Evaluation of the Potential Impact of Seladelpar on the Pharmacokinetics of Midazolam, Tolbutamide, Simvastatin, Rosuvastatin, and Atorvastatin

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Conclusions

- Seladelpar did not significantly impact the pharmacokinetics (PK) of probe substrates including midazolam (cytochrome P450 [CYP] 3A), tolbutamide (CYP2C9), simvastatin (CYP3A and organic anion-transporting polypeptides [OATPs]), rosuvastatin (OATPs and breast cancer resistance protein [BCRP]), and atorvastatin (CYP3A and OATPs) in humans
- Based on these data, seladelpar is not expected to have a clinically relevant impact on the PK of drugs that are substrates of CYP3A, CYP2C9, OATPs, or BCRP

Plain Language Summary

- Sometimes, people may need to take several drugs at the same time
- These drugs can affect one another and how the body breaks them down into parts
- Seladelpar is a drug used to treat people with primary biliary cholangitis
- This study tested whether taking seladelpar affects how the body breaks down other drugs and whether taking seladelpar with other drugs could change the amount of those drugs in the body
- This study also tested whether taking seladelpar with other drugs causes side effects
- The study found that taking seladelpar with other drugs did not greatly change how the body breaks down other drugs
- The study did not find safety concerns related to taking seladelpar and other drugs

References: **1.** Livdelzi. US prescribing information. Gilead Sciences, Inc.; 2024. **2.** Livdelzi. UK Summary of Product Characteristics. Gilead Sciences, Inc.; 2024. **3.** Seladelpar Gilead. EMA prescribing information. Gilead Sciences, Inc.; 2025.

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Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Introduction

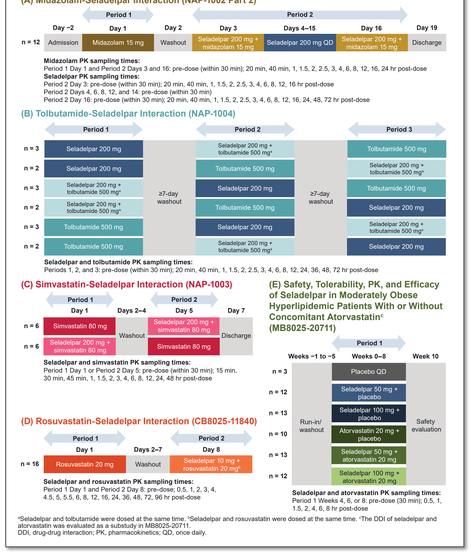
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients who are unable to tolerate UDCA[1-3]
- Seladelpar is mainly metabolised by CYP2C9, and to a lesser extent by CYP2C8 and CYP3A[1]
- Seladelpar is primarily eliminated in the urine as metabolites (M1, M2, and M3), which are not expected to have clinically relevant pharmacological activities[1]
- During the clinical development of seladelpar, the drug-drug interaction (DDI) potential of seladelpar was evaluated in different clinical studies, which found that seladelpar does not affect the PK of drugs that are substrates of CYP3A, CYP2C9, OATPs, and BCRP[1]

Objective

- To report in more detail the effects of seladelpar on CYP3A, CYP2C9, OATPs, and BCRP by using midazolam (CYP3A; study identifier: NAP-1002 Part 2), tolbutamide (CYP2C9; NAP-1004), simvastatin (CYP3A and OATPs; NAP-1003), rosuvastatin (OATPs and BCRP; CB8025-11840), and atorvastatin (CYP3A and OATPs; MB8025-20711 sub-study) as probe substrates across 5 clinical DDI studies

Methods

Figure 1. Study Designs for Evaluating DDI With Seladelpar



*Seladelpar and tolbutamide were dosed at the same time. [a]Seladelpar and rosuvastatin were dosed at the same time. †The DDI of seladelpar and atorvastatin was evaluated as a substudy in MB8025-20711.
DDI, drug-drug interaction; PK, pharmacokinetics; QD, once daily.

