Official title: ***Levothyroxine replacement with liquid gel capsules or tablets in post-thyroidectomy low risk differentiated thyroid cancer patients.***

NCT number: ***NCT02946918***

Document date: 12/16/2018, Version 03

Summary of Proposed Protocol Amendments: 2/7/19

- **Cover page:**
  - **Removal of Lindsay Jacobs as sub-investigator (no longer employed at UT Southwestern)**
  - **Akrimax has sold Tirosint to IbSA Pharma**
- **Given that levothyroxine (both in tablets and gelcaps are only available in specific dosages, the initial dose of medication is amended to allow a range (1.5-1.8 mcg/kg) rather than a specific weight based target of 1.7 mcg/kg**
- **Study Objectives 2.1**
  - "Descriptive statistics are of primary interest as this feasibility study is not powered to formally test a statistical hypothesis." Added to primary objective to emphasize the feasibility/pilot nature of this trial.
- **Study Eligibility 3.0**
  - **Inclusion criteria:**
    - **Preoperative cytology definition clarified to include suspicious as well as presumed differentiated thyroid cancer (surgical pathology is acknowledged as "gold standard" for diagnosis of malignancy)**
  - **Exclusion criteria:**
    - **To provide clarification, concomitant medications that are not permissible for study participation due to effects on absorption or metabolism of thyroid hormone are listed specifically.**
    - **Clarification of prior use of levothyroxine to state within one year of enrollment**
- **Study Procedures: 5.1.6**
  - **Remove respirations from measured vital signs**
- **Section 5.2 Time and Events Table**
  - **Screening procedures, enrollment and informed consent procedures allowed within 14 days**
  - **Visit 2, telephone contact can be made within 7 days of surgery**
  - **Thyroid treatment satisfaction questionnaire only at week 18 (not applicable prior to treatment)**
  - **Remove "dispensing study medication" at 18 week visit as a prescription is given instead**
  - **Postoperative visits will be given +/- 1 week to facilitate follow up visits**
- **Address changes made to reflect relocation to West Campus Building 3**

Levothyroxine replacement with liquid gel capsules or tablets in post-thyroidectomy low risk differentiated thyroid cancer patients.

Pilot feasibility study, randomized, double blinded, stage 1 and 2

Principal Investigator: **Alexander Tessnow, MD**
UT Southwestern
5323 Harry Hines Blvd, Dallas, Texas, 75390-882
Phone 214-645-2868
Fax 214-645-2828
Alex.Tessnow@utsouthwestern.edu

Biostatistician: Beverley Huet, MS, PSTAT
UT Southwestern
5323 Harry H Hines Blvd, Dallas, Texas, 75390-882
Phone 214-648-2788
Beverley.Huet@utsouthwestern.edu

Study Drug: Levothyroxine, Tirosint
Levothyroxine, Synthroid

Funding Source: IBSA Pharma, Inc

Initial version: 1.0, 04/03/2015

Revised versions: 2.0, 09/20/2018
3.0, 12/16/2018

UT Southwestern Medical Center (UTSW)
West Campus Building 3, 8th Floor
Attn: Division of Endocrinology
2001 Inwood Rd
Dallas, Texas 75390-8872

