

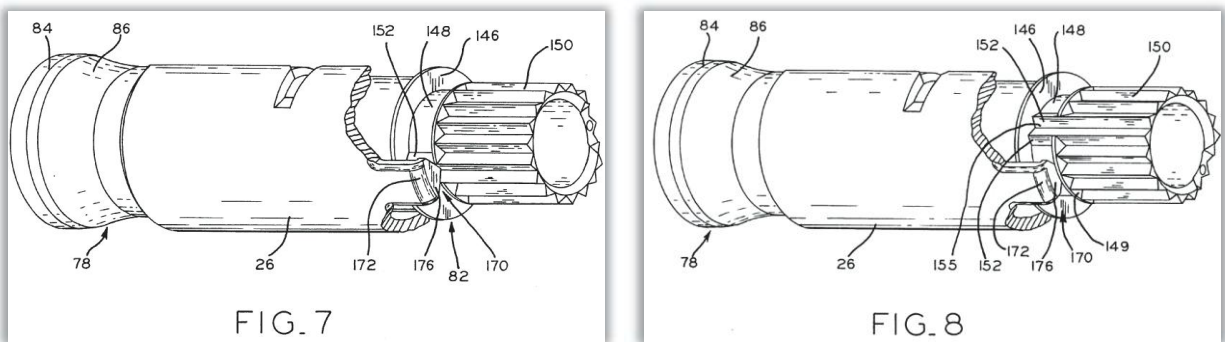
IN RE: OZEMPIC (SEMAGLUTIDE)	)	MDL No. 22-3038-CFC
PATENT LITIGATION	)	ANDA CASE
	)	
NOVO NORDISK INC. and NOVO NORDISK	)	
A/S,	)	
	)	
Plaintiffs,	)	C.A. No. 22-294-CFC
	)	CONSOLIDATED
v.	)	ANDA CASE
	)	
RIO BIOPHARMACEUTICALS INC., et al.,	)	
	)	
Defendants.	)	
NOVO NORDISK INC. and NOVO NORDISK	)	
A/S,	)	
	)	
Plaintiffs,	)	C.A. No. 22-1040-CFC
	)	ANDA CASE
v.	)	
	)	~~CONFIDENTIAL~~
MYLAN PHARMACEUTICALS INC.,	)	
	)	
Defendant.	)	

Pursuant to Paragraph 6 of the Scheduling Order, Defendants Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. ("DRL"), Alvogen, Inc. ("Alvogen"), Rio Biopharmaceuticals Inc. and EMS S/A (collectively, "Rio"), Sun Pharmaceutical Industries Ltd. and Sun Pharmaceutical Industries, Inc. (collectively, "Sun"), and Zydus Worldwide DMCC, Zydus Pharmaceuticals (USA) Inc., Zydus Lifesciences Limited, (collectively, "Zydus"), and Mylan Pharmaceuticals Inc. ("MPI") (each individually a "Defendant Group" and collectively, "Defendants") hereby submit to Plaintiffs Novo Nordisk Inc. and Novo Nordisk A/S (collectively, "Novo") its invalidity contentions for the asserted claims of United States Patent Nos. 8,114,833

Id. at FIG. 5-6.

Burroughs '642 also discloses an end-of-dose audible signal. Specifically, “[o]ne of the two flexible fingers of the dial assembly has an extension which, when the button is pressed, is pushed radially out. This finger falls within a separate groove in the housing as the ‘end-of-dose’ stop surface of the dial engages the corresponding stop surface on the housing, thereby producing an audible ‘click’ indicating that the entire dosage has been injected.” *Id.* at 3:18-23. This is an advantage because it “provide[s] increased accuracy of an end of dose.” *Id.* at 3:50-53.

Figure 7 “is a perspective view, in partial section, of a housing part in engagement with the dial assembly, particularly showing the unit click finger in the zero position.” *Id.* at 5:1-3. Figure 8 “is a view of FIG. 7, except that the unit click finger is behind the end-of-dose flange.” *Id.* at 5:4-5.



