Summaries of Reza Band Clinical Studies

Pivotal Study: A Multi-Center, Non-Randomized, Prospective Study of the Reza Band™ Upper Esophageal Sphincter (UES) Assist Device for the Treatment of Esophagopharyngeal Reflux

Objective

The objective of the study was to assess the safety and effectiveness of the *Reza Band* when worn by subjects that had been clinically diagnosed with laryngopharyngeal reflux disease (LPR) (i.e., chronic cough, choking, aspiration, chronic post nasal drip, globus, sore throat, throat clearing). The subjects wore the *Reza Band* at bedtime and took it off upon waking.

Methods

A non-randomized, prospective, open label trial of 95 patients treated at 5 investigational sites was conducted. Subjects that had been clinically diagnosed with LPR with extraesophageal symptoms (i.e., chronic cough, choking, aspiration, chronic post nasal drip, globus, sore throat, throat clearing) and who met the inclusion and exclusion criteria were enrolled into the study and fit with the Reza Band.

The primary effectiveness endpoint was the percent reduction in the Reflux Symptom Index (RSI) from Baseline to Week 4. The RSI is a validated nine-item patient-administered outcome questionnaire designed to document the symptoms and severity of LPR. Patients were instructed to rate how the nine symptoms affected them on a scale of 0 (no problem) to 5 (severe problem), with a maximum total score of 45.

The safety of the Reza Band was evaluated by assessing the incidence, type, duration and severity of adverse events observed in all patients. Effectiveness was assessed by the evaluation of patient and physician satisfaction, patient response to the Reflux Symptom Index, additional validated questionnaires and patient diaries.

Safety Results

The adverse events that were reported during the study were generally mild, short in duration and the majority of those events were not related to the device. Those events that were related to the device were also generally mild and short in duration. Device related adverse events did not result in reduced outcomes in relation to the change of the RSI score from baseline to Visit 3 (Week 4), as they were consistent with the overall population. There were no deaths in the study, there were no unexpected adverse events, and none of the subjects withdrew from the study due to an adverse event.

The table below summarizes the incidence of adverse events with the reported relationship to the device.

Adverse Events
Relationship to Device
Through 1 Month Follow-up
Safety Patients
N = 95

	Definitely (n/%)	Possibly	Probably Not	Definitely Not
Dysphagia	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
Odynophagia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pain	5 (5.3%)	2 (2.1%)	1 (1.1%)	0 (0.0%)
Globus	1 (1.1%)	0 (0.0%)	1 (1.1%)	5 (5.3%)
Laryngospasm	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
Regurgitation	0 (0.0%)	0 (0.0%)	1 (1.1%)	2 (2.1%)
Choking	5 (5.3%)	2 (2.1%)	1 (1.1%)	2 (2.1%)
Nausea	1 (1.1%)	0 (0.0%)	2 (2.1%)	0 (0.0%)
Dyspepsia	0 (0.0%)	1 (1.1%)	1 (1.1%)	1 (1.1%)
Hoarseness	0 (0.0%)	2 (2.1%)	3 (3.2%)	3 (3.2%)
Cough	0 (0.0%)	2 (2.1%)	2 (2.1%)	7 (7.4%)
Difficulty Breathing	0 (0.0%)	1 (1.1%)	3 (3.2%)	5 (5.3%)
Unable to Belch	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unable to Vomit	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin Reaction	5 (5.3%)	1 (1.1%)	2 (2.1%)	1 (1.1%)
Reza Band Problem	14 (14.7%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
External Manometer Problem	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Effectiveness Results

The Primary Effectiveness endpoint was defined as the percent change in RSI from Baseline (Visit 1) to End of Study (Week 4). Table 2 provides the percent change in the RSI from the baseline for Visit 2 (2 weeks) and Visit 3 (4 weeks) for the Intent-to-Treat subjects. Subjects that did not provide any post-baseline RSI assessments were excluded from the ITT population. Eighty-nine (89) subjects were therefore defined as being included in the ITT population. The six subjects that were excluded from the ITT population did not return for Visit 2 (2 weeks) or Visit 3 (4 weeks).

The change in the RSI from baseline was statistically improved for both Visit 2 and Visit 3, as well as the last post-baseline visit ($p<0.0001$).