Signature Page

Protocol Version 3.0, 12/16/2018

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

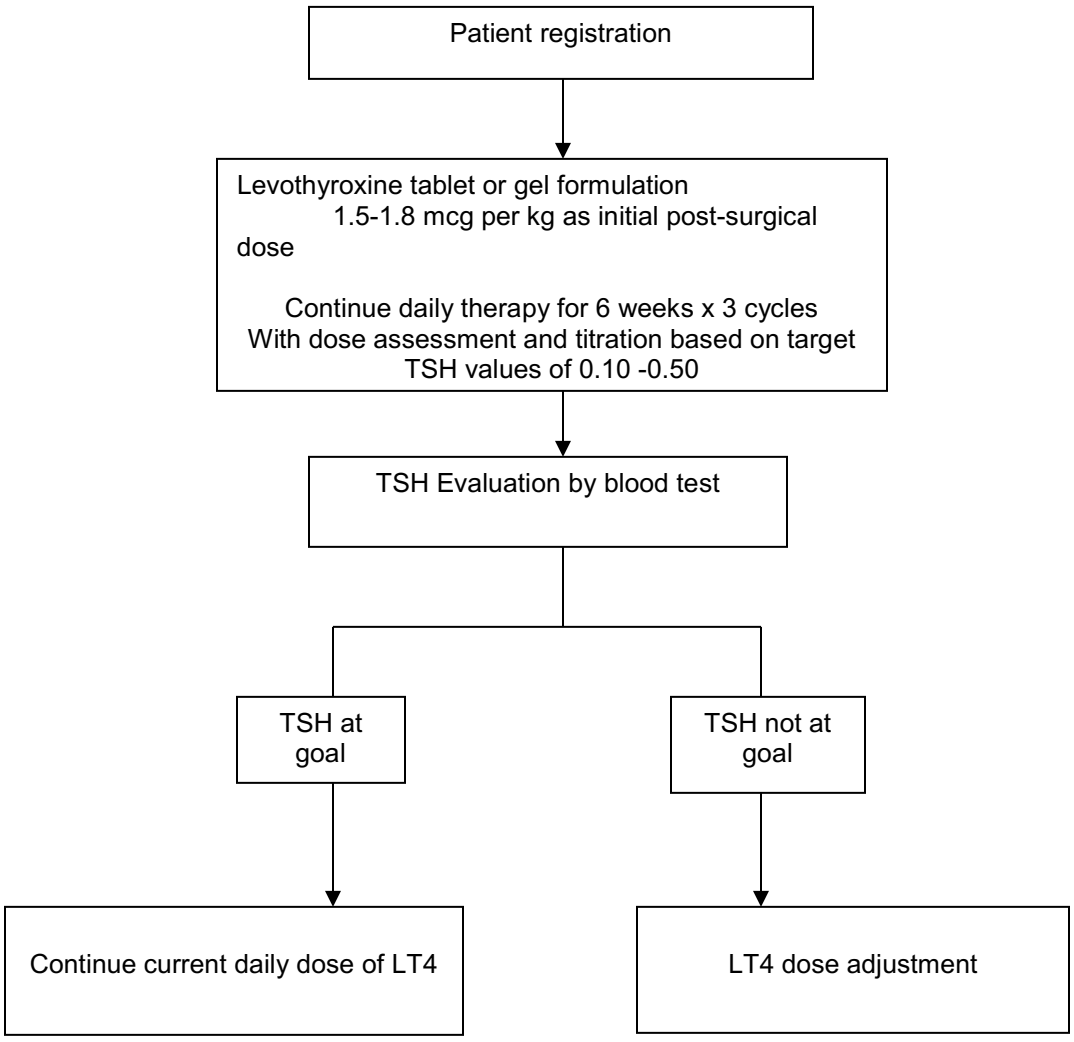
Date:_____

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

FT4	Free T4
LT4	Levothyroxine
QoL-Thyroid	Thyroid version Quality of Life Questionnaire
TFT	Thyroid Function Tests (TSH and FT4)
TSH	Thyroid Stimulating Hormone
ThyTSQ	Underactive Thyroid Treatment Satisfaction Questionnaire

STUDY SCHEMA



STUDY SUMMARY

Title	Levothyroxine replacement with liquid gel capsules or tablets in post-thyroidectomy low risk differentiated thyroid cancer patients.
Short Title	Post-surgical LT4 replacement gelcap vs tablet in patients with stage 1 and 2 Differentiated Thyroid Cancer
Protocol Number	3.0
Phase	pilot, feasibility study
Methodology	double blinded; randomized
Study Duration	4 years
Study Center(s)	Single-center
Objectives	The aim of this investigation is to compare the use of levothyroxine in liquid gel capsules to tablet form for TSH suppression following thyroidectomy for presumed stage I/II differentiated thyroid cancer.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	AJCC Stage I/II differentiated thyroid cancer, post-thyroidectomy
Study Product(s), Dose, Route, Regimen	Synthroid and Tirosint levothyroxine formulations. Initial dose 1.5-1.8 mcg per kg, orally and daily
Duration of administration	18 weeks
Statistical Methodology	Continuous variables will be summarized with mean and standard deviation; medians and ranges will be reported for skewed variables. We will construct 95% confidence intervals will be used to estimate liquid gel capsule treatment and tablet treatment responses at each study visit and to estimate differences between groups or visits within groups.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Globally, the incidence of differentiated thyroid cancer has increased considerably over the past 25 years. Numerous international studies have demonstrated this trend in Europe, Australia, South America and the Middle East. Domestically the US has seen a steady annual increase in differentiated thyroid cancer from approximately 3.5 cases per 100,000 observed from 1988-1998 to now approximately 8.7 cases per 100,000. Not only are more patients being diagnosed with thyroid cancer but there is also a documented increase in the number of large tumors in these patients. Despite this increasing trend, the 10-year disease specific survival rate remains high at over 90%. The overall positive prognosis of differentiated thyroid cancer can be attributed to the slow growing and rarely aggressive nature of this disease as well as the streamlined guidelines provided by the American Thyroid Association that are used in the treatment and management of these patients.

