CLINICAL STUDY PROTOCOL

A PHASE 1, SINGLE-CENTER, OPEN-LABEL, NON-RANDOMIZED, FIXED-SEQUENCE, DRUG-DRUG INTERACTION STUDY TO ASSESS THE EFFECT OF REPEATED DOSES OF INTRAVENOUS CEFTOBIPROLE ON THE PHARMACOKINETICS OF ORAL PITAVASTATIN (OATP1B SUBSTRATE) AND ON PLASMA LEVELS OF COPROPORPHYRIN I (OATP1B BIOMARKER) IN HEALTHY SUBJECTS

CONFIDENTIAL

Sponsor code: BPR-CP-101

ICON code: 0680-0062

EU CT number: 2024-518592-60-00

Ceftobiprole OATP1B interaction study

Investigational product:	Ceftobiprole medocaril sodium
Clinical phase:	Phase 1 study
Indication to be studied:	Not applicable
Sponsor:	Basilea Pharmaceutica International Ltd, Allschwil Hegenheimermattweg 167b 4123 Allschwil Switzerland
Contract Research Organization	ICON Early Clinical & Bioanalytical Solutions Van Swietenlaan 6 9728 NZ Groningen The Netherlands

Version 1.0, 30-Sep-2024

This study will be performed in compliance with the principles of Good Clinical Practice.

SPONSOR AUTHORIZATION OF CLINICAL STUDY PROTOCOL

The Sponsor and the Contract Research Organization agree to conduct the study as outlined in this clinical study protocol. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Contract Research Organization and must be documented in writing.

Name/Position: Date: Signature:

Sponsor: Basilea Pharmaceutica International Ltd, Allschwil

PPD

AUTHORIZATION OF CLINICAL STUDY PROTOCOL BY CONTRACT RESEARCH ORGANIZATION

The Sponsor and the Contract Research Organization agree to conduct the study as outlined in this clinical study protocol. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Contract Research Organization and must be documented in writing.

Name/Position: Date: Signature:

Contract Research Organization: ICON Early Clinical & Bioanalytical Solutions

Jart Oosterhaven, MD, PhD ....
Principal Investigator
Pharmaceutical Research Associates Group BV, an ICON company

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In the event of a serious adverse event (see Appendix 8.2), the Principal Investigator or designee must send a report within 24 hours of notification to:

Sponsor's Pharmacovigilance Service Provider
PrimeVigilance Limited
The Surrey Research Park
1 Occam Court Guildford
Surrey GU2 7HJ, UK
Email: Basilea@primevigilance.com
Copy: drug.safety@basilea.com

SYNOPSIS

Study Title

A PHASE 1, SINGLE-CENTER, OPEN-LABEL, NON-RANDOMIZED, FIXED-SEQUENCE, DRUG-DRUG INTERACTION STUDY TO ASSESS THE EFFECT OF REPEATED DOSES OF INTRAVENOUS CEFTOBIPROLE ON THE PHARMACOKINETICS OF ORAL PITAVASTATIN (OATP1B SUBSTRATE) AND ON PLASMA LEVELS OF COPROPORPHYRIN I (OATP1B BIOMARKER) IN HEALTHY SUBJECTS

Short Study Title

Ceftobiprole OATP1B interaction study

Study Codes

Sponsor code : BPR-CP-101
ICON code : 0680-0062
EU CT number : TBD

Sponsor

Basilea Pharmaceutica International Ltd, Allschwil, Hegenheimermattweg 167b, 4123 Allschwil, Switzerland

Contract Research Organization

ICON Early Clinical & Bioanalytical Solutions, Van Swietenlaan 6, 9728 NZ Groningen, The Netherlands

Objectives and Endpoints

Objectives	Endpoints
Primary	Primary
• To assess the pharmacokinetics (PK) of a single oral dose of pitavastatin administered without and with intravenous (iv) ceftobiprole in healthy subjects.	• Plasma PK parameters of pitavastatin including C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf}, CL/F, and V_z/F, as appropriate.
Secondary	Secondary
• To assess the pharmacodynamic (PD) effect of iv ceftobiprole on the diurnal plasma level profile of coproporphyrin I (CP-I) in healthy subjects.	• Plasma exposure parameters of CP-I, including $AUEC_{0-25.5h}$, C_{max}, t_{max}, C_{trough}, and $C_{25.5h}$.
• To describe the systemic exposure of iv ceftobiprole without and with oral administration of pitavastatin in healthy subjects.	• Plasma exposure parameters of ceftobiprole, including C_{trough}, C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-8h}, CL, and V_z, as appropriate.
• To assess the single-dose plasma PK of the pitavastatin metabolite pitavastatin lactone after a single oral dose of pitavastatin, administered without and with iv ceftobiprole in healthy subjects.	• Plasma PK parameters of pitavastatin lactone including C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf}, as appropriate. • Ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} of pitavastatin lactone over parent drug.
• To assess the safety and tolerability of ceftobiprole without and with administration of a single oral dose of pitavastatin in healthy subjects.	• Type, frequency, severity, timing, and relationship to study drug of any adverse events (AEs). • Abnormalities and changes vs. baseline in clinical laboratory, vital signs, and 12-lead electrocardiogram (ECG) parameters, as appropriate.

Design and Treatments

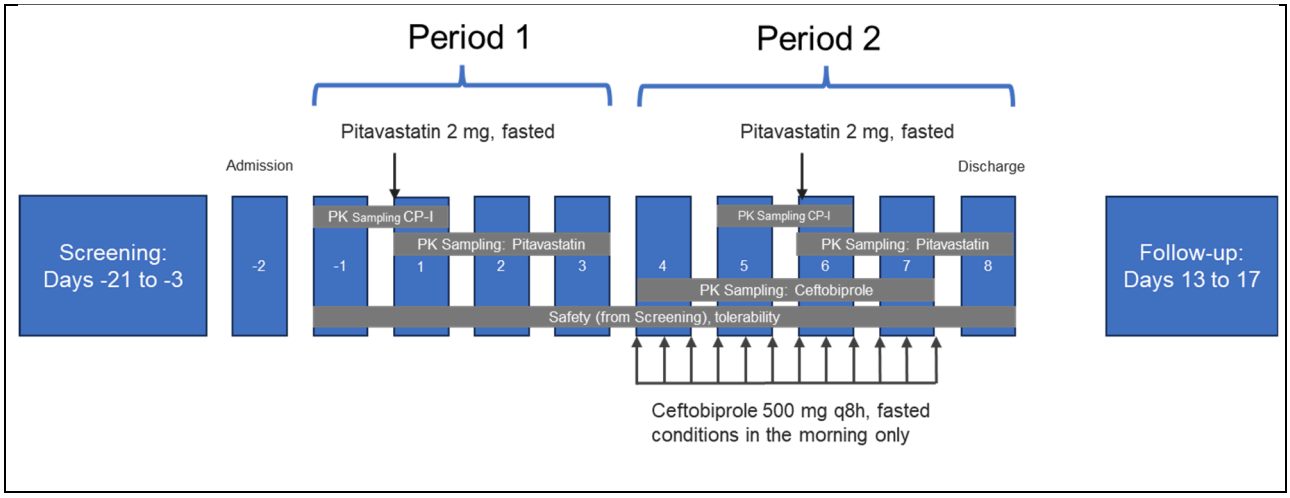
This will be a Phase 1, single-center, open-label, non-randomized, fixed-sequence, drug-drug interaction study in healthy male or female subjects to assess if there is an inhibitory effect of ceftobiprole on the hepatic organic anion-transporting polypeptide 1B (OATP1B) activity. Pitavastatin will be used as an OATP1B substrate in this study. The PK of oral pitavastatin will be assessed when administered alone and when administered together with iv ceftobiprole in a study design including two treatment periods. In addition, the PD effect of repeated doses of iv ceftobiprole on the diurnal plasma levels of coproporphyrin I (CP-I) will be assessed in this study as CP-I is an endogenous biomarker for hepatic OATPB1 activity.

The following treatments are planned to be administered in two periods: Period 1 (from Day −1 to Day 3): 'pitavastatin single dose'; and Period 2 (from Day 4 to Day 8): 'pitavastatin single dose + ceftobiprole q8h':

- On Day 1, a single oral dose of 2 mg pitavastatin will be administered in the morning under fasted conditions.
- From Day 4 to Day 7, 500 mg ceftobiprole (as the prodrug ceftobiprole medocaril sodium)[1] will be administered as a 2-hour iv dose every 8 hours (q8h) under fasted conditions in the morning, and irrespective of timing of food intake further on the day.
- On Day 6, a single oral dose of 2 mg pitavastatin will be coadministered with ceftobiprole 30 minutes prior to the end of the first iv dose of 500 mg ceftobiprole under fasted conditions.

A schematic overview of the study design is provided in Figure 1.

Figure 1 Study design



Study Schedule

Screening:	Between Day −21 and Day −3
Admission:	Day -2
Treatment period:	Period 1 (from Day −1 to Day 3): 'pitavastatin single dose' Period 2 (from Day 4 to Day 8): 'pitavastatin single dose + ceftobiprole q8h'
Discharge:	Day 8
Follow-up/Early Termination:	Day 15 ± 2 days/at the time of Early Termination

Duration of Participation

Up to 38 days

Subjects

A total of 12 healthy male or female subjects.

[1] Unless referring specifically to the prodrug, the term 'ceftobiprole' is used throughout the remainder of this protocol, and all doses are of ceftobiprole equivalents. 500 mg of ceftobiprole is dosed as 667 mg of ceftobiprole medocaril sodium.

Main Criteria for Inclusion

Sex:	Male or female
Age:	18 years to 65 years, inclusive, at Screening
Body mass index:	18.0 to 30.0 kg/m^2, inclusive, at Screening

Study Drug

Active Medication

Active substance:	Ceftobiprole
Mechanism of action:	Beta-lactam antibiotic with bactericidal activity
Approved in the US for the treatment of:	• Adult patients with *Staphylococcus aureus* bloodstream infections (bacteremia) (SAB), including those with right-sided infective endocarditis • Adult patients with acute bacterial skin and skin structure infections (ABSSSI) • Adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP)
Approved in the EU for the treatment of:	The following infections in adults, term neonates, infants, children and adolescents: • Hospital-acquired pneumonia, excluding ventilator-associated pneumonia • Community-acquired pneumonia
Dosage form:	Single dose vial containing lyophilized powder for reconstitution for iv infusion
Strength:	500 mg of ceftobiprole (as 667 mg of ceftobiprole medocaril sodium) per vial
Manufacturer:	Sourced by Sponsor

OATP1B probe substrate

Active substance:	Pitavastatin
Mechanism of action:	3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor
Approved for:	Hyperlipidemia; hypercholesterolemia
Dosage form:	Oral tablet
Strength:	2 mg
Manufacturer:	Sourced by Sponsor

Assessments

Pharmacokinetics:	Blood sampling for pitavastatin, its metabolite pitavastatin lactone, and ceftobiprole concentrations in plasma
Pharmacodynamics:	Blood sampling for diurnal CP-I levels in plasma
Safety:	AEs, clinical laboratory, vital signs, 12-lead ECG

Statistical Methods

Sample size calculation: This is an exploratory study where no prospective calculations of statistical power have been made. The sample size is based on obtaining adequate PK, PD, safety, and tolerability, data to achieve the objectives of the study.