Id. at FIG. 7-8. “The movement of edge 95 (FIG. 4) of dial finger 94 past housing edge 157 (FIG. 4) and into groove 154 (FIG. 10) creates an audible ‘click’ sound, thereby providing an audible confirmation that the entire dosage has been injected.” *Id.* at 9:43-49.

13. Deacon

Published in 1998, the publication C. F. Deacon et al., *Dipeptidyl Peptidase IV Resistant Analogues of Glucagon-Like Peptide-1 which have Extended Metabolic Stability and Improved*

Biological Activity, 41 *Diabetologia* 271 (1998) (“Deacon”) is prior art to the ’343 patent and the ’122 patent under at least § 102(a) and (b).

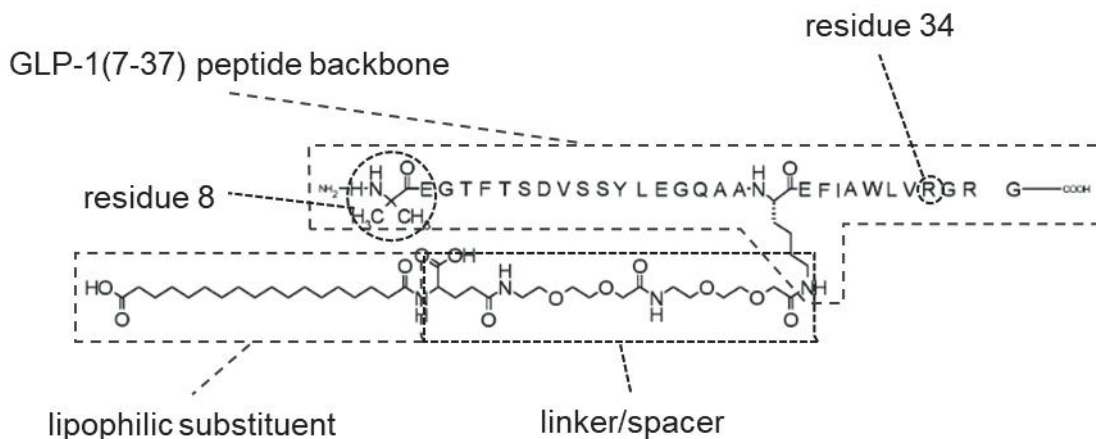
Deacon taught that GLP-1 has “great potential in diabetes therapy.” Deacon at 271. Deacon also explained that GLP-1 is “the product of tissue-specific post-translational processing of the glucagon precursor, proglucagon (PG) in the L-cells of the gastrointestinal mucosa.” *Id.* This resulted in two truncated forms that are found in humans, namely GLP-1(7-36)amide and GLP-1(7-37). *Id.* Deacon also proposed the use of modified GLP-1 peptides. Deacon explained several reasons to modify natural GLP-1 derivatives: for instance, the natural variants undergo rapid degradation. *Id.* However, Deacon explained that because degradation is done by an enzyme with structural specificity, modifications can be made to confer resistance while retaining GLP-1’s biological activity. *Id.* at 271-72. Deacon generated various GLP-1 analogues with improved pharmacokinetic properties. One such analogue was the Aib⁸ substitution. *See id.* at 274. Deacon explained that this analogue was the most potent of all the analogues, and was as potent as the natural form. *Id.* at 274. Thus, Deacon identified particular alterations to GLP-1 that confer resistance to degradation but retain biological activity. *Id.* at 275.

14. Dimarchi

Filed March 19, 2003, and published November 4, 2004, International Patent Application Publication No. WO 2004/093823 A2 (“Dimarchi”), titled “Polyethylene Glycol Link GLP-1 Compounds,” is prior art to the ’343 and the ’122 patent at least under § 102(a) and (e).

