risks

Risks: adverse reactions at screening/baseline

Burdens:
Cycle 1:
- physical examination at baseline/screening
- check vital signs
- completion of diary card (daily) during 6 days by the patients and their parents
- 3x ECG (screening, Day 1 and during the follow up visit)
- 3x blood sampling per central procedures for safety lab sampling: approx. 1,1 mL at the screening visit, approx. 0,6 mL during visit 2 and approx. 1,1 mL at follow up visit.
- urine pregnancy test if applicable
- administration of fosaprepitant with ondansetron or placebo with ondansetron with or without dexamethason.

Cyclus 2-6:
- physical examination at baseline/screening
- check vital signs
- 2x blood sampling for pharmacokinetics on Day 1 (in total approx. 2 mL). If the patient is still at the site or is returning at the site additional PK samples will be collected at up to 2 additional timepoints on day 2 en day 3.
- Administration fosaprepitant with 5-HT3 antogonist administration with or without dexamethason.

Contacts

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US

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

In order to be eligible for participation in this trial, the subject must, for cycle 1:;1.have parent/legal guardian (legally authorized representative) agreement to the subject*s participation as indicated by parent/legal guardian signature on the informed consent form. Subject 12 to 17 years of age, or as required by local regulation, assents and has the ability to understand the nature and intent of the study including the ability to comply with study procedures, complete study diary, and is willing to keep scheduled study visits. ;2.be 0 (at least 37 weeks gestation) to 17 years of age at time of randomization.;3.have a Lansky Play Performance score >=60 (subjects <=16 years of age) or a Karnofsky score >=60 (subjects >16 years of age) as defined in Section 12.4 -Lansky and Karnofsky Performance Status Scales.;4.have a predicted life expectancy >=3 months.;5.be receiving chemotherapeutic agent(s) associated with moderate or high risk of emetogenicity for a documented malignancy, or a chemotherapy regimen not previously tolerated due to vomiting. ;Cycle 1 only: If a subject*s chemotherapy regimen has multiple chemotherapies with different emetogenic potential, then the most emetogenic agent must be part of the Day 1 regimen. ;6.have a preexisting functional central venous catheter available for study drug administration.;7.Meet one of the following:;If the subject is a female who is of reproductive potential, the subject must: have a negative urine pregnancy test prior to fosaprepitant dosing in a cycle; must agree to avoid becoming pregnant in the 28 days prior to receiving study drug, while receiving study drug and for at least 30 days (or local standard of care if longer) after the last dose of study drug (including the optional cycles) by complying with one

of the following: (1) practice abstinence from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity.;The subject is a male.;The subject is a female who is not of reproductive potential, defined as a female who either: (1) has not begun menses; (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.;In order to be eligible for participation in an optional cycle, subject must meet inclusion criteria 5, 6 and 7 above in addition to the following:;8.have completed the preceding study cycle and related study procedures satisfactorily, have no unresolved drug related adverse events and continued participation in an optional cycle poses no unwarranted risk to the subject as determined by the investigator. ;9.have parent/legal guardian (legally authorized representative) or subject (if subject is 18 years old) agreement to the subject*s participation as indicated by parent/legal guardian or subject (if subject is 18 years old) signature on the informed consent form for the optional cycles. Subject 12 to 17 years of age, or as required by local regulation, assents and has the ability to understand the nature and intent of the study including the ability to comply with study procedures and is willing to keep scheduled study visits.;Refer to Protocol for complete list