- To test the effect of seladelpar on CYP3A, CYP2C9, OATPs, and BCRP, healthy participants received a single dose of midazolam (15 mg), tolbutamide (500 mg), simvastatin (80 mg), or rosuvastatin (20 mg) with or without seladelpar coadministration (single or multiple doses) in crossover studies (**Figure 1A-D**)
- The effect of seladelpar on CYP3A and OATPs was also assessed in moderately obese participants with hyperlipidemia in a parallel group design comparing atorvastatin (20 mg) with or without seladelpar (**Figure 1E**)
- Samples were analysed using a validated liquid chromatography–tandem mass spectrometry method
- Primary PK parameters included maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC) from zero extrapolated to infinity ($AUC_{0\text{-}inf}$), or inclusive of all time points above the limit of quantitation (AUC_{all}; for atorvastatin-seladelpar interaction study only), time to peak drug concentration (T_{max}), and terminal half-life
  - Summary statistics (mean, standard deviation [SD], median, minimum, maximum) are presented
  - Geometric least-squares mean (GLSM) ratios and 90% confidence intervals (CIs) were obtained using analysis of variance (ANOVA) model on the log-transformed PK parameters
- Safety was assessed via the incidence and severity of adverse events (AEs)

Results

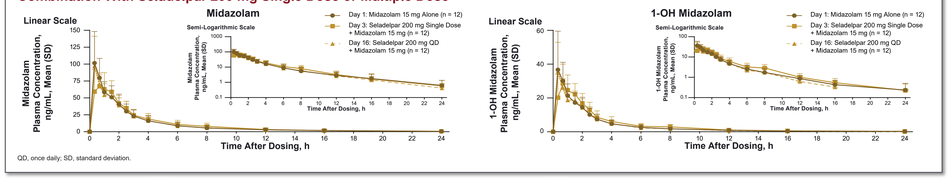
Table 1. Statistical Comparisons of Exposure for Midazolam and 1-OH Midazolam After Administration of Midazolam 15 mg Alone vs With Seladelpar 200 mg Single Dose or Multiple Dose

Parameter	Midazolam			1-OH Midazolam[a]		
	Day 1 Midazolam 15 mg Alone (n = 12)	Day 3 Seladelpar 200 mg Single Dose + Midazolam 15 mg (n = 12)	Day 16 Seladelpar 200 mg QD + Midazolam 15 mg (n = 12)	Day 1 Midazolam 15 mg Alone (n = 12)	Day 3 Seladelpar 200 mg Single Dose + Midazolam 15 mg (n = 12)	Day 16 Seladelpar 200 mg QD + Midazolam 15 mg (n = 12)
C_{max} (ng/mL), mean (SD)	109 (39.6)	82 (21.1)	102 (38.3)	41 (18.9)	33 (9.1)	38 (13.8)
GLSM ratio[b] (90% CI)	-	0.78 (0.69–0.88)	0.94 (0.84–1.06)	-	0.85 (0.72–1.01)	0.97 (0.82–1.15)
$AUC_{0\text{-}inf}$ (ng*h/mL), mean (SD)	251 (99.8)	258 (93.7)	241 (78.1)	78 (25.3)[c]	93 (31.3)	76 (22.5)[c]
GLSM ratio[b] (90% CI)	-	1.04 (0.96–1.12)	0.98 (0.91–1.06)	-	1.14 (1.05–1.23)	0.98 (0.91–1.06)
T_{max} (h), median (min–max)	0.33 (0.33–1.50)	0.85 (0.33–1.53)	0.33 (0.33–2.50)	0.34 (0.33–1.50)	0.85 (0.35–1.53)	0.33 (0.33–0.67)
Terminal half-life (h), mean (SD)	4.3 (1.2)	3.7 (1.0)	3.9 (0.8)	4.6 (0.9)[c]	4.2 (1.2)	3.6 (1.0)[c]

[a]1-OH midazolam is a metabolite of midazolam. [b]GLSM ratio was calculated as day 16/day 1 and day 3/day 1, respectively. [c]n = 11.
$AUC_{t\text{-}inf}$, area under the concentration-time curve from zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean; max, maximum; min, minimum; QD, once daily; SD, standard deviation; T_{max}, time to peak drug concentration.

