

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

Supplemental Table 1
Secondary Outcomes in Years 1-5, By Randomization Assignment

For 113 Patients (excluding 6 without 12-month data and 1 who died) Fitted Values from a Longitudinal Mixed Model Adjusted for Baseline Values and Site Treating Patient as a Random Effect* **					
<u>Outcome</u>	<u>Year</u>	<u>Mean (95% CI)</u>		<u>Difference (95% CI) RYGB minus IMM</u>	
		<u>IMM</u>	<u>RYGB</u>	<u>Difference*</u>	<u>P</u>
HbA _{1c} (%)	0	9.6 (9.3,10.0)	9.6 (9.3, 9.8)	-0.1 (-0.5, 0.3)	
	1	7.8 (7.4, 8.2)	6.3 (5.9, 6.7)	-1.5 (-2.0, -0.9)	<.001
	2	8.4 (8.0, 8.8)	6.4 (6.0, 6.8)	-1.9 (-2.5, -1.4)	<.001
	3	8.7 (8.3, 9.1)	6.7 (6.3, 7.1)	-2.0 (-2.5, -1.4)	<.001
	4	9.1 (8.7, 9.6)	7.0 (6.6, 7.4)	-2.2 (-2.7, -1.6)	<.001
	5	8.7 (8.3, 9.1)	7.1 (6.7, 7.5)	-1.6 (-2.2, -1.0)	<.001
Systolic BP (mm Hg)	0	132 (129, 136)	127 (123, 131)	-5 (-11, 0)	
	1	123 (120, 127)	115 (112, 119)	-8 (-13, -3)	.002
	2	124 (121, 127)	118 (115, 122)	-6 (-10, -1)	.02
	3	129 (125, 132)	122 (119, 126)	-7 (-12, -2)	.01
	4	129 (125, 132)	122 (118, 125)	-7 (-12, -2)	.01
	5	130 (126, 134)	124 (121, 127)	-6 (-11, -1)	.02
LDL-C (mg/dL)	0	102 (91, 113)	102 (92, 111)	-1 (-15, 13)	
	1	89 (81, 97)	83 (76, 91)	-6 (-17, 5)	.29
	2	86 (78, 94)	82 (75, 90)	-3 (-14, 7)	.53
	3	106 (97, 114)	92 (84, 99)	-14 (-25, -2)	.02
	4	99 (90, 108)	88 (80, 95)	-11 (-23, -0)	.05
	5	98 (90, 107)	83 (75, 91)	-15 (-27, -4)	.01
Weight Loss% From baseline	0	0	0	0	
	1	7.8 (5.5, 10.1)	26.1 (23.8, 28.4)	18.3 (15.0, 21.5)	<.001
	2	7.3 (5.0, 9.9)	23.9 (21.6, 26.2)	16.7 (13.4, 19.9)	<.001
	3	8.5 (5.1, 10.9)	22.0 (19.7, 24.3)	13.5 (10.2, 16.8)	<.001
	4	8.7 (6.2, 11.1)	21.7 (19.4, 24.0)	13.0 (9.7, 16.4)	<.001
	5	9.6 (7.2, 12.0)	21.8 (19.5, 24.1)	12.2 (8.9, 15.5)	<.001

Supplemental Table 2
Directly observed data By Randomization Assignment
For 113 Patients (excluding 6 without 12-month data and 1 who died)*

<u>Number of Patients With Data</u>		
<u>Year</u>	<u>IMM</u>	<u>RYGB</u>
0	56	57
1	56	57
2	54	56
3	44	55
4	42	54
5	43	55

“Year 0” is baseline.

Part A: Primary Outcomes			
<u>Outcome</u>	<u>Year</u>	<u>N (%) Success</u>	
		<u>IMM</u>	<u>RYGB</u>
Triple Endpoint**	0	0 (0%)	0 (0%)
	1	11 (20%)	28 (49%)
	2	8 (15%)	26 (46%)
	3	4 (9%)	15 (27%)
	4	2 (5%)	14 (26%)
	5	3 (7%)	15 (27%)
HbA1c < 7%	0	0 (0%)	0 (0%)
	1	18 (32%)	43 (75%)
	2	13 (24%)	42 (76%)
	3	9 (20%)	31 (56%)
	4	5 (12%)	31 (57%)
	5	9 (21%)	30 (55%)
Systolic BP<130mmHg	0	25 (45%)	29 (51%)
	1	44 (80%)	48 (84%)
	2	40 (74%)	47 (84%)
	3	25 (57%)	41 (75%)
	4	27 (64%)	40 (74%)
	5	22 (51%)	38 (69%)
LDL<100 mg/dl	0	30 (54%)	29 (51%)
	1	38 (70%)	45 (79%)
	2	39 (72%)	43 (77%)
	3	25 (57%)	38 (69%)
	4	22 (55%)	36 (67%)

