MRI liver proton density fat fraction in patients with type 2 diabetes mellitus following treatment with Duodenal Mucosal Resurfacing

– results from a randomised, double-blind, sham-controlled, prospective, multicentre study –

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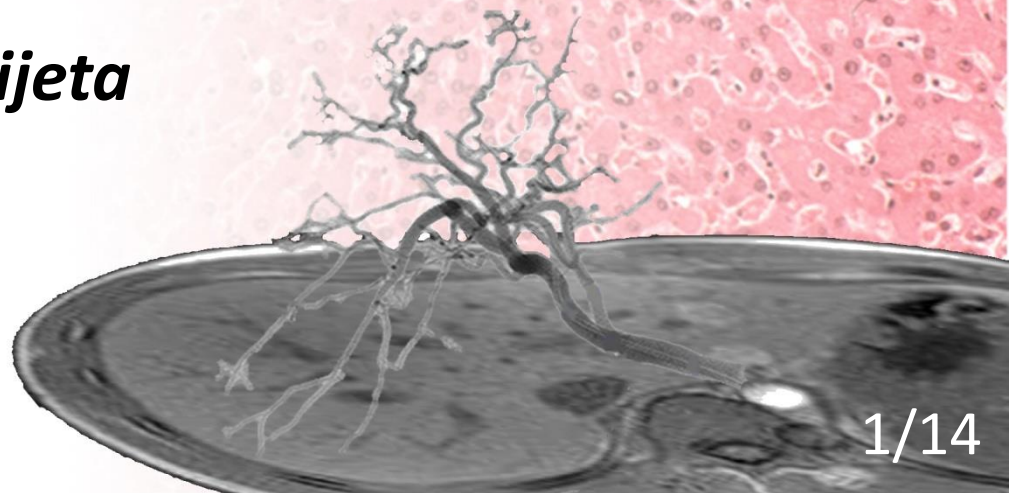
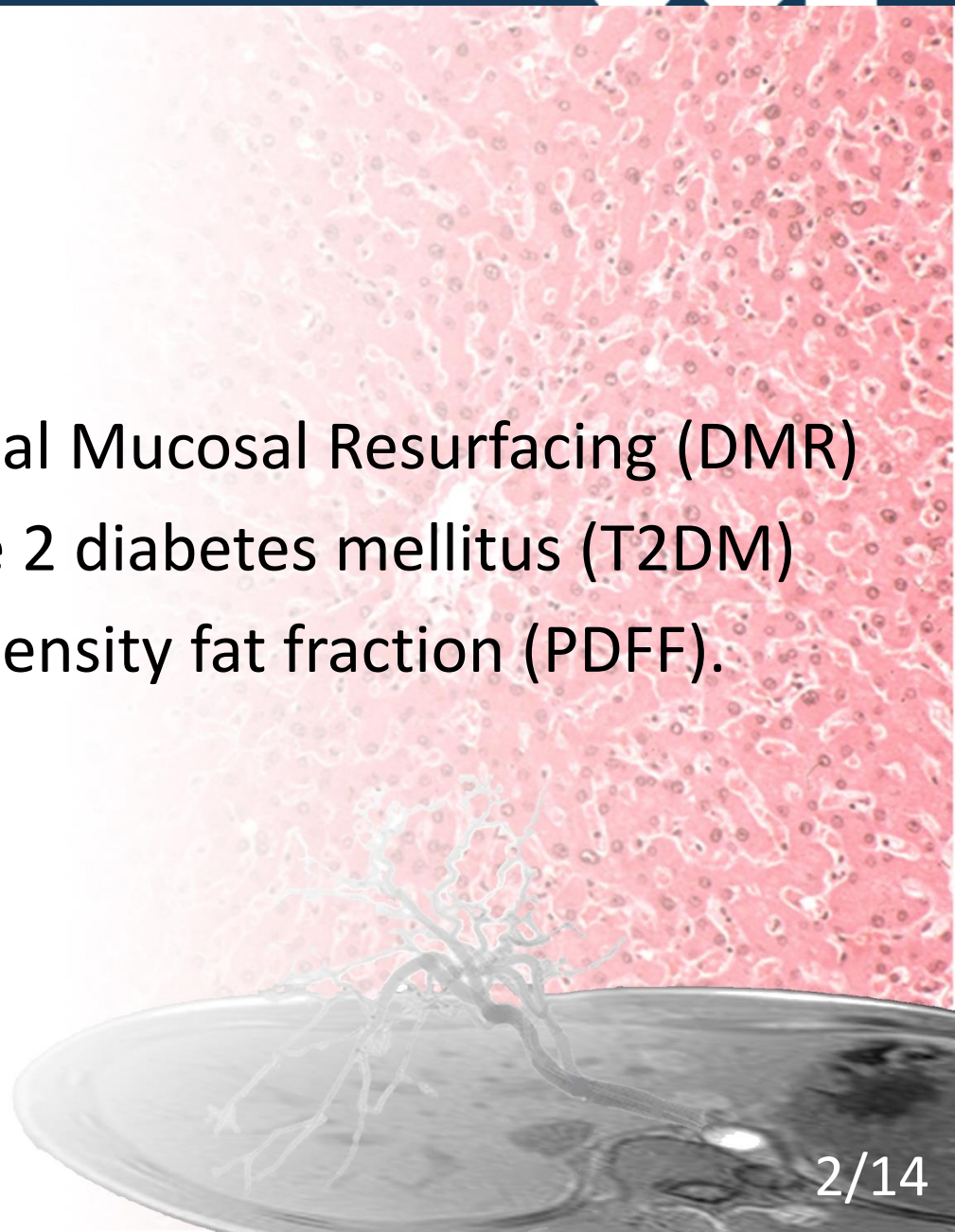


