A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Multiple Escalating Doses of Intravenous WCK 4282 in Healthy Adult Human Subjects

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To evaluate the safety and tolerability of multiple escalating doses of intravenous WCK 4282 in healthy, adult, human subjects.To evaluate the pharmacokinetics (PK) of multiple escalating doses of 1g:1g (1 vial) of intravenous (IV) WCK 4282 every 8...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON41090

Source
ToetsingOnline

Brief title
WCK 4282 Phase 1 MAD Study

Condition

- Bacterial infectious disorders

Synonym
Bacterial infections

Research involving

Human

Sponsors and support

Primary sponsor: Wockhardt Bio AG
Source(s) of monetary or material Support: Wockhardt Bio AG

Intervention

Keyword: pharmacokinetics, randomized, safety, tolerability

Outcome measures

Primary outcome

Safety, tolerability and pharmacokinetics

Secondary outcome

N.A.

Study description

Background summary

The Investigational Product (IP) is WCK 4282, Wockhardt*s proprietary injectable, antibacterial combination product consisting of cefepime and tazobactam. Each vial of WCK 4282 is available in a fixed dose combination of 1g cefepime and 1 g tazobactam. Cefepime is a *fourth generation* cephalosporin with an extended spectrum of activity against Gram-negative and Gram-positive pathogens. Cefepime was introduced in clinical practice in 1994. Cefepime is approved for the treatment of moderate to severe infections such as pneumonia, empiric therapy for febrile neutropenia, uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, and complicated intraabdominal infections (United States, Food and Drug Administration [FDA] approved indications). Cefepime doses for the treatment of the above-mentioned indications range from 0.5 to 2 g every 8 to 12 hours (q8h to q12h) daily for approximately 7 to 10 days.

Unlike other extended spectrum cephalosporins, the methylpyrrolidinium group of cefepime confers a zwitterionic charge that enhances bactericidal activity by rapid penetration through porin channels in the outer membrane of Gram-negative pathogens. Being a fourth generation cephalosporin, cefepime is more potent than third generation cephalosporins such as ceftazidime. Most importantly, it

tends to be superior to even ceftazidime against Pseudomonas strains. One of the important attributes of cefepime is that it withstands the hydrolysis by varieties of extended spectrum lactamase enzymes (ESBLs). In particular, Enterobacteriaceae that harbor inducible chromosomal AmpC Beta-lactamases, such as Citrobacter, Enterobacter, Proteus, Serratia, etc, are typically resistant to third generation cephalosporins, but demonstrate susceptibility to cefepime. Even Enterobacteriaceae which are high-level producers of AmpC Beta-lactamases, and are ceftazidime resistant, may still show a moderate rise in cefepime minimum inhibitory concentration (MIC). Consequently, cefepime is an attractive choice for combining with an appropriate lactamase inhibitor active against both class A and class C enzymes. Such a combination is also likely to remain effective even against strains co-expressing Class A and Class C lactamases.

Tazobactam, triazolyl-substituted penicillanic acid sulphone, is a Beta-lactamases inhibitor that has been successfully combined with piperacillin to protect this antibiotic from Class A ESBLs which mediate hydrolysis. Tazobactam is safe and has been used extensively clinically in combination with piperacillin by various manufacturers, including under the brand name Zosyn, which is approved for a range of indications. United States FDA approved indications include appendicitis/peritonitis, uncomplicated and complicated skin and soft tissue infections, postpartum endometritis, community-acquired pneumonia, and nosocomial pneumonia. The usual daily dose of Zosyn for adults is 3.375 g every 6 hours totaling 13.5 g (12 g piperacillin and 1.5 g tazobactam). The recommended dose for nosocomial pneumonia subjects is 4.5 g every 6 hours totaling 18 g (16 g piperacillin and 2 g tazobactam).