Safety: Descriptive statistics.

Pharmacokinetics: Individual PK parameters will be estimated using non-compartmental analysis, as follows:

- Pitavastatin and pitavastatin lactone on Day 1 and Day 6: C_{max}, t_{max}, k_{el}, $t_{1/2,}$ AUC_{0-t}, AUC_{inf}, CL/F (pitavastatin only), Vz/F (pitavastatin only), as appropriate; ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} of pitavastatin lactone over parent drug; AUC and C_{max} ratio Day 6/Day 1 for pitavastatin and pitavastatin lactone
- Ceftobiprole on Day 5 and Day 6: C_{trough}, C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-8h}, CL, and V_z, as appropriate

Descriptive statistics for all plasma concentrations and PK parameters.

A mixed-effects model with subject as a random effect and treatment as a fixed effect will be performed on the following natural logarithm (ln)-transformed PK parameters of pitavastatin and pitavastatin lactone: C_{max}, AUC_{0-t}, and AUC_{0-inf}. The ratio of geometric least squares means, expressed as test (coadministration of pitavastatin + ceftobiprole)/reference (pitavastatin alone), and corresponding 90% confidence intervals (CIs) will be presented.

Pharmacodynamics: Individual PD parameters will be estimated, as follows:

- $AUEC_{0-25.5h}$, C_{max}, t_{max}, C_{trough}, and $C_{25.5h}$ on Days −1 to 1 and Days 5 to 6; C_{max}, $AUEC_{0-25.5h}$, C_{trough} and $C_{25.5h}$ ratio between Days 5 to 6/Days −1 to 1, and shift (if any) of t_{max} on Days 5 to 6 versus Days −1 to 1.

Descriptive statistics for CP-I plasma levels and PD parameters.

A mixed-effects model with subject as a random effect and treatment as a fixed effect will be performed on the following natural logarithm (ln)-transformed PK parameters of CP-I: C_{max}, and $AUEC_{0-25.5h}$. The ratio of geometric least squares means, expressed as test (during administration of ceftobiprole/reference (CP-I baseline), and corresponding 90% CIs will be presented.

Table 1 Schedule of Assessments

Phase	Screening	Treatment period										Follow-up / Early termination
Study day	**−21 to −3**	**−2**	**−1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15 ± 2 days**
Ambulatory visit	X											X
Admission		X										
Confinement		X	X	X	X	X	X	X	X	X	X	
Discharge											X	
Informed consent	X											
Medical history	X											
Demographics	X											
Physical examination[a]	X											
Bodyweight, height, and BMI calculation	X											
Serology (HBsAg, anti-HCV, anti-HIV 1 and 2)	X											
Drug and alcohol screen	X	X										
Pregnancy test (females only)	X	X										X
12-lead ECG[b,d]	X	X					X		X			X
Vital signs[c,d]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory[e]	X	X			X			X		X		X
Eligibility check	X	X										
Inclusion[f]				X								
Study drug administration (pitavastatin)[g]				X					X			
Study drug administration (ceftobiprole medocaril sodium)[h]							X	X	X	X		
PK blood sampling for pitavastatin and metabolite[i,d]				X	X	X			X	X	X	
PK blood sampling for ceftobiprole[j,d]							X	X	X	X		
PD blood sampling for CP-I[k]			X	X				X	X			
Previous and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X

For abbreviations and footnotes, see next page.

AE=adverse event; BMI=body mass index; CP-I=coproporphyrin I; ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV= hepatitis C virus; HIV= human immunodeficiency virus; ICF=informed consent form; LH=luteinizing hormone; PD=pharmacodynamic(s); PK=pharmacokinetic(s)

a. Complete physical examinations will be conducted at Screening. Symptom-driven physical examinations may be conducted at any time, per the Investigator's discretion.

b. 12-lead ECG: at Screening, on Day -2, on Days 4 and 6 (prior to terminating the first 2-hour infusion of ceftobiprole on those days), and at Follow-up/Early Termination. 12-lead ECGs will be obtained after at least 5 minutes of rest in a supine position. ECGs may be repeated at the discretion of the Investigator to rule out erroneous readings.

c. Vital signs (blood pressure [systolic and diastolic], pulse, respiratory rate, and body temperature): at Screening, on Days −2 and −1, on Day 1 (predose and 2 hours postdose of pitavastatin), on Days 4 and 6 (prior to the start of the first ceftobiprole infusion and prior to terminating the first 2-hour infusion of ceftobiprole on those days), in the morning of Days 2, 3, 5, 7 and 8 (predose when applicable), and at Follow-up/Early Termination. All parameters will be obtained after at least 5 minutes of rest in a supine position. Note: Table 2 provides the vital signs time points relative to Day 1 pitavastatin administration.

d. If multiple assessments are scheduled at the same timepoint, procedures should be performed in the following order: ECGs, vital sign measurements, PK blood sampling for pitavastatin and ceftobiprole, and blood sampling for PD markers. Note that PK blood sampling should be kept as close as possible to the specified timepoint.

e. Clinical laboratory tests (including clinical chemistry, hematology, and urinalysis) at Screening, on Day −2, in the mornings of Days 2, 5, and 7, and at Follow-up/Early Termination. Results of the tests on Day −2 must be reviewed prior to inclusion. A fasting period of at least 4 hours is required before obtaining clinical laboratory blood samples at all time points.

f. Inclusion of subjects will be done at predose on Day 1. This implies that beside other screening assessments, reserve subjects will have blood sampling for OATP1B activity marker CP-I in plasma on Day -1 (see footnote k).

g. OATP1B probe drug (pitavastatin) will be administered orally on Days 1 and 6 under fasted conditions (i.e., after an overnight fast [no foods and drinks, except water] of at least 10 hours). Drug intake will take place with approximately 240 mL of noncarbonated water. Water intake (except for the water to be given to swallow the tablet) will not be allowed from at least 1 hour prior to dosing until 1 hour after dosing. After dosing, fasting is required until a scheduled lunch at 4 hours postdose. On Day 6, OATP1B probe drug will be administered within 30 minutes prior to end of the first 2-hour ceftobiprole infusion on Day 6.

h. Study drug (ceftobiprole medocaril sodium) will be administered q8h, by 2-hour infusion, on Days 4 to 7. The first infusion on each of Days 4 to 7 will be after an overnight fast. Water intake will be ad libitum, and food intake will be according to the clinic meal planning.

i. Blood sampling for PK of pitavastatin and its metabolite pitavastatin lactone in plasma on Day 1 (before pitavastatin dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after pitavastatin dosing), Day 2 (24 and 36 hours after pitavastatin dosing), and Day 3 (48 hours after pitavastatin dosing), and on Day 6 (before pitavastatin dosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours after pitavastatin dosing), Day 7 (24 hours and 36 after pitavastatin dosing), and Day 8 (48 hours after pitavastatin dosing). Note: Table 2 provides the PK sampling time points relative to Day 1 pitavastatin administration.

j. Blood sampling for ceftobiprole PK in plasma on Day 4: predose and 2 hours (immediately after infusion stop) after start of the first infusion on Day 4; on Day 5: predose and 1, 2 (immediately after infusion stop), 4, 6, and 8 hours (predose prior to the second infusion on Day 5) after start of the first infusion on Day 5; on Day 6 (predose), and 1, 2 (immediately after infusion stop), 4, 6, and 8 hours (predose for the second infusion on Day 6) after start of the first infusion on Day 6, and on Day 7 (predose, prior to the first infusion on Day 7). Note: Table 2 provides the PK sampling time points relative to Day 1 pitavastatin administration.

k. Blood sampling for OATP1B activity marker CP-I in plasma: on Day 5 prior to the start of the first ceftobiprole infusion in the morning, at 2, 4, 6, and 8 hours after the start of the first ceftobiprole infusion on Day 5 (8-hour sample just prior to the start of the second ceftobiprole infusion), at 16 hours after the start of the first ceftobiprole infusion on Day 5 (just prior to the start of the third ceftobiprole infusion on Day 5), and prior to pitavastatin dosing on Day 6 (approximately 25.5 hours after the start of the first ceftobiprole infusion on Day 5) (total of 7 samples). On Day −1 and Day 1, a total of 7 samples will be taken at the corresponding clock times as are planned for Day 5 and Day 6. Note: Table 2 provides the sampling time points relative to Day 1 pitavastatin administration.

Table 2 Detailed Schedule of Administration of Pitavastatin and Ceftobiprole, and Assessments With Time Points Relative to Day 1 Pitavastatin Dosing

Day	Time Point With Day 1 Pitavastatin Dosing as Baseline (hours)	Dose	PK of Pitavastatin and Metabolite	Ceftobiprole PK	CP-I Bood Sampling	12-Lead ECG	Vital Signs
Screening						X	X
−2						X	X
−1	−25.5				X		X
	−23.5				X		
	−21.5				X		
	−19.5				X		
	−17.5				X		
	−9.5				X		
1	Predose Pitavastatin		X		X		X
	0	Day 1 Pitavastatin Dosing					
	0.25		X				
	0.5		X				
	0.75		X				
	1		X				
	1.5		X				
	2		X				X
	2.5		X				
	3		X				
	4		X				
	6		X				
	8		X				
	10		X				
	12		X				
2	24		X				X
	36		X				
3	48		X				X
4	Predose Ceftobiprole			X			X
	70.5	Start Day 4 First Ceftobiprole Infusion					
	72.5	End Day 4 First Ceftobiprole Infusion		X (Immediately After Stopping Day 4 First Ceftobiprole Infusion)		X (Prior to Stopping Day 4 First Ceftobiprole Infusion)	X (Prior to Stopping Day 4 First Ceftobiprole Infusion)
	78.5	Start Day 4 Second Ceftobiprole Infusion					

Day	Time Point With Day 1 Pitavastatin Dosing as Baseline (hours)	Dose	PK of Pitavastatin and Metabolite	Ceftobiprole PK	CP-I Bood Sampling	12-Lead ECG	Vital Signs
	80.5	End Day 4 Second Ceftobiprole Infusion					
	86.5	Start Day 4 Third Ceftobiprole Infusion					
	88.5	End Day 4 Third Ceftobiprole Infusion					
5	Predose Ceftobiprole			X	X (Prior to Starting Day 5 First Ceftobiprole Infusion)		X (Prior to Starting Day 5 First Ceftobiprole Infusion)
	94.5	Start Day 5 First Ceftobiprole Infusion					
	95.5			X			
	96.5	End Day 5 First Ceftobiprole Infusion		X (Immediately After Stopping Day 5 First Ceftobiprole Infusion)	X		
	98.5			X	X		
	100.5			X	X		
	Predose Ceftobiprole			X (Prior to Starting Day 5 Second Ceftobiprole Infusion)	X (Prior to Starting Day 5 Second Ceftobiprole Infusion)		
	102.5	Start Day 5 Second Ceftobiprole Infusion					
	104.5	End Day 5 Second Ceftobiprole Infusion					
	Predose Ceftobiprole				X (Prior to Starting Day 5 Third Ceftobiprole Infusion)		
	110.5	Start Day 5 Third Ceftobiprole Infusion					

