First-in-Human Testing of a Wirelessly Controlled Drug Delivery Microchip

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The first clinical trial of an implantable microchip-based drug delivery device is discussed. Human parathyroid hormone fragment [hPTH(1-34)] was delivered from the device in vivo. hPTH(1-34) is the only approved anabolic osteoporosis treatment, but requires daily injections, making patient compliance an obstacle to effective treatment. Furthermore, a net increase in bone mineral density requires intermittent or pulsatile hPTH(1-34) delivery, a challenge for implantable drug delivery products. The microchip-based devices, containing discrete doses of lyophilized hPTH(1-34), were implanted in 8 osteoporotic postmenopausal women for 4 months and wirelessly programmed to release doses from the device once daily for up to 20 days. A computer-based programmer, operating in the Medical Implant Communications Service band, established a bidirectional wireless communication link with the implant to program the dosing schedule and receive implant status confirming proper operation. Each woman subsequently received hPTH(1-34) injections in escalating doses. The pharmacokinetics, safety, tolerability, and bioequivalence of hPTH(1-34) were assessed. Device dosing produced similar pharmacokinetics to multiple injections, and had lower coefficients of variation. Bone marker evaluation indicated that daily release from the device increased bone formation. There were no toxic or adverse events due to the device or drug, and patients stated that the implant did not impact quality of life.

INTRODUCTION

Implantable medical devices are routinely used in many medical specialties, including cardiology, orthopedics, and neurology. Devices such as pacemakers, joint replacements, and pain pumps perform an electronic, mechanical, or fluidic function to help patients return to a healthier anatomical or physiological state. Over the past decade, device manufacturers have incorporated chemicals or drugs into medical implants with the objective to improve efficacy and reduce morbidity. Drug-eluting stents, for example, reduce in-stent restenosis when compared with bare-metal stents (1). The United States Food & Drug Administration (FDA) has defined products that combine devices, drugs, or biological products as “combination products”. Other approved combination products include drug-releasing transdermal patches, absorbable sponges or meshes impregnated with antibiotics, and bone grafts consisting of protein solution with an absorbable structure or scaffold.

One class of combination products featuring on-demand drug-release capabilities was first described by Santini et al., who developed a microchip with many reservoirs containing discrete doses of drug (2–4). However, adapting the microchip technology for human use posed significant challenges. First, hermetic sealing of each reservoir at or near room temperature was critical to prevent degradation of the drug’s composition. A compression welding process was developed to provide a long-term hermetic seal (5). Second, a reliable means to protect and expose the contents of each reservoir on command was required. An impermeable, thin metallic membrane was developed as an integral component of the reservoir. This membrane can be removed by electrothermal ablation (6). The drug is then released in a controlled, pulsatile manner. Third, aseptic filling and lyophilization of clinical doses of a drug in the microchip needed to be developed (7, 8). Implanted drug delivery systems based on the multi-reservoir microchip—with all of these optimized features—are particularly well-suited for delivery of polypeptides based on a predefined or even improvised dosing schedule. Furthermore, despite the microchip’s capability to deliver drugs in vitro, once implanted into the body a fibrous, collagen-based membrane...
can develop around the device (9–11). The presence of this fibrous capsule may impact the resulting pharmacokinetics by slowing systemic absorption because the drug needs to diffuse across the membrane. One of the aims of this study was to determine the clinical relevance of this capsule.

Human parathyroid hormone fragment (1-34) [hPTH(1-34)] is used to treat osteoporosis. Osteoporosis is an imbalance in bone resorption and bone formation processes, where the resulting loss of bone mineral density and disrupted bone microarchitecture lead to an increase in fractures. The World Health Organization estimates 9 million osteoporotic fractures occur annually worldwide, with a significant contribution to disability rates (12). The total cost for treatment of these fractures in the United States in 2015 is projected to be more than $20 billion (13). There are two classes of drugs used to treat osteoporosis: bone resorption inhibitors, such as estrogens, bisphosphonates, and calcitonin, and anabolic agents, such as human parathyroid hormone [hPTH(1-84)] and teriparatide [hPTH(1-34)], the hormone’s 34 amino acid N-terminal fragment. In 2002, the FDA approved Eli Lilly and Company’s teriparatide (U.S. and EU trade names FORTEO and FORSTEO, respectively), which contains hPTH(1-34) as the active pharmaceutical ingredient. This drug is indicated to treat both men and postmenopausal women with osteoporosis who are at high risk for fracture. There were approximately 50,000 teriparatide users in the U.S. in 2010 (14).

Continuous hPTH(1-34) administration promotes osteoclast activity, with resultant bone loss (15, 16). Conversely, intermittent or pulsatile delivery of hPTH(1-34) provides anabolic therapy because it stimulates osteoblast cellular activity (bone formation) more than osteoclast cellular activity, thus increasing bone mass and bone mineral density (17). Subcutaneous injections of 20 to 40 µg doses of hPTH(1-34) administered daily for up to two years have resulted in a decrease in the incidence of fractures and have an acceptable safety profile (18, 19). Teriparatide has therefore become an accepted drug for increasing bone mass and reconstituting bone structure and strength, but has poor patient compliance because of the need for daily subcutaneous injections (20).