Part A: Primary Outcomes			
<u>Outcome</u>	<u>Year</u>	<u>N (%) Success</u>	
		<u>IMM</u>	<u>RYGB</u>
	5	20 (49%)	40 (73%)

Part B: Secondary Outcomes			
<u>Outcome</u>	<u>Year</u>	<u>Mean (Standard Deviation)</u>	
		<u>IMM</u>	<u>RYGB</u>
HbA _{1c} (%)	0	9.6 (1.2)	9.6 (1.0)
	1	7.8 (1.5)	6.3 (0.9)
	2	8.4 (1.9)	6.5 (0.9)
	3	8.5 (1.9)	6.8 (1.2)
	4	8.9 (2.0)	7.0 (1.4)
	5	8.5 (1.9)	7.1 (1.5)
Systolic BP (mm Hg)	0	132 (14)	127 (15)
	1	123 (11)	115 (14)
	2	124 (13)	118 (14)
	3	128 (14)	122 (13)
	4	128 (14)	122 (15)
	5	130 (17)	124 (13)
LDL-C (mg/dL)	0	102 (41)	102 (35)
	1	89 (31)	83 (25)
	2	86 (33)	82 (28)
	3	104 (37)	91 (26)
	4	97 (29)	87 (27)
	5	97 (35)	83 (29)
BMI(kg/m ²)	0	34.4 (3.2)	34.9 (3.0)
	1	31.6 (3.8)	25.8 (3.5)
	2	31.8 (4.5)	26.5 (3.5)
	3	31.4 (4.6)	27.3 (3.8)
	4	31.5 (4.8)	27.5 (3.8)
	5	31.2 (4.7)	27.4 (3.9)
Weight Loss% From baseline	0	0 (0)	0 (0)
	1	8 (8)	26 (9)
	2	7 (9)	24 (9)
	3	9 (9)	22 (9)
	4	8 (9)	22 (9)
	5	9 (9)	22 (9)
Glucose(mg/dL)	0	205 (54)	222 (75)
	1	152 (59)	111 (34)
	2	172 (71)	114 (30)

Part B: Secondary Outcomes			
<u>Outcome</u>	<u>Year</u>	<u>Mean (Standard Deviation)</u>	
		<u>IMM</u>	<u>RYGB</u>
	3	174 (71)	130 (40)
	4	178 (63)	127 (45)
	5	161 (55)	132 (52)
Diastolic BP(mm Hg)	0	79 (10)	78 (12)
	1	74 (9)	68 (9)
	2	75 (8)	69 (10)
	3	76 (10)	71 (11)
	4	76 (10)	72 (10)
	5	77 (12)	72 (10)
HDL-C(mg/dL)	0	41 (8)	41 (11)
	1	42 (9)	50 (14)
	2	43 (11)	50 (13)
	3	45 (9)	52 (12)
	4	44 (9)	53 (13)
	5	45 (10)	52 (13)
T-cholesterol(mg/dL)	0	186 (42)	181 (38)
	1	162 (40)	153 (32)
	2	169 (41)	154 (35)
	3	187 (45)	164 (29)
	4	176 (37)	161 (31)
	5	176 (39)	159 (34)
Triglycerides(mg/dL)	0	250 (221)	258 (393)
	1	182 (150)	104 (48)
	2	257 (300)	110 (77)
	3	236 (324)	111 (58)
	4	197 (141)	112 (64)
	5	183 (123)	117 (99)
Number of Triple Endpoint Medications	0	4.3 (1.5)	4.1 (1.9)
	1	4.9 (2.1)	1.7 (1.8)
	2	4.6 (2.0)	1.9 (1.9)
	3	3.8 (2.2)	1.7 (1.6)
	4	3.9 (1.9)	1.9 (1.6)
	5	4.3 (2.1)	2.0 (1.6)

