Long-Term Sustained Delivery Of Liothyronine (L-T3) With Subdermal ProNeura™ Implants

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OBJECTIVE

A subcutaneous implantable product that can continuously provide sustained, non-fluctuating L-T3 hormone replacement therapy for 6-12 months from a single application.

INTRODUCTION

Tetraiodothyronine (T4) and triiodothyronine (T3) are important for development and normal function of many organ systems. T3 is the active hormone, largely produced in the body by peripheral conversion of T4. While treatment with daily oral levothyroxine (L-T4) alone is effective in most hypothyroid patients, about 15% report feeling not adequately treated and are often prescribed a combination of liothyronine (L-T3) with L-T4. Due to its short half-life and narrow therapeutic window, L-T3 alone is infrequently prescribed because wide peak-to-trough variations in serum T3 levels from oral dosing can result in adverse effects. Therapeutic substitution of L-T3 for L-T4 has been evaluated in hypothyroid subjects in a blinded crossover study with a multiple daily dosing scheme, and comparison of L-T3 and L-T4 doses that produce equivalent steady-state thyroid-stimulating hormone (TSH) levels additionally resulted in L-T3-mediated weight loss and positive changes to lipid profiles without appreciable side-effects (1,2). A sustained-release L-T3 formulation could avoid issues of noncompliance to multiple daily dosing regimens.

1. Celi FS, et al. The pharmacodynamic equivalence of levothyroxine and liothyronine: a randomized, double blind, cross-over study in thyroidectomized patients. Clin Endocrinol (Oxf). 2010 May;72(5):709-15.
2. Celi FS, et al. Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine. J Clin Endocrinol Metab. 2011 Nov;96(11):3466-74.

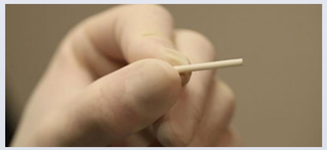

Figure 1. Titan's Proprietary ProNeura Technology

Matchstick-sized non-erodible implants formulated by blending and extruding a drug of choice with Ethylene Vinyl Acetate (EVA).

Implants can be formulated with different drug/EVA ratios and dimensions in order to control the amount of drug released as well as the duration of release.

The drug is uniformly distributed throughout the EVA matrix and released into interstitial fluid in the subcutaneous space through pores in the matrix in a continuous, non-fluctuating manner through dissolution-controlled diffusion that follows pseudo-zero order kinetics.

ADVANTAGES OF PRONEURA-BASED IMPLANTS

- Inserted subcutaneously in the upper arm in a brief, simple, office-based procedure
- Controlled rate of drug delivery, 100% bioavailable, bypasses first-pass metabolism
- Continuous sustained, round-the-clock long-term outpatient treatment
- Stable level of medication in the blood, avoiding peaks and troughs from oral dosing
- Low inter- and intra-subject variability; No reservoir, no risk of drug dumping
- Implants easily removed and replaced at the end of each treatment period

The ProNeura implant platform has been validated in multiple clinical trials of Probuphine®, the first product approved by the US FDA for maintenance treatment of opioid dependence that is designed to release buprenorphine HCl continuously for 6 months maintaining stable serum levels of the medication.

METHODS

ProNeura-based L-T3-containing implants were extruded, washed, sterilized, and tested for release characteristics in thyroidectomized/parathyroidectomized Sprague Dawley rats and in normal beagle dogs. Pharmacokinetics of T3, T4, and TSH levels in serum samples taken pre- and post-implantation were assessed with varying implant formulations and doses.

