A Multicentre, Randomized, Double-Blind, Double Dummy, Crossover Study to Evaluate the Safety and Efficacy of AD 923 (Fentanyl Sublingual) in Comparison to Morphine Sulphate Immediate Release (MSIR) for the Treatment of Breakthrough Pain in Subjects with Malignancies

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To evaluate the efficacy of AD 923 in comparison to MSIR in the management of breakthrough pain in subjects with malignicies who are taking a stable dose of background opioids.

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

Summary

ID

NL-OMON32360

Source
ToetsingOnline

Brief title
P-AD923-005 study

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Breakthrough cancer pain

Research involving
Human

Sponsors and support

Primary sponsor: i3 Research
Source(s) of monetary or material Support: Sosei R & D Ltd

Intervention

Keyword: AD 923 (fentanyl sublingual) Fentanyl Citrate, Breakthrough Cancer Pain, MSIR

Outcome measures

Primary outcome

AD 923 sublingual

safety and efficacy of AD 923 in comparison to MSIR

to show the usually rapid relief of pain with AD 923

to assess patient tolerability of AD 923

physical examination, including vital signs

laboratory assessments

assessment of mucositis

Secondary outcome

not applicable

Study description

Background summary

Title of te study

A study to see if AD 923 (fentanyl sprayed under the tongue) works and is safe

in patients with uncontrolled pain due to cancer.

Sosei R&D Ltd. has begun a research study of an investigational drug called AD 923 (fentanyl sublingual), as a possible treatment for breakthrough pain in patients with cancer.

Fentanyl is a potent opioid that has been in clinical use for many years in anaesthesia and for the treatment of pain and is approved by the Food and Drug Administration (FDA) and in Europe for different ways of administration.
The active ingredient of AD 923 is fentanyl, but sublingual (under the tongue) delivery is not registered yet.

Previous studies have shown that AD 923 may relieve breakthrough pain in patients with cancer and that pain relief was usually rapid. In terms of benifits, safe, effective, easily administered treatment is needed for BTP in patients with malignicies where the onset of pain is typically very quick. Additionally, the mode of delivery, including the option for administration by a caregiver, has the potential to overcome some of the problems faced by this population, including difficulty in swallowing or lack of dexterity.

Study objective

To evaluate the efficacy of AD 923 in comparison to MSIR in the management of breakthrough pain in subjects with malignicies who are taking a stable dose of background opioids.

Study design

A multicentre, randomised, double-blind, double-dummy, active comparator, crossover study.

Intervention

The evaluation of the efficacy of AD 923 (fentanyl sublingual) in comparison to MSIR in the management of BTP in subjects with malignancies who are taking a stable dose of background opiods.

Study burden and risks

Screening
1.questions will be asked to the subject about the medical history including; concomitant diseases and conditions, smoking history, a detailed history of pain condition, date of diagnosis of malignancy
2. physical examination
3. recording height and weight
4. vital signs

5. laboratory samples, where appropriate urine pregnancy test
6. a 12-lead ECG
7. record all concomitant medication
8. manifestations of opiods overdose
9. administer HADS and Breakthrough Pain Questionnaire
MSIR:
1. reconfirm all entry criteria are still met
2. record AEs
3. dispense MSIR after reviewing all laboratory and ECG results
4. issue diary and provide instructions and training in diary use
5. advise on safe use and storage of MSIR
during the MSIR baseline phase, the site will contact the subject by telephone daily to perform the following assessments:
1. review completed diary information
2. record AEs
3. record concomitant and rescue medications
4. review instructions for diary use
5. confirm diary connectivity and operation
6. assess compliance
AD 923 Titration Visit:
1. reconfirm all entry criteria are still met and assess additional inclusion criteria
2. record concomitant medications
3. draw blood for routine clinical laboratory tests
4. record vital signs
5. record AEs
6. review completed diary information
7. collect all study drug containers and assess compliance
8. review diary information from previous phase
9. provide instructions and training in diary use for next phase
10. confirm diary connectivity and operation
11. advise about the safe use and storage of AD 923
AD 923 Titration and Stabilisation phase:
1. discuss and review treatment
2. implement titration of dose, if needed and assess compliance
3. all steps mentioned in MSIR baseline phase, contact the subject by telephone
Treatment period 1:
1. reconfirm all entry criteria are still met and assess inclusion criteria for randomisation
2. confirm dose of MSIR and AD 923 for Crossover Phase
3. record concomitant medications
4. record vital signs
5. record AEs
6. review diary information from previous phase
7. randomly assign subject to treatment
8. collect all study drug containers and assess compliance
9. provide instructions and training in diary use for next phase

