A PHASE 1, OPEN-LABEL, DRUG-DRUG INTERACTION STUDY DESIGNED TO EVALUATE THE EFFECT OF RELACORILANT ON THE PHARMACOKINETICS OF THE SENSITIVE P-gp SUBSTRATE DABIGATRAN ETEXILATE IN HEALTHY SUBJECTS

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T1330-02-12

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PURPOSE

Background

- Relacorilant (CORT125134) is an orally administered selective glucocorticoid receptor modulator (SGRM) without affinity for the progesterone receptor.
- Relacorilant is in development for the treatment of endogenous hypercortisolism (Cushing syndrome).[1,2]
- Additionally, relacorilant is being studied for the treatment of solid tumors, including ovarian cancer,[3,4] in combination with chemotherapy agents.
- In vitro, relacorilant exhibited inhibition of the efflux transporter P-glycoprotein (P-gp) in Caco-2 monolayer cellular assay.

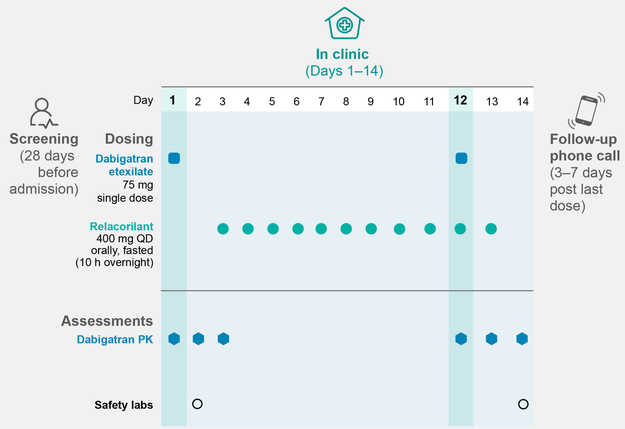
Objective

- The current drug-drug interaction (DDI) study was designed to evaluate the potential effect of relacorilant on the pharmacokinetics (PK) of the sensitive P-gp substrate dabigatran etexilate in healthy participants.

METHODS

- Relacorilant was investigated as a P-gp inhibitor of digoxin transport in vitro in a Caco-2 cell monolayer system over a concentration range of 0.01 to 10.0 µM.
- Relacorilant was investigated as a P-gp inhibitor in vivo in a single center, open-label, non-randomized, single sequence, DDI study in fasted healthy participants between the ages of 18 and 55 years with a BMI of 19.0–32.0 kg/m^2 and body weight ≥50.0 kg.
- Participants were administered a single oral dose of dabigatran etexilate 75 mg in the absence (Day 1) or presence (Day 12) of steady state plasma exposures of relacorilant 400 mg, which was administered orally QD on Days 3 to 13.
  - 400 mg relacorilant is the highest clinical dose studied.
- Blood samples were collected at 0 (pre-dose) through 48 h post-dose of dabigatran etexilate on Days 1 and 12.
- Plasma concentrations of free and total dabigatran were determined using a validated LC-MS/MS method. The lower limits of quantification were 1.01 ng/mL (free dabigatran) and 1.00 ng/mL (total dabigatran).
- PK parameters for free and total dabigatran were estimated and a formal statistical analysis was performed on exposure parameters.
- Geometric least square mean ratios (GMR) and 90% confidence intervals (CI) were generated for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max}. The geometric mean $\%AUC_{extrap}$ was low with <4%.
- Safety was assessed throughout the study.

Clinical DDI Study Design



PK, pharmacokinetics; QD, once a day.

RESULTS

Pharmacokinetics

- Relacorilant inhibited P-gp in vitro with an IC_{50} value of 1.3 µM.
- Following administration of 75 mg dabigatran etexilate alone (Day 1) and in the presence of 400 mg QD relacorilant (Day 12) to healthy participants, the free and total dabigatran plasma concentrations vs time profiles are shown in Figure 1 and the plasma PK parameters in Table 1.
- The similar plasma concentrations (Figure 1) and exposures (Table 1) of free and total dabigatran alone (Day 1) and in the presence of relacorilant (Day 12) support the use of P-gp substrates with no dose adjustment in the presence of relacorilant.

