https://doi.org/10.1038/s42255-025-01383-x

# A salute to innovation: exenatide in diabetes and obesity drug development at Amylin Pharmaceuticals

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The glucagon-like peptide 1 receptor agonist (GLP-1RA) class of medicines has emerged as transformative for the treatment of diabetes, obesity and other diseases. On the twentieth anniversary of the approval of exenatide (Byetta), three former employees of Amylin Pharmaceuticals acknowledge the contributions of some of the individuals and the innovation responsible for delivering the first approved GLP-1RA — the forerunner to the modern blockbuster drugs.

Gila monster hatching.

GLP-1RAs have emerged as the most effective agents thus far for the treatment of obesity. The recognition of other benefits including reduction of cardiovascular risk and amelioration of heart failure, chronic kidney disease, obstructive sleep apnoea, osteoarthritic pain and so on, has taken many by surprise. Several of these other benefits have become labelled indications. Other conditions being investigated, including infertility, addictive disorders, inflammatory diseases and neurodegeneration, indicate that this class of therapeutics has potential beyond metabolic disease. All of the currently approved GLP-1RAs began as antidiabetic agents, which as a class exhibited unprecedented safety and efficacy. When a class of drugs with as extraordinary an effect on society as that of GLP-1RAs emerges, there is a justifiable curiosity about how that class emerged.

In his recent book *Diet, Drugs and Dopamine*[1], David A. Kessler attempts to lay out the background of weight-loss treatments, and especially GLP-1RA development, which has taken decades of work by many in both academia and industry. He covers the discovery of proglucagon in the 1980s to the tissue-specific expression of different cleavage products and the identification of the biologically active moiety. He describes the frustration of Pfizer and other companies with the pharmaceutical intractability of human GLP-1 per se, owing to its vanishingly small half-life, even though infusion studies provided many clues of its potential utility. However, this otherwise excellent book entirely omits the discovery and development of the first GLP-1RA, exenatide, which preceded the development of other GLP-1RAs by approximately 5 years. Other than in a couple of examples of investigative journalism[2,3], the story of how exenatide set a benchmark for antidiabetic drugs and pointed the way to subsequent uses of GLP-1RA therapies has not been well described.

Here, 29 years after exenatide entered development, and 20 years after its first approval as Byetta, we wish to acknowledge the scientific innovation, talent, courage and faith of some of the individuals and teams that brought it to the market. The therapeutic promise that the approval of exenatide represented preceded the wave of subsequent innovation in peptide chemistry, formulation, process chemistry and devices that led to today's GLP-1RA medicines.

The isolation and discovery of exenatide (originally named exendin-4) from salivary proteins in the Gila monster[4], and its characterization as a GLP-1RA[5] by John Eng and others is relatively well known. Its effects on glucose-stimulated insulin release from pancreatic preparations and on glucose and HbA1c lowering in diabetic rodents[6,7] have been described in several reviews[8–10]. Less well known is that John privately patented and funded the development of the molecule when his employer (the US Government) declined to do so, that virtually every large company developing antidiabetic treatments either ignored him or passed on the opportunity, and that the general scientific and diabetes communities fared no better when they ignored his posters at scientific meetings[2].

Amylin Pharmaceuticals was established in San Diego, USA, in 1987 to develop the hormone amylin, which was discovered and named by Garth Cooper from New Zealand[11]. In 1996, Amylin Pharmaceuticals was a cash-strapped startup struggling to develop the first amylin agonist, pramlintide. In possibly his final chance to present his exendin-4 data, John Eng presented a poster at the July 1996 scientific conference of the American Diabetes Association in San Francisco, USA. Several employees (Andrew Young, Will Vine, Orville Kolterman and advisor John Buse) independently noted the importance of these foundational exendin-4 data. The key observation was a

profound, dose-dependent and (importantly) durable reduction of plasma glucose by administration of exendin-4 in diabetic mice[6]. Andrew Young, a physician–scientist also from New Zealand, campaigned Amylin Pharmaceuticals' leadership to internalize the programme. Within three months, Amylin Pharmaceuticals had extended the characterization of exendin-4 and discovered further relevant and interesting biological effects in preclinical models. A deal was subsequently struck with John Eng and exendin-4 was licensed to Amylin Pharmaceuticals.

