CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-924

MEDICAL REVIEW(S)

The action letter will contain a reference to the recent recommendations made at the joint advisory committee meeting such that the company will be informed that should the specifications be narrowed, the shelf-life for Tirosint® capsules will likely be shortened significantly such that re-formulation may be necessary.

Office of Compliance has completed its inspection of the manufacturing facility and has reported a satisfactory inspection report.

Conclusions

Pending changes to the label, carton and package presentations, Tirosint® 25, 50, 75, 100, 125 and 150 mcg capsules should be approved under NDA 21-924.

Tirosint® 12.5 mcg capsule should not be approved. Recommendations should be conveyed to the applicant that a different low dosage strength (e.g., 13 mcg) that would unlikely be confused with a higher dosage strength may address the potential for medication errors raised with the 12.5 mcg dosage strength.

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/s/

Mary Parks
10/6/2006 06:44:11 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMO

NDA#:	21-924
Sponsor:	Institut Biochimique SA (IBSA)
Drug:	Tirosint 12.5, 25, 50, 75, 100, 125 & 150 mcg
Indication:	Hypothyroidism Pituitary TSH suppression
Date of Submission:	December 5, 2005

I. Introduction and Background

IBSA has submitted this 505(b)(2) new drug application for Tirosint (levothyroxine sodium soft capsule at doses of 0.0125mg, 0.025mg, 0.050mg, 0.075mg, 0.10mg, 0.125mg and 0.150mg) seeking approval for treatment of hypothyroidism and pituitary TSH suppression. The basis for approval is study AA05227: Comparative, randomized, single-dose, 2-way, crossover, bioavailability study of levothyroxine sodium soft capsules and synthroid levothyroxine sodium tablets following oral administration of a 600 mcg total dose in healthy adults volunteers under fasting conditions; and study AA05228: Comparative, randomized, single-dose, 3-way, crossover, dosage form proportionality study of levothyroxine sodium soft capsules following oral administration of a 600 mcg total dose in healthy adults volunteers under fasting conditions.

Current levothyroxine sodium products available include Synthroid (NDA 21-402), Levoxyl (NDA 21-301), Levo-T (NDA 21-342), Novothyrox (NDA 21-292), Unithroid (NDA 21-210), Levolet (NDA 21-137) and Levothroid (NDA 21-116) and generics. All levothyroxine sodium products are available in tablet form at doses of 0.025mg, 0.05mg, 0.075mg, 0.088mg, 0.1mg, 0.112mg, 0.125mg, 0.137mg, 0.15mg, 0.175mg, 0.2mg and 0.3mg, except Unithroid which does not have a 0.137mg dose. IBSA is proposing to market Tirosint soft gel capsule in doses of 0.0125mg, 0.025mg, 0.050mg, 0.075mg, 0.10mg, 0.125mg and 0.150mg. Compared to the majority of currently available levothyroxine agents, this levothyroxine soft capsule is missing dosage strengths for 0.088mg, 0.112mg, 0.137mg, 0.175mg, 0.2mg and 0.3mg. However, Tirosint will have a new dose strength of 0.0125mg which will allow for the use of multiple capsules to achieve appropriate levothyroxine doses.

II. Clinical Efficacy

No clinical efficacy studies have been submitted with this 505 (b)(2) NDA.

III. Clinical Safety

Clinical pharmacology studies AA05227 and AA05228 were reviewed for safety. Please refer to Appendix A (study AA05227) and Appendix B (study AA05228) for the complete study reviews.

Exposure: In study AA05227, subjects received 600mcg levothyroxine in each of the two study periods (four 150mcg levothyroxine soft capsules and four 150mcg Synthroid tablets capsules) for a total of 1200mcg levothyroxine. Twenty-five subjects received both doses of levothyroxine study drug, for a total of 1200 mcg levothyroxine. Three subjects received study drug at Period 1 only, for a total of 600mcg levothyroxine.

