Public Comments Received on "*Controversies in Obesity Management*" by June 9, 2015

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FROM: Matthew L. Maciejewski, PhD
TO: CTAF Review Staff
DATE: June 3, 2015
RE: Written Comments on CTAF's Controversies in Obesity Management

I submit these written comments to the very comprehensive review of evidence for bariatric, device and medication interventions. Comments are provided initially for the executive summary and then the main report.

Executive Summary Comment

1) ES5: In the statement of "moderate certainty of a substantial net health benefit of bariatric surgery", it would be helpful to state which procedures appear to provide the greatest net health benefit for patients with a BMI of 35 and above. That would be consistent with the qualification provided in the summary for patients with BMI 30-34.9.

Comment on the Main Report

1) Pages 30-31: Clearly state the duration of follow-up for Figures 8 and 9. In the discussion and the figures themselves, the meta-analytic results do not state the duration of follow-up for these pooled treatment effects. It is critical to qualify the duration of follow-up in each trial in Figures 8 and 9, so the reader has a clear sense of how little evidence there is for weight loss beyond 2-3 years.

2) Page 41: The discussion of procedure volume and its association with patient outcomes fails to report results by Dimick and Nicholas published in JAMA (Feb 2013; Oct 2013) showing that center of excellence designation, which is partly related to patient volume, showed no difference in outcomes. Those results are important to include, since CMS reversed its coverage policy regarding centers of excellence in part based on these results.

3) Page 67: The discussion of the Padwal 2011 systematic review does not examine the specific studies underlying that review, several of which use matched controls that conducted matching in a profoundly flawed way. That is, several studies (Cremieux, Finkelstein) matched surgical patients to non-surgical controls on the basis of pre-surgical expenditures, which were accelerating in the 12 months prior to surgery due to pre-surgical work-up or emergent issues that put the future surgical patients on the path to bariatric surgery. Non-surgical controls with similar pre-surgical "spikes" are likely not generalizable to eligible non-surgical controls, but represent outliers in their pre-surgical expenditure trends and, more importantly, not generalizable in their post-surgical expenditure trends. In sum, matching on pre-surgical expenditures set up a false comparison that ended up making expenditures of bariatric patients look better in comparison than they might have in the absence of matching on pre-surgical expenditures. This is a subtle point that would

benefit from empirical verification in a general US population, but I am (almost) convinced that this must be true.

4) Page 68: It would be worth noting in the summary of the Weiner 2013 paper that only 10% of the original study sample was followed out to 6 years.

5) Page 68: I was surprised that this review of the literature did not reference the 2012 Archives of Surgery by my colleagues and I published. While expenditure analyses on veterans may not generalize to non-VA populations, it should be mentioned given that restriction to non-veterans did not appear to be an inclusion criteria.

6) Page 68-69: Further, there were two commentaries about the lack of cost savings in bariatric surgery (Maciejewski and Arterburn, 2013 JAMA; Goldfine, Vernon and Zinner 2014 JAMA Surgery) that may merit summarizing as well.

7) Simulation Model: The cost-effectiveness results to 10 years hinges critically on the assumption of the decrease in expenditures per unit of BMI decrease (3%, page 76). This assumption should be subject to sensitivity analysis, given that Neovius (2012 JAMA) and Weiner (2013 JAMA Surg) found that expenditures did not decline over time at a 3% rate per unit of BMI decrease and appeared to plateau. A range of scenarios should be assessed in terms of how quickly cost reductions plateau and the percentage reduction per unit of BMI decrease. I would guess that results are highly sensitive to these two assumptions that are not clearly stated in the decision model assumption section.

All in all, this is a tremendously useful report and I will be using it as a reference for some time to come. If you have any questions, please don't hesitate to contact me at mlm34@duke.edu or 919-286-0411 ext 5198. Thank you for the opportunity to comment on this report.

My name is Jaime Ponce and I am the Medical Director for the Bariatric Surgery program at Hamilton Medical Center, in Dalton, Georgia, and Memorial Hospital in Chattanooga, Tennessee. I have been a practicing bariatric surgeon since 1998 with extensive experience in Bariatric Surgery. I am a Fellow of the American College of Surgeons and the American Society for Metabolic and Bariatric Surgery (ASMBS) and a member of the ASMBS, IFSO, SAGES and AOA. Additionally, I served as the Chair of the Bariatric Surgical Review Committee, which established guidelines for Bariatric Centers of Excellence and in 2012-2013 served as President of the ASMBS.

I am pleased to offer comments on the California Technology Assessment Forum (CTAF)/Institute for Clinical and Economic Review (ICER) review on objective evidence to improve the quality and value of health care in the session on "Controversies in Obesity Management," which includes bariatric surgery, pharmaceuticals, traditional weight management and medical devices. The main focus of these comments is my concern that the review is too focused on a backward looking metric of absolute weight loss, to the exclusion of medically relevant weight loss consistent with patient's goals and objectives.

CTAF/ICER has proposed what appears to be a very comprehensive review of the landscape for medical obesity treatment. On the surface, that is a very positive outcome as this review not only covers existing surgical treatment options that are either restrict food intake or are malabsorptive, but includes recently approved technologies, such as the vagal blocking system that creates satiety. The review even includes temporary intragastric balloon systems that are awaiting a FDA approval decision very soon and duodenal-jejunal bypass liner products that are still under FDA clinical trials.

As a treating physician, what I need is to be able to offer my patients the most appropriate and highest standard of care. This review fails if an expanded armamentarium – more treatments with greater variety of mechanisms of action, differing reward/risk profiles and expanded therapeutic possibilities that allow for as much individualized treatment planning as possible – is not the outcome.

The goal of this meeting – and other similar technical reviews – should NOT be an exercise in determining which diet, drug, device or surgery holds the promise of the most absolute weight

loss, but rather, what mechanisms of action of those diets, drugs, devices and/or surgeries are most appropriately applied to which patients that hold the highest likelihood of being the most effect treatment for their individual cause of obesity at the lowest acceptable level of risk.

Also, it needs to be understood and acknowledged that Obesity is a "chronic disease" that will always need treatment tools to manage it at different degrees of severity. People that suffer from overweight (BMI 25-29) may be treated with diet, exercise, and even medications. Other people suffering from more severe obesity (BMI over 35) might be more clear candidates for some type of surgical procedure. But there is a gap of treatment modalities for many patients in the moderate obesity category (BMI 30-40) that have exhausted the non-surgical options and are equally not quite ready for surgical treatments. Many of the endoscopic temporary modalities might have a beneficial effect to continue the treatment for these patients. So, not one therapy fits all patients and we need more tools to decide what is best for each individual case.

Each of the treatments reviewed at this meeting – alone or in conjunction with one another – has a place in my treatment armamentarium to provide medically meaningful weight loss. Each treatment, when properly applied, can arrest the upwardly trending weight gain of the morbidly obese, in most cases reverse the trend and reset the patient's weight at a healthier level. With proper treatment, most of my patients will experience fewer of the co-morbid effects of obesity – resulting in lower costs for the patient and the healthcare system through fewer drugs being prescribed to treat diabetes, high cholesterol and congestive heart failure, lower risks for cancer as well as the need for fewer new knee and hip replacement implants.

All of these treatments need to be paired with a commitment to a continued post-operative/post-treatment weight management program. This vital inclusion is critical to the success of any weight loss therapy.

What concerns me the most in my read of the "Scoping Documents" for this Review that all of the procedures, whether existing, newly approved or still investigational, are being measured against "absolute weight loss" instead of examining the resolution of comorbid conditions or even just quality of life. My patients do not succeed if the outcome doesn't include fewer diabetes drugs, a lower risk of cardiovascular events, increase employability, or reduced cancers – all improvements coming with an acceptable risk/reward consideration.

The traditional "dollars-per-pound lost" measure used by Payors as a surrogate measure of efficacy has no place in this critical analysis. Sound medical management of obesity requires a realistic, achievable patient outcome that is focused on the health effects of the treatment and not just the total weight loss.

For example, Roux-en-Y Gastric Bypass is an excellent treatment option for a patient with severe Class III obesity and life threatening co-morbid issues that require aggressive resolution. Both the surgical and longer-term risks of this procedure are outweighed by the need for aggressive intervention. For younger Class II/III patients that have failed diet and/or pharmaceuticals but need a surgical treatment, or who are concerned about the long-term effects of the malabsorptive surgical procedures – as well as older patients Class II/III obese patients that seek a less risky approach – a newer surgical technology such as vBloc therapy or even temporary endoscopic therapies like intragastric balloons that could be very useful tools in a variety of approaches in patients seeking moderate, medically relevant weight loss or as bridging technology to a more invasive procedure.

Obesity treatment must be considered dynamic, and the Scoping Document at first read fails that test by appearing too static in its review and too focused on surrogate markers of absolute weight loss versus comorbid resolution of the diseases of obesity. By telling a patient that obesity treatment was about how many pounds you can lose as opposed to how much healthier you can become, we failed to treat the disease. CTAF/ICER has the opportunity to relook at obesity treatments with a different approach – one that accepts the new technologies alongside the existing procedures. No two patients are alike, no one treatment works for every patient and there are no silver bullets.

CTAF/ICER should support each of the reviewed treatment options for the right patient, at the right time for the optimal outcome as determined by their physician and their own long-term goals.

Thank you

My name is Sajani (Sunny) Shah and I am a Surgeon in the department of Bariatric and Minimally Invasive Surgery at Tufts Medical Center and Assistant Professor at the Tufts University School of Medicine.

I am pleased to have the opportunity to comment on the California Technology Assessment Forum (CTAF)/Institute for Clinical and Economic Review (ICER), review on objective evidence to improve the quality and value of health care in its session on "Controversies in Obesity Management," which includes bariatric surgery, pharmaceutical therapy, traditional weight management and medical devices.