Andrew Young and Kathryn Prickett co-led the early development of exenatide, supported by discovery research teams. In particular, the in vivo pharmacology team including Will Vine, Sunil Bhavsar, Richard Pittner, Slava Gedulin and David Parkes characterized novel biological actions. The peptide chemistry team including Nigel Beeley, Kathryn Prickett and Soumitra Ghosh explored pharmaceutical and pharmacological optimization. In the end, none of the approximately 400 analogues of exenatide that were synthesized and tested showed superior pharmaceutical properties to those of the peptide naturally expressed in the Gila monster. Exenatide (synthetic exendin-4) became the development candidate, AC-2993.

Amylin Pharmaceuticals leveraged its expertise in physiology and in vivo pharmacology to extensively characterize the actions of exenatide. For example, whereas subcutaneous injection of native mammalian GLP-1 had failed to show a reduction in food intake[12], a dose-dependent reduction was observed with exenatide (US Patent 8,288,338). This anorexigenic response was associated in chronic rodent studies with weight loss and was affirmed in 1999 in acute clinical studies[13]. By the early 2000s, it became apparent that weight loss was a consistent feature of chronic exenatide administration in humans[14,15]. Other actions identified at Amylin Pharmaceuticals included glucose-sensitive slowing of gastric emptying (US Patent 6,858,576) and suppression of nutrient-stimulated (but not hypoglycaemia-stimulated) glucagon secretion (US Patent 6,872,700). Observations of cardiotropic effects predicted a benefit in heart failure (US Patent 8,759,291), and additional potassium-sparing natriuresis (US Patent 7,298,065) predicted a benefit in renal disease. Treatment of polycystic ovary syndrome (US Patent 7,105,490) predicted an enhancement in fertility. Benefits in metabolic dysfunction-associated steatohepatitis were also identified (US Patent 8,389,472). These observations all preceded the similar observations made with other GLP1-RAs, including semaglutide, and apparently surprised many, leading to depictions of the latter (and also tirzepatide and retatrutide) as a 'panacea'.

Early clinical studies with AC-2993 were led by Orville Kolterman, an experienced endocrinologist, with assistance from Mark Fineman and others. The clinical group worked hand-in-hand with preclinical scientists in the sequence and design of the phase I and phase IIa studies, which confirmed not only the glycaemic benefits (including insulin-independent benefits) observed in preclinical models but also other metabolic benefits including lipid-lowering, anti-hypertensive and weight loss effects.

Toxicology studies were primarily led by Richard Hiles and Denis Roy. These were the first pivotal non-clinical studies to establish the safety of exenatide with chronic treatment over months to years. Contrary to the predictions of many, who still regarded it as a component of a venom, exenatide proved remarkably safe. In 14 toxicology studies, including one with acute dosing up to 200,000 times the therapeutic dose, there was not a single drug-related death. When Richard Hiles reported the occurrence of tumours following 2 years of exenatide dosing in carcinogenicity studies, he was asked what had occurred in the vehicle-treated control group. His response was that the last member of this group had died several months earlier – the exenatide-treated animals had apparently outlived the control group long enough to develop tumours. These data showing the life-extending effect of exenatide were shown by Jens Juuls Holst during the closing ceremony of the 2011 EASD (47th Annual Meeting of the European Association for the Study of Diabetes).

The recruitment of Alain Baron, an endocrinologist and researcher at Indiana University, was a coup for Amylin Pharmaceuticals; he was sought by many companies in the field, including Indianapolis-based Eli Lilly. Baron saw the therapeutic potential of GLP-1RAs in a space that sorely needed innovation, and he was persuaded to join Amylin Pharmaceuticals after seeing early clinical data obtained with exenatide. He assumed leadership of exenatide development and worked closely with Orville Kolterman, Mark Fineman and other clinical researchers to complete the pivotal phase II and phase III trials with exenatide within approximately 4 years.

Exenatide (as a twice-daily subcutaneous injection) was approved as the first GLP-1RA for the treatment of type 2 diabetes on 28 April 2005. Amylin Pharmaceuticals had collaborated with development and regulatory personnel at Eli Lilly (who went on to develop separate GLP-1 therapies) while outpacing other pharmaceutical companies in the field, including the Danish giant Novo Nordisk. This achievement, together with a strong rate of adoption, encouraged other companies to develop further GLP-1-based therapeutics, with the potential to benefit what was approaching 30 million patients with diabetes. Liraglutide (Victoza) for type 2 diabetes, developed by Novo Nordisk, was next to be approved, nearly 5 years later in 2010. It differed from exenatide in requiring only one daily injection and exhibited superior antidiabetic efficacy. Amylin Pharmaceuticals also pioneered the development of the first once-weekly GLP-1RA with the approval of extended-release exenatide (Bydureon) in 2012.

