REVITA-1 study

Evaluation of the Duodenal Mucosal Resurfacing (DMR) for the Treatment of Type 2 Diabetes

Trial Rationale and Design

F. Holleman

Objective

To demonstrate the

efficacy and safety of the

Fractyl Revita DMR procedure compared to a sham procedure for the

treatment of type 2 diabetes

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Multicenter trial

Single arm phase:

- ≥ 25 patients DMR treatment
- 3-month follow-up
- Establish safety, feasibility, approximate effect size & SD

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Randomization phase:

- Up to 240 patients
- Randomized 2:1 double blind to DMR or sham
- At 3 months primary endpoint: Reduction in HbA1c
- After 3 months unblinding: Sham patients also DMR
- Follow-up 3 years: durability of effect

Inclusion criteria

- Age 28-75 years
- Type 2 diabetes ≤ 10 years
- HbA1c 59-97 mmol/mol (7.5-11.0%)
- BMI ≥ 24 and ≤ 40 kg/m^2
- On at least 1 stable oral glucose lowering drug for at least 3 months

Exclusion criteria (1)

- Insulin production failure
  - fasting C-peptide < 1ng/mL (333 pmol/l)
- Current use of insulin or GLP-1 analogues
- Hypoglycaemia unawareness or a history of severe hypoglycaemia
- Known autoimmune disease
- Previous GI surgery (that affects ability to treat duodenum)
- History of chronic or acute pancreatitis

Exclusion criteria (2)

- Known active hepatitis or active liver disease
- Symptomatic gallstones or kidney stones
- History of coagulopathy or upper gastro-intestinal bleeding conditions
- Specific medications
- Persistent anaemia (Hb < 10 mg/dl)
- eGFR or MDRD < 60 ml/min/1,73m^2
- Active systemic infection
- Active malignancy < 5 years

- *Additional exclusion criteria at 2nd (baseline) and 3rd (endoscopy) visit*

Screening period

Visit 1: Screening:

- Verification primary in- and exclusion criteria

4-week medication run-in:

- Glucose concentration-independent insulin secretagogues (sulfonylureas and meglitinides) discontinued
- Adding DPP-IV inhibitors optional (investigator's discretion)
- Other medication maintained stable
- Home blood glucose monitor
- Keeping glycaemia diary

Screening period

Visit 2: Baseline:

- Medication / Compliance,
- Glycaemia diary, DTSQs,
- Blood analysis and urine analysis (MA)

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Additional exclusion criteria:

- HbA1c < 7.5% (59) or > 11.0% (97) after run-in
- Hyperglycaemic events
  - 3x FBG > 15 mmol/L (270 mg/dL) or NFBG > 20 mmol/L (360 mg/dL)
  - Confirmed by laboratory blood test since Visit 1
- Hypoglycaemic events
  - FBG < 3.1 mmol/L (56 mg/dL) and/or 3rd party assistance

Endoscopic Screening

Visit 3: Endoscopic screening

- Assessment of the esophagus, stomach, duodenum and associated structures

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Additional exclusion criteria:

- Active and uncontrolled GERD (≥ grade III esophagitis)
- Abnormalities GI tract preventing access to duodenum
- Abnormalities duodenum precluding completion of the DMR procedure
- Malignancy
- Upper GI bleeding conditions

Endoscopic Treatment

Visit 3: Endoscopic treatment

- Randomization: DMR or sham (2:1)
- Followed by diet for 2 weeks
- PPI 5weeks from procedure

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3-month follow-up phase:

- Stable medication
- Record hypo- and hyperglycaemic events in glycaemia diary

Follow-up

Visit 4: Phone call (day 7)

Visit 5 – 13: Office visits

- 1, 3, 6, 9, 12, 18, 24, 30, 36 months
- Anamnesis & physical exam
- Blood analysis & urine analysis
- Medication use
- DTSQs (additional DTSQc at 3 months)