As a bariatric surgeon and clinician, I am experienced with, and use all of the approved techniques and treatments under discussion at this meeting. I am concerned in my review of the "Scoping Documents" for this Review that all of the procedures – both traditional, newly approved and those still in the FDA pipeline – are being measured against an out-of-date and decidedly non-medical standard of "absolute weight loss." The financial analysis in the Scoping Document appears to further cloud a medical analysis by adopting a "dollars-per-pound lost" paradigm that does not reflect sound medical management of obesity, does not promote realistic patient outcome of treatment goals nor is it an appropriate intervention evaluator when physicians must determine how to treat the multi-factorial disease of obesity.

The treatment paradigm of obesity has been – and appears to be repeated here – as a "one-size-fits-all" approach that places maximal weight loss as the ultimate clinical outcome. While aesthetic weight loss has it place, as a stand-alone goal, it has become obsolete. As a bariatric surgeon, I strive to work individually with each of my patients to design a treatment plan that will provide for sustained, medically meaningful weight loss. My objectives for my patients are improved cardiovascular function, lowered HbA1c, and LDL, an increased capacity for physical activity with correspondingly lowered impact on hips and knees. No solitary treatment will, by itself solve my patient's obesity each therapy requires a commitment by the patient to post-operative medical management, life style modification supported by experienced clinicians.

Bariatric physicians and surgeons are treating an ever-growing case load, not only as relates to volume, but also to patient complexity. Consequently, we require enhanced treatment options with different reward/risk paradigms, different mechanisms of action to align with different

patient disease states and interventional approaches whose outcomes are focused on the expanded paradigm of medically meaningful weight loss.

One such option under review at this session is vBloc therapy. Just a few days before submitting this letter, I performed the first U.S. commercial implant of this newly approved medical device.. As an investigator in the clinical trial that led to FDA approval of this promising treatment, I now have an option to offer a select group of my patients whose health requires an intervention, have failed diet and exercise, failed pharmaco-therapy and are unwilling to accept the risk of conventional gastric bypass or gastric sleeve. As is the case with the other therapeutic approaches in our armamentarium, vBloc is not for all my patients – one size does not fit all. But for the right patient – a younger patient that is 60 - 100 pounds overweight, has unremitting hunger issues, has failed diet, exercise and pharmacologic avenues and is, unwilling or has significant contraindications to bypass/sleeve options – vBloc may be a life changing choice.

vBloc has been demonstrated to have an enhanced safety profile when compared to traditional bariatric surgical methods, while patients that used the device per the clinical protocol lost approximately 28% of their excess weight at 12 months, and that weight loss has been maintained through reported 24 and 30 month time periods, thereby providing an additional, novel alternative that I can offer my obese patients who are in need of treatment options.

My experience treating obese patients has taught me that to ensure successful treatment, patients should have access to a variety of alternative and complementary therapies. Additionally, my professional experience has documented that shared-decision making concerning specific weight-loss interventions involving the physician along with the patient and his/her social network in choosing the right weight loss intervention for each patient will help to enhance efficacy over the long-term.

What concerns me the most about the design and construct of this review is that ICER traditional relies on long-term, peer-reviewed, published clinical data to issue a supportive rating. It is not a system that is well-designed for the evaluation of newer, evolving technologies. vBloc, a promising technology that is working for my patients, is such a technology that has been recently approved by the FDA – January 14, 2015. It is premature for CTAF/ICER to form definitive conclusions on vBloc's durability and effectiveness, as outlined in the scoping documents, based on currently available data. But it is equally true that it is equally premature for CTAF/ICER to

reach a negative conclusion based on the lack of published long term data due to the very recent regulatory approval for commercial use of vBloc.

The most appropriate outcome for the CTAF/ICER evaluation is to accurately note the strong safety profile of vBloc with its promise of medically relevant weight loss, acknowledge that it is a new device awaiting the publication of longer term data. It would also appear prudent for CTA/ICER to recognize that vBloc is a technology with promise when targeted to appropriate patient populations.

Thank you for your consideration.

For years I struggled with maintaining my weight. When I was in my twenties, I had no problems staying at a healthy weight. But once I hit thirty, I started gaining weight. No matter what I did, what I ate, I gained weight. I tried various diets, shakes, pills, exercise programs, all to no avail. The one constant that sabotaged my efforts was uncontrollable hunger. I would diet and exercise and lose weight but as soon as I went back to eating normally, I would gain it all back plus. I could never stay on an eating plan long term because I always felt insatiably hungry. I still ate a healthy diet most of the time but the urge to snack or being hungry would cause me to choose foods that were quick and accessible rather than healthy. Plus I would eat too many calories and never be satisfied.

I became very discouraged and had resigned myself to the fact that I would never be able to permanently lose weight. So I focused on trying to eat healthy and exercise and maintaining my health. I was lucky that I did not have any health issues but I was afraid that being obese would cause issues long term. I felt better when I exercised but I did not see any results from it which was discouraging and I was hungrier than ever! I had researched the various surgical options but I did not feel like that was the answer. I felt like it would not solve the problem and would lead to more issues in the long run. I was so concerned with maintaining my health and preventing disease and I felt that there must be some way to do that without destroying my digestive system. One day I was commuting home and I heard the advertisement for the VBloc study. I called the number and went to the orientation. What I heard made me hope! I decided that this might be the answer. I liked that it was something that was reversible and that it was presented as a tool not a magic bullet. So I filled out the forms and hoped I would be selected for the study. I was so happy when I was selected as a participant. The surgery went well and the recovery time was very short with hardly any discomfort or pain.

Once the device started to work, I could feel the difference! I felt in control, no more insatiable hunger! This helped me be able to stick to making good food choices and changing my eating patterns so that I was eating healthy all the time. It is so much easier to make good choices when you are not feeling like you are starving all the time! With the nutrition counseling and food journaling, I was able to take control. I felt like exercising again and now I am actually seeing results! I committed myself to developing good eating habits and a regular exercise routine and found it much easier to stick to my goals. Now I work out at least five days a week and I have a much easier time making good food choices. I feel my body changing and becoming stronger and healthier and smaller! I have more muscle and even when the scale does not go down quickly, I see the results in lost inches. I am gaining muscle and losing fat. I am no longer discouraged and hungry. I am much more active and have a lot of energy and I feel great.

The thing I most like about this tool is that it puts me in control instead of hunger. When you are not constantly thinking about eating and being hungry you can focus on being healthy and mindful. That one shift makes it possible to set and reach goals in relation to nutrition and exercise. I now feel empowered and in control and able to reach my goals. I still have a way to go on my journey but I know I will reach my goal and maintain it.

An Evidence-Based Response to the Draft Report on "Controversies in Obesity Management" that support an Informed Assessment on vBloc Neurometabolic Therapy

June 9, 2015

What follows are specific references to data discrepancies concerning lack of evidence for vBloc Neurometabolic Therapy found in the May 26, 2015 CTAF "Controversies in Obesity Management" Draft Report

1) Table ES1: "Strength of Evidence by BMI Category" indicates that there is no certainty of the evidence that vBloc is effective in the 35 to 39.9 BMI category.

    - The ReCharge study did assess this BMI range and an abstract has recently been accepted for oral presentation at the 2015 international federation for Surgery for Obesity (IFSO) meeting in Vienna, Switzerland. Data from 53 patients with BMI 35 to 40 kg/m^2 demonstrated 34%EWL at 12 months with no device-related serious adverse events. Statistically significant improvements were observed in systolic blood pressure, total cholesterol, triglycerides, blood glucose and heart rate (see attachment 1).

2) Pages ES6 and ES7 summary of Vagus Nerve Block (Maestro) summarizes the state of evidence of vBloc. The following comments regarding that summary are relevant to Draft Document discrepancies and misstatements:

    - Note that the first RCT conducted, the EMPOWER Trial, evaluated an earlier generation device and provided supporting evidence of primarily safety of vBloc therapy only. Efficacy was confounded by inconsistent hours of therapy delivery and an unintended therapeutic effect in the control group from electrical impedance and safety checks. The lack of evidence of effectiveness in this study needs to be considered in this context in addition to the fact that the device evaluated in the EMPOWER Trial was an early generation Maestro RF System and not the FDA approved Maestro Rechargeable System.

    - While outcomes related to improvements in comorbidities have not been published to date, data through 2 years are in the process of being reviewed by The Obesity Society for the 2015 meeting in November (see attachment 2). Those data demonstrate 21%EWL with systolic blood pressure (BP), diastolic BP, and resting heart rate reductions from baseline of 5.5mmHg, 3.0mmHg, and 4.4 bpm, respectively. Waist circumference reduced by 8.4cm from baseline and 50 and 47% of subjects with pre-diabetes and metabolic syndrome at baseline, respectively, no longer had those conditions at 2 years. Improvements in Impact of Weight on Quality of Life-lite questionnaire and all factors of the three factor eating questionnaire were also observed. Clearly, a clinically meaningful weight loss was maintained that resulted in improvements in comorbid conditions and quality of life.

- A statement is made that 3.4 to 4.4% of patients experienced serious complications related to the device, implantation, or revision. The primary safety endpoint, which was the serious adverse event rate related to the implant/revision procedure, device or therapy in the EMPOWER and ReCharge Trials was 3.0% and 3.7%, respectively. Importantly, these events did not cause life-threatening serious complications similar to what is observed with traditional bariatric surgery such as anastomic leak, bleeding and bowel obstruction and were events such as neuroregulator site pain requiring neuroregulator repositioning within the subcutaneous pocket, atelectasis, neuroregulator revision due to malfunction not causing harm to the patient (which became serious due to investigator decision to keep the patient in the hospital overnight), gallbladder surgery and emesis requiring a hiatal hernia repair.

- We also do not agree with the statement "that there was a not-inconsequential rate of device removal." Only two patients in 162 randomized to the vBloc group in the ReCharge trial had their device removed for an adverse event (one with pain at the neuroregulator site and one with heartburn). The other 3 patients left due to subject decision, but not for complications or adverse events, which is always their right to do in a clinical trial setting.