- When midazolam was coadministered with seladelpar, either with a single dose of seladelpar 200 mg (day 3) or after multiple doses of seladelpar 200 mg once daily (for 16 days), plasma PK of midazolam and its primary metabolite via CYP3A oxidation (1-OH midazolam) were not affected (**Table 1**; **Figure 2**)
- These data suggested that seladelpar is not a CYP3A inhibitor nor a CYP3A inducer
- The PK of seladelpar did not appear to be affected by coadministration of midazolam (data not shown)

Figure 2. Midazolam and 1-OH Midazolam Plasma Concentration vs Time for Participants Administered Midazolam 15 mg Alone or in Combination With Seladelpar 200 mg Single Dose or Multiple Dose



QD, once daily; SD, standard deviation.

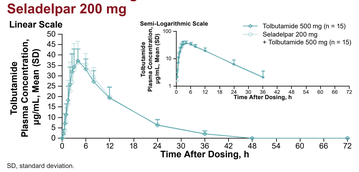
Table 2. Statistical Comparisons of Exposure for Tolbutamide After Administration of Tolbutamide 500 mg Alone vs With Seladelpar 200 mg

Parameter	Tolbutamide	
	Tolbutamide 500 mg Alone (n = 15)	Seladelpar 200 mg + Tolbutamide 500 mg (n = 15)
C_{max} (μg/mL), mean (SD)	39 (5.0)	41 (7.3)
GLSM ratio[a] (90% CI)	1.03 (0.97–1.09)	
$AUC_{0\text{-}inf}$ (μg*h/mL), mean (SD)	545 (123)	546 (121)
GLSM ratio[a] (90% CI)	1.00 (0.98–1.03)	
T_{max} (h), median (min–max)	4.00 (3.00–6.00)	4.00 (2.50–6.00)
Terminal half-life (h), mean (SD)	7.4 (1.7)	7.1 (1.6)

[a]GLSM ratio was calculated as seladelpar + tolbutamide/tolbutamide alone.
$AUC_{t\text{-}inf}$, area under the concentration-time curve from zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean; max, maximum; min, minimum; SD, standard deviation; T_{max}, time to peak drug concentration.

- Results indicated that coadministration of seladelpar 200 mg with tolbutamide did not affect the plasma PK of tolbutamide as exemplified in the GLSM ratios of C_{max} and $AUC_{0\text{-}inf}$ (**Table 2**; **Figure 3**)
- The PK of seladelpar was unaffected by concomitant administration of tolbutamide (data not shown)

Figure 3. Tolbutamide Plasma Concentration vs Time for Participants Administered a Single Dose of Tolbutamide 500 mg Alone or in Combination With Seladelpar 200 mg



SD, standard deviation.

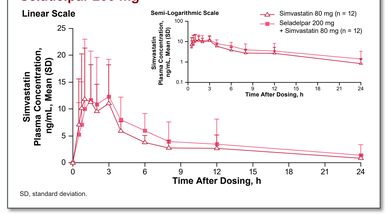
Table 3. Statistical Comparisons of Exposure for Simvastatin After Administration of Simvastatin 80 mg Alone vs With Seladelpar 200 mg

Parameter	Simvastatin	
	Simvastatin 80 mg Alone (n = 12)	Seladelpar 200 mg + Simvastatin 80 mg (n = 12)
C_{max} (ng/mL), mean (SD)	18 (8.5)	18 (9.6)
GLSM ratio[a] (90% CI)	0.95 (0.78–1.14)	
$AUC_{0\text{-}inf}$ (ng*h/mL), mean (SD)	84 (39.6)[b]	90 (38.9)[c]
GLSM ratio[a] (90% CI)	1.17 (0.97–1.41)	
T_{max} (h), median (min–max)	1.50 (0.75–3.00)	2.99 (1.00–3.93)
Terminal half-life (h), mean (SD)	6.3 (2.0)[b]	6.5 (3.0)[c]

[a]GLSM ratio was calculated as seladelpar + simvastatin/simvastatin alone. [b]n = 8. [c]n = 9.
$AUC_{t\text{-}inf}$, area under the concentration-time curve from zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean; max, maximum; min, minimum; SD, standard deviation; T_{max}, time to peak drug concentration.

- Simvastatin levels were not significantly changed by seladelpar coadministration (**Table 3**; **Figure 4**)

Figure 4. Simvastatin Plasma Concentration vs Time for Participants Administered a Single Dose of Simvastatin 80 mg Alone or in Combination With Seladelpar 200 mg



SD, standard deviation.