In study AA05228, subjects received 600mcg levothyroxine in each of the three study periods (twelve 50mcg levothyroxine soft capsules, six 100mcg levothyroxine soft capsules, and four 150mcg levothyroxine soft capsules). Overall, 25 subjects received all three doses for a total of 1800mcg levothyroxine, four subjects completed Periods 1 and 2, for a total of 1200mcg levothyroxine and one subject completed only Period 1, receiving a total of 600 mcg levothyroxine.

Deaths: There were no deaths reported in studies AA05227 and AA05228.

Serious Adverse Events: There were no serious adverse events reported in these two studies.

Adverse Events Leading to Withdrawal or Dose Alteration: There were no adverse events related to levothyroxine therapy leading to withdrawal or dose alteration in these two studies.

Adverse Events: In study AA05227, 13 of 28 subjects (46%) reported at least one adverse event during the study. There were twice as many events reported with the levothyroxine soft capsules than with the levothyroxine tablets. However, given the small number of subjects in this trial, it is difficult to reach any conclusions regarding a difference in safety signals between these two agents. The most common adverse events were headache (5 subjects) and dizziness (3 subjects). Symptoms that could be attributed to high dose levothyroxine therapy, including chest pain, feeling jittery and dizziness, occurred in three subject following Synthroid tablets and four subjects following levothyroxine soft capsules.

In study AA05228, 12 of 30 subjects (40%) reported at least one adverse event during the study. Events were reported during all periods of the study. The most common adverse events were headache (4 subjects) and body ache (3 subjects). Symptoms that could be attributed to high dose levothyroxine therapy, including muscle aches, fatigue, loose stools, palpitations, heart pounding and dizziness, occurred in eight subjects.

Laboratory: In study AA05227 and study AA05228, TSH was measured at Hour 0 and Hour 48 for each treatment period. TSH decreased after administration of 600 mcg levothyroxine in both studies. In study AA05227, there was no significant difference in the TSH values or change in TSH seen with the soft capsule compared to the Synthroid tablet. Similar results were obtained for each study period. In study AA05228, there was no significant difference in the TSH values or change in TSH seen with the various strengths of levothyroxine soft capsules. Similar results were obtained for each study period.

Vital Signs: In study AA05227 and study AA05228, blood pressure and pulse were monitored at baseline and Hours 2, 4, 8 and 24 after study drug administration. No significant changes in systolic or diastolic blood pressure were noted in either study. In study AA05227, heart rate increased after administration of 600mcg levothyroxine, as would be expected. The excursion in heart rate peaked at Hours 8 and 24. There was no significant difference in the change in heart rate between the levothyroxine soft capsules or the Synthroid tablet. In study AA05228, there was no significant difference in the change in heart rate between the levothyroxine soft capsule dosage groups

IV. Pharmacology/Toxicology

There are no new Pharmacology / Toxicology data submitted in this 505 (b)(2)NDA.

V. Clinical Pharmacology

Clinical Pharmacology data submitted in this NDA have been reviewed by Dr. Chung and include the two pivotal studies AA05227 and AA05228. The relative bioavailability of levothyroxine soft capsules compared to Synthroid tablets was evaluated in a two-way crossover study. The pharmacokinetics of the two levothyroxine products were comparable, with an AUC_{0-t} ratio (test/reference) of 103.0% (90% CI: 92.8 – 114.4) and Cmax ratio of 106.8% (90% CI: 100.7 – 113.2). Therefore, it was concluded that levothyroxine soft capsules (Tirosint) are bioequivalent to Synthroid tablets. Dosage form equivalence was evaluated in a three-way cross-over study using 50mcg, 100mcg and 150mcg of levothyroxine sodium soft capsules. It was concluded that the dosage forms were equivalent.

VI. CMC

Chemistry data submitted in this NDA were reviewed by Dr. Sheldon Markofsky. A discipline review letter was sent to the sponsor on February 10, 2006. The company submitted satisfactory responses to the deficiencies noted and these responses have been reviewed. Dr. Markofsky is recommending approval of this NDA, pending an acceptable cGMP status for the relevant manufacturing and testing facilities.