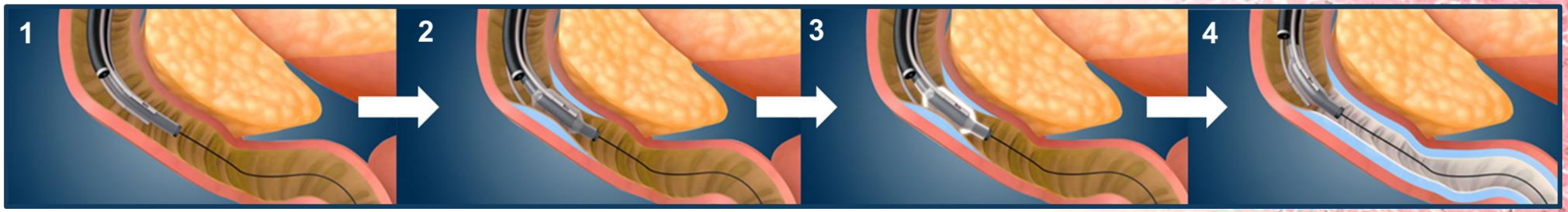
Purpose

To investigate the effects of endoscopic Duodenal Mucosal Resurfacing (DMR) in patients with sub-optimally controlled type 2 diabetes mellitus (T2DM) on liver fat fraction (FF) using MRI proton density fat fraction (PDFF).



Background – Duodenal Mucosal Resurfacing

- DMR catheter is designed to perform submucosal lift and hydrothermal ablation of hyperplastic duodenal mucosa, promote healthy epithelial regrowth within 12 weeks, and reduce insulin resistance and hyperinsulinemia[1,2]