While ESBL inhibition by tazobactam is comparable to clavulanic acid for most Class A enzymes such as SHV and TEM, it is many folds superior to clavulanic acid with respect to inhibition of Class C enzymes such as AmpC. However, this property of tazobactam (i.e., AmpC inhibition) has not been clinically realizable since it was combined with readily hydrolyzable Beta-lactams such as piperacillin and cephalosporins such as ceftriaxone and ceftazidime (combinations available in India and emerging markets). Additionally, the lower proportion [cephalosporin: tazobactam = 8:1] of tazobactam in these current combinations does not result in the in vitro activity against Class C ESBL producing strains. Therefore, the present product of WCK 4282 was designed using the unique properties of cefepime and tazobactam such as high potency, relative ESBL stability, and AmpC inhibition. Moreover, the increased proportion [1:1] of tazobactam in the combination of WCK 4282 translates into clinically relevant synergy against AmpC and Klebsiella pneumoniae carbapenemase (KPC) strains in addition to Class A ESBL strains. An important consideration for choosing cefepime is the higher susceptibility breakpoint (8 micro g/mL) assigned to it, which suggests very favorable pharmacokinetics (PK) pharmacodynamics (PD), which in turn could be useful in harnessing synergistic interactions based on the higher proportion of tazobactam found in WCK 4282.

WCK 4282 could find significant clinical utility in the treatment of inhibitor

resistant ESBLs, AmpC, KPCs and derepressed ESBLs which are not treatable by currently marketed cephalosporin based combinations and other combinations such as piperacillin-tazobactam, ampicillin-sulbactam, and amoxicillin-clavulanic acid. Moreover, owing to multidrug resistant features of ESBL producing organisms, fluoroquinolones and aminoglycosides would likely also have very limited clinical use against such pathogens. The wider coverage of pathogens by WCK 4282 could circumvent the need of carbapenem usage as the first line of treatment (*carbapenem sparing*) for infections caused by ESBL pathogens and would be expected to address all indications which are currently approved for cefepime. The established safety profile of both cefepime and tazobactam along with significant coverage of ESBL could lead to empiric use particularly for complicated urinary tract infections, pneumonia, complicated intraabdominal infections, and acute bacterial skin and skin structure infections.

Study objective

To evaluate the safety and tolerability of multiple escalating doses of intravenous WCK 4282 in healthy, adult, human subjects.

To evaluate the pharmacokinetics (PK) of multiple escalating doses of 1g:1g (1 vial) of intravenous (IV) WCK 4282 every 8 hours (q8h), and 2g:2g (2 vials) of WCK 4282 every 12 hours (q12h) and every 8 hours (q8h) in healthy, adult, human subjects.

Study design

This study is a Phase 1, randomized, double-blind, single center, prospective, placebo-controlled, comparative, sequential, cohort study in 30 healthy male and female subjects

Intervention

The study will start with a screening visit. During the screening visit standard medical assessments including safety laboratory tests (blood draw, urine collection), an alcohol breath test, urine drug screen, a physical examination, ECG and a vital signs measurement will be performed.

During study the subjects will enter the clinic, will receive medication q8h or q12h, will be asked on a regular basis for possible side effects, blood will be drawn for safety and PK measurements, urine will be collected for safety and PK measurements and vital signs and ECG will be checked regularly during the confinement period.

Finally a follow-up examination will be performed. During this visit the subjects will be asked for possible side effects, blood will be drawn for safety, the vital signs/ECG will be checked and a physical examination will be

conducted.

Study burden and risks

The risk is small. The subjects will be closely monitored. The subjects will be regularly questioned for any side effects and regular safety tests are scheduled (ECG / Vital Signs/Lab). In addition the subjects will be asked to report, as soon as possible, any changes in physical and/or mental well being.

The blood collection procedure is not dangerous, but may cause discomfort or bruising. Occasionally fainting or an infection at the blood sampling site may occur.

