1. Cover/Title Page

Medtronic	
Clinical Investigation Plan Title	A prospective, multi-center, single arm non-comparative pilot study of BiZact™ on adults undergoing tonsillectomy.
Clinical Investigation Plan Identifier	COVBZTS0562
Study Product	BiZact™ (BZ4112)
ClinicalTrials.gov Identifier	NCT02876575
Sponsor/Local Sponsor	Covidien-Medtronic Minimally Invasive Therapies Group Surgical Innovations 5920 Longbow Dr. Boulder, CO 80301 Covidien Services Europe (an indirect, wholly owned subsidiary of Medtronic plc.) Block G, Ground Floor Cherrywood Business Park Loughlinstown, Dublin 18, Ireland
Key Entities	Ron J Karni, University of Texas Health Science Center at Houston Luciano Mazzaro, Clinical Study Manager, MITG Sylvain Anselme, Biostatistics, MITG

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	A prospective, multi-center, single arm non-comparative pilot study of BiZact™ on adults undergoing tonsillectomy.
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Sponsor/Local Authorized Representative	Covidien-Medtronic Minimally Invasive Therapies Group Surgical Innovations 5920 Longbow Dr. Boulder, CO 80301 Covidien Services Europe *(an indirect, wholly owned subsidiary of Medtronic plc.)* Medtronic plc., Block 3090-3094, Lake Drive Citywest Business Campus Co. Dublin, D24 XN47 Ireland
Document Version	4.0 Final dated 20-Mar-2018

1. Investigator Statement

Study product Name	BiZact™ (BZ4112)
Sponsor/Local Authorized Representative	Covidien-Medtronic Minimally Invasive Therapies Group Surgical Innovations 5920 Longbow Dr. Boulder, CO 80301, USA Covidien Services Europe *(an indirect, wholly owned subsidiary of Medtronic plc.)* Medtronic plc., Block 3090-3094, Lake Drive Citywest Business Campus Co. Dublin, D24 XN47 Ireland
Clinical Investigation Plan Identifier	COVBZTS0562
Version Number/Date	Version 4.0 dated 20-Mar-2018
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with United States Food and Drug Administration regulations (US) or ISO 14155:2011 (EU) and any regional or national regulations, as appropriate. I agree to comply with the ethical principles that have their origin in the Declaration of Helsinki 2013 and the clinical trial agreement. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

Table of Contents

2. Glossary

Term	Definition
ADE	Adverse device effect
ADL	Activities of daily living
AE	Adverse event
CIP	Clinical Investigation Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
ENT	Ear, nose and throat
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full Analysis Set
Focal infection	Infection confined to a single organ or tissue; certain focal infections, as in tonsillar crypts or periodontal tissues, are a source of systemic disease as a result of blood-stream dissemination of the offending pathogen according to Dorland's Illustrated Medical Dictionary 1976.
GCP	Good Clinical Practice
Hemostasis	The arrest of bleeding, whether it be by normal vasoconstriction (the vessel walls closing temporarily), by an abnormal obstruction (such as a plaque) or by coagulation or surgical means (such as ligation).
ICMJE	International Committee of Medical Journal Editors
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
PETG	Polyethylene terepthalate glycol

Term	Definition
QOL	Quality of Life (survey)
RDC	Remote Data Capture
RF	Radiofrequency
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
WHO	World Health Organization

3. Synopsis

Title	A prospective, multi-center, single arm non-comparative pilot study of BiZact™ on adults undergoing tonsillectomy.
Clinical Study Type	Post-market interventional, prospective, multi-center, single arm, non-comparative pilot
Product Name	BiZact™ (BZ4112)
Sponsor	Covidien-Medtronic Minimally Invasive Therapies Group Surgical Innovations 5920 Longbow Dr. Boulder, CO 80301, USA
Local Authorized Representative	Covidien Services Europe *(an indirect, wholly owned subsidiary of Medtronic plc.)* Medtronic plc., Block 3090-3094, Lake Drive Citywest Business Campus Co. Dublin, D24 XN47 Ireland
Indication under investigation	Adult tonsillectomy
Investigation Purpose	The purpose of this study is to assess the severity of post-operative pain following the use of the BiZact™ device in adult (≥22 years of age in United States and ≥18 years of age in Europe) tonsillectomy procedures.
Product Status	Food and Drug Administration (FDA) 510(k) clearance and Conformité Européene (CE) Mark clearance
Primary Objective(s)	The primary objective of this study is to assess the severity of post-operative pain following the use of the BiZact™ device in adult (≥22 years of age in United States and ≥18 years of age in Europe) tonsillectomy procedures using the Visual Analogue Scale (VAS) at days 1 through 7, 10 and 14.
Secondary Objective(s)	The secondary objective of this study is to assess bleeding, and post-operative ability to return to normal diet and activity up to 14 days.
Study Design	Prospective, multi-center, single-arm non-comparative pilot study to assess the severity of post-operative pain with the use of BiZact™ for tonsillectomy.

Sample Size	A minimum of 48 subjects may be enrolled at up to 3 sites in the United States and Europe with competitive enrollment not to exceed 24 subjects per site.
Inclusion/Exclusion Criteria	**Subjects are eligible to be enrolled in the study only if they meet all of the following criteria:** *Inclusion Criteria:* 1. Adults (male or female) ≥22 years of age in United States and ≥18 years of age in Europe 2. Scheduled to undergo tonsillectomy 3. Signed informed consent by subject **Subjects will be excluded from the study if they meet any of the following criteria:** *Exclusion Criteria* 1. Subjects undergoing: a. Simultaneous adenoidectomy b. Tonsillectomy as a result of cancer c. Unilateral tonsillectomy d. Current participation in other clinical trials 2. Subjects with: a. Current tobacco use b. Known bleeding disorders c. History of peritonsillar abscess d. Craniofacial disorders e. Down syndrome (Trisomy 21) f. Cerebral palsy g. Major heart disease (including but not limited to; right-sided heart failure, left-sided heart failure, congestive heart failure, coronary artery disease, arrhythmias, chronic heart failure, acute heart failure, etc.) h. Subjects unable to comply with the required study follow-up visits i. Pregnancy 3. The subject has comorbidities which, in the opinion of the investigator, will not be appropriate for the study or the subject has an estimated life expectancy of less than 6 months

	4. Any subject who is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity) 5. The subject has participated in any drug or device research study within 30 days of enrollment
Study Procedures and Assessments	**Pre-operative & Operative Assessments**: • Histories: Medical, Surgical, Medication • Urine Pregnancy test for females of child bearing potential (US only) • Intra-operative bleeding volume-volume of stomach juices and blood should be measured prior to stomach draining • Irrigant volume – volume to be recorded of operative field irrigant used during procedure • Operative time-time from the first incision to complete hemostasis of the tonsillar bed (excluding closing time) • Subjects will be followed for 2 weeks post tonsillectomy procedure. **Follow-up Assessments** (Form filled out by subject on post-operative days 1-7, 10 and 14): • Pain level • Analgesic consumption • Ability to return to normal diet • Ability to return to normal activity • Incidence of post-operative hemorrhage - any primary (≤24 hrs) and secondary (>24hrs) bleeding • Incidence of post-operative readmission
Safety Assessments	• Adverse events (AEs), Serious Adverse Events (SAEs), Adverse device effects (ADE) and Unanticipated serious adverse device effects (USADE) • Device deficiencies • Focal Infection
Statistics	• Pain levels will be captured at post-operative days 1-7, 10, and 14 for each subject. Paired tests may be used to test whether there is a mean change along the follow-up. • For operative time and intra-operative bleeding volume a sample value will be calculated. Incidence of post-operative

	hemorrhage and post-operative readmission will be summarized using frequency and percentages. This study does not have a statistically powered hypothesis. There will be no sample size calculations since the study is not hypothesis-driven. The number of enrolled subjects is pre-defined, and all the results will be summarized in a descriptive manner which will be further defined in the statistical analysis plan with the following measures utilized: • Mean, standard deviations, medians, minimum and maximum for quantitative variables. • Numbers and percentages for qualitative variables. The following aspects will be used to assess safety: • Adverse events (AEs), Serious Adverse Events (SAEs), Adverse device effects (ADE) and Unanticipated serious adverse device effects (USADE) • Device deficiencies • Focal Infection

4. Introduction

4.1. Background

Tonsillectomy is one of the most frequently performed otorhinolaryngologic procedures with more than 4.5 million procedures performed annually. Aside from the conventional technique of cold steel and electrocautery dissection, the introduction of numerous energy based tools and techniques allow for the simultaneous dissection and sealing of vessels, significantly improving safety and reducing the complications of the procedure (1-3). Generally thought of as safe and effective, energy based devices such as laser, Shaw scalpel, electrosurgical devices (needle, scissor, or knife), radiofrequency needle ablation device, thermal welding, and Coblator, use heat energy to denature protein, leading to vascular tamponade and hemostasis. Unfortunately, a byproduct of using this energy during surgery is the lateral heating of the surgical area, which can damage adjacent structures, delay wound healing, increase post-operative pain, and increase the subject's time to return to normal diet and activity (4).

In order to address these concerns, Covidien (Covidien LP is an indirect wholly owned subsidiary of Medtronic plc.) has developed BiZact™, a bipolar electrosurgical instrument intended for use in open surgical procedures, such as tonsillectomies, where ligation and division of vessels, tissue bundles and lymphatics is desired. BiZact™ is designed as a pistol grip radiofrequency (RF) sealer/dissector for use with vessels up to and including 3mm. Compatible with the already in use Valleylab™ (LS10) energy platform, BiZact™ employs bipolar electrosurgical RF energy and pressure to ligate vessels interposed between its jaws which can then be transected using the built in knife deployed by the device trigger. Based off

Ligasure™ technology, bipolar electrosurgical devices have been shown to be safe and effective for tonsillectomy procedures, providing adequate hemostasis while minimizing postoperative pain (5, 6).

In summary, biocompatibility testing and animal model studies have found BiZact™ to be safe and effective in achieving hemostasis and reducing lateral thermal spread potentially resulting in reduced post-operative pain. Full details of biocompatibility testing and prior investigations can be found in Section 4.3.

The primary objective of this study is to assess the severity of post-operative pain and return to normal diet and activity for up to 14 days following the use of the BiZact™ device in adult (≥22 years of age in United States and ≥18 years of age in Europe) tonsillectomy procedures. At the conclusion of this study, data will be used for publication.

4.2. Purpose

The purpose of this study is to assess the severity of post-operative pain following the use of the BiZact™ device in adult (≥22 years of age in United States and ≥18 years of age in Europe) tonsillectomy procedures.

The results of this study will be offered for publication at the conclusion of the study, if participating investigators believe the data warrants publication in an appropriate journal.

4.3. Report of Prior Investigations

4.3.1. Biocompatibility Evaluation

Biocompatibility testing for a device having tissue/bone/blood contact was conducted per ISO 10993: Biological evaluation of medical devices and met the necessary requirements. This testing was performed utilizing BiZact™ (BZ4112) and included cytotoxicity, sensitization and irritation, toxicity (acute) and hemo-compatibility testing.

4.3.2. Animal Evaluations

Table 1. Animal Trial Schematics

Study	Type and Number of Animals/ Study Duration	Methods/Summary	Endpoints	Results
Verification of the BiZact™ (BZ4112) Devices in an Acute	1 pig 204 seals total	One (1) female porcine underwent various procedures to assess acute sealing	• Intraoperative hemostasis	• The mean lateral thermal spread from the BiZact™ (BZ4112) device

Table 1. Animal Trial Schematics

Study	Type and Number of Animals/ Study Duration	Methods/Summary	Endpoints	Results
Hemostasis Porcine Study (RE00033410)	• 102 seals – BiZact™ (BZ4112) • 102 seals – LF1212 Duration • 1-day	performance by the BiZact™ (BZ4112) device as well as the LF1212 control device. Efficacy was defined by: • Mean lateral thermal spread • Time to hemostasis (TTH) Evaluations and records: • Clinical observations • Clinical pathology parameters • Body weight • Seal Evaluation • Histopathology / Thermal spread analysis	• Histopathology / Thermal spread analysis	was statistically lower than the predicate LF1212 device. • There was no statistical difference between the rate of hemostatic seals between BiZact™ (BZ4112) and the predicate LF1212 device.

Table 1. Animal Trial Schematics

Study	Type and Number of Animals/ Study Duration	Methods/Summary	Endpoints	Results
Verification of the BiZact™ (BZ4112) Devices in a Chronic Hemostasis Porcine Study (RE00030667)	6 pigs 245 seals total using BiZact™ (BZ4112) Duration 21-days	Six (6) female porcine underwent a total ovariohysterectomy and splenectomy in which as many appropriately sized vessels (4.0 mm and smaller) as possible were sealed. Efficacy was defined by: • Long term seal quality over 21 days Evaluations and records: • Clinical observations • Clinical pathology parameters • Body weight • Gross observation of seal at time of necropsy	• Gross observation of seal at time of necropsy	• At necropsy chronic hemostasis was confirmed and there was no evidence of post-operative bleeding, peritoneal cavity hematoma formation, or free intraperitoneal blood in any of the six animals.
Verification of the BiZact™ (BZ4112) Devices in a Fresh Renal Burst Pressure Study (RE00031977)	118 porcine renal artery seals 60 seals - BiZact™ (BZ4112) 58 seals – LF1212	Freshly excised renal arteries underwent ligation and resection with either BiZact™ (BZ4112) or the control LF1212. Burst pressure (mmHg) was then monitored Efficacy was defined by: • Number of bursts • Burst Pressure	• Number of bursts • Burst Pressure	• There was no statistical difference in sealing performance between BiZact™ (BZ4112) and the control LF1212. • BiZact™ (BZ4112) had a statistically significant faster renal activation time than the

Table 1. Animal Trial Schematics

Study	Type and Number of Animals/ Study Duration	Methods/Summary	Endpoints	Results
		Evaluations and records: • Vessel size • Total Bursts • Burst pressure (mmHg)		LF1212 control device.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The primary objective of this study is to assess the severity of post-operative pain following the use of the BiZact™ device in adult (≥22 years of age in United States and ≥18 years of age in Europe) tonsillectomy procedures using the Visual Analogue Scale (VAS) at days 1 through 7, 10 and 14.