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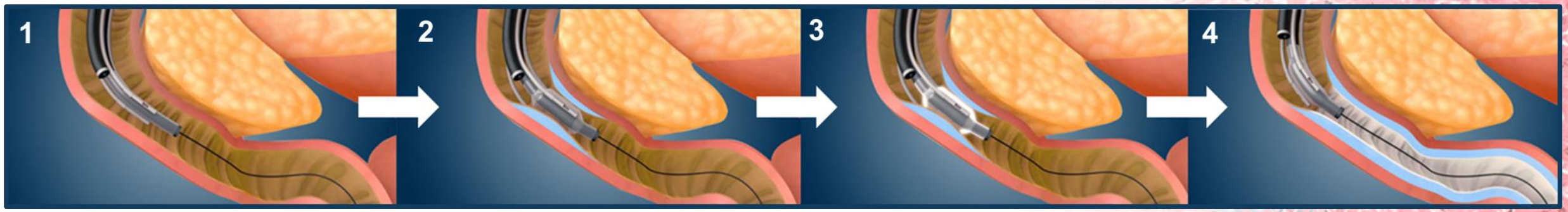
1. Hadefi A et al., *Dig Dis*. 2018;36:322-324.2. Rajagopalan H et al., *Diabetes Care*. 2016. 3. Cherrington A et al., *Gastrointest Endoscopy Clin N Am*. 2017;27:299-311. 4. Van Baar A et al., *Gut*. 2019; pii: gutjnl-2019-318349. 5. Haidry R et al., *GIE*. 2019; 673 - 681.e2. 6. van Baar ACG et al., DTM 2019 poster VAN 19122D.
REVITA-2 NCT02879383; DMR = duodenal mucosal resurfacing; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2D = type 2 diabetes.

Background – Duodenal Mucosal Resurfacing

- DMR is a well-tolerated procedure with few, self-limited side effects[3-5]
- Prior studies (eg, REVITA-1) showed a single DMR procedure durably improves hepatic and glycemic parameters through 2 years in patients with T2D, indicating potential benefit in T2D with concomitant NAFLD/NASH[3-6]



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Materials and methods – REVITA-2

Prospective, sham-controlled study of the effect of DMR on hepatic and glycaemic parameters in patients with sub-optimally controlled T2D across 11 sites (9 in EU, 2 in Brazil)

Objective

Demonstrate DMR efficacy and safety compared with sham for the treatment of suboptimally controlled T2D

Key Inclusion Criteria

- Aged 28 – 75 years
- T2D with evidence of preserved insulin secretion (fasting insulin > 7.0 µU/ mL)
- HbA1c 7.5 – 10%
- BMI ≥ 24 and ≤ 40 kg/m2
- On ≥ 1 oral antidiabetic medication (≥ 1 must be metformin)
- No medication or dose changes 12 weeks prior to study entry
- Able to comply with study and understand/sign informed consent

Key Exclusion Criteria

- Current use of insulin or GLP-1
- History of severe hypoglycemia
- Known autoimmune disease
- Active *H. pylori* infection
- Previous GI surgery (including bariatric)
- Participating in another ongoing clinical trial of an investigational drug or device

