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

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.

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.

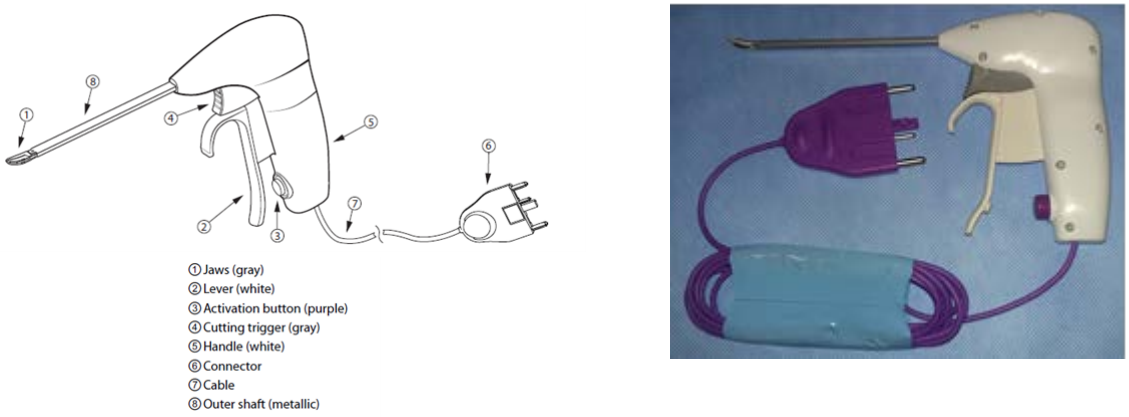

Figure 1: BiZact™ (BZ4112) schematic diagram (left), and device photo (right)

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

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

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.

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.

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

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.

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

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	

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)

	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

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

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.

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)

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;

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.

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.

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

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.

- 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.

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
Document Version	SAP v3.0 Final