2 SYNOPSIS

Name of Sponsor/Company: Bracco S.p.A., Via E. Folli 50, I-20134 Milan, Italy

Name of Active Ingredient: T3 Sulfate (T3S)– Sodium Salt

Name of Finished Product: Not applicable

Title of the study: Pharmacokinetics of orally administered single doses (40-60-80 mcg) of T3 Sulfate (TS3)-sodium salt. A single-blind, randomized, placebo- controlled clinical study in healthy subjects

Investigators: one principal investigator in Italy

Study centres: one investigational study site in Italy

Publication (reference): None

Study period: First subject enrolled: May 26, 2011; last subject completed: July 06, 2011

Phase of development: II

Objectives: The primary objective of this study was to evaluate the gastrointestinal absorption of T3S after a single oral dose (40/60/80 μg) in healthy volunteers and relevant absorption pattern.

The secondary objectives of the study were: to define the serum profile of TT3 and FT3 after oral administration of T3S; to confirm the safety after T3S oral administration

Methodology:
This was a single-blind, randomized, placebo-controlled, single-center study. The study was conducted at the Clinical Pharmacology Centre for Drug Experimentation of University Hospital of Pisa, Department of Internal Medicine, via Roma, 67 – 56126 Pisa, Italy.
Healthy volunteers were randomly administered a single dose of placebo or 40 or 60, or 80 μg of T3S. The four dose groups consisted of six patients each. Inside each group, three male subjects and three female subjects were to be enrolled; the treatment was randomized by sex also. The gastrointestinal absorption, fate and transformation of T3S was assessed by measuring serum levels of T3S, FT3 and TT3. Serum levels of FT_4 and TSH were measured also. Blood sampling was performed before the administration of T3S tablets (time -0,5; baseline) and 1, 2, 4, 8, 12, 24, 48, 72, 96 h after.

A phone safety check 7 days after IMP dosing and a follow-up safety visit 15 days after the IMP dosing were performed

Number of subjects (total and in each arm):

	Evaluable for safety	**Evaluable for absorption**	**Completers**
Total	24	24	24
00 μg (placebo)	6	6	6
40 μg	6	6	6
60 μg	6	6	6
80 μg	6	6	6

Diagnosis and main criteria for inclusion:

Subjects were healthy subjects. They were enrolled if they met all the following criteria: provided written informed consent and willing to comply with protocol requirements; age between 18 and 40 years; subject of either gender; BMI ranging between 20 and 25 kg/mq.

Test product, dose and mode of administration, batch no:

The Investigational product T3S (40-60-80 μg) and the placebo were administered as a single dose (one tablet) via oral route. The administration was performed after at least 12 hours fasting, and the tablet was taken with half a glass of natural water. Food intake was restrained for 2 hours post-dose.

Batches numbers:

strenght	*batch*
placebo	TFR11127
40 μg	TFR11128
60 μg	TFR11129
80 μg	TFR11130

Duration of treatment: single doses

Reference therapy, dose and mode of administration, batch no: Not applicable.

Criteria for evaluation:

Pharmacokinetics variables:

The following thyroid hormones were dosed at the indicated time points:

T3S, TT_3 and FT_3 serum levels were dosed before the administration of T3S tablets (time -0,5; baseline) and 1, 2, 4, 8, 12, 24, 48, 72, 96 h after. Additionally, free T_4 (FT_4) and TSH were dosed at baseline and at time 96 h.

Safety variables:

The safety variables were: ECG, incidence of adverse events, physical examination and vital signs (heart rate and blood pressure).

Statistical methods:

The absorption analysis population consisted of all subjects dosed and who had blood samples collected at each of the post-dose time points. The safety analysis population consisted of all subjects who were dosed. A subset analysis by dose was performed. Summary tables were provided for the number of subjects who had been screened, dosed and completed according to the protocol guidelines, as well as for the actual dose received. Summary tables were also provided for demographic and baseline characteristics, including age, sex, race, height, and weight and for baseline characteristics, such as medical history, concomitant medication and vital signs. Anova was performed on demographic data and vital signs to test baseline homogeneity among dose groups. The baseline values were defined as the pre-dose values. Descriptive statistics of vital signs by time, stratified by dose of investigational product were carried out and repeated measure anova was conducted. Changes (pre-dose to post-dose) in ECG results were presented by frequency tables. Adverse events absolute and relative count were presented as well as number of SAEs and number of subjects with AE. Phisical examination and concomitant medications where presented in data listings. The efficacy was assessed by T3S blood sampling performed at the times foreseen by the study protocol. Other efficacy variables were serum levels of TT_3, FT_3, FT_4 and TSH. Descriptive table and graphs were supplied for native values, baseline-corrected values and % changes from baseline values. For T3S summary tables and graphs were provided for 70 kg weight normalized baseline corrected values also. A non compartimental analysis based on baseline-corrected values was performed and C_{max}, T_{max}, AUC_{0-96} and $t_{1/2beta}$ were estimated. AUCs were calculated using trapezoidal method. Linear regression between dose/kg and C_{max}, between dose/kg and AUC, between ln/dose and lnAUC where performed to check the dose proportionality, both in total treated population and in the population stratified by gender. A secondary PK analysis was performed on time interval 0-12.

