The REDUCE Pivotal Trial

A Prospective, Randomized Multicenter Study to Evaluate the Safety and Efficacy of the Dual Balloon System in Obese Subjects
(SOARD 2015 in press)

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Dalton GA
Disclosures

- ReShape Medical: FDA clinical trial investigator, consultant
- USGI Medical: FDA clinical trial investigator
- Apollo Endosurgery: consultant, proctor
- Gore: consultant, speaker
- ConMed: consultant, speaker
- Ethicon: consultant
- Olympus: speaker, consultant
- Obalon: research

REDUCE Pivotal Trial
# Clinical Sites

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
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<td>University of Texas Medical School, Houston, TX</td>
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<td>University of Texas Medical School, Houston, TX</td>
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<td>Marquette General Hospital, Marquette, MI</td>
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<td>Sayeed Ikramuddin, MD</td>
<td>University of Minnesota, Minneapolis, MN</td>
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<td>Steven Edmundowicz, MD Shelby Sullivan, MD</td>
<td>Washington University, St Louis, MO</td>
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</table>
Background

• Saline-filled intragastric balloons:
  – Are endoscopically delivered, temporary devices that cause weight loss by occupying space in the stomach, inducing satiety and reducing food intake.
  – Used outside the U.S. since 1997, and result in 25%-40% percent excess weight loss (%EWL) at 6 months.

• Meet an unmet need for BMI 30-40 patients who don’t want or qualify for bariatric surgery

• Not intended to replace or compete with surgery
Device
Dual Balloon

- Two silicone balloons connected by a flexible shaft for migration resistance, large volume and tolerance
- Trans-oral endoscopic delivery over a guidewire
- Inflated with saline / methylene blue solution by a powered pump to a total volume of 750 - 900cc
Removal Procedure

- Left in stomach for up to 6 months
- Controlled, rapid emptying with suction catheter
- Secure capture and removal using standard snare
REDUCE Pivotal Trial Design

• Randomized, double-blinded, sham-controlled comparison:
  – DUO (Balloon, diet, exercise) vs. DIET (diet, exercise)
• Obese subjects (BMI 30-40 kg/m$^2$) with one or more obesity-related comorbidities
• Monthly counseling per NHLBI Guideline (2000)
• Assessments included weight, AEs, labs and quality of life measures
Co-Primary Endpoints:
1) $\%\text{EWL}_{\text{DUO}} > \%\text{EWL}_{\text{DIET}} + 7.5\%$
2) DUO Responder $\geq 25\%\text{EWL} > 35\%$
Subject Flow Chart

Weeks 0 – 24 Randomized Period

DUO Subjects (n = 187)
- 164 entered Weeks 24 - 48
- 167 completed 24 weeks of follow-up

DIET Subjects (n = 139)
- 77 implanted with Duo device
- 126 completed 24 weeks of follow-up

Randomization

594 screened

326 enrolled

Weeks 24 – 48 Follow-up Period

- 20 LTFU
- 13 LTFU

164 entered Weeks 24 - 48

28 LTFU

136 completed 48 weeks of follow-up

3 LTFU at Week 24

126 completed 24 weeks of follow-up

48 decline / ineligible 1 failed Duo insertion

13 LTFU

64 completed 48 weeks of follow-up

Weeks 24 – 48 Optional Duo Period

- 90% follow-up for primary endpoints
- Total of 187 + 77 = 264 dual balloon-treated subjects for safety

REDUCE Pivotal Trial
# Baseline Subject Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DUO subjects (187)</th>
<th>DIET Subjects (139)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.8 ± 9.5</td>
<td>44.0 ± 10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>95%</td>
<td>95%</td>
<td>NS</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>82%</td>
<td>86%</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kgs)</td>
<td>95.1 ± 11.7</td>
<td>96.9 ± 11.6</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>130.4 ± 13.9</td>
<td>133.2 ± 14.0</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>81.8 ± 10.1</td>
<td>82.8 ± 10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>200.3 ± 37.7</td>
<td>195.7.1 ± 39.8</td>
<td>NS</td>
</tr>
<tr>
<td>LDL</td>
<td>121.0 ± 33.1</td>
<td>119.9 ± 34.8</td>
<td>NS</td>
</tr>
<tr>
<td>HDL</td>
<td>52.0 ± 13.9</td>
<td>50.6 ± 13.0</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>140.9 ± 86.6</td>
<td>136.9 ± 88.3</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.0%</td>
<td>7.2%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Procedural Data

• Total of 531 insertion/retrieval procedures
• Insertions 99.6% successful
  – Mean duration 8.0 ± 3.4 minutes
• All dual balloon devices retrieved successfully
  – Mean duration 14.0 ± 10.4 minutes
• Three (1.1%) post-retrieval related SAEs:
  – Pneumonia (1, hosp/antibx), contained perforation of cervical esophagus (1, hosp/antibx), proximal esophageal mucosal tear (1, hemostatic clips)
%EWL Primary Endpoint Met: DUO significantly > DIET + 7.5%
Responder Rate Primary Endpoint Met: DUO responders significantly > 35%
Sham Blinding

### Treatment Subjects

<table>
<thead>
<tr>
<th>Bang Index:</th>
<th>Post-proc</th>
<th>Week 4</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Unblinded&quot;</td>
<td>41% 13% 47%</td>
<td>93% 2% 6%</td>
<td>93% 3% 5%</td>
</tr>
</tbody>
</table>

- **Correct**
- **Incorrect**
- **Unknown**

### Control Subjects

<table>
<thead>
<tr>
<th>Bang Index:</th>
<th>Post-proc</th>
<th>Week 4</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Unblinded&quot;</td>
<td>41% 9% 50%</td>
<td>67% 17% 17%</td>
<td>84% 6% 10%</td>
</tr>
</tbody>
</table>

