OPEN ACCESS

Dose selection for a phase III study evaluating gepotidacin (GSK2140944) in the treatment of uncomplicated urogenital gonorrhoea

Nicole E Scangarella-Oman ,[1] Mohammad Hossain,[1] Caroline R Perry,[1] Courtney Tiffany,[1] Marcy Powell,[2] Brandon Swift,[2] Etienne F Dumont[1]

[1]GSK Collegeville, Collegeville, Pennsylvania, USA
[2]GSK, Research Triangle Park, North Carolina, USA

Correspondence to
Dr Nicole E Scangarella-Oman, GSK Collegeville, Collegeville, PA 19426, USA; nicole.e.scangarella-oman@gsk.com

This work was previously presented as a poster presentation at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2021).

Received 5 May 2022
Accepted 30 September 2022

To cite: Scangarella-Oman NE, Hossain M, Perry CR, *et al*. *Sex Transm Infect* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/sextrans-2022-055518

ABSTRACT

Background Gepotidacin is a novel, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action and is active against most strains of *Neisseria gonorrhoeae* (*N. gonorrhoeae*). Phase II data suggested higher exposures were needed for efficacy and to suppress resistance development. A translational approach using in vitro pharmacokinetic/pharmacodynamic (PK/PD) and clinical data was used to select a gepotidacin dose for a phase III study. In this narrative review of previously shown data, we summarise how a translational approach based on in vitro PK/PD and population PK modelling and simulation data was undertaken to select a dosing regimen for the ongoing phase III gepotidacin study in participants with uncomplicated urogenital gonorrhoea.

Methods For dose selection, prior in vitro minimum inhibitory concentrations (MICs) and PK/PD data were available. PK modelling was conducted to determine a dose that would limit plasma concentrations to less than 14 µg/mL (as concentrations above this are associated with QT prolongation and effects associated with acetylcholinesterase inhibition) while maintaining ≥90% probability of target attainment (PTA) for efficacy and resistance suppression against *N. gonorrhoeae* isolates with gepotidacin MICs ≤1 µg/mL.

Results Two 3000 mg gepotidacin doses, administered 10–12 hours apart, resulted in PTA of ≥97.5% and ≥91.7% for gepotidacin MICs ≤1 µg/mL for the ratio of the area under the free drug plasma concentration–time curve over 24 hours to the MIC ($fAUC_{0-24}$/MIC) efficacy, and resistance suppression targets of 40 and 46, respectively, but limited the occurrence of maximum plasma concentrations ≥14 µg/mL.

Conclusions Two gepotidacin 3000 mg oral doses 10–12 hours apart provide ~2-fold higher systemic exposures, increase efficacy for higher gepotidacin MIC *N. gonorrhoeae* isolates, reduce resistance potential and limit plasma concentrations of potential safety concern, compared with higher doses.

Key messages

Rationale

⇒ Gepotidacin phase II data indicated higher exposures were needed to suppress resistance development to gepotidacin in *Neisseria gonorrhoeae* (*N. gonorrhoeae*). A translational approach using in vitro pharmacokinetic/pharmacodynamic (PK/PD) and clinical data was used to select the gepotidacin dose for a phase III study.

Main findings

⇒ Using the hollow-fibre infection model, we confirmed resistance suppression thresholds and identified 2 doses of 3000 mg gepotidacin given 10–12 hours apart were required to achieve 90% probability of target attainment for the necessary minimum inhibitory concentration (MIC).

Implications

⇒ Adding a second gepotidacin dose led to ~2-fold higher systemic exposures, increased efficacy potential for *N. gonorrhoeae* isolates with higher gepotidacin MICs and reduced resistance risk, compared with lower doses evaluated in phase II while mitigating the probability of plasma concentrations exceeding the threshold of potential safety concern with higher doses.

Limitations

⇒ The phase II study was limited by sample size and did not include a comparator; microbiologically evaluable samples were from US participants only; the hollow-fibre infection model only tested one isolate and the PK/PD target for dose selection was based on limited clinical and in vitro data rather than traditional in vivo models.

INTRODUCTION

Gonorrhoea is a common sexually transmitted disease caused by the bacterium *Neisseria gonorrhoeae (N. gonorrhoeae)*. Gonorrhoea is increasingly prevalent across many regions of the world, including America, Asia and Europe.[1] The World Health Organization (WHO) estimates that 82 million new cases of gonorrhoea are acquired each year in 15–49 year olds worldwide.[1] Gonococcal infections left untreated are a cause of serious sequelae including pelvic inflammatory disease which can lead to serious outcomes in women such as ectopic pregnancy and infertility.[2] However, a major challenge in treating patients with gonorrhoea is the emergence of multidrug-resistant *N. gonorrhoeae*, prompting the US Centers for Disease Control and Prevention (CDC) and WHO to label drug-resistant *N. gonorrhoeae* as an 'urgent

threat' and a 'high priority', respectively.[3 4] Effective and accessible antimicrobial treatment is essential for gonorrhoea management, but antimicrobial resistance has emerged in all previous first-line therapies.[5–8] Current CDC guidelines recommend a single 500 mg intramuscular dose of ceftriaxone administered in the clinic,[9] but strains with decreased susceptibility or increased resistance to ceftriaxone have been reported globally, and these strains may continue to spread.[10] Pharmacokinetic/pharmacodynamic (PK/PD) data for ceftriaxone have been used to alter doses of ceftriaxone.[11 12] However, drug-resistant *N. gonorrhoeae* strains globally continue to spread; therefore, new antibiotics for the treatment of gonorrhoea are urgently needed.[3 13]