One concern raised by Dr. Markofsky is the lack of ability to distinguish the various dosage strengths of the levothyroxine sodium soft capsules. The drug product is a liquid form inside the soft gel capsule. In contrast to other levothyroxine products which are tablets, there is no distinguishing color for each levothyroxine dose strength with the soft capsule. This raises the concern of accidental overdose for patients taking more than one capsule strength daily. The company now proposes to package Tirosint in boxes of [redacted]

[redacted]. The blister packs, not the individual capsules, will be color coded by strength. While the risk of accidental overdose is not completely removed, this approach is adequate to prevent prolonged overdose exposure for the individual patient who requires two separate daily dose strengths of Tirosint.

VII. Other Regulatory Requirements

VIIa. Financial Disclosure

Financial disclosure information, provided for both study AA05227 and study AA05228, was reviewed. These studies were conducted by [redacted] The same team of one investigator and 3 sub-investigators conducted both studies. No investigator or sub-investigator reported any financial interests in IBSA.

VIIb. Pediatrics

The sponsor requests a pediatric waiver similar to the one granted Synthroid on 7/24/2002. The company believes that the same exemption from the requirement to perform clinical trial(s) in the pediatric population is warranted. This request appears reasonable. It should be noted that the levothyroxine soft capsules cannot be crushed to facilitate administration to young patients and may pose a choking hazard to pediatric patients who have difficulty swallowing. The sponsor has proposed the following statement be added to the Contraindications section of the Tirosint label: *TIROSINT is also contraindicated for anyone who may be unable to swallow a soft capsule (e.g., infants, small children)*. This reviewer believes it would also be prudent to have that statement repeated in the Pediatric subsection of the Precautions section of the Tirosint label.

VIIc. Clinical Audits/Inspections

No DSI audit was conducted for this NDA. The [redacted] clinical and analytical study sites used to conduct both protocols for this application were previously inspected in 2003-2004 for another levothyroxine product application (Levo-T, NDA 21-342 s-003) and a follow-up DSI inspection was not considered necessary.

VIII. Conclusions and Recommendations

VIII.a. Conclusions

The sponsor has demonstrated that Tirosint (levothyroxine soft capsules) are bioequivalent to Synthroid levothyroxine tablets. In addition, the sponsor has adequately demonstrated that the dosage forms of Tirosint (levothyroxine soft capsules) were equivalent.

There were no unexpected safety signals noted in the small population of subjects enrolled in the two pharmacokinetic studies. There was no significant difference in the adverse events seen with the Tirosint soft capsule compared to the Synthroid tablet. There was no significant difference in systolic and diastolic blood pressure, heart rate or change

in heart rate, the TSH values or change in TSH seen with the Tirosint soft capsule compared to the Synthroid tablet.

The concern regarding the lack of ability to distinguish the various dosage strengths of the levothyroxine sodium soft capsules has been adequately addressed. Although the capsules themselves will have no distinguishing color or features to allow dose strength discrimination, the product will be packaged in blister packs which will be color coded by strength. While the risk of accidental overdose is not completely removed, this approach should prevent prolonged overdose exposure for the individual patient who requires two separate daily dose strengths of Tirosint.

The additional statement added to the Contraindications section of the Tirosint label (*TIROSINT is also contraindicated for anyone who may be unable to swallow a soft capsule (e.g., infants, small children)* is acceptable and consideration should be given to add the same statement to the Pediatric subsection of the Precautions section of the Tirosint label.

VIIIb. Recommendation

The reviewer recommends approval of Tirosint (levothyroxine sodium soft capsules), pending agreed-upon labeling changes and an adequate cGMP inspection of the relevant manufacturing and testing facilities.

Appendix A
Study AA05227: Comparative, randomized, single-dose, 2-way crossover bioavailability study of softgel levothyroxine sodium capsules and Synthroid levothyroxine sodium tablets following oral administration of a 600mcg total dose in healthy adult volunteers under fasting conditions

Objectives: The objective of this study was to assess the bioavailability of softgel levothyroxine sodium capsules in comparison with Synthroid levothyroxine sodium tablets following oral administration of a single 600mcg total dose in healthy volunteers under fasting conditions

Study Design: This was an open-label, randomized, 2-way crossover, comparative bioavailability study under fasting conditions. A single oral 600mcg dose (four 150mcg softgel levothyroxine capsules or four 150mcg Synthroid tablets) was administered with 240 mL of water. There was a planned wash-out period of at least 35 days between doses. Subjects were admitted to the clinical research unit (CRU) at least 10 hours prior to the first dose of study medication, remained in the CRU until the 24-hour post dose assessments, were discharged and then returned for the 48 hour post dose assessments.