The closure of Amylin Pharmaceuticals as an independent organization when it was acquired by AstraZeneca and Bristol-Myers Squibb in 2012, and later wholly by AstraZeneca in 2013, left two notable legacies: the first approved GLP-1RA and the first approved amylin receptor agonist (pramlintide (Symlin), for insulin-using type 1 and type 2 diabetes). Both of these classes of agent are now the leading approaches for the treatment of obesity and other indications, with amylin-based therapeutics in late-stage clinical trials at multiple pharmaceutical companies.

Drug development is a team sport. Several functions, even cultures, may reside within the walls of a pharmaceutical company. Although the chemist who made the successful molecule may become well known, the many hands that touched the molecule through its long journey to become a medicine, and the many more necessary to ensure its commercial success, all had essential roles. We have tried to recognize some of the key individuals at Amylin Pharmaceuticals who made critical contributions in the development and commercialization of exenatide. Many not mentioned here, but who, for example, identify themselves as one of the 1,250 members of the Amylin Pharmaceuticals Alumni on LinkedIn, as well as the professionals and patients with whom they worked, recall with satisfaction the foundational effort they provided. It was on their shoulders that future innovators in the GLP-1 space could stand to deliver to patients some of the most innovative and improved therapies our industry has ever seen.

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Published online: 25 September 2025

## References

1. Kessler, D. A. *Diet, Drugs, and Dopamine: The New Science of Achieving a Healthy Weight* (Flatiron Books, 2025).
2. Delaye, F. Le monstre qui a ouvert le marché de la minceur, episode no. 6. *Heidi News* https://www.heidi.news/explorations/minceur-sur-ordonnance/le-monstre-qui-a-ouvert-le-marche-de-la-minceur-medicalisee (2024).
3. Winkler, R. & Cohen, B. Monster diet drugs like Ozempic started with actual monsters: studies of Gila monsters and anglerfish laid the groundwork for today's blockbusters. *Wall Street Journal* https://www.wsj.com/health/pharma/ozempic-mounjaro-gila-monster-anglerfish-8c9c1ff2 (2023).
4. Eng, J., Kleinman, W. A., Singh, L., Singh, G. & Raufman, J. P. *J. Biol. Chem.* **267**, 7402–7405 (1992).
5. Raufman, J. P., Singh, L., Singh, G. & Eng, J. *J. Biol. Chem.* **267**, 21432–21437 (1992).
6. Eng, J. *Diabetes* **45** (suppl. 2) 152A (1996).
7. Young, A. A. et al. *Diabetes* **48**, 1026–1034 (1999).
8. Yap, M. K. K. & Misuan, N. *Basic Clin. Pharmacol. Toxicol.* **124**, 513–527 (2019).
9. Parkes, D. G., Mace, K. F. & Trautmann, M. E. *Expert Opin. Drug Discov.* **8**, 219–244 (2013).
10. Bhavsar, S., Mudaliar, S. & Cherrington, A. *Curr. Diabetes Rev.* **9**, 161–193 (2013).
11. Cooper, G. J. S. et al. *Proc. Natl Acad. Sci. USA* **85**, 7763–7766 (1988).
12. Turton, M. D. et al. *Nature* **379**, 69–72 (1996).
13. Young, A., Gottlieb, A., Fineman, M. & Kolterman, O. *Diabetologia* **42** (suppl. 1), A40 (1999).
14. Blonde, L. et al. *Diabetes Obes. Metab.* **8**, 436–447 (2006).
15. Riddle, M. C. et al. *Diabetes Metab. Res. Rev.* **22**, 483–491 (2006).

## Competing interests

All authors are former employees of Amylin Pharmaceuticals Inc. J.L.T is an employee and shareholder of Eli Lilly and Co. A.A.Y is an employee of i20 Therapeutics. D.G.P. receives consulting fees from Epirium, Prolynx, Neurocrine, Pioneering Medicine and UCSD.