- The statement that there is a small net benefit for the vBloc device compared to sham device needs to be qualified with the unexpected high weight loss response observed with the sham device. That response was deemed to be likely related to the placebo effect of surgery, daily self-monitoring reinforced by interaction with the sham device to recharge the battery and participation in the weight management program. Importantly, the sham was found to not be durable and patients gained back 40% of what they had lost at 12 months by 18 months post-implantation. Even with these factors, weight loss was superior in the vBloc group to sham control at every visit post-implant and the weight loss observed in the vBloc group is clinically meaningful. Lastly, the sham is not a therapy and cannot be prescribed. It was custom designed specifically for the ReCharge Study.

- Finally, the ReCharge Study did evaluate patients with a BMI < 40 as described above. Those patients had a greater %EWL than the higher BMI patients.

3) On page ES10, the statement was made that "device removal for AEs or other reasons are not uncommon."

- This statement is misleading. Of fact, only 2 of 162 patients in the vBloc group had their devices removed due to an adverse event, yielding a "device removal" rate of 1.2%.

4) Also, the statement of a "small net benefit of vBloc over sham" needs to be put into its proper context of 1) an uncommon sham surgery, 2) a "fully functioning" sham device and 3) a very active sham effect. Lastly, as the vBloc neurometabolic therapy patients achieved almost exactly the pre-trial specified weight loss of 25% EWL (24.4% ITT observed/26.1% multiple imputation model), the context of the sham was to ensure the therapeutic level of treatment reached clinical meaningfulness. At a p-value of .002, superiority of weight loss was demonstrated and the achieved weight loss was identical to the pre-specified trial design assumption.

In summary, the ReCharge Trial demonstrated superior weight loss of 24.4% in the vBloc group compared to 15.9% in the sham control group at 12 months (p=.002). The pre-specified super-superiority margin of 10% was not met due to a sham control response of 3 times greater than expected (5% EWL expected versus 16% observed). However, the vBloc group achieved the EWL expected of almost 25%. The pre-specified responder rate was almost met with over 50% of subjects achieving 20% EWL at 12 months. Improvements in obesity-related risk factors such as blood pressure, heart rate, cholesterol, HDL, LDL, triglycerides and waist circumference were observed on average in all vBloc therapy subjects with greater improvements observed with corresponding greater weight losses.

At 18 months, %EWL was 23% for the vBloc group and 10% for Sham group ($p<0.0001$). VBLOC patients largely maintained their 12-month weight loss of 24%.[1] Sham patients regained over 40% of the 16% excess weight by 18 months with most of the weight regain proceeding unblinding. The most common adverse events related to VBLOC through 18 months were heartburn/dyspepsia and abdominal pain; 98% of events were reported as mild or moderate in severity and 79% had resolved. Weight loss with VBLOC was sustained through 18 months, while the Sham group regained weight between 12 and 18 months.

These results clearly support vBloc neurometabolic therapy as an effective obesity intervention with a low rate of serious complications and served as the basis for the FDA device approval based on the demonstrated safety and efficacy of treatment.

Thank you for your consideration and review. I welcome any questions and further dialogue on the statements provided herein and can be reached directly at: (651)-335-2205.

Katherine Tweden, PhD
Sr. Vice President, Research
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1 Shikora et al. Can J of Diabetes 2015;39:S36

Abstract Proof:

Title: Sustained Improvements in Cardiovascular and Metabolic Risk Factors and Quality of Life at Two Years with Vagal Nerve Block in the ReCharge Trial

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Track 3: Interventional and Clinical Studies

Title:

Sustained Improvements in Cardiovascular and Metabolic Risk Factors and Quality of Life at Two Years with Vagal Nerve Block in the ReCharge Trial

Background:

Vagal nerve blocking reduces appetite and creates weight loss. The vagal nerve block device recently received FDA approval for the treatment of obesity based on 18-month data from the ReCharge Trial. This report assesses the metabolic benefits through 24 months.

Methods:

The double-blind period of the ReCharge Trial has completed and transitioned to a 5-year, open-label study of the safety and effectiveness of vagal blocking. We report on improvements among patients randomized to the active arm of the trial who attended the two-year visit (n=102).

Results:

Two year weight loss was 21%EWL or 8%TBL. Metabolic parameter improvement was sustained to 24 months. Systolic blood pressure (BP), diastolic BP, and resting heart rate were reduced from baseline by 5.5mmHg (95%CI 2.7 to 8.2), 3.0mmHg (95%CI 1.2 to 4.9), and 4.4 bpm (95% CI 2.4 to 6.3), respectively. Waist circumference reduced by 8.4cm from baseline (95% CI 6.3 to 10.6). At baseline 34 subjects were pre-diabetic and not on diabetic medications (5.79% HbA1c, 95%CI 5.2 to 6.3); at 2 years, 17 (50%) had improved to normal (5.31%, 95%CI 4.9 to 5.6). Additionally, 16 (47%) of the 34 subjects with metabolic syndrome at baseline (5.56% HbA1c, 95%CI 4.7 to 6.5) improved to normal at 2 years (5.27% HbA1c, 95%CI 4.4 to 6.9). Mean scores on Impact of Weight on Quality of Life-Lite significantly improved by 35% (57 to 77; 0-100 scale). All scales of Three Factor Eating Questionnaire showed significant improvements from baseline with mean scores on Cognitive Restraint of Eating improved by 58% (9.5 to 15; 0-21 scale), Disinhibition decreased by 28% (10.3 to 7.4; 0-16 scale) and Hunger decreased by 51% (8.0 to 3.9 on 1-14 scale).

Conclusions:

At two years, data from the ReCharge Trial demonstrate that weight loss with vagal blocking continues to provide significant and clinically meaningful improvements in cardiovascular risk factors, pre-diabetes, metabolic syndrome, weight-related quality of life and eating behaviors.

Keywords: Bariatric surgery

Reversible Vagal Nerve Blocking (VBLOC) in Patients with Moderate Obesity and an Obesity Related Co-morbid Condition: The ReCharge Study

Scott Shikora[1,2], Katherine Tweden[2], Mark Knudson[2]

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Introduction: Twelve month results from the randomized, controlled ReCharge Clinical Trial of 239 obese patients with BMI 40 to 45 or BMI 35 to 40kg/m^2 with at least one obesity-related condition(s) were reported previously.

Methods: Moderately obese subjects with at least one co-morbid condition were randomized to the VBLOC device (n=53) or sham group (n=31). Percent excess weight loss (%EWL), blood pressure, heart rate, lipids and safety are reported through 12 months.

Results: VBLOC group demographics were 79% female, BMI 38±2kg/m^2, age 53±8 years and sham demographics were 81% female, BMI 38±2kg/m^2, age 51±7 years (mean±SD). Baseline subject conditions: 59% hypertension, 70% dyslipidemia, 30% sleep apnea, 8% type 2 diabetes. 46 and 27 subjects presented for 12 month visit in the VBLOC and sham group, respectively. Mean EWL at 12 months in the per-protocol group (defined as subjects with 12 mo data, correct treatment randomization, received treatment within 45 days of implant) was 34±26% (95%CI, 26 to 41) in VBLOC group and 19±18% (95%CI, 12 to 27) in sham group. Improvements in blood pressure, heart rate and lipids in

VBLOC group are shown. Improvements were observed in the sham group commensurate with weight loss. No serious device-related complications were observed the first year.

Parameter	Baseline	12Month	Change	95%CI
SBP(mmHg)	130±11	124±13	-5.6±13	[-9.5, -1.6]
DBP(mmHg)	80±9	78±8	-2.7±9	[-5.4, 0.1]
Fasting Glucose(mg/dL)	101±20	93±14	-7.3±15	[-12.1, -2.5]
HR(bpm)	76±10	70±8	-6.4±10	[-9.3, -3.6]
Total Cholesterol(mg/dL)	216±36	202±37	-13.2±34	[-23.6, -2.9]
HDL(mg/dL)	55±16	55±13	0.2±9	[-2.6, 3.0]
LDL(mg/dL)	131±35	123±34	-6.6±33	[-16.7, 3.4]
TG(mg/dL)	150±62	117±53	-34.0±57	[-51.3, -16.6]

Mean+S.D.

Conclusions: Reversible vagal nerve blocking with the implantable Maestro System results in medically meaningful weight loss and improved obesity-related risk factors in moderately obese subjects with co-morbidities.

June 5, 2015

To Whom It May Concern,

My name is Erica Roy-Nyline. I am 49 years old and live in St. Paul, MN. I am among the approximately 96 million people in the US with a BMI over 30, but not for long. In the past year I have brought my BMI down from 40 to 32. I have lost 45 pounds. My blood pressure has decreased from 130/110 to 90/74 and my A1C has lowered from 9 to 5.5.

I have struggled with weight most of my adult life. In my late 20's I gained a great deal of weight due to thyroid disease and polycystic ovary syndrome. Over the years I have found losing weight virtually impossible and have tried many different approaches. Therapies I have tried include, Weight Watchers (three times), Xenical, Meridia, Medifast, and numerous individual diet plans. I was able to lose moderate amounts of weight with several of these interventions, but always found I could not adhere to the program and would gain the weight right back. Furthermore, both Meridia and Xenical caused side effects that were too severe to live with on an extended basis.

At one point I seriously considered Lap Band and Bariatric surgeries. After talking with patients, surgeons and dieticians I decided these more invasive procedures were not an option for me. I was afraid I would never enjoy food again. I was afraid of device slippage, malabsorbtion and painful digestive complications. I did not feel the urgency to "go that far", and yet, the effects of obesity were making me an unhealthy person.

This changed for me on February 25, 2014 when I had a vBlock device implanted at the University of Minnesota. From the first week with the device my relationship with food changed. I feel less hungry at meals and throughout the day. I eat much smaller portions, less frequently and make better choices about the food I eat. My stress and urgency surrounding food is much less. I am naturally living as a person who is more indifferent to food. Over this past year I have enjoyed food, but have not been controlled by it.

vBlock was the perfect therapy choice for me as a weight loss tool. I can still enjoy all the foods I did before vBlock. I receive full nutritional absorption from the food I eat. I have had no pain or any feeling from the device or therapy. It works on decreasing my desire for food, easing food related stress. My weight loss has been slow and steady and permanent. With vBlock I feel confident about maintaining my weight loss for life. I easily decided to try vBlock because it presented me with a physically less invasive and lifestyle altering option than other Bariatric surgeries. It presented me with a socially and emotionally more acceptable intervention for my weight loss. vBlock has helped me achieve the weight loss of a bariatric intervention without "going that far". vBlock gives me the appetite control and satiety of a medication without chemicals and side effects.