Gepotidacin is a novel, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action,[14 15] which confers activity against most strains of *N. gonorrhoeae*, including those resistant to current antibiotics.[16–18] Gepotidacin previously demonstrated efficacy in a phase II study (NCT02294682) of adults with gonorrhoea, where single oral doses of 1500 mg and 3000 mg gepotidacin were at least 95% efficacious against *N. gonorrhoeae* from urogenital infections.[19] Previous studies of antibiotics have demonstrated that attaining a target exposure that correlates with bacterial reduction endpoints in preclinical models is predictive of good clinical outcomes in participants with bacterial infections.[20] However, due to a lack of validated preclinical models for *N. gonorrhoeae*, the PK/PD index and magnitude predictive of gepotidacin efficacy have not been established for this bacterium.

Gepotidacin is currently being evaluated for the treatment of uncomplicated urogenital gonorrhoea in adults and adolescents in a phase III clinical trial (NCT04010539). In this narrative review, we summarise how a translational approach based on in vitro PK/PD (from an in vitro hollow-fibre infection model and the phase II uncomplicated urogenital gonorrhoea clinical trial) and population PK modelling and simulation data was undertaken to select a dosing regimen for the ongoing phase III gepotidacin study in participants with uncomplicated urogenital gonorrhoea.

METHODS

This narrative review drew on papers with prior in vitro minimum inhibitory concentrations (MICs) data and PK/PD data available from clinical data and the hollow-fibre infection model.[19 21–24] Population PK modelling including phase II data and simulation was conducted to determine a dose that would limit the occurrence of maximum plasma concentrations of ≥14 µg/mL (as is necessary from a safety perspective due to the plasma concentrations above this threshold correlating with QT/corrected QT (QTc) and adverse events associated with acetylcholinesterase inhibition), while maximising the probability for efficacy against *N. gonorrhoeae* isolates with gepotidacin MICs ≤1 µg/mL and preventing the emergence of resistance. Probability of target attainment (PTA) for efficacy and resistance suppression PK/PD targets was determined using Monte Carlo simulations (200 trials of 50 subjects) that used a population PK model developed using phase II data (NCT04079790).

Clinical efficacy and PK/PD data from the phase II gonorrhoea clinical study

Of 69 participants in the phase II study, single oral doses of 1500 mg and 3000 mg gepotidacin were ≥95% efficacious for bacterial eradication of *N. gonorrhoeae* in adults with urogenital gonorrhoea.[19] Three participants failed therapy at the urogenital body site (all with baseline *N. gonorrhoeae* isolate with a gepotidacin MIC of 1 µg/mL and a pre-existing D86N substitution in the *parC* gene).[19 21] Post-treatment culture analysis identified 2 isolates with an additional substitution, A92T in the *gyrA* gene, which resulted in reduced susceptibility to gepotidacin (gepotidacin MICs ≥32 µg/mL).[21] Resistance to gepotidacin is likely to emerge if the combination of *parC* D86N and *gyrA* A92T mutations occur.[25 26] The highest reported prevalence of the *parC* D86N mutation was 38.6% of ciprofloxacin-resistant *N. gonorrhoeae* isolates.[27] Currently, no published genomic databases report frequencies for the *gyrA* A92T mutation.[26]

Table 1 Microbiological success by *f*AUC/MIC against urogenital *Neisseria gonorrhoeae* at baseline in a phase II study evaluating single oral doses of gepotidacin

*f*AUC/MIC (range)	n/N	Microbiological success (%)
≥198	27/27	100
95 to 103	25/25	100
48 to 49	9/9	100
24 to 25	4/6	67
12	1/2	50
Total	**66/69**	**96**

Table reproduced with permission from Scangarella-Oman *et al*,[21] under the Creative Commons Attribution License. Full terms at: https://creativecommons.org/licenses/by/4.0/.
fAUC/MIC, ratio of the area under the free-drug concentration–time curve to the MIC; MIC, minimum inhibitory concentration; n/N, number of subjects with culture-confirmed eradication of *N. gonorrhoeae* out of total microbiologically evaluable subjects.