Aside from radioactive iodine ablation, TSH suppression is one of the most basic yet effective postsurgical therapies used in the treatment of patients with thyroid cancer. By maintaining higher than normal T4 levels with exogenous thyroid hormone replacement, the TSH is down regulated to lower than normal levels, which subsequently decreases remaining thyroidal cell activity and growth. As recommended by the American Thyroid Association's most recent published guidelines, TSH suppression of 0.1 – 0.5 mU/L is recommended for all patients with low risk of reoccurrence. A large majority of stage I and II differentiated thyroid cancer patients fall into this low risk category. Careful titration of levothyroxine is used to appropriately manage these patient's TSH levels into this therapeutic window.

There is limited data on the use of liquid gel capsules for the use of levothyroxine replacement and TSH suppression in post thyroidectomy patients with a history of thyroid cancer. Studies have suggested that in some patients, levothyroxine liquid gel capsules demonstrate superior absorption than the tablet option. Impaired absorption of thyroid hormone directly correlates to higher and more unpredictable TSH levels. We therefore hypothesize that following thyroidectomy the gel capsule levothyroxine formulation will provide more predictable TSH results and in turn require fewer dose adjustments to achieve optimal hormone levels in the postoperative period.

1.2 Study Agent(s) Background and Associated Known Toxicities

Both study agents are FDA approved formulations of levothyroxine. These therapies are considered safe and regularly used in the postsurgical management of hypothyroidism.

1.3 Rationale

Patients with AJCC Stage I/II differentiated thyroid cancer are recommended to have TSH suppression (goal 0.1-0.5 mU/L) during the immediate postoperative period to prevent recurrence. As many of these patients do not have pre-existing thyroid synthetic dysfunction, they represent a treatment naïve population well suited to study initiation of levothyroxine therapy.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 The aim of this investigation is to compare the use of levothyroxine in liquid gel capsules to tablet form for TSH suppression (target 0.1-0.5 MIU/L) following thyroidectomy for presumed stage I/II differentiated thyroid cancer. This will be

achieved by evaluating the number of patients in each group at the predefined target TSH range at each time interval (6, 12, and 18 weeks (+/- 1 week for each interval) postoperatively). Descriptive statistics are of primary interest as this feasibility study is not powered to formally test a statistical hypothesis.

2.2 Secondary Objectives

2.2.1 To quantify the mean number of dose adjustments, and compare the two study agent group outcomes

2.2.2 To assess and compare quality of life differences between study groups using scores on QoL-Thyroid and ThyTSQ surveys

2.3 Endpoints

The 18 week post-operative visit will serve as the endpoint of this study.

3.0 Subject ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Preoperative cytology suspicious of or positive for differentiated thyroid cancer

3.1.2 Presumed AJCC tumor stage I or II

3.1.3 Planned total, near-total or completion thyroidectomy requiring lifelong thyroid hormone replacement.

3.1.4 Planned goal TSH suppression 0.1-0.5 mU/L for at least 18 weeks postoperatively

3.1.5 Normal serum TSH within 12 months preceding surgery

3.1.6 Age ≥ 18 years.

3.1.7 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 AJCC Stage III/IV differentiated thyroid cancer

3.2.2 Undifferentiated, Anaplastic or Medullary thyroid cancer

3.2.3 Planned postoperative TSH goal different than 0.1-0.5 mU/L

3.2.4 History of gastrointestinal mal-absorption or gastric bypass surgery

3.2.5 Pregnancy

3.2.6 Concurrent use of phenobarbital, carbamazepine, rifampin, amiodarone, or tyrosine kinase inhibitors

3.2.7 Use of levothyroxine within 12 months of enrollment

3.2.8 Anticipated RAI treatment within 18 weeks of treatment

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.2 Initial dose of medication will be dispensed upon enrollment (Visit 1). Refills will be dispensed at the Aston based research pharmacy at subsequent follow up visits.