Day	Time Point With Day 1 Pitavastatin Dosing as Baseline (hours)	Dose	PK of Pitavastatin and Metabolite	Ceftobiprole PK	CP-I Bood Sampling	12-Lead ECG	Vital Signs
	112.5	End Day 5 Third Ceftobiprole Infusion					
6	Predose Ceftobiprole			X (Prior to Starting Day 6 First Ceftobiprole Infusion)			X (Prior to Starting Day 6 First Ceftobiprole Infusion)
	118.5	Start Day 6 First Ceftobiprole Infusion					
	119.5			X			
	Predose Pitavastatin		X		X (Prior to Day 6 Pitavastatin Dosing)		
	120	Day 6 Pitavastatin Dosing					
	120.25		X				
	120.5	End Day 6 First Ceftobiprole Infusion	X	X (Immediately After Stopping Day 6 First Ceftobiprole Infusion)		X (Prior to Stopping Day 6 First Ceftobiprole Infusion)	X (Prior to Stopping Day 6 First Ceftobiprole Infusion)
	120.75		X				
	121		X				
	121.5		X				
	122		X				
	122.5		X	X			
	123		X				
	124		X				
	124.5			X			
	126		X				
	Predose Ceftobiprole			X (Prior to Starting Day 6 Second Ceftobiprole Infusion)			
	126.5	Start Day 6 Second Ceftobiprole Infusion					
	128		X				
	128.5	End Day 6 Second Ceftobiprole Infusion					
	130		X				

Day	Time Point With Day 1 Pitavastatin Dosing as Baseline (hours)	Dose	PK of Pitavastatin and Metabolite	Ceftobiprole PK	CP-I Bood Sampling	12-Lead ECG	Vital Signs
	132		X				
	134.5	Start Day 6 Third Ceftobiprole Infusion					
	136.5	End Day 6 Third Ceftobiprole Infusion					
7	Predose Ceftobiprole			X (Prior to Starting Day 7 First Ceftobiprole Infusion)			X (Prior to Starting Day 7 First Ceftobiprole Infusion)
	142.5	Start Day 7 First Ceftobiprole Infusion					
	144		X				
	144.5	End Day 7 First Ceftobiprole Infusion					
	156		X				
	150.5	Start Day 7 Second Ceftobiprole Infusion					
	152.5	End Day 7 Second Ceftobiprole Infusion					
	158.5	Start Day 7 Third Ceftobiprole Infusion					
	160.5	End Day 7 Third Ceftobiprole Infusion					
8	168		X				X
Follow-up/Early Termination						X	X

CP-I=coproporphyrin I; ECG=electrocardiogram; PK=pharmacokinetic(s)

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LIST OF ABBREVIATIONS

ABSSSI	acute bacterial skin and skin structure infections
AE	adverse event
BCRP	breast cancer resistance protein
BMI	body mass index
CABP	community-acquired bacterial pneumonia
CFU	colony forming unit
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
CP-I	coproporphyrin I
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration required to inhibit 50% of the activity
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
iv	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
OAT	organic anion transporter
OATP1B	organic anion-transporting polypeptide 1B
OATP1B1	organic anion-transporting polypeptide 1B1
OATP1B3	organic anion-transporting polypeptide 1B3
OCT	organic cation transporter
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
q8h	every 8 hours
S. aureus	*Staphylococcus aureus*
SAB	*Staphylococcus aureus* bacteremia
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T>MIC	Time that drug concentration exceeds MIC
TEAE	treatment-emergent adverse event
tid	three times a day
WMA	World Medical Association

Note: Definitions of pharmacokinetic (PK) and/or pharmacodynamic (PD) parameters are provided in Section 3.6.2

1. INTRODUCTION

1.1 Background

A detailed description of the pharmacology, PK, safety, and toxicology of ceftobiprole from nonclinical and clinical studies is provided in the Investigator's Brochure (IB).[1] Details most relevant for the current study are summarized below.

Ceftobiprole is a beta-lactam antibiotic with bactericidal activity against a broad spectrum of Gram-positive bacteria, including methicillin-resistant Staphylococcus species, vancomycin-resistant *Staphylococcus aureus* (*S. aureus*), and penicillin-resistant *Streptococcus pneumoniae*. Ceftobiprole also demonstrates in vitro activity against Gram-negative bacteria, including *Pseudomonas aeruginosa*. Ceftobiprole binds tightly to penicillin-binding proteins that are related to beta-lactam resistance in staphylococci and pneumococci.

1.1.1 Overview of the Ceftobiprole Clinical Program

The completed ceftobiprole clinical development program includes 20 Phase 1 studies, and the following five Phase 3 studies: 1) in pediatric patients aged 3 months to < 18 years with either hospital-acquired bacterial pneumonia (HABP) or community-acquired bacterial pneumonia (CABP) requiring hospitalization and treatment with intravenous (iv) antibiotics (N=138); 2) in patients with HABP (N=772); 3) in patients with CABP (N=632); 4) in patients with acute bacterial skin and skin structure infections (ABSSSIs) (N=676); and 5) in patients with *S. aureus* bloodstream infection (SAB) (N=389). (The number of patients refers to the Safety population in the respective studies).

1.1.1.1 Pharmacokinetics, Product Metabolism, and Tissue Distribution in Humans

The PK of ceftobiprole in adult subjects are predictable, linear, and time-independent across the dose range of 125 to 1000 mg, and variability is low (<30%). Steady-state drug concentrations are attained on the first day of dosing (3 times daily [tid]), and no appreciable accumulation is observed in subjects with normal renal function. The volume of distribution at steady-state of ceftobiprole is approximately 18 L, suggesting that distribution is restricted to the extracellular water compartment. The total body clearance of ceftobiprole is approximately 5 L/h, and the apparent elimination half-life ($t_{1/2}$) is 3 to 4 hours.

Ceftobiprole is eliminated primarily unchanged by renal excretion, with minimal metabolism to an open-ring metabolite, BAL1029, which accounts for approximately 4% of total exposure. The predominant mechanism responsible for elimination is glomerular filtration. The distribution of ceftobiprole in lung epithelial lining fluid, bone, muscle, and adipose tissue is similar to that of other cephalosporins. Following administration of 500 mg ceftobiprole tid for 7 days, ceftobiprole could not be detected in the feces of healthy subjects, there were no significant changes in the aerobic or anaerobic intestinal microflora, and no new colonizing aerobic or anaerobic bacteria resistant to ceftobiprole were observed.

1.1.1.2 Pharmacokinetics/Pharmacodynamics and Target Attainment

The probabilities of target attainment were obtained using a population PK/PD model developed for unbound ceftobiprole based on data from clinical studies of healthy subjects and patients.

Overall and for the recommended clinical dose regimen of ceftobiprole of 500 mg as a 2-hour iv infusion every 8 hours, percent probabilities of PK/PD target attainment on the first dosing day based on free-drug plasma %T minimum inhibitory concentration (MIC) targets associated with net bacterial stasis (ABSSSI only) and with 1-$\log_{10}$ colony forming unit (CFU) reduction from baseline

(CABP only), weighted over the MIC distributions for the isolate collections evaluated, were >99.9% for *S. aureus*, 100% for *Staphylococcus pneumoniae* (CABP only), 100% for Streptococcus species (ABSSSI only), and approximately 87% Enterobacterales. In patients with *S. aureus* bacteremia, the highest MIC value at which percent probabilities of PK/PD target attainment on Days 1 and 10 approached or exceeded 90% based on nonclinical ceftobiprole free-drug plasma % time that drug concentration exceeds MIC (T>MIC) targets associated with net bacterial stasis and a 1-$\log_{10}$ CFU reduction from baseline for *S. aureus* was at least 4 µg/mL (the MIC value inhibiting 100% of methicillin-resistant *S. aureus* and all *S. aureus* isolates). Overall and for the recommended clinical dose regimen of ceftobiprole of 500 mg as a 2-hour iv infusion every 6 hours for the first 8 days and every 8 hours from Day 9, percent probabilities of PK/PD target attainment on Days 1 and 10 based on free-drug plasma %T>MIC targets associated with net bacterial stasis and a 1-$\log_{10}$ CFU reduction from baseline for *S. aureus*, weighted over the MIC distributions for the 13,715 *S. aureus* isolates collected from centers in the US from 2016 to 2020, were >99.9%.

1.2 Risk-benefit Assessment and Risk Mitigation

Up to 22 Jan 2024, the estimated overall cumulative exposure to ceftobiprole in clinical studies supportive of the currently approved indications is 1779 subjects/patients, comprising 1606 adult subjects (including 305 healthy subjects) and 173 pediatric patients. The observed safety profile is consistent with that of the cephalosporin class as a whole. Based on clinical Phase 3 studies in adults, the most common adverse reactions occurring in ≥ 1% of patients treated with ceftobiprole were nausea, diarrhea, vomiting, headache, hyponatremia, phlebitis, dysgeusia, alanine aminotransferase increased, and rash.

Important identified risks include hepatic enzymes increased, hyponatremia, hypersensitivity reactions including anaphylactic reactions, and convulsions.

The additional identified risks of nausea and vomiting, and *Clostridium difficile* colitis (including pseudomembranous colitis) are of low frequency, considered manageable, reversible, and therefore without significant impact on the benefit-risk of ceftobiprole. Section 6 of the IB serves as the Reference Safety Information for ceftobiprole.

There is no expected clinical benefit for the healthy subjects who will participate in this study. The information obtained in this study can be used to provide an indication for a possible effect of ceftobiprole on blood concentrations of drugs eliminated by OATP1B1 and OATP1B3.

Overall, on the basis of the available nonclinical and clinical data, and prior knowledge, the risk-benefit profile of ceftobiprole is judged acceptable for the proposed clinical study.

1.3 Study Rationale

In vitro studies demonstrated that ceftobiprole is an inhibitor of the hepatocyte uptake transporters organic anion-transporting polypeptide 1B1 (OATP1B1) and organic anion-transporting polypeptide 1B3 (OATP1B3) with IC_{50}s of 67.6 µM and 44.1 µM, respectively, but is not an inhibitor of P-glycoprotein (P-gp), breast cancer resistant protein (BCRP), multidrug resistance mutation 1, multidrug resistance-associated protein 2, organic anion transporter (OAT) 1 and 3, organic cation transporter (OCT) 1 and 2. Since the concentration required to inhibit 50% of the activity (IC_{50}) values of OATP1B1 and OATP1B3 inhibition are in the order of magnitude of systemic ceftobiprole levels after efficacious clinical dose levels, ceftobiprole may increase concentrations of drugs eliminated by OATP1B1 and OATP1B3, such as statins (pitavastatin, pravastatin, and rosuvastatin), glyburide,

and bosentan. Ceftobiprole is potentially a weak substrate of the renal tubule cells uptake transporters OAT1 and OCT2.