10. confirm diary connectivity and operation
11. dispense double-blind study drug for Treatment Periods 1 and 2
Treatment period 2:
1. record concomitant medications
2. record vital signs
3. record AEs
4. review diary information from previous period
5. confirm diary connectivity and operation
6. review diary insructions
7. collect all study drug containers and assess compliance
at the investigator's discretion, this visit may be conducted by telephone
Treatment period 3:
1. record concomitant medications
2. record vital signs
3. record AEs
4. review diary information from previous period
5. confirm diary connectivity and operation
6. review diary insructions
7. collect all study drug containers and assess compliance
8. dispense double-blind study drug for Treatment Perios 3 and 4
Treatment period 4:
the same assessments as treatment period 2
End of Treatment:
1. record concomitant medications
2. perform physical examination
3. perform mucositis assessment
4. record vital signs
5. draw blood for routine clinical laboratory tests
6. perform urine pregnancy test for all women of childbearing potential
7. administer 12-lead ECG
8. administer HADS
9. administer Breakthrough Pain Questionnaire
10. collect and review diary
11. collect all study drug containers and assess compliance
12. record AEs
13. for subjects wishing to continue with open-label Ad 923, review inclusion and exclusion criteria for Protocol P-AD923-006
Follow-up:
subjects who choose not to enter the open-label extension study will be assessed at an additional follow-up visit, 1 week after completion of double-blind treatment for safety purposes
1. record concomitant medications
2. perform physical examination
3. perform mucositis assessment
4. record vital signs
5. draw blood for routine clinical laboratory tests
6. perform urine pregnancy tests for all women of childbearing potential

7. administer 12-lead ECG
8. record AEs

Contacts

Public
i3 Research

Gevers Deynootweg 93L
2586 BK, Den Haag
Nederland
Scientific
i3 Research

Gevers Deynootweg 93L
2586 BK, Den Haag
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. male or female subjects, 18 years of age and older
2. subjects has a malignancy, receiving opioid therapy, and is tolerant to the opioid therapy. the dose of opioid therapy must be stable for at least 7 days prior to screening visit and should not be changed during the study. mimimum dose of opioid therapy should be 60 mg of morphine or morphine equivalent or 50 µg/hour transdermal fentanyl
3. subject has established an optimal stable dose of MSIR for the treatment of BTP (range 10-60 mg per dose) and has been on this dose for at least 3 consecutive days
4. subject has 2-6 episodes of target BTP per day that require treatment. Breakthrough pain

