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BEXICASERIN HAS NEGLIGIBLE CYP OR P-GLYCOPROTEIN INTERACTION POTENTIAL, MINIMIZING THERAPEUTIC COMPLEXITY IN EPILEPSY PATIENTS WITH A HIGH BURDEN OF POLYPHARMACY

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BACKGROUND

- Given the common nature of complex polypharmacy in patients with developmental and epileptic encephalopathies, avoiding drug–drug interactions (DDIs) is of particular importance in this population[1,2]
- CYP enzymes can be inhibited and/or induced by many antiseizure medications resulting in clinically relevant drug-drug interactions, notably the enzymes CYP2D6, CYP3A4, and CYP2C19[3]
- Bexicaserin was designed to minimize dependency on CYP metabolism but rather promote it as a substrate for metabolism via UDP-glucuronosyltransferase (UGT) to form the glucuronide metabolite, M20. The pharmacokinetics (PK) of bexicaserin has been characterized in first-in-human studies[4]
- Confirmatory victim evaluation potential for bexicaserin was conducted in both in vitro and in vivo studies
  - **In vitro study**: standard in vitro metabolism screen to determine the intrinsic clearance of bexicaserin for various CYP and UGT enzymes
  - **In vivo study**: a unique clinical study was designed and conducted in 2 parts in healthy subjects

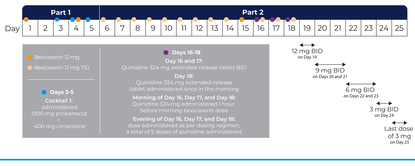
OBJECTIVES

- The clinical study was designed to determine the following:
  - Confirm metabolism of bexicaserin via glucuronidation by UGT to form M20
  - Assess bexicaserin disposition and potential to be affected by renal transporters
  - Characterize the likelihood of bexicaserin to be affected by P-glycoprotein (P-gp) efflux or by DDIs through the CYP metabolic pathway
- An in vitro evaluation was conducted to understand the victim potential of bexicaserin for CYPs and UGTs

METHODS

- The **in vivo clinical study** was conducted in 2 parts (**Figure 1**):
  - **Part 1**: the UGT metabolic pathway and the role of renal transporters was assessed using a single 12-mg dose of bexicaserin in the presence of Cocktail 1, comprising a UGT inhibitor (probenecid 1000 mg) and a renal transport inhibitor (cimetidine 400 mg) compared with bexicaserin alone (**Figure 1**)
  - **Part 2**: the PK of steady-state bexicaserin 12 mg administered 3-times daily was assessed with a CYP and P-gp inhibitor (quinidine 324 mg) compared with bexicaserin alone (**Figure 1**)
    - Serial plasma samples were collected in both parts of the study for PK assessment for bexicaserin and M20
    - Safety parameters were monitored throughout
- In an **in vitro study**, standard screens were employed to assess the victim potential of bexicaserin in CYP screens, and M20 formation was assessed using various UGTs

Figure 1. Study Design



RESULTS

Participants

- 19 healthy adult volunteers were included in this study (**Table 1**)

Table 1. Participant Demographics Summary

		Total N = 19
Age, years	Mean (SD)	37.0 (9.8)
	Median (minimum–maximum)	37.0 (22–60)
Sex, n (%)	Male	12 (63.2)
Race, n (%)	Asian	1 (5.3)
	Black or African American	9 (47.4)
	Other	1 (5.3)
	White	8 (42.1)
Ethnicity, n (%)	Hispanic or Latino	6 (31.6)
	Not Hispanic or Latino	13 (68.4)
Weight, kg	Mean (SD)	75.5 (13.79)
	Median (minimum–maximum)	74.5 (50–95)
Height, cm	Mean (SD)	171.4 (8.50)
	Median (minimum–maximum)	174.5 (156–184)

Part 1

- Maximum plasma concentration (C_{max}) and area under the curve (AUC) values were higher for bexicaserin and lower for M20 with bexicaserin alone (day 1) versus bexicaserin in the presence of Cocktail 1 (probenecid/cimetidine; day 4), as reflected in the geometric mean ratio (GMR) (**Figure 2** and **Figure 3**)

Figure 2. Forest Plot of UGT Pathway

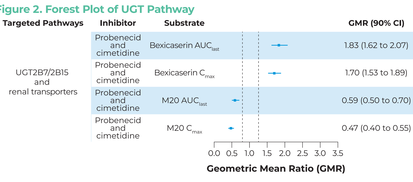
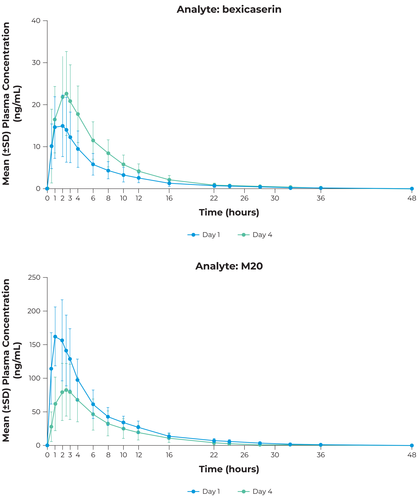
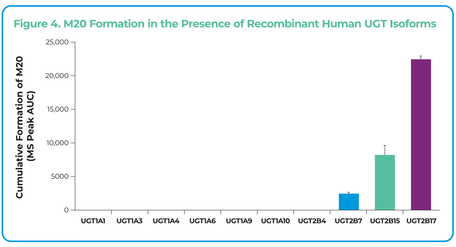