Bacterial eradication was 100% when the ratio of the area under the unbound plasma concentration–time curve over 24 hours to the MIC ($fAUC_{0-24}$/MIC) was ≥48, and all 3 of the microbiological failures had an $fAUC_{0-24}$/MIC of ≤24.[21] In prior studies, $fAUC_{0-24}$/MIC has been shown to be the PK/PD index most closely associated with gepotidacin efficacy against other bacteria, specifically *Escherichia coli*, *Staphylococcus aureus* and *Streptococcus pneumoniae*.[22 23] Based on these phase II clinical study results, the preliminary gepotidacin efficacy PK/PD target for gonorrhoeae in plasma was estimated to be an *f*AUC/MIC between 24 (failure) and 48 (success, defined as culture-confirmed eradication of *N. gonorrhoeae*).[21] Due to the limited number of isolates with a pre-existing single-step mutation, a resistance suppression target could not be identified from the phase II clinical study. In addition, 7% of the isolates from the phase II clinical study had a gepotidacin MIC of 1 µg/mL,[21] highlighting the importance of demonstrating efficacy against *N. gonorrhoeae* isolates with higher gepotidacin MICs. Therefore, the microbiological failures from this study demonstrated the need to optimise the gepotidacin dose to increase efficacy and prevent the emergence of bacterial resistance (table 1 and table 2).

Previous research looking at body sites where gonorrhoea infections have been identified evaluated the PK, safety and exploratory efficacy of gepotidacin 1500 mg 2 times daily for 5 days and found that urinary exposure over the dosing interval ($AUC_{0-\tau}$) increased from 3742 µg/mL/hour (day 1) to 5973 µg/mL/hour (day 4), with trough concentrations of 322 to 352 µg/mL from day 3 to day 5 and provided >600-fold higher concentrations in urine than in free plasma at steady state.[28] Previous research also investigated exploratory PK assessment of the collection of cervical, rectal and pharyngeal swab specimens on day 4 predose and 2 hours postdose, with blood

Table 2 Characterisation of urogenital *Neisseria gonorrhoeae* isolates from microbiological failures in the phase II study

Participant no. (sex)	GEP dose (mg)	Microbiological response	Visit	Mutation*				MIC (µg/mL)†							
				GyrA			ParC	GEP‡	CIP	CRO	SPT	PEN	AZI§	TET	CFM
4 (male)	3000	Failure	Baseline	S91F	D95G		D86N	1	8	0.06	8	4	0.5	2	0.06
			TOC	S91F	A92T	D95G	D86N	>32	8	0.06	32	1	0.5	2	0.06
6 (male)	3000	Failure	Baseline	S91F	D95G		D86N	1	4	0.06	16	1	0.5	2	0.06
			TOC	S91F	A92T	D95G	D86N	32	4	0.03	8	0.5	0.25	1	0.03
7 (male)	1500	Failure	Baseline	S91F	D95A		D86N	1	16	0.03	8	2	2	2	0.03
			TOC	S91F	D95A		D86N	1	16	0.03	8	2	2	2	0.03

*Sequencing of quinolone resistance–determining region only.
†Dark, light and no shading indicate resistant, intermediate and susceptible, respectively, according to M100-S27 CLSI breakpoints.
‡No breakpoints are currently available for GEP.
§The CLSI non-wild-type epidemiological cut-off value was applied.
AZI, azithromycin; CFM, cefixime; CIP, ciprofloxacin; CLSI, Clinical and Laboratory Standards Institute; CRO, ceftriaxone; GEP, gepotidacin; MIC, minimum inhibitory concentration; PEN, penicillin; SPT, spectinomycin; TET, tetracycline; TOC, test of cure.

samples taken at these same timepoints as part of a study in patients with uncomplicated urinary tract infection following multiple oral doses of gepotidacin 1500 mg 2 times daily for 5 days.[28] In the cervical site, the distribution of gepotidacin was 1.30 µg/mL in predose samples and 1.03 µg/mL in postdose samples. In rectal samples, 6.04 µg/mL of gepotidacin was found in predose and 12.3 µg/mL in postdose. Lastly, in pharyngeal samples, 0.0330 µg/mL of gepotidacin was found in predose and 1.40 µg/mL in postdose. In free plasma samples, 0.618 µg/mL of gepotidacin was found predose and 3.94 µg/mL postdose.[28]

Concentration-driven QT prolongation and acetylcholinesterase inhibition with gepotidacin

A potential for QT prolongation was identified during in vitro studies, and although in vitro prolongation potentials were not realised in in vivo dog studies, slight prolongations in QT interval corrected for heart rate (QTc; 4% to 9%) were observed in an in vivo intravenous cardiovascular study in monkeys (unpublished data). A thorough QT study (NCT02257398) in humans showed that an infusion of gepotidacin at a dose of 1000 mg and 1800 mg over 2 hours caused a mild heart rate acceleration of approximately 7 bpm and 10 bpm, respectively, and QT prolongation measured as ΔΔQT corrected by Fridericia's formula (QTcF) of 12 ms to 22 ms, respectively.[29] The QT prolongation evolved during the infusion and was reversed over 2 hours after the end of the infusion. Gepotidacin did not have a clinically relevant effect on cardiac conduction (PR and QRS intervals). A statistically significant effect on the QTcF interval was demonstrated with a slope of the relationship between gepotidacin plasma concentrations and ΔΔQTcF of 1.45 ms/µg/mL (90% CI: 1.30 to 1.61). A gepotidacin plasma concentration was established to not exceed 14 µg/mL to decrease the occurrence of QTc prolongation, predicted to correlate to a 20 ms increase in the QT interval.[29] In previous research, one instance of arrythmia (1/13; 8%) was reported following a dose of 3000 mg 12 hours apart, which was mild in severity and deemed not related to gepotidacin.[30] The plasma concentration ceiling also reduces the likelihood of adverse effects driven by acetylcholinesterase inhibition as observed in phase I and II studies,[24 29] as in vitro studies have shown that gepotidacin is a rapidly reversible inhibitor of acetylcholinesterase (unpublished data).