This paper describes the first human trial of an implantable drug delivery device based on microchip reservoir technology that is wirelessly programmable over the Medical Implant Communications Service (MICS) band to deliver an anti-osteoporosis drug at precise times (Fig. 1, A–C). The primary objective of this clinical trial was to assess the pharmacokinetics (PK) of hPTH(1-34) released from implantable devices in vivo in patients with osteopenia or osteoporosis, with the PK after development of a fibrous capsule of specific interest. Safety measures included evaluation of the biological response to the implant and monitoring indicators of drug toxicity. Secondary objectives were to assess the bioactivity of the drug, based on changes in serum markers of bone formation and resorption, and to evaluate the reliability and reproducibility of releasing peptide from the device. The result of this effort was the demonstration of a programmable implant that was able to deliver hPTH(1-34) at scheduled intervals, with PK similar to multiple subcutaneous injections and without the pain and burden of daily injections.

RESULTS

Clinical trial design

The clinical trial for the microchip-based drug delivery device focused on assessing the PK profiles of drug released from the implant encapsulated with fibrous tissue in comparison to subcutaneous injections of FORSTEO. hPTH(1-34) releases were therefore initiated eight weeks postimplantation to ensure a fully developed tissue capsule. In addition to assessing the PK parameters, bone formation markers were evaluated to determine improvement to bone formation owing to hPTH(1-34) dosing from the implanted device. Comparator injections of FORSTEO were scheduled after device-mediated dosing was complete. These subcutaneous injections were administered at two doses: 20 µg and 40 µg. The 20 µg doses were administered prior to explanting the device, while the 40 µg doses were administered after explanting these devices as part of an amendment to the original protocol. The detailed protocol and study rationale are further described in the Materials and Methods section. Fig. 1D summarizes the sequence and timing of the protocol.

hPTH(1-34) pharmacokinetics

Pharmacokinetic (PK) profiles were obtained by measuring hPTH(1-34) in venous blood samples drawn periodically during the 6 h following hPTH(1-34) release. For each subject (n = 7), hPTH(1-34) delivery from the implant was characterized by four PK profiles on days 60, 65, 70, and 84 (Fig. 2A); whereas two PK profiles each were determined for 20 and 40 µg injections of FORSTEO on days 91 and 96 and days 131 and 138, respectively (Fig. 2B). (The 40 µg dose was administered as two sequential 20 µg injections from the delivery pen and is hereinafter denoted “2 × 20 µg”.) The interpatient differences in maximum concentration were attributed to the differences in patient weight (table S1). The average concentration profiles from all implant deliveries and all 2 × 20 µg subcutaneous injections are presented in Fig. 2C.

Noncompartmental analysis was conducted to determine the PK parameters characterizing hPTH(1-34) administration. These parameters included Cmax (observed peak concentration), Tmax (time to peak concentration), AUC (area...
under the curve), and \( T_{1/2} \) (terminal half life). The averages of these parameters by study day and by patient are presented in Tables 1 and 2A. The resulting intrapatient PK parameters of the microchip implanted devices were reproducible for PK days 60, 65, 70, and 84 (Table 2; Fig. 2A): coefficient of variance for \( C_{\text{max}} \) ranged from 7 to 22% and the coefficient of variance for AUC ranged from 2 to 20%. The corresponding intrapatient PK parameters for the FORSTEO injections are summarized in Table 2B and Fig. 2B. The coefficients of variance for the \( 2 \times 20 \mu g \) injections for \( C_{\text{max}} \) ranged from 2 to 45% and the coefficient of variance for AUC ranged from 2 to 34%. These data show that the coefficients of variance for \( C_{\text{max}} \) and AUC were lower for the device releases than for the subcutaneous injections. Similarly, the coefficients of variance for \( T_{\text{max}} \) and \( T_{1/2} \) were lower for the implant releases than for the subcutaneous injections.

The average PK parameters for different modes of drug administration, based on this clinical study and published literature \((21)\), are summarized in Table 3. PK parameter comparisons between microchip device-mediated release and subcutaneous injection can also be evaluated as a ratio of each delivery mode (average PK parameter for implant releases divided by average PK parameter for injections).

Ratios of the average implant PK parameters for the 40 \( \mu g \) FORSTEO injections were: \( C_{\text{max}} = 88\% \), AUC = 98\%, \( T_{\text{max}} = 77\% \) (Table 3). These ratios indicate that the resulting average implant \( C_{\text{max}} \) was 12\% lower than that for the injection. The average implant AUC was approximately equal (within 2\%) to that of the injections. The average time to maximum concentration for the implant was 1.3-fold faster than the time for the injections.

Ratios comparing the average values for the implant release to the \( 2 \times 20 \mu g \) injections were also calculated: \( C_{\text{max}} = 101\% \), AUC = 157\%, \( T_{\text{max}} = 196\% \), \( T_{1/2} = 132\% \) (Table 3). The average implant \( C_{\text{max}} \) was approximately equal (within 1\%) to that of the \( 2 \times 20 \mu g \) injections. The average implant AUC was approximately 1.6-fold higher than that of the \( 2 \times 20 \mu g \) injections. The average time to maximum concentration for the implant was approximately twice that of the \( 2 \times 20 \mu g \) injections. The average terminal half life for the implant dosing was approximately one third longer than that of the \( 2 \times 20 \mu g \) injections.