Population: This study enrolled healthy adult men and women.

Inclusion Criteria

- Healthy adult male or female volunteers, 18-50 years of age
- Weighing at least 52 kg for males and 45 kg for females and within 15% of their ideal body weights
- Medically healthy with clinically normal laboratory profiles and ECGs
- Females of childbearing potential should be either sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using an acceptable method of birth control (listed). Postmenopausal women with amenorrhea for > than 1 year and confirmed by FSH level $\geq$ 40 IU/mL
- Voluntary consent to participate in the study

Exclusion Criteria

- History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease.
- In addition, history or presence of:
    - hypothyroidism or hyperthyroidism
    - alcoholism or drug abuse within the past 2 years
    - seizures
    - hypersensitivity or idiosyncratic reaction to thyroid hormones
- Female subjects who are pregnant or lactating
- Subjects who have been on a special diet (for whatever reason) during the 28 days prior to the first dose and throughout the study

- Subjects who have made a donation (standard donation amount or more) of blood or blood products (with the exception of plasma as noted below) within 56 days prior to the study
- Subjects who have made a plasma donation with 7 days prior to the study
- Subjects with hemoglobin less than 12.0 g/dL
- Subjects who have participated in another clinical trial within 28 days prior to the first dose

COMMENT: The inclusion and exclusion criteria appear appropriate.

Study Medication: Subjects received two 600 mcg doses of levothyroxine during the study: one as four 150mcg softgel levothyroxine capsules and one as four 150mcg Synthroid tablets. Each dose was administered with 240 mL of water.

Efficacy Measures: No clinical efficacy measures were evaluated in this study. Pharmacokinetic blood samples for T4 were collected at Hours -0.5, -0.25, -0.083, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 48 for each study period. Blood samples for TSH measurement were collected at baseline and Hour 48 or each study period.

Safety Measures: Safety was assessed by adverse events. Vital signs (seated blood pressure and heart rate) were measured at baseline and Hours 2, 4, 8, and 24 post-dose for each study period. ECGs were collected at baseline for each study period. Safety laboratories were collected at baseline for each study period.

Withdrawal criteria: Patients had the right to withdraw from the study at any time for any reason. Subjects could also be withdrawn by the investigator for adverse events, difficulties in blood collection or protocol violations.

Protocol Amendments: The protocol was amended once prior to study initiation in order to change the study site location from Montréal Canada to phoenix Arizona. In addition, the number of subjects was increased from 24 to 28 and other minor modifications to the protocol were made.

Results

Patient Disposition: The planned sample size was 24 subjects and statistical and pharmacokinetic analyses were to be performed on data from 24 subjects. The protocol was amended to allow for an additional four subjects to be enrolled as alternates. A total of 28 subjects (14 men and 14 women) were enrolled in the study and 25 subjects (12 men and 13 women) completed the study. Three subjects were discontinued on Day 1 of Period 2: one for a positive pregnancy test, one due to a positive cocaine drug screen and one due to an elevated WBC count. These subjects were not included in the PK analyses and were replaced by 3 alternate subjects. Data from the fourth alternate subject was not used.

Protocol Violations: All subjects experienced at least one protocol violation. A total of 9 different protocol violations occurred, mostly related to timing of blood draws and sample clot time deviations. None of the protocol violations were thought to affect the pharmacokinetic results and conclusions of the study.

Demographics: The average age of enrollees is 32 years with a range of 21 – 45 years. The racial mix is 54% Caucasian, 43% Hispanic and 3% Black. The mean weight of enrollees was 62 kg for women and 74 kg for men. The mean height of enrollees was 164 cm for women and 173 cm for men.