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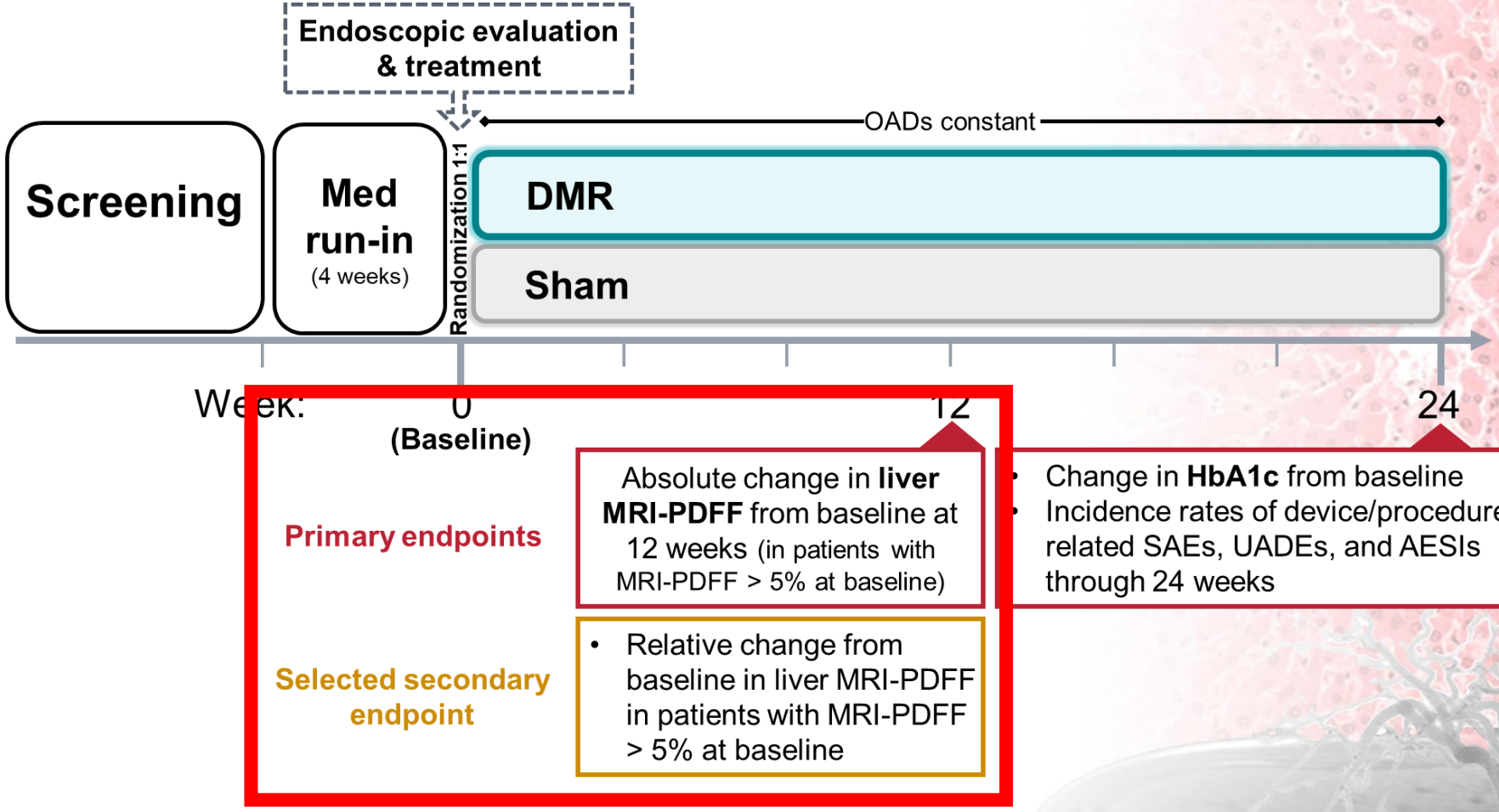
Data on File, Fractyl Laboratories Inc.
BMI = body mass index; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; T2D = type 2 diabetes.

Materials and methods – REVITA-2

Sham-controlled multi-site, multi-scanner vendor cross-over study of the effect of DMR with MRI derived primary and secondary endpoints



AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BG = blood glucose; BMI = body mass index; DMR = duodenal mucosal resurfacing; MRI-PDFF = magnetic resonance imaging proton density fat fraction; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OAD = oral antidiabetic medication; SAE = serious adverse event; T2D = type 2 diabetes; UADE = unanticipated adverse device effects.

Materials and methods – REVITA-2 – Image acquisition

- MRI-based proton density fat fraction (PDFF) can be used to quantify liver fat.

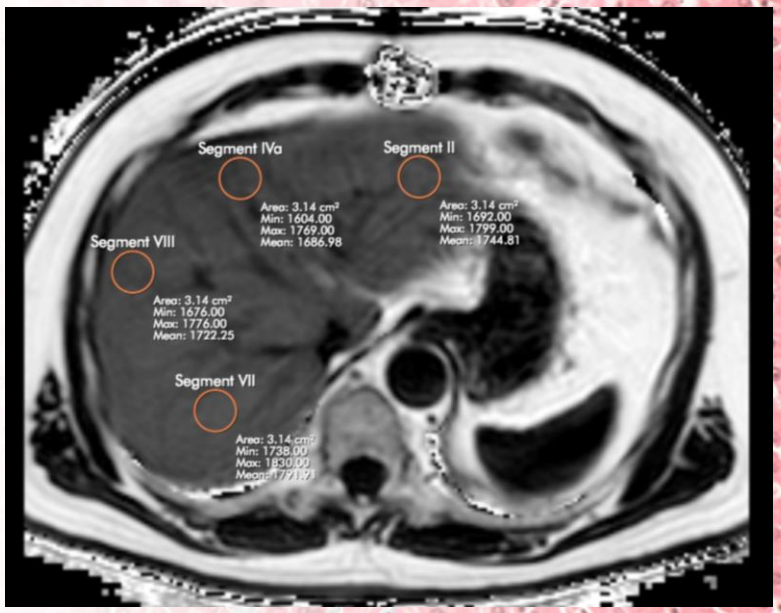
- Vendor-derived PDFF sequences (e.g. Philips mDixonQuant, GE IDEAL-IQ) were used for multi-site, multi-vendor, multi-field strength studies