**Bone markers**

Changes in bone formation and bone resorption were evaluated by measuring serum type I collagen pro-peptide (P1NP) and type I collagenolysis fragment (CTX), respectively. Blood samples to assess these two bone markers were obtained from each patient at screening, two weeks following device implant, on the first day of hPTH(1-34) dosing (day 57), and at each of the eight PK profile procedures (days 60, 65, 70, 84, 91, 96, 131, 138). Serum P1NP progressively increased during the period of daily dosing (days 57 to 75) from the implant (Fig. 3A). The mean increase between the first day of dosing and the fourteenth day of dosing was 143\% \((P = 0.01, \text{pairwise } t\text{-test})\). An increase in P1NP is consistent with anabolic increase in bone formation, which is essential to increasing bone mineral density. The significance of increasing P1NP during device dosing confirms that the hPTH(1-34) delivery from the device was clinically effective. Pairwise \( t\)-tests between the average P1NP levels at screening (approximately 2 weeks prior to implantation) and those at study days 60, 65, 70, and 84 all had a \( P \) value less than 0.05. P1NP levels began to fall after completion of the daily dosing from the implant (> day 75). The P1NP levels at day 91 and day 96, which were the 20-µg dosing days, had a \( P \) value less than 0.05 (pairwise \( t\)-test).

The marker for bone resorption, serum CTX, was normal and did not vary during the interval of hPTH(1-34) dosing (Fig. 3A).

**Safety assessment**

Safety assessment was based on evaluating the biological response to the implant and the absence of any indications for drug toxicity. The laboratory assessment of drug toxicity indicated the drug and device combination were safe, and there were no abnormalities reported as part of the adverse events/serious adverse events (AE/SAE) procedures. Uric acid, creatinine, and blood urea nitrogen (BUN) values were measured during the dosing period in order to assess kidney function (table S2). No change in mean uric acid concentration was observed \((P > 0.05, \text{pairwise } t\text{-test})\)

The average concentrations of creatinine and BUN were also unchanged over the course of the study (both \( P > 0.05 \), pairwise \( t\)-test), providing evidence of the safety of the treatment on kidney function. Routine liver panel assessments [aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total protein, and albumin (ALB)] were also performed at dosing visits to ensure normal liver function (table S3). All results were within the normal limits.

Serum total calcium was measured in venous blood samples drawn immediately preceding and 1, 2, 4, and 6 h after each dose delivered from the implant and after each subcutaneous injection of FORSTEO. The baseline value \((t = -5\text{ min})\) during the dosing period represented approximately the 24 h time point with respect to the dose delivered on the previous day. A transient increase of serum calcium that is expected after dosing should return to the patient’s typical range within 24 h. Calcium levels increased slightly after dosing, but remained below the upper limit of normal, which is 2.6 mM \((22)\) (Fig. 3B). The increase in serum calcium levels at the 6 h time point were statistically significant \((P < 0.05, \text{pairwise } t\text{-test})\) as compared to the predose calcium.
levels from both the implant and FORSTEO injections (2 × 20 µg). Calcium levels 18 or more hours after teriparatide administration were all lower than baseline serum calcium measured before any teriparatide was administered (Fig. 3C).

**Tissue capsule histology**

Potential local effects of drug delivery were assessed for abnormal tissue reactions at the time of explantation by macroscopic evaluation of the capsule tissue surrounding the implant (Fig. 4, A and B) and by histological and cellular morphological analysis of this tissue (Fig. 4, C–H). The histology of the excised tissue capsules indicated that 6 of the 7 capsules showed a normal wound healing response, with few inflammatory cells (scores of 0 and 1 on a scale of 0 to 5, with 0 being no visible cells in field of view at 400×). These cells included neutrophils, lymphocytes, and macrophages as identified by histological and cellular morphological analysis (fig. S1). The seventh tissue capsule showed a higher amount of macrophages (scores of 0 to 3), but was still considered a normal wound healing response (23). Microscopic examination showed minimal, if any, evidence of giant cells, edema, congestion, necrosis, hemorrhage, or granulation tissue cells. Histology showed no signs of degeneration, bacterial infection, or malignancy in any of the capsules (fig. S1).

The tissue capsule thickness over the microchip where the drug was released was consistent with the capsule thickness over the entire device. The capsule thickness over the microchip varied across the patients from 0.2 to 0.7 mm (Fig. 4, E and F). The average distance to the neovascularization bed across all patients was 0.1 mm, with a minimum and maximum distance of 0.05 mm and 0.35 mm, respectively. The relative size of the neovascularization bed was scored by assessing the width of the area from the implant/tissue interface to the unaffected areas that had the characteristics of normal tissue and normal vascularity.

**Device functionality**

The devices were inspected after explant to determine if the reservoirs had opened properly by noting the number of apertures opened per reservoir. A total of 132 doses of drug were delivered from the seven devices. The electrothermal activation process was designed to simultaneously remove the 20 membranes that were sealing each of the reservoir’s 20 apertures. Of the 132 reservoirs opened, 116 had all 20 membranes cleared. The number of membranes successfully removed from the remaining 16 reservoirs ranged from 9 to 19. Only 3 of these reservoirs were opened on days when the PK was assessed. The number of apertures opened for these three releases were 19, 16, and 15; however, only the latter case appeared to impact the resulting PK (patient MC-0002, day 70), as indicated by a slightly decreased C_{max} (Fig. 2A).

The instances of partially opened reservoirs were limited to two of the seven devices. These have been correlated to high resistance connections on a particular lot of printed circuit boards and are not design-related.

