An Open Label, Phase 1/2a Trial to Evaluate the Efficacy, Safety, and Tolerability of KU002 Given as Intravesical Instillations in Subjects with Interstitial Cystitis (IC)/Bladder Pain Syndrome (BPS)*

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Primary Objective:The primary objective of this study is to evaluate the safety, tolerability and PK profile following intravesical administration of KU002 in subjects with a diagnosis of BPS/IC.Secondary Objective(s):The secondary objective of the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON52788

Source
ToetsingOnline

Brief title
Phase 1/2a Evaluation of Safety and Efficacy of KU002 in BPS/IC

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
Bladder Pain Syndrome, Interstitial Cystitis

Research involving

Human

Sponsors and support

Primary sponsor: Kuste Biopharma
Source(s) of monetary or material Support: Kuste Biopharma

Intervention

Keyword: BPS/IC, Intravesical Instillations, KU002, safety and efficacy

Outcome measures

Primary outcome

-Incidence and severity of AEs over the course of the study.

• Hematology, biochemistry, and urinalysis. While total white blood cell (WBC) count will be expressed in absolute values, differential count will be expressed as both absolute count and percentage of WBCs.

• Absolute change from baseline to EoT+1 in ECG readings.

• ECG parameters of interest include ventricular rate, QT interval, corrected QT interval, PR interval, and QRS duration.

• Absolute change from baseline to each visit in standardized cuff systolic and diastolic blood pressure and radial heart rate.

• Pharmacokinetics: Determination of concentration of KU002 in plasma at the given time points, presented descriptively.

Secondary outcome

-Absolute change in pain, measured as mean value over 3 days, on the 11-point Numerical Rating Scale from baseline to EoT+1.

• Change in O*Leary Sant ICSI-ICPI participant reported questionnaire from baseline to EoT+1.

• Responder analysis: Proportion of subjects who have at least a 2-point

reduction in pain score measured by NRS between baseline and EoT+1.

• Change in the maximum daily pain score from baseline to EoT+1.

• Change in Subject*s Global Response Assessment (GRA) at EoT+1.

• Change in NRS, O*Leary Sant ICSI-ICPI after 3 instillations and to EoT+1.

• Change in 3-day voiding diary from baseline to EoT+1.

• A visual inspection of Hunner*s lesion before and after treatment to

determine any effect on the lesion.

Study description

Background summary

IC is a condition which can have a significant negative impact on the psychological well-being, social functioning and overall quality of life (QoL) of those affected, and very limited medical treatment options are available. The two main approaches are oral medications and bladder instillations used with the intention to alleviate pain and inflammation.
KU002 is an investigational anti-inflammatory compound exerting its effect in the JNK pathway. The JNK pathway, which is central to the inflammatory cascade, may serve as a modulator for the disease pathology/symptomatology in IC. Treatment effects were evaluated in a model of cyclophosphamide-induced IC in the rat and demonstrated an effect to increase the nociceptive threshold in treated animals. While this model represents an established experimental model to screen potential compounds for biologic effect, it is not predictive of effects in humans. The purpose of this clinical proof of concept study is to gain a first experience in subjects as to whether KU002, acting on JNK in the inflammatory cascade, could be administered safely and with acceptable tolerability while also providing the benefit to relieve symptoms of pain and visually indicate any effect on the pre-existing Hunner*s lesions

Study objective

Primary Objective:
The primary objective of this study is to evaluate the safety, tolerability and PK profile following intravesical administration of KU002 in subjects with a diagnosis of BPS/IC.

Secondary Objective(s):
The secondary objective of the study is to evaluate the efficacy of KU002 in subjects with a diagnosis of BPS/IC.

Study design

This is an open-label exploratory study. All subjects will enter the Screening Period during which eligibility will be assessed. Eligible subjects will receive KU002 intravesically 6 times through bladder catheterization. The subjects will be asked to hold the instillation for at least 30 min, and max 2 h. The time of urination post-instillation will be recorded.
Figure 1: Study Design
All subjects will start treatment with 25 mg KU002 (baseline, week 0), followed by 50 mg (week 2) and 100 mg (week 4). PK samples will be taken after each dose. The escalation to the next dose will be decided based on safety and PK parameters; the dose increase will only occur until plasma levels reaches 4000 ng/mL at Cmax or 500 ng/mL at the 4h timepoint. The decision to escalate the dose will be taken by the Investigator based on any AE reported and the results of the PK analyses in the subject.
The dose for the remaining 3 instillations in each subject will be the dose with a PK measure within the limit 4000 ng/mL at Cmax or 500 ng/mL at 4h; the maximal dose will be 100 mg/administration. These 3 instillations will be given at weekly intervals (week 6, 7 and 8).
If the subject has a PK exposure higher than indicated, the following instillations will be given at the previous (lower) dose level. If the subject does not tolerate the lowest dose level (25 mg) they will be discontinued from the study.
Final assessments of safety, tolerability and efficacy will be conducted 1 week after the last administration in each subject, referred to as End-of-Treatment +1 week [EoT+1].
All subjects will return to the clinic for a safety follow-up visit 4 weeks after their last administration of study drug (EoT+4).
Thirteen patients have gone through phase 1as described above. The measured PK values **after each instillation have been measured, a maximum of 43 ng/ml has been measured. This is 100x lower than the allowed plasma level (4000 ng/ml). This is reason to add a new cohort of 4-6 patients who will receive a dose 2x as high as the maximum dose in the first phase (highest dose phase 1 = 100 mg, phase 2: 1x 100 mg, then 6X 200 mg , if safety allows, PK level okay, and no side effects).
Further setup of phase 2 is the same as for phase 1.

Intervention

The investigational medicinal product (IMP) is KU002 (active pharmaceutical ingredient is brimapitide), given intravesically through bladder catheterization. All subjects in this study will receive the IMP.