Dimarchi discloses “GLP-1 compounds coupled to at least one polyethylene glycol molecule or derivative thereof, resulting in a biologically active peptide with an extended half-life and a slower clearance when compared to that of unPEGylated peptide.” *Id.* at Abstract.

substituent (17-carboxyheptadecanoyl, octadecanedioic (ODDA), ω -carboxyheptadecanoyl, or other chemically equivalent names):¹⁰



The prior art disclosed the GLP-1(7-37) peptide backbone. *See, e.g.*, Knudsen at Abstract, 1:23-26, 1:56-2:50, 4:48-60, 8:33-51, 9:22-11:34; *see also* Deacon at 271-72; This backbone would have been known to a POSA.; *See, e.g., id.*; Sturis 2003 at 124. Further, the prior art disclosed using GLP-1 derivatives to treat type 2 diabetes, and this also would have been known to a POSA. *See, e.g.*, Knudsen at 4:36-38, 169:50-170:10, 172:12-16, claims 39-40; Deacon at 271-72, 277; Kim at 751; Dimarchi at p. 15 ll. 23-32; Sturis 2003 at 123. The prior art also disclosed doing so with a pharmaceutical composition containing a pharmaceutically acceptable excipient, and discloses using an effective amount. *See, e.g.*, Knudsen at 4:36-38, 5:7-15, 167:63-170:35, 169:50-170:10, 172:12-16, claims 28-40; Dimarchi at p. 15 ll. 23-32, p. 24 l. 28-p. 26 l. 5, p. 27 l. 23-p. 28 l. 17, claim 13.

The prior art also disclosed a GLP-1 derivative containing an Arg34 substitution. *See, e.g.*, Knudsen at claims 1-40. The prior art also disclosed a GLP-1 derivative containing an Aib8 substitution. *See, e.g.*, Deacon at 271-76.

¹⁰ A POSA would either understand chemical names or would know how to look up the structural names/formulas of compounds.

Deacon studied GLP-1 analogs with the specific intent to address both issues with GLP-1 mentioned above—an active agent that maintained the functional effect of GLP-1 while extending the plasma half-life. Deacon’s Table 1 (pg. 274) presented data for the GLP-1 analogs prepared and studied therein, all of which satisfy these criteria. The data illustrated that Aib⁸-GLP-1(7-37) had the highest percentage of intact peptide after a 20-minute infusion *in vivo* (Table 1). There was no cross-reactivity on the N-terminal end of the modified peptide for Aib⁸-GLP-1(7-37), while all other modifications exhibited cross-reactivity and degradation. The other three GLP-1 analogs had degradation occurring at both the C-terminus and N-terminus of the modified peptide chain, while Aib⁸-GLP-1(7-37) only had degradation at the C-terminus (Table 2). Aib⁸-GLP-1(7-37) also had the slowest rate of degradation (i.e., the longest half-life) of the different analogs on the C-terminal end, where some degradation occurred. Most significantly, Table 3 and Figure 2 present data for the binding affinity of these analogs to the GLP-1 receptor. Aib⁸-GLP-1(7-37) had the best binding affinity (i.e., lowest IC₅₀) out of all four analogs and was even better than GLP-1 itself.

Aib⁸-GLP-1(7-37) appears to be the best GLP-1 analog tested, even binding to the GLP-1 receptor better than GLP-1 itself. Thus, based on the teachings of Deacon, Aib⁸-GLP-1(7-37) would have been a strong choice for the lead compound in the development of a diabetes treatment.

iv. Other GLP-1 derivatives

The three potential lead compounds listed above are examples. Numerous other GLP-1 derivatives would have been candidates as well given the well-understood importance of GLP-1 for treatment of diabetes. GLP-1 is an endogenous gut hormone known to be responsible for regulating glucose metabolism, and would be an ideal starting compound for the development of a drug to treat diabetes. For example, Knudsen taught that GLP-1 is “a product of the proglucagon, is one of the youngest members of the secretin-VIP family of peptides, but is already established as an important gut hormone with regulatory function in glucose metabolism and gastrointestinal

secretion and metabolism.” Knudsen at 2:19-23. The variety of GLP-1 derivatives in clinical trials at the time of the alleged invention would have given a POSA a reasonable expectation of success in choosing such compounds as starting points.