In vitro hollow-fibre infection model

The predicted gepotidacin exposure necessary to prevent the amplification of gepotidacin-resistant *N. gonorrhoeae* was assessed using an in vitro hollow-fibre infection model.[31] This in vitro model was undertaken to fill a gap in the phase II gonorrhoea study resistance development data due to the lack of isolates with a pre-existing mutation and *f*AUC/MICs between 24 and 96. A set of duplicate, 7-day, hollow-fibre infection model studies was completed using an *N. gonorrhoeae* isolate from the phase II clinical trial with a gepotidacin MIC of 1 µg/mL and a *parC* D86N mutation, to determine the $fAUC_{0-24}$/MIC exposure of gepotidacin needed to prevent the amplification of a gepotidacin-resistant subpopulation when a pre-existing single-step mutation affecting gepotidacin activity was already present. The gepotidacin resistance suppression PK/PD target for *N. gonorrhoeae* in plasma was an *f*AUC/MIC of 46, based on the data from the hollow-fibre infection model, which was able to replicate the efficacy and resistance development seen in the phase II gonorrhoea study. Using this approach, the hollow-fibre infection model confirmed that total daily doses of ≥4500 mg (including 2 gepotidacin 3000 mg doses administered either 8 or 12 hours apart, as evaluated in the hollow-fibre infection model) prevented resistance amplification to gepotidacin in *N. gonorrhoeae* (figure 1).[24 31] Notably, the gepotidacin isolates with reduced susceptibility recovered from the hollow-fibre infection model studies and contained target-site mutations consistent with those identified from the 2 gepotidacin-treated patients enrolled in the phase II study whose postbaseline *N. gonorrhoeae* isolates developed reduced the susceptibility to gepotidacin.[19] The variable efficacy/resistance amplification of the 3000 mg dose seen in the hollow-fibre infection model studies was also consistent with the results for the 3000 mg single dose in the phase II clinical study, thereby providing confidence in this model's ability to replicate the efficacy and resistance development seen in the clinical trial. These concurring findings were particularly useful for the selection of a dose which minimised resistance risk potential for the phase III clinical study in uncomplicated urogenital gonorrhoea.

Population PK modelling and simulation

A population PK model was developed using plasma PK data from a randomised, fixed-sequence, 3-period study of oral gepotidacin in 14 healthy adults, and a 2-period study in 13 healthy adolescent subjects (NCT04079790). Subjects received gepotidacin as a single 1500 mg dose, followed by 2×3000 mg doses given at a 12-hour interval (adults only) and 2×3000 mg doses given at a 6-hour interval (adults and adolescents).[30] A 2-compartment model with first-order absorption and elimination containing transit compartments was used to describe the PK of gepotidacin. Based on this model, a Monte Carlo simulation approach was

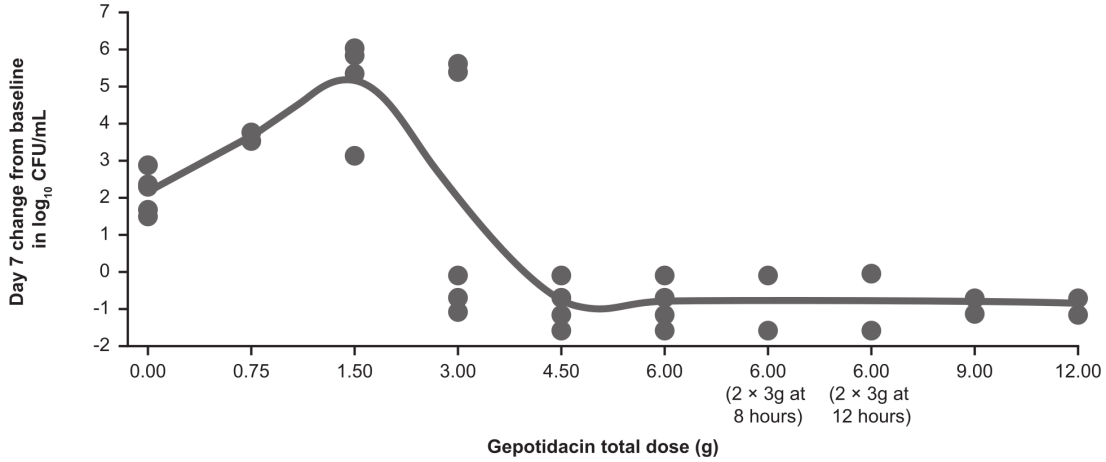

Figure 1 Gepotidacin exposure and change in $\log_{10}$ colony-forming unit per millilitre (CFU/mL) from baseline of the gepotidacin-resistant subpopulation. Figure adapted with permission from VanScoy *et al*,[31] under the Creative Commons Attribution License. Full terms at: https://creativecommons.org/licenses/by/4.0/.