4.1.2 The initial dose of both levothyroxine formulations will be based on the patient's actual body weight: 1.5-1.8 mcg per kg. Medication dose will be adjusted at each follow up visit and titrated until goal TSH of 0.10 -0.50 is reached.

4.1.2 Treatment will be administered on an outpatient basis.

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Trial Therapy Length**
Synthroid	Take on an empty stomach first thing in the morning. Do not eat/drink or take other vitamins or medications within one hour of taking this medication.	Initial dose: 1.5-1.8 mcg per kg	PO in the a.m.	daily	18 weeks
Tirosint	Take on an empty stomach first thing in the morning. Do not eat/drink or take other vitamins or medications within one hour of taking this medication.	Initial dose: 1.5-1.8 mcg per kg	PO in the a.m.	daily	

These medications will be self-administered. At every clinical follow up visit a pill count will be inventoried to confirm compliance.

4.2 Dose Modifications

Levothyroxine doses will be titrated to achieve optimal suppression of TSH levels (0.10 – 0.50). Dose adjustments will be made at 6 and 12 week postoperative visits utilizing available levothyroxine doses or combinations thereof listed in section 7.1.

4.3 Duration of Therapy

- As thyroid hormone replacement is necessary for life following thyroidectomy, these patients will be treated with levothyroxine indefinitely. According to the American Thyroid Association guidelines, levothyroxine is the treatment of choice for thyroid hormone replacement.

4.4 Duration of Follow Up

Subjects will not be followed after removal from treatment, as this therapy is standard of care and imposes no additional risk to the patients. Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.5 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per protocol.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 14 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history, history of infections

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height (initial visit only) and weight*

Vital signs (temperature, pulse, blood pressure), weight

5.1.7 *Serum chemistries – if not performed within the prior 12 months*

TSH
FT4

5.1.8 *Urine tests*

Pregnancy test (if female of child-bearing potential)

5.1.9 Patient Quality of Life Questionnaires

QoL-Thyroid

5.2 Time and Events Table [When appropriate, this may be referenced and included in the appendices rather than within the body of the protocol. Consider landscape format when necessary to include all of the appropriate procedures and tests]

Visit	**1**	**2**	**3**	**4**	**5**
Time	**Within 14 days preop**	**Postoperative Day #1-7**	**5-7 weeks**	**11-13 weeks**	**17-19 weeks**
Type	**Office**	**Phone**	**Office**	**Office**	**Office**
Consent	x				
I&E criteria	x				
Randomization	x				
Physical exam	x		x	x	x
Height	x				
Vitals (weight, BP, pulse)	x		x	x	x
Labs (TSH, Free T4)	X if not done within 12 months		x	x	x
Dispense trial drug	x		x	x	
QoL questionnaires (QoL –Thyroid and ThyTSQ)	X (QOL ONLY)				X
AE and SAE assessment			x	x	x
Pregnancy test (if applicable)	x		x	x	x
Answer Study Related Questions	x	x	x	x	x

5.3 Removal of Subject/Withdrawal from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.3.1 Subject voluntarily withdraws from treatment;

5.3.2 Subject withdraws consent (termination of treatment and follow-up);

5.3.3 Subject is unable to comply with protocol requirements;

5.3.4 Treating physician determines that the continuation on the study would not be in the subject's best interest;

5.3.5 Lost to follow-up

5.3.6 Patient becomes pregnant during this study (this is a dose based study and pregnancy can affect hormone titration)

6.0 ADVERSE EVENTS

6.1 Experimental Therapy

Synthroid and Tirosint are not experimental drugs. Levothyroxine therapy is standard of care.

6.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

6.2.1 Definition

Adverse Events will be reported as indicated by the appropriate following table (see below).

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily

associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study. Refer to the UTSW IRB website at http://www.utsouthwestern.net/intranet/research/research-administration/irb/study-management/adverse-events.html to determine when a serious adverse event requires reporting to the IRB.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

6.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be assessed for 18 weeks and followed up according to good medical practices.

6.3 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment *(alternatively, to the end of the acute adverse events reporting period as defined in section XX*). Any event that occurs more than 30 days after the last dose of treatment (*alternatively, during the late adverse event period as defined in section XX*) and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

6.3.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to:

Primary Investigator: Alexander Tessnow (if fax report is not available) within 1 working day to 214-645-2868
Written reports to: Primary Investigator: Alexander Tessnow Email: Alex.Tessnow@utsouthwestern.edu Fax: 214-645-2828 or deliver to West Campus Building 3, 8th floor Endocrine Office UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combined.pdf.