This study has therefore been designed to determine whether ceftobiprole impacts the single dose PK of the OATP1B1 and OATP1B3 substrate pitavastatin[2]. Further to the evaluation of ceftobiprole dosing on the levels of pitavastatin as organic anion-transporting polypeptide 1B (OATP1B) probe drug, this study will evaluate the effects of ceftobiprole on the systemic levels of coproporphyrin-1 (CP-I) as endogenous marker for OATP1B activity.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	Primary
• To assess the PK of a single oral dose of pitavastatin, administered without and with iv ceftobiprole in healthy subjects.	• Plasma PK parameters of pitavastatin including C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf}, CL/F, and V_z/F, as appropriate.
Secondary	Secondary
• To assess the PD effect of iv ceftobiprole on the diurnal plasma level profile of CP-I in healthy subjects.	• Plasma exposure parameters of CP-I, including $AUEC_{0-25.5h}$, C_{max}, t_{max}, C_{trough}, and $C_{25.5h}$.
• To describe the systemic exposure of iv ceftobiprole without and with oral administration of pitavastatin in healthy subjects.	• Plasma exposure parameters of ceftobiprole, including C_{trough}, C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-8h}, CL, and V_z, as appropriate.
• To assess the single-dose plasma PK of the pitavastatin metabolite pitavastatin lactone after a single oral dose of pitavastatin, administered without and with iv ceftobiprole in healthy subjects.	• Plasma PK parameters of pitavastatin lactone including C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf}, as appropriate. • Ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} of pitavastatin lactone over parent drug.
• To assess the safety and tolerability of ceftobiprole without and with administration of a single oral dose of pitavastatin in healthy subjects.	• Type, frequency, severity, timing, and relationship to study drug of any adverse events (AEs). • Abnormalities and changes vs. baseline in clinical laboratory, vital signs, and 12-lead electrocardiogram (ECG) parameters, as appropriate.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

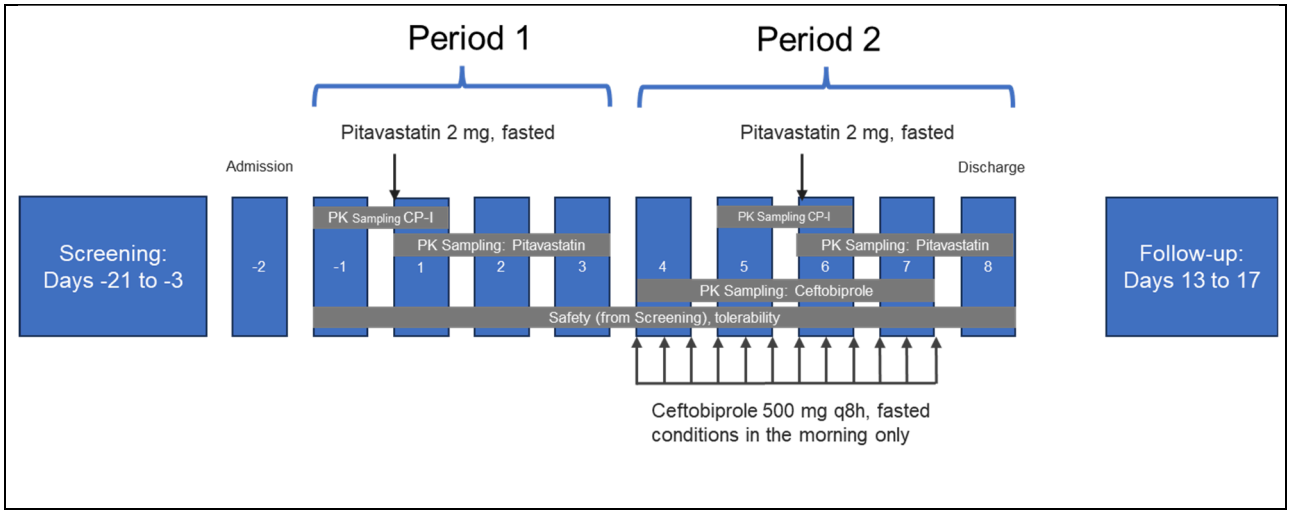
3.1.1 Type of Study

This will be a Phase 1, single-center, open-label, non-randomized, fixed-sequence, drug-drug interaction study in healthy male or female subjects to assess if there is an inhibitory effect of ceftobiprole on the hepatic OATP1B activity. Pitavastatin will be used as an OATP1B substrate in this study. The PK of oral pitavastatin will be assessed when administered alone and when administered together with intravenous (iv) ceftobiprole in a study design including two treatment periods. In addition, the PD effect of repeated doses of iv ceftobiprole on the diurnal plasma levels of CP-I will be assessed in this study as CP-I is an endogenous biomarker for hepatic OATPB1 activity.

The treatments planned in this study are described in Section 3.4.1.

A schematic overview of the study design is provided in Figure 1.

Figure 1 Study Design



CP-I=coproporphyrin 1; PK=pharmacokinetics; q8h=every 8 hours

3.1.2 Screening Period

Subjects will report to the medical screening facility/clinical site for the eligibility screening (see Section 3.3 for inclusion and exclusion criteria) within 3 weeks prior to the first drug administration.

Subjects will sign the study specific Informed Consent Form (ICF) prior to any study-specific screening procedures being performed. The written informed consent will be obtained for all subjects, regardless of their eligibility for the study; the signed ICFs will be retained and archived at the ICON and a copy will be provided to the subject.

Eligibility screening will consist of the assessments as presented in the schedule of assessments (Table 1).

3.1.3 Treatment Periods

Subjects will be admitted to the clinical research center on Day −2, which is 2 days prior to Day 1, the day of the first drug administration, and 1 day prior to characterization of the CP-I baseline profile on Day −1. They will be discharged on Day 8 after completion of the assessments.

The study design will comprise two treatment periods, with Period 1 for pitavastatin alone (from Day −1 to Day 3), and Period 2 for pitavastatin + ceftobiprole (from Day 4 to Day 8).

Assessments during the treatment periods will be performed as presented in the schedule of assessments (Table 1).

Inclusion of subjects will be done at predose on Day 1. This implies that reserve subjects will have blood sampling for OATP1B activity marker CP-I in plasma on Day −1.

3.1.4 Follow-up / Early Termination

The follow-up assessments will be performed 5 to 9 days after discharge on Day 8 (Day 15 ± 2 days) or 5 to 9 days after the time of Early Termination.

Assessments during Follow-up/Early Termination will be performed as presented in the schedule of assessments (Table 1).

3.1.5 Start and End of Study and Duration of the Study

The start of the study is defined as the date on which the first subject provides informed consent.

A subject is considered to have completed the study if he/she has completed all study visits.

The end of the study is defined as the date of the last visit or last procedure of the last subject in the study.

The total duration of the study from Screening until Follow-up for subjects will be up to 38 days.

3.2 Discussion of Study Design

The fixed-sequence design was chosen to allow each subject to serve as his/her own control with respect to pitavastatin PK characteristics with and without ceftobiprole coadministration.

A washout period of 5 days between the days of pitavastatin administration is considered sufficient in view of the elimination half-life of pitavastatin (approximately 12 hours).

Strong OATP1B inhibitors are known to increase the CP-I blood concentrations. Therefore, changes in plasma CP-I concentrations can be used as a sensitive and selective endogenous biomarker for OATP1B activity and provide an indication for a possible drug-drug interaction, with the note that CP-I appears informative by its own merit, without apparent need for, or advantage of, adding further markers like coproporhyrin-III (CP-III).[3][4][5] In the present study OATP1B activity will be assessed by comparing baseline CP-I levels to CP-I levels after multiple doses of ceftobiprole.

3.2.1 Other

For this exploratory study, no prospective calculations of statistical power have been made. The sample size has been based on the desire to obtain adequate PK, PD, safety, and tolerability, data to achieve the objectives of the study.

The intended sample size of 12 subjects is considered adequate to fully address the primary objective of the study, given the precedence of earlier studies with pitavastatin as probe substrate. Prueksaritanont and colleagues (2014) demonstrated in a sample of eight subjects the notable increase of pitavastatin exposure by a single dose of rifampin.[2] In samples of six subjects with mild liver cirrhosis and six subjects with moderate liver cirrhosis, Hui and colleagues (2015) demonstrated an unambiguous difference in pitavastatin exposure in relation to liver function, after a single oral dose of 2 mg of pitavastatin.[6]

Healthy subjects have been chosen as the study population due to the study design and the low risk of clinically significant toxicity at anticipated exposure levels. Additionally, the short duration of exposure will not be able to provide clear therapeutic benefit and justify patients discontinuing current therapies. Moreover, use of healthy subjects as opposed to patients will allow a clearer interpretation of the study results, as there will be no confounding factors resulting from changes in disease state and/or concomitant medications.

The Investigator will take all the usual precautions necessary for studies at an early stage in the development of a new drug.

3.3 Selection of Study Population

A total of 12 healthy male or female subjects are planned to be included in the study.

3.3.1 Inclusion Criteria

Note: Restrictions that apply to the period after admission are described in Section 3.4.8 except when they concern a statement of willingness.

The following inclusion criteria must be met for a subject to be eligible for inclusion in the study:

1. Sex: male or female
2. Age: 18 years to 65 years, inclusive, at Screening.
3. Body mass index (BMI): 18.0 to 30.0 kg/m^2, inclusive, at Screening.
4. Good physical and mental health on the basis of medical history, physical examination, clinical laboratory, ECG, and vital signs at Screening and admission to the clinical research center, as assessed by the Investigator.
5. Normal renal function (creatinine clearance ≥90 mL/min as determined by the Cockcroft-Gault equation) at Screening and admission to the clinical research center.
6. Females can be of nonchildbearing potential or of childbearing potential:
   a) Female participants of nonchildbearing potential: defined as either surgically sterilized or physiologically incapable of becoming pregnant, or at least 1 year postmenopausal (amenorrhea duration of 12 consecutive months). All female participants should have a negative serum pregnancy test at Screening and admission to the clinical research center.
   b) Female participants of childbearing potential must not be pregnant or lactating and should have a negative serum pregnancy test at Screening and admission to the clinical research center. Additionally, they must agree not to donate ova, not to attempt to become pregnant, and, if engaging in sexual intercourse with a fertile male partner, must agree to use adequate contraception from at least 4 weeks prior to the first administration of the study drug until after discharge from the clinical research center. Adequate contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least one of the following forms of contraception: a diaphragm, a cervical cap, or a condom. Total abstinence from heterosexual intercourse, in accordance with the lifestyle of the participant, is also acceptable.
7. Male subjects, if not surgically sterilized, must agree to use adequate contraception and not donate sperm from admission to the clinical research center until after discharge from the clinical research center. Adequate contraception for the male subject (and his female partner, if she is of childbearing potential) is defined as using hormonal contraceptives or an intrauterine device combined with at least one of the following forms of contraception: a diaphragm, a

cervical cap, or a condom. Total abstinence from heterosexual intercourse, in accordance with the lifestyle of the subject, is also acceptable.
8. All prescribed medication must have been stopped at least 30 days prior to admission to the clinical research center. An exception is made for hormonal contraceptives, which may be used throughout the study.
9. All over-the-counter medication, vitamin preparations and other food supplements, or herbal medications (e.g., St. John's wort) must have been stopped at least 14 days prior to admission to the clinical research center. An exception is made for paracetamol that is allowed up to admission to the clinical research center (up to 2 g/day for no more than 3 consecutive days).
10. Ability and willingness to abstain from alcohol from 48 hours (2 days) prior to Screening and admission to the clinical research center.
11. Ability and willingness to abstain from methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks) from 48 hours (2 days) prior to admission to the clinical research center.
12. Willing and able to sign the inform consent form.

