2 SYNOPSIS

Name of Sponsor/ Company: **Inserm** - Pôle Recherche Clinique (PRC) / Clinical Research Department Biopark, Bâtiment A, 8 rue de la Croix Jarry, 75013 Paris (FRANCE)	
Name of Investigational Medicinal Product: Gepotidacin (GSK2140944)	
Name of active ingredient(s): Gepotidacin tablets [GSK2140944E (mesylate salt dihydrate) 750mg]	
Title of Study Penetration of the innovative antibiotic gepotidacin into prostate and tonsillar tissue.	
Investigator(s): **Site AKH Vienna**: Markus ZEITLINGER, MD, Department of Clinical Pharmacology Medical University Vienna Spitalgasse 23 1090 Vienna, AUSTRIA **Site Vienna Klinik Donaustadt**: Peter FRANZ, MD, Department of Ear, Nose and Throat Diseases, Langobardenstraße 1220 Vienna, AUSTRIA **Site CHU of Tours**: Franck BRUYÈRE, MD, Urology Department, CHU de Tours 2 Boulevard Tonnellé, 37000 Tours, FRANCE **Sites CHU of Poitiers**: Xavier DUFOUR, MD, ENT Department & Thomas CHARLES, MD, Urology Department, CHU de Poitiers, 2 Rue de la Milétrie, 86021 Poitiers; FRANCE	
Study Centers: **Site AKH Vienna**: Department of Clinical Pharmacology Medical University Vienna Spitalgasse 23 1090 Vienna, AUSTRIA **Site Vienna Klinik Donaustadt**: Department of Ear, Nose and Throat Diseases, Langobardenstraße 1220 Vienna, AUSTRIA **Site CHU of Tours**: Department of Urology, CHU de Tours 2 Boulevard Tonnellé, 37000 Tours, FRANCE **Sites CHU of Poitiers**: Department of ENT and Department of Urology, CHU de Poitiers, 2 Rue de la Milétrie, 86021 Poitiers, FRANCE	
Publication (reference):	
Study period (years): 3 years *(date of first enrolment)* 29 Jan 2021 *(date of last completed)* 27 May 2023	**Phase of Development:** Phase II

Objectives:

Primary Objectives

- To obtain pharmacokinetic data of gepotidacin in plasma and interstitial space fluid of prostate and tonsillar tissue after the administration of a single oral dose of 1500 mg gepotidacin

Secondary Objectives

- Pharmacokinetic/pharmacodynamic (PK/PD) calculations in relation to common pathogens and possible breakpoints.
- Collection of safety data of gepotidacin

Methodology:

Prospective, open-labelled, randomized and multi-centre study.

Main activities during study period:

· Administration of gepotidacin prior to surgery

· Ex-vivo microdialysis in removed prostate or tonsil

· Plasma sampling

Number of participants (planned and analyzed):

Planned:

Cohort A: Male participant with localized prostate cancer scheduled to undergo radical prostatectomy and participant with benign prostate hyperplasia scheduled to undergo simple prostatectomy (n=30)

Cohort B: Male and female participants undergoing complete tonsillectomy (n=30)

Number of participants analyzed (subjects who received the study treatment):

Cohort A: 30

Cohort B: 18

Inclusion Criteria:

<u>Cohort A only</u>

- Clinically localized prostate cancer or benign prostate hyperplasia
- Male participant scheduled for prostatectomy

<u>Cohort B only</u>

- Male or female participant scheduled for complete tonsillectomy
- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

→ Is not a woman of childbearing potential (WOCBP) or

→ Is a WOCBP with a highly sensitive negative pregnancy test

Both Cohorts

- Age: above18 years
- Body weight ≥40 kg and body mass index (BMI) within the range 18.5 – 32.0 kg/m2
- A signed and dated written informed consent form
- The subject is able to understand and willing to comply with protocol requirements and timetables, instructions and protocol-stated restrictions
- Negative serology (human immunodeficiency virus, hepatitis B-AG and C-AB) at screening
- Participant with a social security or health insurance (if applicable according to the local regulation

Exclusion Criteria:

Cohort A only

- Any concerns of the investigator or the treating urologists that the participation in the study might impair histological assessment of the prostate tissue such as (but not limited to): lack of representative histology via previous biopsy AND inability to safely insert microdialysis probes in tissue with sufficient distance to the tumor (e.g. large or diffuse tumor, lack of MRI or PET image to locate tumor within the organ)