Figure 3. Mean (±SD) Bexicaserin and M20 Plasma Concentrations Versus Time for Probenecid: Single Doses on Day 1 (without Cocktail 1) and Day 4 (with Cocktail 1)



- The observed ~80% increase in bexicaserin exposure is consistent with, and supportive of, in vitro data indicating the disposition of bexicaserin via UGT, and a low likelihood of being affected by renal transport inhibitors
- In vitro investigations for UGTs indicated the major role of UGT2B17 and UGT2B15, and the minor role of UGT2B7 in the formation of M20 (**Figure 4**)

Figure 4. M20 Formation in the Presence of Recombinant Human UGT Isoforms



Part 2

- The plasma profiles of bexicaserin were comparable without quinidine (day 15) and with quinidine (day 18) coadministration (**Figure 5**)
- The Forest plot (**Figure 6**) indicated that the GMR was contained within 80% to 125%, which shows the lack of quinidine effect on exposure

Figure 5. Mean (±SD) Bexicaserin Plasma Concentrations Versus Time for Quinidine: Multiple TID Dosing on Day 15 (without quinidine) and Day 18 (with quinidine)

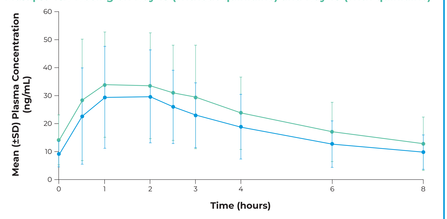
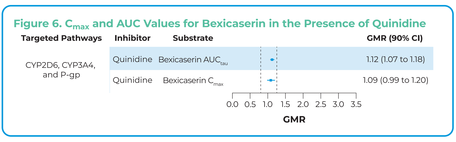
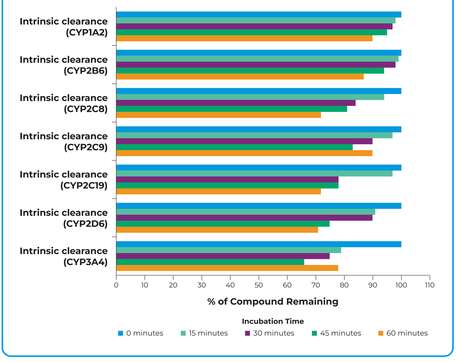


Figure 6. C_{max} and AUC Values for Bexicaserin in the Presence of Quinidine



- In vitro investigations for various CYPs indicated the low victim potential for bexicaserin (**Figure 7**)

Figure 7. In vitro CYP Victim Data



Safety

- Overall, 14 participants reported treatment-emergent adverse events (TEAEs). No serious TEAEs were reported
- The most common TEAEs were nausea, chills, fatigue, dizziness, attention disturbance, somnolence, euphoric mood, and constipation
- 3 participants discontinued due to an adverse event

CONCLUSIONS

- **Clinical study data (part 1) confirmed the involvement of the UGT pathway in the disposition of bexicaserin because bexicaserin concentrations increased and M20 decreased in the presence of probenecid, a known UGT inhibitor**
- **Definitive in vitro investigations measuring M20 further confirmed that bexicaserin is a victim for a few specific UGTs**
- **In vitro investigations confirmed that bexicaserin has a low victim potential for various CYP enzymes involved in clinical DDIs**
- **Clinical study data (part 2) unequivocally confirmed that CYP2D6 and CYP3A4 do not affect bexicaserin metabolism**
- **Furthermore, data from parts 1 and 2 support a low likelihood of renal transporters or P-gp interactions in the disposition of bexicaserin**
- **Overall, data confirm the role of UGT, but not CYPs, in the disposition of bexicaserin and the low likelihood for bexicaserin to have CYP-mediated clinical DDI potential**
- **Bexicaserin was safe and generally well tolerated, alone or in combination with other probe substrate**

Abbreviations **AUC**, area under the curve; **CI**, confidence interval; C_{max}, maximum plasma concentration; **DDI**, drug–drug interaction; **GMR**, geometric mean ratio; **P-gp**, P-glycoprotein; **PK**, pharmacokinetics; **SD**, standard deviation; **TEAE**, treatment-emergent adverse event; **TID**, 3-times daily; **UGT**, UDP-glucuronosyltransferase.

References **1.** Van Wilder L et al. *Prev Chronic Dis.* 2022;19:E50. **2.** Raga S et al. *Epileptic Disord.* 2021;23(1):40-52. **3.** Johannessen SI et al. *Curr Neuropharmacol.* 2010;8(3):254-267. **4.** Parasrampuria D et al. *Neurology.* 2022;98(18):1771.

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