3.3.2 Exclusion Criteria

Note: Restrictions that apply to the period after admission are described in Section 3.4.8 except when they concern a statement of willingness.

A subject who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Employee of ICON or the Sponsor.
2. History of relevant drug and/or food allergies, particularly to antibiotics.
3. Subject received a known potent inhibitor of OATP1B activity (e.g., cyclosporin A or rifampin) within 30 days prior to admission to the clinical research center.
4. Subject received a potential inducer of OATP1B activity (e.g., carbamazepine) within 30 days prior to admission to the clinical research center.
5. Subject has signs of, or frequently recurring, fungal infections.
6. Subject has a history of seizures.
7. Subject has a history of frequent diarrhea.
8. Smoking more than 5 cigarettes, 1 cigar, or 1 pipe daily; the use of tobacco products in the 48 hours (2 days) prior to admission to the clinical research center is not allowed.
9. History of alcohol abuse or drug addiction (including soft drugs like cannabis products) within 12 months prior to Screening.
10. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits).
11. Positive drug and/or alcohol screen (opiates, methadone, cocaine, amphetamines, methamphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol) at Screening or at admission to the clinical research center.
12. Positive screen for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibodies, or human immunodeficiency virus (HIV) 1 and 2 antibodies at Screening.
13. Participation in a drug study within 30 days prior to the first pitavastatin administration on Day 1 of the current study. Participation in four or more other drug studies in the 12 months prior to the first pitavastatin administration on Day 1 of the current study.

14. Donation or loss of more than 450 mL of blood within 60 days prior to the first pitavastatin administration on Day 1 of the current study. Donation or loss of more than 1.5 liters of blood (for male subjects)/more than 1.0 liters of blood (for female subjects) in the 10 months prior to the first pitavastatin administration on Day 1 of the current study.
15. Significant and/or acute illness within 5 days prior to the first pitavastatin administration on Day 1 that may impact safety assessments, in the opinion of the Investigator.
16. Unsuitable veins for iv infusion or blood sampling.

Subjects should refrain from consumption of any foods containing poppy seeds within 48 hours prior to Screening and admission to the clinical research center to avoid false positive drug screen results. In addition, they should refrain from strenuous exercise within 96 hours prior to Screening and admission as this could result in abnormal clinical laboratory values. If subjects indicate that they have violated these restrictions, but this does not lead to deviating laboratory values, subjects can still be eligible for participation at the Investigator's discretion.

3.3.3 Removal of Subjects from Assessment

Participation in the study is voluntary. A subject has the right to withdraw from the study at any time for any reason.

The Investigator has the right to terminate participation of a subject for any of the following reasons: difficulties in obtaining blood samples, violation of the protocol, severe AEs or serious adverse events (SAEs), or for any other reason relating to the subject's safety or integrity of the study data.

If a subject is withdrawn from the study, the Sponsor and/or study monitor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned.

After signing informed consent, subjects who drop out or withdraw for any reason without completing all screening evaluations successfully as well as subjects who drop out or withdraw prior to the first dose of study drug will be considered screening failures.

A subject who is withdrawn or voluntarily withdraws from the study for any reason, whether related to the study drug or not, after having received the first dose of study drug, will be considered an early-termination subject. If a subject is withdrawn for a reason related to the study drug, according to the judgment of the Investigator, the early-termination subject will not be replaced. If a subject does not complete the study for a reason not related to the study drug, the early-termination subject may be replaced after mutual agreement between the Sponsor and ICON.

The decision regarding the replacement of subjects will be documented.

ICON will make every effort to ensure that early-termination subjects who have received study drug complete the early-termination assessments/safety follow-up assessments.

3.3.3.1 Stopping Rules for Individual Subjects

Dosing of a subject will be stopped at any time during the study if any of the following circumstances occurs:

- A drug-related serious adverse reaction (i.e., an SAE considered at least possibly related to the study drug administration).
- A drug-related severe adverse reaction (i.e., severe nonserious AEs considered at least possibly related to the study drug administration).

- Other findings that, at the discretion of the Investigator and/or Sponsor's Medical Monitor, indicate that further dosing should be stopped.

3.4 Treatments

3.4.1 Treatments Administered

The following treatments are planned to be administered in two periods: Period 1 (from Day −1 to Day 3): 'pitavastatin single dose'; and Period 2 (from Day 4 to Day 8): 'pitavastatin single dose + ceftobiprole q8h':

- On Day 1, a single oral dose of 2 mg pitavastatin will be administered in the morning under fasted conditions.
- From Day 4 to Day 7, 500 mg ceftobiprole (as the prodrug ceftobiprole medocaril sodium)[2] will be administered as a 2-hour iv dose every 8 hours (q8h) under fasted conditions in the morning, and irrespective of timing of food intake further on the day.
- On Day 6, a single oral dose of 2 mg pitavastatin will be coadministered with ceftobiprole 30 minutes prior to the end of the first iv dose of 500 mg ceftobiprole under fasted conditions.

3.4.2 Identity of Investigational Products

Active Medication

Active substance:	Ceftobiprole
Mechanism of action:	Beta-lactam antibiotic with bactericidal activity
Approved in the US for the treatment of:	• Adult patients with SAB, including those with right-sided infective endocarditis • Adult patients with ABSSSI • Adult and pediatric patients (3 months to less than 18 years old) with CABP
Approved in the EU for the treatment of:	The following infections in adults, term neonates, infants, children and adolescents: • Hospital-acquired pneumonia, excluding ventilator-associated pneumonia • Community-acquired pneumonia
Dosage form:	Single dose vial containing lyophilized powder for reconstitution and iv infusion
Strength:	500 mg of ceftobiprole (as 667 mg of ceftobiprole medocaril sodium) per vial.
Manufacturer:	Sourced by Sponsor.

[2] Unless referring specifically to the prodrug, the term 'ceftobiprole' is used throughout the remainder of this protocol, and all doses are of ceftobiprole equivalents. 500 mg of ceftobiprole is dosed as 667 mg of ceftobiprole medocaril sodium.

OATP1B probe substrate

Active substance:	Pitavastatin
Mechanism of action:	3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor
Approved for:	Hyperlipidemia; hypercholesterolemia
Dosage form:	Oral tablet
Strength:	2 mg
Manufacturer:	Sourced by Sponsor

Details of study drug preparation by the ICON Pharmacy are described in the Pharmacy Preparation Record prepared by the ICON Pharmacy.

The active medication and the probe substrate are commercially obtained by Sponsor.

For details concerning drug storage and drug accountability, see Appendix 8.1.

3.4.3 Method of Assigning Subjects to Treatment Groups

All subjects signing informed consent will be assigned a subject number in Electronic Data Capture (EDC). After signing informed consent, subjects who drop out or withdraw for any reason without completing all screening evaluations successfully, as well as subjects who drop out or withdraw prior to the first dose of study drug, will be considered screening failures. A minimal set of screen failure information will be collected: demography, screen failure details, eligibility criteria, and any SAE.

On Day 1, subjects eligible for treatment will be assigned an enrollment number (01–12). In the event that a subject would need to be replaced (see Section 3.3.3), the replacement subject will receive the enrollment number of the subject to be replaced, increased by 100 (e.g., 101 replacement number for enrollment number 01), and will be administered the same treatments in the same order.

3.4.4 Selection of Doses in the Study

The selected dose of ceftobiprole of 500 mg administered as a 2-hour iv infusion q8h is the recommended dose of ceftobiprole for adult patients with ABSSSI, for adult and pediatric patients with CABP, and as maintenance dose in adult patients with SAB. This regimen results in systemic ceftobiprole exposure that is well in the ranges of IC_{50} values for OATP1B inhibition, and thereby considered appropriate for the objectives of the present study. A more intense dosing regimen with dosing every 6 hours as in the early phase of SAB treatment is therefore not proposed for the current study.

Based on the safety profile of multiple iv doses (tid) seen in previous studies, 500 mg tid (total 1,500 mg/day) is considered a safe dose in this study.[1]

Regarding pitavastatin as OATP1B probe drug, a dose of 2 mg is proposed for the present study, considering its successful use when discriminating pitavastatin exposures in small samples of subjects with mild and moderate liver impairment (Hui et al. 2004).[6] The 2-mg dose level is expected to provide a more complete characterization of the full PK profile of pitavastatin, compared to the 1-mg dose level deployed previously by Prueksaritanont et al. (2014) to assess the OATP1B inhibiting effect of rifampin.[2] The 2-mg dose remains in the range of linearity of pitavastatin PK.[7] The intended single 2-mg dose provides a more than 30-fold safety margin versus the 64-mg dose evaluated clinically previously in a repeated dosing setting[8], and is therefore expected to be a safe single dose, also in case of a major interaction.

3.4.5 Timing of Doses in the Study

On Day 1 and Day 6, pitavastatin will be administered to subjects between 08:00 and 12:00 hours in the morning under fasted conditions. Subjects will fast overnight for at least 10 hours following a light supper.

The study drug will be swallowed together with approximately 240 mL water (room temperature). The study drug should not be chewed.

On Days 4 to Day 7, ceftobiprole will be administered as a 2-hour iv infusion 3 times a day every 8 hours (q8h). The morning dose will be administered following an overnight fast of at least 10 hours.

On Day 6, a single oral dose of pitavastatin will be coadministered the morning with a single iv dose of dose of ceftobiprole under fasted conditions. Pitavastatin will be administered 30 minutes prior to the end of the 2-hour ceftobiprole infusion.

On Days 1 and 6 only, fasting will continue for a period of 4 hours after administration of pitavastatin, i.e., until scheduled lunch. On Days 4, 5 and 7, a non-standardized breakfast will be given 1 hour after the end of the first ceftobiprole infusion of that day.