Part C: Post-hoc			
<u>Outcome</u>	<u>Year</u>	<u>N(%) Success or True</u>	
		<u>IMM</u>	<u>RYGB</u>
HbA1c < 6.0%	0	0 (0%)	0 (0%)
	1	5 (9%)	25 (44%)
	2	3 (6%)	21 (38%)
	3	3 (7%)	15 (27%)
	4	2 (5%)	13 (24%)
	5	2 (5%)	11 (20%)
Full or Partial Remission ^a	0	Not applicable	Not applicable
	1	Not applicable	Not applicable
	2	0 (0%)	22 (39%)
	3	0 (0%)	21 (38%)
	4	2 (5%)	20 (37%)
	5	2 (5%)	15 (27%)
Full Remission ^a	0	Not applicable	Not applicable
	1	Not applicable	Not applicable
	2	0 (0%)	12 (21%)
	3	0 (0%)	10 (18%)
	4	0 (0%)	9 (17%)
	5	0 (0%)	7 (13%)
Fasting Glucose < 100 mg/dl	0	1 (2%)	0 (0%)
	1	7 (13%)	25 (44%)
	2	5 (10%)	19 (34%)
	3	3 (9%)	12 (27%)
	4	2 (5%)	9 (20%)
	5	2 (5%)	15 (29%)
Using Insulin	0	24 (43%)	35 (61%)
	1	24 (43%)	10 (18%)
	2	24 (44%)	10 (18%)
	3	20 (45%)	8 (15%)
	4	15 (36%)	7 (13%)
	5	16 (37%)	8 (15%)
Using Non-Insulin Diabetes Medications	0	53 (95%)	49 (86%)
	1	55 (98%)	20 (35%)
	2	50 (93%)	24 (43%)
	3	37 (84%)	23 (42%)
	4	38 (90%)	22 (41%)

Part C: Post-hoc			
<u>Outcome</u>	<u>Year</u>	<u>N(%) Success or True</u>	
		<u>IMM</u>	<u>RYGB</u>
	5	38 (88%)	23 (42%)
Systolic BP <140 mm Hg	0	39 (70%)	46 (81%)
	1	51 (93%)	54 (95%)
	2	48 (89%)	53 (95%)
	3	35 (80%)	52 (95%)
	4	33 (79%)	51 (94%)
	5	35 (81%)	49 (89%)
Using Anti-hypertensives	0	41 (73%)	38 (67%)
	1	40 (71%)	21 (37%)
	2	34 (63%)	22 (39%)
	3	27 (61%)	21 (38%)
	4	26 (62%)	24 (44%)
	5	29 (67%)	26 (47%)
Using Dyslipidemia Meds	0	33 (59%)	31 (54%)
	1	36 (64%)	21 (37%)
	2	37 (69%)	24 (43%)
	3	21 (48%)	20 (36%)
	4	19 (45%)	23 (43%)
	5	23 (53%)	22 (40%)

*The current paper reports fitted values based on data from all 5 years. In contrast, the 1st year paper was based on data available at the time. Fitted values take into account missing data and are thus consistent with an intent to treat analysis. The 5y paper is based on the patients with 1 year visits, excluding one patient who died shortly after the 1y visit. The longitudinal mixed model that formed the backbone for this paper modeled changes from the 1-year visit; it was not practical to include patients without 1-year data. The 1y paper focused on early outcomes in the 120 randomized patients, using multiple imputation to fill in data for any missing 12-month visits. The differences in available data and analytic techniques (required by an intent-to-treat analysis) create differences in reported 1st year results

**“Triple Endpoint” = simultaneous achievement of HbA1c < 7.0%, Systolic BP < 130mmHg, and LDL < 100 mg/dl

**Supplemental Table 3
Details on Crossovers**

Total of 11 crossovers:

3 early crossovers (< 4 months post randomization): included in as-treated analyses using their chosen treatment

7 later crossovers (> 4 months post randomization) with data through 5 years: excluded from as-treated analyses

1 later crossover (> 4 months post randomization) lost to follow-up after 36 months: excluded from all 5-year as-treated and as-randomized analyses except adverse events