used to simulate 10 000 virtual subjects for different gepotidacin dosing regimens (200 trials with 50 subjects in each trial).[24] For each simulated plasma–concentration time profile, AUC_{0-24} was calculated using the linear-up log-down trapezoidal method. The individual AUC_{0-24} estimates were corrected for protein binding by multiplying by the unbound fraction (f_u=0.67) and then dividing by the MIC values ranging from 0.125 to 4 µg/mL to calculate *f*AUC/MIC ratio, the PK/PD index for gepotidacin. The PTA was determined within each dose based on the proportion of the 10 000 virtual subjects above the PK/PD targets for efficacy (40) and resistance suppression (46) (figure 2). These simulations were conducted to evaluate doses that could maximise the probability of efficacy against *N. gonorrhoeae* isolates with gepotidacin MICs ≤1 µg/mL, while minimising the potential for emergence of resistance.[20] In addition, the simulations were used to identify a dose that would limit the occurrence of maximum plasma concentrations exceeding 14 µg/mL, which is necessary from a safety perspective due to the increased risk of QTc interval prolongation and acetylcholinesterase inhibition side effects.[24 29]

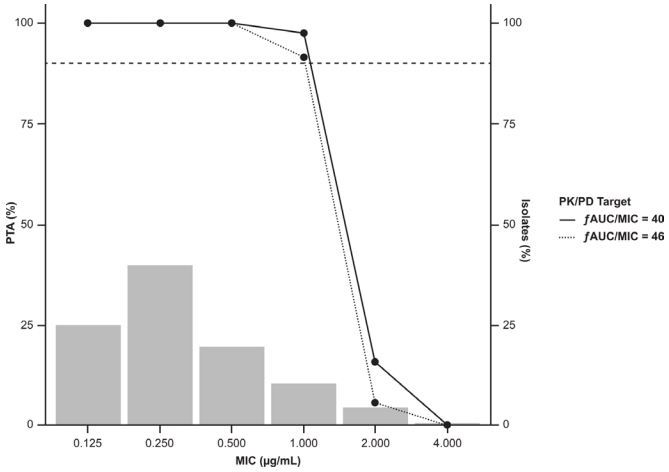

Figure 2 Percentage probabilities of PK/PD target attainment by MIC for gepotidacin oral dosing regimen based on the evaluation of $fAUC_{0-24}$/MIC targets associated with efficacy and resistance suppression, overlaid on the gepotidacin MIC distribution for *Neisseria gonorrhoeae*. Dashed line represents 90% PTA. Adapted with permission from Singh *et al*.[24] $fAUC_{0-24}$/MIC, ratio of the area under the free-drug plasma concentration–time curve over 24 hours to the MIC; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetics/pharmacodynamics; PTA, probability of target attainment.

Summarising dose regimen selection for the phase III gonorrhoea study

Based on the phase II clinical study results,[21] when all isolates were considered, the preliminary gepotidacin efficacy PK/PD target for *N. gonorrhoeae* in plasma was an *f*AUC/MIC between 24 (failure) and 48 (success, defined as culture-confirmed eradication of *N. gonorrhoeae*). However, for the purposes of modelling, an *f*AUC/MIC target of 40 was chosen, for a total daily dose of 6000 mg (3000 mg given twice). The gepotidacin resistance suppression PK/PD target for *N. gonorrhoeae* in plasma was determined to be an *f*AUC/MIC of 46, based on the in vitro hollow-fibre model.[24 31] This in vitro model was specifically undertaken to fill a gap in the phase II gonorrhoea study with regards to resistance development, due to a limited subset of isolates with a pre-existing single-step mutation.[19] Results of the PK modelling and simulation demonstrated that a dosing strategy of 2 gepotidacin 3000 mg oral doses administered 12 hours apart resulted in PTA of approximately 97.5% and 91.7% for gepotidacin MICs ≤1 µg/mL for the efficacy and resistance suppression PK/PD targets of an *f*AUC/MIC of 40 and 46, respectively.[24 32] Furthermore, 2 gepotidacin 3000 mg doses resulted in a limited occurrence of exceeding the QTc threshold of 14 µg/mL.[30] In previous research that studied the dose of 3000 mg 12 hours apart (mean observed maximum concentrations of 10–11 µg/mL; less than the 14 µg/mL), 77% experienced an adverse event, 62% experienced diarrhoea and 31% had abdominal discomfort.[30]

CONCLUDING REMARKS

The overarching aim of the studies described herein was to evaluate gepotidacin-dosing regimens to support dose selection for a pivotal phase III clinical study of gepotidacin in patients with uncomplicated urogenital gonorrhoea. The gepotidacin dose and dosing regimen was guided by modelling and simulation, using a population PK model and applying efficacy and resistance suppression PK/PD targets determined from an in vitro hollow-fibre infection model and phase II clinical data,