Reflux Symptom Index (RSI)
Percent Change in RSI From Visit 1
Intent-to-Treat Subjects
N = 89

Time Point	Statistic	RSI	% Change from Visit 1 - Baseline
Visit 1	n	89	N/A
	Mean	26.0	
	Standard Deviation	6.8	
	Median	25.0	
	Minimum	14.0	
	Maximum	42.0	
Visit 2	n	86	86
	Mean	14.6	-43.8
	Standard Deviation	9.2	31.1
	Median	12.5	-50.0
	Minimum	0.0	-100.0
	Maximum	41.0	35.7
	p-Value (1)		<0.0001
	p-Value (2)		<0.0001
Visit 3	n	86	86
	Mean	12.0	-54.3
	Standard Deviation	8.6	-27.1
	Median	10.5	-57.8
	Minimum	0.0	-100.0
	Maximum	42.0	7.7
	p-Value (1)		<0.0001
	p-Value (2)		<0.0001
Last Post-Baseline Visit	n	89	89
	Mean	12.1	-54.2
	Standard Deviation	8.6	27.5
	Median	10.0	-57.9
	Minimum	0.0	-100.0
	Maximum	42.0	7.7
	p-Value (1)		<0.0001
	p-Value (2)		<0.0001

(1) p-Value based on paired t-test to test hypothesis of no mean percent change.
(2) p-value based on one-sided one sample t-test to test hypothesis of mean change >25%.

Conclusion

The results of this clinical study demonstrate that the *Reza Band* is safe and effective for its intended use, in that it is a non-invasive treatment for LPR that provides improvement in symptoms within the first two weeks, and this benefit was maintained through the 4-week follow-up.

Safety Study: Safety of an Intentionally Displaced Reza Band™ Upper Esophageal Sphincter (UES) Assist Device

Objective

The safety of the *Reza Band*™ UES Assist Device (*Reza Band*) was evaluated when worn as intended over the cricoid, as well as when intentionally displaced laterally over each side of the neck, based on changes in heart rate, blood pressure, cardiac rhythm and intraocular pressure (IOP), as compared to when the *Reza* Band was not being worn.

Methods

Twenty (20) subjects who met the inclusion and exclusion criteria were enrolled in the study, and were representative of the intended *Reza Band* patient population. The study population consisted of 60% males and 40% females (95% Caucasian and 5% African-American subjects), with a mean age of 46.3 years, and a mean Body Mass Index (BMI) of 28.7.

Measurements of heart rate, blood pressure, cardiac rhythm and IOP were taken immediately after the *Reza Band* was placed on the neck in each of the specified scenarios (cricoid, right displacement and left displacement), 5 minutes after placement (except for IOP) and again 15 minutes after placement. The *Reza Band* was removed and 3 minutes later, IOP was again measured in each placement scenario.

After the fitting of the *Reza Band*, the Comfort Dial was fully actuated, to achieve the maximum pressure. The maximum pressure with the Comfort Dial fully actuated was also measured with the *Reza Band* displaced laterally over the vascular structures on both sides of the of the neck.

Results

The results showed that there was no effect on heart rate, blood pressure, cardiac rhythm or IOP, when the *Reza Band* when worn as intended as well as when the *Reza* Band was intentionally displaced laterally, as compared to the baseline. No adverse events were reported during this study.

Analyses of Variance (One Way) were conducted on heart rate, blood pressure and intraocular pressure to determine whether there was any effect of the *Reza Band* being placed as intended or laterally displaced, when compared to not wearing the Reza Band. The summaries in the table following show that there was no significant difference for any of the measurements at any time point, when compared to the baseline values.

Analysis of Variance (One Way)
Patient Parameters

Parameter	p-Value
Heart Rate	0.7130
Diastolic Blood Pressure	0.8508
Systolic Blood Pressure	0.9691
Left Eye IOP	0.9981
Right Eye IOP	0.9999

Additionally, electrocardiograms (ECGs) were evaluated to determine whether there was any impact on cardiac rhythm, when the *Reza Band* was placed as intended, or intentionally displaced, over the jugular and carotid vasculature. It was determined that there was no change in the ECGs for any of the subjects at any time during the study, when comparing the baseline ECG, to any other ECG.

When the *Reza Band* is set to apply its maximal pressure with the Comfort Dial fully actuated, and then displaced laterally, the pressure being applied is significantly reduced (mean of 59.2%, when displaced laterally to the left and a mean of 55.2%, when displaced laterally to the right), as compared to the applied pressure over the cricoid. This further reduces the risk of increased pressure to the sensitive structures of the neck.