Lifestyle/Intense Medical Management = LS/IMM; RYGB = Addition of Roux-en-Y Gastric Bypass

Details for 11 Patients who Crossed Over (Including those who did so after the treatment protocol ended)			
<u>Randomization Assignment</u>	<u>Yr Had Surgery</u>	<u>Early Crossover</u>	<u>Completed 5y Visit?</u>
LS/IMM	1	*	Yes
RYGB	Never	*	Yes
RYGB	Never	*	Yes
LS/IMM	3		Yes
LS/IMM	2		Yes
LS/IMM	3		Yes
LS/IMM	3		Yes
LS/IMM	3		Yes
LS/IMM	3		Yes
LS/IMM	2		Lost to follow-up after 3y visit
LS/IMM	4		Yes

5-year Outcomes Data for 11 Patients who Crossed Over						
<u>Randomization Assignment</u>	<u>Yr Had Surgery</u>	<u>HbA1c</u>	<u>LDL</u>	<u>Systolic BP</u>	<u>Triple Endpoint*</u>	<u>% WtChg</u>
LS/IMM	1	7.4	66	101	No	-37%
RYGB	Never	8.2	52	125	No	7% gain
RYGB	Never	5.9	46*	122	Yes	-8%
LS/IMM	3	6.1	107	132	No	-15%
LS/IMM	2	8.0	156	166	No	-17%
LS/IMM	3	9.5	126	116	No	-11%
LS/IMM	3	7.5	141	115	No	-13%
LS/IMM	3	8.1	76	120	No	-23%
LS/IMM	3	5.6	80	100	Yes	-27%
LS/IMM	2				Lost to follow-up after 3y visit. At last report, HbA _{1c} =8.7; LDL=77; Systolic BP=125; PctWtChg=-34%.	
LS/IMM	4	5.5	76	163	No	-29%

*LDL (40-78 mg/dL) from 9 months through 48 months, and 46 mg/dL at 48 months. Data are missing at the 5y visit. The triple endpoint is treated as “missing” in as-randomized analyses.

**“Triple Endpoint” = simultaneous achievement of HbA_{1c} < 7.0%, Systolic BP < 130mmHg, and LDL < 100 mg/dl

Supplemental Table 4
Expanded Adverse Events on an As-treated Basis with crossovers (red) included

Adverse Events on an As-Treated Basis* --- IMM ONLY						
Years 1 Serious Events, 2: Clinically Important Events²; Year 3-5: Serious Events						
	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Year 4</u>	<u>Year 5</u>	<u>(Mix) Total</u>
Gastrointestinal						
Acute Pancreatitis	1	2	1	2		6
Pancreatic carcinoma	2	-	-			2
Cholelithiasis/cholecystectomy	-	-	1	-	1	2
Abdominal pain	1	-	-			1
Reflux esophagitis	2	-	-			2
Gastritis or Duodenitis	1	-	-	-	1	2
Bowel perforation	-	-	-	1	-	1
Cardiovascular						
Deep venous thrombosis	-	-	-			0
Congestive heart failure	-	1	-			1
Shortness of breath	-	-	-	1	-	1
Acute myocardial infarction	-	-	-			0
Retinal Vascular Occlusion	-	-	1			1
Retinopathy	-	-	-	-	1	1
Renal						
Nephrolithiasis	1	-	-			1
Acute renal insufficiency	-	-	-	1	-	1
Metabolic						
Diabetic ketoacidosis	-	1	-			1
Hyperglycemia	-	-	-	-	1	1
Musculoskeletal						
Below the knee amputation	-	-	-	-	-	0
Toe amputation	-	-	-	-	-	0
Foot amputation	-	-	-			0
Osteoarthritis	-	-	-	1	-	1
Neurologic						
Herniated spinal disc	-	-	-	-	-	0
Multiple sclerosis	-	-	-	-	-	0
Partial 3 rd cranial nerve palsy	1	-	-	-	-	1
Psychiatric						
Depression	-	1	-	-	-	1
Suicide attempt	1	-	-	-	-	1
Miscellaneous						
Fall with fracture or injury	3	-	-	-	-	3
Laceration with tendon injury	-	-	-	1	-	1
Inguinal hernia	-	-	-	-	1	1
Hypertension w/ hospitalization	-	-	-	-	-	1
Abdominoplasty	-	-	-	-	-	1
Infection or cellulitis	-	-	2	-	1	3
Allergic reaction	-	-	-	1	-	1
Gynecologic						
Unwanted pregnancy	-	-	-	-	-	1
Abnormal uterine bleeding	1	-	-			
Totals	14	5	5	8	6	38

