Introduction
Use of glucagon-like peptide-1 (GLP1) receptor agonists is now well established in the treatment of type 2 diabetes, particularly for use in overweight patients with suboptimal glycaemic control. Current preparations are available as daily, twice-daily or weekly subcutaneous injections and, as with many diabetes drugs, poor patient concordance and adverse side effect profile can limit clinical effectiveness. ITCA 650 is a device which delivers continual drug delivery is improved patient concordance with guaranteed drug delivery and possible reduction in adverse events by removing the initial higher drug concentrations present with current bolus methods.

Pharmacology
Exenatide is a GLP1 receptor agonist which acts to improve insulin secretion, slow gastric emptying and increase satiety, promoting improved glycaemic control and weight loss. ITCA 650 is an injection-free preparation delivering exenatide via a mini osmotic pump placed in the subdermal tissue of the abdominal wall. The pump is sterile, single use and is placed under aseptic conditions and local anaesthetic.

ITCA 650 uses novel technology comprising a 44mm titanium rod with internal drug reservoir. The pump uses osmosis to achieve zero order pharmacokinetics with stable and continuous release of exenatide into the subcutaneous tissue.

Once placed in the subdermal region, extracellular fluid enters the pump at one end through a semi-permeable membrane into an osmotic salt engine. This area then reliably and predictably expands to drive the pump piston at the other end, in turn forcing the contained drug through an exit port in a continuous motion (Figure 1).

Pharmacokinetic studies have suggested stability for over 12 months at body temperatures with rapid reduction in exenatide levels 24 hours following removal of the pump. ITCA 650 is currently being used in trials for six months before replacement or removal via a short sterile procedure.

Trials of safety and efficacy in diabetes
An early trial examined ITCA 650 at varying doses in 44 patients over a 28-day period, demonstrating significant reduction in fasting glucose levels (p<0.05) and reduction in HbA1c (p<0.001) from baseline to

Figure 1. ITCA 650 osmotic pump design

Semi-permeable membrane
Piston
Drug reservoir

Osmotic engine
Drug formulation
end point. Adverse events included gastrointestinal upset and local inflammation but were generally described as mild to moderate. Twelve patients developed anti-exenatide antibodies but this did not appear to affect the pharmacokinetics of the drug.1

A later open-label study examined the effectiveness of ITCA 650 versus twice-daily subcutaneous exenatide in patients with suboptimal diabetes control already on conventional oral treatments.2 The trial was conducted in two parts with stage 1 randomising 155 patients to ITCA 650 20µg/day, ITCA 650 40µg/day or conventional twice-daily exenatide for 12 weeks. All treatment groups demonstrated a significant (p<0.001) reduction in HbA1c from baseline with changes of -0.90% (10.7mmol/mol), -0.95% (10.4mmol/mol), and -0.72% (7.9mmol/mol), respectively. In stage 2, patients within the ITCA 650 arms were re-randomised to stay at the same dose or increase to 60 or 80µg/day. Patients in the twice-daily exenatide arm were re-randomised to receive ITCA 650 40 or 60µg/day. Further significant (p<0.05) reductions in HbA1c were seen in the patients switched to ITCA 650 from injections and in patients receiving a higher ITCA 650 dose than previously.

In terms of side effects, patients on ITCA 650 reported less and more transient problems with nausea versus exenatide twice-daily injections. Discontinuation of treatment was reported in 3.9% of patients on ITCA 650 versus 5.7% of patients on injectable exenatide.2

Two of the phase 3 efficacy and tolerability outcomes have recently been published. The FREEDOM-I trial3 was a double-blind randomised placebo controlled trial conducted over a 39-week period. A total of 460 patients with established type 2 diabetes and HbA1c between 58–86mmol/mol were recruited from 126 sites in the USA and were randomised to receive ITCA 650 40µg/day, ITCA 650 60µg/day or identically placed mini pumps containing placebo. The primary end point evaluated change in HbA1c at 39 weeks and results demonstrated a statistically and likely clinically significant improvement in glycaemic control, with mean reductions in HbA1c 12.2mmol/mol, 13.2mmol/mol and 1.3mmol/mol in the ITCA 650 40µg/day, ITCA 650 60µg/day and placebo groups, respectively (p=0.001 versus placebo).3 Pre-defined secondary end points were also examined. Mean weight losses of 2.3kg and 3.0kg were demonstrated in the ITCA 650 arms versus 1.0kg loss with placebo (p=0.015). At the end point, 37%, 44% and 9% of patients achieved an HbA1c of ≤53mmol/mol in the 40µg/day, 60µg/day and placebo groups, respectively (p<0.001 versus placebo).3

Adverse events were reported in large percentages of patients in each group, with 82.4% and 85.1% of patients in treatment arms reporting at least one adverse event, versus 71.1% in the placebo group. The majority of side effects were related to mild gastrointestinal upset in the form of nausea, vomiting and diarrhoea, with no episodes of pancreatitis reported. Episodes of local inflammation were reported across study arms but only 1.3% of patients overall were treated for a related infection. Despite frequent side effects, discontinuation rates were relatively low, with premature removal of the device occurring in 7.2% of ITCA 650 patients versus 1.3% of placebo treated patients.3

The FREEDOM-I HBL open-label trial4 has subsequently been published evaluating ITCA 650 in 80 patients not eligible for FREEDOM-I due to high initial HbA1c above 86mmol/mol. Clinical effectiveness was also demonstrated in this group with mean reduction in HbA1c of 30.5mmol/mol, 90% of patients achieving a fall in HbA1c of >10.9mmol/mol and 25% of patients reaching a target HbA1c <7.8mmol/mol within the 39-week trial period. Discontinuation rates were low at 6.7%.

There are two further phase 3 trials awaiting formal publication. FREEDOM-2 compared the effectiveness of ITCA 650 versus oral sitagliptin, while FREEDOM-CVO examined the cardiovascular safety of ITCA 650.

Discussion
ITCA 650 is the first device developed to provide continuous stable delivery of GLP1 receptor agonist treatment for type 2 diabetes. Efficacy trials have shown favourable glucose lowering and weight loss outcomes versus placebo. Side effects including gastrointestinal upset appear common but generally mild and data suggest low rates of discontinuation for drug-related effects. More trials are awaited to further examine effectiveness versus current available treatments and cardiovascular safety.

Pending FDA and EMEA approval, ITCA 650 may provide a novel treatment strategy for people with type 2 diabetes, addressing common limitations surrounding drug adherence and tolerability.

Declaration of interests
There are no conflicts of interest declared.

References