DRUG DELIVERY

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 (1–34) [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 eight 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 affect 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 U.S. Food and 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 multireservoir 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 affect the resulting pharmacokinetics (PK) 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 that 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 European Union 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 about 50,000 teriparatide users in the United States in 2010 (*14*).

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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 2 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 to C). The primary objective of this clinical trial was to assess the 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 on the basis of 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 8 weeks after implantation 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 and 40 μg. The 20-μg doses were administered before explanting the device, whereas 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 Materials and Methods. Figure 1D summarizes the sequence and timing of the protocol.

hPTH(1–34) PK

PK profiles were obtained by measuring hPTH(1–34) in venous blood samples drawn periodically during the 6 hours after 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

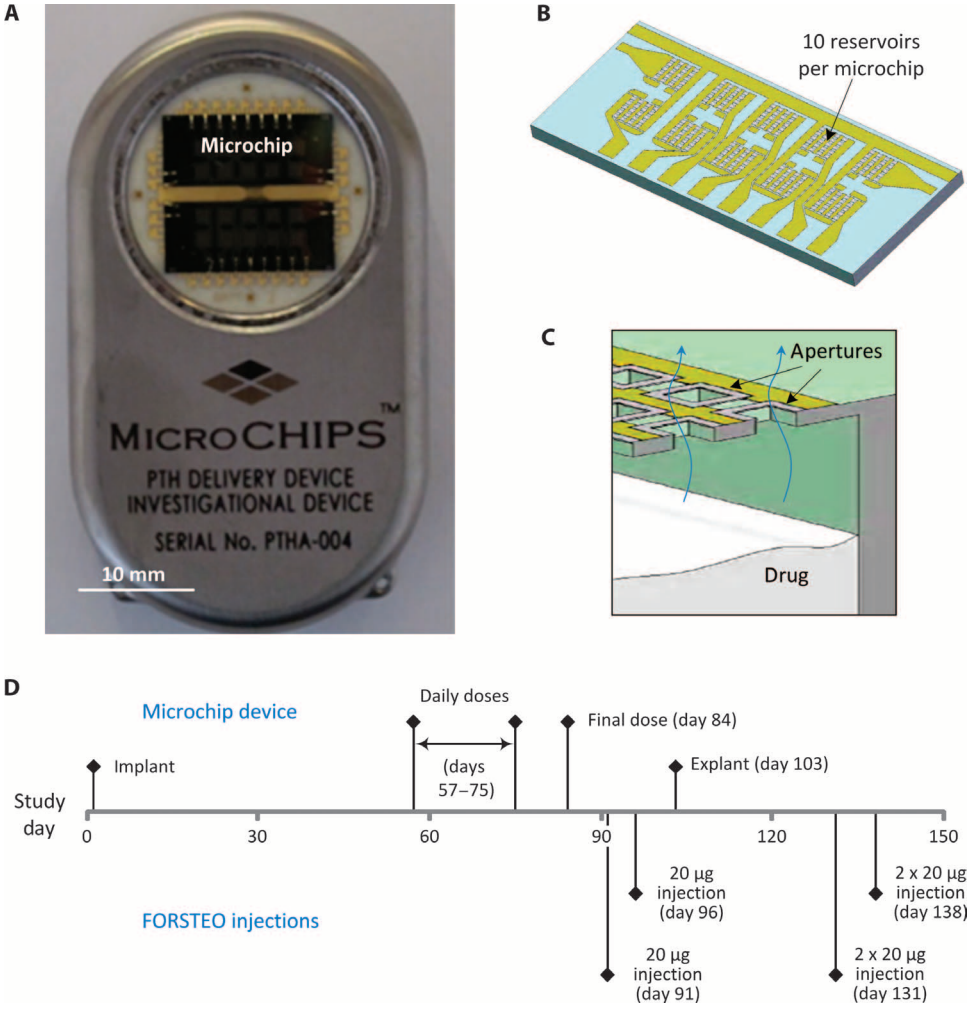

Fig. 1. The microchip-based drug delivery device and overview of study design. (**A** and **B**) Microchip-based hPTH(1–34) drug delivery device (54 mm × 31 mm × 11 mm, $l \times w \times h$) (A) containing two microchips with 10 reservoirs each (13.0 mm × 5.4 mm × 0.5 mm, $l \times w \times h$) (B).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