Shaving may be required for proper placement of the ECG patches. This may cause irritation or bleeding of the skin. The ECG patches may cause redness of the skinn, itching or rash. In addition when the paches are removed hairloss may occur.

Contacts

Public
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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. Male or female, 18-65 years of age both inclusive
2. Have a body Mass Index (BMI) between 18 to 30 kg/m2 (both inclusive) calculated as weight (kg) / height (m2)
3. Medical history without any major pathology
4. Resting supine blood pressure 90-139 (systolic) / 40-89 (diastolic) mmHg, a resting pulse rate of 40-100 beats per minute or higher, computerized 12-lead electrocardiogram (ECG) recording without signs of clinically relevant pathology and showing no clinically relevant deviations as judged by the Principal Investigator
5. Glomerular filtration rate (GFR) > 80 mL/min.
6. All values for blood and urine tests within the normal range or showing no clinically relevant deviations as judged by the Principal Investigator. Re-screening may be allowed only once.
7. Abstain from alcohol, methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, "powerdrinks"), grapefruit or grapefruit (juice) from 48 hours prior to entry in the clinical research center (Day -1) until discharge
8. Females must be non-pregnant and not breast feeding (non-pregnancy will be confirmed by a serum pregnancy test conducted at screening and prior to any dosing period), or of no childbearing potential at screening.
9. In sexually active subjects, willingness to use 2 effective methods of contraception, of which one must be a physical barrier method (a condom, a diaphragm or cervical/vault cap), and other could be oral contraceptives, intra-uterine device or spermicidal jelly. Since a systemic or individual effect of WCK 4282 on the PK of oral contraceptives cannot not be ruled out, females on oral contraceptives will be informed of a possible effect and asked to continue their contraceptive daily between screening and the last follow-up (i.e., also continue with contraceptive during a possible planned stop week).
10. Males should not donate sperm until 90 days after the follow-up visit.
11. Willing to sign the Informed Consent Form and adhere to the study restrictions and assessment schedule.

Exclusion criteria

1. Receipt of WCK 4282 in the past.
2. History or evidence of clinically relevant pathology which might compromise the haemopoietic, renal, hepatic, endocrine, pulmonary, central nervous, cardiovascular, immunological, dermatological, gastrointestinal or any other body system.
3. History of epilepsy

4. Active Candida infection
5. Cystic fibrosis
6. Mental handicap
7. History of relevant drug and/or food allergies particularly known hypersensitivity to cefepime or tazobactam, cephalosporins or penicillins.
8. Receipt of a prescription or non-prescription drug within 14 days prior entry into clinical research centre (Day -1) except for acetaminophen (paracetamol) which is allowed for up to 3 days prior entry into clinical research centre (Day -1). Multivitamins and vitamin C are allowed up to 7 days before entry into the clinical research centre (Day -1).
9. Smoking within 60 days prior to drug administration and through the follow-up visit.
10. History of alcohol abuse and/or drug addiction (including soft drugs like cannabis products)
11. Intake of more than 21 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 30 mL of spirits)
12. Participation in a drug study within 90 days prior study start.
13. Donation of blood (500 mL or more) within 90 days prior to study start (Day -1).
14. Positive drug screen (opiates, methadone, cocaine, amphetamines, cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol)
15. Positive screen on hepatitis B surface antigen (HBsAg), anti hepatitis C virus (HCV) antibodies or anti human immunodeficiency virus (HIV) 1/2 antibodies
16. Illness within 5 days prior to drug administration that may impact safety assessments, in the opinion of the Principal Investigator
17. Strenuous activity (e.g., sports) is not allowed from 96 hours (4 days) prior to entry into the clinical research center (Day -1) and throughout the study (until the final follow-up visit has been conducted)

Study design

Design

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):	04-08-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N.A.
Generic name:	Cefepime / Tazobactum

Ethics review

Approved WMO Date:	21-07-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-07-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-08-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2014-002633-55-NL
CCMO	NL49891.056.14