Follow-up

Visit 6: Primary endpoint visit

- 3 months
- Unblinding

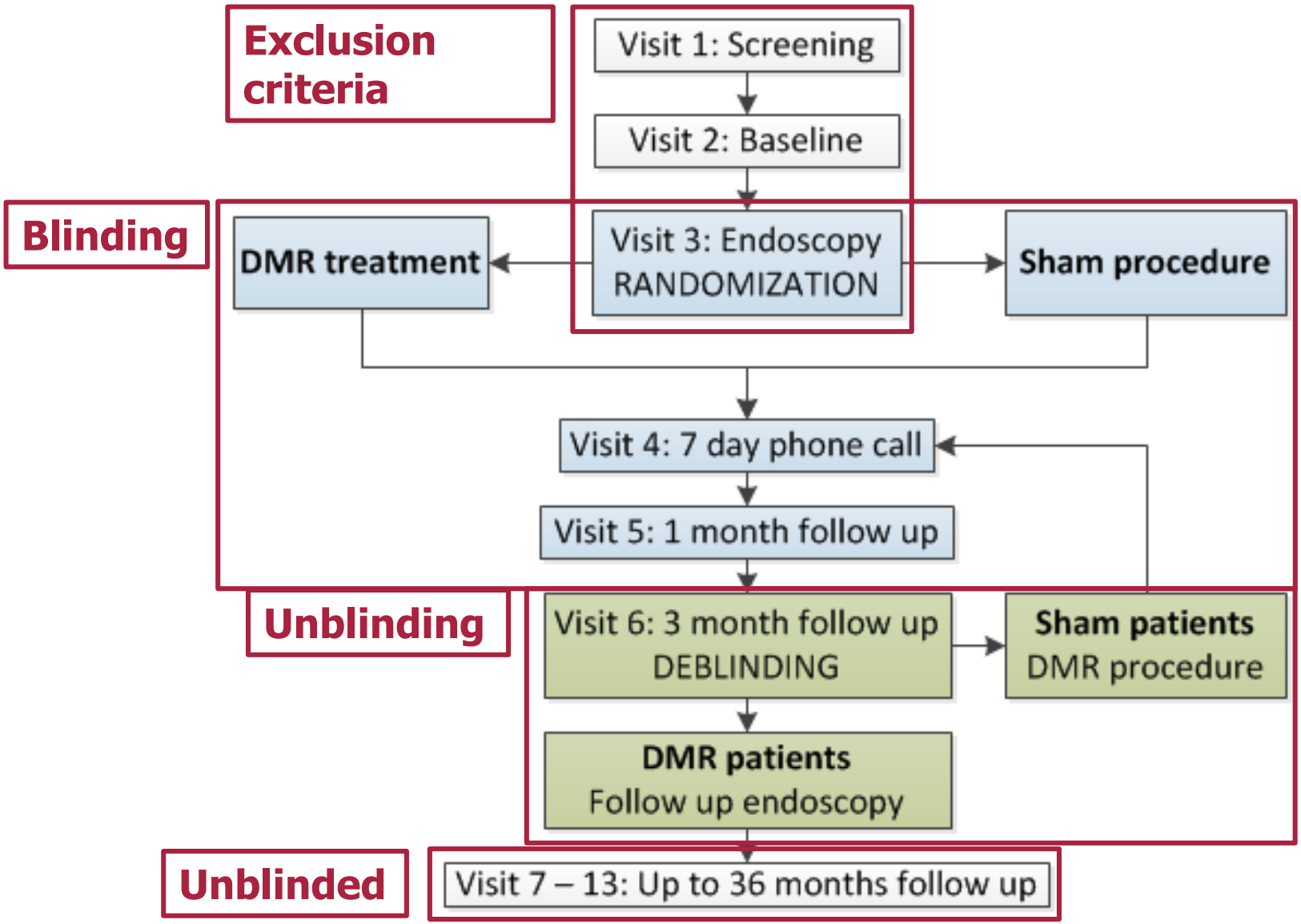
DMR patients:

- Follow up endoscopy and standard follow up
- Medication regimen intensively managed (changes allowed)

Sham patients:

- DMR treatment and restart follow up from visit 4

Overview


Exclusion criteria
Visit 1: Screening
Visit 2: Baseline
Blinding
DMR treatment
Visit 3: Endoscopy RANDOMIZATION
Sham procedure
Visit 4: 7 day phone call
Visit 5: 1 month follow up
Unblinding
Visit 6: 3 month follow up DEBLINDING
Sham patients DMR procedure
DMR patients Follow up endoscopy
Unblinded
Visit 7 – 13: Up to 36 months follow up

Efficacy endpoints

Primary (at 3 months):

- Reduction HbA1c from baseline

Secondary (at 3 months):

- Achievement of ≥1% reduction in HbA1c
- Reduction in FBG
- Reaching a target HbA1c ≤ 7%
- Weight loss (Kg and % EW)
- DTSQ (s and c)

Exploratory (up to 36 months)

Safety endpoints

Primary (through 3 months post randomization):

- Incidence rate SAEs
- Incidence rate UADEs
- Incidence rate hypoglycaemic events

Secondary:

- Incidence rate of all SAEs and UADEs
- Device performance
- Successful completion of submucosal expansion
- Successful completion of ablation

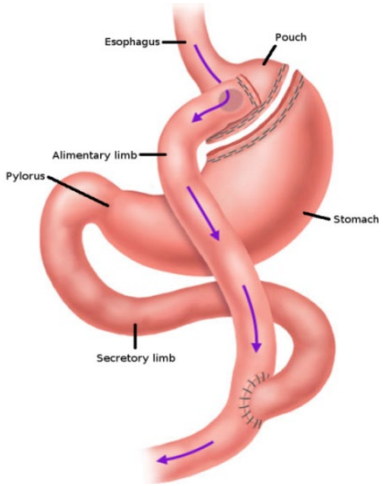
Questions?