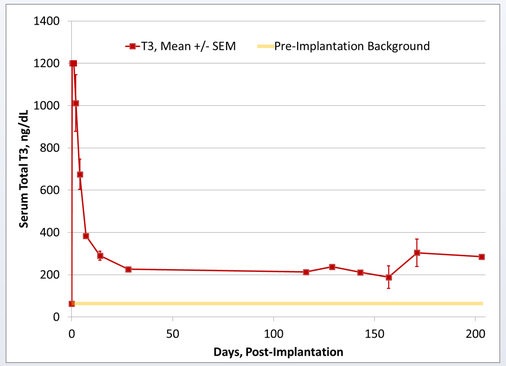

Figure 2. Pharmacokinetics of L-T3 Release in Thyroidectomized Rats

One L-T3 implant (119 mg L-T3/implant, 3 x 40 mm) was placed subcutaneously in the dorsal-scapular region of each male Sprague Dawley thyroidectomized/parathyroidectomized rat (n=2, Charles Rivers Laboratories), and samples were drawn over a 7.25 month period and sera assayed for total T3 with the IMMULITE® 2000 immunoassay system (Siemens).

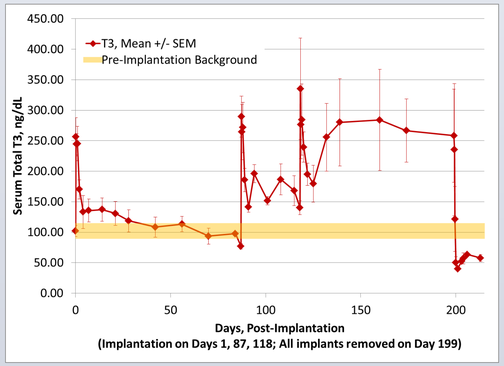

Figure 3. Dose Response Pharmacokinetics of L-T3 Release in Dogs

Three L-T3-containing implants were sequentially placed subcutaneously in the dorsal-scapular region of each male dog (n=3) for a total of 9 implants/animal. On day 0, each dog received 3 implants (119 mg L-T3/implant, 3 x 40 mm). At 3 months (Day 87) and at 4 months (Day 118) 3 additional L-T3 implants (172 mg L-T3/implant, 3 x 60 mm) were sequentially placed to step up the implant dose from 3 to 6 to 9 implants/dog. Samples were drawn over a period of about 7.5 months and sera assayed for total T3, T4 and TSH with the IMMULITE® 2000 immunoassay system. At 7 months post-implantation (Day 199) all 9 implants were removed and sampling continued for 2 weeks post-removal.

RESULTS

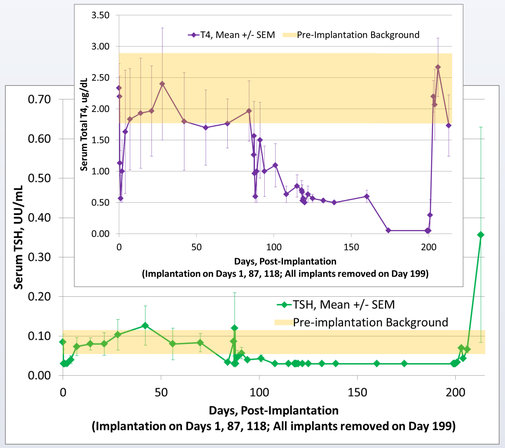

Figure 4. Pharmacokinetics of TSH and Total T4 Levels in Implanted Dogs

Endogenous levels of serum TSH and total T4 (inset) were quantified with the IMMULITE® 2000 immunoassay system in dogs (n=3) sequentially implanted each time with 3 L-T3 implants for a total of 9 implants/animal.

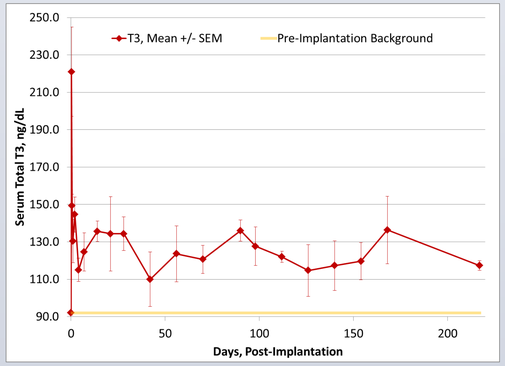

Figure 5. Long-Term Continuous Release of L-T3 in Dogs

One reformulated L-T3 implant (227 mg L-T3/implant, 3 x 26 mm) was placed subcutaneously in the dorsal-scapular region of each male dog (n=3), and samples were drawn over an 8 month period and sera assayed for total T3 with the IMMULITE® 2000 immunoassay system. Implants were removed on Day 217.