Conclusion

In the event the *Reza Band* is displaced laterally, the likelihood of impacting sensitive structures of the neck is low. There was no effect on heart rate, blood pressure, cardiac rhythm, or intraocular pressure, either when the *Reza Band* is placed as intended over the cricoid cartilage, or when it is laterally displaced, over the jugular and carotid vasculature. It was concluded that based on the results of this study, the *Reza Band* is safe, when worn as intended and if it were to be were to be displaced laterally.

Supportive Study: Prevention of Esophagopharyngeal Reflux by Augmenting the UES Pressure Barrier

Objective

Incompetence of the upper esophageal sphincter (UES) is fundamental to the occurrence of extraesophageal reflux, and development of supraesophageal manifestations of reflux disease. The objective was to determine if reflux events can be prevented by application consistent external pressure applied at the cricoid.

Methods

Fourteen (14) subjects diagnosed with extraesophageal reflux (mean age of 57 years, 8 females) and 12 healthy controls (mean age of 26 years, 7 females) were studied by concurrent esophageal slow infusion, (1 mL/s) of 60 mL of HCl, and pharyngoscopic and manometric technique without and with the application of a sustained predetermined cricoid pressure to induce, detect, and prevent extraesophageal reflux, respectively.

Results

Slow esophageal infusion resulted in 16 objectively confirmed extraesophageal reflux events in 9 extraesophageal reflux patients, and no events in the healthy controls. All subjects developed subjective sensation of regurgitation. Sustained cricoid pressure resulted in a significant UES pressure augmentation in all participants. During application of sustained cricoid pressure, slow esophageal infusion resulted in only one extraesophageal reflux event ($p<0.01$).

Conclusion

The application of 20-30 mmHg of external pressure to the cricoid significantly increases the UES intraluminal pressure, and prevents pharyngeal reflux, induced by esophageal slow liquid infusion. The slow infusion was able to demonstrate that when the device is applying the sustained pressure, extraesophageal reflux was prevented, as well as significantly reducing the subjective sensation of regurgitation.

Supportive Study - Difference in Reflux Events With and Without the UES Assist Device Using Pharyngeal pH and Impedance Monitoring

Objective

The objective of the study was to compare the incidence of extraesophageal reflux, as measured by changes in pH and impedance, for subjects diagnosed with LPR and compare that incidence to healthy subjects. Both groups were evaluated with and without the UES assist device in place.

Methods

Pharyngeal pH and impedance monitoring was obtained in both healthy and reflux subjects, comparing the changes in pH and impedance, with and without the device in place. Pharyngeal pH events were identified using criteria published by Szczesniak, et al[1].

Based on the duration of pharyngeal pH events, the events were categorized into two entities. To differentiate between a transient pH drop and an EPR event, the following definitions were used:

- Transient pH drop: A brief swallow related pharyngeal pH drop of more than 3 pH units, to a pH below 4, lasting for less than 3 seconds.
- EPR: A sustained pharyngeal pH drop of more than 3 pH units, to less than 4, and lasting for longer than 3 seconds

The reduction of both types of events (transient and sustained) are important, in that even with shorter durations of refluxate, the hypopharynx is exposed to acidic contents.

Impedance is the change in resistance (Ohms) to alternating electrical current when a bolus passes by a pair of metallic rings mounted on a catheter. In the esophagus, the electrical current between the two metallic rings is conducted by the few ions present in and on the esophageal mucosa. Liquid containing boluses with an increased number of ions has a higher conductivity. Therefore, when a bolus (i.e., refluxate) is at the location of the metallic rings, the impedance value is reduced. The impedance stays at the lower value as long as the bolus is present and returns to baseline once it is cleared. The clearing by contraction of the esophagus produces a slight increase in impedance above the baseline due to a decrease in luminal cross-section. Decease in the impedance indicates the presence of reflux.

In twelve (12) reflux subjects and 7 healthy subjects, reflux was simulated by the slow infusion (1ml/sec) of HCI (0.1 N) in the distal esophagus. The pharynx was monitored endoscopically for occurrence of reflux events, by the change in pH and impedance. This was done for both reflux and healthy subjects, with and without the device in place.