Sincerely,

Erica Roy-Nyline
vBlock Patient, 2014
St. Paul, MN
612 849-8680
eroynyline@gmail.com

To whom it may concern,

My name is Mike Magnant and I live in Carver Massachusetts. I would like to comment on my struggle with obesity for all of my adult life.

I have tried just about everything out there to try and lose weight. I have gone to Weight Watchers a number of times. I tried Atkins, Jenny Craig, South Beach, and even tried a gym membership. All to no avail. Sure I could lose 20 or 30 pounds with no problem. Then after a couple of months my brain would take over and let me know that I had to eat to feel better. So I did. Before you'd know it, I would have gained back all of the weight and then some. I struggled with this all of my life.

Being obese is not fun. There were many things that I could not do. Tie my shoes for one. Sit comfortably in a plane. Sit in a booth at a restaurant. I like to think of myself as an active person and I would like to try a zip line tour in through the White Mountains of New Hampshire. Sorry, no, you can't do that, the maximum weight allowed on a zip line tour is 250 pounds. One time I took my twin granddaughters to an amusement park and I told them that grandpa would go on every ride with them. And I did. Except when we came to the biggest and baddest roller coaster in the park. I could not get the safety bar to latch around me. The safety operator of the ride told me I could not ride and I had to step aside and watch my granddaughters ride alone. This was heartbreaking.

In 2011 when I was 59 years old I achieved a lifetime high of 291 pounds. My legs hurt, I was out of breath. I had high blood pressure, high cholesterol, sleep apnea, my doctor told me that if I didn't take of the weight that my health would worsen and I was in a downward spiral.

I researched bariatric surgery as an option. I found out that this type of surgery was invasive and it was not reversible. Most patients were out of work for up to 6 weeks and some had debilitating side effects. There seemed to be no hope for me and my 60th birthday was right around the corner. My future was dim.

Then I heard a commercial on the radio about a new scientific device to help people lose weight. Tufts University in Boston was looking for trial patients for a product call vBloc. I called the number, was interviewed, tested and was fortunate enough to be accepted in the trial.

I had my surgery for the vBloc implant on Friday morning December 2, 2011. I went home that afternoon and recovered for the weekend. I returned back to work Monday morning with little to no discomfort. This surgery is noninvasive, safe, effective and reversible. I am 3 ½ years out and have lost 70 pounds. The most impressive part of this experience for me is that I don't have the hunger that I used to. I have never been nauseous, had headaches or any discomfort with the device. It is very easy to maintain. I charge regularly every 2 to 3 days. It is much easier than

charging my cell phone. Most impressive is that I have been able to maintain my weight loss and keep it off.

My medications have been reduced and or eliminated. My blood pressure is normal and my cholesterol is great. I used to see my doctor every 4 to 6 weeks. Now I see him every 6 months.

This summer I intend to take that zip line tour in the White Mountains. I can tie my shoes. When my wife and I go out to eat we always sit in a booth and very comfortably. I am also looking forward to returning to the amusement park with my twin granddaughters to ride that rollercoaster.

I am now 63 years old and I can see much furthur into the future. Because of my weight loss with vBloc I am looking forward to a longer and healthier life.

Respectfully,

Mike Magnant
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Carver, MA 02330

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Evidence-Based Response on CTAF/ICER Draft Report on
"Controversies in Obesity Management"

June 9, 2015

The majority of people with the disease of obesity are either untreated or receive sub-optimal treatment. Unfortunately, for most individuals with Class I, II or III obesity, diet and exercise alone does not result in clinically meaningful and sustainable weight loss. In general, only 15-20% of patients who use conservative treatments (e.g., behavioral therapy, diet and exercise) achieve meaningful sustained weight loss.[i,ii,iii] It is our position that the evidence for comparative clinical effectiveness for vBloc neurometabolic therapy fits into the "promising, but inconclusive category" established by ICER. This view is based on the clinically meaningful weight loss demonstrated at 12 months of 24.4% (intent-to-treat analysis) and 26.1% (multiple imputation model), combined with the low rate of related serious adverse events (all which were resolved with no sequelae). Data on weight loss and safety have been published on the trial results through 18 months from the pivotal study ReCharge. Data is in the process of being published on improvements in obesity risk factors, quality of life and longer duration safety and effectiveness in patients with a BMI between 35 and 45 kg/m^2. These data continue to support the promise of vBloc neurometabolic therapy as a durable, less invasive and safer option compared to bariatric surgical interventions.

The vBloc neurometabolic therapy's clinical evidence has demonstrated to be an effective intervention for moderate to severe obesity through 36 months. Three trials have contributed to this assessment of safety and efficacy. EMPOWER was a randomized controlled trial in which 294 subjects with BMI 35 to 40 kg/m^2 with at least one obesity-related co-morbid condition or BMI 40 to 45 kg/m^2 with or without obesity-related co-morbid conditions were randomized in a 2 to 1 allocation of treatment to control.[iv] Therapy was delivered via external components using radio frequency methods. This trial provided *supporting* evidence of the safety of vBloc Therapy with a 3% implant procedure, device or therapy-related serious adverse event (SAE) rate at 12 months. Note that the device used in this trial is not the device that received approval by the FDA on January 14, 2015. Neuroregulator pocket infection, device revision for malfunction and neuroregulator repositioning for pain at the neuroregulator site which resulted in an overnight hospital stay were the most common SAEs. None of the SAEs was life-threatening, required emergency operation, or necessitated removing the subject from the study. No subject in either group developed abnormalities in their ECG, such as abnormalities in the PR interval, QRS duration, or the ventricular repolarization interval (QTcF interval), and no abnormalities were noted with Holter monitoring.

The efficacy analysis was confounded by variable hours of therapy delivery and an unanticipated therapeutic effect. The variable hours of therapy was a result of device technology and not trial design -- patients effectively were able to control the time of use due to the use of the external battery. The therapy design was for optimally12 hours of use per day, but many patients failed to comply. However, clinically important weight loss of 23%EWL was observed, *post hoc*, with at least 9 hours therapy delivery per day in a per protocol subgroup. In addition, improvements in patient reported outcomes with vBloc Therapy were observed using the SF-36 questionnaire ($p=.01$ change from baseline) and the Impact of Weight on the Quality of Life (IWQOL, $p<.001$

change from baseline). Control over hunger and appetite relative to baseline were observed using Three Factor Eating Questionnaire (cognitive control and hunger specifically, $p<0.0001$) and Visual Analogue Scales for appetite and hunger.[iv] The overall changes in the responses to questions were consistent with a decrease in hunger and an increase in early fullness in the treated group.

The second trial which provides support for the safety and efficacy of vBloc is VBLOC-DM2 which was a prospective, open-label, multi-center trial evaluating 28 subjects with obesity, type 2 diabetes and a BMI of 30 to 40 kg/m^2. This trial evaluated the Maestro Rechargeable System, where power is delivered from an internal battery and external components were used to recharge the device a few times per week. Data to 36 months post-implantation have been published.[v,vi] This study has shown approximately 24%EWL through 36 months post-implant with related SAEs of pain at the neuroregulator site and device malfunction. As with the EMPOWER study, these SAEs were not life threatening nor did they require emergency operation. Importantly, patients reduced their baseline HbA1c by 1 percentage point at 12 months and maintained a drop of 0.6 percentage points at 3 years. Similar improvements in fasting plasma glucose were also observed. Significant reductions in waist circumference of 11 and 7 cm were observed at 12 months and 36 months, respectively.

The pivotal trial that resulted in FDA approval of the Maestro Rechargeable System is the ReCharge trial. This trial is a double-blind, randomized controlled clinical trial in 8 centers in the United States and 2 in Australia, including 239 participants with body mass index (BMI) 40 to 45 kg/m^2 or BMI 35 to 40 kg/m^2 with one or more obesity-related conditions.[vii] Interventions comprised of either implantation with a Maestro Rechargeable System to deliver vBloc therapy or a sham surgery with implantation of a non-functional neuroregulator (Sham). Both groups received weight management counseling. FDA required that vBloc be superior to sham control by a 10% super-superiority margin and that the related serious adverse event rate (SAE) be less than 15%.

This trial provided proof of the safety of the vBloc therapy with a 3.7% implant/revision procedure, device or therapy-related SAE rate at 12 months, statistically lower than the performance goal of 15%. Neuroregulator revision for malfunction, neuroregulator repositioning for pain, vomiting, atelectasis and gallbladder disease which resulted in overnight or prolonged hospital stays were the related SAEs. Prolonged hospital stay due to nausea was the most commonly observed general surgery SAE. None of the SAEs necessitated removing the subject from the study.

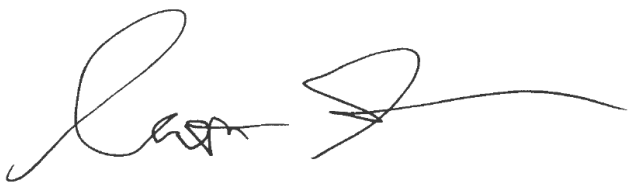
Superior weight loss of 24.4% was observed in the vBloc group compared to 15.9% in the sham control group at 12 months ($p=.002$). The pre-specified super-superiority margin of 10% was not met due to a sham control response of 3 times greater than expected (5% EWL expected versus 16% observed). However, the vBloc group achieved the expected EWL of almost 25%. The pre-specified responder rate was almost met with over 50% of subjects achieving 20% EWL at 12 months. Improvements in obesity-related risk factors such as blood pressure, heart rate, cholesterol, HDL, LDL, triglycerides and waist circumference were observed on average in all vBloc therapy subjects with greater improvements observed with corresponding greater weight losses.