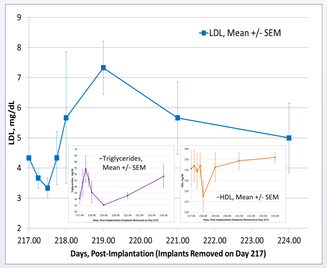

Figure 6. Change in Serum Lipids in Dogs Following Implant Removal

Serum levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides were quantified with the MODULAR® P analytics system (Roche) in dogs (n=3) before and after removal of L-T3 implants (227 mg L-T3/implant, 3 x 26 mm) on Day 217 post-implantation.

DISCUSSION

Results showed these L-T3 implants continuously released sustained levels of T3 in both rats and dogs, in a dose dependent manner for over 6 months. There were no observable safety issues seen during the studies, including no signs of tachycardia in dogs. On study termination, there were also no signs of skin irritation, inflammation or fibrotic capsule formation detected at the site of implantation.

Following implantation, there was a brief initial peak of release of surface drug followed by a sustained period of relatively stable and constant release. This initial peak can be substantially reduced by controlled washing of implants during the manufacturing process.

Fig. 2: In thyroidectomized rats, which have little to no endogenous T3, the steady state serum levels (Css) of total T3 averaged 247 ng/dL. Cmax for the initial peak is unknown as the bioassay upper limit of quantitation is 1,200 ng/dL. Residual content analysis of implants removed on post-implantation Day 203 indicated that they released an average of 27% of the original L-T3 content after 7.25 months *in vivo*.

Fig. 3: In beagle dogs, the sequential implantation of L-T3 implants resulted in a stepwise increase in the Css for total T3 levels from 119 ng/dL (3 implants) to 167 ng/dL (6 implants) to 269 ng/dL (9 implants). Total T3 dropped sharply upon implant removal at Day 199.

Fig. 4: Sequential implantation of L-T3 implants in dogs resulted in a stepwise decrease in serum TSH and total T4 (inset) levels. Total T4 levels rose sharply to pre-implantation baseline levels at 48 hours after implant removal (inset). Serum TSH levels hovered around pre-implantation baseline levels at Day 4 post-removal before rising sharply at Week 2.

Fig. 5: In beagle dogs, which closely match implant-derived serum levels seen in humans, the initial peak release from 3 implants (Cmax = 221 ng/dL,Tmax = 6 hours) was about 1.7-times that of the Css (128 ng/dL), which was sustained from 12 hours post-implantation through Month 8. Residual content analysis of implants removed on post-implantation Day 217 indicated that an average of 21% of the original L-T3 content was released. Assuming similar release characteristics in humans, 1 implant (227 mg L-T3/implant, 3 x 26 mm) will release the equivalent of ~25 mcg oral L-T3/day for >3 years following a single treatment.

Fig. 6: Serum samples taken before and after implant removal from dogs on Day 217 were also assayed for LDL, HDL and triglycerides levels. LDL levels went up from 4 mg/dL to 7 mg/dL, peaking at 48 hours post-implant removal. Triglycerides levels also rose from 31 mg/dL to 54 mg/dL, peaking at 12 hours post-implant removal (inset), and HDL levels dropped from 131 mg/dL to 118 mg/dL, with a trough at 24 hours post-removal (inset).

CONCLUSION

This successful demonstration of a long-term, sustained-release implant formulation for L-T3 provides initial data that support further studies to evaluate the potential therapeutic substitution of, or combination with L-T4 for the treatment of hypothyroidism.