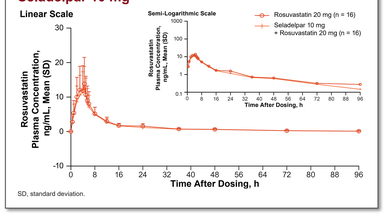
Table 4. Statistical Comparisons of Exposure for Rosuvastatin After Coadministration of Seladelpar 10 mg and Rosuvastatin 20 mg vs Rosuvastatin Alone

Parameter	Rosuvastatin	
	Rosuvastatin 20 mg Alone (n = 16)	Seladelpar 10 mg + Rosuvastatin 20 mg (n = 16)
C_{max} (ng/mL), mean (SD)	14 (7.5)[a]	13 (6.8)[b]
GLSM ratio[c] (90% CI)	0.86 (0.69–1.07)	
$AUC_{0\text{-}inf}$ (ng*h/mL), mean (SD)	164 (56.4)[d]	137 (46.5)[b]
GLSM ratio[c] (90% CI)	0.87 (0.70–1.07)	
T_{max} (h), median (min–max)	4.48 (2.98–5.00)[a]	4.48 (2.00–5.00)[b]
Terminal half-life (h), mean (SD)	22.9 (10.3)[a]	24.5 (11.6)[b]

[a]n = 14. [b]n = 13. [c]GLSM ratio was calculated as seladelpar + rosuvastatin/rosuvastatin alone. [d]n = 12.
$AUC_{t\text{-}inf}$, area under the concentration-time curve from zero extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean; max, maximum; min, minimum; SD, standard deviation; T_{max}, time to peak drug concentration.

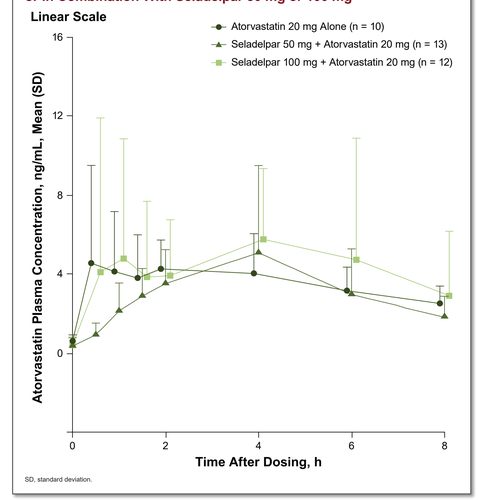
- Coadministration of seladelpar with rosuvastatin did not significantly impact the PK of rosuvastatin (**Table 4**; **Figure 5**)

Figure 5. Rosuvastatin Plasma Concentration vs Time for Participants Administered a Single Dose of Rosuvastatin 20 mg Alone or in Combination With Seladelpar 10 mg



SD, standard deviation.

Figure 6. Atorvastatin Plasma Concentration vs Time for Participants Administered Single Doses of Atorvastatin 20 mg Alone or in Combination With Seladelpar 50 mg or 100 mg



SD, standard deviation.

Table 5. Statistical Comparisons of Exposure for Atorvastatin, o-Hydroxyatorvastatin, and p-Hydroxyatorvastatin After Administration of Atorvastatin 20 mg With Seladelpar 50 mg or 100 mg Relative to Atorvastatin 20 mg Alone