is defined as a transitory flare of moderate to severe pain (on a 4-point scale from 1 to 4; mild, moderate, severe, excruciating) that occurs on a background of persistent pain controlled to moderate intensity or less (as defined by the Breakthrough Pain Questionnaire) by th opioid regimen. if a subject has more than 1 type of BTP, or has BTP in more than 1 location, only 1 of the pains will be identified as a ' target' BTP
5. if female, the subject has a negative urine pregnancy test and is not lactating, or has not been of childbearing potential for at least 3 months prior to study drug administration (postmenopausal for at least 2 years, have had a hysterectomy or bilateral tubal ligation, or be proven to be otherwhise incapable of pregnancy. if of childbearing potential, the subject must have been participating one of the following methods of contraception consistently for at least 1 month prior to study entry and agree to continue participating it during the study: hormonal contraceptives, intrauterine device, spermicide and barrier, spouse/partner sterility; or is practicing abstinence and agrees to continue abstinence or to start an acceptable method of contraception from the above list if sexual activity commences
6. subject is able and willing to understand the study and cooperate with all study instructions
7. subject is able and willing to provide written informed consent
8. subject has a Karnofsky score of *60
9. subject has a life expectancy of *3 months
10. subject or his her caregiver has easy, reliable access to a telephone
Additional Inclusion Criteria for the AD 923 Titration and Stabilization Phase
In addition, subjects must meet all of the following criteria prior to entering the AD 923 Titration and Stabilisation Phase
1. subject continues to meet the critera listed above
2. subject has established an optimal stable dose of MSIR for the treatment of BTP (range of 10-60 mg per dose) and has been on this dose for at least 3 consecutive days. optimal dose of MSIR is defined as the dose that provides, in the subject's and investigator's opinion, the best balance between relief and target pain (in particular without requiring rescue medication) and side effect profile; the selected dose should be stable across 3 consecutive days
3. subject is skilled and compliant with completion of the daily diary for at least 3 consecutive days during the Screening and MSIR Baseline Phase
Inclusion Criteria for Randomisation
in addition, subjects must meet all of the following criteria prior to randomisation and entering the Double-blind Crossover Phase
1. subjects continues to meet criteria 'a' through 'j' listed above
2. subject has been on an optimal stable dose of AD 923 for at least 3 days, optimale stable dose is defined as the dose that provides, in subject's and investigator's opinion, the best balance between relief to target pain (in particular without requiring rescue medication) and side effect profile; the selected dose should be stable across 3 consecutive days
3. subject is at least 80% compliant with completion of the daily diary for at least 3 consecutive days during the AD 923 Titration and Stabilisation Phase

Exclusion criteria

1. subject is a female who is pregnant or lactating
2. subject has any respiratory or cardiac condition that, in the opinion of the investigator, may be clinically worsened by opioids
3. subject has an allergy to the AD 923 product or excipients, namely: fentanyl, dehydrated alcohol, menthol, saccharin, and citrate buffer; or to the MSIR product excipients, namely: morphine sulphate, lactose (anhydrous), pregelatinized maize starch, povidone, purified water, magnesium stearate, talc, and tablet coatings
4. subject has any neurological or psychiatric disease that, in the opinion of the investigator, would compromise data collection
5. subject has uncontrolled or rapidly escalating pain
6. subject has a history of alcohol or substance abuse within the last 2 years
7. subject has hepatic dysfunction as shown by liver function tests (i.e., ALT, AST, ALP, or bilirubin) elevated more than 5 times the upper limit of normal
8. subject has renal dysfunction as shown by creatinine elevated more than 1.5 times the upper limit of normal
9. subject has any significant laboratory test results that, in the opinion of the investigator, will compromise subject safety or the conduct of the study
10. subject has uncontrolled infection
11. subject has received treatment with an investigational drug or has participated in a clinical study within 4 weeks of the screening visit
12. subject has had treatment with radiotherapy to a painful site within 14 days prior to study entry or has had any therapy that could alter pain or response to pain medication
13. subject is taking intrathecal or epidural forms of opioids
14. subject is taking any prohibited medications as described in the concomitant medication section
15. subjects has plans to undergo chemotherapy, radiotherapy, or surgery during the treatment period. the exception is that subjects may continue chemotherapy over the study period, provided it is not expected to alter the pain state or response to pain medication

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2007
Enrollment:	33
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Does not yet exist
Generic name:	Sublingual Fentanyl Spray
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sevredol®
Generic name:	Morphine Sulphate Immediate Release tablets

Ethics review

Approved WMO

Date:	05-11-2007
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

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	EUCTR2007-000558-30-NL
CCMO	NL20007.028.07