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1 Szczesniak MM, Williams RB, Cook IJ. Mechanisms of esophago-pharyngeal acid regurgitation in human subjects. PLoS One. 2011;6(7):e22630. doi: 10.1371/journal.pone.0022630. Epub 2011 Jul 22.

Results

Twelve (12) reflux subjects underwent a total of 69 infusions. A vast majority of the subjects were seen to have either a transient pH drop (75.0%) and/or a reflux event (90.0%) when not wearing the device. However, when wearing the device, the number of both transient pH drops and reflux events was significantly reduced (33.3% and 16.7%, respectively). See the table immediately following.

Occurrence of pH Drop and/or EPR Events
By Subject
Reflux Subjects

		Transient pH drop		EPR	
	N	n	%	n	%
Without Device	12	9	75.0%	10	90.0%
With Device	12	4	33.3%	2	16.7%

Seven (7) healthy subjects underwent a total of 21 infusions. As would be expected, the number of transient pH drops in the healthy subjects was rare, and there were no incidences of a reflux event. Table 2c.iii and Table 2c.iv below summarize those incidences. When healthy subjects had the device in place, neither a transient pH drop nor an EPR event was recorded. See the table immediately following.

Occurrence of pH Drop and/or EPR Events
By Subject
Healthy Subjects

		Transient pH Drop		EPR	
	N	n	%	n	%
Without Device	7	1	14.3%	0	0.0%
With Device	7	0	0.0%	0	0.0%

For the healthy subjects, it was found that there were no changes in pH. This is not unexpected, since in the healthy subjects, the UES is functioning as intended, and the absence of pH changes indicates that there was not a presence of refluxate in the extraesophageal area. In healthy subjects, this was observed independent of the device being in place.

In addition to evaluating the change of pharyngeal pH, the change in pharyngeal impedance was also evaluated.

As with pH, impedance was measured for both the reflux and the healthy subjects with and without the device in place. The impedance results were similar to the pH results, in that when the device was in place for the reflux subjects, the number of impedance drops that were transient was significantly greater when not wearing the device (66.7%) as compared to when the device was in place (23.2%). The number of sustained impedance drops, or reflux events, was also significantly greater when not wearing the

device (46.0%) when compared to when the device was worn (4.7%). The table following summarizes the impedance results.

Occurrence of Impedance Change
Reflux Subjects

		Transient Impedance Drop		Sustained Impedance Drop	
	N	n	%	n	%
Without Device	63	42	66.7%	29	46.0%
With Device	43	10	23.2%	2	4.7%

The number of transient impedance drops and/or reflux events in the reflux subjects, when not wearing the device, was significantly greater, as compared to the incidence of events, when the reflux subjects were wearing the device. In addition, when the reflux subjects were wearing the device, the incidence of both a transient pH drop and a reflux event was similar to those of healthy subjects.

Conclusion

The results of this study demonstrate that reflux is impeded from passing through the UES into the pharynx in reflux subjects when external cricoid pressure is applied, resulting in a safe and effective method for controlling extraesophageal reflux. In essence, when the UES has the assist from the device, it performs as a healthy UES.

Supportive Study: Correlation of Externally Applied Cricoid Pressure with Luminal Upper Esophageal Sphincter Pressure Augmentation

Objective

This study was conducted on 14 subjects to evaluate the effect of predefined external pressures on cricoid cartilage on intraluminal UES pressure. The purpose of the study was to:

- Determine the relationship between externally applied pressure, as displayed by the Somna External Manometer when connected to the Somna Pressure Sensor device and the intraluminal UES pressure as measured by esophageal manometry.

- Determine the effect of the presence of the Pressure Sensor device on the intraluminal UES pressure.

Methods

External pressure to the cricoid was applied using two methods:

- Manually for approximately 10 seconds (represents typically three respiratory cycles) each continuously adjusted to sustain pressures of 10, 20, 30, 40 and 50 (±3) mmHg. At each pressure, three measurements were recorded.

- Each subject had pressure applied by the Somna *Reza Band* UES Assist Device positioned over the cricoid region. Pressures of 10, 20, 30, 40 and 50 mmHg were applied to the cricoid region with the *Reza Band* (without the need for continuous adjustment) as measured by the Somna External Manometer/Pressure Sensor. At each pressure, three measurements were recorded.