Study burden and risks

This study is for adults (aged over 18 years) with a confirmed IC diagnosis. IC has been shown to have a significant negative impact on the psychological well-being, social functioning, and overall QoL of those affected. The positive effects of brimapitide on pain score, which is a key feature in patients with IC, have been demonstrated in non-clinical studies. Therefore, the Risk/Benefit for the use of brimapitide in the proposed study is considered acceptable.

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. Be at least 18 years of age.

2. Willing to provide written informed consent.
3. Willing and able to comply with study requirements and visit schedule.
4. Have a diagnosis of IC/BPS for at least 6 weeks prior to screening.
5. Have undergone a cystoscopy and have visible signs of Hunner*s lesion (photo documented) within 6 weeks prior to study inclusion. If the cystoscopy was not performed within 6 weeks of study inclusion, a new cystoscopy (incl photo of the Hunner*s lesion) must form part of the screening eligibility procedure.
6. Have an average daily pain score (recorded over 3 days) > 4 but <9 on the 11-point Numerical Rating Scale (NRS) in the 3 days prior to inclusion.
7. Be ambulatory and able to use the toilet independently.
8. Have a body mass index >=19 kg/m2 but <=35 kg/m2.
9. Have a pre-dose mean systolic/diastolic blood pressure of <=140/90 mmHg before randomization can occur.
10. Must not be pregnant, lactating, or actively trying to become pregnant, Subjects who are premenopausal and of childbearing potential must have a negative pregnancy test at Screening (serum) and at Day 0 (urine) and must use a medically acceptable and effective method of birth control for the duration of the study, which can include:
a. Having a male partner who is sterile prior to the female subject*s entry into the study and is the sole sexual partner for that female subject.
b. Use of double-barrier methods of contraception; condoms with the use of caps (with spermicide) and intra-uterine devices are acceptable.
c. Use of hormonal contraceptives (oral, depots, patches, etc.) with double-barrier methods of contraception as outline above.
d. True abstinence: When this is in line with the preferred and usual lifestyle of the subject (period abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).
e. Male study participants must use a condom for sexual intercourse from screening until at least 90 days after last dose of study drug, unless they have been surgically sterilized (vasectomy).

Exclusion criteria

1. Current or recent (30 days prior to screening) change in any pharmacologic agent or invasive procedure (e.g. fulguration) used to treat the IC/BPS condition. Patient is eligible to participate in the study if their treatment for IC/BPS has remained stable for the past month prior to entry.
2. Concurrent (at Screening), recent (within 30 days), chronic, or recurrent (>4 per year) urinary tract infections (positive dipstick for urinary tract infection and abnormal microscopic evaluation, signs and symptoms) or unevaluated microhematuria.
3. Having a history of previous procedure that affects bladder function (e.g. augmentation, cystoplasty, cystectomy, partial bladder resection, cystolysis etc.).

4. History of cyclophosphamide or chemical cystitis, urinary tuberculosis, radiation cystitis or history of pelvic irradiation.
5. Electrostimulation, biofeedback, or bladder training therapy (behavioral therapy), during the previous month prior to Screening, or the intention to initiate such therapies during the study.
6. Postvoid residual (PVR) urine volume >150 mL.
7. Diagnosis of dementia.
8. Subjects with uncontrolled hypertension.
9. Documented history of myocardial infarction, unstable angina, and/or has undergone coronary artery bypass surgery and/or percutaneous transluminal coronary angioplasty in the past year.
10. Congestive heart failure (New York Heart Association Class III or IV heart failure).
11. Any concurrent condition or any clinically significant abnormality on the Screening physical examination, laboratory tests, electrocardiogram (ECG; including ischemic heart disease), Hepatitis B or C, which, in the opinion of the Investigator, may affect the interpretation of efficacy or safety data, or which otherwise contraindicates participation in a clinical study with KU002.
a) Hypersensitivity to KU002 or any of its ingredients.
b) History of clinically significant drug hypersensitivity.
c) History of urogenital neoplasms or malignancies including bladder, urethra, uterine, cervical or vaginal cancer.
d) For men: history of prostate surgery (transurethral resection of the prostate [TUR-P], transurethral resection of tumor, [TUR-T], transurethral incision of the prostate [TUIP], transurethral needle ablation [TUNA]), history of prostate cancer or currently (within 30 days) being treated for chronic bacterial prostatitis.
e) Subjects with neuropathology that could affect the lower urinary tract or nerve supply, including but not limited to multiple sclerosis, stroke, Parkinsonism, or spinal cord injury.
f) Clinically significant or unstable endocrine, hepatic, renal, immunologic (incl immune suppressive and autoimmune) disease or malignancy other than non-melanomatous skin cancer.
12. Severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73m2).
13. Hepatic impairment (Child-Pugh B or greater).
14. Use of medications for BPH (eg Tamsulosin, silodosin, alfulozin and finasteride) within a month prior to study entry.
15. History of an addiction to drugs or alcohol within the last 2 years prior to Screening as determined by the Investigator.
16. Participation in a clinical study within a month prior to Screening, or exposure to an investigational drug which has not washed out for at least 5 half-lives since the last administration prior to Screening.
17. Participation in any clinical study of an investigational drug that may affect bladder function within 3 months prior to Screening.
18. In the opinion of the Investigator, is at risk of non-compliance with study procedures, or cannot read, understand, or complete study-related materials,

particularly informed consent.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-11-2020
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KU002
Generic name:	brimapitide

Ethics review

Approved WMO Date:	18-05-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-09-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	21-10-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-07-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2020-001729-29-NL
CCMO	NL73909.091.20

Study results

Date completed: 03-05-2023

Results posted: 03-08-2023

First publication
24-07-2023