6.4 Stopping Rules

There are no stopping rules

7.0 DRUG INFORMATION

7.1 Levothyroxine

- Other names for the drug(s): Tirosint, Synthroid
- Classification - type of agent: Thyroid hormone
- Mode of action: Synthetic levothyroxine is identical to that produced naturally in the human thyroid gland.
- Storage and stability: room temperature
- Protocol dose: Starting dose will be 1.5-1.8 mcg per kg, using the patient's actual weight. Dose will be rounded to the nearest available incremental dose of the randomized formulation. Dose will be adjusted to next higher or next lower dose during follow up visits based on TSH values. Doses can be initiated or adjusted by single or combination of preparations listed below. Note: if dose requires use of 12.5 mcg or 13 mcg, exact dose will be determined based on the brand to which the subject was randomized. This is due to gel capsules only available in 13 mcg while tablets can only be split to 12.5 mcg.
- Route of administration for this study: oral
- Incompatibilities: Must be taken on an empty stomach. Must wait at least 1 hour before taking food/water/other medications or vitamins
- Availability: commercially available, both formulations will be encapsulated in a fashion to allow double blinding. The available strengths above (including 12.5 mcg split from 25 mcg Synthroid) will be encapsulated by an outside compounding pharmacy. The medication will be shipped directly to the Aston research pharmacy (8th floor) that will dispense all medication and will not be blinded. The Aston pharmacy will be given the randomization code for the patient by the study statistician, Beverley Huet. The pharmacy will dispense medication according to the randomization.
- Side effects: Adverse Reactions associated with levothyroxine therapy are symptoms of hyperthyroidism due to therapeutic over-dosage.
- Nursing implications: none

- Pharmacokinetics – from package inserts of Tirosint and Synthroid which is identical except for absorption.
    - Absorption:
        - Absorption of orally administered T_4 from the gastrointestinal (GI) tract ranges from 40% to 80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of TIROSINT capsules compared to another marketed levothyroxine sodium tablet is approximately 103%. The relative bioavailability of SYNTHROID tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 93%.T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybeans. Dietary fiber decreases the bioavailability of T_4. Absorption may also decrease with age. In addition, many drugs and foods affect T_4 absorption.
    - Distribution
        - Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and thyroxine-binding albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T_4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T_4 compared to T_3. Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins
    - Metabolism
        - T_4 is slowly eliminated. The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of circulating T_3 is derived from peripheral T_4 by monodeiodination. The liver is the major site of degradation for both T_4 and T_3, with T_4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and reverse T_3 (r T_3). T_3 and r T_3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.
    - Elimination
        - Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T_4 is eliminated in the stool. Urinary excretion of T_4 decreases with age.

7.1.1 Return and Retention of Study Drug

The remaining drugs will be destroyed according to the UT Southwestern pharmacy policy.

7.1.2 Subject's compliance with the study agents will be assessed at every clinical appointment. A pill count will be inventoried by the practitioner and recorded in the patient's electronic medical record.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

This is a double blinded, randomized, single center study. The study will end at the 18 week post-surgical follow up appointment.

.

8.2 Sample Size and Accrual

As this is a feasibility study it will only include 20 total, study-completed participants. Each arm of the study will include 10 patients. Descriptive statistics are of primary interest as this study is not powered to formally test a statistical hypothesis.

8.3 Data Analyses Plans

Continuous variables will be summarized with mean and standard deviation; medians and ranges will be reported for skewed variables. We will construct 95% confidence intervals will be used to estimate liquid gel capsule treatment and tablet treatment responses at each study visit and to estimate differences between groups or visits within groups. This study has repeated measurements and these longitudinal data will be evaluated using a mixed linear model approach for repeated measures. Due to the pilot nature of study any hypothesis testing will be interpreted cautiously. The primary analysis data set will be the intention-to-treat analysis data set consisting of all randomized subjects who have at least one post-randomization study visit. All available data, including cases with missing data, will be included in the statistical analysis. Categorical variables, including any adverse events, will be summarized in detail with descriptive statistics. P values of < 0.05 will be considered statistically significant.

