Introduction
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are now well established in the treatment of type 2 diabetes. Initially, GLP-1 RAs were injected either once or twice daily. A once-weekly formulation of exenatide is available with the perceived benefit of the reduced frequency of administration with a once-weekly preparation. Two other once-weekly GLP-1 RAs have recently been approved by the EMEA (albiglutide, dulaglutide) and these should be available shortly for clinical use. Taspoglutide was being developed as a once-weekly GLP-1 RA for patients with type 2 diabetes, but development was halted because of unacceptable side effects.

Pharmacology
The main actions of GLP-1 RAs are to stimulate insulin secretion from the pancreas, suppress glucagon secretion, reduce gastric emptying and increase satiety. The prolonged action of once-weekly exenatide is achieved by encapsulating exenatide in biodegradable polymer microspheres that slowly degrade and release their contents. Albiglutide and dulaglutide achieve prolonged pharmacodynamic profiles through attachment to larger protein molecules – albiglutide through bonding with human albumin and dulaglutide through bonding with an inactivated human IgG4-Fc immunoglobulin molecule.

Taspoglutide was a 30-amino acid derivative of native GLP-1 which achieved a prolonged pharmacodynamic profile through amino acid substitutions at position 8 (aminoisobutyric acid substituted for alanine), which resisted degradation by dipeptidyl-peptidase-4, and at position 35 (aminoisobutyric acid substituted for glycine) which resisted degradation by other plasma proteases such as plasmin and kallikrein. This analogue was fully resistant to enzymatic cleavage, stable in plasma, and had similar binding affinity for the human GLP-1 receptor and activated this receptor with similar potency. It was then commercially produced as a sustained-release once-weekly formulation by the addition of zinc chloride. When injected subcutaneously the sustained-release formulation peaked at 24 hours after injection and plasma levels were sustained for over 14 days.
Taspoglutide

Trials of efficacy
The T-emerge trial programme was a large Phase 3 programme of taspoglutide to determine the efficacy and safety of taspoglutide in patients with type 2 diabetes.

T-emerge 1 was a randomised 24-week, double-blind, placebo-controlled study that recruited 373 patients with type 2 diabetes who had not been on any previous diabetes medications, and randomised them to weekly taspoglutide vs placebo. As expected, there was an HbA1c reduction in the treatment arm vs the placebo arm at 24 weeks. HbA1c improvements with taspoglutide 10mg, taspoglutide 20mg vs placebo were -1.01% (SE 0.07), -1.18% (0.06) and -0.99% (0.07), respectively. As with other GLP-1 RAs there were also weight reductions of -1.45kg (0.32) with taspoglutide 10mg, -2.25kg (0.30) with taspoglutide 20mg, and -1.23kg (0.31) with placebo.

T-emerge 2 was a direct head-to-head trial to compare the efficacy of taspoglutide with twice-daily exenatide. The investigators recruited 1189 overweight type 2 diabetic adults who were taking metformin with or without a thiazolidenedione and were failing treatment based on an HbA1c of 7–10% (53–86mmol/mol). They were randomised to either taspoglutide 10mg weekly, taspoglutide 20mg weekly, or standard dose exenatide 10μg twice-daily. Following 24 weeks of treatment, both doses of taspoglutide achieved statistically superior HbA1c reductions vs exenatide: taspoglutide 10mg -1.24%; taspoglutide 20mg -1.31%; exenatide -0.98%. There was also a comparable weight loss achieved with taspoglutide (taspoglutide 10mg: -1.6kg; taspoglutide 20mg: -2.3kg) compared with exenatide (-2.3kg).

There were several other trials in the T-emerge series investigating taspoglutide. Five further studies compared taspoglutide with placebo as second-line and as third-line therapy, and three head-to-head studies compared taspoglutide with sitagliptin, pioglitazone and insulin, and as additional therapy in patients already on existing diabetes treatments. A large cardiovascular safety study was also started.

Side effects and adverse events
Throughout the T-emerge trial programme, side effects were common and clinically important. The most common side effects that occur with GLP-1 RAs are gastrointestinal (GI) side effects. These were more common in taspoglutide-treated patients than with exenatide (nausea: taspoglutide 10mg 53%, taspoglutide 20mg 59%, and exenatide 35%; vomiting: taspoglutide 10mg 33%, taspoglutide 20mg 37%, and exenatide 16%).

Other side effects reported in the T-emerge 1 trial include abdominal pain and distension, dyspepsia, and diarrhoea.

An unexpected side effect that was identified throughout the T-emerge series was local injection site reactions. There were more injection site reactions than compared to placebo in the T-emerge 1 trial (taspoglutide 10mg 36%, taspoglutide 20mg 34%, placebo 11%). These included: nodule formation (taspoglutide 10mg 12%, taspoglutide 20mg 9%, placebo 1%); induration (taspoglutide 10mg 5%, taspoglutide 20mg 5%, placebo 1%); and pruritus (taspoglutide 10mg 4%, taspoglutide 20mg 5%, placebo 0%).

As a consequence of injection site reactions and GI side effects, there was a higher withdrawal rate from the studies in the taspoglutide group than in the control groups (taspoglutide 34% compared to exenatide 16% dropout rate). In the T-emerge 2 trial, post-baseline anti-taspoglutide antibody levels were measured in the majority of patients. These were positive in 43% of the taspoglutide 10mg group and in 55% of the taspoglutide 20mg group. The proportion of patients with strongly positive anti-taspoglutide antibody tests also increased from 16% at week 12 to 39% at week 24, with no further increase at week 52.

Discussion
Taspoglutide was being developed as a new, longer-acting GLP-1 RA with the potential benefit of reduced frequency of dosing. With regard to efficacy, taspoglutide was more effective than twice-daily exenatide in reducing HbA1c and similar in reducing weight. No trials were undertaken comparing once-weekly taspoglutide to the once-weekly preparation of exenatide, or to other GLP-1 RAs. Studies comparing the different GLP-1 RAs give useful clinical information, and differences are starting to emerge within the class in terms of efficacy in reducing HbA1c, efficacy in reducing weight, and side effects.

Due to the higher incidence of adverse reactions, including common class effects such as GI disturbance and unexpected ones such as local hypersensitivity reactions, taspoglutide did not make it to market. In September 2010, Roche voluntarily stopped further dosing in Phase 3 trials due to the higher than expected discontinuation rates, and to address the serious hypersensitivity reactions observed. Roche continued to work on the root cause analysis and ultimately returned the product to the originator Ipsen.

Roche had identified an association between the noted hypersensitivity reactions and the development of anti-drug antibodies. These anti-taspoglutide antibodies were measured in significant numbers of study patients, and antibody measurement may have a role in predicting the incidence of hypersensitivity reactions in other long-acting GLP-1 RAs. Exenatide has similar rates of anti-body formation and appeared to demonstrate a higher incidence of injection site reactions in antibody positive patients vs the antibody negative patients. It is noted that lixaglutide has significantly lower rates of development of anti-lixaglutide antibodies compared to exenatide or taspoglutide.

Declaration of interests
Prof Fisher has done advisory boards for AstraZeneca, Eli Lilly, GlaxoSmith Klein, Novo Nordisk, Roche, Sandofi.

References
References are available online at www.practicaldiabetes.com.
References