Concomitant Medications: One subject was taking a concomitant medication during the study, an oral contraceptive.

Efficacy Outcomes
There are no clinical efficacy outcomes associated with this trial. Please see Dr. Sang Chung's review for a detailed analysis of the pharmacokinetic parameters.

Safety

Events Rates: Overall, thirteen (46%) subjects experienced adverse events during the study. There were no withdrawals due to adverse events, except for a 34-year-old woman who was withdrawn pre-dose at Period 2 due to a positive pregnancy test.

Exposure: Both doses of study drug were taken under the supervision of clinic personnel. Twenty-five subjects received both doses of levothyroxine study drug, for a total of 1200 mcg levothyroxine. Three subjects received study drug at Period 1 only: two received 600 mcg of levothyroxine softgel capsules and one received 600 mcg of Synthroid levothyroxine tablets.

Deaths: There were no deaths reported during this study.

Serious Adverse Events: There were no serious adverse events reported during this study.

Adverse Events Leading to Withdrawal or Dose Alteration: There were no adverse events leading to withdrawal or dose alteration reported during this study.

Adverse Events: Overall, thirteen (46%) subjects experienced seventeen adverse events during the study. The number of subjects experiencing adverse events was evenly distributed between men (7) and women (6). As outlined in the table below, adverse events were reported during all periods of the study (2 events during Screening, 8 events during Period 1, and 7 events during Period 2). There were twice as many events reported with the levothyroxine soft gel capsules than with the levothyroxine tablets. The most common adverse events were headache (5 subjects) and dizziness (3 subjects).

Study AA005227: Adverse Events					
Period	Gender	Age	Wgt (kg)	Drug	AE
Screen	F	27	58.5	none	headache
Screen	F	27	58.5	none	nausea
1	M	33	69.4	Synthroid tab	dizziness
1	M	33	69.4	Synthroid tab	sore throat
1	F	34	66.5	Synthroid tab	unintended pregnancy
1	M	29	58.1	Soft gel capsule	dizziness
1	M	29	58.1	Soft gel capsule	nausea
1	F	38	66	Soft gel capsule	feels jittery
1	M	24	57.6	Soft gel capsule	headache
1	F	34	66.7	Soft gel capsule	vaginal spotting
2	M	30	72.1	Synthroid tab	headache
2	M	45	74.2	Synthroid tab	heart racing
2	M	27	87.8	Soft gel capsule	chest pain
2	F	27	62.1	Soft gel capsule	dizziness
2	F	27	62.1	Soft gel capsule	mouth blister
2	M	41	79.4	Soft gel capsule	headache
2	F	24	59.4	Soft gel capsule	headache

Laboratory: TSH was measured at Hour 0 and Hour 48 for each treatment period. As outlined in the table below, TSH decreased after administration of 600 mcg levothyroxine. There was no significant difference in the TSH values or change in TSH seen with the soft gel capsule compared to the Synthroid tablet. Similar results were obtained for each study period.

Study AA005227: TSH values			
	Baseline	**Hour 48**	**Change**
Overall			
Levothyroxine Soft Gel Capsule	1.7 ± 0.8	0.6 ± 0.6	-1.1 ± 0.6
Synthroid Tablet	1.4 ± 0.9	0.5 ± 0.4	-0.9 ± 0.7
p value	0.143	0.431	0.224
Period 1			
Levothyroxine Soft Gel Capsule	1.6 ± 0.8	0.6 ± 0.8	-1.0 ± 0.7
Synthroid Tablet	1.4 ± 0.9	0.5 ± 0.4	-0.9 ± 0.8
p value	0.401	0.562	0.635
Period 2			
Levothyroxine Soft Gel Capsule	1.8 ± 0.8	0.5 ± 0.4	-1.3 ± 0.6
Synthroid Tablet	1.4 ± 0.9	0.4 ± 0.5	-0.9 ± 0.7
p value	0.238	0.587	0.197

Vital Signs: Blood pressure and pulse were monitored at baseline and Hours 2, 4, 8 and 24 after study drug administration. No significant changes in systolic or diastolic blood pressure were noted. As noted, heart rate increased after administration of 600mcg levothyroxine, as would be expected. The excursion in heart rate peaked at Hours 8 and

24. There was no significant difference in the change in heart rate between the levothyroxine soft gel capsules or the Synthroid tablet.