while also limiting plasma concentrations of potential safety concern.[19 24 29 31] Despite a lack of validated preclinical models for *N. gonorrhoeae*, the use of this translational approach permitted informed selection of an appropriate gepotidacin dose likely to provide safe and effective exposure, and overcome resistance development in the pivotal phase III clinical trial. It was through this evaluation that we found the optimal regimen to be 2 oral 3000 mg doses of gepotidacin 10–12 hours apart, rather than the single 3000 mg oral dose used in a phase II trial.[19] In terms of gepotidacin systemic exposure, 2 oral 3000 mg doses 10–12 hours apart provided approximately twice the systemic exposure of the single 3000 mg dose, allowing more reliable efficacy coverage of *N. gonorrhoeae* isolates with gepotidacin MICs of 1 µg/mL and resistance suppression.[19 21] PK modelling and simulation demonstrated that for the 2 oral gepotidacin 3000 mg doses, taken 12 hours apart, the PTA was ≥97.5% when applying the efficacy PK/PD target of an *f*AUC/MIC of 40 (based on the preliminary target from the phase II clinical trial and achievable PK levels for a total daily dose of 6000 mg (3000 mg given 2 times)), and ≥91.7% when applying the resistance suppression PK/PD target of an *f*AUC/MIC of 46 (based on the in vitro hollow-fibre infection model) for gepotidacin MICs ≤1 µg/mL. The second 3000 mg dose given 10–12 hours later as compared with the single dose used in phase II trials provided reliable efficacy while simultaneously preventing the development of resistance. PK modelling and simulation with the selected dosing regimen also predicted maximum plasma concentrations that would limit exceeding the exposure threshold of 14 µg/mL, which correlates with a potential to increase the QTc interval and acetylcholinesterase inhibitory effects.[24 29]

On the basis of these results, the ongoing phase III randomised, open-label study is currently evaluating gepotidacin administered as an initial 3000 mg oral dose followed by another 3000 mg oral dose 10–12 hours later. The original protocol designated an interval of 6–12 hours for the second dose. Subsequent data from the completion of a phase I study in adults and adolescents[30] resulted in lengthening the second-dose interval via a protocol amendment to 10–12 hours to mitigate any potential safety concerns from plasma concentrations exceeding the exposure threshold of ≥14 µg/mL. Gepotidacin will be compared with ceftriaxone plus azithromycin in individuals (planned sample size of 600) with urogenital gonorrhoea; the study is currently recruiting.[33] Of note, the study started prior to the CDC-recommended change in the standard of care, and as such uses ceftriaxone plus azithromycin, rather than ceftriaxone alone.[34]

Public health control of gonorrhoea relies on appropriate antimicrobial treatment, together with targeted prevention, and the use of effective diagnostics and surveillance. The aim of therapy should be to cure individual cases to reduce the risk of potentially severe complications and prevent transmission. The prospect of multidrug-resistant *N. gonorrhoeae*, including resistance to ceftriaxone, the only remaining option for first-line therapy in many settings, is the cause for trepidation.[3] There is some concern around adherence to antibiotic treatment regimens requiring >1 dose per day, which may result in poorer outcomes, emergence of drug-resistant strains and increased healthcare costs. Meta-analyses have shown that patients who received antibiotic treatment once daily had higher compliance than those who received antibiotic treatment multiple times daily.[35] However, regimens, where treatment is received for a short period of time, may lead to a high overall compliance to treatment. Apart from the frequency of daily dosing, other factors such as patient age, gender, health literacy, therapy-related factors (treatment-related adverse events, taste or odour of medication), factors associated with healthcare (lack of accessibility, long waiting times, difficulty filling prescriptions) and disease severity can affect treatment compliance.[36] Strategies to improve adherence should also consider the needs of the patient. For example, contact between patient and doctor during treatment may result in higher compliance.[37]

The studies used to inform the phase III gepotidacin dosing regimen for evaluation in patients with urogenital gonorrhoea had several limitations. The phase II multicentre, open-label, dose-ranging study was limited by sample size (n=69 microbiologically evaluable) and did not include a comparator. Although both men and women were enrolled, only 3% of the microbiologically evaluable samples were from women. An additional limitation of the phase II study was that microbiologically evaluable samples were from US participants only; therefore, the results may not reflect the global epidemiology of *N. gonorrhoeae*, and different patterns of resistance may be observed in other geographic regions.[19] A limitation of the in vitro hollow-fibre infection model was that only one isolate was evaluated, and it was therefore not possible to test interisolate variability in the gepotidacin exposure associated with resistance prevention.[31] Another limitation was that the PK/PD target (ie, *f*AUC/MIC) for dose selection was based on unbound plasma exposures rather than local exposures in the infected tissues, such as the pharynx or rectum, and systemic exposures may not be reflective of these additional target tissue sites.[31] Since the start of the phase III trial in uncomplicated urogenital gonorrhoea, an animal model has been developed that may be informative for future dose selection studies in gonorrhoea.[11]

Using a translational approach, a regimen of 2 oral gepotidacin doses of 3000 mg administered 10–12 hours apart was selected for the treatment of individuals with gonorrhoea in the ongoing phase III clinical study in uncomplicated urogenital gonorrhoea (NCT04010539). This regimen is predicted to provide appropriate systemic exposure to achieve efficacy with consideration of QT prolongation safety limits while reducing the risk of resistance emergence to gepotidacin in *N. gonorrhoeae* in the clinic. Additional data derived from this study will allow for further study of the gepotidacin dose regimen as it relates to a greater understanding of gepotidacin efficacy in a larger and more geographically diverse patient population.