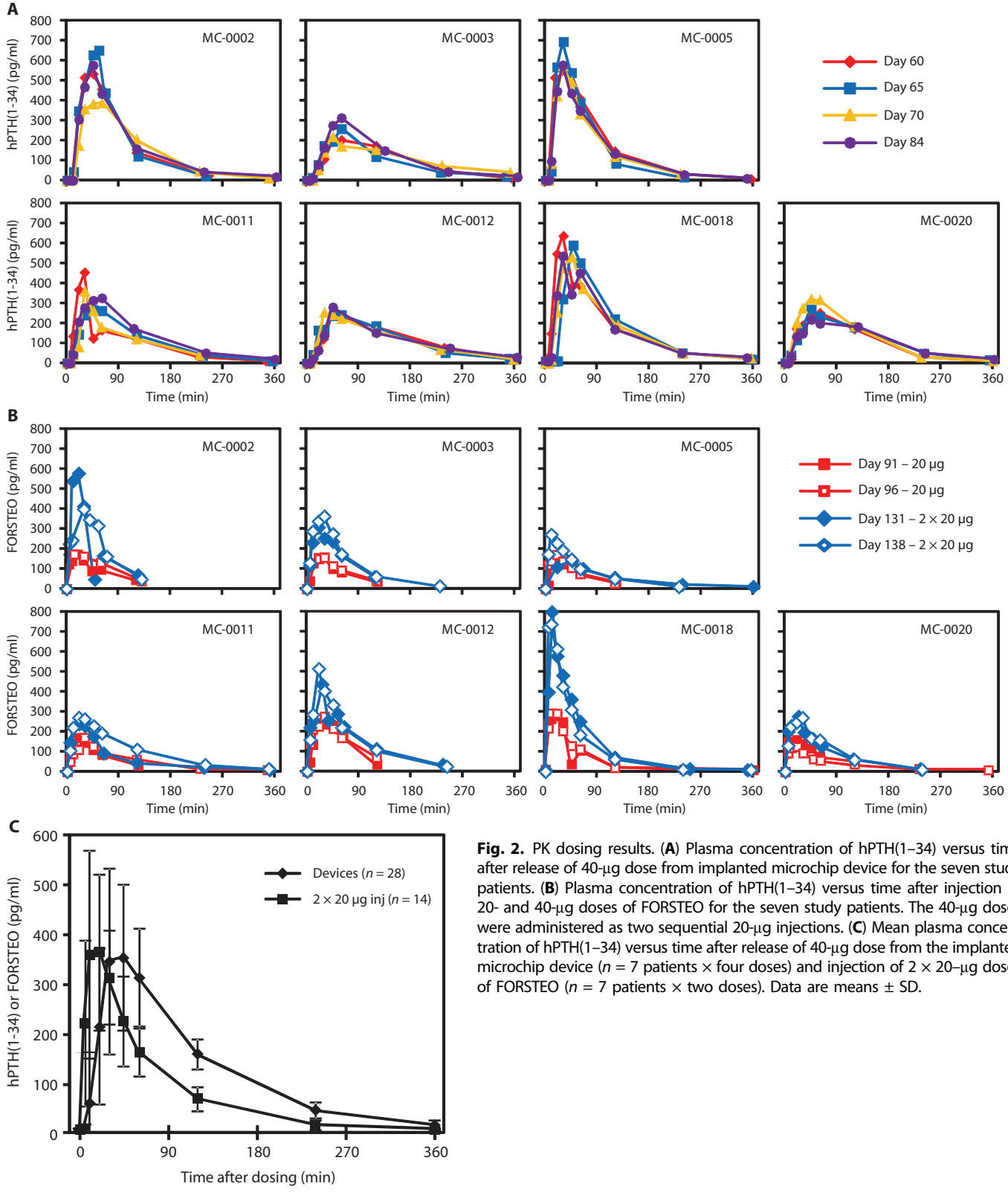

Fig. 2. PK dosing results. (**A**) Plasma concentration of hPTH(1–34) versus time after release of 40-µg dose from implanted microchip device for the seven study patients. (**B**) Plasma concentration of hPTH(1–34) versus time after injection of 20- and 40-µg doses of FORSTEO for the seven study patients.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