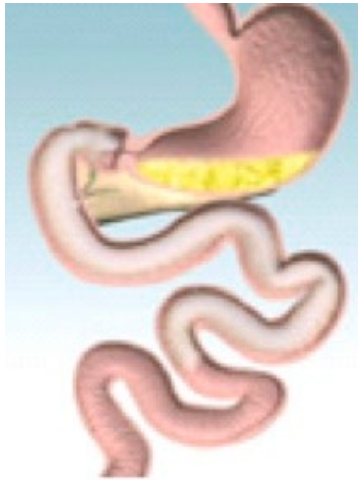
Background

Type 2 diabetes: Most prevalent and costly pandemic of our time

GI tract largest endocrine organ

Bariatric surgery and GI Dynamics Endobarrier: Anti-diabetic effect



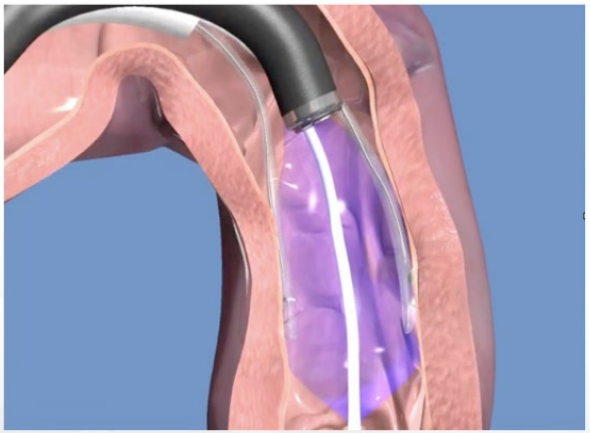


In duodenum cellular and hormonal changes in type 2 diabetes

Bypass duodenum: GLP-1 ↑ and GIP ↓

DMR procedure

DMR: Duodenal Mucosa Resurfacing



Endoscopic outpatient treatment (sedation)

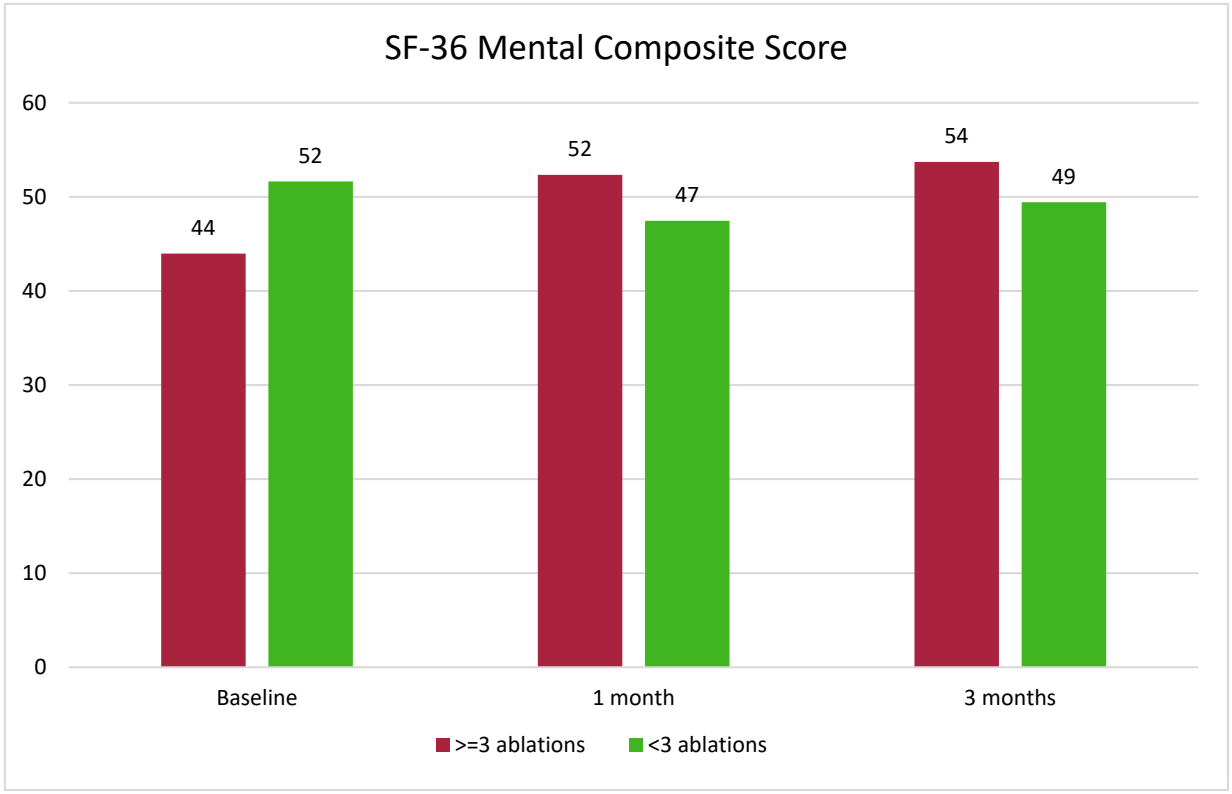
Submucosal injection of saline

Thermal mucosal ablation (3 segments of 3 cm)

Alter the hormonal response to food intake similar to bariatric surgery and GI Dynamics Endobarrier

Clinical experience

33 patients treated in Santiago, Chile



1 complication: duodenal stenosis (resolved after endoscopic dilatation)