At 18 months, %EWL was stable at 23% for the vBloc group and deceased to 10% for Sham group ($p<0.0001$). vBloc patients largely maintained their 12-month weight loss of 24%.[viii] Sham patients regained over 40% of the 16% excess weight by 18 months with most of the weight regain proceeding unblinding. The most common adverse events related to vBloc through 18 months were heartburn/dyspepsia and abdominal pain; 98% of events were reported as mild or moderate in severity and 79% had resolved. Weight loss with vBloc was sustained through 18 months, while the Sham group regained weight between 12 and 18 months. These results support vBloc as an effective obesity intervention with a low rate of serious complications.

Results of the ReCharge trial at the 18-month time point provide important context for weighing the benefits and risks of vBloc therapy. First, the trial continues to demonstrate sustained weight loss with vBloc therapy. Second, vBloc appears to have a favorable safety profile with a low risk of serious complications, and non-serious complications were typically mild or moderate sensations of the therapy that were resolved with little to no intervention. Interestingly, weight loss in the Sham group was considerably diminished within 6 months of the 12-month endpoint, despite continued blinding of the study past the 12-month visit and ongoing weight management counseling. These 18-month data were the topic of a meeting of the FDA Gastroenterology and Urology Devices Panel in June 2014 to consider US regulatory approval of the Maestro Rechargeable System to deliver vBloc therapy. The independent panel voted that the benefits of vBloc therapy outweighed the risks, and FDA subsequently granted approval the Maestro Rechargeable System in January 2015.

Thank you for your consideration and review. I welcome any questions and further dialogue on the statements provided herein and can be reached directly at: (339) 364-0949.

Sincerely,



Scott Shikora, MD
Executive Vice President and Chief Medical Officer
EnteroMedics

[i] Sacks FM, Bray GA, Carey VJ, et al. Comparison of Weight-loss Diets with Different Compositions of Fat, Protein and Carbohydrates. N Engl J Med 2009;360:859-873.
[ii] McGuire MT, Wing RR, Hill JO. The Prevalence of Weight Loss Maintenance Among American Adults. Int J Obes Relat Metab Disord 1999;23:1314-1319.
[iii] Kraschnewski JL, Boan J, Esposito J, et al. Long-term Weight Loss Maintenance in the United States. Int J Obes 2010;34:1644-1654.
[iv] Sarr et al. Obesity Surgery 2012;22:1781
[v] Shikora et al. Journal of Obesity 2013;doi:10.1155/2013/245683
[vi] Shikora et al. Obesity Surgery 2014;24:1148.
[vii] Ikramuddin et al. JAMA 2014;312:915-922
[viii] Shikora et al. Can J of Diabetes 2015;39:S36

Karen K Shore, PhD
Program Director
California Technology Assessment Forum
Institute for Clinical and Economic Review

Via Electronic Submission
RE: "Controversies in the Management of Obesity" – Additional Comments

Dear Dr. Shore:

Eisai Inc. appreciates the opportunity to provide comments related to your upcoming meeting, "Controversies in the Management of Obesity".

In your new document released on May 26th, we noted several statements specific to lorcaserin (marketed by Eisai in the United States as BELVIQ®) that need to be corrected for the record. Herein we provide comments and supporting evidence in response to those statements and request that a re-evaluation of the lorcaserin data be considered, based upon the data provided.

- **CTAF draft report suggesting lack of evidence for lorcaserin in patients with common obesity-related comorbidities:**
    - Page ES8: *"There is moderate certainty because while three good quality studies reported consistent weight-loss results, two studies excluded patients with common obesity-related comorbidities."*
    - Pages 58, 59, 60: *"Two of the three studies excluded patients with certain comorbidities, including hypertension and T2DM."*

  Eisai Inc. Response: In the BLOOM and BLOSSOM phase 3 trials a significant number of subjects: BLOOM (45.5%) and BLOSSOM (42%) did have comorbid conditions. The majority had dyslipidemia (33.3% and 27.7%, respectively), followed by hypertension (21.3% and 23.6%, respectively), sleep apnea (4% and 4.3%, respectively), glucose intolerance (1% and 1.5%, respectively) and CV disease (0.3% and 1.1%, respectively) .[1-2] Patients with hypertension were only excluded if they had persistent, uncontrolled hypertension .[1-3]

  In addition, BLOOM-DM was a 1-year study in adult patients with BMI greater than or equal to 27 kg/m2 with the comorbidity of inadequately controlled type 2 diabetes (HBA1C range 7-10%). [3] Patients also had other co-morbid conditions present at baseline, primarily hypertension (34.6%) and dyslipidemia (34.8%).[4]

- **CTAF report suggesting lack of evidence to support use of lorcaserin in patients with BMI<35 or ≥40:**
    - Page ES8 and Page 60: *We found no evidence of lorcaserin's benefits in populations with BMI levels ≤35 or ≥40.*

  Eisai Inc. Response: We are puzzled by the CTAF report's statement since another section of the draft report has clearly evaluated the weight loss effect of lorcaserin in those BMI categories and concluded that "Outcomes did not differ for patients in any BMI category for either the lorcaserin or placebo groups." (page 59)

  To further substantiate the beneficial effect of lorcaserin across different BMI

categories, below is a summary of weight changes stratified by baseline BMI.

Percentage of Patients Responding to Treatment by BMI Subgroup and Diabetic Status[5]

Obesity Classification (BMI Subgroup)	Patients Without T2DM		Patients With T2DM	
	PBO-DE % (n/N)	LOR-DE % (n/N)	PBO-DE % (n/N)	LOR-DE % (n/N)
Overweight (BMI <30 kg/m²)				
Subjects achieving ≥5% weight loss	24.6 (30/122)	58.3* (84/144)	13.8 (4/29)	50.0* (12/24)
Subjects achieving ≥10% weight loss	8.2 (10/122)	31.3* (45/144)	6.9 (2/29)	20.8 (5/24)
Class I Obesity (BMI 30 to <35 kg/m²)				
Subjects achieving ≥5% weight loss	24.9 (307/1235)	48.9* (589/1205)	17.3 (14/81)	38.3* (31/81)
Subjects achieving ≥10% weight loss	9.5 (117/1235)	23.6* (284/1205)	4.9 (4/81)	17.3* (14/81)
Class II Obesity (BMI 35 to <40 kg/m²)				
Subjects achieving ≥5% weight loss	20.2 (214/1060)	46.5* (508/1092)	11.4 (10/88)	31.8* (27/85)
Subjects achieving ≥10% weight loss	7.3 (77/1060)	21.7* (237/1092)	1.1 (1/88)	10.6* (9/85)
Class III Obesity (BMI ≥40 kg/m²)				
Subjects achieving ≥5% weight loss	21.9 (136/621)	42.5* (279/657)	24.0 (12/50)	39.3 (24/61)
Subjects achieving ≥10% weight loss	9.7 (60/621)	19.6* (129/657)	8.0 (4/50)	21.3 (13/61)

*p<0.05 ; PBO-DE: Placebo plus diet and exercice, LOR-DE : Lorcaserin plus diet and exercice

- **CTAF reporting suggesting lorcaserin is not recommended for patients with cardiovascular disease**:
  - Page 12: *"lorcaserin is not recommended for patients with cardiovascular disease."*

Eisai Inc. Response: We believe this is a misunderstanding of the Endocrine Society Clinical Practice Guidelines which actually recommend the use of lorcaserin or orlistat in patients with cardiovascular disease, as seen in section titled 'Care of the patient who is overweight or obese': "In patients with cardiovascular disease who seek pharmacological treatment for weight loss, we suggest using medications that are not sympathomimetics such as lorcaserin and/or orlistat." [6]

- **CTAF report suggesting lack of long-term data for lorcaserin:**
  - Page 59: *"All three studies had a follow-up duration of 52 weeks."*

Eisai Inc. Response: The BLOOM study was a 2-year study that enrolled 3182 patients. In Year 2, placebo patients were continued on placebo and lorcaserin patients were re-randomized in a 2:1 ratio to continue lorcaserin or to switch to placebo.[1]

Among patients in the lorcaserin group who had weight loss of 5% or more at year 1, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year 2 than in those who were reassigned to receive placebo. Patients who received lorcaserin in years 1 and 2 had a lower mean body weight than patients who

received placebo in both years and those who received lorcaserin in year 1 then placebo in year 2.[1]

Maintenance of Weight Loss at Year 2[1]

	Lorcaserin BID for 2 years (N=573)	Lorcaserin BID year 1 then Placebo year 2 (N=283)	P-value
Patients (%) who maintained ≥5% weight loss	67.9	50.3	0.001

In addition, recently published post-hoc analyses of the lorcaserin pivotal trials may help further elucidate the benefit of lorcaserin as used in real-world clinical practice.

The lorcaserin prescribing information indicates that lorcaserin should be discontinued if 5% weight loss is not achieved by week 12 (W12).[7] Therefore, the benefits of lorcaserin should be evaluated based upon its use only in those individuals who demonstrate an early (W12) response, as is recommended in the prescribing information.

In the pooled BLOOM and BLOSSOM trials (Completers Population) lorcaserin-treated W12 responders achieved a mean percent weight loss from baseline of 10.8% at Week 52.[7] In the BLOOM-DM trial (Completers Population), lorcaserin-treated W12 responders had a mean percent weight loss from baseline of 9.1% at Week 52.[8]

Obesity Management Questions for Deliberation (July 14, 2105) Public Meeting:

We would also like to point out that there is only one question (Question #6) in the Questions for Deliberation document regarding weight loss medications:

However, based on the above, it would be imprudent to exclude the opportunity to discuss the value of lorcaserin in patients with BMI <35 and ≥40 who could benefit from pharmacotherapy for weight loss.

In summary, we would strongly urge you to 1) update the report and reevaluate the value of lorcaserin and other weight loss medications based on the additional evidence provide and 2) consider adding more questions for deliberation with regard to the value of lorcaserin and other weight loss medications in patients with a BMI<35.