- **Correct**
- **Incorrect**
- **Unknown**

### James Index:

- **"Blinded"**
- **"Unblinded"**
- **"Unblinded"**
Weight Loss Maintenance

• For DUO subjects at Week 48 (24 weeks after dual balloon retrieval):
  – Completers maintained a mean %EWL that was 65% of the %EWL achieved at the time of Week 24 retrieval
  – 36% of subjects maintained a %EWL ≥ 25%
  – 25% of subjects continued to lose weight after dual balloon retrieval, weighing less at Week 48 than they did at Week 24
# Comorbidity Benefits

Significant improvements through 48 weeks of follow-up

<table>
<thead>
<tr>
<th>DUO n=187 Measure</th>
<th>Value at Baseline</th>
<th>Change from Baseline at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Week 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>During dual balloon Tx</td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.7</td>
<td>-0.1</td>
</tr>
<tr>
<td>TG</td>
<td>140.9</td>
<td>-17.9</td>
</tr>
<tr>
<td>HDL</td>
<td>52.0</td>
<td>-0.9</td>
</tr>
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<td>Systolic BP</td>
<td>130.4</td>
<td>-8.2</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>81.8</td>
<td>-2.7</td>
</tr>
<tr>
<td>Waist (in)</td>
<td>42.3</td>
<td></td>
</tr>
<tr>
<td>Hip (in)</td>
<td>47.1</td>
<td></td>
</tr>
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REDUCE Pivotal Trial

Bold figures are significantly better than baseline value
Quality of Life and Patient Satisfaction

- IWQoL, SF-36, patient survey
- DUO QoL significantly better than DIET QoL at 24 weeks
- 64% of all dual balloon subjects would repeat the procedure and 78% would recommend it to a friend

IWQoL, SF-36 benefits continued for 48 weeks
Post-Insertional Symptoms

Symptoms are generally mild to moderate and resolve over first week

Rhodes Index of Nausea and Vomiting
(all implanted subjects)

Abdominal Pain
Visual Analog Scale
(all implanted subjects)
Safety

• In 264 dual balloon-implanted subjects:
  – No deaths, migrations, obstructions or surgery

• Most AEs were GI symptoms which:
  – Occurred ≤ 30 days
  – Were 99% mild / moderate in severity
  – Resolved within days

<table>
<thead>
<tr>
<th>Device-related AEs &gt; 5% frequency:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Gastric ulcer</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Eructation</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Gastritis</td>
</tr>
<tr>
<td>GERD</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
</tbody>
</table>

N=264 dual balloon-implanted subjects
Early Retrievals and Deflations

• 15% of dual balloons were retrieved early
  – 6% were late (>2 months) and associated with ulcers
  – 9% were early device intolerance ≤ 2 months
  – → reduced fill volumes (750cc) for shorter subjects, reducing non-ulcer related intolerance by 60%

• Deflations in 6% of subjects
  – 69% heralded by blue-green urine
  – No migrations, all devices retrieved without incident
Proximal balloon deflated with food bezoar
Proximal balloon deflated
Balloon covered with a microbial biofilm
Balloon with air fluid level
Balloon with air fluid level
Change in Fill Volume

- Disproportionate early retrieval rate in short subjects (stature ≤ 5’ 4””) detected early in trial
- Short subjects treated thereafter with 750cc fills

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>ITT</th>
<th>mITT</th>
<th>Non-Ulcer Early Retrieval % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tall</td>
<td>128</td>
<td>Yes</td>
<td>Yes</td>
<td>8.6 (11)</td>
</tr>
<tr>
<td>Short – 750</td>
<td>93</td>
<td>Yes</td>
<td></td>
<td>6.5 (6)</td>
</tr>
<tr>
<td>Short – 900</td>
<td>43</td>
<td>No</td>
<td></td>
<td>16.3 (7)</td>
</tr>
</tbody>
</table>

Overall non-ulcer early retrieval rate: 7.7%
Gastric Ulceration

- Gastric ulcers were observed in 35.2% (93/264) dual balloon-implanted subjects, 95+% in incisural region

- Clinical impact:
  - 1 GEJ ulcer with bleeding → hemostatic clips, transfusion
  - Remaining ulcers without clinical consequence, and all resolved with device retrieval and PPI treatment

- Cause: distal tip contacting the incisural wall

- Minor changes were made to the device during the trial to make the distal tip lower profile, smoother and softer, which dramatically reduced ulcer rate and size
Reduction in Ulcer Rate and Size

- Total of 107 subjects treated with modified device
- 10.3% ulcer rate, all minor, without clinical impact

All ulcer findings determined by independent CEDMC review of endoscopic images and videos
Superficial ulcer (0.3 cm) at the incisura
Ulcer at the incisura with follow-up endoscopy

3.3 months
Conclusions

• The dual balloon is a reversible intervention for BMI 30-40 patients who do not qualify or are not ready for surgery

• Effective: 25% ITT EWL at 24 weeks, 2.2X that observed in DIET subjects (11%)

• An average of 65% of the 24 week weight loss is sustained through 48 weeks

• Significant benefits seen in comorbidity labs and in quality of life measures through 48 weeks
Conclusions

• Overall safety profile is good
  – Accommodative symptoms occur but can be treated successfully with reassurance, Rx, fluids
  – Small benign ulceration may occur (~10%); and requires vigilance re PPI prophylaxis and late onset ulcer symptoms

• Future applications might include:
  – Sequential use for greater or more prolonged weight loss
  – Combined use with weight loss drugs
  – Adolescents as an early, reversible intervention
  – Morbidly obese patients (BMI 40+) requiring weight loss prior to surgical procedures
Thank You