Cohort B only

- Pregnancy
- Women of childbearing potential who are not employing adequate contraceptive measures

→ Accepted contraceptive measures are (have to be employed for at least 30 days prior to dosing until one week after the final examination):

- intrauterine device
- intrauterine hormone-releasing system
- implantable progestogen-only hormone contraception associated with inhibition of ovulation
- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal, injectable)
- progestogen-only hormone contraception associated with inhibition of ovulation (oral, injectable)
- condoms
- sexual abstinence
- surgical sterilization

- Acute tonsillitis or peritonsillar abscess
- History of peritonsillar abscess

- Tonsillectomy for cervical lymph node metastasis of cancer of unknown primary

Both Cohorts

- Individuals deprived of liberty and protected persons (under guardianship or curatorship).
- Fertile men unwilling or unable to ensure safe contraception for up to 3 months after taking the test substance. (in French protocol only, in Austrian protocol listed as "lifestyle consideration")

Medical Conditions

- Clinically significant abnormality in the past medical history or at the Screening physical examination that in the investigator's opinion may place the participant at risk or interfere with outcome variables of the study. This includes, but is not limited to, history or current cardiac, hepatic, renal, neurologic, gastrointestinal (GI), respiratory, hematologic, or immunologic disease.
- Any surgical or medical condition that may be aggravated by inhibition of acetylcholinesterase, such as:

→ Poorly controlled asthma or chronic obstructive pulmonary disease at baseline and, in the opinion of the investigator, not stable on current therapy

→ Acute severe pain, uncontrolled with conventional medical management

→ Active peptic ulcer disease

→ Parkinson disease

→ Myasthenia gravis

→ A history of seizure disorder requiring medications for control (this does not include a history of childhood febrile seizures)

- Any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study intervention, or any other condition that may place the participant at risk, in the opinion of the investigator.
- Within 2 months before Screening, either a confirmed history of Clostridium difficile diarrhea infection or a past positive C. difficile toxin test.
- Uncompensated heart failure
- Severe left ventricular hypertrophy
- History of significant vasovagal and/or syncopal episodes or episodes of symptomatic bradycardia
- Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
- History of drug and/or alcohol abuse within 6 months before screening, as determined by the investigator

- History of sensitivity to any of the study drug, components thereof, or a history of drug or other allergy that, in the opinion of the investigator contraindicates their participation.
- Participants at high risk for QT/QTc prolongation as defined by:
→ A personal or family history of long QT syndrome (e.g. congenital long QT syndrome or known prolongation of the QTc interval)
→ Other known pro-arrhythmic conditions
→ Risk factors for Torsade de Pointes
→ Family history of sudden cardiac death before the age of 50
→ Heart disease: ischemia or myocardial infarction, uncompensated heart failure, severe left ventricular hypertrophy, cardiomyopathy, conduction disorder in the 6 months prior to inclusion
→ History of arrhythmia (especially ventricular arrhythmias, atrial fibrillation or recent recovery of rhythm after atrial fibrillation
→ Electrolyte disorder that might increase the risk for QT prolongation, in the opinion of the investigator
→ Bradycardia (< 50 beats per minute)
→ Any acute neurologic events (e.g. intracranial or subarachnoid hemorrhage, stroke, intracranial trauma) during the 6 months before inclusion (in French protocol only)
- Subject is taking QT-prolonging drugs or drugs known to increase the risk of torsades de points (TdP) per the www.crediblemeds.org "Known Risk of TdP" category at the time of screening that cannot be discontinued. If discontinued they should be discontinued at screening and can be resumed after the last PK sample. (in Austrian protocol)
- Subject is taking QT-prolonging drugs or drugs known to increase the risk of torsades de points (TdP) per the www.crediblemeds.org "Known Risk of TdP" category at the time of the screening. Even if the drug can be discontinued subject should be excluded. (in French protocol)
- Subject is taking strong cytochrome P450 enzyme 3A4 (CYP3A4) inhibitors CYP3A4 that cannot be discontinued. If discontinued, they should be discontinued at a minimum of 12 hours or 5 half-lifes from the scheduled gepotidacin dose and can be resumed after the last PK sample. (in Austrian protocol only)
- Subject is taking St. John's Wort or strong CYP3A4 inducers that cannot be discontinued. If discontinued, they should be discontinued at a minimum of 14 days before study entry and can be resumed after the final examination visit. (in Austrian protocol)