Study AA005227: Heart Rate					
	Hour 0	**Hour 8**	**Change**	**Hour 24**	**Change**
Overall					
Levothyroxine Capsule	63.4 ± 8.8	68.5 ± 6.9	4.9 ± 7.1	69.2 ± 8.8	5.6 ± 5.4
Synthroid Tablet	61.8 ± 9.9	68.5 ± 10.8	6.7 ± 8.1	70.9 ± 11.5	9.0 ± 7.7
p value	0.493	0.994	0.404	0.550	0.06
Period 1					
Levothyroxine Capsule	63.1 ± 7.1	68.7 ± 5.9	5.6 ± 8.4	68.4 ± 7.2	5.2 ± 5.7
Synthroid Tablet	62.3 ± 9.7	69.1 ± 12.2	6.9 ± 9.7	71.9 ± 12.0	9.6 ± 9.1
p value	0.792	0.907	0.712	0.353	0.138
Period 2					
Levothyroxine Capsule	64.2 ± 10.6	68.3 ± 8.1	4.2 ± 5.6	70.1 ± 10.5	5.9 ± 5.2
Synthroid Tablet	61.3 ± 10.5	67.8 ± 9.3	6.4 ± 6.1	69.7 ± 11.2	8.3 ± 6.0
p value	0.512	0.875	0.348	0.926	0.296

Discussion and Conclusions: When compared to Synthroid levothyroxine tablets, the levothyroxine soft gel capsules exhibited no new or increased safety signals.

Appendix B
Study AA05228: Comparative, randomized, single-dose, 3-way crossover, dosage form proportionality study of softgel levothyroxine sodium capsules following oral administration of a 600mcg total dose in healthy adult volunteers under fasting conditions

Objectives: The objective of this study was to assess the proportionality of three different dosages of softgel levothyroxine sodium capsules (50mcg, 100mcg and 150mcg) following oral administration of a single 600mcg total dose in healthy volunteers under fasting conditions

Study Design: This was an open-label, 6-sequence, 3-way crossover dosage form proportionality study conducted under fasting conditions. A single oral 600mcg dose (twelve 50mcg softgel levothyroxine capsules, six 100mcg softgel levothyroxine capsules or four 150mcg softgel levothyroxine capsules) was administered with 240 mL of water. There was a planned wash-out period of at least 35 days between doses. Subjects were admitted to the clinical research unit (CRU) at least 10 hours prior to the first dose of study medication, remained in the CRU until the 24-hour post dose assessments, were discharged and then returned for the 48 hour post dose assessments.

Population: This study enrolled healthy adult men and women.

Inclusion Criteria

- Healthy adult male or female volunteers, 18-50 years of age
- Weighing at least 52 kg for males and 45 kg for females and within 15% of their ideal body weights
- Medically healthy with clinically normal laboratory profiles and ECGs
- Females of childbearing potential should be either sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using an acceptable method of birth control (listed). Postmenopausal women with amenorrhea for > than 1 year and confirmed by FSH level $\geq$ 40 IU/mL
- Voluntary consent to participate in the study

Exclusion Criteria

- History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease.
- In addition, history or presence of:
    - hypothyroidism or hyperthyroidism
    - alcoholism or drug abuse within the past 2 years
    - seizures
    - hypersensitivity or idiosyncratic reaction to thyroid hormones
- Female subjects who are pregnant or lactating
- Subjects who have been on a special diet (for whatever reason) during the 28 days prior to the first dose and throughout the study

- Subjects who have made a donation (standard donation amount or more) of blood or blood products (with the exception of plasma as noted below) within 56 days prior to the study
- Subjects who have made a plasma donation with 7 days prior to the study
- Subjects with hemoglobin less than 12.0 g/dL
- Subjects who have participated in another clinical trial within 28 days prior to the first dose

COMMENT: The inclusion and exclusion criteria appear appropriate.