c. A POSA would have been motivated to introduce an Aib⁸ modification to Leads A or B

A POSA would have been motivated to introduce an Aib⁸ modification to either Lead A (liraglutide) or Lead B (Lys²⁶(N^ε-(ω-carboxyheptadecanoyl)),Arg³⁴-GLP-1(7-37)). Such motivation was provided by Deacon. For instance, Deacon disclosed that “[a]nalogues, substituted at position 8 of GLP-1 with either threonine (Thr⁸-GLP-1 (7-37)), glycine (Gly⁸-GLP-1 (7-37)), serine (Ser⁸-GLP-1 (7-36) amide) or α-aminoisobutyric acid (Aib⁸-GLP-1 (7-36) amide and Aib⁸-GLP-1 (7-37)) were prepared.” Deacon at 272. One of ordinary skill in the art would have been motivated to substitute Ala⁸ with Aib⁸ because such a substitution was known to improve stability without compromising activity. Deacon taught the vulnerability of GLP-1 derivatives to degradation, particularly by dipeptidyl peptidase IV (DPP IV). *E.g., id.* at 272. But Deacon also taught that Aib⁸ substitution improves stability in plasma, stating that “[i]ncubation of the GLP-1 analogues revealed a significantly ($p < 0.0001$) prolonged $t_{1/2}$ compared to GLP1 (7-36)amide itself.... Degradation of Aib8-GLP1 ($n = 9$) was undetectable after 6 h.” *Id.* at 273. Deacon also taught that Aib⁸ substitution does not alter binding affinities. For example, Deacon states that “[a]ll the analogues bound to the cloned human pancreatic GLP-1 receptor (Fig. 2), but with widely differing binding affinities (IC₅₀; Table 3). The Aib⁸ and Gly⁸ analogues had similar affinities compared to GLP-1 (7-36) amide, while the other two analogues had lower receptor affinities than GLP-1 (7-36) amide.” *Id.* at 274. Further, Deacon taught that Aib⁸ substitution does not decrease the inhibition of glucagon secretion. Deacon stated, “[o]f the analogues, Aib⁸-GLP-1 (7-36) amide was at least as potent as GLP-1 (7-36) amide in stimulating insulin and inhibiting glucagon

grounds set forth above and in Exhibits A-G. Discovery and Defendants' investigation are ongoing, and Defendants reserve the right to modify and/or supplement its Invalidity Contentions as discovery progresses, after claim construction, or otherwise as appropriate.

/s/ Kelly F. Farnan

Kelly E. Farnan (#4395)
Sara M. Metzler (#6509)
RICHARDS, LAYTON & FINGER, P.A.
One Rodney Square
920 North King Street
Wilmington, DE 19801
302-651-7705
farnan@rlf.com
metzler@rlf.com

*Attorneys for Defendants Sun Pharmaceutical
Industries Ltd. and Sun Pharmaceutical
Industries Inc.*

/s/ Pilar G. Kraman

Pilar G. Kraman (#5199)
YOUNG CONAWAY STARGATT
& TAYLOR, LLP
Rodney Square
1000 North King Street
Wilmington, DE 19801
(302) 571-6600
pkraman@ycst.com

*Attorneys for Defendants Zydus Worldwide
DMCC, Zydus Pharmaceuticals (USA) Inc.,
and Zydus Lifesciences Limited*

/s/ Dominick T. Gattuso

Dominick T. Gattuso (#3630)
HEYMAN ENERIO GATTUSO
& HIRZEL LLP
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@hegh.law

*Attorneys for Defendants Dr. Reddy's
Laboratories, Ltd. and Dr. Reddy's
Laboratories, Inc.*

/s/ Stamatios Stamoulis

Stamatios Stamoulis (#4606)
Richard C. Weinblatt (#5080)
STAMOULIS & WEINBLATT LLC
800 N. West Street, Third Floor
Wilmington, DE 19801
(302) 999-1540
stamoulis@swdelaw.com
weinblatt@swdelaw.com

*Attorney for Defendant
Mylan Pharmaceuticals, Inc.*