Handling editor Erica L Plummer

Acknowledgements We thank the study participants, clinical staff and investigators of NCT02294682 for their participation. We also thank Aline Barth (GSK); David Gardiner (GSK) and PPD, part of Thermo Fisher Scientific, for their support and contributions to study conduct and data analysis; Q2 Solutions for laboratory contributions; the University of Alabama for their microbiology analyses; the GSK microbial genetics laboratory for their mutation analyses and ICPD for their hollow-fibre infection model work. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Natasha Tracey, PhD, of Ashfield MedComms (Macclesfield, UK), an Inizio company, and was funded by GSK.

Contributors NES-O, MH, CRP, CT, MP, BS and EFD contributed to the conception and design of the study and acquisition of data. All authors contributed to the analysis and interpretation of the data, substantively revised the manuscript, and approved the submitted version.

Funding This work was supported by GSK. This work was also supported in whole or in part with Federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority (HHSO100201300011C).

Competing interests All authors report employment with and stock/share options in GSK at the time of the study. MH is currently employed by Servier Pharmaceuticals, Boston, Massachusetts, USA. CT is currently employed by Spark Therapeutics, Philadelphia, Pennsylvania, USA. EFD is currently employed by Boston Pharmaceuticals, Cambridge, Massachusetts, USA.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Nicole E Scangarella-Oman http://orcid.org/0000-0003-4211-8261