Parameter	Philips	GE
PDFF manufacturer-supplied package	mDixon Quant	IDEAL IQ
Sequence variant	3D Spoiled Gradient Echo	3D Spoiled Gradient Echo
Imaging Time	Breath-hold (< 20s)	Breath-hold (< 20s)
3D Slab dimensions*	40 Axial slices FH – 240 mm RL – 400 mm AP – 350 mm	40 Axial Slices FH – 240 mm Freq FoV: 400 mm Phase FoV: 0.88
Voxel Dimensions	6 mm axial slices 2-2.5 mm isotropic in plane	6 mm axial slices 2-2.5 mm isotropic in plane
TR	Shortest (5-10 ms)	Shortest (5-10 ms)
Number of echoes	6	6
TE of first echo	Shortest (~1-2ms)	Shortest (~1-2ms)
Echo spacing	Shortest (~1-2ms)	Shortest (~1-2ms)
Flip Angle	3 degrees	3 degrees
Parallel Imagaing Factor	2	2
Number of averages	1	0.5
Number of shots	-	2
Reconstructed images	Fat-only image Water-only image PDFF map T2* map	Fat-only image Water-only image PDFF map T2* map

Materials and methods – REVITA-2 – Image analysis

- Images were analysed using a custom-developed online platform (Ambra Health, New York, USA)

- Circular ROIs measuring upto 20mm diameter were placed on each of the 9 Coinaud liver segments



Materials and methods – REVITA-2 – calibration

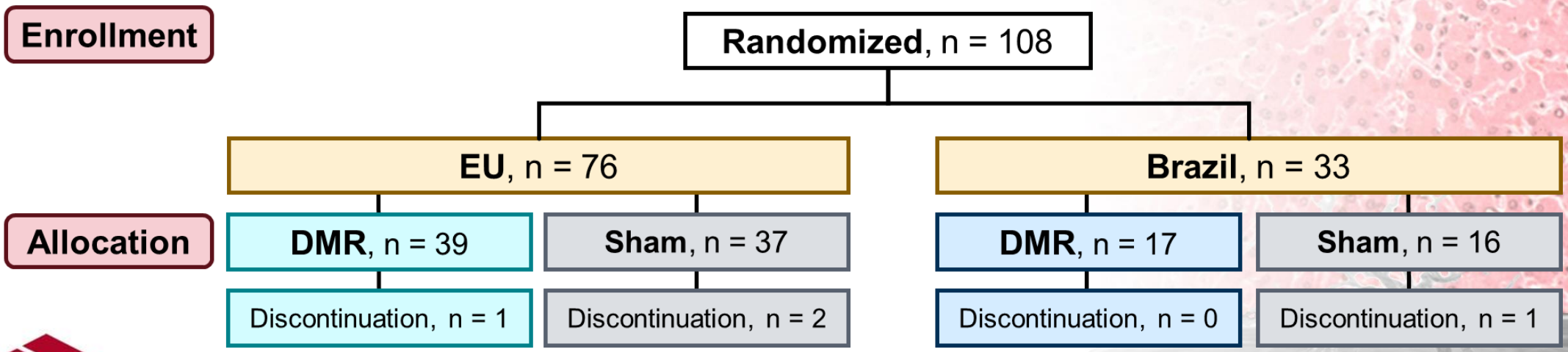
- Longitudinal measurement stability was confirmed using custom-built fat-water liquid-emulsion based phantoms

Results – Study cohort

Prespecified interaction statistical tests **assessed homogeneity** across geographic regions

Brazil not homogeneous to European countries in hepatic and glycemic endpoints, regardless of treatment group

