Apraglutide Has an Extended Duration and Induces a Greater Intestinotrophic Effect Compared with Teduglutide and Glepaglutide

Violetta Dimitriadou[1], Diane M. Hargrove[2], Régent Laporte[2], Alexander P. Posch[2], Pierre J.-M. Rivière[2], Richard Porter[1], Christian Meyer[1], Luca Santarelli[1]

[1]Therachon AG, Basel, Switzerland, [2]Ferring Research Institute, San Diego, USA.

INTRODUCTION

- Teduglutide is the only GLP-2 analog licensed for the treatment of short-bowel syndrome (SBS) in patients requiring parenteral support
- Apraglutide is a new GLP-2 analog with an extended half-life in development for SBS in patients requiring parenteral support
- Glepaglutide is also in development for SBS
- Here we report direct comparisons of the three agents with respect to intestinotrophic effects in rat.

OBJECTIVE

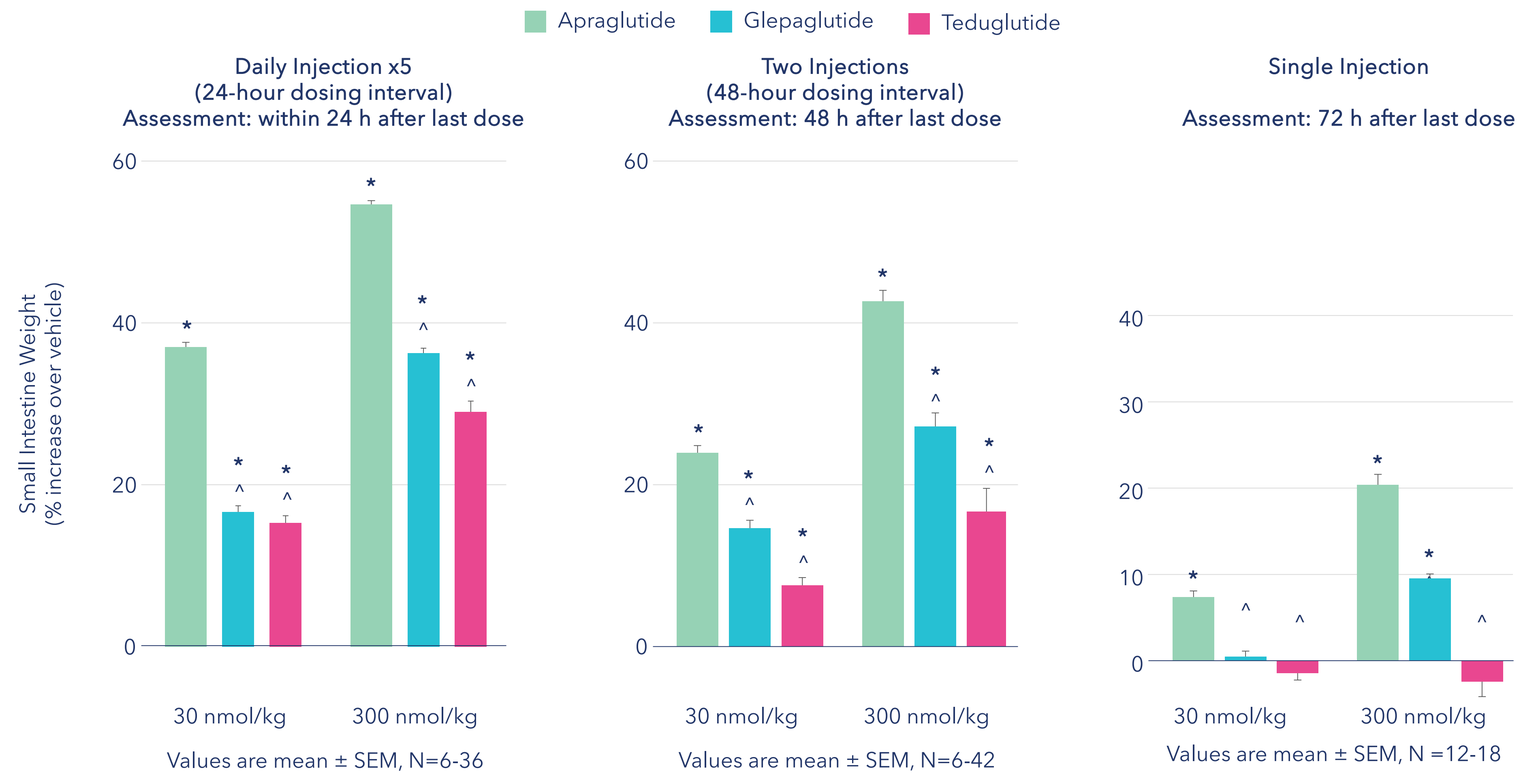
To compare the extent and duration of intestinotrophic effects in a rat model of SBS with apraglutide, teduglutide and glepaglutide

METHODS

- Two studies were conducted; one comparing apraglutide with teduglutide, and one comparing apraglutide, teduglutide and glepaglutide
- The three GLP-2 analogs were administered by subcutaneous (sc) injection at a range of equivalent doses (3 to 1,000 nmole/kg)
- Dosing frequencies of 24, 48 and 72 h were studied (Table 1)
- Each dosing regimen was tested in 6 Sprague-Dawley rats
- Intestinal wet weight was normalized to body weight and was expressed as % increase over a control group run in the same study
- A third study determined pharmacokinetic parameters after single intravenous bolus injection of apraglutide, teduglutide and glepaglutide at a dose of 0.2 free bases/kilogram in Sprague-Dawley rats