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 C_{max} (observed peak concentration), T_{max} (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 2A and Fig. 2A): coefficient of variance for C_{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 × 20–μg injections for C_{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_{max} and AUC were lower for the device releases than for the subcutaneous injections. Similarly, the coefficients of variance for T_{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 averages for the implant releases to the 40-μg FORTEO injections were as follows: C_{max} = 88%, AUC = 98%, T_{max} = 77% (Table 3). These ratios indicate that the resulting average implant C_{max} was 12% lower than that for the injection. The average implant AUC was about 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 × 20–μg injections were also calculated: C_{max} = 101%, AUC = 157%, T_{max} = 196%, $T_{1/2}$ = 132% (Table 3). The average implant C_{max} was about equal (within 1%) to that of the 2 × 20–μg injections. The average implant AUC was about 1.6-fold higher than that of the 2 × 20–μg injections. The average time to maximum concentration for the implant was about twice that of the 2 × 20–μg injections. The average terminal half-life for the implant dosing was about one-third longer than that of the 2 × 20–μg injections.

Bone markers

Changes in bone formation and bone resorption were evaluated by measuring serum type I collagen propeptide (P1NP) and type I collagenolysis fragment (CTX), respectively. Blood samples to assess these two bone markers were obtained from each patient at screening, 2 weeks after 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, and 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 14th day of dosing was 143% (P = 0.01, pairwise t 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