During fasting, no fluids are allowed except water, with the following exception. On Days 1 and 6, water is not allowed from 1 hour before administration of pitavastatin until 1 hour after administration of pitavastatin (apart from the water taken with the dose as described above).

- On Days 4 to 7, water is not allowed from 1 hour before the start of the first ceftobiprole infusion until 1 hour after the end of the first ceftobiprole infusion.

When not fasting, noncaffeinated fluids are allowed ad libitum.

On PK days (Day 1, Day 5, and Day 6) dosing for each individual subject will be at around the same time (±15 minutes) on each dosing day. On other (non-PK) days, a margin of ±30 minutes is allowed.

3.4.6 Meals During the Study

A fasting period of at least 4 hours is required before obtaining clinical laboratory blood samples at all time points.

With the exception of the restrictions with respect to methylxanthine- and alcohol-containing beverages or food as described in Section 3.4.8 and what has been described in Section 3.4.5 there are no special requirements related to food and beverage intake. When not fasting, meals and snacks (such as decaffeinated coffee, herbal tea, fruit, biscuits) will be provided according to the clinical site Standard Operating Procedures (SOPs). A light supper will be provided on the evening before those days where fasting is required until lunch time.

3.4.7 Blinding

This is an open-label study.

3.4.8 Concomitant Medication and Other Restrictions During the Study

Note: Restrictions that apply to the period before admission are described in Section 3.3.1 and Section 3.3.2.

The use of all prescribed medication is not allowed from admission to the clinical research center until Follow-up. An exception is made for hormonal contraceptives, which are allowed throughout the study. The use of all over-the-counter medication, vitamin preparations and other food

supplements, or herbal medications (e.g., St. John's wort) is not allowed from admission to the clinical research center until Follow-up. An exception is made for paracetamol: from admission onwards, the Investigator may permit a limited amount of paracetamol for the treatment of headache or any other pain (up to 2 g/day for no more than 3 consecutive days). Other medication to treat AEs may only be prescribed if deemed necessary by the Investigator. If medication is used, the name of the drug, the dose, and dosage regimen will be recorded in the eCRF.

The use of methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks), and grapefruit (juice) and tobacco products is not allowed during the stay in the clinical research center.

The use of alcohol is not allowed during the stay in the clinical research center and within 48 hours prior to Follow-up.

Strenuous exercise is not allowed from admission to the clinical research center until Follow-up.

Male subjects, if not surgically sterilized, are required to use adequate contraception (see description below) and not donate sperm from admission to the clinical research center until after discharge from the clinical research center.

Female subjects of childbearing potential with a fertile male sexual partner are required to use adequate contraception (see description below) from at least 4 weeks prior to first administration of the study drug until after discharge from the clinical research center.

Adequate contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least one of the following forms of contraception: a diaphragm, a cervical cap, or a condom. Total abstinence from heterosexual intercourse, in accordance with the lifestyle of the subject, is also acceptable.

Subjects must not donate blood during the study until the follow-up visit (other than the blood sampling planned for this study).

3.4.9 Treatment Compliance

Study drug will be administered in the clinical research center. To ensure treatment compliance, administration of the study drug will be supervised by the Investigator or authorized designee. Compliance will be further confirmed by bioanalytical assessment of pitavastatin and ceftobiprole in plasma samples (see Section 3.5.3).

The exact times of study drug administration and the number of units administered must be recorded in the eCRF.

3.5 Pharmacokinetic, Pharmacodynamic, and Safety Assessments

3.5.1 Pharmacokinetic, Pharmacodynamic, and Safety Assessments, and Schedule of Assessments

A schedule of assessments is presented in Table 1.

3.5.1.1 Pharmacokinetic Assessments

3.5.1.1.1 Blood Sampling

At the time points defined in the Schedule of Assessments, blood samples will be taken for the analysis of pitavastatin, the metabolite pitavastatin lactone, and ceftobiprole in plasma samples. The

blood samples will be taken via an indwelling iv catheter or by direct venipuncture. The exact times of blood sampling will be recorded in the eCRF. Ceftobiprole PK samples should not be taken from the ceftobiprole iv infusion line and should be taken from the opposite arm during ceftobiprole infusion.

Details on sample processing, storage, and shipping will be described in the laboratory manual prepared by ICON.

Plasma samples may (in the future) also be used for research purposes such as evaluation of the activity of ceftobiprole, identification of exploratory biomarkers that are predictive of activity, or other exploratory evaluations that may help characterize the molecular mechanisms of ceftobiprole.

3.5.1.2 Pharmacodynamic Assessments

At the time points defined in the schedule of assessments, blood samples will be taken for the analysis of plasma CP-I levels.

Inclusion of subjects will be done at predose on Day 1. This implies that reserve subjects will have blood sampling for OATP1B activity marker CP-I in plasma on Day −1.

3.5.1.3 Safety and Tolerability Assessments

Safety and tolerability assessments will consist of AEs, clinical laboratory, vital signs, 12-lead ECG, and physical examination. Assessments will be performed in accordance with the schedule of assessments.

3.5.1.3.1 Adverse Events

The time period for actively eliciting and collecting AEs and SAEs (‘active collection period’) for each subject begins from the time the subject provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention), up to and including Follow-up.

Any clinically significant observations, as determined by the Investigator, in the results of clinical laboratory tests, 12-lead ECGs, vital signs measurements, or physical examinations will be recorded as AEs.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the first administration of the study drug, or any event already present that worsens in either severity or frequency following exposure to the study drug.

An AE that occurs prior to the first administration of the study drug will be considered a pre-treatment AE.

At several time points before and after drug administration, subjects will be asked non-leading questions to determine the occurrence of AEs. Subjects will be asked in general terms about any AEs at regular intervals during the study. In addition, all AEs reported spontaneously during the course of the study will be recorded. All AEs will be recorded in the eCRF as reported terms.

The severity of the AEs will be graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v5.0); the relationship between the AEs and the study drug will be indicated as related or not related. Details on grading the severity of AEs and assessing the relationship to study treatment are given in Appendix 8.2.

For subjects who are screening failures, the active collection period ends when screening failure status is determined.

If a subject withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a subject either permanently or temporarily discontinues participation in the study because of an AE or SAE, the event must be recorded in the eCRF, and if an SAE, reported using the SAE Report Form.

Investigators are not required to actively seek information on AEs or SAEs after the subject has concluded study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has completed the study, and considers the event to be reasonably related to the study drug, the Investigator must promptly report the SAE to the Sponsor using the SAE Report Form.

Any pregnancy of either a subject or a partner of a male subject must be monitored, until Follow-up if warranted.

3.5.1.3.2 Clinical Laboratory

Blood and urine samples for clinical laboratory assessments will be collected, analyzed, and processed according to the clinical site SOPs.

The following parameters will be measured:

- Clinical chemistry (serum quantitatively):
  total bilirubin, alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase creatinine, creatine kinase, urea, total protein, glucose, inorganic phosphate, sodium, potassium, calcium, and chloride.
  Creatinine clearance will be calculated using the Cockcroft-Gault equation at screening and admission to the clinical research center.
- Hematology (blood quantitatively):
  leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes, absolute partial automated differentiation (lymphocytes, monocytes, eosinophils, basophils, and neutrophils), mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
  Manual differential white blood cell count or red blood cell differentiation will only be performed if there is an abnormality in the blood cell count in accordance with the clinical site SOPs.
- Urinalysis (urine qualitatively):
  specific gravity, pH, hemoglobin, leukocytes, nitrite, protein, glucose, bilirubin, ketones, and urobilinogen.
  Urine sediment examinations will only be performed if there is an abnormality in urinalysis in accordance with the clinical site SOPs.
- Serology:
  HbsAg, HCV antibodies, and HIV 1 and 2 antibodies.
- Drug and alcohol screen (urine or serum qualitatively):
  Urine: opiates, methadone, cocaine, amphetamines, methamphetamines (including ecstasy), cannabinoids, barbiturates, benzodiazepines, and alcohol.
  Serum: tricyclic antidepressants.

- Pregnancy test (females only):
  β-human chorionic gonadotropin in serum.

For screening and admission, clinical laboratory tests may be repeated once if in the judgment of the Investigator there is a reason to believe the initial results are inaccurate.

In the event of an unexplained or unexpected clinical laboratory test value, the test must be repeated as soon as possible and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is found. The clinical laboratory will clearly mark all laboratory test values that are outside the normal range, and the Investigator will indicate which of these deviations are clinically significant. Clinically significant laboratory result deviations must be recorded as AEs, with the relationship to the treatment indicated (see also Appendix 8.2).

3.5.1.3.3 Vital Signs

Systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate should be recorded after the subject has been resting for at least 5 minutes in the supine position. These assessments should be made using an automated device whenever possible.

For screening and admission, vital signs may be repeated once if in the judgment of the Investigator there is a reason to believe the initial results are inaccurate (e.g., white coat hypertension).

3.5.1.3.4 Electrocardiogram

A standard 12-lead ECG is to be recorded after the subject has been resting for at least 5 minutes in the supine position. The ECG will be recorded using an ECG machine equipped with computer-based interval measurements. The following ECG parameters will be recorded: heart rate, PR interval, QRS-duration, QT-interval, QTc-interval (Fridericia's), and the interpretation of the ECG profile by the Investigator.

For screening and admission, ECG may be repeated once if in the judgment of the Investigator there is a reason to believe the initial results are inaccurate.

3.5.1.3.5 Physical Examination

Physical examination including body weight and height will be performed according to the clinical site SOPs.

3.5.1.4 Total of Blood Volume

The total volume of blood drawn for a subject will not exceed 500 mL (except when extra blood samples need to be taken for safety reasons).

3.5.2 Appropriateness of Assessments

The assessments that will be made in this study are standard and generally recognized as reliable, accurate, and relevant.

3.5.2.1 Timing of Assessments

For pitavastatin PK, predose samples will be obtained between waking up and dosing. Postdose samples up to 20 minutes postdose will be obtained with a time window of ±1 minute. Thereafter, postdose samples will be obtained with time margins of ±5% of the time that has passed since dosing.

For ceftobiprole PK, samples prior to the first infusion of a day will be obtained between waking up and the start of the iv infusion. For predose (trough) samples during multiple dosing, a 5% time

window since the last dose is allowed, but the sample must be taken before the next dose. Postdose samples up to 20 minutes after the start of the iv infusion will be obtained with a time window of ±1 minute. Thereafter, postdose samples will be obtained with time margins of ±5% of the time that has passed since the start of the iv infusion.

For CP-I diurnal profiling on Days -1 to 1 and on Days 5 to 6, samples will be obtained within margins of ±15 minutes. On Day 5, the first sample will be obtained prior to the start of the iv infusion with ceftobiprole. On Days 1 and 6, the last CP-I sample will be collected prior to pitavastatin dosing.

For safety assessments, predose assessments will be performed between waking up and dosing / the start of the iv infusion. For safety assessments up to 2.5 hours postdose/after the start of the iv infusion, a time window of ±15 minutes is allowed. Thereafter, serial postdose assessments (e.g., multiple assessments within any given day) must be performed with time margins of ±10% of the time that has passed since (last) dosing/the start of the iv infusion.

When assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that PK and PD blood sampling will be done after the ECG and vital signs recordings have been conducted, with PK blood sampling exactly on time.

3.5.3 Drug Concentration Measurements

The analysis of pitavastatin, metabolite pitavastatin lactone, ceftobiprole, and CP-I in plasma samples will be performed using validated liquid chromatography-mass spectrometry/mass spectrometry methods.

3.5.4 Retention of Blood Samples

Blood and urine samples remaining after clinical laboratory assessments have been performed can be used by ICON to develop and test methods. ICON will process these samples anonymously.

Blood samples remaining after PK and/or PD assessments have been performed will be stored by the Sponsor for research related to this clinical study. The samples will be stored for a maximum period of 12 months, after which they will be destroyed.

3.6 Statistical Procedures and Determination of Sample Size

3.6.1 Analysis Sets

3.6.1.1 Safety Set

All subjects who have received at least one dose of study drug.

3.6.1.2 Pharmacokinetic Set

All subjects who have received at least one dose of study drug and provided sufficient bioanalytical assessment results to calculate reliable estimates of the PK parameters.

3.6.1.3 Pharmacodynamic Set

All subjects for whom the PD data are considered to be sufficient and interpretable.

3.6.2 Statistical and Analytical Plan for Pharmacokinetic, Pharmacodynamic, and Safety Evaluation

A Statistical Analysis Plan (SAP) will be generated by Basilea and finalized prior to database lock. Full details of the analysis to be performed will be included in the SAP.

Any deviation from the SAP will be reported in the section “Changes in Planned Analysis” in the clinical study report (CSR).

3.6.2.1 Pharmacokinetic Evaluation

PK endpoints will be the plasma PK parameters of pitavastatin, pitavastatin lactone, and ceftobiprole. The PK parameters to be determined or calculated using noncompartmental analysis from the plasma concentration-time data for pitavastatin, pitavastatin lactone, and ceftobiprole include, but are not limited to, the parameters as given in Table 3. A complete list of PK parameters and analyses will be provided in the SAP.

Table 3 Pharmacokinetic Parameters

Parameter	Description	Pitavastatin	Pitavastatin lactone	Ceftobiprole
C_{trough}	Trough plasma concentration			X
C_{max}	Maximum observed plasma concentration	X	X	X
t_{max}	Time to attain maximum observed plasma concentration	X	X	X
AUC_{0-t}	Area under the plasma concentration-time curve up to time t, where t is the last point with concentrations above the lower limit of quantification (LLOQ)	X	X	
AUC_{0-8h}	Area under the plasma concentration-time curve up to 8 hours after the start of the first ceftobiprole infusion of the day (prior to the second infusion of the day)			X
AUC_{0-inf}	Area under the plasma concentration-time curve from time 0 to infinity calculated as: $AUC_{0-inf}=AUC_{0-t}+C_{last}/k_{el}$, where C_{last} is the last measurable plasma concentration	X	X	
k_{el}	Terminal elimination rate constant	X	X	X
$t_{1/2}$	Terminal elimination half-life, calculated as $0.693/k_{el}$	X	X	X
CL	Clearance			X
CL/F	Apparent oral clearance, calculated as dose/AUC_{0-inf}	X		
V_z	Volume of distribution at terminal phase			X
V_z/F	Apparent volume of distribution at terminal phase	X		

In addition, ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} of pitavastatin lactone over parent drug will be calculated.

Also, the Day 6/Day 1 ratios will be calculated for AUC and C_{max} for pitavastatin and pitavastatin lactone.

The PK parameters and their statistical evaluation will be included in the CSR for this study.

All data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

A mixed-effects model with subject as a random effect and treatment as a fixed effect will be performed on the following natural logarithm (ln)-transformed PK parameters of pitavastatin and pitavastatin lactone: C_{max}, AUC_{0-t}, and AUC_{0-inf}. The ratio of geometric least squares means, expressed as test (coadministration of pitavastatin + ceftobiprole)/reference (pitavastatin alone), and corresponding 90% confidence intervals (CIs) will be presented.

3.6.2.2 Pharmacodynamic Evaluation

PD endpoints will be the plasma exposure parameters of CP-I. The parameters to be determined or calculated from the plasma level-time data CP-I include, but are not limited to, the parameters as given in Table 4. A complete list of plasma exposure parameters and analysis will be provided in the SAP.

Table 4 Pharmacodynamic Parameters

Parameter	Description
C_{max}	Maximum observed plasma level
t_{max}	Time to attain maximum observed plasma level
C_{trough}	Trough plasma level
$C_{25.5h}$	Plasma level at 25.5 hours after the start of the first ceftobiprole infusion on Day 5 (prior to pitavastatin dosing on Day 6) or at the corresponding clock time on Day 1
$AUEC_{0-25.5h}$	Area under the plasma level-time curve up to time 25.5 hours after the start of the first ceftobiprole infusion on Day 5 (prior to pitavastatin dosing on Day 6) or at the corresponding clock time on Day 1

In addition, C_{max}, $AUEC_{0-25.5h}$, C_{trough} and $C_{25.5h}$ ratio between Days 5 to 6/Days -1 to 1, and shift (if any) of t_{max} on Days 5 to 6 versus Days -1 to 1 will be calculated.

The PD parameters and their statistical evaluation will be included in the CSR for this study.

All data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

Statistical analysis will be performed on PD parameters to compare baseline CP-I plasma concentrations to CP-I plasma concentrations after multiple doses of ceftobiprole. A mixed-effects model with subject as a random effect and treatment as a fixed effect will be performed on the following natural logarithm (ln)-transformed PK parameters of CP-I: C_{max}, and $AUEC_{0-25.5h}$. The ratio of geometric least squares means, expressed as test (during administration of ceftobiprole)/reference (CP-I baseline), and corresponding 90% CIs will be presented.

3.6.2.3 Evaluation of Safety and Tolerability

Safety and tolerability will be assessed through AEs, clinical laboratory, vital signs, ECGs, and physical examination findings.

3.6.2.3.1 Adverse Events

A listing of all individual AEs will be provided. Summary tables of TEAEs will be presented by System Organ Class based on the MedDRA terminology list (Preferred Terms): one containing the number of TEAEs (frequency of occurrence, number of subjects experiencing the event) by treatment and one containing the number of drug-related TEAEs (frequency of occurrence, number of subjects experiencing the event) per treatment. Additional tables of total counts by treatment and relationship and by treatment and severity will be given.

3.6.2.3.2 Clinical Laboratory

Clinical laboratory data will be listed accompanied by an indication if the parameter is outside the reference range. A listing of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable.

3.6.2.3.3 Vital Signs and Electrocardiograms

Vital signs and ECG parameters will be listed and presented descriptively, where applicable.

3.6.2.3.4 Physical Examination

Physical examinations will be listed.

3.6.3 Determination of Sample Size

This is an exploratory study where no prospective calculations of statistical power have been made. The sample size is based on obtaining adequate PK, PD, safety, and tolerability, data to achieve the objectives of the study. For this study, no prospective calculations of statistical power have been made. Any p values to be calculated according to the SAP will be interpreted in the perspective of the explorative character of this study.

3.7 Data Quality Assurance

The study may be audited by the Quality Assurance Department at ICON to assess adherence to the clinical study protocol (CSP) and Quality System. During the conduct of the study, process-related audits may be performed. An audit certificate outlining any audits and other related activities performed may be provided in the appendices of the final CSR.

The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study is conducted according to the relevant regulatory requirements. The eCRF entries will be verified with the source documentation.

Regulatory authorities, the Independent Ethics Committee (IEC), and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. If there are any missing or spurious data, they will be queried by the data manager and/or the study monitor.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed at ICON for all documents that are generated in relation with the study.

An explanation will be given for all missing and spurious data in the relevant sections of the CSR.

4. ETHICS

4.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki.[9]

This study is also designed to comply with International Council for Harmonisation (ICH) E6(R2) Guideline for Good Clinical Practice (GCP) (European Medicines Agency [EMA]/Committee for Medicinal Products for Human Use [CHMP]/ICH/135/1995)[10] and the EU Clinical Trial Regulation (CTR) (Regulation Number 536/2014)[11] and other applicable laws, regulations, and regulatory guidance.

Whenever the term “Investigator” is noted in the CSP text, it may refer to either the Investigator at the site or an appropriately appointed sub-investigator.

4.2 Independent Ethics Committee

The CSP, ICF/subject information leaflet, investigational medicinal product dossier (IMPD), IB and any other documents required by the EU CTR (Regulation Number 536/2014)[11] will be submitted via Clinical Trial Information System (CTIS) to obtain regulatory approval before the clinical study is started. The submission package will be evaluated by Independent Ethics Committees in the Member States concerned.

When applicable, the Sponsor will also submit and obtain approval for substantial modifications to the original approved documents via CTIS. A ‘substantial modification’ is defined in the CTR as any change to any aspect of the clinical study which is made after notification of approval and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical study. Substantial modifications must not be implemented before approval, unless necessary to eliminate hazards to the subjects.

During the study, the Sponsor will notify within 15 days through CTIS each Member State concerned of the following:

- the start of the clinical study in relation to that Member State
- the first visit of the first subject in relation to that Member State
- the end of the recruitment of subjects for a clinical study in that Member State
- the end of a clinical study in relation to that Member State
- the end of a clinical study in all Member States concerned and in all third countries in which the clinical study has been conducted.

In case of a temporary halt of a clinical study in all Member States concerned for reasons not affecting the benefit-risk analysis, the Sponsor will inform each Member State within 15 days through CTIS. If the clinical study is resumed, this will also be notified through CTIS.

The Sponsor will notify early termination of the clinical study for reasons not affecting the benefit-risk balance through CTIS. The reasons for such action and, when appropriate, follow-up measures for the subjects will be provided as well.

The Sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The temporary halt or early termination of a clinical study for reasons of a change of the benefit-risk balance will be notified to the Member States concerned

through the EU portal CTIS without undue delay, but not later than in 15 days of the date of the temporary halt or early termination. The notification will include the reasons for such action and specify follow-up measures. The restart of the clinical study following a temporary halt in this case will be deemed to be a substantial modification subject to the above-described authorization procedure.

4.3 Subject Information and Consent

All subjects will be informed verbally and in writing regarding the objectives, procedures, and risks of study participation. The subjects will have to sign the ICF before any study-related procedures are started. The ICF contains information about the objectives of the study, the procedures followed during the study, and the risks and restrictions of the study, with special reference to possible side effects of the study drug and potential interactions. In addition, insurance coverage provided during the study is explained. The elements addressed in the ICF are according to the ICH E6(R2) Guideline for GCP (EMA/CHMP/ICH/135/1995).[10]

4.4 Privacy

All personal details will be treated as confidential by the Investigator and staff at ICON, the Sponsor, and any subcontractors involved, and handling of personal data will be in compliance with the EU General Data Protection Regulation.[12]

5. STUDY ADMINISTRATIVE STRUCTURE

5.1 Distribution of Activities

5.1.1 Study Drug

The active medication and the probe substrate will be commercially obtained by the Sponsor.