Thank you for your consideration of our additional comments. Please feel free to contact me at randi_fain@eisai.com, or (201) 746-2532.

Best regards,

Randi Fain, MD, FCCP
Group Director, Medical Strategy
Medical & Scientific Affairs
Eisai Inc.

References:

1. Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. NEJM. 2010;363:245-256.
2. Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab. 2011;96:3067-3077.
3. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (2012); 20 (7):1426–1436.
4. Data on File: BLOOM-DM (APD356-010) CSR Page 88, Table 39: Eisai Inc.
5. Deborah Bade Horn, Randi Fain, Alan Glicklich, et al. Analysis of Weight Loss by Baseline Body Mass Index (BMI) in Lorcaserin-Treated Patients Affected by Overweight or Obesity With or Without Type 2 Diabetes Mellitus. Poster presented at ASBP; September 10-13,2014; Austin, TX.
6. Apovian CM, Aronne LJ, Bessesen DH et al. Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(2):342-62.
7. BELVIQ® (lorcaserin hydrochloride) CIV Tablet for Oral Use [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2014.
8. Smith SR, O'Neil PM, Astrup A, et al. Early Weight Loss While on Lorcaserin, Diet, and Exercise as a Predictor of Week 52 Weight-Loss Outcomes. *Obesity.* 2014; 00(00):00-00. doi:10.1002/oby.20841.

With regards to the LAP-BAND®, please include data from the 3-year U.S. pivotal study submitted to the FDA to expand the indication for use to include obese individuals with BMI 30-34 with medical comorbidity. An additional 2 years of follow-up on this same study population, culminating in 5 years of follow-up data (ClinicalTrials.gov NCT 00570505) demonstrated that >76.9% of subjects achieved at least 30% excess weight loss by month 4[1] and at every subsequent time point in the 5-year study.[2] Implantation of the LAP-BAND® resulted in statistically significant decreases in all measures of weight and body mass.[1, 2] Hypertension, dyslipidemia, and Type 2 diabetes improved significantly from baseline to month 60.[2] Laparoscopic adjustable gastric banding (LAGB) has also been shown to resolve metabolic syndrome and improve lipid profile over 5 years in obese patients with BMI 30- 40.[3] Pending publications include data from two FDA-regulated studies that demonstrate the rate of LAP-BAND® removals without replacement has significantly decreased since the original FDA approval for morbid obesity due to improvements in the device, procedure, and aftercare. Fifty-four months after LAP-BAND® placement, in the 5-year Lower BMI study, the rate of explants without replacement was 5.4%. Three-year and partial 4-year data from the HERO Study, an ongoing 5-year U.S. post-marketing study, has also demonstrated a 6.3% removal without replacement rate.

With regards to Intragastric Balloon (IGB), FDA-PMA approval of the OBERA™ Intragastric Balloon is imminent. The U.S. pivotal ORBERA™ trial was recently presented at Digestive Disease Week (DDW) on 5/18/15 by Dr. Barham Abu-Dayyeh from the Mayo Clinic. In this multi-center, prospective, randomized, non-blinded comparative study of obese patients with BMIs 30-40, subjects were randomized to either treatment with ORBERA™ or behavioral modification alone (Control). One hundred sixty (160) patients underwent endoscopic placement

of ORBERA™. The Orbera group experienced a mean 10.5% total body weight loss (TBWL) at 6 months (time of device removal), as compared to the mean 4.7% TBWL in the Control Group. The ORBERA™ group lost twice as much weight as the control group and was able to maintain significant weight loss six months after ORBERA™ removal. Additional information about this study and consultation with the investigators is available upon request. In Europe, the current ORBERA™ design, formerly branded as the Bioenterics Intragastric Balloon (BIB), has been on the market outside of the U.S. (OUS) since 2004. More than 280,000 devices have been distributed to over 80 countries. Ten years of OUS clinical product surveillance, more than 200 peer-reviewed publications, and over 80 global randomized controlled trials have demonstrated that ORBERA™ produces clinically meaningful weight loss and quality of life benefits for patients with BMI ≥ 30 with and without co-morbidities.[4-8] We anticipate similar results post-launch in the United States.

REFERENCES

1. Michaelson R, Murphy DJ, Gross TM, SM W. LAP-BAND for Lower BMI: 2-Year Results from the Multicenter Pivotal Study. Obesity. 2013; **21**: 1148-58.
2. ClinicalTrials.gov. Effectiveness and Safety Study of LAP-BAND Treatment in Subject with BMI >/= 30 kg/m2 and < 40 kg/m2. 2015 March 12, 2015 [cited 2015 June 2, 2015]; Available from: https://clinicaltrials.gov/ct2/show/NCT00570505
3. Heffron S, Singh A, Zagzag J, Youn H, Underberg J, Fielding G, et al. Laparoscopic gastric banding resolved the metabolic syndrome and improves lipid profile over five years in obese patients with body mass index 30-40 kg/m2. Atherosclerosis. 2014 Nov; **237**(1): 183-90.
4. Genco A, Maselli R, Frangella F, Massimiliano C, Michele L, Nicola B. Intragastric balloon for obesity treatment: results of a multicentric evaluation for balloons left in place for more than 6 months. Surg Endosc. Dec 2014.
5. Genco A, Bruni T, Doldi S, Forestieri P, Marino M, Busetto L, et al. BioEnterics Intragastric Balloon: The Italian Experience with 2,515 patients. Obes Surg. 2005; **15**(8): 1161-4.
6. Gottig S, Weiner R, Daskalakis M. Preoperative weight reduction using the intragatric balloon. Obes Facts. 2009; **2 Suppl 1**: 20-3.
7. Sallet J, Marchesini J, Paviva D, Komoto K, Pizani C, Ribeiro M, et al. Brazilian multicenter study of the intragastric balloon. Obes Surg. Aug 2004; **14**(7): 991-8.
8. Mathus-Vliegen E, Alders P, Chuttani R, Scherpenisse J. Outcomes of intragastric balloon placements in a private practice setting. Endoscopy. Dec 2014.

To: California Technology Assessment Forum

From: Steve Chen, MD
Executive Medical Director
Medical Affairs, US Region
Takeda Pharmaceuticals U.S.A., Inc.

Date: June 8, 2015

Re: Comments to "Controversies in Obesity Management" Draft Report (May 26, 2015)

Dear California Technology Assessment Forum:

We appreciate the efforts of CTAF in compiling research on obesity management and bringing this topic to the forefront for discussion. On behalf of Takeda Pharmaceuticals U.S.A., Inc., we want to thank you for the opportunity to respond to the draft report, "Controversies in Obesity Management" dated May 26, 2015 and have provided a summary of our comments below.

Weight Loss Outcomes

- The Contrave prescribing information instructs physicians to discontinue therapy for patients who do not experience a ≥ 5% weight loss after 12 weeks at the maintenance dosage.[1] In the naltrexone/bupropion (N/B) pivotal trials, efficacy results were based on data from all randomized patients with 1 baseline weight measurement and ≥ 1 post-baseline weight measurement, including patients who did not experience significant weight loss and those that discontinued treatment.[2-5] Therefore the efficacy results may not represent current clinical practice.
- Evidence of double-digit weight loss was demonstrated in an integrated analysis of the N/B clinical trials, which evaluated weight loss of early responders defined as ≥ 5% weight loss at week 16 mimicking the Contrave prescribing information.[6] Early responders achieved 11.3% weight loss at 56 weeks, which may more closely represent real world efficacy results. Also at 56 weeks, 85% of patients had ≥ 5% weight loss, 55% had weight loss ≥ 10%, and 30% had ≥ 15% weight loss. Weight loss at week 56 was similar (9.7 kg to 12.4 kg) across four baseline body mass index (BMI) groups: 27-29.9 kg/m^2, 30-34.9 kg/m^2, 35-39.9 kg/m^2, and ≥ 40 kg/m^2.
- On pages ES8 and 62, the draft report assessed N/B as having a "small net benefit" in patients with a BMI from 35-39.9 kg/m^2. In an integrated analysis of the N/B clinical trials where patients on N/B were stratified by baseline BMI groups: 30.0-34.9 kg/m^2, 35.0-39.9 kg/m^2, and ≥40 kg/m^2, weight loss with N/B at week 56 was similar across the 3 obesity classes (N/B range: 6.1% to 7.3%; placebo-corrected range: 4.0% to 5.0%, all $P < 0.001$), as was the categorical weight loss of ≥ 5% weight loss (N/B range: 49% to 54%, odds ratio relative to placebo: 3.5 to 4.3; all $P < 0.001$).[7] Additionally, based on FDA's evaluation of N/B's clinical data, Contrave is indicated for patients with a BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with ≥ 1 comorbidity as an adjunct to diet and exercise for chronic weight management.[1] For these reasons, we request that the draft report reflect the efficacy analysis

of BMI groups from 27 kg/m^2-35 kg/m^2 consistent with the studies presented above and FDA approved labeling.

Evaluated Population and Scope of Draft Report

- According to the analytic framework provided in the draft report on pages ES3 and 18, obesity management was evaluated in adolescents and adults classified as overweight or obese with a BMI of ≥ 25 kg/m^2. The population of interest in the report is inconsistent with the population that was studied in the N/B clinical studies, which included adults (18 to 65 years of age) with a BMI 30-45 kg/m^2 for patients with uncomplicated obesity or a BMI 27-45 kg/m^2 for patients with obesity and controlled hypertension and/or dyslipidemia.[2-5] This study population is reflected in the FDA approved indication.[1] Additionally, the pediatric population was not evaluated and therefore, not recommended for use in this population. We request that the draft report specifically address pharmacotherapy treatment consistent with FDA labeling to provide a balanced picture of the treatment guideline algorithms, which recommend pharmacotherapy treatments prior to considering bariatric surgery and devices.[8-10] Furthermore, we do not believe that the economic and healthcare benefit of pharmacotherapy, surgery, and devices can be compared with each other as they provide treatment options for varying patient populations during different stages of the treatment continuum. We recommend incorporating treatment guideline algorithms in evaluating pharmacotherapy treatment options for patients with BMI ≥ 25-35 kg/m^2.