Study Medication: Softgel levothyroxine sodium capsules (twelve 50mcg capsules, six 100mcg capsules or four 150mcg capsules) for a total dose of 600mcg during each Period, for a total dose of 1800mcg levothyroxine.

Efficacy Measures: No clinical efficacy measures were evaluated in this study. Pharmacokinetic blood samples for T4 were collected at Hours -0.5, -0.25, -0.083, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 48 for each study period. Blood samples for TSH measurement were collected at baseline and Hour 48 or each study period.

Safety Measures: Safety was assessed by adverse events. Vital signs (seated blood pressure and heart rate) were measured at baseline and Hours 2, 4, 8, and 24 post-dose for each study period. ECGs were collected at baseline for each study period. Safety laboratories were collected at baseline for each study period.

Withdrawal criteria: Patients had the right to withdraw from the study at any time for any reason. Subjects could also be withdrawn by the investigator for adverse events, difficulties in blood collection or protocol violations.

Protocol Amendments: The protocol was amended once prior to study initiation in order to change the study site location from Montreal, Canada to Phoenix, Arizona. In addition, the number of subjects was increased from 24 to 30 and other minor modifications to the protocol were made.

Results

Patient Disposition: The planned sample size was 24 subjects and statistical and pharmacokinetic analyses were to be performed on data from 24 subjects. The protocol was amended to allow for an additional six subjects to be enrolled as alternates. A total of 30 subjects (15 men and 15 women) were enrolled in the study and 25 subjects (11 men and 14 women) completed the study. One subject was withdrawn by the investigator prior to Day 1 of Period 2 because of concomitant illness (sore throat, fever, pain on urination) and medication use (Zithromax and Vicodin). Four subjects were discontinued on Day 1 of Period 3: one had moved out of state, two did not return for the scheduled visit and one did not return because of illness (cold symptoms). These subjects were not included in the PK analyses and were replaced by five alternate subjects. Data from the sixth alternate subject was not used.

Protocol Violations: All subjects experienced at least one protocol violation. A total of 13 different protocol violations occurred, mostly related to timing of blood draws and sample clot time deviations. None of the protocol violations were thought to affect the pharmacokinetic results and conclusions of the study.

Demographics: The average age of enrollees is 30 years with a range of 18 – 48 years. The racial mix is 70% Caucasian and 30% Hispanic. The mean (± SD) weight of enrollees was 63 ± 8 kg for women and 74 ± 4 kg for men. The mean (± SD) height of enrollees was 165 ± 8 cm for women and 179 ± 10 cm for men.

Concomitant Medications: Four subjects reported use of concomitant medication during the study: 2 subjects reported use of an oral contraceptive, one subject reported use of Vicodin and Zithromax, and one subject reported use of diphenhydramine cream.

Efficacy Outcomes
There are no clinical efficacy outcomes associated with this trial. Please see Dr. Sang Chung's review for a detailed analysis of the pharmacokinetic parameters.

Safety

Events Rates: Overall, twelve (40%) subjects experienced adverse events during the study. Five subjects withdrew prematurely from the trial. None of these withdrawals were due to adverse events.

Exposure: All three doses of study drug were taken under the supervision of clinic personnel. Twenty-five subjects received all doses of softgel levothyroxine, for a total of 1800 mcg levothyroxine. One subject received 600mcg of levothyroxine at Period 1 only (twelve 50mcg capsules). Four subjects received a total of 1200mcg of levothyroxine for Periods 1 and 2 (two received twelve 50mcg capsules in Period 1 and four 150mcg capsules in Period 2; two received four 150mcg capsules in Period 1 and six 100mcg capsules in Period 2).

Deaths: There were no deaths reported during this study.

Serious Adverse Events: There were no serious adverse events reported during this study.

Adverse Events Leading to Withdrawal or Dose Alteration: There were no adverse events leading to withdrawal or dose alteration reported during this study.