**DISCUSSION**

**Pharmacokinetic profile of implant versus injection**

The primary objective of this study was to determine the PK profiles of hPTH(1-34) when delivered from multi-reservoir microchip implants after a fibrous capsule was formed around the implant. The PK profiles were assessed for reproducibility (day-to-day, interpatient, and intrapatient) and also compared with subcutaneous injections of FORSTEO. A key factor in assessing the bioequivalence of a new drug formulation is the correspondence of the pharmacokinetics. The FDA and the European Medicines Agency (EMA) require the PK profiles once released from the device to be within 80% to 125% of the approved drug’s PK values (24, 25). The results obtained from this first in-human microchip clinical trial indicated that the release profile of 40-µg doses of hPTH(1-34) from a wirelessly controlled microchip implant device was comparable to the profile of subcutaneous injections of 2 × 20 µg FORSTEO and was bioequivalent to the profile of single injections of 40 µg of FORTEO (Table 3). The release of hPTH(1-34) in plasma further showed the pulsatile profile required for anabolic response.

Drug absorption from the implant appeared to be slower than the 2 × 20 µg injections, but faster than the single 40 µg injections, based on observed T_{max} values. There was no evidence that such differences in absorption rate altered skeletal responses to hPTH(1-34), using P1NP as an indicator of bone formation. In this study, the changes in serum calcium, CTX, and PINP during implant therapy qualitatively and quantitatively mimic those reported previously during daily subcutaneous injections of FORSTEO (26). Because bioequivalence has been demonstrated here, future implant designs should be sized for the same dose size as that of the approved dose for injection. Furthermore, the 2 × 20 µg injections indicated that the T_{max} and T_{1/2} values were approximately equal to those of a single 20 µg injection, rather than those of a 40 µg injection. These differences may be attributed to the method of administration of the 2 × 20 µg injections. Two injections versus one drug bolus may increase the surface area, resulting in absorption into the bloodstream, similar to that of a single 20-µg injection. Conversely, drug releases from the implants were reproducible within each patient and more reproducible than the subcutaneous injections. PK data from the microchip implant had lower coefficients of variance than the injections. A possible explanation for this was that the implant environment was more consistent from dose to dose than subcutaneous injection.
injections, because the needle location would have varied with each administration, whereas the implant resides in a stable environment.

Biological markers of bone turnover are used in the treatment of osteoporosis to monitor efficacy and improve fracture risk assessment. Two markers were monitored over the course of the study: P1NP, a widely accepted bone formation marker and a predictor of long-term increase in bone mass, and the bone resorption marker, CTX. Daily hPTH(1-34) released from the microchip implant device progressively and statistically increased P1NP. When daily dosing was terminated, P1NP levels decreased back to levels observed at the start of the trial. Daily hPTH(1-34) released from the microchip implant device did not increase CTX. The increase in P1NP and the constancy of CTX is an indication that the hPTH(1-34) dosing increased bone formation instead of bone resorption, as expected. Furthermore, serum calcium levels and markers for liver and kidney function remained within the clinically accepted ranges.

Histology of the explanted fibrous tissue capsule formed around the microchip implant device was consistent in terms of tissue thickness and composition with capsules of other biocompatible devices, such as pacemakers. The capsule thickness over the microchip varied across the 7 patients, but there were no observable differences in capsule histology for sections directly over the microchip (where the Pt/Ti membranes were electrothermally removed to release the drug) versus sections contacting other inactive components of the implant. This observation implies that the membrane opening and drug release did not alter the capsule locally, and is further evidence of the tolerability and biocompatibility of the drug and device.

Clinical and biological effects of the implant

This study has demonstrated the clinical viability of the microchip-based implantable drug delivery device. The device and hPTH(1-34) drug combination were biocompatible, had no adverse immune reaction, and were well-tolerated and accepted by the patients in this study. The microchip successfully protected and released each dose precisely as programmed. Furthermore, the resulting PK profiles from the implant—even through the fibrous tissue capsule surrounding the implant—were comparable to the PK profiles of multiple subcutaneous injections. These dose releases were anabolic, as evidence showed an increase in the bone formation marker P1NP.

A benefit of this microchip device is that it can be both implanted and explanted in a physician’s office using a local anesthetic. For this study, all of the patients’ surgical incisions healed normally following both the implant and explant surgical procedures. Discomfort associated with each procedure required only acetaminophen or ibuprofen taken for no more than two days after surgery. The microchip implant device was well-tolerated by the patients based on surveys conducted throughout the study (table S4). The patients responded favorably, indicating they would repeat the procedure to implant such a device again; were satisfied with the implant location; the implant site was comfortable; and they tolerated the size of the implant.

Missed drug doses and the few partial reservoir openings were due to printed circuit board fabrication (high resistance or open connections) and did not impact the overall outcome of the trial. The one device that did not release any drug contained a faulty component in the membrane activation circuitry required to release the drug. Specific tests to assess the membrane activation circuitry will become part of the manufacturing inspection process, and will ensure proper operation of implanted devices. Also, although our device contained only 20 reservoirs (for up to 20 doses), a microchip-based device containing a larger number of reservoirs will be needed to deliver daily doses of proteins, peptides, and other drugs over the course of one or more years. These implants will provide effective, scheduled treatment for patients without the disadvantages associated with injection-based drug administration. The cost of an annual drug delivery implant is expected to be equal to other electronic implants, such as pacemakers and implantable cardioverter defibrillators. Indications that will benefit from this implant will be those that require frequent, scheduled dosing, such as anabolic osteoporosis treatment requiring daily teriparatide injections, and multiple sclerosis treatment requiring injections of interferon β-1a every 48 hours to decrease the frequency of exacerbations and to improve physical abilities. Alternatively, one can envision use of such a device to deliver potent drugs on demand in an acute situation.