5.1.2. Secondary Objective(s)

The secondary objective of this study is to assess intra-operative bleeding volume, and ability to return to normal diet and activity up to 14 days post-operative.

5.2. Endpoints

5.2.1. Primary Endpoint

The primary endpoint will be post-operative pain level measured using the VAS at days 1 through 7, 10 and 14.

5.2.2. Secondary Endpoint(s)

- Analgesic consumption
- Ability to return to normal diet (days 1-7, 10, 14)
- Ability to return to normal activity (days 1-7, 10, 14)
- Incidence of post-operative hemorrhage
- Primary (≤24 hrs) bleeding and
- Secondary (>24hrs) bleeding
- Incidence of post-operative readmission
- Intra-operative bleeding volume- volume of stomach juices and blood should be measured prior to stomach draining
- Irrigant volume – volume to be recorded of operative field irrigant used during procedure
- Operative time - time from the first incision to complete hemostasis of the tonsillar bed

5.2.3. Safety Endpoints

- Adverse events (AEs), Serious Adverse Events (SAEs), Adverse device effects (ADE) and Unanticipated serious adverse device effects (USADE)
- Device deficiencies
- Focal Infection

6. Study Design

6.1. Duration

Including enrollment and follow up time, the current study is estimated to progress for up to 1 year. During this time subjects will be pre-screened for the study up to 30 days prior to the procedure. Post-procedure, subjects will be assessed for pain and their ability to return to normal diet and activity via Visual Analog Scale (VAS) and Quality of Life (QoL) questionnaire (EORTC QLQ – H&N35) at days 1 through 7, 10 and 14. These materials can be found in Appendices A and B.

6.2. Rationale

In order to demonstrate the clinical use of BiZact™ (BZ4112) effects post-operative pain and return to normal diet and activity after standard tonsillectomy procedure, Medtronic is performing a prospective, multi-center, single arm non-comparative pilot study of BiZact™ on adults (≥22 years of age in United States and ≥18 years of age in Europe) undergoing tonsillectomy. Post-operative pain, and other quality of life aspects will be collected via questionnaire for up to 14 days following the procedure. As a study with no comparator this study does not utilize any randomization or blinding. The BiZact™ device will only be used during the course of the tonsillectomy procedure and subjects will be followed for up to 14 days to monitor bleeding, pain and return to normal diet and activity. Currently there are no known factors

that may compromise study outcomes or the interpretation of results (*e.g.*, baseline characteristics, concomitant medications, the use of other study products, or subject-related factors such as age, gender or lifestyle). If any adverse occurrences are identified they will be assessed, reported and documented.

7. Product Description

7.1. General

The BiZact™ (BZ4112) is a single use bipolar electrosurgical instrument intended for use with the Valleylab™ (LS10 with V1.1 or V1.2 software) energy platform in general open surgical procedures. It is also indicated for adult ENT procedures, including tonsillectomy, for the ligation and division of vessels, tissue bundles and lymphatics 2-3 mm away from unintended thermally sensitive structures. This instrument creates tissue fusion by application of bipolar electrosurgical RF energy and pressure to vessels/tissue interposed between the jaws of the instrument. The tissue fusion can then be transected using the built in cutting mechanism. The instrument can be used for vessels and lymphatic tissue up to and including 3mm in diameter and tissue bundles. The instrument also incorporates inline RF activation, features for grasping and tips for dissection. The instrument is intended primarily for surgeons performing tonsillectomies. It is also indicated for adult ear, nose and throat (ENT) procedures, including tonsillectomy, for the ligation and division of vessels, tissue bundles and lymphatics 2-3 mm away from unintended thermally sensitive structures.

See Instructions for Use for additional information.

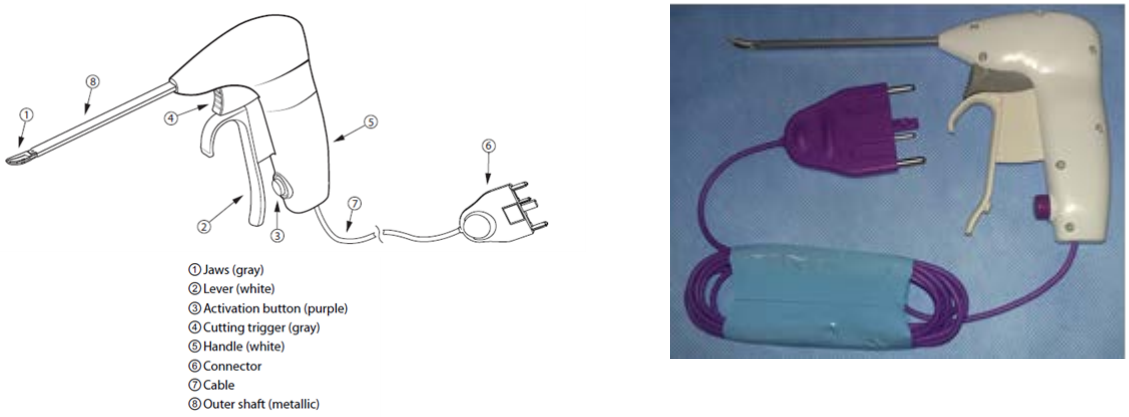

Figure 1: BiZact™ (BZ4112) schematic diagram (left), and device photo (right)

BiZact™ is a pistol grip RF-based sealer/dissectors similar (design, technology and materials) to current Ligasure™ devices. Similar to its predicate device LF1212 (Ligasure™ small jaw), BiZact™ includes a jaw, a deploying knife, a lever to open and close the jaws, and a trigger to deploy the knife and inline activation

of bipolar energy. The device does not include a rotation knob for rotating the jaws, but the device does allow surgeons to perform procedures by switching hands. BiZact™ is compatible with the Valleylab™ (LS10 with V1.1 or V1.2 software) energy platform, which is able to recognize the device utilizing RFID identification capabilities. In total, 96 BiZact™ units will be assigned to this study to account for any situations in which more than one device is needed.

7.2. Dosage Form and Route of Administration

Not applicable.

7.3. Manufacturer

BiZact™ is manufactured by Covidien (Covidien LP is an indirect wholly owned subsidiary of Medtronic plc.).

7.4. Packaging

Each instrument is individually packaged in a single-use polyethylene terephthalate glycol (PETG) tray and sealed with Tyvek lid. Six sealed trays are packaged in one shipper case.

7.5. Intended Population

The BiZact™ (BZ4112) device is indicated for use in general open surgical procedures. The device is also indicated for adult ENT procedures, including tonsillectomy, for the ligation and division of vessels, tissue bundles and lymphatics.

7.6. Equipment

BiZact™ devices are single-use disposable products. For this study, BiZact™ will be used in combination with a Valleylab™ (LS10 with V1.1 or V1.2 software) energy platform. No maintenance or calibration of this equipment is required.

7.7. Product Use

The BiZact™ (BZ4112) is a single use bipolar electrosurgical instrument intended for use with the Valleylab™ (LS10 with V1.1 or V1.2 software) energy platform in general open surgical procedures. It is also indicated for adult ENT procedures, including tonsillectomy, for the ligation and division of vessels, tissue bundles and lymphatics 2-3 mm away from unintended thermally sensitive structures.

The BiZact™ device has not been shown to be effective for tubal sterilization or tubal coagulation for sterilization procedures and should not be used for these procedures.

7.8. Product Training Requirements

Each Investigator participating in the clinical trial and the associated clinical study staff will receive training on the clinical protocol, as well as the BiZact™ device. Investigators will be trained on device characteristics, shelf life and storage requirements, device use, and warnings, precautions, contraindications, etc.

7.9. Product Receipt and Tracking

BiZact™ and a Valleylab™ (LS10 with V1.1 or V1.2 software) energy platform will be shipped to each site and each site will document the date received, quantity, expiration date, model number and lot number of each product upon receipt. For each procedure, the serial number of the device being used will be recorded in the eCRF as well as the date of use and date of disposal or return.

7.10. Product Storage

The devices will be labeled "Exclusively for Clinical Investigations" and should be stored in a secure (locked) area under the appropriate storage conditions (room temperature). Access should be limited to designated study staff only.

7.11. Product Return

It is the site's responsibility to return the Valleylab™ (LS10) energy platform to Medtronic within 30 days of the End of Study as well as any unopened BiZact™ devices. Date of return should be documented in the eCRFs.

7.12. Product Accountability

BiZact™ and a Valleylab™ (LS10 with V1.1 or V1.2 software) energy platform will be provided to each site upon Sponsor collection and approval of all required regulatory documentation. Device accountability logs will be provided to the site. It is the site's responsibility to document the receipt (maintain shipping logs), disposition of the product (per subject use, including amount used, amount remaining, etc.), transfer (if applicable) and return of all unopened study devices.

8. Selection of Subjects

8.1. Study Population

A minimum of 48 adult subjects (males and females ≥22 years of age in United States and ≥18 years of age in Europe) undergoing tonsillectomy surgery will be enrolled in the study.

8.2. Subject Enrollment

After being informed of the nature of the study, the subject will provide written informed consent that has been approved by the sponsor and the appropriate IRB/EC of the respective clinical site. A minimum of 48 subjects will be enrolled in the study at up to 3 sites with competitive enrollment not to exceed 24 subjects per site. Subjects' participation in the study will last 14 days (+3) post procedure.

A subject is considered enrolled in the study when ICF is signed, and must be followed for the full 14 days follow-up regardless of whether or not the subject received treatment with the study device.

The procedure will be performed per the institution's standard practice. Subjects will be considered for the study if they meet specific preoperative and intraoperative inclusion/exclusion criteria. The criteria for enrollment must be followed explicitly.

8.3. Inclusion Criteria

Subjects are eligible to be enrolled in the study only if they meet **all** of the following inclusion criteria:

1. Adults (male or female) ≥22 in United States and ≥18 years of age in Europe years of age
2. Scheduled to undergo tonsillectomy
3. Signed informed consent by subject

8.4. Exclusion Criteria

Subjects will be excluded from the study if they meet **any** of the following exclusion criteria:

- Subjects undergoing;
- Simultaneous adenoidectomy
- Tonsillectomy as a result of cancer
- Unilateral tonsillectomy
- Current participation in other clinical trials
- Subjects with;
- Current tobacco use
- Known bleeding disorders
- History of peritonsillar abscess
- Craniofacial disorders
- Down syndrome (Trisomy 21)
- Cerebral palsy
- Major heart disease
- Subjects unable to comply with the required study follow-up visits
- Pregnancy

- The subject has comorbidities which, in the opinion of the investigator, will not be appropriate for the study or the subject has an estimated life expectancy of less than 6 months
- Any subject who is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity)
- The subject has participated in any drug or device research study within 30 days of enrollment that would interfere with this study

9. Study Procedures

9.1. Schedule of Events

9.1.1. Study Schematic

Subjects who meet the eligibility criteria will be considered for study participation. The schematic of the trial is presented in the table below.

Table 1: Study Schematic

	Screening / Baseline Day -30 to 0	Surgery (Day 0)	Post-Op Follow-Up Day 1 – Day 7 (Home)	Post-Op Follow-Up Day 10 (Home)	Post-Op Follow-Up Day 14 (+3 days)
Informed Consent Form[1]	X	x			x
Eligibility Criteria	x	x			
Urine pregnancy test (female Pts; US only)[2]	x	x			
Demographic data	x				
Medical history	x				
Surgical history	x				
Medication history	x				
Concomitant medications		x	x	x	X
Type of admission		x			
Physical Examination		x			
Intra-operative bleeding volume		x			
Tonsil measurement		x			
Surgical technique		x			
Operation time		x			
Device ease of use		x			
Dissection assessment		x			
Alternate device used (if any)		x			
Post-operative bleeding			x	x	x
AE, SAE, ADE, USADE Assessment & Device Deficiencies[3]		x	x	x	x
Readmission			x	x	x
QOL Home survey (EORTC QLQ – H&N35) • Ability to return to normal diet • Ability to return to normal activity			x	x	x
Pain via VAS scale (Appendix B)			x	x	x
Return to clinic follow-up visit					x
Return VAS and QoL questionnaire					x
Device accountability		x			
Protocol deviation collection	x	x			x

[1] No study procedures will be performed until informed consent form has been completed.
[2]Urine pregnancy test (US only): unless female subject is surgically sterile or postmenopausal for at least 2 years. Confirmed by PI judgment and subject signature and noted in medical history and eCRF.
[3]AEs/SAEs must be followed to resolution or 30 days post EOS, whichever is first.

9.1.2. Screening / Baseline Visit

A screening/baseline visit will be performed within 30 days up to/on the day of the scheduled procedure. Subjects will be consented prior to enrollment in the study before any procedures specific to the study are undertaken. The purpose and all aspects of the study will be explained to the subject. Subjects who

agree to study participation must sign and personally date the sponsor and an IRB/EC-approved informed consent form prior to participating in any study activities.
Once informed consent has been signed and eligibility is confirmed, the subject's demographics and medical history will be assessed to include: age, gender and weight.

- Relevant medical history will be assessed based on clinical condition categorized by category codes specified in the electronic case report form (eCRF).
- Female subjects will be assessed for childbearing potential, and if they do have childbearing potential, they will undergo a urine pregnancy test (US only). If the test is positive, they will be withdrawn from the study. If the pregnancy test is negative, these subjects should practice contraceptive methods through the course of the study. Additional urine pregnancy test will be performed on the day of surgery (US only). In Europe female subjects of childbearing potential will be asked pregnancy status. Women who respond as pregnant will not be included.

The following assessments will be performed within 30 days prior to the scheduled surgical procedure and the results recorded on the appropriate subject eCRFs:

- Verification of preoperative eligibility criteria
- Verification of surgical candidacy
- Demographic data
- Medical history, including concomitant medications and comorbidities
- Surgical history
- Medication history
- Pregnancy test, if applicable (US only)
- Concomitant medication(s)

  Note: All medications will be coded using the World Health Organization (WHO) drug coding dictionary.