Intraluminal UES pressure was measured using a solid-state circumferential sensor manometry catheter with outer diameter of 2.7mm. External pressure was measured using the Somna External Manometer connected to the Somna Pressure Sensor.

The UES intraluminal pressure was analyzed in 2 ways:

- UES Nadir Pressure: The relevant pressure of UES as a dynamic defensive mechanism against esophageal contents, as it is the lowest pressure during UES relaxation.
- Average UES Pressure: Takes into account fluctuations of the UES pressure over three respiratory cycles.

Results

When the *Reza Band* was applying external pressure at the cricoid, the Nadir luminal UES pressure was highly correlated to external cricoid pressure ($p<0.0001$). Externally applied manual pressure at the cricoid region of 20 and 30 mmHg, resulted in 17 (±5) mmHg and 23 (±7) mmHg luminal UES pressure increase, respectively. When the *Reza Band* was fit to externally apply the same external pressure of 20 and 30 mmHg, it also

resulted in consistent intraluminal UES pressure increase. The presence of the Somna Pressure Sensor had no affect on the intraluminal UES pressure.

Conclusion

Based on the results of this study, it was concluded that the UES intraluminal pressure increase is significantly correlated with externally applied pressure by the *Reza Band* at the cricoid region, irrespective of patient position, type of pressure application or measurement technique. Therefore, the external pressure being applied by the *Reza Band* is transferred to the intraluminal pressure at the UES.

Supportive Study: Efficacy of a "Novel UES Assist Device" in Management of Supraesophageal Complications of Reflux Disease

Objective

The objective of this study was to determine the effect of the *Reza Band* on subjects diagnosed with LPR. The study used the validated Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire (N-GSSIQ). Even though this questionnaire was developed for the evaluation of nocturnal symptoms due to the presence of GERD, it was determined that it would provide meaningful data for those diagnosed with extraesophageal reflux. The N-GSSIQ was chosen specifically for this 2-week study as it targets those patients with nocturnal symptoms due to extraesophageal reflux, that result in the disruption of sleep and a negative impact on the quality of life.

Methods

Twenty-four (24) subjects with extraesophageal reflux were enrolled into the study, with 19 subjects completing the study. For those that did not complete the study, 2 subjects were lost to follow-up, 2 subjects did not tolerate the therapeutic setting of the device and 1 subject dropped out due to their report that the device did not work after a single night's use. The validated N-GSSIQ was used to assess changes in subject symptoms by comparing the N-GSSIQ baseline score to the scores after wearing the device with sub-therapeutic pressure (5-10 mmHg) as well as with therapeutic pressure (20-30 mmHg).

Results

When comparing the baseline N-GSSIQ score to the N-GSSIQ score with the device set to apply sub-therapeutic pressure, significant differences for the Nocturnal Impact domain ($p=0.002$), the Morning Impact domain ($p=0.014$) and the total N-GSSIQ score ($p<0.0001$) were observed. Significant differences were also demonstrated when comparing the baseline N-GSSIQ score to when the device was set to therapeutic pressure, for the Nocturnal Impact domain ($p<0.0001$), the Morning Impact domain ($p<0.0001$), the Patient Concern domain (<0.0001) and the total score ($p<0.0001$).

When comparing the N-GSSIQ score when the device was set to sub-therapeutic pressure, to the N-GSSIQ score when the device was set to therapeutic pressure, the N-GSSIQ score showed a significant difference for the Nocturnal Impact domain ($p=0.001$), the Morning Impact domain ($p=0.014$) and the total score ($p<0.0001$). The table following is summary of the results.

N-GSSIQ
Baseline vs. Sub-Therapeutic and Therapeutic Pressure

Baseline vs. Sub-therapeutic Pressure	p-Value
Nocturnal Impact	0.002
Morning Impact	0.014
Patient Concern	0.060
Total	<0.001
Baseline vs. Therapeutic Pressure	
Nocturnal Impact	<0.001
Morning Impact	<0.001
Patient Concern	<0.001
Total	<0.001
Sub-therapeutic Pressure vs. Therapeutic Pressure	
Nocturnal Impact	0.001
Morning Impact	0.014
Patient Concern	0.060
Total	<0.001

Conclusion

It was concluded that the UES Assist Device is safe and well tolerated, significantly improves extraesophageal reflux symptoms and would be a simple and effective therapeutic modality for some subjects with extraesophageal manifestations of reflux disease.