9.0 STUDY MANAGEMENT

9.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

9.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been

provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

9.3 Required Documentation (for multi-site studies)

Not applicable

9.4 Registration Procedures

Not applicable

9.5 Data Management and Monitoring/Auditing

Trial monitoring will be conducted by no less than annually and refers to a regular interval review of trial related activity and documentation performed by the study team, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Toxicity and dose escalation reviews will be performed by the primary investigator, Dr. Tessnow at each follow up visit. These reviews will be documented in the visit note and electronic medical record.

9.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.6.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

9.6.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

➢ **Reporting requirement**: Emergency deviations must be promptly reported

to the IRB within 5 working days of occurrence.

9.6.3 Major Deviations (also called **violations**): include any departure from IRB-approved research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

9.6.4 Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

9.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

9.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.0 REFERENCES

1. Rego-Iraeta A, Perez-Mendez LF, Mantinan B, Garcia-Mayor RV. Time trends for thyroid cancer in northwestern Spain: true rise in the incidence of micro and larger forms of papillary thyroid carcinoma. Thyroid. 2009;19(4):333-40. doi: 10.1089/thy.2008.0210. PubMed PMID: 19355823.
2. Burgess JR. Temporal trends for thyroid carcinoma in Australia: an increasing incidence of papillary thyroid carcinoma (1982-1997). Thyroid. 2002;12(2):141-9. doi: 10.1089/105072502753522374. PubMed PMID: 11916283.
3. Cordioli MI, Canalli MH, Coral MH. Increase incidence of thyroid cancer in Florianopolis, Brazil: comparative study of diagnosed cases in 2000 and 2005. Arq Bras Endocrinol Metabol. 2009;53(4):453-60. PubMed PMID: 19649384.
4. Sisson JC. The increasing incidence of thyroid cancer in Saudi Arabia. Ann Saudi Med. 1995;15(6):557-8. PubMed PMID: 17589008.
5. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988-2005. Cancer. 2009;115(16):3801-7. doi: 10.1002/cncr.24416. PubMed PMID: 19598221.
6. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214. Epub 2009/10/29. doi: 10.1089/thy.2009.0110. PubMed PMID: 19860577.
7. Vita R, Fallahi P, Antonelli A, Benvenga S. The administration of L-thyroxine as soft gel capsule or liquid solution. Expert opinion on drug delivery. 2014;11(7):1103-11. doi: 10.1517/17425247.2014.918101. PubMed PMID: 24896369.
8. Wenzel KW, Kirschsieper HE. Aspects of the absorption of oral L-thyroxine in normal man. Metabolism: clinical and experimental. 1977;26(1):1-8. PubMed PMID: 834138.
9. McMillan CV, Bradley C, Woodcock A, Razvi S, Weaver JU. Design of new questionnaires to measure quality of life and treatment satisfaction in hypothyroidism. Thyroid. 2004;14(11):916-25. doi: 10.1089/thy.2004.14.916. PubMed PMID: 15671770.
10. Ferrell BR, Hassey-Dow K, Grant M. Measurement of the QOL in Cancer Survivors. Quality of Life Research. 1995; 4:523-531.

11.0 APPENDICES

11.1 ThyTSQ

Treatment Satisfaction Survey

1. How satisfied are you with the current treatment for your underactive thyroid?

Very Dissatisfied	Dissatisfied		Neutral		Satisfied	Very Satisfied
0	1	2	3	4	5	6
O	O	O	O	O	O	O

2. How well do you feel the treatment is working?

Very Dissatisfied	Dissatisfied		Neutral		Satisfied	Very Satisfied
0	1	2	3	4	5	6
O	O	O	O	O	O	O

3. How convenient have you found your treatment to be recently (e.g. remembering to take the medication, getting prescriptions)?

Very Dissatisfied	Dissatisfied		Neutral		Satisfied	Very Satisfied
0	1	2	3	4	5	6
O	O	O	O	O	O	O

4. How satisfied are you with your understanding of your underactive thyroid?

Very Dissatisfied	Dissatisfied		Neutral		Satisfied	Very Satisfied
0	1	2	3	4	5	6
O	O	O	O	O	O	O

5. Would you encourage someone else with underactive thyroid to have your kind of treatment?

Very Dissatisfied	Dissatisfied		Neutral		Satisfied	Very Satisfied
0	1	2	3	4	5	6

O	O	O	O	O	O	O

6. How well do you feel that the treatment is controlling symptoms of underactive thyroid?

Very Dissatisfied	Dissatisfied		Neutral		Satisfied	Very Satisfied
0	1	2	3	4	5	6
O	O	O	O	O	O	O

7. How satisfied would you be to continue with your present treatment and dose?

Very Dissatisfied	Dissatisfied		Neutral		Satisfied	Very Satisfied
0	1	2	3	4	5	6
O	O	O	O	O	O	O

8. Are there any other features of your recent treatment for underactive thyroid, causing either satisfaction or dissatisfaction, that have ***not*** been covered by the questionnaire?