9.1.3. Surgical Procedure (Day 0)

The Study Investigator should perform the surgical procedure according to the appropriate standard procedures and practices at his/her institution using BiZact™. BiZact™, in conjunction with other non-energy surgical tools (e.g. Allis clamp), should be used to complete the entire procedure unless it is medically necessary to use another device. Additionally, the following procedures and assessments will be performed:

- Type of admission
- AE/SAE assessment
- Pre-operative procedure specific physical examination
  - Including assessment of heart/lungs, neurological, ENT, immune system and vital signs (blood pressure, respiration rate, heart rate, temperature)

- Pregnancy test, if applicable (US only)
- Intra-operative bleeding volume
    - Record volume of any irrigant used
    - Record presence of gastric fluids
    - Record amount of fluid in suction container prior to stomach drainage
- Surgical performance parameters
    - Surgical technique
    - Operation time
    - Device ease of use
    - Dissection assessment
    - Other non-study device alternative procedural devices used (if any),
        - Operation time used
        - Tonsil location (Left/Right)
        - Reason for use
    - Tonsil size measurement (Measured via water displacement)
        - Using a graduated container that has 1mL markings, fill container to half full with water note mL level. Put the first tonsil into the water and record the mL level. The difference equals the volume of the first tonsil. Remove the first tonsil and note water level. Put the second tonsil into the water and record how much the water level rises. The difference equals the volume of the second tonsil.
- Device accountability
- Concomitant medications

    Note: All medications will be coded using the World Health Organization (WHO) drug coding dictionary.

9.1.4. Post-Operative Follow-up: Days 1 through 7, Day 10 and Day 14

Post-operative hospital stay and AE/SAE assessment will take place by delegated study personnel. Additionally, during post-operative days 1 through 7, day 10 and day 14 the following will be assessed via an at home survey form (EORTC QLQ – H&N35, Appendix A):

- Pain assessment
    - VAS (see Appendix B)
    - Consumption of recommended standard of care analgesic pain regimen;
        - 10 mg dose dexamethasone intra-operative
        - Ibuprofen 800 mg q8hrs
        - Hydrocodone/acetaminophen 10/325 mg q4 hrs PRN
        - Any modifications to recommended pain regimen will be noted in the eCRF
- Postoperative AEs and SAEs

- Readmission
- Ability to return to normal diet
- Ability to return to normal activity
- Day 14 (+3) days clinical visit for follow-up and to return VAS and QoL questionnaires
- Concomitant medications
- Post-operative bleeding – Any bleeding that occurs, from the presence of blood in saliva to bleeding that requires re-operation

9.2. Prior and Concomitant Medications

All concomitant medications will be managed by the investigator per their standard of care and will be recorded on the appropriate eCRFs from Screening/Baseline through end of study.

Consumption of recommended standard of care analgesic pain regimen post-procedure is as follows;

- 10 mg dose dexamethasone intra-operative
- Ibuprofen 800 mg q8hrs
- Hydrocodone/acetaminophen 10/325 mg q4 hrs PRN
- Any modifications to recommended pain regimen will be noted in the eCRF

9.3. Subject Consent

Subjects will be consented prior to enrollment in the study before any procedures specific to the study are undertaken. The principal investigator or his/her authorized designee will provide the subjects with a description of the device and procedure; risks, benefits, and alternative procedures; length of participation required; method and amount of compensation, if applicable; and information regarding injury and confidentiality with ample time given to consider their participation in the clinical study. Subjects will be informed that their participation in this study is voluntary and they may refuse to participate or discontinue from the study at any time. Subjects will be given the opportunity to ask the investigator questions so that they are adequately informed about the research. The informed consent form must be in a native non-technical language and must be personally signed and dated by subject and investigator at time of consent. The principal investigator or his/her authorized designee shall avoid any coercion or undue improper influence on, or inducement of, the subject to participate. The informed consent process will be documented in the source records and a copy of the consent will be provided to the subject.

If new information becomes available that may affect a subject's decision to continue to take part in the study, this information will be discussed with the subject by the investigator and new consent will be obtained in writing. A revised consent will be first reviewed and approved by Medtronic and the IRB/EC. The informed consent form must be personally signed and dated by subject and investigator at time of

consent. The informed consent process will be documented in the source records and a copy of the consent will be provided to the subject.

9.4. Randomization and Treatment Assignment

No randomization will occur during the course of the study.

9.5. Medication Compliance

A recommended standard of care analgesic pain regimen is listed in section (9.2). Compliance to this regimen will be monitored via the at home survey (EORTC QLQ – H&N35, Appendix A).

9.6. Assessment of Efficacy

Procedure time, pain relief, bleeding details patient outcomes and QOL will be recorded in the eCRF and used to assess efficacy of the BiZact™ device.

9.7. Assessment of Safety

Safety will be assessed by monitoring the occurrence of adverse events (AEs), serious adverse events (SAEs), death, adverse device effects (ADE), unanticipated serious adverse device effects (USADE), device deficiencies or the presence of focal infection. Assessments will take place during the procedure through post-operative day 14 and will be recorded in the eCRF.

9.8. Recording Data

This study will utilize an electronic database and eCRF. All data requested on the eCRF are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified. The Principal Investigator or authorized designee(s) must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate eCRFs. The Investigator's electronic signature for specific eCRFs will be documented in compliance with local regulations. Changes to data previously submitted to the sponsor will require a new electronic signature by the Investigator to acknowledge/approve the changes.

9.9. Deviation Handling

A study deviation is an event where the Investigator or site personnel did not conduct the clinical study according to the Clinical Investigational Plan or Clinical Investigation Agreement. The Investigator is not allowed to deviate from the above-mentioned documents except under emergency circumstances to protect the rights, safety and well-being of human subjects. No changes to the protocol will be permitted without the written approval from Medtronic, the IRB/EC and Competent Authority. The investigator must

notify Medtronic and the reviewing IRB/EC of any deviation, which will be recorded in the eCRF, from the Investigational Plan when specific to the protection of the life or physical well-being of a subject in an emergency. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency has occurred. Except in such an emergency, prior written approval by Medtronic is required for changes in or deviations from the Investigational Plan. If these changes or deviations affect the scientific soundness of the Investigational Plan or the rights, safety, or welfare of human subjects the IRB/EC will also be notified. All other deviations will be reported per the site's IRB/EC deviation policy. Should any deviations from the Investigational Plan occur, these will be reviewed by Medtronic for their clinical significance and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases, freeze enrolment or ultimately terminate the Investigator's participation in the clinical study.

9.10.Screen Failure

A subject is considered enrolled in the study when ICF is signed, and must be followed regardless of whether or not the subject received treatment with the study device unless considered a screen failure or withdrawn due to physician decision. Subjects who provide study consent, but then are determined to be ineligible prior to study procedure will be considered a screen failure and will not require additional study follow-up visits. The reason for the screening failure will be clearly delineated on the applicable eCRFs.

Subjects in whom the procedure is begun but not completed will be considered "discontinued" and will be followed until discharge. These subjects will only contribute AE data intraoperatively until discharge (no additional follow-up).

9.11.Subject Withdrawal or Discontinuation

The reason for study exit, including screen failure, will be documented on the applicable electronic case report form (eCRF). In the event the subject withdraws consent during the study, the date of withdrawal will be documented. If the Study Investigator voluntarily removes a subject from further study participation, supporting documentation must be in place for the rationale and date of removal. Follow up to subjects withdrawn or discontinued will be deemed by the standard of care for a standard tonsillectomy procedure. Every attempt will be made to contact subjects that are noncompliant with study procedures. Subjects will be considered lost to follow-up once the following steps have been taken:

- Two phone calls should be made to the subject. Each attempt should be clearly documented in the source documents and the response or lack thereof should be captured.

- If there is no response to the phone calls, then an official, certified letter should be written to the subject. A copy of the letter and return or delivery receipts should be retained in the subject's source document.
- Additionally, the site should attempt to reach out to the primary care practitioner to determine the status of the subject.
- When all due diligence attempts to contact have been made, after a period of two (2) weeks, the subject will be considered Lost to Follow-up. The Sponsor should be notified and the End of Study (EOS) form should be completed.

9.12. Selection of Investigators

Surgeons who are qualified by training (board certified in otolaryngology in accordance with US/European and hospital guidelines), education, and relevant experience appropriate to the use of the product and associated procedures will be considered for participation as investigators in this study. Investigators/sites must have adequate time and resources to conduct the study throughout the duration of the study and have access to an adequate number of eligible subjects. Investigators/sites must be able to comply with applicable Institutional Review Board (IRB)/Ethics Committee (EC) and regulatory requirements. Investigator is not debarred, disqualified, or working under sanctions in applicable regions. Qualifications are verified through valid CV and current licensing and maintained with study documentation.

10. Risks and Benefits

10.1. Potential Risks

The potential risks associated with the standard tonsillectomy procedure include but are not limited to: reaction to anesthesia, swelling, bleeding, infection and pain.

The potential risks associated with BiZact™ include, but are not limited to: unintended cutting or bruising, arcing, pinching, tearing of tissue, inadequate/no seal, pain, bleeding, nausea, vomiting, and headache. Results from preclinical testing and the instructions for use (IFU) will be used to mitigate risk.

Reproductive and developmental toxicology studies in animals to evaluate the potential for AEs on reproductive ability and effects on the embryo/fetus have not been conducted. As with any device, there is always a risk of a rare or previously unknown side effect developing from the treatment.

The risk analysis assumes the system is operated by properly trained personnel. The overall residual risk after design risk mitigation strategies and/or design control was deemed acceptable in the Risk Management Report for the BiZact™ system.

10.2. Potential Benefits

The potential benefits associated with BiZact™ device usage include, but are not limited to: reduction in pain and decreased time to return to normal diet and activity post tonsillectomy procedure.

10.3. Risk-Benefit Rationale

Post-operative pain and delayed time to normal diet and activity are common challenges after tonsillectomy procedures. Aside from conventional cold steel and electrocautery dissection, the introduction of numerous energy based tools and techniques allow for the simultaneous dissection and sealing of vessels significantly improving safety and reducing the complications of the procedure. In most cases however, these energy based devices use heat to establish hemostasis, which can lead to lateral heating and damage to adjacent structures delaying wound healing and increasing post-operative pain.

A positive risk/benefit ratio has been demonstrated with BiZact™ as evidenced by preclinical and biocompatibility testing. BiZact™ was safely tolerated in animals and there were no apparent adverse systemic or local effects in any of the preclinical studies. BiZact™ is also based off Ligasure™ technology which historically has been shown to be safe and effective for tonsillectomy procedures providing adequate hemostasis while minimizing postoperative pain.

The product design, as well as the results of these studies, shows that BiZact™ is a promising class 2 FDA and CE-mark approved product. Consequently, with respect to performance and safety, BiZact™ presents a favorable risk/benefit ratio to the subject. Results from preclinical testing, the device instructions for use (IFU) and experienced surgeons will be used to mitigate risk. There are currently no known interactions between the BiZact™ device and concurrent medical interventions.

11. Adverse Events and Device Deficiencies

Adverse event (AE) definitions used in this study are based on ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice).

11.1. Definitions/Classifications

11.1.1. Adverse Event (AE)

In alignment with ISO 14155:2011 (Section 3.2), an Adverse Event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

This definition includes events related to the investigational medical device and the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

For study purposes, the following occurrences are considered to be expected observations and will not be considered reportable Adverse Events, as long as the event is not associated with significant sequelae, does not prolong hospitalization and responds to standard medical therapy:

- Postoperative transient nausea determined to be procedure and/or medication related.
- Postoperative transient emesis determined to be procedure and/or medication related.
- Postoperative inflammation determined to be a part of every healing process.
- Postoperative headaches determined to be procedure and/or medication related.
- Postoperative constipation determined to be procedure and/or medication related.
- Postoperative pain that the Investigator considers common and within normal limits for the procedure and is well-managed with medication.
    - Pain that the investigator considers outside normal, or is not well-managed with medication, as well as pain that is severe (score 7 or higher on the VAS) and ongoing at the end of study will be reported as an AE in the eCRFs.

AEs will be collected and documented at baseline and 0 to 14 days follow-up.

11.1.2. Serious Adverse Event (SAE)

In alignment with ISO 14155:2011 (Section 3.37), a serious adverse event (SAE) is any AE that has:

- led to death,
- led to serious deterioration in the health of the subject that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
- led to fetal distress, fetal death, or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered an SAE.

SAEs will be collected and documented at baseline and 0 to 14 days follow-up.

11.1.3. Adverse Device Effect (ADE)

In alignment with ISO 14155:2011 (Section 3.1), an Adverse Device Effect is an adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse Device Effects will be reported by the Investigator(s). If escalation is required, ADEs will be reviewed by medical affairs as part of Medtronic's Post-Market Vigilance program. Both confirmed and possible device related events will be included in the study report.

Examples of adverse device effects include but are not limited to: unintended cutting, unintended electrical path, fire or explosion, or arching.

ADEs will be collected and documented at baseline and 0 to 14 days follow-up.

11.1.4. Serious Adverse Device Effect (SADE)

In alignment with ISO 14155:2011 (Section 3.36), a Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

SADEs will be collected and documented at baseline and 0 to 14 days follow-up.

11.1.5. Unanticipated Serious Adverse Device Effect (USADE)

In alignment with ISO 14155:2011 (Section 3.42), an Unanticipated Serious Adverse Device Effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

USADEs will be collected and documented at baseline and 0 to 14 days follow-up.

11.1.6. Adverse Event Severity Classification

Severity will be defined according to the following criteria:

Mild	Awareness of event, but easily tolerated
Moderate	Discomfort enough to cause some interference with activities of daily living (ADL)
Severe	Incapacitating, with an inability to perform ADL
Death	Death related to AE

An AE can be classified as severe and not deemed an SAE. Similarly, an SAE is not automatically severe in nature.