Study population:

The study population included 24 subjects in total: 6 patients (2 male, 4 female) received the 40 µg dose, 6 (3 male, 3 female) received the 60 µg dose, 6 (3 male, 3 female) received the 80 µg dose, and 6 (4 male, 2 female) received the zero µg dose (placebo). All the 24 enrolled subjects regularly completed the entire study procedures.

Extent of exposure and compliance:

The investigational study drug was administered as single dose. The compliance to study medication was ensured by on-site administration under the Investigator's supervision.

Efficacy results:

Serum levels by groups

Placebo group

No significant changes of T3S, FT_3, FT_4 and TSH serum levels were observed; the TT_3 levels showed a waving trend, with three peaks at 8, 48 and 72h.

T3S 40 µg group

No significant variations of FT_3, FT_4 and TSH serum levels were observed. The T3S serum levels increased from baseline to time 4 (mean change: 5,58 ng/dL), decreased until time 12 (mean change from baseline: -1,6) and slowly increased until time 96 (mean change from baseline: 2,6 ng/dL). The TT3 serum levels increased from baseline to time 8 (mean change: 26,8 pg/mL), decreased until time 24 (mean change from baseline: 14,6 ng/dL) and slowly increase until time 96 (mean change from baseline: 51,59).

T3S 60 µg group

No significant variations of FT3, FT4 and TSH serum levels were observed. The T3S serum levels increased from baseline to time 4 (mean change: 12,70 ng/dL) then decreased at baseline value, remaining around zero line until time 96. The TT3 levels showed a waving trend like that observed in the placebo group, with two peaks at 24 and 72 h.

T3S 80 µg group

No significant variations of FT3, FT4 and TSH serum levels were observed. The T3S serum levels increased from baseline to time 1 (mean change: 11,03 ng/dL) and thereafter decreased until baseline values from time 8. The TT3 serum levels increased from baseline to time 8 (mean change from baseline: 37,7 ng/dL) and remained almost stable until time 72, decreasing to the 23,6 value at time 96.

Serum levels between groups

The serum levels of T3S remained almost unchanged in the placebo group. An absorption curve was observed in the T3S-treated subjects starting from 1h, with the time-to-peak around 4h in the 40 and 60 µg groups and 1h in the 80 µg group. In the T3S-treated subjects, the lower levels were observed in the 40 µg-treated subjects, being the 60 and 80 µg levels similar. The serum levels of T3S returned at the baseline values at T12 in all T3S groups; thereafter, remained around the baseline values until 96 h. In all group an increase of TT_3 levels was observed starting from baseline; serum levels remained above the baseline values until T96. No significant changes of the FT_3, FT_4 and TSH values were observed in all groups.

PK parameters

A linear correlation among the T3S dose and the Cmax was found, but not among the T3S dose and the AUC0-96h. Moreover, the analysis of T3S serum levels showed that the absorption and elimination phases were completed within 12 hours after dosing, seeming the following variations of the T3S serum levels biological fluctuations of the endogenous substance. Therefore the PK parameters were calculated in the time frame 0-12h also. The T3S AUC 0-12 was higher in the 60 than in 40 μg group -both higher than in placebo group; in the 80 μg group was not significantly different from 60 μg group. A linear dose-response relationship was found. A linear correlation with the dose was found also for T3S Cmax. The time-to-peak (Tmax) was 2h (median; min 1-max 4) in the placebo group ; 3 (1-8) hours in the 40 μg group, 4 (1-4) in the 60 μg group and 1,5 (1-2) in the 80 μg group

Safety results:

Adverse events:
Height subjects (4 male and 4 female) complained of a total 12 not serious AE: headache (n=6); diarrhea (n=1), nausea (n=1), vomiting (n=1); dysmenorrea (n=1), exfoliative dermatitis (n=1), weariness (n=1). Four subjects suffering from headache required a single dose of oral antalgics drugs. Two subjects were dosed with placebo, 3 with T3S 60 μg and 3 with T3S 80 μg. The causality assessment was judged as unknown in all subjects.
Vital signs:
The results of vital signs (blood pressure and heart rate) did not show changes from baseline with all treatment doses.
ECG:
The results of ECG did not show changes from baseline with all treatment doses.

Conclusions:

The analysis of the serum concentrations show that in healthy subjects orally administered single doses of T3S (40-60-80 μg) are absorbed in a proportional fashion from the gastrointestinal tract. This datum confirms the findings observed in hypothyroid patients. The FT3, FT4 and TSH serum levels were not affected by T3S administration. The TT3 serum levels showed an increase of baseline values but an erratic trend .

The PK analysis confirmed that the orally admnistered T3S

is adsorbed in proportional fashion to the dose;

the absorption phase is completed within 4h and

the elimination phase is completed within 12 h after dosing.

The safety results showed that treatments with T3S tablets at the tested single doses are safe and well tolerated in terms of adverse event profile and effects on vital signs (blood pressure and heart rate).