Despite the current limitations, a microchip-based drug delivery device has several advantages, including custom pharmacokinetics to achieve desired efficacy, as well as the ability to achieve injection-like pharmacokinetic profiles without repeated needle injections. In addition, the device can be implanted in various body compartments for more localized delivery to maximize delivery to target tissue while minimizing the systemic side effects. Future applications involving closed-loop control may be possible since the implant can be triggered to release a drug based on feedback from sensors in the body to achieve needed therapy or drug delivery. Patients will further benefit from the programmable and automatic drug delivery functionality without fear of overdosing, underdosing, and will be 100% compliant without having to intervene or remember to take their medication.

MATERIALS AND METHODS
Study design
The clinical trial was conducted in Denmark in accordance with the principles of the Declaration of Helsinki from the International Conference on Harmonization (ICH). A clinical research organization (CRO), CCBR-SYNARC, was contracted to facilitate regulatory approval, patient recruiting and management, and overall study execution. The trial was approved by the CRO’s Research Ethics Committee and the Danish Medicines Agency (DKMA). The trial was registered in the European Clinical Trials Database (EudraCT, number 2010-020040-35), and a MedDRA account was established to record adverse events. All patients provided informed consent.

Patients
Patients \( (n = 7) \) participating in the study were osteoporotic postmenopausal women between the ages of 65 and 70, in good health, with a body mass index ranging from 18.5 to 30.2, and normal thyroid function. Patient weights varied from 45.3 to 80.7 kg (table S1). Dual-energy x-ray absorptiometry (DXA) was used to screen for osteoporosis. Subjects who had taken bone active drugs in the preceding six months were excluded from the study, as were those with any illness relating to bone or calcium metabolism (e.g. kidney and urinary tract stones, hepatitis, or compromised immune function). Potential subjects with active implantable medical devices were also excluded. Patients were asked to participate in periodic surveys to assess noticeable pain and their satisfaction level with an implantable drug delivery device. A total of four surveys were conducted with a 100% response rate. An eighth patient was enrolled in the study, but on-board diagnostics for that device reported that the drug was not released. All results from the eighth patient were excluded from the analysis.

Implantable device
The implantable drug delivery system consisted of the implant and a personal computer-based programmer. The implant (Fig. 1A) integrated two drug-containing microchip assemblies on the surface of a titanium housing that contained control and communication electronics. Each microchip assembly (Fig. 1, B, C) contained ten individual 40-µg doses of lyophilized hPTH(1-34) formulation, for a total of 20 doses per device. A drug dose could be released immediately upon receipt of a command from the programmer, or at a pre-specified time in the future. The programmer, operating in the Medical Implant Communication Service (MICS) band, wirelessly transmitted instructions, such as dose scheduling, to the implant. The bidirectional communications link permitted the upload of implant status information, including dose delivery confirmation and battery voltage.

Devices and drug were manufactured with systems consistent with Good Manufacturing Practices (GMP). The assembled and packaged devices were sterilized by ethylene oxide gas at a maximum temperature of 36°C. Device verification tests for active implants (including ISO 14708, IEC 60601-1-2, FCC 47CFR 95, ETSI EN 301 839-1, -2, -3) were conducted prior to trial submission and approval to ensure functionality, safety, and electrical and radio frequency compliance. The device was classified as a tissue-contacting implant for long implant duration (≥30 days). All biocompatibility tests were performed in compliance with ISO 10993 and the FDA Blue Book Memorandum G95. The drug was tested for toxicity, stability, and impurities. Nonclinical tests were conducted per Good Laboratory Practice (GLP) standards by Toxikon Corporation. Electrical, emissions, safety, and transportation testing were conducted by a certified laboratory (Intertek).

Microchip
The key component of the microchip assembly was a 13.0 mm × 5.4 mm × 0.5 mm (l × w × h) silicon chip having 10 individually addressable, 600-nL reservoirs. The microchip’s reservoirs were filled with drug solution and lyophilized (see “Drug formulation”). A mating chip made of silicon was then joined to the silicon chip to hermetically seal the individual reservoirs by a room temperature compression welding process. The tissue-contacting face of the reservoirs was perforated with twenty 0.1-mm diameter apertures, each covered by a composite membrane of titanium and platinum. Circuit traces, connecting the 20 membranes and wired to the internal electronics, provided the path for a current pulse to ablate individual membranes and to expose their reservoir’s contents to tissue fluid surrounding the device. The silicon microchips were fabricated by Micralyne, Inc.

Drug formulation
We formulated an hPTH(1-34) solution to meet the requirements of the multi-reservoir microchip delivery device. The requirements included: (i) concentrated (> 50 mg/ml) solutions to fill the microreservoirs and achieve a clinically relevant dose; (ii) rapid dissolution (seconds) and release of the dosage form to mimic pulsatile pharmacokinetics of a subcutaneous injection; and (iii) stability at 37°C for the duration of the study.