11.1.7. Adverse Event Relationship Classification

Causality assessments define the relationship between the use of the medical device (including the medical-surgical procedure) and the occurrence of each adverse event, according to MEDDEV (Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting). The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to **the investigational medical device or procedures**:

Not related: relationship to the device or procedures can be excluded when:

1. the event is not a known side effect of the product category the device belongs to or of similar devices and procedures
2. the event has no temporal relationship with the use of the device or the procedures;
3. the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
4. the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
5. the event involves a body-site or an organ not expected to be affected by the device or procedure;
6. the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
7. the event does not depend on a false result given by the device used for diagnosis, when applicable;
8. harms to the subject are not clearly due to use error;

9. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the serious event is associated with the device or with procedures beyond reasonable doubt when:

1. the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
2. the event has a temporal relationship with device use/application or procedures;
3. the event involves a body-site or organ that
    a. the device or procedures are applied to;
    b. the device or procedures have an effect on;
4. the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
5. the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
6. other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
7. harm to the subject is due to error in use;
8. the event depends on a false result given by the device used for diagnosis, when applicable;
9. In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Sponsor and the Investigators will distinguish between the serious adverse events related to the device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the subjects also in the absence of device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as "possible".

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

11.1.8. Adverse Event Outcome Classification

Outcome of the event will be defined according to the following:

- ***Fatal:*** This event is determined to be the cause of death.
- ***Not Recovering/Not Resolved***: The event has retained pathological conditions resulting from the prior disease or injury.
- ***Recovered/Resolved:*** The event has fully resolved at the end of the study.
- ***Recovering/Resolving:*** The event is ongoing at the end of the study.
- ***Unknown***: The event has been unclassified at the end of the study.

11.2. Reporting of Adverse Events

The following events are generally considered reportable during the course of this study and should be reported in a timely manner to the sponsor:

- any ADE, SADE, SAE, or USADE
- any Device Deficiency that might have led to an SADE if
- suitable action had not been taken or
- intervention had not been made or
- if circumstances had been less fortunate
- new findings/updates in relation to already reported events

Events will be reviewed by the sponsor to determine any reporting obligations to National Competent Authorities and IRBs/ECs.

SAEs need to be reported to the sponsor within 24 hours of becoming aware.

11.3.Adverse Event Recording

Assessment of the occurrence of an AE will be based on changes in the subject's physical examination, laboratory results and/or signs and symptoms. Adverse events will be monitored until a subject completes the study unless the Investigator determines the event is related to the device, in which case they will be monitored until resolution if possible. Medical care will be provided, as defined in the informed consent, for any AE related to study participation. Adverse events will be collected on an AE eCRF and applicable source documentation. To the extent possible, the event to be recorded and reported is the event diagnosis as opposed to event symptoms (e.g., fever, chills, nausea and vomiting in the presence of a clinically diagnosed infection is to be reported as infection only). For the purposes of this protocol, AEs will collected and documented in a timely manner at baseline and 0 to 14 days follow-up.

The following should not be considered an AE:

- A condition requiring a preplanned procedure unless the condition worsened since screening
- A preexisting condition found as a result of screening, unless the condition has worsened since enrollment.

All responses to the above events that require treatment beyond the institution's standard procedures will be reported as AEs.

All AEs observed during the course of this study, regardless of severity or relationship to the device will be recorded on the appropriate eCRF except for what is noted in Section 11.1.1.

11.4. Study Contact Information

Questions regarding safety or medical procedures should be directed to Medtronic MITG Medical Affairs. All other questions should be directed to Medtronic MITG Surgical Innovations, Clinical Research.

Clinical Research	Medical Affairs
Kelley Kennedy Director, Clinical Research Medtronic MITG Surgical Innovations 555 Long Wharf Drive New Haven, CT 06511 USA Phone: (001 if Ex-US) 203-821-4743 Kelley.e.Kennedy@Medtronic.com	Matthew Savary, MD Associate Director of Medical Affairs Medtronic MITG Surgical Innovations 5920 Longbow Dr. Boulder, CO 80301 USA Phone: (001 if Ex-US) 203-530-1395 Matthew.Savary@medtronic.com

11.5. Device Deficiencies

In alignment with ISO14155:2011 (Section 3.15), a Device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

All BiZact™ device deficiencies will be documented on the appropriate Device malfunction eCRF and the device should be returned to Medtronic for analysis, if possible. Instructions for returning the device will be provided. Device deficiencies should also be documented in the subject's medical record.

Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate eCRF.

12. Data Review Committees

There will be no use of data review committees in this study. Instead, a steering committee and an internal safety review committee will monitor the trial's progress including trends of data over time and scientific relevance of the data collected. Please see section 15.10 on the review of data for this study. These groups will provide oversight in terms of scientific validity and the safe conduct of the study.

By nature, this study's focus is about the level of post-operative pain. Additionally, this is a study of two sites with forty-eight subjects, with no planned interim analysis, and as such, has a less burden in terms of severity of implications, and degree of data review and analysis compared to a larger study with interim data review needs or a study focusing on severe complications or mortality. Per FDA guidance (OMB Control No 0910-0581 "The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors" Data Monitoring Committees (DMCs) are "generally

recommended for any controlled trial of any size that will compare rates of mortality or major morbidity but a DMC is not required or recommended for most clinical studies." The guidance goes on to list conditions wherein a DMC may offer additional protections to study participants. This study does not meet any of the criteria listed wherein a DMC would provide added benefit.

13. Statistical Design and Methods

13.1. Statistical Test Methods

Continuous variables will be summarized using counts, means, standard deviations, medians, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. Changes to the planned statistical analysis as defined in the protocol will be documented in the statistical analysis plan and clinical study report.

13.2. Sample Size Determination

This study does not have a statistically powered hypothesis. There will be no sample size calculations since the study is not hypothesis-driven. The number of enrolled subjects is pre-defined at a minimum of 48, which is adequate to reflect the study purposes. All the results will be summarized in a descriptive manner which will be further defined in the statistical analysis plan with the following measures utilized:

- Mean, standard deviations, medians, minimum and maximum for quantitative variables.
- Numbers and percentages for qualitative variables.

13.3. Analysis Populations

The analyses will be done based on the subjects who are enrolled and have the intended procedure.

13.4. Statistical Analysis of Endpoints

13.4.1. Primary Endpoint

To assess pain, pain levels will be captured at post-operative days 1-7, 10, and 14 for each subject using the VAS. For each defined post-operative time point, paired tests will be used to test whether there is a mean change along the follow-up.

13.4.2. Secondary Endpoints

To assess procedure details, operative time and intra-operative bleeding volume a sample value and margin of error (95% confidence level) will be calculated.

Incidence of post-operative hemorrhage, and post-operative readmission will be summarized using frequency and percentages.

13.5. Statistical Analyses of Safety Endpoints

- Focal Infection
- Other intra/post-operative complications (complications related to device deficiency)
- Incidence and severity of adverse events

13.6. Handling of Missing Data

No data imputation will be performed for missing data. All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. Since endpoints are assessed intra-operatively, it is anticipated that there will be minimal missing data for these endpoints.

13.7. Interim Analysis

Currently no interim analysis is planned for this study however this is subject to change.

14. Ethics

14.1. Statement(s) of Compliance

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki 2013, the clinical trial agreement and any regional or national regulations such as FDA regulations (US) or ISO 14155:2011 (EU), as appropriate. All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the patient informed consent process, IRB/EC approval, clinical study training, clinical study registration, publication policy.
The clinical investigation will not begin until all necessary approvals/favorable opinions are obtained from the appropriate IRB/EC or regulatory authority, as appropriate. Should an IRB/EC or regulatory authority impose any additional requirements, they will be followed. Information regarding the study and study data will be made available via publication on clintrials.gov.

15. Study Administration

15.1. Monitoring

Site visits will be conducted by an authorized Medtronic representative to monitor study data, subjects' medical records, and eCRFs in accordance with current applicable regulations and standards and the

respective local and national regulations and guidelines (if applicable). The Study Investigator and the investigating site will permit authorized clinical research personnel and clinical monitors employed by Medtronic to review completed eCRFs, IRB/EC decisions, and Investigator and clinical site records at regular intervals throughout the study as well as permit study-related monitoring, audits, IRB/EC review, and regulatory inspection(s) by providing direct access to source data/documents. Additionally, subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. In instances where data protection regulations prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor. Monitoring, including site initiation visits, interim monitoring visits, and closeout visits may be performed with in person visits or remotely, when applicable.

To ensure the rights, safety, and welfare of study subjects are being maintained, the monitor will maintain assurance that all study staff are trained on the study protocol and use of the study devices. If the monitor discovers that an investigator is not complying with the signed Investigator Agreement, the Investigational Plan, applicable laws, or any conditions of approval imposed by the reviewing IRB/EC, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, device shipments to the investigator may be discontinued and the investigator's participation in the investigation terminated. The monitor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

15.2. Data Management

Visual and/or computer data review will be performed to identify possible data discrepancies. The investigator will clearly mark clinical record to indicate that the subject is enrolled in this clinical investigation (in regions where applicable). Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document. Manual and/or automatic queries will be created in the Oracle remote data capture (RDC) system and will be issued to the site for appropriate response. The site staff will be responsible for resolving all queries in the database. Medications will be coded under the WHO dictionary while Medical History, Surgical History and/or Adverse Events will be coded in Medical Dictionary for Regulatory Activities (MedDRA).

This study will be using a 21 CFR Part 11 compliant electronic data capture system. All system level validation documentation is retained within the Information Systems group.

15.3. Direct Access to Source Data/Documents

Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/EC review, and regulatory inspection(s), and provide direct access to source data/documents as per local policies and regulations.

15.4. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will be kept confidential. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated. In cases were the local law does not allow using the subject initials, an identifying number will be assigned. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, IRBs/ECs, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. Subjects will also be informed that information regarding the study that does not include subject identifiers will be posted on clinicaltrials.gov.

If the results of the trial are published, the subject's identity will remain confidential.

The investigator will maintain a master list to enable subjects' records to be identified.

15.5. Liability

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC.

Covidien Services Europe is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC.

15.6. CIP Amendments

A CIP amendment will be prepared when there are revisions that are significant changes or corrections, or modifications that impact subject safety, ethical conduct, data integrity or trial design. CIP amendments must undergo review and approval by the sponsor, IRB/EC and any appropriate regulatory authority, and will be logged in the document version history (Section 18). IRB/EC approval, regulatory authority

approval, site training and a new Acknowledgement form will be signed and returned before any new procedures take place.

15.7. Record Retention

The investigator and the sponsor will maintain the records of the study including all pertinent correspondence, the study protocol with any/all amendments, all correspondence with and approval from the IRB/EC, the clinical trial agreement, the Investigator Agreement, device accountability records, individual subject records, and signed informed consent forms. Subject files, other source data and essential documentation kept in the Investigator study files, must be kept for a period of not less than 2 years after the latter of the following two dates: the date on which this investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket application. Records may need to be maintained by the Principal Investigator for a longer duration if national regulations require or if agreed to in writing with Medtronic. All data and documents should be made available if requested by relevant authorities.

15.8. Publication and Use of Information

The Medtronic Publication and Authorship Policy is aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). Medtronic will seek to publish, in appropriate peer-reviewed journals and scientific conferences, results of clinical studies where human subjects are involved, regardless of outcome. While study results are owned by Medtronic, all data on which a publication is based will be made available to all authors as required for their participation in the publication process. Furthermore, data may be published or used by study investigators provided that such publication or use is in accordance with this this protocol, the Medtronic Publication and Authorship Policy, and the Clinical Investigation Agreement. Investigators must submit a copy of all manuscripts and/or abstracts to Medtronic for review and comment 30 days prior to planned submission. Medtronic acknowledges that its right to review and comment shall relate solely to the proprietary, licensing, and/or confidential rights Medtronic may have in such proposed publication, rather than whether such results and/or opinions are favorable to Medtronic.

The publication of post-hoc analyses, regional results, or single-center experiences based on multicenter clinical studies should not precede that of the primary multicenter publication, and should cite the primary publication whenever possible, as required by specific journal and scientific meeting guidelines.

Medtronic involvement in a publication (e.g., funding of the study; sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be disclosed according to journal-specific policies, submission requirements, and prevailing editorial standards, in addition to those specified by International Committee of Medical Journal Editors. Authors must ensure that an

acknowledgement/disclosure statement is included in the body of the manuscript for Medtronic to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal/conference requirements.

To enable health care providers, payers, and subjects access to the wealth of Medtronic's research, Medtronic will report its scientific data in accordance with the principles outlined in the Guidance Document on Registration and Reporting Results of Company-Sponsored Clinical Trials Under FDAAA 2007 (Title VIII).

15.9. Suspension or Early Termination

Medtronic or appropriate regulatory authorities reserve the right to suspend or discontinue the study at any stage, with written notice to all investigators, all institutions, all reviewing IRBs (US), any investigator(s) in communication with the EC (EU), all subjects and subjects' personal physicians and any applicable regulatory agencies. Similarly, investigators may withdraw from the study at any time, subject to providing written notification to Medtronic 30 days prior to the date they intend to withdraw. However, Medtronic and investigators will be bound by their obligation to complete the follow-up of subjects already participating in the study. The subjects must be followed according to the clinical protocol, and information obtained during subject follow-up shall be reported to Medtronic on the appropriate eCRF.

15.10. Safety Committees

The Sponsor will employ a comprehensive safety plan for this study comprised of the following components: Independent Medical Monitor and Steering Committee.

15.10.1. Independent Medical Monitor

The Sponsor will utilize an Independent Medical Monitor to provide an independent medical review and adjudication of pre-specified adverse events in support of protocol defined endpoint data. The Independent Medical Monitor will be a qualified, board-certified otolaryngology surgeon that is not affiliated with an investigative center.

During the review of adverse events, the Independent Medical Monitor will be blinded to the treatment and investigational site.

15.10.2. Steering Committee

The Steering Committee will consist of Investigators participating in this study, as well as relevant members of Medtronic Clinical and Medical Affairs. The role of the Steering Committee is to make recommendations on the design and conduct of the study, the analysis of data, and the communication

of results in alignment with the Medtronic Publication and Authorship Policy. The Steering Committee will also review aggregate adverse event data on an as needed basis, as described in the Steering Committee Charter.