Exclusion criteria

The subject must be excluded from participating in the trial if:;Exclusion criteria for Cycle 1 only:;1.has vomited in the 24 hours prior to chemotherapy initiation on Treatment Day 1.;2.has a symptomatic primary or metastatic central nervous system (CNS) malignancy with nausea and/or vomiting. Subject who is asymptomatic is allowed to participate.;3.has abnormal laboratory values as follows:;•peripheral absolute neutrophil count (ANC) <1000/mm3;•platelet count < 75,000/mm3;•aspartate aminotransferase (AST) > 5.0 x upper limit of normal (ULN) for age;•alanine aminotransferase (ALT) > 5.0 x ULN for age;•bilirubin > 1.5 x ULN for age;•creatinine > 1.5 x ULN for age;4.will be receiving stem cell rescue therapy in conjunction with study related course of emetogenic chemotherapy or during the 14 days following administration of fosaprepitant/placebo for fosaprepitant. ;5.has received or will receive total body irradiation or radiation therapy to the abdomen (includes the level of the diaphragm and below) or pelvis in the week prior to Treatment Day 1 and/or during the diary reporting period (120 hours following initiation of chemotherapy).;6.has had benzodiazepine (potential to alleviate nausea and vomiting), opioid or opioid like (e.g., tramadol hydrochloride) therapy (potential to enhance nausea and vomiting) initiated within 48 hours prior to study drug administration, or is expected to receive within 120 hours following initiation of chemotherapy, except for single daily doses of midazolam, temazepam or triazolam. Continuation of chronic benzodiazepine, opioid or opioid like therapy is permitted provided it was initiated at least 48 hours prior to study drug administration.;7.has been started on systemic corticosteroid therapy within 72 hours prior to study drug administration or is expected to receive a corticosteroid as part of the chemotherapy regimen.;Exceptions:;subject who is receiving chronic (>72 hours), daily steroid therapy can be enrolled provided the steroid dose is not >0.14 mg/kg (up to 10 mg) of prednisone daily or equivalent.;for supportive care, subject is permitted to receive a single dose of corticosteroid within 3 days prior (but not on the day of study drug administration) provided it is less than

the equivalent of 20 mg of prednisone.;8.is currently taking, or has taken within 48 hours of Treatment Day 1 the following drugs with antiemetic properties: 5-HT3 antagonists (e.g., ondansetron), benzamides (e.g., metoclopramide), butyrophenones (e.g., haloperidol), cyclizine, domperidone, herbal therapies with potential antiemetic properties, olanzapine, phenothiazines (e.g., prochlorpenzine), scopolamine. ;Exclusion criteria for Cycle 1 and optional Cycles 2 to 6:;9.is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial. ;10.is currently a user of any recreational or illicit drugs (including marijuana) or has current evidence of drug or alcohol abuse or dependence as determined by the investigator.;11.is mentally incapacitated or has a significant emotional or psychiatric disorder that, in the opinion of the investigator, precludes study entry.;12.is pregnant or breast feeding. ;13.is allergic to fosaprepitant, aprepitant, ondansetron, or any other 5-HT3 antagonist.;14.has a known history of QT prolongation or is taking any medication that is known to lead to QT prolongation. ;15.has an active infection (e.g., pneumonia), congestive heart failure, bradyarrythmia, any uncontrolled disease (e.g., diabetic ketoacidosis, gastrointestinal obstruction) except for malignancy, or has any illness which in the opinion of the investigator, might confound the results of the study or pose unwarranted risk in administering study drug or concomitant therapy to the subject.;16.has ever participated in a previous study of aprepitant or fosaprepitant or has taken a non-approved (investigational) drug within the last 4 weeks. Note: Subjects in investigational studies with marketed chemotherapeutic agents (whether explicitly for children or only marketed for adults and usually administered in children with the appropriate dose adjustments) are allowed to enroll if they fulfill all other entry criteria. Previous or current participation in an observational study is acceptable.;17.is currently taking, or has taken a CYP3A4 inducer (within 30 days of Treatment Day 1), a CYP3A4 substrate or inhibitor (within 7 days of Treatment Day 1) or is expected to receive within 120 hours following initiation of chemotherapy. Or, is currently taking warfarin or is expected to receive within 2 weeks following initiation of chemotherapy;Refer to Protocol for complete list

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:	Recruiting
Start date (anticipated):	04-03-2016
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fosaprepitant
Generic name:	IVEMEND
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:	25-08-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	21-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2016
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	EUCTR2014-001783-34-NL
CCMO	NL53748.078.15
Other	Nog niet bekend