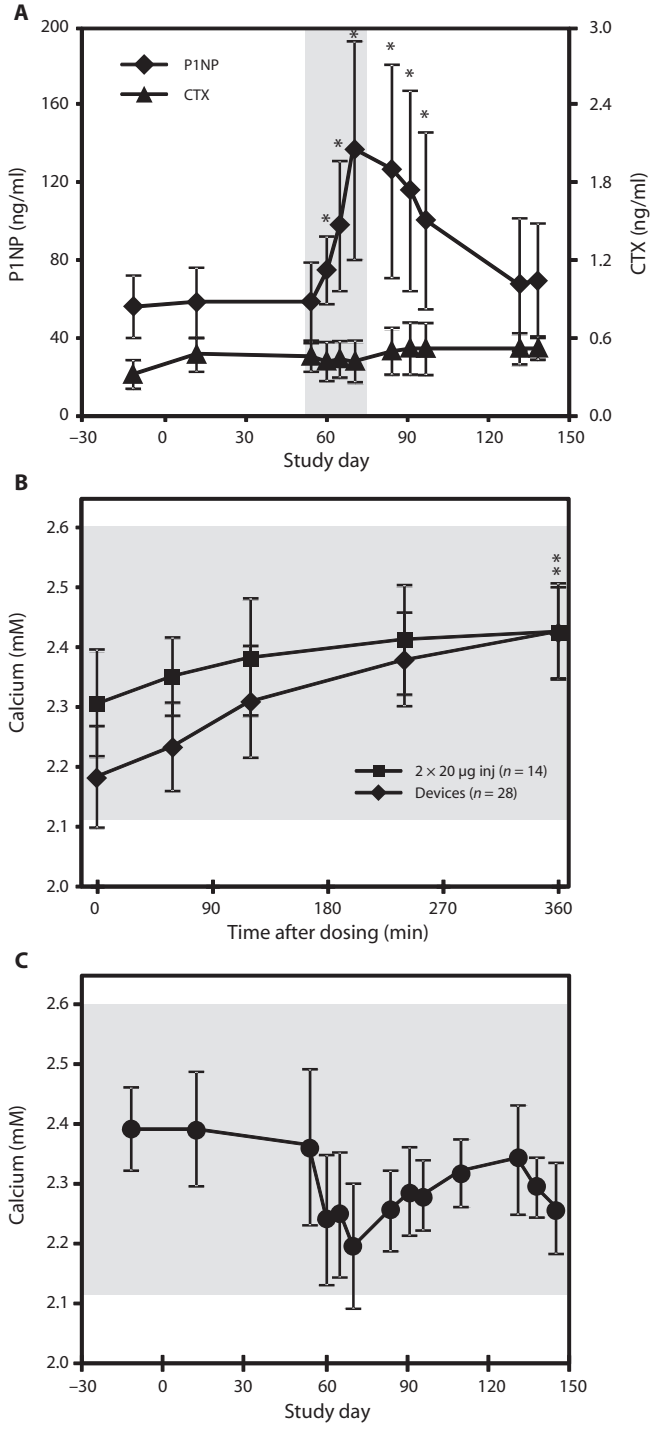

Fig. 3. Bone marker and calcium measurements. (**A**) P1NP and CTX bone marker concentrations in serum before, during, and after implant-mediated drug dosing. The shaded area encloses the 2 weeks during which individual 40-μg doses of hPTH(1–34) were released from the implant once daily. Data are means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

the average P1NP levels at screening (about 2 weeks before implantation) and those at study days 60, 65, 70, and 84 all had a P value of less than 0.05. P1NP levels began to fall after completion of the daily dosing from the implant (day >75). The P1NP levels at days 91 and 96, which were the 20-μg dosing days, had a P value of 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).

Table 1. PK parameters throughout the device dosing period. Data are means ± SD (n = 7).

Day	C_{max} (ng/ml)	T_{max} (min)	AUC (ng·min/ml)	$T_{1/2}$ (min)
60	410 ± 175	44 ± 13	44 ± 10	66 ± 16
65	426 ± 209	49 ± 10	44 ± 9	64 ± 20
70	378 ± 133	41 ± 11	43 ± 9	75 ± 27
84	405 ± 154	45 ± 12	46 ± 6	76 ± 16

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.

Patient	C_{max} (ng/ml)	T_{max} (min)	AUC (ng·min/ml)	$T_{1/2}$ (min)
A. Implant [hPTH(1–34)]				
MC-0002	538 ± 111	51 ± 8	51 ± 2	51 ± 11
MC-0003	249 ± 49	56 ± 8	36 ± 4	89 ± 28
MC-0005	598 ± 67	32 ± 3	48 ± 4	48 ± 7
MC-0011	353 ± 79	41 ± 14	36 ± 7	69 ± 4
MC-0012	255 ± 19	45 ± 12	41 ± 1	91 ± 8
MC-0018	575 ± 51	39 ± 10	57 ± 2	68 ± 5
MC-0020	266 ± 43	49 ± 8	40 ± 3	72 ± 12
B. Injection (FORSTEO)				
MC-0002	489 ± 127	26 ± 6	26 ± 1	39 ± 13
MC-0003	335 ± 39	25 ± 7	24 ± 5	44 ± 5
MC-0005	206 ± 93	28 ± 26	18 ± 1	64 ± 19
MC-0011	255 ± 23	21 ± 1	27 ± 9	77 ± 7
MC-0012	476 ± 56	23 ± 4	37 ± 1	61 ± 4
MC-0018	770 ± 43	11 ± 17	41 ± 3	45 ± 2
MC-0020	273 ± 5	27 ± 5	22 ± 1	49 ± 6

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 that the drug and device combination were safe, and there were no abnormalities reported as part of the adverse event/serious adverse event procedures.

Uric acid, creatinine, and blood urea nitrogen (BUN) values were measured during the dosing period to assess kidney function (table S2). No change in mean uric acid concentration was observed (P > 0.05, pairwise t 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, alanine transaminase, γ-glutamyl transpeptidase, alkaline phosphatase, total protein, and albumin) 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 hours after each dose delivered from the implant and after each subcutaneous injection of FORSTEO. The baseline value (t = −5 min) during the dosing period represented about the 24-hour 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 hours. 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-hour time point was statistically significant (P < 0.05, pairwise t test) compared to the predose calcium levels from both the implant and the 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 to H). The histology of the excised tissue capsules indicated that six of the seven 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

Table 3. Average PK parameters for hPTH(1–34) from the microchip device compared to 2 × 20–μg and single 20-μg FORSTEO injections. Data are means ± SD. ND, not determined.