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17. Appendices

17.1. APPENDIX A: Post-operative home survey forms

Subjects will receive a minimum of 9 copies of the following survey, and be asked to fill out the survey on post-operative days 1-7, 10 and 14 to assess their return to normal diet and activity. All surveys will be returned during their 14 day post-operative follow-up visit.

17.1.1. EORTC QLQ-H&N35 (English)

ENGLISH

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had a painful throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you choked when swallowing?	1	2	3	4
39. Have you had problems with your teeth?	1	2	3	4
40. Have you had problems opening your mouth wide?	1	2	3	4
41. Have you had a dry mouth?	1	2	3	4
42. Have you had sticky saliva?	1	2	3	4
43. Have you had problems with your sense of smell?	1	2	3	4
44. Have you had problems with your sense of taste?	1	2	3	4
45. Have you coughed?	1	2	3	4
46. Have you been hoarse?	1	2	3	4
47. Have you felt ill?	1	2	3	4
48. Has your appearance bothered you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you had trouble eating?	1	2	3	4
50. Have you had trouble eating in front of your family?	1	2	3	4
51. Have you had trouble eating in front of other people?	1	2	3	4
52. Have you had trouble enjoying your meals?	1	2	3	4
53. Have you had trouble talking to other people?	1	2	3	4
54. Have you had trouble talking on the telephone?	1	2	3	4
55. Have you had trouble having social contact with your family?	1	2	3	4
56. Have you had trouble having social contact with friends?	1	2	3	4
57. Have you had trouble going out in public?	1	2	3	4
58. Have you had trouble having physical contact with family or friends?	1	2	3	4
59. Have you felt less interest in sex?	1	2	3	4
60. Have you felt less sexual enjoyment?	1	2	3	4

During the past week:	No	Yes
61. Have you used pain-killers?	1	2
62. Have you taken any nutritional supplements (excluding vitamins)?	1	2
63. Have you used a feeding tube?	1	2
64. Have you lost weight?	1	2
65. Have you gained weight?	1	2

17.1.2. EORTC QLQ-H&N35 (Spanish)

SPANISH

EORTC QLQ - H&N35

Los pacientes a veces dicen que tienen los siguientes síntomas o problemas. Por favor, indique hasta qué punto ha experimentado usted estos síntomas o problemas durante la semana pasada. Por favor, responda rodeando con un círculo el número que mejor se aplique a su caso.

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
31. ¿Ha tenido alguna molestia en su boca ?	1	2	3	4
32. ¿Ha sentido dolor en su mandíbula ?	1	2	3	4
33. ¿Ha tenido su boca irritada ?	1	2	3	4
34. ¿Ha tenido un dolor fuerte en la garganta ?	1	2	3	4
35. ¿Ha tenido problemas al tragar líquidos ?	1	2	3	4
36. ¿Ha tenido problemas al tragar alimentos en puré ?	1	2	3	4
37. ¿Ha tenido problemas al tragar alimentos sólidos ?	1	2	3	4
38. ¿Se ha atragantado cuando tragaba ?	1	2	3	4
39. ¿Ha tenido problemas con sus dientes ?	1	2	3	4
40. ¿Ha tenido problemas al abrir mucho su boca ?	1	2	3	4
41. ¿Ha tenido la boca seca ?	1	2	3	4
42. ¿Ha tenido la saliva pegajosa ?	1	2	3	4
43. ¿Ha tenido problemas con su sentido del olfato ?	1	2	3	4
44. ¿Ha tenido problemas con su sentido del gusto ?	1	2	3	4
45. ¿Ha tosido ?	1	2	3	4
46. ¿Ha estado ronco/a ?	1	2	3	4
47. ¿Se ha sentido enfermo/a ?	1	2	3	4
48. ¿Se le ha hecho molesto su aspecto ?	1	2	3	4

Por favor, continúe en la página siguiente

SPANISH

Durante la semana pasada:	En absoluto	Un poco	Bastante	Mucho
49. ¿Ha tenido dificultad al comer ?	1	2	3	4
50. ¿Ha tenido dificultad al comer delante de su familia?	1	2	3	4
51. ¿Ha tenido dificultad al comer delante de otras personas ?	1	2	3	4
52. ¿Ha tenido dificultad al disfrutar de sus comidas ?	1	2	3	4
53. ¿Ha tenido dificultad al hablar con otras personas ?	1	2	3	4
54. ¿Ha tenido dificultad al hablar por teléfono ?	1	2	3	4
55. ¿Ha tenido dificultad al relacionarse con su familia?	1	2	3	4
56. ¿Ha tenido dificultad al relacionarse con sus amigos?	1	2	3	4
57. ¿Ha tenido dificultad al salir en público ?	1	2	3	4
58. ¿Ha tenido dificultad al tener contacto físico con su familia o amigos ?	1	2	3	4
59. ¿Ha sentido menos interés en el sexo ?	1	2	3	4
60. ¿Ha disfrutado menos con el sexo ?	1	2	3	4

Durante la semana pasada:	No	Sí
61. ¿Ha tomado medicinas para el dolor ?	1	2
62. ¿Ha tomado algún suplemento nutritivo (excluyendo vitaminas) ?	1	2
63. ¿Ha utilizado un tubo de alimentación ?	1	2
64. ¿Ha perdido peso ?	1	2
65. ¿Ha ganado peso ?	1	2

17.1.3. EORTC QLQ-H&N35 (Swedish)

SVENSKA

EORTC QLQ - H&N35

Patienter rapporterar ibland att de har följande symptom eller problem. Ange i vilken utsträckning du har upplevt dessa symtom eller problem under den senaste veckan. Svara genom att ringa in den siffra som bäst passar in på dig.

Under den senaste veckan:		Inte alls	Lite	Ganska mycket	Väldigt mycket
31.	Har du känt smärta i munnen?	1	2	3	4
32.	Har du känt smärta i käkarna?	1	2	3	4
33.	Har du varit öm i munnen?	1	2	3	4
34.	Har du haft ont i halsen?	1	2	3	4
35.	Har du upplevt problem med att svälja vätska?	1	2	3	4
36.	Har du upplevt problem med att svälja mosad mat?	1	2	3	4
37.	Har du upplevt problem med att svälja mat i fast form?	1	2	3	4
38.	Har du satt i halsen när du svalt?	1	2	3	4
39.	Har du haft problem med tänderna?	1	2	3	4
40.	Har du haft problem med att öppna munnen vidöppen?	1	2	3	4
41.	Har du varit torr i munnen?	1	2	3	4
42.	Har du haft klibbig saliv?	1	2	3	4
43.	Har du haft problem med luktsinnet?	1	2	3	4
44.	Har du haft problem med smaksinnet?	1	2	3	4
45.	Har du haft hosta?	1	2	3	4
46.	Har du varit hes?	1	2	3	4
47.	Har du mått illa?	1	2	3	4
48.	Har ditt utseende stört dig?	1	2	3	4

Gå till nästa sida

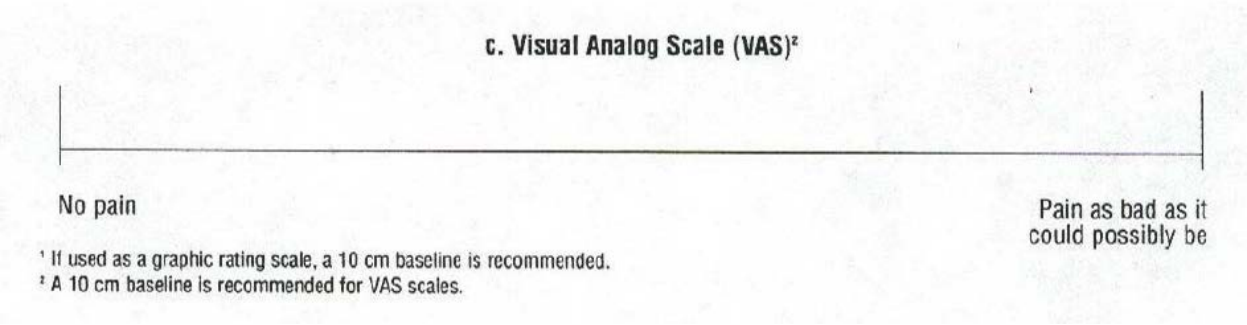
SVENSKA

Under den senaste veckan:		Inte alls	Lite	Ganska mycket	Väldigt mycket
49.	Har du haft problem med att äta?	1	2	3	4
50.	Har du haft problem med att äta inför din familj?	1	2	3	4
51.	Har du haft problem med att äta inför andra människor?	1	2	3	4
52.	Har du haft svårigheter att njuta av dina måltider?	1	2	3	4
53.	Har du haft svårt för att tala med andra människor?	1	2	3	4
54.	Har du haft svårigheter att tala i telefon?	1	2	3	4
55.	Har du haft svårigheter i den sociala kontakten med din familj?	1	2	3	4
56.	Har du haft svårigheter i den sociala kontakten med vänner?	1	2	3	4
57.	Har du haft svårt för att vara ute offentligt?	1	2	3	4
58.	Har du haft svårigheter i den fysiska kontakten med familj eller vänner?	1	2	3	4
59.	Har du känt mindre intresse för sex?	1	2	3	4
60.	Har du känt mindre sexuell njutning?	1	2	3	4

Under den senaste veckan:		Nej	Ja
61.	Har du använt smärtstillande?	1	2
62.	Har du tagit kosttillskott (med undantag av vitaminer)?	1	2
63.	Har du använt matningssond?	1	2
64.	Har du gått ner i vikt?	1	2
65.	Har du gått upp i vikt?	1	2

17.2.APPENDIX B: Visual Analogue Scale (VAS)

Subjects will receive at least nine copies of the VAS scale (below) where the lines are printed exactly 10cm in length. Prior to the subject receiving the scale, the subject ID will be written on the pages. On post-operative days 1 through 7, 10 and 14, each day the subjects will be instructed to place a vertical mark on the line, along with the date and time, to indicate their degree of pain. Rulers will be provided to each site and after their return on post-operative day 14 (+3), the vertical marks will be rounded to the nearest whole centimeter and entered into the eCRF. Marks which fall directly between two whole numbers will be rounded to the larger number; *i.e.* 3.5 would be rounded to 4.



17.3.APPENDIX C: List of Investigators and Institutions

Investigator	Institution Address
Dr. Ron Karni, MD	University of Texas Health Science Center – Houston Memorial Hermann 6400 Fannin Street #2700 Houston, TX 77030 USA
Dr. Per Attner, MD, PhD	Sophiahemmet Hospital ENT Department Valhallavägen 91 11486, Stockholm Sweden

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• New Document	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Sections reordered per CIP template 056-F275 (Table of Contents)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Local Sponsor for EU CAE added and Coordinating Investigator removed from Clinical Investigation Plan cover page	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Added ISO 14155:2011 and location specificity to Investigator Statement (Section 2)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Updated Primary Objective and added Post-market interventional to Clinical Study Type, Primary Endpoint, Secondary Endpoints and Secondary Objectives to Synopsis (Section 4).	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Sample size revised to "a minimum of 48" throughout document	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Updated the definition of Hemostasis in the Glossary (Section 3)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Deleted "or the legally authorized representative" from Inclusion Criteria (Sections 4 and 9.3)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Additional detail regarding justification, rationale and summary of clinical evaluation added to Background (5.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Secondary Objectives added to Section 6.1.2	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Additional details were added to Rationale (Section 7.2)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• V1.2 software was added to LS10 description in General Product Description (Section 8.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications

1.1	• "lot number" changed to "serial number" in Product Receipt and Tracking (Section 8.7)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Added "(room temperature)" to Product Accountability (Section 8.8)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Added "the sponsor and" , "(+3)", and "for the full 14 days follow-up" to Subject Enrollment (Section 9.2)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• 'Device Accountability' removed from Study Schematic (Section 10.1.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• QOL home survey removed from Screening/Baseline in Study Schematic (Section 10.1.1) and Screening/Baseline Visit section (10.1.2)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• "Return to clinic follow-up visit" added to '14 days' in study schematic (Section 10.1.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Added "Protocol deviation collection" to Study Schematic (Table 1, Section 10.1.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Screening/Baseline Visit (Section 10.1.2) was edited for clarity and consistency	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• "(+3) days" and "Post-operative bleeding – Any bleeding that occurs, from the presence of blood in saliva to bleeding that requires re-operation" added to Post-Operative Follow-up: Days 1 through 7, Day 10 and Day 14 (Section 10.1.4)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Subject Consent (Section 10.2) was updated for clarity and consistency	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Details of Assessment of Efficacy (Section 10.4) were added	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Medication Compliance section was added (Section 10.3)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Assessment of Safety section was added (Section 10.5)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications

1.1	• "or authorized designee(s)" was added to Recording Data (Section 10.6)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Deviation Handling section edited for clarity (Section 10.7)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Additional detail added to Selection of Investigators (Section 10.10)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Risks of tonsillectomy procedure added to Potential Risks (Section 11.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Potential Benefits section added (Section 11.2)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Additional details added to Risk-Benefit Rationale (Section 11.3)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• "which is aligned with MEDDEV 2.7/3 Revision 3, May 2015 (Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting)." was removed from Adverse Event Assessments (Section 12)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• References to ISO 14155:2011 added to Adverse Event Assessment definitions (Sections 12.1.1 to 12.1.5 and 12.5	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Removed "During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Clinical Evaluation Report and the Risk Management Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there." from Adverse Event Relationship Classification (Section 12.1.7)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Removed "Reporting to National Competent Authorities will occur within the timelines described in the study Safety Plan." And added "SAEs need to be reported to the sponsor within 24 hours of becoming aware." to Reporting of Adverse Events (Section 12.2)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Sample size Determination (Section 14.2) edited for clarity and consistency	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications

1.1	• Added Interim Analysis (Section 14.7)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• "Changes to the planned statistical analysis as defined in the protocol will be documented in the statistical analysis plan and clinical study report." Added to Statistical Test Methods (Section 14.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Statistical Primary and Secondary Endpoint sections were edited for clarity (14.4.1-2)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Interim Analysis edited for clarity in Synopsis and Interim Analysis (Sections 4 and 14.7)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Statements of Compliance (Section 15.1) edited for clarity	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Protocol Compliance (Section 15.2) edited for clarity	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Added "Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC." to Liability (Section 15.3)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• "Site visits will be conducted by an authorized Medtronic representative to inspect study data, subjects' medical records, and eCRFs in accordance with current ICH GCPs and the respective local and national government regulations and guidelines (if applicable)." and "as well as permit study-related monitoring, audits, MEC/IRB review, and regulatory inspection(s) by providing direct access to source data/documents." Added to Statement(s) of Compliance (Section 16.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• "and initials" was deleted from Confidentiality (Section 16.4)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• CIP Amendments edited for clarity (Section 16.5)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications

1.1	• Record Retention (Section 16.6) edited for clarity and additional detail	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Publication and Use of Information edited for clarity (Section 16.7)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Suspension or Early Termination edited for clarity and updated for suspension of study (Section 16.8)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Safety Committees (Section 16.9) edited for clarity	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Steering Committee (Section 16.9.2) was edited for clarity	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Removed "Subjects will also be asked to complete the form prior to the procedure on Day 0)" (Section 18.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• "subject's name" replaced with "subject ID" and "(+3)" in Appendix B (Section 18.2)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• EORTC QLQ H&N35 (Spanish) added to Section 18.1.2	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
1.1	• Added "List of Investigators and Institutions" section (Section 18.3)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
2.0	• Updated Study Schematic Screening/Baseline Days (Section 10.1.1) and Screening/Baseline Visit (Section 10.1.2) to allow for screening to take place on the procedure day	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
2.0	• Pre-operative procedure specific physical examination moved from Screening/Baseline Visit (Section 10.1.2.) to Surgical Procedure (Section 10.1.3) and added to Study Schematic (Section 10.1.1)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
2.0	• Visual Analog Scale (VAS) image replaced and text updated (Section 18.2)	Nicholas Paquette, Ph.D. Senior Medical Writer, Scientific Communications
3.0	• Clarify age of adult in the US (≥22) and Europe (≥18) (Section 5.1, 5.2, 6.1.1, 7.2, 9.1, 9.3, 10.1.1 and Synopsis)	Caitlin Gibbons, Clinical Study Manager

3.0	• Remove "non-elective" under tonsillectomy inclusion criteria (Section 9.1, 9.3 and Synopsis)	Caitlin Gibbons, Clinical Study Manager
3.0	• Remove Elective Tonsillectomy exclusion criteria (Section 9.4 and Synopsis)	Caitlin Gibbons, Clinical Study Manager
3.0	• Clarify urine pregnancy tests are only for females in the United States (Section 10.1.1. 10.1.2, Study Schematic and Synopsis)	Caitlin Gibbons, Clinical Study Manager
4.0	• Transferred to 056-F275 Clinical Investigation Plan Template v3.0 and updated all revised Section/Appendix references throughout the document (Summary of Changes moved to end of document, Additional headings in Sections 7 & 9)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Corrected Local Sponsor/Authorized Representative Address (Cover Page, Section 1, 3 and 15.5)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Compliance Statement revised (Section 1 and 14.1)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Clarified Statistical Tests (Section 3 and 13.4.1)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Clarified Device Deficiencies (Section 3, 5.2.3, and 9.7)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Aligned purpose with Synopsis and described publication intent (Section 4.2)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Clarified timeline of Primary Endpoint (Section 5.2.1)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Modified Reference to VAS and QoL (Section 6.1, 9.1.4, and 9.5)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Added device deficiencies to Table 1 (Section 9.1.)	Luciano Mazzaro, Clinical Study Manager &

		Nicole Brini, Clinical Research Specialist
4.0	• Added additional ISO14155 elements to subject consent (Section 9.3)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Added Deviation definition and escalation of repetitive non-compliance (Section 9.9)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Clarified when to follow subjects (Section 9.10)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Add AE Reporting guidelines (Section 11.1.1)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Clarified Adverse Event Recording (Section 11.3)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Revised Clinical Research point of contact (Section 11.4)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Clarified phone number for ex-US callers (Section 11.4)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Added rationale for not using a Data Review Committee (Section 12)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Removed Protocol Compliance section (Section 14.2) as it is duplicated in Section 9.9	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Clarifications made to Monitoring responsibilities (Section 15.1)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist

4.0	• Clarified documentation in clinical records and use of original electronic records as source (Section 15.2)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Added Covidien Services Europe Liability language (Section 15.5)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Added Swedish EORTC QLQ-H&N35 (Section 17.1.3)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist
4.0	• Added List of Investigators and Institutions (Section 17.3)	Luciano Mazzaro, Clinical Study Manager & Nicole Brini, Clinical Research Specialist

Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	A prospective, multi-center, single arm non-comparative pilot study of BiZact™ on adults undergoing tonsillectomy.
Clinical Investigation Plan Identifier	COVBZTS0562
Clinical Investigation Plan Version	CIP_V4.0 Final 13MAR2018
Sponsor/Local Sponsor	Medtronic Minimally Invasive Therapies Group 5920 Longbow Dr. Boulder, CO 80301
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1. Version History

Version	Summary of Changes	Author(s)/Title
1	First version	Sylvain Anselme, Sr. Biostatistician
2	· Definition of primary/secondary bleeding · Update Subjects' participation in the study will last 14 days 14 (+3) post-procedure · Process of primary endpoint revised	Sylvain Anselme, Sr. Biostatistician
3	· Section 3: biocompatibility testing and animal model studies conclusion developed · Add of 95% Agresti-Coull Confidence Intervals · Center pooling section updated · Adjustments for Multiple Comparisons updated · Demographic, treatment characteristics, safety evaluation updated · References updated · Changes to planned analysis updated · Validation Requirement Level I added	Sylvain Anselme, Sr. Biostatistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
ADL	Activity of Daily Living
CIP	Clinical Investigational Plan
eCRF	Electronic Case Report Form
EORTC QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Head & Neck cancer module
FAS	Full Analysis Set
ITT	Intent-to-treat
PPAS	Per-Protocol Analysis Set
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
USADE	Unanticipated Adverse Device Effect
VAS	Visual Analogue Scale

3. Introduction

Tonsillectomy is one of the most frequently performed otorhinolaryngologic procedures with more than 4.5 million procedures performed annually. The introduction of numerous energy based tools and techniques allow for the simultaneous dissection and sealing of vessels, significantly improving safety and reducing the complications of the procedure. Generally thought of as safe and effective, energy based devices such as laser, Shaw scalpel, electrosurgical devices (needle, scissor, or knife), radiofrequency needle ablation device, thermal welding, and Coblator, use heat energy to denature protein, leading to vascular tamponade and hemostasis. Unfortunately, a byproduct of using this energy during surgery is the lateral heating of the surgical area, which can damage adjacent structures, delay wound healing, increase post-operative pain, and increase the subject's time to return to normal diet and activity. In order to address these concerns, Medtronic (formerly Covidien) has developed BiZact™, a bipolar instrument intended for use in open surgical procedures, such as tonsillectomies, where ligation and division of vessels, tissue bundles and lymphatics is desired. BiZact™ is designed as a pistol grip radiofrequency (RF) sealer/dissector for use with vessels up to and including 3mm. Compatible with the already in use Valleylab (LS10) energy platform, BiZact™ employs bipolar electrosurgical RF energy and pressure to ligate vessels interposed between its jaws which can then be transected using the built in knife deployed by the device trigger. Based off LigaSure technology, bipolar electrosurgical devices have been shown to be safe and effective for tonsillectomy procedures, providing adequate hemostasis while minimizing postoperative pain.

In summary, biocompatibility testing and animal model studies have found BiZact™ to be safe and effective in achieving hemostasis and reducing lateral thermal spread potentially resulting in reduced post-operative pain.

4. Study Objectives

The study population consists of patients being treated with BiZact™ device for tonsillectomy.

4.1. Primary objective

The primary objective of this study is to assess the severity of post-operative pain following the use of the BiZact™ device in adult tonsillectomy procedures using the Visual Analogue Scale (VAS) at days 1 through 7, 10 and 14.

4.2. Secondary objectives

Several secondary hypotheses will be analyzed:

- To assess the incidence of patients with post-operative analgesic consumption
- To assess the ability to return to normal diet and normal activity after operation:
    - Time between dates of operation and return to a normal situation
    - Incidence of patients returning to a normal situation

- To assess the incidence of patients with of post-operative hemorrhage
    - Incidence of patients with primary bleeding, occurring at the latest 24 hours after operation.
    - Incidence of patients with secondary bleeding, occurring more than 24 hours after operation.

- To assess the incidence of patients with post-operative readmission

- To assess the quantity of intra-operative bleeding volume

- To assess the quantity of intra-operative irrigant volume

- To assess the operative time from the first incision to complete hemostasis of the tonsillar bed (procedure duration and device use duration)

5. Investigation Plan

This is a Prospective, multi-center, single-arm non-comparative pilot study to assess the severity of post-operative pain with the use of BiZact™ for tonsillectomy.
A minimum of 48 subjects being treated with BiZact™ for tonsillectomy may be enrolled at up to 3 sites in the United States and Europe with competitive enrollment not to exceed 24 subjects per site.

Subjects' participation in the study will last 14 days 14 (+3) post-procedure. Assessments of pain, quality of life, safety, readmission, concomitant medications, ability to return to normal diet and activity will be performed. An at home survey form during post-operative days 1 through 7 and day 10 will be used. At day 14 (+3) these parameters will be evaluated via a clinical follow-up visit in the sites.

5.1 Inclusion criteria

Subjects are eligible to be enrolled in the study only if they meet **all** of the following inclusion criteria:

1. Adults (male or female) ≥22 years of age in United States and ≥18 years of age in Europe
2. Scheduled to undergo non-elective tonsillectomy
3. Signed informed consent by subject or the legally authorized representative

5.2 Exclusion criteria

Subjects will be excluded from the study if they meet **any** of the following exclusion criteria:

Subjects undergoing;

a. Simultaneous adenoidectomy
b. Tonsillectomy as a result of cancer
c. Unilateral tonsillectomy
d. Current participation in other clinical trials

Subjects with;

e. Current tobacco use
f. Known bleeding disorders
g. History of peritonsillar abscess
h. Craniofacial disorders
i. Down syndrome (Trisomy 21)
j. Cerebral palsy
k. Major heart disease
l. Subjects unable to comply with the required study follow-up visits
m. Pregnancy

The subject has comorbidities which, in the opinion of the investigator, will not be appropriate for the study or the subject has an estimated life expectancy of less than 6 months

Any subject who is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity)

The subject has participated in any drug or device research study within 30 days of enrollment that would interfere with this study

6 Determination of Sample Size

This study does not have a statistically powered hypothesis. There will be no sample size calculations since the study is not hypothesis-driven. The number of enrolled subjects is pre-defined and all the results will be summarized in a descriptive manner.

7 Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Screen, consented, eligible, intent-to-treat patients (ITT), operated patients (Full Analysis Set - FAS) and per-protocol patients (PP) will be summarized by frequency, as well as patients early withdrawn.
Early withdrawal reasons will be presented by related reason and listed. Protocol deviations, post-operative assessment completions and length of follow-up will be reported (frequency and percentage from Full Analysis Set population).

Subjects who provide study consent, but then are determined to be ineligible prior to study procedure will be considered a screen failure and will not require additional study follow-up visits as well as subjects withdrawn due to physician decision. The reason for the screening failure will be clearly delineated.

Subjects in whom the procedure is begun but not completed will be considered "discontinued" and will be followed until discharge. These subjects will only contribute to Adverse Event data intraoperatively until discharge (no additional follow-up). They will only be part of the ITT analysis set.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Full-list of protocol deviations will be reported and major violations to be excluded from Per-Protocol Analysis Set (PPAS) will be reviewed and discussed with the study team prior to run statistical analysis.

7.1.3 Analysis Sets

Three analysis sets will be created for study purpose:

1. Intent-To-Treat. ITT includes all subjects:
   - who signed the informed consent
   - who satisfied the eligibility criteria
   - who began the procedure

Subjects in whom the procedure is begun but not completed will be considered "discontinued" and will be followed until discharge. These subjects will only contribute AE data intraoperatively until discharge (no additional follow-up).

2. Full Analysis Set. FAS is a subset of the ITT, restricted to subjects:
   - who signed the informed consent
   - who satisfied the eligibility criteria
   - who were operated with BiZact™ procedure successfully completed

3. Per Protocol Analysis Set. PPAS is a subset of the FAS, restricted to subjects who adhere to the protocol and do not have major protocol violation.

7.2 General Methodology

Continuous variables will be summarized using counts, means, 95% Agresti-Coull Confidence Intervals, standard deviations, medians, minimum and maximum.
Categorical variables will be summarized using frequencies and percentages.

7.3 Center Pooling

Subgroup analyses for primary and secondary endpoints will be presented by clinical center.

7.4 Handling of Missing Data and Dropouts

No method of imputation will be used for missing data. A summary of missing data will be provided according to the number of subjects, the time points where the data are missing and clinical center. For each clinical center, number and percent of subjects with no missing data will be presented in tabular form.

7.5 Adjustments for Multiple Comparisons

Only one analysis will be performed then no adjustment for multiple comparison will be performed.

7.6 Demographic and Other Baseline Characteristics

Patient's characteristics and other baseline data will be summarized for the FAS and reported using statistical methods described above (see section 7.2 General Methodology).

7.7 Treatment Characteristics

The Study Investigator should perform the surgical procedure according to the appropriate standard procedures and practices at his/her institution using BiZact™. Additionally, the following procedures and assessments will be performed:

- Type of admission
- Adverse Events/Serious Adverse Events assessment
- Intra-operative bleeding volume
    - Record volume of any irrigant used
    - Record presence of gastric fluids
    - Record amount of fluid in suction container prior to stomach drainage
- Surgical performance parameters
    - Surgical technique
    - Operation time
    - Device ease of use
    - Dissection assessment
    - Other alternative devices used (if any)
        - Operation time used
        - Side
        - Reason for use
    - Tonsil size measurement (Measured via water displacement)
        - Using a graduated container that has 1mL markings, fill container to half full with water note mL level. Put the first tonsil into the water and record the mL level. The difference equals the volume of the first tonsil. Remove the first tonsil and note

water level. Put the second tonsil into the water and record how much the water level rises. The difference equals the volume of the second tonsil.