Comorbidities and Related Outcomes

- In the N/B pivotal trials, secondary markers of cardiovascular and metabolic risk factors besides glycosylated hemoglobin (A1C) were assessed as secondary endpoints.[2-5] Due to the implications of improving comorbid conditions as a result of weight loss, we recommend providing additional results that summarize the significant effect of N/B on cardiovascular and other metabolic biomarkers (eg, lipid panel, waist circumference).
- Also, please consider adding additional information related to the benefits of modest weight loss on other comorbidities not included in the report (eg, osteoarthritis, gastroesophageal reflux disease, urinary incontinence, polycystic ovary syndrome/infertility).[11-22] A list of citations has been provided in the reference section for your review.

Economic Outcome Measures

- While the methodology used to develop the one and ten-year models of clinical and economic outcomes is transparent and reasonable, we suggest that CTAF consider revisions to several critical assumptions upon which these models are based. As previously discussed, assumed use of N/B in the analysis does not reflect the FDA approved label. N/B's label recommends that patients discontinue treatment if they do not achieve ≥ 5% weight loss after 12 weeks at the maintenance dosage.[1] The base case one-year model assumes WAC – 23.1% rebate for N/B's price of 12 months at 100% adherence ($1,645).[23] According to the N/B pivotal trials, 33% of patients exposed to N/B (32 mg/360 mg) discontinued treatment by week 16. Consequently the cost of N/B used in the base case is far greater than it is in actuality, once dropouts are removed from the analysis. Given the N/B label discontinuation guidance, the treatment sequencing sensitivity analysis depicts a greater likelihood of N/B use in clinical practice, and we recommend that this analysis be considered the base case.

- Second, while the prevalence of eligible Medi-Cal adult enrollees is appropriately estimated from NHANES, the assumptions regarding the percentage of patient who would opt for obesity treatment is not robust.[23] According to the US 2013 National Health and Wellness Survey (NHWS), independently conducted by Kantar Health, of individuals with either a BMI of $\geq$ 30 kg/m^2 or with a BMI $\geq$ 27 kg/m^2 and an obesity-related comorbidity, only 19.9% spoke to their physician regarding their weight during the previous 12 months. Of these, 5% were prescribed weight loss medications, and 3% and 1% received either a surgical or surgical band procedure, respectively. Consequently, the budget impact estimate for any obesity intervention should be far less than that projected in the CTAF report.
- Finally, we recommend including the cost of lifetime follow-up care such as nutritional supplements and laboratory testing for individuals receiving bariatric surgery, even if some of these costs are borne by the patient. Severe and costly complications can occur without this continuing treatment and follow-up.

Other Comments

- Page ES8. N/B is described as "naltrexone (sustained release, 32 mg daily) combined with bupropion (immediate release, 360 mg daily)". Both naltrexone and bupropion in N/B are extended release formulations.[1]
- Page ES8. The total weight loss range from Contrave clinical studies is noted as 5-7.8% with N/B vs 1.2-4.9% with placebo. In four NB pivotal trials, weight loss ranged from 5-9.3% with N/B vs 1.2-5.1% with placebo as specified on page 61.[2-5]
- Page 9. Please revise the wording for the mechanism of action of N/B and reference the primary source (Contrave prescribing information).
- Page 9 and 62 reference the Light Study, a cardiovascular (CV) outcomes trial that terminated early. We recommend referencing Takeda's press release on this topic instead of tertiary sources (ie, Fierce Pharma and Herper).[24] The Herper 2015 resource could not be found in the reference section of the draft report. Another option would be to remove reference to this study until final data have been published as it does not provide additional evidence related to CV safety.
- Page 60. Please clarify how baseline characteristics (eg, age and gender) were calculated. For the 4 pivotal trial populations combined, the mean age was 46 years and 83% female.[2-5]

We are interested in collaborating with CTAF to create a balanced assessment of obesity management and appreciate the review of our comments. Should you have any questions or comments, please feel free to contact me.

Thank you,

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References

1. Contrave [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.;2014.

2. Greenway FL, Fujioka K, Plodkowski RA, et al; COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2010;376(9741):595-605.

3. Apovian CM, Aronne L, Rubino D, et al; COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity.* 2013;21(5):935-943.

4. Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity.* 2011;19(1):110-120.

5. Hollander P, Gupta AK, Plodkowski R, et al; COR-Diabetes Study Group. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care.* 2013;36(12):4022-4029.

6. Plodkowski RA, Walsh B, Berhanu P, Shan K, Cerasoli F, Fujioka K. Early achievement of significant weight loss with naltrexone/bupropion is associated with additional weight loss at one year – an integrated analysis of four Phase 3 trials [poster T-740-P]. Poster presented at: The Obesity Society Annual Scientific Meeting; November 12-16, 2013; Atlanta, GA.

7. Apovian CM, Burns C, Walsh B, Taylor K. An integrated analysis of weight loss with combination naltrexone/bupropion therapy by BMI (obesity) classification [poster 1130-P]. Poster presented at: the American Diabetes Association Meeting; June 21-25, 2013; Chicago, IL.

8. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation.* 2013. doi: 10.1161/01.cir.0000437739.71477.ee.

9. American Association of Clinical Endocrinologists. Consensus Conference on Obesity. March 23-24, 2014; Washington, DC. Available at: https://www.aace.com/consensus_conference_on_obesity. Accessed April 14, 2014.

10. Department of Veterans Affairs and Department of Defense. VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity. Version 2.0 - 2014.

11. Singh M, Lee J, Gupta N, et al. Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: a prospective intervention trial. *Obesity*. 2013;21(2):284-290.

12. Kumar AA, Palamaner Subash Shantha G, Kahan S, et al. Intentional weight loss and dose reductions of anti-diabetic medications – A retrospective cohort study. *PLoS One.* 2012;7(2):e32395.

13. Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care.* 2011;34(7):1481-1486.

14. Wing, RR, Creasman JM, West DS, et al. Improving urinary incontinence in overweight and obese women through modest weight loss. *Obstet Gynecol.* 2010;116(2 Pt 1):284–292.

15. Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis (NASH): a randomized prospective trial. *Hepatol.* 2009;49:80-86.

16. Subak LL, Wing R, West DS, et al. Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med*. 2009;360(5):481-490.

17. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis.* 2007;66:433–439.

18. Grunstein RR, Stenlöf K, Hedner JA, Peltonen M, Karason K, Sjöström L. Two year reduction in sleep apnea symptoms and associated diabetes incidence after weight loss in severe obesity. *Sleep*. 2007;30(6):703–710.

19. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care.* 2006;29(9):2102-2107.

20. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. *Osteoarthr Cartil*. 2005;13:20–27.

21. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. *Hum Reprod Update*. 2004;10(3):267-280.

22. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women: The Framingham Study. *Ann Intern Med*. 1992;116:535–539.

23. Data on file. Takeda Pharmaceuticals, 2013.

24. Takeda Pharmaceuticals and Orexigen Therapeutics Announce Termination of the Cardiovascular Outcomes Study (Light Study) of the Obesity Drug Contrave®(naltrexone HCl and bupropion HCl). May 12, 2015. Available at: http://www.takeda.us/newsroom/press_release_detail.aspx?year=2015&id=334. Accessed June 6, 2015.

June 9, 2015

VIA Electronic Mail: ctaf@icer-review.org

California Technology Assessment Forum
c/o Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109

Re: Controversies in Obesity Management Draft Report

To Whom It May Concern,

Novo Nordisk Inc. (henceforth referred to as "Novo Nordisk") is pleased to submit the following comment letter to the California Technology Assessment Forum (CTAF) regarding the organization's Controversies in Obesity Management Draft Report released on May 26, 2015. Headquartered in Denmark, and with over 5,000 U.S. employees, Novo Nordisk is a global health care company with over 90 years of innovation and leadership in diabetes, obesity, hemophilia, and growth hormone disorders. Our organization is firmly committed to ensuring that all patients have access to high quality and effective health care, and we look forward to working with CTAF as it delves into the topic of improving obesity treatment.

Our comment letter focuses on the following: (1) Including only studies for liraglutide for obesity treatment and excluding studies of liraglutide for treatment of type 2 diabetes; (2) Accounting for the dynamic nature of the obesity treatment option landscape and relative availability of long-term data for emerging treatments; and (3) Consistently addressing all interventions of interest throughout the review, or clearly identifying why interventions were omitted.

Novo Nordisk addresses these comments in more detail below.

Specific Comments

(1) Novo Nordisk recommends the exclusion of studies of Victoza® (liraglutide) from review given those studies apply to use of liraglutide up to 1.8mg for treatment of type 2 diabetes rather than treatment of obesity

In December of 2014 Saxenda® (liraglutide) was approved by the Food and Drug Administration (FDA) at a dosage of 3mg as a treatment option for adults with either a body

mass index (BMI) of 30 or greater or with a BMI of 27 or greater in combination with at least one weight related condition. While Saxenda® and Victoza® are both based on the same active ingredient (liraglutide), Victoza® data is derived from studies where it is used as an adjunct to diet and exercise to improve glycemic control for type 2 diabetes patients and is delivered at lower doses (1.2 or 1.8 mg) than Saxenda® (liraglutide 3.0 mg). In CTAFs analysis of liraglutide, studies comparing lower doses (i.e., less than 3mg) of liraglutide to placebo to gauge effects on blood glucose control, should not be included to assess effects on obesity or weight loss. To accurately assess the efficacy of liraglutide on obesity, Novo Nordisk recommends that CTAF only include the three identified studies, listed in the references below, related to Saxenda® (i.e., liraglutide dosed at 3mg for obesity treatment) in their review and exclude the remaining studies of Victoza® (i.e., liraglutide dosed at 1.2 or 1.8mg for type 2 diabetes).

(2) CTAF should account for the dynamic nature of the obesity treatment landscape and make appropriate accommodations when making any comparisons across treatment modalities given the differences in availability of long-term data on emerging therapeutic options.