REFERENCES

1 World Health Organization. Sexually transmitted infections (STIs), 2021. Available: https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis) [Accessed 3 Mar 2022].
2 Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2018, 2019. Available: https://www.cdc.gov/std/stats18/STDSurveillance2018-full-report.pdf [Accessed 13 Oct 2021].
3 Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Available: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf
4 World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics, 2017. Available: https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf [Accessed 1 Mar 2022].
5 Unemo M, Shafer WM. Antimicrobial resistance in *Neisseria gonorrhoeae* in the 21st century: past, evolution, and future. *Clin Microbiol Rev* 2014;27:587–613.
6 Wi T, Lahra MM, Ndowa F, *et al*. Antimicrobial resistance in *Neisseria gonorrhoeae*: global surveillance and a call for international collaborative action. *PLoS Med* 2017;14:e1002344.
7 World Health Organization. WHO guidelines for the treatment of *Neisseria gonorrhoeae*, 2016. Available: https://apps.who.int/iris/bitstream/handle/10665/246114/9789241549691-eng.pdf
8 World Health Organization. WHO global action plan to control the spread and impact of antimicrobial resistance in *Neiserria gonorrhoeae*, 2012. Available: http://apps.who.int/iris/bitstream/handle/10665/44863/9789241503501_eng.pdf?sequence=1
9 St Cyr S, Barbee L, Workowski KA, *et al*. Update to CDC's treatment guidelines for gonococcal infection, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1911–6.
10 European Centre for Disease Prevention and Control. Gonorrhoea - annual epidemiological report for 2018, 2020. Available: https://www.ecdc.europa.eu/en/publications-data/gonorrhoea-annual-epidemiological-report-2018
11 Connolly KL, Eakin AE, Gomez C, *et al*. Pharmacokinetic Data Are Predictive of *In Vivo* Efficacy for Cefixime and Ceftriaxone against Susceptible and Resistant *Neisseria gonorrhoeae* Strains in the Gonorrhea Mouse Model. *Antimicrob Agents Chemother* 2019;63:e01644–18.
12 Thompson J, Marijam A, Mitrani-Gold FS, *et al*. 1415. allergies to antimicrobial agents among US females with uncomplicated urinary tract infection. *Open Forum Infect Dis* 2021;8:S792–3.
13 World Health Organization. Antibiotic-resistant gonorrhoea on the rise, new drugs needed, 2017. Available: https://www.who.int/news/item/07-07-2017-antibiotic-resistant-gonorrhoea-on-the-rise-new-drugs-needed [Accessed Nov 2021].
14 Gibson EG, Bax B, Chan PF, *et al*. Mechanistic and structural basis for the actions of the antibacterial gepotidacin against *Staphylococcus aureus* gyrase. *ACS Infect Dis* 2019;5:570–81.
15 Bax BD, Chan PF, Eggleston DS, *et al*. Type IIA topoisomerase inhibition by a new class of antibacterial agents. *Nature* 2010;466:935–40.
16 Jacobsson S, Golparian D, Scangarella-Oman N, *et al*. *In vitro* activity of the novel triazaacenaphthylene gepotidacin (GSK2140944) against MDR *Neisseria gonorrhoeae*. *J Antimicrob Chemother* 2018;73:2072–7.
17 Farrell DJ, Sader HS, Rhomberg PR, *et al*. *In vitro* activity of gepotidacin (GSK2140944) against *Neisseria gonorrhoeae*. *Antimicrob Agents Chemother* 2017;61:e02047–16.
18 Mushtaq S, Vickers A, Sadouki Z. *In-vitro* activities of gepotidacin, a novel triazaacenaphthylene and topoisomerase IV DNA gyrase inhibitor, against gram-negative bacteria and *Staphylococcus saprophyticus*. Poster p1849. Amsterdam, The Netherlands ECCMID; 2019.
19 Taylor SN, Morris DH, Avery AK, *et al*. Gepotidacin for the treatment of uncomplicated urogenital gonorrhea: a phase 2, randomized, dose-ranging, single-oral dose evaluation. *Clin Infect Dis* 2018;67:504–12.
20 Ambrose PG, Bhavnani SM, Rubino CM, *et al*. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clin Infect Dis* 2007;44:79–86.
21 Scangarella-Oman NE, Hossain M, Dixon PB, *et al*. Microbiological analysis from a phase 2 randomized study in adults evaluating single oral doses of gepotidacin in the treatment of uncomplicated urogenital gonorrhea caused by *Neisseria gonorrhoeae*. *Antimicrob Agents Chemother* 2018;62:e01221–18.
22 Bulik CC, Okusanya O, Lakota EA, *et al*. Pharmacokinetic-pharmacodynamic evaluation of gepotidacin against gram-positive organisms using data from murine infection models. *Antimicrob Agents Chemother* 2017;61:e00115–6.
23 VanScoy BD, Lakota EA, Conde H, *et al*. Gepotidacin pharmacokinetics-pharmacodynamics against *Escherichia coli* in the one-compartment and hollow-fiber *in vitro* infection model systems. *Antimicrob Agents Chemother* 2021;65:e0012221.
24 Singh R, Dumont E, Powell M, *et al*. Assessing safety and efficacy to determine the gepotidacin probability of pharmacological success in urogenital gonorrhea. Presented at the 12th Annual Congress of the American Conference on Pharmacometrics, 2021.
25 Preib MT, Marijam A, Mitrani-Gold FS, *et al*. 1422. real-world study of the effects of inappropriate or suboptimal treatment on the burden of illness among patients with uncomplicated urinary tract infection and high-risk comorbid conditions in the United States. *Open Forum Infect Dis* 2021;8:S794–5.
26 Vegvari C, Grad YH, White PJ, *et al*. Using rapid point-of-care tests to inform antibiotic choice to mitigate drug resistance in gonorrhoea. *Euro Surveill* 2020;25:1900210.
27 Garnett GP, Mertz KJ, Finelli L, *et al*. The transmission dynamics of gonorrhoea: modelling the reported behaviour of infected patients from Newark, New Jersey. *Philos Trans R Soc Lond B Biol Sci* 1999;354:787–97.
28 Overcash JS, Tiffany CA, Scangarella-Oman NE, *et al*. Phase 2a pharmacokinetic, safety, and exploratory efficacy evaluation of oral gepotidacin (GSK2140944) in female participants with uncomplicated urinary tract infection (acute uncomplicated cystitis). *Antimicrob Agents Chemother* 2020;64:e00199–20.
29 Hossain M, Zhou M, Tiffany C, *et al*. A phase I, randomized, double-blinded, placebo- and moxifloxacin-controlled, four-period crossover study to evaluate the effect of gepotidacin on cardiac conduction as assessed by 12-lead electrocardiogram in healthy volunteers. *Antimicrob Agents Chemother* 2017;61:e02385–16.
30 Barth A, Hossain M, Brimhall DB, *et al*. Pharmacokinetics of oral formulations of gepotidacin (GSK2140944), a triazaacenaphthylene bacterial type II topoisomerase inhibitor, in healthy adult and adolescent participants. *Antimicrob Agents Chemother* 2022;66:e0126321.
31 VanScoy BD, Scangarella-Oman NE, Fikes S, *et al*. Relationship between gepotidacin exposure and prevention of on-therapy resistance amplification in a *Neisseria gonorrhoeae hollow-fiber in vitro infection model*. *Antimicrob Agents Chemother* 2020;64:e00521–20.
32 Scangarella-Oman N, Hossain M, Perry C, *et al*. Dose selection for a phase 3 study evaluating gepotidacin (GSK2140944) in the treatment of gonorrhoea. Presented at the 31st Annual Congress of the European Society for Clinical Microbiology and Infectious Diseases, virtual, 9–14 July, 2021.
33 ClinicalTrials.gov. NCT04010539. A study to evaluate efficacy and safety of gepotidacin compared with ceftriaxone plus azithromycin in the treatment of uncomplicated urogenital gonorrhea, 2019. Available: https://clinicaltrials.gov/ct2/show/NCT04010539 [Accessed Nov 2021].
34 Workowski KA, Bachmann LH, Chan PA, *et al*. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep* 2021;70:1–187.
35 Falagas ME, Karagiannis AKA, Nakouti T, *et al*. Compliance with once-daily versus twice or thrice-daily administration of antibiotic regimens: a meta-analysis of randomized controlled trials. *PLoS One* 2015;10:e0116207.
36 Jin J, Sklar GE, Min Sen Oh V, *et al*. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag* 2008;4:269–86.
37 Zanichelli V, Tebano G, Gyssens IC, *et al*. Patient-Related determinants of antibiotic use: a systematic review. *Clin Microbiol Infect* 2019;25:48–53.