- Concomitant medications - medications used during procedure, used for Averse Events and used for the treatment of pain (including but not limited to analgesics, anti-inflammatories, etc.)

Surgical procedure data will be summarized on the FAS and reported using statistical methods described above (see section 7.2 General Methodology).

7.8 Interim Analyses

No interim analysis is planned.

7.9 Evaluation of Objectives

7.9.1 Primary objective

The severity of pain will be analyzed at each post-operative assessment: at days 1 through 7, 10 and 14. This pain score will be assessed quantitatively using the VAS scale and qualitatively using the below subgroups:

- No Pain: VAS= 0
- Mild Pain: VAS > 0 and < 4
- Moderate: VAS ≥ 4 and < 7
- Severe: VAS ≥ 7

Friedman's test will be performed so as to assess the distribution of the VAS along the follow-up and testing whether the VAS per visits are from a same population:

- H_0: $M_1 = M_2 = M_3 = M_4 = M_5 = M_6 = M_7 = M_{10} = M_{14}$ (the distribution of the VAS is the same in all timepoints)
- H_a: There is at least one paire (i,j) such as $M_i \neq M_j$.

Subgroup analyses will be performed according to the use of pain killers.

Primary objective analysis will be run on both FAS and PPAS.

7.9.2 Secondary objectives

- The incidence of patients with analgesic consumption will be assessed at each timepoint and globally using frequency and percentages. On the whole follow-up the total consumption of analgesics (narcotics and non-narcotics analgesics) will be assessed. Patients with analgesics will be identified based on dosing diary.
- Ability to return to normal diet and normal activity and patients quality of life after operation will be presented:
    - Calculating the time (counts, means, standard deviations, medians, minimum and maximum) between the operation and the return to normal diet or activity dates.
    - Calculating the incidence of patients being returned to normal diet or activity after operation.
    - Using the **EORTC QLQ-H&N35 questionnaire:**

The head & neck cancer module is meant for use among a wide range of patients with head & neck cancer, varying in disease stage and treatment modality (i.e. surgery, radiotherapy and chemotherapy) (Bjordal and Kaasa, 1992; Bjordal et al., 1994, 1999, 2000) (1-3). The module comprises 35 questions assessing symptoms and side effects of treatment, social function and body image/sexuality. The module has been

developed according to the guidelines, and pretested on patients from Norway, Sweden, Denmark, the UK and French-speaking Belgium. It has been field tested in Norway, Sweden and The Netherlands, and in a large cross-cultural study involving more than ten countries (EORTC Protocol 15941).

Scoring of the head & neck cancer module
The head & neck cancer module incorporates seven multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact and sexuality. There are also eleven single items. **For all items and scales, high scores indicate more problems** (i.e. there are no function scales in which high scores would mean better functioning).
Friedman's test will be applied to assess the distribution of the scores along the follow-up timepoint:

- H_0: $M_1 = M_2 = M_3 = M_4 = M_5 = M_6 = M_7 = M_{10} = M_{14}$ (The distribution of the Symptom score is the same in all timepoints)
- H_a: There is at least one paire (i,j) such as $M_i \neq M_j$.

Scale name	Scale	Number of items	Item range*	QLQ-H&N35 Item numbers
Symptom scales / items				
Pain	HNPA	4	3	1-4
Swallowing	HNSW	4	3	5-8
Senses problems	HNSE	2	3	13, 14
Speech problems	HNSP	3	3	16, 23, 24
Trouble with social eating	HNSO	4	3	19-22
Trouble with social contact	HNSC	5	3	18, 25-28
Less sexuality	HNSX	2	3	29,30
Teeth	HNTE	1	3	9
Opening mouth	HNOM	1	3	10
Dry mouth	HNDR	1	3	11
Sticky saliva	HNSS	1	3	12
Coughing	HNCO	1	3	15
Felt ill	HNFI	1	3	17
Pain killers	HNPK	1	1	31
Nutritional supplements	HNNU	1	1	32
Feeding tube	HNFE	1	1	33
Weight loss	HNWL	1	1	34
Weight gain	HNWG	1	1	35

* Item range is the difference between the possible maximum and the minimum response to individual items.

Example:

Pain	RawScore = (Q1 + Q2 + Q3 + Q4)/4
	Pain Score = {(RawScore-1)/Item range}*100
	Questions scores
Not at all = 1	No = 1
A little = 2	Yes = 2
Quite a bit = 3	
Very much = 4	

- The incidence of patients having a post-operative hemorrhage, primary and secondary bleeding, and post-operative readmission along the follow-up will be assessed.
- Intra-operative bleeding, irrigant volumes and operative time will be calculated (counts, means, standard deviations, medians, minimum and maximum).

Secondary objectives will be run on both FAS and PPAS.

7.10 Safety Evaluation

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

This definition includes events related to the investigational medical device and the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Events may include but are not limited to pain, bleeding, nausea, vomiting, and headache.

AEs will be reported by frequencies and percentages of subjects by categories of AEs and by count of each AE. A listing will also be provided.

AEs will be collected and documented at baseline and 0 to 14 days follow-up. AEs will be presented globally and based on their occurrence periods: PRE-PROCEDURE, DURING PROCEDURE and POST-PROCEDURE. The MedDRA coding system will be used so as to report the AEs in the statistical tables.

Safety analysis will be run on the whole ITT population and on the FAS.

7.10.1 Serious Adverse Event

A serious adverse event (SAE) is any AE that has:

- led to death,
- led to serious deterioration in the health of the subject that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
- led to fetal distress, fetal death, or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered an SAE.

SAEs will be collected and documented at baseline and 0 to 14 days follow-up.

7.10.2 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse Device Effects will be reported by the Investigator(s). If escalation is required, ADEs will be reviewed by medical affairs as part of Medtronic's Post-Market Vigilance program. Both confirmed and possible device related events will be included in the study report.

7.10.3 Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

SADEs will be collected and documented at baseline and 0 to 14 days follow-up.

7.10.4 Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

USADEs will be collected and documented at baseline and 0 to 14 days follow-up.

7.10.5 Adverse Event Severity Classification

Severity will be defined according to the following criteria:

Mild	Awareness of event, but easily tolerated
Moderate	Discomfort enough to cause some interference with activities of daily living (ADL)
Severe	Incapacitating, with an inability to perform ADL
Death	Death related to AE

An AE can be classified as severe and not deemed an SAE. Similarly, an SAE is not automatically severe in nature.
In this study, the incidence of patients by AEs category will be summarized by worst severity.

7.10.6 Adverse Event Relationship Classification

Causality assessments define the relationship between the use of the medical device (including the medical-surgical procedure) and the occurrence of each adverse event, according to MEDDEV 2.7/3 Revision 3, May 2015 (Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting). During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Clinical Evaluation Report and the Risk Management Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures:

Not related: relationship to the device or procedures can be excluded when:

1. the event is not a known side effect of the product category the device belongs to or of similar devices and procedures
2. the event has no temporal relationship with the use of the device or the procedures;
3. the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
4. the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
5. the event involves a body-site or an organ not expected to be affected by the device or procedure;
6. the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
7. the event does not depend on a false result given by the device used for diagnosis, when applicable;
8. harms to the subject are not clearly due to use error;
9. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the serious event is associated with the device or with procedures beyond reasonable doubt when:

1. the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
2. the event has a temporal relationship with device use/application or procedures;
3. the event involves a body-site or organ that
    a. the device or procedures are applied to;
    b. the device or procedures have an effect on;
4. the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
5. the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
6. other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
7. harm to the subject is due to error in use;
8. the event depends on a false result given by the device used for diagnosis, when applicable;
9. In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

In this study, the incidence of patients with AEs related with study procedure or study device will be calculated. For each patients having at least one AE, their worst relationship will be identified. An AE will be considered as related when it is coded as:

Relationship	
Study CRF	**Final code used (Not related/Related)**
NOT RELATED	Not related
UNLIKELY	Related
POSSIBLE	Related
PROBABLE	Related
CAUSAL RELATIONSHIP	Related

7.10.7 Adverse Event Outcome Classification

Outcome of the event will be defined according to the following:

- ***Fatal:*** This event is determined to be the cause of death.
- ***Not Recovering/Not Resolved***: The event has retained pathological conditions resulting from the prior disease or injury.
- ***Recovered/Resolved:*** The event has fully resolved at the end of the study.
- ***Recovering/Resolving:*** The event is ongoing at the end of the study.
- ***Unknown***: The event has been unclassified at the end of the study.

7.10.8 Device Deficiency

A Device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

All BiZact™ device deficiencies will be documented on the appropriate Device malfunction eCRF and the device should be returned to Medtronic for analysis, if possible. Instructions for returning the device will be provided. Device deficiencies should also be documented in the subject's medical record.

Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate eCRF.

Device deficiencies will be reported by frequencies and percentages, and listing will also be provided.

7.11 Health Outcomes Analyses

Health outcomes have been previously described.

7.12 Changes to Planned Analysis

Analysis corresponds to the planned analysis in the CIP. Any deviations from this statistical plan will be justified in future revisions to this document or in the final report, as appropriate.

8 Validation Requirements

Level I validation will be performed for all the analysis output. Level I is defined as that the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

9 References

1. Bjordal K., Kaasa S. Psychometric validation of the EORTC Core Quality of Life Questionnaire, 30-item version and a diagnosis-specific module for head and neck cancer patients. Acta Oncol. 1992;31:311-21.

2. Bjordal K, Ahlner-Elmqvist M, Tolleson E, el al. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. EORTC Quality of Life Study Group. Acta Oncol. 1994;33:879-85

3. Bjorda K. Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire H&N35. J Clin Oncol. 1999;17:1008-19.

10 Statistical Appendices

Appendix 1: Table shells (provided in a separated file)

Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	A prospective, multi-center, single arm non-comparative pilot study of BiZact™ on adults undergoing tonsillectomy.
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CIP	Clinical Investigational Plan
eCRF	Electronic Case Report Form
EORTC QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Head & Neck cancer module
FAS	Full Analysis Set
ITT	Intent-to-treat
PPAS	Per-Protocol Analysis Set
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
USADE	Unanticipated Adverse Device Effect
VAS	Visual Analogue Scale

3. Introduction

Tonsillectomy is one of the most frequently performed otorhinolaryngologic procedures with more than 4.5 million procedures performed annually. The introduction of numerous energy based tools and techniques allow for the simultaneous dissection and sealing of vessels, significantly improving safety and reducing the complications of the procedure. Generally thought of as safe and effective, energy based devices such as laser, Shaw scalpel, electrosurgical devices (needle, scissor, or knife), radiofrequency needle ablation device, thermal welding, and Coblator, use heat energy to denature protein, leading to vascular tamponade and hemostasis. Unfortunately, a byproduct of using this energy during surgery is the lateral heating of the surgical area, which can damage adjacent structures, delay wound healing, increase post-operative pain, and increase the subject's time to return to normal diet and activity. In order to address these concerns, Medtronic (formerly Covidien) has developed BiZact™, a bipolar instrument intended for use in open surgical procedures, such as tonsillectomies, where ligation and division of vessels, tissue bundles and lymphatics is desired. BiZact™ is designed as a pistol grip radiofrequency (RF) sealer/dissector for use with vessels up to and including 3mm. Compatible with the already in use Valleylab (LS10) energy platform, BiZact™ employs bipolar electrosurgical RF energy and pressure to ligate vessels interposed between its jaws which can then be transected using the built in knife deployed by the device trigger. Based off LigaSure technology, bipolar electrosurgical devices have been shown to be safe and effective for tonsillectomy procedures, providing adequate hemostasis while minimizing postoperative pain.

In summary, biocompatibility testing and animal model studies have found BiZact™ to be safe and effective in achieving hemostasis and reducing lateral thermal spread potentially resulting in reduced post-operative pain.

4. Study Objectives

The study population consists of patients being treated with BiZact™ device for tonsillectomy.

4.1. Primary objective

The primary objective of this study is to assess the severity of post-operative pain following the use of the BiZact™ device in adult tonsillectomy procedures using the Visual Analogue Scale (VAS) at days 1 through 7, 10 and 14.

4.2. Secondary objectives

Several secondary hypotheses will be analyzed:

- To assess the incidence of patients with post-operative analgesic consumption
- To assess the ability to return to normal diet and normal activity after operation:
    - Time between dates of operation and return to a normal situation
    - Incidence of patients returning to a normal situation

- To assess the incidence of patients with of post-operative hemorrhage
    - Incidence of patients with primary bleeding, occurring at the latest 24 hours after operation.
    - Incidence of patients with secondary bleeding, occurring more than 24 hours after operation.

- To assess the incidence of patients with post-operative readmission

- To assess the quantity of intra-operative bleeding volume

- To assess the quantity of intra-operative irrigant volume

- To assess the operative time from the first incision to complete hemostasis of the tonsillar bed (procedure duration and device use duration)

5. Investigation Plan

This is a Prospective, multi-center, single-arm non-comparative pilot study to assess the severity of post-operative pain with the use of BiZact™ for tonsillectomy.
A minimum of 48 subjects being treated with BiZact™ for tonsillectomy may be enrolled at up to 3 sites in the United States and Europe with competitive enrollment not to exceed 24 subjects per site.

Subjects' participation in the study will last 14 days 14 (+3) post-procedure. Assessments of pain, quality of life, safety, readmission, concomitant medications, ability to return to normal diet and activity will be performed. An at home survey form during post-operative days 1 through 7 and day 10 will be used. At day 14 (+3) these parameters will be evaluated via a clinical follow-up visit in the sites.