Drug, method of delivery	Dose (μg)	Number of samples	C_{max} (pg/ml)	T_{max} (min)	AUC_{0-last} (ng·min/ml)	$T_{1/2}$ (min)	Reference
hPTH(1–34), implant	40	28	405 ± 161	45 ± 11	44 ± 8	70 ± 20	This study
FORSTEO, injection	2 × 20	14	400 ± 194	23 ± 10	28 ± 9	53 ± 15	This study
FORTEO, injection*	40	34	460 (146–875)	58 (40–91)	46 (17–69)	ND	(*21*)
FORSTEO, injection	20	14	192 ± 55	22 ± 6	14 ± 4	55 ± 16	This study
FORTEO, injection	20	22	151 ± 57	32 ± 15	10 ± 4	90 ± 107	(*21*)

*Range shown in parentheses.

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 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 whether 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 three 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 affect 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 were not design-related.

DISCUSSION

PK profile of implant versus injection

The primary objective of this study was to determine the PK profiles of hPTH(1–34) when delivered from multireservoir 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 PK. The FDA and the European Medicines Agency 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. Here, the changes in serum calcium, CTX, and P1NP 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 about 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

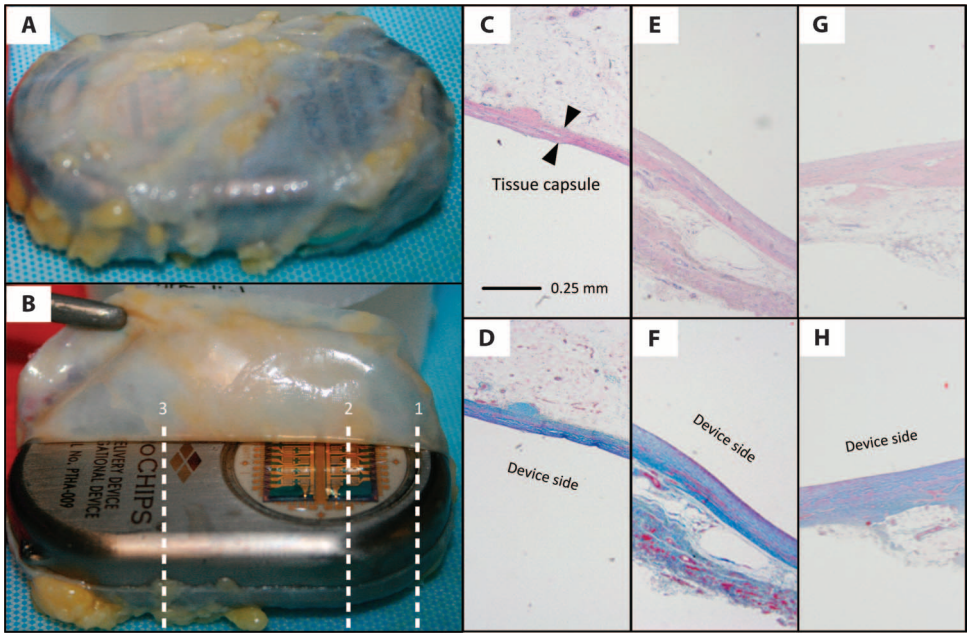

Fig. 4. Tissue histology results from a representative patient, MC-0012. (**A** and **B**) Two representative macroscopic images of the tissue capsule surrounding the device after explantation. (**C** to **H**) Micrographs of the tissue capsule from each patient consisted of three total images from both the dorsal (antenna, toward skin) and the ventral (microchip, toward muscle) sides. Top row, H&E stain; bottom row, Masson's trichrome stain. (C and D) Cross-section 1 at the microchip and titanium interface (dorsal). (E and F) Cross-section 2 over the microchip (ventral). (G and H) Cross-section 3 over the titanium case (ventral).