Figure 1. Free and total dabigatran plasma concentrations following single oral dose of 75 mg dabigatran etexilate (Day 1) and in presence of 400 mg QD relacorilant (Day 12)

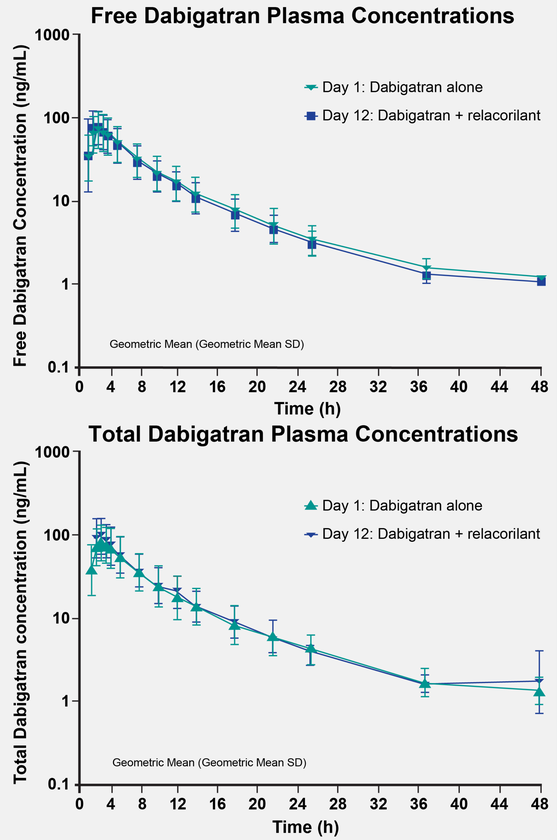


Table 1. Plasma PK parameters for free and total dabigatran following a single oral dose of 75 mg dabigatran etexilate (Day 1) and in presence of 400 mg QD relacorilant (Day 12)

	FREE DABIGATRAN			TOTAL DABIGATRAN		
Parameter	**Day 1 (alone)**	**Day 12 (+ relacorilant)**		**Day 1 (alone)**	**Day 12 (+ relacorilant)**	
N	30	24	—	30	24	—
	Geometric mean (Geometric CV%)		GMR (90%CI)	Geometric mean (Geometric CV%)		GMR (90%CI)
C_{max} (ng/mL)	76.5 (51.4)	83.8 (47.4)	113.21 (92.07–139.21)	90.6 (52.5)	111 (53.3)	123.95 (99.45–154.50)
$AUC_{0\text{-last}}$ (ng*h/mL)	501 (50.8)	480 (46.0)	101.53 (82.72–124.62)	598 (56.0)	647 (50.1)	112.58 (90.55–139.97)
$AUC_{0\text{-inf}}$ (ng*h/mL)	522 (48.2)	503 (42.9)	102.02 (84.16–123.67)	629 (49.2)	673 (48.1)	110.70 (91.00–134.66)
T_{max} (h) median	2.0 (1.5–4.0)	1.5 (1.5–2.5)	—	2.0 (1.5–3.0)	1.5 (1.0–3.0)	—

AUC, area under the curve; C_{max}, maximum measured concentration; CI, confidence interval; CV%, coefficient of variation; GMR, adjusted geometric mean ratio; T_{max}, time to peak drug concentration.

RESULTS

Safety & Tolerability

- 75-mg dabigatran etexilate doses were found to be well tolerated and 400-mg relacorilant doses administered QD were found to be moderately tolerated under the conditions of the study.
- Of the 30 participants enrolled in the study
  - 24 completed the study.
  - 5 withdrew consent due to a treatment emergent adverse event (TEAE) (upper abdominal pain in 4 participants, nausea in 1 participant, and back pain in 1 participant), and 1 was withdrawn due to a TEAE (mild influenza) that occurred prior to relacorilant dosing.
- The most commonly reported TEAEs considered to be related to relacorilant were upper abdominal pain, back pain, headache and nausea and were mild or moderate in severity.
- There was no meaningful change to the relacorilant safety profile when administered with dabigatran etexilate, compared with relacorilant administered alone. No new safety findings were identified.
- There were no clinically significant trends in laboratory parameters, ECGs, vital signs, body weight or physical examination findings throughout the study.

CONCLUSIONS

- Following a single oral dose of 75 mg dabigatran etexilate, the free and total dabigatran plasma exposures ($AUC_{0\text{-inf}}$) were similar in the absence and presence of 400 mg QD relacorilant.
- There were small numeric increases in free and total dabigatran plasma C_{max} in the presence of relacorilant compared to dabigatran alone; these increases are not considered to be clinically relevant.
- Overall, 400 mg QD relacorilant had minimal-to-no impact on the free and total dabigatran plasma exposures, suggesting no dose adjustments are needed for P-gp substrates in the presence of relacorilant.
- Dabigatran + relacorilant showed no change in TEAE profile when co-administered, compared with relacorilant administered alone.

REFERENCES

1. Pivonello et al. Poster P108 presented at ENDO 2024, June 1–4, 2024, Boston, MA.
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DISCLOSURES

JK, HH, JC: employees of and own stock in Corcept Therapeutics. KD: employee of Jade Consultants (Cambridge) Ltd, which provides consultancy services to Corcept Therapeutics.

ACKNOWLEDGEMENTS

This study is sponsored by Corcept Therapeutics Incorporated**.** Poster layout assistance by R&R Healthcare, LLC.