- Subject is taking St. John's Wort or strong cytochrome P450 enzyme 3A4 (CYP3A4) inhibitors. Even if the drug can be discontinued subject should be excluded. (in French protocol)
- Subject is planned to receive antibiotic prophylaxis before and/or during surgery that may interfere with gepotidacin (e.g. potential or known drug interaction), in the opinion of the investigator. (in French protocol)

Prior/Concurrent Clinical Study Experience

- Previous exposure to gepotidacin. Participant has participated in a clinical trial and has received an investigational product prior to gepotidacin administration within 30 days, 5 half-lives, or twice the duration of the biological effect of investigational product (whichever is longer) non-interventional studies are excepted.

Diagnostic assessments

- Alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN).
- Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
- History of any kidney disease or current or chronic history of impaired renal function as indicated by an estimated creatinine clearance <60 mL/min.
- History of regular alcohol consumption within 6 months of screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or an average weekly intake of >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 270 mL of full-strength beer, 470 mL of light beer, 30 mL of spirits, or 100 mL of wine.
- Clinically significant abnormal findings in serum chemistry, hematology, or urinalysis results obtained at screening at investigators discretion
- Baseline corrected QT interval using the Fridericia formula (QTcF) of >450 msec. (in Austrian protocol)
- Baseline corrected QT interval using the Fridericia formula (QTcF) of ≥440 msec for men and women. (in French protocol)

Other Exclusions

- Participant has donated blood in excess of 500 mL within 12 weeks prior to dosing or participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.
- Participant is unable to comply with all study procedures, in the opinion of the investigator.

- Participant should not participate in the study, in the opinion of the investigator or sponsor.

Test product, dose and mode of administration, batch number:

- Gepotidacin Tablets, 750 mg
- Tablets containing mesylate salt dihydrate 750 mg (GSK2140944E) and inactive formulation excipients
- Dose: 2x 750 mg single dose
- Mode of administration: oral
- Batch number (s):

  Site Clinic Donaustadt: Lot No. 212425514

  Site AKH: Lot No. 202418189 and Lot No. 212425514

  Site Tours: Lot No. 202418189 and Lot No. 212425514

  Sites Poitiers: Lot No. 212425514

Duration of treatment:

Single dose

Reference therapy, dose and mode of administration, batch number:

Not applicable

Criteria for Evaluation:

Efficacy

Efficacy was not evaluated.

Safety

Adverse events were documented, graded and compared to already known adverse events.

Pharmacokinetic/Pharmacodynamic (PK/PD)

- Area under the concentration time curve (AUC) from zero to last observed concentration (AUC0-t), AUC from zero to infinity (AUC0-∞), maximum drug concentration (Cmax), half-life (t1/2), time to reach maximum drug concentration (tmax) in tissue (calculated with a population pharmacokinetic model)
- Area under the concentration time curve (AUC) from zero to last observed concentration (AUC0-t), AUC from zero to infinity (AUC0-∞), Cmax, t1/2, tmax, apparent volume of distribution (Vd), Clearance (Cl) in plasma (calculated using non-compartmental analysis and a population pharmacokinetic model)
- Penetration ratio calculated as the ratio between the plasma (Ct, plasma) and tissue (Ct, tissue) free drug concentrations collected at the same time.

- PK/PD parameters Cmax/MIC, AUC/MIC, T>MIC in tissue and plasma (if applicable) considering currently established/discussed susceptibility breakpoints of relevant pathogens

Statistical Methods:

Descriptive statistics and population pharmacokinetic modelling.

Summary-Conclusion:

Pharmacokinetic Results

Tissue/unbound plasma AUC ratios are equal to 1. Concentration profiles in tissues are flatter than in plasma with a lower peak that is delayed when compared with the plasma peak.

Safety Results

During the conduct of this study no new safety issues with gepotidacin were identified. The study participants tolerated a single oral dose of gepotidacin, without any serious adverse events.

Conclusion

With this study, an innovative method for determining tissue pharmacokinetics was successfully established. It was shown that gepotidacin penetrates well in the interstitium of prostate and tonsillar tissue.

Date of report: 12 Feb 2024

Par délégation du Président-Directeur général
Inserm - Pôle Recherche Clinique
Responsable Promotion

Couffin-Cadiergues Sandrine Signature numérique de Couffin-Cadiergues Sandrine
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