Brazilian and European populations not poolable, analyses were stratified **by region**



Results – Patient demographics and baseline characteristics

Characteristic	DMR (N = 39)	EU Sham (N = 36)	p value*
Age, years	59.0 (40.0, 72.0)	56.5 (35.0, 75.0)	0.62
Male, n (%)	30 (76.9)	28 (77.8)	0.93
Weight, kg	93.1 (64.8, 155.0)	94.5 (66.6, 113.4)	0.66
BMI, kg/m^2	31.4 (23.6, 39.5)	30.4 (24.2, 39.6)	0.16
Liver MRI-PDFF, %	16.5 (5.5, 33.0)	16.1 (5.6, 33.8)	0.50
> 5% at baseline, n (%)	N=33 (85%)	N=27 (75%)	0.25
ALT, U/L	31.0 (11.0, 76.0)	29.0 (12.0, 162.0)	0.65
AST, U/L	21.0 (11.0, 44.0)	19.5 (10.0, 131.0)	0.31
Fasting glucose, mg/dL	191.0 (122.0, 313.0)	185.5 (110.0, 344.0)	0.68
HbA1c, %	8.1 (7.5, 10.0)	8.2 (7.5, 10.0)	0.45
C-peptide, ng/mL	2.5 (0.7, 4.9)	2.3 (1.5, 5.0)	0.48
Fasting insulin, mU/L	9.8 (2.4, 22.6)	8.4 (3.9, 17.6)	0.08

All data cited as median (min, max), unless stated

*Mann-Whitney U test for continuous variables due to non-normality and chi-squared test (or Fisher's exact test when appropriate) for categorical variables, unless otherwise specified.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; HbA1c = hemoglobin A1c

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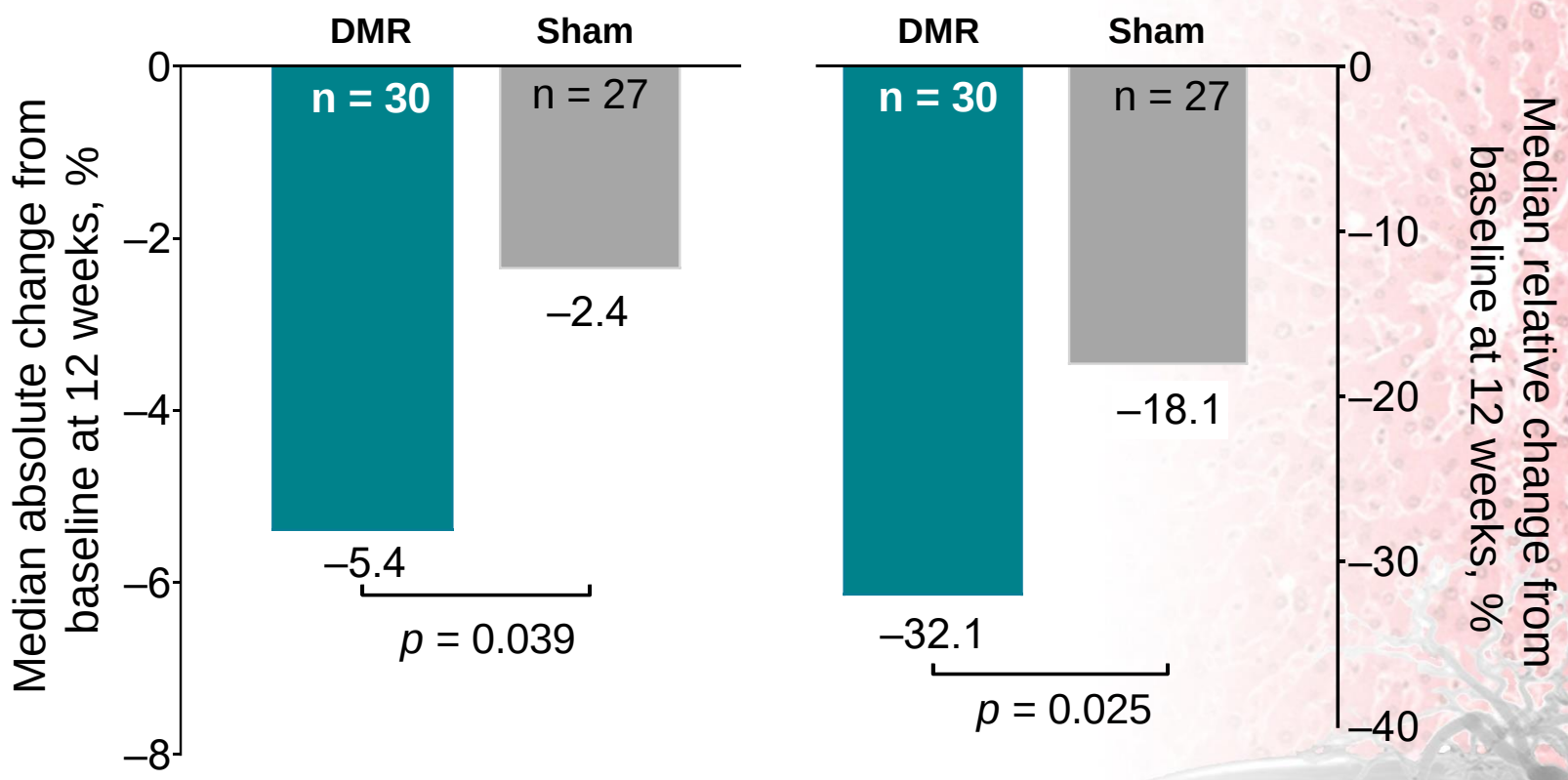
Results – MRI-PDFF