5.1.2 Electronic Case Report Form Design

The eCRF design will be performed by the Sponsor or designee.

5.1.3 Data Management

Data management will be performed by the Sponsor or designee.

5.1.4 Statistics

A SAP will be provided by the Sponsor or designee. The safety analysis and the statistical evaluation of PK and PD parameters will be conducted by the Sponsor or designee. Statistical analysis will be performed with the computer program SAS® (SAS Institute Inc, Cary, NC, US). PK and PD parameters will be calculated using Phoenix WinNonlin (Certara, Princeton, NJ, US). Additional PK or PD computations can also be performed in SAS®.

5.1.5 Clinical Study Report Writing

The CSR, structured in accordance with the guideline "Structure and Content of Clinical Study Reports ICH E3"[13] will be written by ICON.

5.2 Documentation

5.2.1 Archiving

All documents concerning the study will be kept on file in the Central Archives of ICON for at least 25 years after conduct of the study. The Sponsor will receive the completed eCRFs (upon request, as PDF file).

5.2.2 Recording of Data in Source Documents and Electronic Case Report Forms

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data entered in the eCRF that are from source documents must be consistent with the source documents, or the discrepancies must be explained. If necessary, the Investigator may request previous medical records or transfer records. Current medical records must be available. A study-specific source document identification list will be finalized with the Sponsor prior to the start of the clinical phase of the study.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents when applicable; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

For screening failures and participants who are eligible for inclusion in the study but do not receive the study drug, only applicable data will be entered in the eCRFs, such as informed consent, demographics, reason for screen failure, and SAEs, if any.

6. CONFIDENTIALITY AND PUBLICATION POLICY

All information generated in this study is considered confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor, unless the disclosure is to authorized regulatory officials, the Sponsor, or the Sponsor's authorized representatives under applicable laws and regulations.

All study subjects must be informed that their personal study-related data will be handled by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject, who will be required to give consent for their data to be used as described in the ICF. The subjects must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

Identification of subjects and eCRFs must be by unique subject numbers only.

All relevant aspects regarding publication will be part of the contract between the Sponsor and ICON.

7. REFERENCES

1. Investigator's Brochure Ceftobiprole medocaril (BAL5788), Edition 23, 24 April 2024.
2. Prueksaritanont et al. Pitavastatin is a more sensitive and selective organic anion-transporting polypeptide 1B clinical probe than rosuvastatin. Br J Clin Pharmacol 2014;78:587–98.
3. Mori D, Kimoto E, Rago B, Kondo Y, King-Ahmad A, Ramanathan R, Wood LS, Johnson JG, Le VH, Vourvahis M, David Rodrigues A, Muto C, Furihata K, Sugiyama Y, Kusuhara H. Dose-Dependent Inhibition of OATP1B by Rifampicin in Healthy Volunteers: Comprehensive Evaluation of Candidate Biomarkers and OATP1B Probe Drugs. Clin Pharmacol Ther 2020;107:1004–1013.
4. Suzuki et al. Relationship of hemoglobin level and plasma coproporphyrin- I concentrations as an endogenous probe for phenotyping OATP1B. Clin Transl Sci. 2021;14:1403–11.
5. Kunze A, Ediage EN, Dillen L, Monshouwer M, Snoeys J. Clinical Investigation of Coproporphyrins as Sensitive Biomarkers to Predict Mild to Strong OATP1B-Mediated Drug-Drug Interactions. Clin Pharmacokinet. 2018;57:1559–70.
6. Hui CK, Cheung BM, Lau GK. Pharmacokinetics of pitavastatin in subjects with Child-Pugh A and B cirrhosis. Br J Clin Pharmacol. 2005;59:291–7.
7. Luo Z, Zhang Y, Gu J, Feng P, Wang Y. Pharmacokinetic Properties of Single- and Multiple-Dose Pitavastatin Calcium Tablets in Healthy Chinese Volunteers. Curr Ther Res Clin Exp. 2015;77:52–7.
8. Center for Drug Evaluation and Research. Application Number: 22-363. Clinical Pharmacology and Biopharmaceutics Review(S). 2009 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022363s000_ClinPharmR_P1.pdf)
9. World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (18th WMA General Assembly 1964), revised at 64th WMA General Assembly, Fortaleza, Brazil, Oct 2013.
10. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E6(R2): Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice. Adopted by the European Medicines Agency (EMA), Committee for Human Medicinal Products, Document Reference EMA/CHMP/ICH/135/1995), 14 Jun 2017.
11. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, Official Journal of the European Union, 57: 1-76.
12. The General Data Protection Regulation (GDPR). Regulation (EU) 2016/679 of the European Parliament and the Council of the European Union, 27 Apr 2016, applicable as of 25 May 2018.
13. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E3: Structure and Content of Clinical Study Reports. Note for Guidance on Structure and Content of Clinical Study Reports. Adopted by the Committee for Human Medicinal Products, European Medicines Agency (EMA), Document Reference CPMP/ICH/137/95, Jul 1996.
14. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Note for Guidance on Clinical Safety Data Management. Adopted by the Committee for Human Medicinal Products, European Medicines Agency (EMA), Document Reference CPMP/ICH/377/95, Jun 1995.

8. APPENDICES

8.1 Drug Accountability

Upon receipt of the study drug, it will be inspected and counted by the responsible pharmacist. If necessary, all study drug will be repacked per dosing occasion and labeled according to the clinical site SOPs.

All study drug must be kept in the ICON Pharmacy or in a locked and secured storage facility accessible only to the pharmacist and other pharmacy staff.

The responsible pharmacist must keep an inventory which includes a description of the formulation and quantity of study drug received for the study, and a record of what is dispensed, to whom, and when.

On termination of the study, the responsible pharmacist must conduct a final inventory of the study drug supply and record the results of this inventory in the Drug Accountability Form. Unused study drug will be returned to the Sponsor at the end of the study or will be locally destroyed according to the clinical site standard procedures.

8.2 Adverse Events and Serious Adverse Events Evaluation and Reporting

8.2.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AE definitions will be followed as stated in the “Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” (ICH topic E2A)[14]

All AEs reported by the subjects or apparent from their physical appearance during the clinical study will be reported on the AE eCRF page.

The Investigator will assess severity for each AE and SAE reported during the study and assign it to one of the following categories, according to CTCAE 5-point scale (version 5.0). Grade refers to the severity of the AE with unique clinical descriptions of severity for each AE based on this general guideline:

- **Mild (Grade 1)**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2)**: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- **Severe (Grade 3)**: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Life-threatening (Grade 4)**: Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5)**: Death related to AE.

If an AE has multiple aspects, the aspect with the highest severity will be graded.

It is emphasized that the term severe is a measure of severity; thus, a severe AE is not necessarily serious. An event is defined as ‘serious’ when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. For example, itching for several days may be rated as severe, but may not be clinically serious.

In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., laboratory, x-ray, ECG) should also be recorded as AEs.

Any abnormal laboratory test results that meet any of the conditions below must be considered as "clinically significant":

- Are associated with accompanying symptoms, and/or
- Require additional diagnostic testing or medical/surgical intervention, and/or
- Lead to a change in study dosing or discontinuation from the study; result in the addition of significant additional concomitant drug treatment or other therapy, and/or
- Lead to any of the outcomes included in the definition of an SAE, and/or
- Are considered to be an AE by the Investigator or Sponsor.

Reporting as an AE should not be triggered by:

- Merely repeating an abnormal test, or
- Any abnormal test result that is determined to be an error.

The relationship of any AE to the study drug will be assessed and graded as related or not related.

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The Investigator will use clinical judgment to determine the relationship.
- A 'reasonable possibility' of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The Investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the Investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assesses causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

If the Investigator does not know whether the study intervention caused the event, then the event will be handled as 'related to study intervention' for reporting purposes, as defined by the Sponsor. In addition, if the Investigator determines that an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the SAE Report Form and in accordance with the SAE reporting requirements.

8.2.2 Serious Adverse Events

An SAE is any untoward medical occurrence that, on the basis of medical and scientific judgment:

- Results in death, or
- Is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), or
- Requires inpatient hospitalization for a medical reason or prolongation of existing hospitalization (this refers to hospital admission required for treatment of the AE). (Note: this does not include confinement in, for example, a respite unit; a skilled nursing unit; rehabilitation facility; the clinical research center; or confinement due to planned or unplanned reason unrelated to study), or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Medically significant: Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

SAEs will be collected from the time of informed consent until Follow-up. SAEs that are related to the investigational drug and continue beyond the normal collection period (i.e., are ongoing at the time a subject exits the study) will be followed until resolution or until stabilized with or without sequelae. SAEs that begin after the subject's participation in the study is complete, but that the Investigator considers to be related to study drug, may be reported at any time.

The Investigator or clinical site personnel must notify the Sponsor's pharmacovigilance service provider, the Sponsor's Pharmacovigilance Unit and Medical Monitor of all SAEs, regardless of relationship to the investigational drug, immediately within 24 hours of clinical site personnel becoming aware of the event. The Investigator will provide the initial notification by sending a completed "Safety Report Form", which must include the Investigator's assessment of the relationship of the event to investigational drug and must be signed by the Investigator.

In addition, notification is sent by ICON to the IEC and the subject's General Practitioner, if applicable.

SAEs should be reported on the SAE Report Form, which is to be sent to the Sponsor's pharmacovigilance service provider PrimeVigilance, as shown below.

Pharmacovigilance service provider

PrimeVigilance Limited
The Surrey Research Park
1 Occam Court Guildford
Surrey GU2 7HJ, UK
Email: Basilea@primevigilance.com
Copy: drug.safety@basilea.com

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly as specified above.

All SAE reports should be sent to the contacts provided on Page 4: SAE Contact Information.

8.2.3 Suspected Unexpected Serious Adverse Reactions

An SAE that is also an unexpected adverse event related to study drug or when causality is unknown is called a suspected unexpected serious adverse reaction (SUSAR). Unexpected adverse reactions are adverse reactions of which the nature or severity is not consistent with the applicable product information (IB Section 6 for ceftobiprole, the Summary of Product Characteristics or USPI for pitavastatin).

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IECs, and Investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. An Investigator who receives SUSARs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the study documentation and will notify the IEC, if appropriate according to local requirements.

Expedited reporting will occur no later than 15 calendar days after the Sponsor or its representative has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be maximally 7 calendar days for a preliminary report with another 8 calendar days for completion of the report.

8.2.4 Follow-up of Adverse Events

All AEs and SAEs are followed up until the end of the study (FU/Early termination) or until resolution/stabilization or death. All SAEs considered related to study medication will be reported regardless of time on study, even if the study has been closed (see Section 8.2.2).