5.1 Inclusion criteria

Subjects are eligible to be enrolled in the study only if they meet **all** of the following inclusion criteria:

1. Adults (male or female) ≥22 years of age in United States and ≥18 years of age in Europe
2. Scheduled to undergo non-elective tonsillectomy
3. Signed informed consent by subject or the legally authorized representative

5.2 Exclusion criteria

Subjects will be excluded from the study if they meet **any** of the following exclusion criteria:

Subjects undergoing;

a. Simultaneous adenoidectomy
b. Tonsillectomy as a result of cancer
c. Unilateral tonsillectomy
d. Current participation in other clinical trials

Subjects with;

e. Current tobacco use
f. Known bleeding disorders
g. History of peritonsillar abscess
h. Craniofacial disorders
i. Down syndrome (Trisomy 21)
j. Cerebral palsy
k. Major heart disease
l. Subjects unable to comply with the required study follow-up visits
m. Pregnancy

The subject has comorbidities which, in the opinion of the investigator, will not be appropriate for the study or the subject has an estimated life expectancy of less than 6 months

Any subject who is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity)

The subject has participated in any drug or device research study within 30 days of enrollment that would interfere with this study

6 Determination of Sample Size

This study does not have a statistically powered hypothesis. There will be no sample size calculations since the study is not hypothesis-driven. The number of enrolled subjects is pre-defined and all the results will be summarized in a descriptive manner.

7 Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Screen, consented, eligible, intent-to-treat patients (ITT), operated patients (Full Analysis Set - FAS) and per-protocol patients (PP) will be summarized by frequency, as well as patients early withdrawn.
Early withdrawal reasons will be presented by related reason and listed. Protocol deviations, post-operative assessment completions and length of follow-up will be reported (frequency and percentage from Full Analysis Set population).

Subjects who provide study consent, but then are determined to be ineligible prior to study procedure will be considered a screen failure and will not require additional study follow-up visits as well as subjects withdrawn due to physician decision. The reason for the screening failure will be clearly delineated.

Subjects in whom the procedure is begun but not completed will be considered "discontinued" and will be followed until discharge. These subjects will only contribute to Adverse Event data intraoperatively until discharge (no additional follow-up). They will only be part of the ITT analysis set.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Full-list of protocol deviations will be reported and major violations to be excluded from Per-Protocol Analysis Set (PPAS) will be reviewed and discussed with the study team prior to run statistical analysis.

7.1.3 Analysis Sets

Three analysis sets will be created for study purpose:

1. Intent-To-Treat. ITT includes all subjects:
   - who signed the informed consent
   - who satisfied the eligibility criteria
   - who began the procedure

Subjects in whom the procedure is begun but not completed will be considered "discontinued" and will be followed until discharge. These subjects will only contribute AE data intraoperatively until discharge (no additional follow-up).

2. Full Analysis Set. FAS is a subset of the ITT, restricted to subjects:
   - who signed the informed consent
   - who satisfied the eligibility criteria
   - who were operated with BiZact™ procedure successfully completed

3. Per Protocol Analysis Set. PPAS is a subset of the FAS, restricted to subjects who adhere to the protocol and do not have major protocol violation.

7.2 General Methodology

Continuous variables will be summarized using counts, means, 95% Agresti-Coull Confidence Intervals, standard deviations, medians, minimum and maximum.
Categorical variables will be summarized using frequencies and percentages.

7.3 Center Pooling

Subgroup analyses for primary and secondary endpoints will be presented by clinical center.

7.4 Handling of Missing Data and Dropouts

No method of imputation will be used for missing data. A summary of missing data will be provided according to the number of subjects, the time points where the data are missing and clinical center. For each clinical center, number and percent of subjects with no missing data will be presented in tabular form.

7.5 Adjustments for Multiple Comparisons

Only one analysis will be performed then no adjustment for multiple comparison will be performed.

7.6 Demographic and Other Baseline Characteristics

Patient's characteristics and other baseline data will be summarized for the FAS and reported using statistical methods described above (see section 7.2 General Methodology).

7.7 Treatment Characteristics

The Study Investigator should perform the surgical procedure according to the appropriate standard procedures and practices at his/her institution using BiZact™. Additionally, the following procedures and assessments will be performed:

- Type of admission
- Adverse Events/Serious Adverse Events assessment
- Intra-operative bleeding volume
    - Record volume of any irrigant used
    - Record presence of gastric fluids
    - Record amount of fluid in suction container prior to stomach drainage
- Surgical performance parameters
    - Surgical technique
    - Operation time
    - Device ease of use
    - Dissection assessment
    - Other alternative devices used (if any)
        - Operation time used
        - Side
        - Reason for use
    - Tonsil size measurement (Measured via water displacement)
        - Using a graduated container that has 1mL markings, fill container to half full with water note mL level. Put the first tonsil into the water and record the mL level. The difference equals the volume of the first tonsil. Remove the first tonsil and note

water level. Put the second tonsil into the water and record how much the water level rises. The difference equals the volume of the second tonsil.

- Concomitant medications - medications used during procedure, used for Averse Events and used for the treatment of pain (including but not limited to analgesics, anti-inflammatories, etc.)

Surgical procedure data will be summarized on the FAS and reported using statistical methods described above (see section 7.2 General Methodology).

7.8 Interim Analyses

No interim analysis is planned.

7.9 Evaluation of Objectives

7.9.1 Primary objective

The severity of pain will be analyzed at each post-operative assessment: at days 1 through 7, 10 and 14. This pain score will be assessed quantitatively using the VAS scale and qualitatively using the below subgroups:

- No Pain: VAS= 0
- Mild Pain: VAS > 0 and < 4
- Moderate: VAS ≥ 4 and < 7
- Severe: VAS ≥ 7

Friedman's test will be performed so as to assess the distribution of the VAS along the follow-up and testing whether the VAS per visits are from a same population:

- H_0: $M_1 = M_2 = M_3 = M_4 = M_5 = M_6 = M_7 = M_{10} = M_{14}$ (the distribution of the VAS is the same in all timepoints)
- H_a: There is at least one paire (i,j) such as $M_i \neq M_j$.

Subgroup analyses will be performed according to the use of pain killers.

Primary objective analysis will be run on both FAS and PPAS.

7.9.2 Secondary objectives

- The incidence of patients with analgesic consumption will be assessed at each timepoint and globally using frequency and percentages. On the whole follow-up the total consumption of analgesics (narcotics and non-narcotics analgesics) will be assessed. Patients with analgesics will be identified based on dosing diary.
- Ability to return to normal diet and normal activity and patients quality of life after operation will be presented:
    - Calculating the time (counts, means, standard deviations, medians, minimum and maximum) between the operation and the return to normal diet or activity dates.
    - Calculating the incidence of patients being returned to normal diet or activity after operation.
    - Using the **EORTC QLQ-H&N35 questionnaire:**

The head & neck cancer module is meant for use among a wide range of patients with head & neck cancer, varying in disease stage and treatment modality (i.e. surgery, radiotherapy and chemotherapy) (Bjordal and Kaasa, 1992; Bjordal et al., 1994, 1999, 2000) (1-3). The module comprises 35 questions assessing symptoms and side effects of treatment, social function and body image/sexuality. The module has been

developed according to the guidelines, and pretested on patients from Norway, Sweden, Denmark, the UK and French-speaking Belgium. It has been field tested in Norway, Sweden and The Netherlands, and in a large cross-cultural study involving more than ten countries (EORTC Protocol 15941).

Scoring of the head & neck cancer module
The head & neck cancer module incorporates seven multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact and sexuality. There are also eleven single items. **For all items and scales, high scores indicate more problems** (i.e. there are no function scales in which high scores would mean better functioning).
Friedman's test will be applied to assess the distribution of the scores along the follow-up timepoint:

- H_0: $M_1 = M_2 = M_3 = M_4 = M_5 = M_6 = M_7 = M_{10} = M_{14}$ (The distribution of the Symptom score is the same in all timepoints)
- H_a: There is at least one paire (i,j) such as $M_i \neq M_j$.

Scale name	Scale	Number of items	Item range*	QLQ-H&N35 Item numbers
Symptom scales / items				
Pain	HNPA	4	3	1-4
Swallowing	HNSW	4	3	5-8
Senses problems	HNSE	2	3	13, 14
Speech problems	HNSP	3	3	16, 23, 24
Trouble with social eating	HNSO	4	3	19-22
Trouble with social contact	HNSC	5	3	18, 25-28
Less sexuality	HNSX	2	3	29,30
Teeth	HNTE	1	3	9
Opening mouth	HNOM	1	3	10
Dry mouth	HNDR	1	3	11
Sticky saliva	HNSS	1	3	12
Coughing	HNCO	1	3	15
Felt ill	HNFI	1	3	17
Pain killers	HNPK	1	1	31
Nutritional supplements	HNNU	1	1	32
Feeding tube	HNFE	1	1	33
Weight loss	HNWL	1	1	34
Weight gain	HNWG	1	1	35

* Item range is the difference between the possible maximum and the minimum response to individual items.

Example:

Pain	RawScore = (Q1 + Q2 + Q3 + Q4)/4
	Pain Score = {(RawScore-1)/Item range}*100
	Questions scores
Not at all = 1	No = 1
A little = 2	Yes = 2
Quite a bit = 3	
Very much = 4	

- The incidence of patients having a post-operative hemorrhage, primary and secondary bleeding, and post-operative readmission along the follow-up will be assessed.
- Intra-operative bleeding, irrigant volumes and operative time will be calculated (counts, means, standard deviations, medians, minimum and maximum).

Secondary objectives will be run on both FAS and PPAS.

7.10 Safety Evaluation

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

This definition includes events related to the investigational medical device and the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Events may include but are not limited to pain, bleeding, nausea, vomiting, and headache.

AEs will be reported by frequencies and percentages of subjects by categories of AEs and by count of each AE. A listing will also be provided.

AEs will be collected and documented at baseline and 0 to 14 days follow-up. AEs will be presented globally and based on their occurrence periods: PRE-PROCEDURE, DURING PROCEDURE and POST-PROCEDURE. The MedDRA coding system will be used so as to report the AEs in the statistical tables.

Safety analysis will be run on the whole ITT population and on the FAS.

7.10.1 Serious Adverse Event

A serious adverse event (SAE) is any AE that has:

- led to death,
- led to serious deterioration in the health of the subject that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
- led to fetal distress, fetal death, or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered an SAE.

SAEs will be collected and documented at baseline and 0 to 14 days follow-up.

7.10.2 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse Device Effects will be reported by the Investigator(s). If escalation is required, ADEs will be reviewed by medical affairs as part of Medtronic's Post-Market Vigilance program. Both confirmed and possible device related events will be included in the study report.

7.10.3 Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

SADEs will be collected and documented at baseline and 0 to 14 days follow-up.

7.10.4 Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

USADEs will be collected and documented at baseline and 0 to 14 days follow-up.

7.10.5 Adverse Event Severity Classification

Severity will be defined according to the following criteria:

Mild	Awareness of event, but easily tolerated
Moderate	Discomfort enough to cause some interference with activities of daily living (ADL)
Severe	Incapacitating, with an inability to perform ADL
Death	Death related to AE

An AE can be classified as severe and not deemed an SAE. Similarly, an SAE is not automatically severe in nature.
In this study, the incidence of patients by AEs category will be summarized by worst severity.

7.10.6 Adverse Event Relationship Classification

Causality assessments define the relationship between the use of the medical device (including the medical-surgical procedure) and the occurrence of each adverse event, according to MEDDEV 2.7/3 Revision 3, May 2015 (Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting). During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Clinical Evaluation Report and the Risk Management Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures:

Not related: relationship to the device or procedures can be excluded when:

1. the event is not a known side effect of the product category the device belongs to or of similar devices and procedures
2. the event has no temporal relationship with the use of the device or the procedures;
3. the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
4. the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
5. the event involves a body-site or an organ not expected to be affected by the device or procedure;
6. the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
7. the event does not depend on a false result given by the device used for diagnosis, when applicable;
8. harms to the subject are not clearly due to use error;
9. In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the serious event is associated with the device or with procedures beyond reasonable doubt when:

1. the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
2. the event has a temporal relationship with device use/application or procedures;
3. the event involves a body-site or organ that
    a. the device or procedures are applied to;
    b. the device or procedures have an effect on;
4. the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
5. the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
6. other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
7. harm to the subject is due to error in use;
8. the event depends on a false result given by the device used for diagnosis, when applicable;
9. In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

In this study, the incidence of patients with AEs related with study procedure or study device will be calculated. For each patients having at least one AE, their worst relationship will be identified. An AE will be considered as related when it is coded as:

Relationship	
Study CRF	**Final code used (Not related/Related)**
NOT RELATED	Not related
UNLIKELY	Related
POSSIBLE	Related
PROBABLE	Related
CAUSAL RELATIONSHIP	Related

7.10.7 Adverse Event Outcome Classification

Outcome of the event will be defined according to the following:

- ***Fatal:*** This event is determined to be the cause of death.
- ***Not Recovering/Not Resolved***: The event has retained pathological conditions resulting from the prior disease or injury.
- ***Recovered/Resolved:*** The event has fully resolved at the end of the study.
- ***Recovering/Resolving:*** The event is ongoing at the end of the study.
- ***Unknown***: The event has been unclassified at the end of the study.

7.10.8 Device Deficiency

A Device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

All BiZact™ device deficiencies will be documented on the appropriate Device malfunction eCRF and the device should be returned to Medtronic for analysis, if possible. Instructions for returning the device will be provided. Device deficiencies should also be documented in the subject's medical record.

Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate eCRF.

Device deficiencies will be reported by frequencies and percentages, and listing will also be provided.

7.11 Health Outcomes Analyses

Health outcomes have been previously described.

7.12 Changes to Planned Analysis

Analysis corresponds to the planned analysis in the CIP. Any deviations from this statistical plan will be justified in future revisions to this document or in the final report, as appropriate.

8 Validation Requirements

Level I validation will be performed for all the analysis output. Level I is defined as that the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

9 References

1. Bjordal K., Kaasa S. Psychometric validation of the EORTC Core Quality of Life Questionnaire, 30-item version and a diagnosis-specific module for head and neck cancer patients. Acta Oncol. 1992;31:311-21.

2. Bjordal K, Ahlner-Elmqvist M, Tolleson E, el al. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. EORTC Quality of Life Study Group. Acta Oncol. 1994;33:879-85

3. Bjorda K. Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire H&N35. J Clin Oncol. 1999;17:1008-19.

10 Statistical Appendices

Appendix 1: Table shells (provided in a separated file)