The active pharmaceutical ingredient, hPTH(1-34) acetate lyophilizate (PolyPeptide Laboratories), was prepared by adding 150 mg of hPTH(1-34) to 1670 µl of an aqueous solution of 4.4 M glacial acetic acid, 0.20 M citric acid, and 0.39 M histidine. After filtering through a 0.2-µm filter, a custom robotic system was used to aseptically dispense 500 nl into each microchip reservoir. The microchips were placed into a lyophilizer (Genesis 25 EL, VirTis Inc.) to remove
water and acetic acid, leaving a solid dosage form. The hPTH(1-34) content of each dose, determined by HPLC analysis, was 40 ± 2 µg.

The microchip assemblies were sealed with a cold-compression weld and then tested for hermeticity. Reservoirs that did not pass the hermeticity specification (3 x 10^-10 atm cc/s) were opened in sterile saline to release the drug. The microchip assemblies were then attached to the devices, resulting in the following number of reservoirs per device per patient: patient MC-0018 device had 20 doses; patients MC-0002, MC-0003, MC-0011, MC-0012, and MC-0020 devices had 19 doses each; patient MC-0005 device had 17 doses. This resulted in a total of 132 doses for the study.

Surgical procedures
The drug delivery device was implanted in a surgeon’s office during an outpatient visit. The implant location was the subcutaneous space of the abdomen, just below the waistline. Patients were given injections of lidocaine as a local anesthetic. A 2.5 cm–long incision was made through the dermis followed by blunt dissection to create a pocket of equal size to the device. Each device was placed in the pocket with the microchip facing the muscle fascia, and was anchored with two suture loops to minimize micromotion in the subcutaneous space. The sutures used to anchor the device were nonabsorbable polypropylene, and the incision was approximated with a nylon suture. Patients were instructed to take acetaminophen or ibuprofen to manage post-surgical pain. The condition of the implant site was documented during follow-up visits with a physician at 1 and 2 weeks after surgery.

The device explant procedure was also performed during an outpatient visit at the surgeon’s office. The devices and their encapsulating fibrous tissue were removed under local anesthetic. The explanted tissue and device were placed in 10% buffered formalin for approximately 7 weeks prior to analysis. The device within the capsule was stored in 10% buffered formalin in preparation for histological examination. Follow-up visits took place at approximately 1 and 6 weeks following explant.

Study procedure
Eight weeks were allowed to pass after device implantation before drug release was initiated, to ensure formation of a stable fibrous capsule around the implant. The implant delivered up to 19 daily doses of 40 µg of hPTH(1-34) per patient during days 57 through 75. The final implant dose was released approximately one week later, on day 84. The first of these doses was administered while the patient was under observation at the clinic. Four of the remaining doses were delivered while the patient was at the clinic for PK analysis (days 60, 65, 70, and 84). All other doses were released automatically at a predetermined time under control of the implant. Two doses of teriparatide (FORSTEO, Eli Lilly) were administered on days 91 and 96 to determine the comparative PK of a subcutaneous injection. The microchip was explanted on day 103. Two additional FORSTEO PK analyses were carried out on days 131 and 138 (after explant), during which patients were given two sequential injections (2 × 20 µg) of FORSTEO for a total dose of 40 µg.

Pharmacokinetics determination
hPTH(1-34) PK analyses were carried out in the clinic. The patients’ vital signs were measured and a peripheral intravenous line inserted. A baseline blood sample was drawn within 5 min of dosing. A command was sent wirelessly to the microchip implant to release the drug. For subcutaneous injections, FORSTEO was administered using the manufacturer’s injector pen. The 40-µg FORSTEO doses were accomplished by injecting a second dose at the same site without removing the pen. These are denoted “2 × 20 µg” in the results. Blood samples for hPTH(1-34) determination were then collected at 5, 10, 20, 30, 45, 60, 120, 240, and 360 min following the dose. Serum calcium kinetics were determined using samples drawn at -5, 60, 120, 240, and 360 min.

Blood sampling and assays
Laboratory procedures conducted in Denmark were managed by CCBR-Synarc Research Laboratory. The concentration of hPTH(1-34) in the plasma samples was measured by Intertek ALTA Analytical Laboratory (San Diego, CA) using High Sensitivity ELISA kit (60-3900, Immutopics). Method validation for the kit was conducted according to FDA Good Laboratory Practices. The assay was qualified to a lower limit of quantitation (LLOQ) of 7.5 pg/ml, with a cross-reactivity to endogenous hPTH(1-84) of less than 6.5 wt% [for assay specifications for cross-reactivity, see (27)]. Endogenous PTH levels were measured at screening and found to be within the normal range (15-65 pg/ml) for all seven patients, so any contribution of hPTH(1-84) to the response was expected to be below the LLOQ. Synarc Research Laboratory (Rødovre, DK) conducted the sample analyses for serum calcium, P1NP, and CTX. The serum calcium test was qualified to an LLOQ of 0.25 mM. The LLOQs for P1NP and CTX were 5 ng/mL and 0.010 nM, respectively.