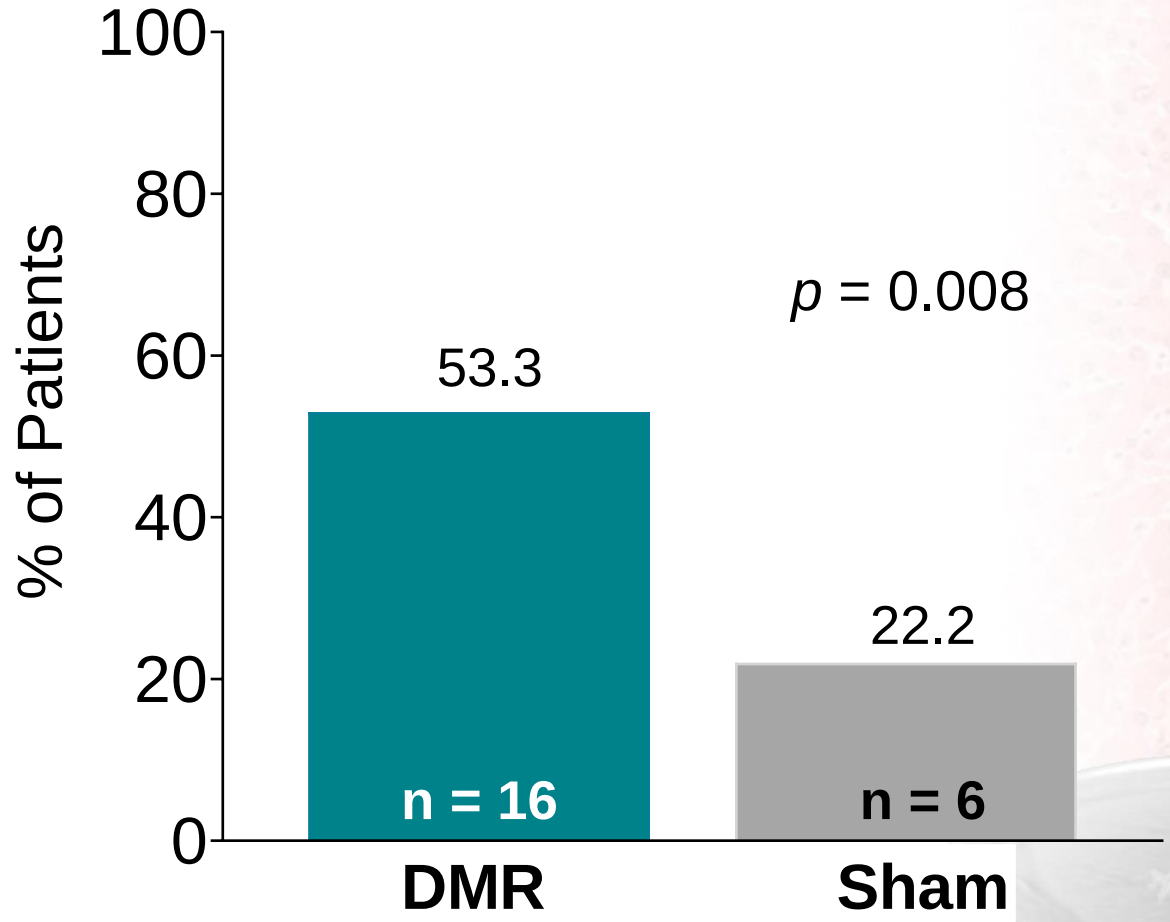
Changes in Liver MRI-PDFF in Patients with > 5% Liver Fat Content at Baseline (mITT)