Adverse Events on an As-Treated Basis* --- IMM ONLY

Years 1 Serious Events, 2: Clinically Important Events^a; Year 3-5: Serious Events

	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Year 4</u>	<u>Year 5</u>	<u>(Mix)</u> <u>Total</u>
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Adverse Events on an As-Treated Basis* --- RYGB ONLY

Years 1-2: Clinically Important Events; Year 3-5: Serious Events

	<u>Clinically Important</u> <u>Year 1</u>	<u>Year 2</u>	<u>Serious</u> <u>Year 3</u>	<u>Year 4</u>	<u>Year 5</u>	<u>(Mix)</u> <u>Total</u>
Surgical Complications						
Anastomotic leak	2 ¹	-	-	-	-	2
Anastomotic ulcer	1	3	-	-	-	4
Anastomotic stricture	2	-	-	-	-	2
Wound infection	1	-	-	-	-	1
Wound hematoma	1	-	-	-	-	1
Pouch gastritis	1	-	-	-	-	1
Small bowel obstruction	2	-	-	-	1	3
Gastrointestinal						
Acute Pancreatitis	-	-	-	-	-	0
Pancreatic carcinoma	-	-	-	-	-	0
Cholelithiasis	-	1	-	-	-	1
Abdominal pain	4	4	2	1	-	11
Reflux esophagitis	-	3	-	-	-	3
Gastritis or Duodenitis	-	-	-	-	-	0
Cardiovascular						
Deep venous thrombosis	-	1	-	-	-	1
Congestive heart failure	-	-	-	-	-	0
Chest congestion	-	-	-	1	-	1
Acute myocardial infarction	-	-	1	-	-	1
Retinal Vascular Occlusion	-	-	-	-	-	-
Retinopathy	-	-	-	1	-	1
Renal						
Nephrolithiasis	1	-	2	1	-	4
Metabolic						
Diabetic ketoacidosis	-	-	-	-	-	0
Dehydration/Altered mentation	-	-	-	1	-	1
Musculoskeletal						
Below the knee amputation	1	-	-	-	-	1
Toe amputation	1	-	1	-	-	2
Foot amputation	-	-	1	1	-	2
Osteoarthritis	-	-	-	1	-	1
Neurologic						
Herniated spinal disc	1	-	-	-	-	1
Multiple sclerosis	-	1	-	-	-	1
Partial 3 rd cranial nerve palsy	-	-	-	-	-	-
Diabetic neuropathy	-	-	-	-	1	1
Psychiatric						
Depression	-	-	-	-	-	0
Suicide attempt	-	-	-	-	-	0
Opioid Addiction	-	-	-	-	1	1
Miscellaneous						
Fall with fracture or injury	3	4	-	-	-	7
Fall with other injury	-	-	-	-	1	1

Adverse Events on an As-Treated Basis* --- RYGB ONLY**Years 1-2: Clinically Important Events; Year 3-5: Serious Events**

	<u>Clinically Important</u>		<u>Serious</u>	<u>Year 4</u>	<u>Year 5</u>	<u>(Mix)</u>
	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>			<u>Total</u>
Inguinal hernia	-	-	-	1	-	1
Hypertension w/ hospitalization	1	-	-	-	-	1
Abdominoplasty	-	-	1	-	-	1
Infection or cellulitis	-	-	2	-	-	2
Ventral Hernia	-	-	-	1	-	1
Gynecologic**						
Unwanted pregnancy	1	-	-	-	-	1
Abnormal uterine bleeding	-	-	-	-	-	0
Ovarian Cyst	-	-	-	1	-	1
Miscarriage	-	-	-	1	-	1
Breast Cancer	-	-	-	1	-	1
Totals	23	17	10	13	4	67

*Excluded the patients with non-serious adverse events

** Cross over patient year 4 with endometriosis and fibroids in the same year as cross over- will not count a Clinically important events included any event that required treatment or change of treatment plan