Tissue capsule histology
Tissue samples were excised at the time of device explant. The device within the capsule was stored in 10% buffered formalin for approximately 7 weeks prior to analysis. The devices were shipped to Toxikon Corporation (Bedford, MA), and histological analysis was performed on each capsule. Once the device was removed from the capsule, three cross sections were taken in the following locations: the edge of the microchip, the center of the microchip, and over the titanium
Masson’s trichrome

Biological reaction was assessed by light microscopic histological analysis for the presence of an inflammatory response (PMN cells, lymphocytes, plasma cells, macrophages, giant cells, and necrosis). The healing response was scored by the amount of neovascularization and fibrosis. Neovascularization was identified by the distinct morphological appearance of blood vessels and fibrosis was identified by the distinct morphological appearance and pattern of collagen deposition. The ventral (toward the skin) and dorsal (toward the muscle) sides of the capsule were scored separately. Scores were based on a five point scale (fig. S1).

Statistical analysis

Summary statistics (mean, standard deviation, coefficient of variance), the identification of maximum hPTH(1-34) concentration ($C_{\text{max}}$) and the time to reach $C_{\text{max}}$ ($T_{\text{max}}$) from tabulated data, and the determination of the area under the PK curve (AUC) by application of the linear trapezoidal rule array.

catabolic bone effects of human parathyroid hormone (1-34) are predicted by duration of hormone exposure. Bone. 33, 372–379 (2003).


Acknowledgments: We thank C. S. Teglbjærg and the staff at CCBR-Synarc in Denmark for their assistance in conducting the clinical trial. Funding: This study was sponsored by MicroCHIPS, Inc. Author contributions: All authors have contributed in one or more of the following ways: development of the microchip-based device, protocol development, conducting portions of the study, and data collection (R.F., N.F.S., L.M.); data analysis (R.F., N.F.S., L.M., R.M.N, J.M.A.); preparing the manuscript (R.F., N.F.S., L.M., R.M.N, J.M.A., J.T.S., M.J.C, R.L.). Competing interests: R.F., N.F.S., L.M. are employees of MicroCHIPS, Inc. R.L. is a board member and R.M.N., M.J.C. are paid consultants of MicroCHIPS, Inc. N.F.S., J.T.S., M.J.C., and R.L. hold patents in various aspects of the microchip. The authors declare that their spouses, partners, or children have no financial relationships that may be relevant to the submitted work and none of the authors have any nonfinancial interests that may be relevant to the submitted work. Accession numbers: European Clinical Trials Database (EudraCT, Number 2010-020040-35).

Submitted 29 September 2011
Accepted 15 December 2011
Published 16 February 2012
10.1126/scitranslmed.3003276


Fig. 1. The microchip-based drug delivery device and overview of study design. (A, B) Microchip-based hPTH(1-34) drug delivery device (54 mm × 31 mm × 11 mm, 1 × w × h) (A) containing two microchips with 10 reservoirs each (13.0 mm × 5.4 mm × 0.5 mm, 1 × w × h) (B). (C) schematic cross-section of microchip assembly showing drug releasing from a reservoir. (D) Timeline of study events.

Fig. 2. PK dosing results. (A) Plasma concentration of hPTH(1-34) versus time following release of 40 µg dose from implanted microchip device, for the 7 study patients. (B) Plasma concentration of hPTH(1-34) versus time following injection of 20 µg and 40 µg doses of FORSTEO, for the 7 study patients. The 40 µg doses were administered as two sequential 20 µg injections. (C) Mean plasma concentration of hPTH(1-34) versus time following release of 40 µg dose from the implanted microchip device (n = 7 patients × 4 doses) and injection of 2 × 20 µg doses of FORSTEO (n = 7 patients × 2 doses). Data are means ± SD; *P < 0.05 compared to

Fig. 3. Bone marker and calcium measurements. (A) P1NP and CTX bone marker concentrations in serum before, during, and after implant-mediated drug dosing. The shaded area encloses the two weeks during which individual 40-µg doses of hPTH(1-34) were released from the implant once daily. Data are means ± SD (n = 7).
day -12 (screening visit), pairwise $t$-test. (B) Serum calcium levels during dosing from the microchip implant ($n = 28$) and the $2 \times 20 \mu g$ injections ($n = 14$). *$P < 0.05$ compared to predose calcium levels, pairwise $t$-test. (C) Baseline serum calcium levels over the course of the study ($n = 7$). Grey shaded area in (B, C) represents range of normal serum calcium values. Data are means ± SD.

**Fig. 4.** Tissue histology results from a representative patient, MC-0012. (A, B) Two representative macroscopic images of the tissue capsule surrounding the device after explantation. (C to H) Micrographs of the tissue capsule from each patient consisted of three total images from both the dorsal (antenna, toward skin) and ventral (microchip, toward muscle) sides. Top row: hematoxylin & eosin stain; bottom row Masson’s trichrome stain. (C, D) Cross-section 1 at the microchip and titanium interface (dorsal). (E, F) Cross-section 2 over the microchip (ventral). (G, H) Cross-section 3, over the titanium case (ventral). Scale bar, 0.25 mm.
Table 1. PK parameters throughout the device dosing period. Data are means ± SD (n = 7).

<table>
<thead>
<tr>
<th>Day</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (min)</th>
<th>AUC (ng-min/ml)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (min)</th>
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<tr>
<td>60</td>
<td>410 ± 175</td>
<td>44 ± 13</td>
<td>44 ± 10</td>
<td>66 ± 16</td>
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<tr>
<td>65</td>
<td>426 ± 209</td>
<td>49 ± 10</td>
<td>44 ± 9</td>
<td>64 ± 20</td>
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<tr>
<td>70</td>
<td>378 ± 133</td>
<td>41 ± 11</td>
<td>43 ± 9</td>
<td>75 ± 27</td>
</tr>
<tr>
<td>84</td>
<td>405 ± 154</td>
<td>45 ± 12</td>
<td>46 ± 6</td>
<td>76 ± 16</td>
</tr>
</tbody>
</table>

Table 2. Results of PK parameters by patient. (A) Doses delivered by the implant (n=4). (B) Doses delivered as 2 × 20 µg injections (n=2). Data are means ± SD.