Dosing interval	Day of drug administration	Day tissue collected
Study 1		
24 hours	1, 2, 3, 4, 5	5
Study 2		
24 hours	1, 2, 3, 4, 5	5
48 hours	1 and 3	5
72 hours	1	4

Figure 1. Apraglutide Induced a Greater Intestinotrophic Effect Compared to Teduglutide or Glepaglutide



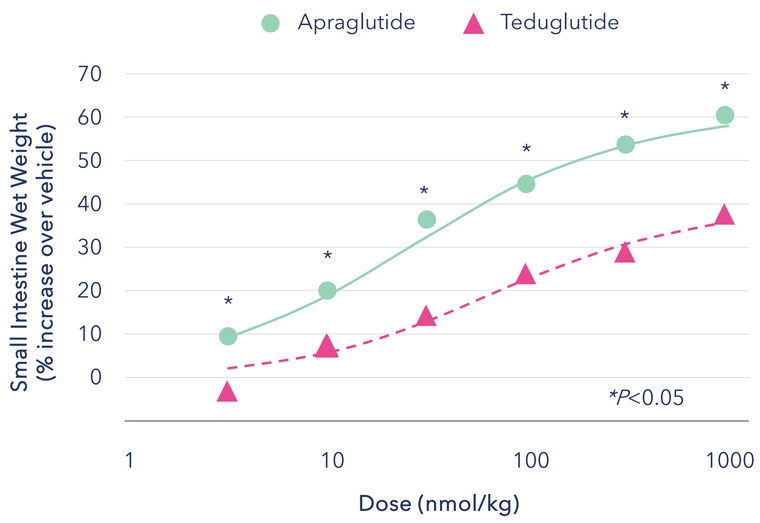
*P<0.05 versus vehicle control; ^P<0.05 versus corresponding apraglutide treatment group (ANOVA with Newman-Keuls post hoc pair-wise comparisons); SEM, standard error of the mean

RESULTS

Intestinotrophic effects

- Apraglutide induced a greater intestinotrophic effect than identical doses of teduglutide and glepaglutide at 24-, 48- and 72-hour dosing intervals (Figure 1)
- With a 96-hour dosing interval (not tested with glepaglutide), apraglutide significantly increased intestinal wet weight compared with teduglutide, which decreased intestine weight (Figure 2)

Figure 2. Dose Response with 96-hour Dosing Interval: Apraglutide vs Teduglutide



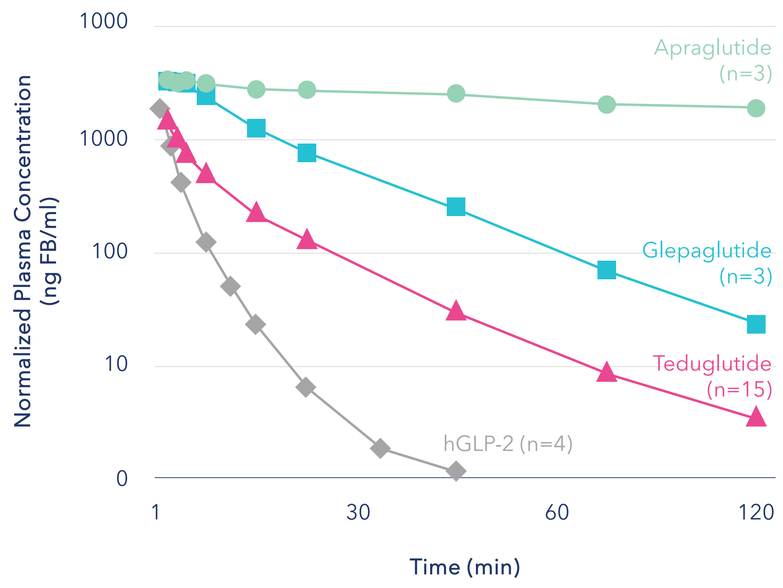
	ED_{50}		Emax	
	nmole/kg	95% CI	%	95% CI
Apraglutide	25	(21–30)	63	(60–66)
Teduglutide	68	(39–97)	41	(36–46)

CI, confidence interval; ED_{50}, dose providing 50% of maximum effect
Emax, maximum response

Pharmacokinetics

- Apraglutide had a longer elimination half-life and lower clearance than teduglutide and glepaglutide after a single intravenous dose (Figure 3)
- Half-life of apraglutide was ~30 hours compared with ~2–3 hours for teduglutide

Figure 3. Pharmacokinetic Profiles GLP-2 Analogs after Single IV Injection in Rats



CONCLUSIONS

- Apraglutide induced a greater intestinotrophic effect than teduglutide and glepaglutide in rats at the same dose and dosing intervals
- Apraglutide showed a prolonged duration of effect, most likely due to its extended half-life of ~30 hours
- These data indicate that apraglutide has the most robust and longest lasting pharmacodynamic effect of the compounds tested

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

VD is a consultant to Therachon AG; RP, LS and CM are employees of Therachon AG; DH, RL, AP and PR are employees of Ferring Pharmaceuticals