Treatment comparison one-sided *p* value based on ANCOVA model with Multiple Imputation on the rank values (modified ridit scores). Via multiple imputation, analysis is based on all patients in the population of interest where post-rescue values are first set to missing.

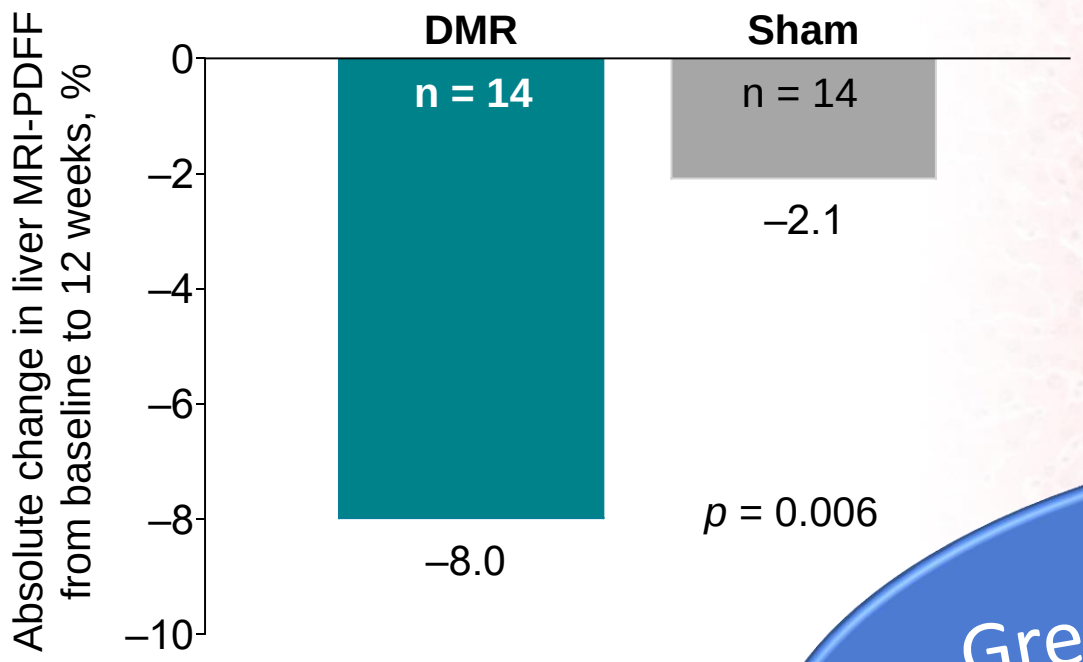
Results – MRI-PDFF responder analysis

>30% reduction in relative liver MRI-PDFF from baseline to week 12



Results - Patients with baseline fasting plasma glucose ≥180 mg/dL

Baseline median (min, max) liver MRI-PDFF: 20.3 (8.0, 35.8)



Greater benefit in patients with higher FPG at baseline

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Conclusion

DMR elicits favourable effects on liver PDFF at 12 weeks, in patients with sub-optimally controlled T2DM.