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 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 are indications 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 seven 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, because 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 after both the implant and the explant surgical procedures. Discomfort associated with each procedure required only acetaminophen or ibuprofen taken for no more than 2 days after surgery. The microchip implant device was well tolerated by the patients on the basis of surveys conducted throughout the study (table S4). The patients responded favorably, indicating that they would repeat the procedure to implant such a device again, they 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 affect 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 1 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 that of 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-β1a 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 PK to achieve desired efficacy, as well as the ability to achieve injection-like PK 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 because 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 and 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. A clinical research organization (CRO), Center for Clinical and Basic Research (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. 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 with normal thyroid function. Patient weights varied from 45.3 to 80.7 kg (table S1). Dual-energy x-ray absorptiometry was used to screen for osteoporosis. Subjects who had taken bone-active drugs in the preceding 6 months were excluded from the study, as were those with any illness relating to bone or calcium metabolism (for example, 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 PC–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 and C) contained 10 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 prespecified 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. 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 before 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 standards by Toxikon Corp. 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 ($l \times w \times h$) 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 multireservoir 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 PK 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 high-performance liquid chromatography 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 (3×10^{-10} atm cm^3/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 postsurgical 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 in preparation for histological examination. Follow-up visits took place at about 1 and 6 weeks after explant.

Study procedure

Figure 1D summarizes the sequence and timing of the study. 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 to 75. The final implant dose was released about 1 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.

PK determination

hPTH(1–34) PK analyses were carried out in the clinic. The patients' vital signs were measured and a peripheral intravenous line was 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 with 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 section. Blood samples for hPTH(1–34) determination were then collected at 5, 10, 20, 30, 45, 60, 120, 240, and 360 min after the dose. Serum calcium kinetics were determined with 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) with High Sensitivity ELISA (enzyme-linked immunosorbent assay) kit (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 weight percent (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 to 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, Denmark) 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 about 7 weeks before analysis. The devices were shipped to Toxikon Corp., 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 case. The sections were embedded in paraffin, and histologic slides were prepared and stained with both hematoxylin and eosin (H&E) and Masson's trichrome.

Biological reaction was assessed by light microscopic histological analysis for the presence of an inflammatory response (polymorphonuclear 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, SD, coefficient of variance), the identification of maximum hPTH(1–34) concentration (C_{max}) and the time to reach C_{max} (T_{max}) from tabulated data, and the determination of the area under the PK curve (AUC) by application of the linear trapezoidal rule were performed with Microsoft Excel (version 12.0). Values of hPTH(1–34) that were below the LLOQ were not included in the PK analysis.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/4/122/122ra21/DC1

Fig. S1. Overview of the histological analysis performed on the tissue capsule for each patient.

Table S1. Patient history collected at screening visit (day −12).

Table S2. Results of routine kidney panel assessment (n = 7 patients).

Table S3. Results of routine liver panel assessment (n = 7 patients).

Table S4. Survey questions and responses conducted throughout the study.

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

Robert Farra, Norman F. Sheppard, Jr., Laura McCabe, Robert M. Neer, James M. Anderson, John T. Santini, Jr., Michael J. Cima and Robert Langer

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Forget About It

"Remind me to take my medicine" are often the famous last words of someone who, incidentally, forgets to take his or her medication. Adherence to a treatment plan, or "compliance," is a major challenge for complicated drug regimens, where patients may be ingesting or injecting several medications per day; sometimes, for years. Now, Farra and colleagues have made great strides in solving this compliance problem by developing an implantable microchip that delivers drugs for you. The best part about this device? It is wirelessly controlled by your doctor, so you can literally forget about your daily doses.

In this first-in-human trial, Farra *et al.* implanted a drug delivery microchip subcutaneously into eight postmenopausal women with osteoporosis. The microchip-based device is only about the size of a watch face, but was able to deliver microgram quantities of an anti-osteoporosis drug once daily for up to 3 weeks. A computer-based programmer communicated wirelessly with the device to confirm proper operation (no malfunction). The authors monitored the pharmacokinetics of the drug during patient visits to the clinic and found that the profiles were similar after implant-mediated release or after multiple injections of the drug. Finally, by measuring several bone markers, the authors indicated that not only was the device releasing intact drug on schedule, but also that the drug was performing its intended function: promoting bone growth to reverse the loss that is characteristic of osteoporosis.

The women in the clinical trial reported that they were satisfied with the size and function of the device, that the implant site was comfortable, and that they would repeat the procedure to implant a "fresh" microchip. Although the implanted device needs additional engineering for higher number of doses, this controlled-release microchip developed by Farra and colleagues represents an important shift in drug delivery, wherein patients with chronic diseases, such as diabetes or osteoporosis, can adhere to their complex treatment plan without compromising quality of life.

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