Parameter	Atorvastatin			o-Hydroxyatorvastatin			p-Hydroxyatorvastatin		
	Atorvastatin 20 mg Alone (n = 10)	Seladelpar 50 mg + Atorvastatin 20 mg (n = 13)	Seladelpar 100 mg + Atorvastatin 20 mg (n = 12)	Atorvastatin 20 mg Alone (n = 10)	Seladelpar 50 mg + Atorvastatin 20 mg (n = 13)	Seladelpar 100 mg + Atorvastatin 20 mg (n = 12)	Atorvastatin 20 mg Alone (n = 10)	Seladelpar 50 mg + Atorvastatin 20 mg (n = 13)	Seladelpar 100 mg + Atorvastatin 20 mg (n = 12)
C_{max} (ng/mL), mean (SD)	6.8 (3.9)	6.1 (4.0)	9.8 (7.9)	4.3 (1.6)	4.9 (2.3)	6.2 (3.2)	0.5 (0.2)	0.8 (0.6)	1.0 (0.6)
GLSM ratio[a] (90% CI)	-	0.88 (0.54–1.43)	1.27 (0.77–2.09)	-	1.07 (0.73–1.58)	1.32 (0.89–1.95)	-	1.39 (0.89–2.17)	1.78 (1.13–2.79)
AUC_{all} (ng*h/mL), mean (SD)	28.7 (10.8)	26.0 (14.4)	35.5 (22.1)	22.8 (9.0)	23.3 (9.9)	27.2 (12.5)	3.1 (1.3)	4.3 (2.9)	5.1 (2.8)
GLSM ratio[a] (90% CI)	-	0.85 (0.57–1.27)	1.13 (0.76–1.69)	-	1.00 (0.69–1.43)	1.15 (0.80–1.67)	-	1.24 (0.81–1.90)	1.56 (1.01–2.41)

[a]GLSM ratio was calculated as seladelpar + atorvastatin/atorvastatin alone.
AUC_{all}, area under the concentration-time curve inclusive of all time points above the limit of quantitation; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean; SD, standard deviation.

- Atorvastatin levels were similar with or without seladelpar (**Table 5**; **Figure 6**)
- Following coadministration of seladelpar 50 mg, C_{max} and AUC_{all} for atorvastatin and o-hydroxyatorvastatin were similar to those without seladelpar coadministration; C_{max} and AUC_{all} for p-hydroxyatorvastatin were slightly higher in the presence of seladelpar 50 mg compared with in the absence of seladelpar, but the differences were not statistically significant
- Following coadministration of seladelpar 100 mg, C_{max} and AUC_{all} for atorvastatin and its metabolites, o-hydroxyatorvastatin and p-hydroxyatorvastatin, were slightly higher than those without seladelpar coadministration
- The evaluated doses of seladelpar were 5- or 10-fold higher than the therapeutic dose of 10 mg; based on the results of this study, seladelpar 10 mg is not expected to affect the PK of atorvastatin and its metabolites
- In this study, the effect of atorvastatin on the PK of seladelpar was also evaluated; the results suggested that atorvastatin 20 mg did not affect the PK of seladelpar (data not shown)

Safety

Midazolam-Seladelpar:

- One participant experienced 2 mild AEs of nasal congestion and folliculitis

Tolbutamide-Seladelpar:

- Eleven of 15 participants (73%) reported at least 1 AE, with incidences of 33% (5 of 15) and 47% (7 of 15) for tolbutamide and seladelpar alone, respectively; the incidence of AEs was similar (47% [7 of 15]) when the 2 drugs were co-administered
  - The most common AE was headache (40% [6 of 15]); all cases were mild

Simvastatin-Seladelpar:

- All 12 participants reported at least 1 AE: 2 (17%) following simvastatin alone and 12 (100%) following simvastatin plus seladelpar
  - The most common AE was dysgeusia, reported in all participants following dosing with simvastatin plus seladelpar (the latter in a reconstituted liquid form)

Rosuvastatin-Seladelpar:

- The proportion of participants with AEs was generally comparable in those receiving rosuvastatin (33%) or rosuvastatin with seladelpar (43%), and most events were mild or moderate in severity
  - One severe AE of syncope occurred in the blood draw setting

Atorvastatin-Seladelpar:

- 74%, 60%, and 57% of participants reported an AE in the atorvastatin plus placebo, atorvastatin plus seladelpar 50 mg, and atorvastatin plus seladelpar 100 mg groups, respectively; incidence was similar across the placebo (65%), placebo plus seladelpar 50 mg (59%), and placebo plus seladelpar 100 mg (63%) groups
  - The patient incidence of muscle toxicity AEs (by predefined search strategy) was generally similar across treatment groups: atorvastatin plus placebo (13%), atorvastatin plus seladelpar 50 mg (7%), atorvastatin plus seladelpar 100 mg (10%), placebo (6%), placebo plus seladelpar 50 mg (10%), and placebo plus seladelpar 100 mg (6%)
- Overall, seladelpar alone and when administered with these various DDI probes appeared generally safe and well tolerated

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