Adverse Events: Overall, twelve (40%) subjects experienced 26 adverse events during the study. As outlined in the table below, adverse events were reported during all periods of the study (one event during Screening, seven events during Period 1, nine events during Period 2, and eight events during Period 3). The most common adverse events were headache (4 subjects) and body ache (3 subjects). Symptoms that could be

attributed to high dose levothyroxine therapy, including muscle aches, fatigue, loose stools, palpitations, heart pounding and dizziness, occurred in eight subjects.

Study AA005228: Adverse Events					
Period	Gender	Age	Wgt (kg)	Drug	AE
Screen	F	36	70	none	neck pain
1	M	21	75	12 x 50mcg	fractured thumb
1	M	25	76	4 x 150mcg	headache
1					sore throat
1					body aches
1					pain on urination
1					fever
1	F	41	61	12 x 50mcg	lower back pain
1					nausea
2	F	38	53	4 x 150mcg	eye redness
2	M	26	65	4 x 150mcg	cough
2					headache
2	F	38	65	12 x 50mcg	muscle aches
2					fatigue
2	F	22	53	4 x 150mcg	headache
2					palpitations
2					hives
2	F	36	70	12 x 50mcg	heart pounding
3	M	41	78	6 x 100mcg	loose stools
3	M	24	81	12 x 50mcg	dizziness
3	F	25	70	4 x 150mcg	loose stools
3	F	38	71	4 x 150mcg	headache
3					back ache
3	F	38	65	6 x 100mcg	sore throat
3					muscle pain
3					palpitations

Laboratory: TSH was measured at Hour 0 and Hour 48 for each treatment period. As outlined in the table below, TSH decreased after administration of 600 mcg levothyroxine. There was no significant difference in the TSH values or change in TSH seen with the various soft gel capsules. Similar results were obtained for each study period.

Study AA005228: TSH values following Levothyroxine Soft Gel Capsules			
	Baseline	**Hour 48**	**Change**
Overall			
Soft Gel Caps 12 x 50mcg	1.5 ± 1.0	0.4 ± 0.3	-1.0 ± 0.8
Soft Gel Caps 6 x 100mcg	1.4 ± 0.7	0.4 ± 0.2	-1.0 ± 0.6
Soft Gel Caps 4 x 150mcg	1.4 ± 0.9	0.4 ± 0.3	-1.0 ± 0.9
Period 1			
Soft Gel Caps 12 x 50mcg	1.3 ± 0.5	0.5 ± 0.2	-0.8 ± 0.4
Soft Gel Caps 6 x 100mcg	1.2 ± 0.5	0.4 ± 0.2	-0.8 ± 0.3
Soft Gel Caps 4 x 150mcg	1.9 ± 1.3	0.5 ± 0.4	-1.4 ± 1.3
Period 2			

Study AA005228: TSH values following Levothyroxine Soft Gel Capsules			
	Baseline	**Hour 48**	**Change**
Soft Gel Caps 12 x 50mcg	1.2 ± 0.7	0.4 ± 0.2	-0.8 ± 0.6
Soft Gel Caps 6 x 100mcg	1.9 ± 1.0	0.5 ± 0.2	-1.5 ± 0.8
Soft Gel Caps 4 x 150mcg	1.2 ± 0.6	0.5 ± 0.4	-0.7 ± 0.5
Period 3			
Soft Gel Caps 12 x 50mcg	2.0 ± 1.5	0.4 ± 0.4	-1.5 ± 1.3
Soft Gel Caps 6 x 100mcg	1.1 ± 0.3	0.4 ± 0.3	-0.7 ± 0.3
Soft Gel Caps 4 x 150mcg	1.2 ± 0.5	0.3 ± 0.1	-0.9 ± 0.5

Vital Signs: Blood pressure and pulse were monitored at baseline and Hours 2, 4, 8 and 24 after study drug administration. No significant changes in systolic or diastolic blood pressure were noted. Heart rate increased after administration of 600mcg levothyroxine, and peaked at Hours 8 and 24. There was no significant difference in the change in heart rate between the levothyroxine soft gel capsule dosage groups

Discussion and Conclusions: There were no significant safety differences between the three soft gel capsule dosage groups assessed.

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/s/

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