Yes	No
O	O

If yes, please describe:

_____

_____

_____

_____

_____

11.2 QoL-Thyroid

Quality of Life Scale/THYROID
Directions: We are interested in knowing how your experience of having thyroid cancer affects your quality of life. Please answer all of the following questions based on how you have been feeling **during the previous week.**

Physical Well Being
1. To what extent have the following been a problem during your illness and treatment?
a) Fatigue
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

b) Appetite changes
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

c) Aches or pain
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

d) Sleep changes
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

e) Constipation
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

f) Menstrual changes or fertility
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

g) Weight gain
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

h) Tolerance to cold or heat
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

i) Dry skin or hair changes
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

j) Voice changes
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

k) Motor skills/coordination
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

l) Swelling/fluid retention
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

2. Rate your overall physical health:
extremely poor 0 1 2 3 4 5 6 7 8 9 10 **excellent**

Psychological Well Being Items

3. How difficult is it for you to cope with your disease and treatment?
not at all difficult 0 1 2 3 4 5 6 7 8 9 10 **very difficult**

4. How good is your quality of life?
Extremely poor 0 1 2 3 4 5 6 7 8 9 10 **excellent**

5. How much happiness do you feel?
none 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

6. Do you feel like you are in control of things in your life?
None at all 0 1 2 3 4 5 6 7 8 9 10 **completely**

7. How satisfying is your life?
not at all 0 1 2 3 4 5 6 7 8 9 10 **completely**

8. How is your present ability to concentrate or to remember things?
extremely poor 0 1 2 3 4 5 6 7 8 9 10 **excellent**

9. How useful do you feel?
not at all 0 1 2 3 4 5 6 7 8 9 10 **extremely**

10. Has your illness or treatment caused changes in your appearance?
not at all 0 1 2 3 4 5 6 7 8 9 10 **extremely**

11. Has your illness caused changes in your self-concept (the way you see yourself)?
not at all 0 1 2 3 4 5 6 7 8 9 10 **extremely**

12. How distressing were the following aspects of your illness and treatment:
a) Initial diagnosis
not at all distressing 0 1 2 3 4 5 6 7 8 9 10 **very distressing**

b) Surgeries
not at all distressing 0 1 2 3 4 5 6 7 8 9 10 **very distressing**

c) Time since my treatment was completed
not at all distressing 0 1 2 3 4 5 6 7 8 9 10 **very distressing**

13. How much anxiety do you have?
none at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

14. How much depression do you have?
none at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

15. To what extent are you fearful of:
a) Future diagnostic tests
no fear 0 1 2 3 4 5 6 7 8 9 10 **extreme fear**

b) A second cancer
no fear 0 1 2 3 4 5 6 7 8 9 10 **extreme fear**

c) Recurrence of your cancer
no fear 0 1 2 3 4 5 6 7 8 9 10 **extreme fear**

d) Spreading (metastasis) of your cancer
no fear 0 1 2 3 4 5 6 7 8 9 10 **extreme fear**

Social Concerns

16. How distressing has your illness been for your family?
none at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

17. Is the amount of support you receive from others sufficient to meet your needs?
none at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

18. Is your continuing health care interfering with your personal relationships?
none at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

19. Is your sexuality impacted by your illness?
none at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

20. To what degree has your illness and treatment interfered with your employment?
a) Motivation to work
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**
b) Time away from work
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

c) Productivity at work
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

d) Quality of work
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

21. To what degree has your illness and treatment interfered with your activities at home?
a) Driving a car
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

b) Household chores
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

c) Preparing meals
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

d) Leisure activities
no problem 0 1 2 3 4 5 6 7 8 9 10 **severe problem**

22. How much isolation do you feel is caused by your illness and treatment?
none at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**

23. How much financial burden have you incurred as a result of your illness and treatment?
none at all 0 1 2 3 4 5 6 7 8 9 10 **a great deal**