Within the report, in the Clinical Effectiveness Summary, CTAF notes that given the dynamic nature of obesity the efforts to treat and manage the disease continues to grow as the prevalence also increases. The report does a good job of identifying the challenges associated with the individual types of treatment, including surgical procedures, devices and medications. While all important, Novo Nordisk asks that CTAF not compare each of these differences, as the evidence and patient population for each specific type of treatment will vary. Rather, we ask that CTAF consider comparisons within a treatment path, rather than comparisons across all treatments. Additionally, the data presented to support medications for weight loss needs to consider long-term results related to improvement in co-morbidities, long-term weight trends and health related quality of life. Although this data may not be available today, many of these products are new to the market and will have additional supportive data in the future. This data should be considered and updated to reflect the value of specific medications for this report.

(3) Throughout the report, CTAF should make every effort to address all interventions of interest via the same methods of analysis; in instances where this is not possible, the report should clearly explain why specific treatments are omitted.

Novo Nordisk applauds CTAF for taking a comprehensive approach when reviewing treatment options for obesity as the review is intended to cover surgical, device, and pharmaceutical approaches to obesity management. While the report clearly lays out the surgical procedures of interest, the three devices, and four pharmaceutical agents of interest, the full complement of therapeutic options are not necessarily addressed in each section of the report. For example, in Section 5, Model of Clinical and Economic Outcomes, when discussing prior published evidence of cost effectiveness of interventions of interest (other than surgical interventions), the report notes only the Maestro vBloc device (and no other

devices) and N/B therapy (and no other drug therapies) as "the other treatment options of interest in this review". The exclusion of other device options and the three other FDA-approved pharmaceutical treatments for obesity is inconsistent with the overall focus of the report. We recommend that all stated treatment options of interest be included in each section of CTAF's review. When this is not possible (e.g., newness of product dictates a lack of sufficient evidence of interest), CTAF should clearly outline why specific treatment options were omitted in the specific section for consistency and clarity throughout the entire review.

Conclusion

We appreciate the opportunity to provide comments on CTAF's Controversies in Obesity Management Draft Report. Novo Nordisk shares CTAF's unwavering commitment to improving the quality and effectiveness of care for all patients. We look forward to reviewing the Final Report and assisting in any way possible as your organization continues to evaluate this topic. If you have any questions or need any further information related to our comments, please do not hesitate to contact me at 609-786-4167 or TDDH@novonordisk.com.

Sincerely,

Todd Hobbs, MD
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References:

Pi-Sunyer X, Astrup A, Fujioka K et al. Efficacy and safety of liraglutide 3 mg for weight management in overweight and obese adults: the SCALE™ Obesity and Prediabetes, a randomized, double-blind and placebo-controlled trial. Abstract 700 presented at the 23rd Annual Scientific and Clinical Congress of the American Association of Clinical Endocrinologists (AACE). May 14-18, 2014; Las Vegas, NV.

Davies M, Bode BW, Kushner RF et al. Liraglutide 3.0 mg for weight management in obese/overweight adults with type 2 diabetes: results from the SCALE Diabetes 56-week randomized, double-blind, placebo-controlled trial. Diabetes. 2014;63(suppl 1):A26. Abstract 97-OR.

Wadden T, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie diet-induced weight loss: the SCALE™ Maintenance randomized study. *Int J Obesity (Lond)*. 2013;37(11):1443-1451.

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The staff of the Comprehensive Weight Control Center has been involved in obesity treatment and research for more than 25 years. We are compelled to comment on the California Technology Assessment Forum (CTAF)/Institute for Clinical and Economic Review (ICER) draft report on "Controversies in Obesity Management," published recently.

Obesity is one of the most serious health problems afflicting Americans. The recognition that obesity is a disease of hypothalamic signaling and adipose tissue hormone and metabolite production is becoming clear. The causal relationship between obesity and more than 50 illnesses is also clear.

We would like to point out a number of issues about the report.

1. **The title strongly implies that there is a controversy around obesity treatment. However, the word controversy is mentioned only twice in the report, once to describe bariatric surgery, around which there is no controversy – it is effective, and cost effective. At the end of the Executive Summary there is mention of controversy over the significance of BMI values of 25-35 kg/m2. The age adjusted relative risk of Type II Diabetes Mellitus increases with higher BMI values starting at a BMI of 24 kg/m2 (Diabetes Care 1994;17:961-969). The fact is, there is no controversy. Obesity is a disease, which should be treated. Given the complexity of body weight regulation, the difficulty has been in finding effective treatments. The major obstacle is a lack of coverage for much of what we do: behavioral obesity treatments to complement medical and surgical therapies, high co-pays and prior authorizations for medications, and various barriers including, in some cases, complete lack of coverage for surgical procedures.**
2. **The concerns about whether weight loss will be maintained if a patient stops an FDA approved obesity medicine as mentioned in the liraglutide section is**

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inconsistent with our understanding of body weight regulation and management of obesity as a chronic disease. Disease states such as diabetes, hyperlipidemia, or hypertension would recur if medicines for those were stopped. One of the purposes of the AMA's decision to recognize obesity as a disease state is to recognize that it would require long-term management with lifestyle intervention, diet, exercise, as well as long term use of medicine, devices or surgery to control the hormonal/neurologic abnormalities defining the disease.

3. **Package inserts for the medications recommend not continuing medications past 3-4 months if the patient does not lose 4-5% of body weight. Only those who benefit with medically significant weight loss continue on medication. This increases the benefit and minimizes risk and cost to those who do not respond. This factor does not appear to have been taken into consideration.**
4. **Given the complexity of the weight-regulating mechanisms, combinations of treatment will be needed and treatments with unique mechanisms of action will be critical. For example, the vBloc Maestro device which you mention has a unique mechanism of action, impacting vagal nerve signaling and affecting afferent weight regulating pathways. The promise of the vBloc Maestro device in combination with a centrally active drug which could produce significantly greater weight loss. This and other minimally invasive therapies that produce consistent results will open up treatment to more patients. Your analysis minimizes the potential benefit, and maximizes the cost and risk of such therapies.**

Sincerely,

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June 9, 2015

Dear CTAF Members:

As Principle Investigator of the team investigating vBloc at the Mayo Clinic in Rochester, I have been impressed by the short-term safety and clinical efficacy. Although on average the weight loss is not on par with traditional bariatric procedures, it has a much more favorable safety profile.

The options for treating obesity are generally limited to medical/behavioral treatment and bariatric surgery. Medical/behavioral treatment is generally very safe but is not very effective for patients who are beyond overweight and are in the obese category (e.g. body mass index > 30 kg/m2). Bariatric surgery is the most effective treatment for obesity but necessarily has the risks associated with a major surgery. Moreover, obesity is a complex disease and optimal management will almost certainly involve a variety of different treatments that consider a patient's specific needs. Commitment to a continued post-operative weight management program is critical to the success of any weight loss therapy and vBloc is no exception.

In clinical trials vBloc technology has shown much promise as a treatment option that is safe and effective. Despite exciting short-term results, it is premature to form definitive conclusions regarding the durability and long-term effectiveness of vBloc based on the data currently available, since the device was recently FDA approved and commercial experience and additional data are limited at this point.

In summary, current treatment options for obesity are severely limited. vBloc therapy is a technology that has the potential to add an important and novel treatment option for the treatment of this complex and widespread disease.

Sincerely,

Todd Andrew Kellogg, M.D.

TAK/tas

Response to the technology assessment prepared for the CTAF on Controversies in Obesity Management

Professor John B Dixon, Head of Clinical Obesity Research, Baker IDI Heart and Diabetes Institute Melbourne, Australia.

1) This technical assessment has some important flaws and inconsistencies but also some very important attributes. The literature review has failed to fully assess the literature. For example, it is hard to exclude the SOS study and have questionable conclusions about surgery and long-term sustained weight loss. There are many examples of duplicates of single studies getting into your analysis and others missing. When dealing with weight loss, use one measure and choose a measure that allows comparisons of different interventions and different cohorts. Actual weight loss favours heavier subjects, percentage excess weight lighter smaller. Percentage weight loss is widely advised as it is balanced for baseline BMI and actually gives us valuable information about health. How could there be two systems for surgery and devices versus lifestyle and medications? Even the leading surgical journals do not permit %EWL as a sole weight loss measure and it has never had an evidence based reason for existing. Please standardize how you express the most basic outcome. The CE analysis appears inadequate, unsophisticated, and brief given its importance to the questions. The focus is surgery and devices but fails to adequately consider the most common lifestyle interventions and drug therapy. The analysis is stratified by BMI but health costs are driven by obesity complications not BMI – Diabetes, CV events, physical disability, and OSA. The productivity and community costs need also to be evaluated. The cost of treating diabetes for example may actually be reduced by choosing surgery as suggested in studies of propensity matched groups.
2) Table ES1 is very important and really provides the answers to the key questions you are examining. Question – What is the place for any intensive therapies under a BMI of 30? Is there a disconnect between this chart and recommendations from the various US associations? Why is this not a key question? With limited resources why not deliver to those with at least low to moderate evidence? This table has another key anomaly that needs addressing. How do you distinguish devices from surgery? LAGB is classified surgery and vBloc a device. How can this be? There are many examples that will challenge these arbitrary divisions as we move forward. It is important to have clarity as, for example, a beneficial attribute of a device is its removability-reversibility. Strangely, removability (reversibility) by surgeons is seen as a downside, but physicians and patients often see this as a logical and positive attribute. This consideration is important when treating those with class I obesity, younger patients, more elderly patients and those with high risk specific comorbidity. Permanent change, as is clearly the case with sleeve gastrectomy, may not be seen as a positive attribute when we have negligible long term data and an increasing range of medications and devices in the pipeline.
3) I would urge the evidence based availability for effective therapies in the class I obese range. Serious obesity related comorbidity, current evidence regarding regulation and defence of energy balance, and the early life determinants of weight trajectory , and individuals with rapidly rising weight trajectory despite lifestyle interventions provide clear evidence of a chronic, often progressive, process that needs intervention beyond lifestyle – needing medication, devices and surgery.