(A) Implant [hPTH(1-34)]

<table>
<thead>
<tr>
<th>Patient</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (min)</th>
<th>AUC (ng-min/ml)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (min)</th>
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<tbody>
<tr>
<td>MC-0002</td>
<td>538 ± 111</td>
<td>51 ± 8</td>
<td>51 ± 2</td>
<td>51 ± 11</td>
</tr>
<tr>
<td>MC-0003</td>
<td>249 ± 49</td>
<td>56 ± 8</td>
<td>36 ± 4</td>
<td>89 ± 28</td>
</tr>
<tr>
<td>MC-0005</td>
<td>598 ± 67</td>
<td>32 ± 3</td>
<td>48 ± 4</td>
<td>48 ± 7</td>
</tr>
<tr>
<td>MC-0011</td>
<td>353 ± 79</td>
<td>41 ± 14</td>
<td>36 ± 7</td>
<td>69 ± 4</td>
</tr>
<tr>
<td>MC-0012</td>
<td>255 ± 19</td>
<td>45 ± 12</td>
<td>41 ± 1</td>
<td>91 ± 8</td>
</tr>
<tr>
<td>MC-0018</td>
<td>575 ± 51</td>
<td>39 ± 10</td>
<td>57 ± 2</td>
<td>68 ± 5</td>
</tr>
<tr>
<td>MC-0020</td>
<td>266 ± 43</td>
<td>49 ± 8</td>
<td>40 ± 3</td>
<td>72 ± 12</td>
</tr>
</tbody>
</table>

(B) Injection (FORSTEO)

<table>
<thead>
<tr>
<th>Patient</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (min)</th>
<th>AUC (ng-min/ml)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (min)</th>
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<tbody>
<tr>
<td>MC-0002</td>
<td>489 ± 127</td>
<td>26 ± 6</td>
<td>26 ± 1</td>
<td>39 ± 13</td>
</tr>
<tr>
<td>MC-0003</td>
<td>335 ± 39</td>
<td>25 ± 7</td>
<td>24 ± 5</td>
<td>44 ± 5</td>
</tr>
<tr>
<td>MC-0005</td>
<td>206 ± 93</td>
<td>28 ± 26</td>
<td>18 ± 1</td>
<td>64 ± 19</td>
</tr>
<tr>
<td>MC-0011</td>
<td>255 ± 23</td>
<td>21 ± 1</td>
<td>27 ± 9</td>
<td>77 ± 7</td>
</tr>
<tr>
<td>MC-0012</td>
<td>476 ± 56</td>
<td>23 ± 4</td>
<td>37 ± 1</td>
<td>61 ± 4</td>
</tr>
<tr>
<td>MC-0018</td>
<td>770 ± 43</td>
<td>11 ± 17</td>
<td>41 ± 3</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>MC-0020</td>
<td>273 ± 5</td>
<td>27 ± 5</td>
<td>22 ± 1</td>
<td>49 ± 6</td>
</tr>
</tbody>
</table>
Table 3. Average PK parameters for hPTH(1-34) from the microchip device compared to $2 \times 20 \mu g$ and single $20 \mu g$ FORSTEO injections. Data are means ± SD. ND, not determined.

<table>
<thead>
<tr>
<th>Drug, method of delivery</th>
<th>Dose (µg)</th>
<th>Number of samples</th>
<th>$C_{\text{max}}$ (pg/ml)</th>
<th>$T_{\text{max}}$ (min)</th>
<th>$\text{AUC}_{0-\text{last}}$ (ng-min/ml)</th>
<th>$T_{1/2}$ (min)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>hPTH(1-34), implant</td>
<td>40</td>
<td>28</td>
<td>405 ± 161</td>
<td>45 ± 11</td>
<td>44 ± 8</td>
<td>70 ± 20</td>
<td>This study</td>
</tr>
<tr>
<td>FORSTEO, injection</td>
<td>$2 \times$ 20</td>
<td>14</td>
<td>400 ± 194</td>
<td>23 ± 10</td>
<td>28 ± 9</td>
<td>53 ± 15</td>
<td>This study</td>
</tr>
<tr>
<td>FORTEO, injection*</td>
<td>40</td>
<td>34</td>
<td>460 (146 – 875)</td>
<td>58 (40 – 91)</td>
<td>46 (17 – 69)</td>
<td>ND</td>
<td>(21)</td>
</tr>
<tr>
<td>FORTEO, injection</td>
<td>20</td>
<td>14</td>
<td>192 ± 55</td>
<td>22 ± 6</td>
<td>14 ± 4</td>
<td>55 ± 16</td>
<td>This study</td>
</tr>
<tr>
<td>FORTEO, injection</td>
<td>20</td>
<td>22</td>
<td>151 ± 57</td>
<td>32 ± 15</td>
<td>10 ± 4</td>
<td>$90 \pm 107$</td>
<td>(21)</td>
</tr>
</tbody>
</table>

* Range shown in parentheses.
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Sci Transl Med published online 16 February 2012