Final Results of the CATALYST Trial

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Disclosures

- **Research Support (to Tulane):** Grants from Novo Nordisk
- **Honoraria for Consulting and Lectures:** Regeneron, Abbott, Corcept, Eli Lilly
- **Stock Options:** Mellitus Health, BRAVO4Health
- **Stock:** Vertex
- **Patents Pending:** BRAVO risk engine for predicting diabetes complications; PAX4 gene therapy for type 1 diabetes

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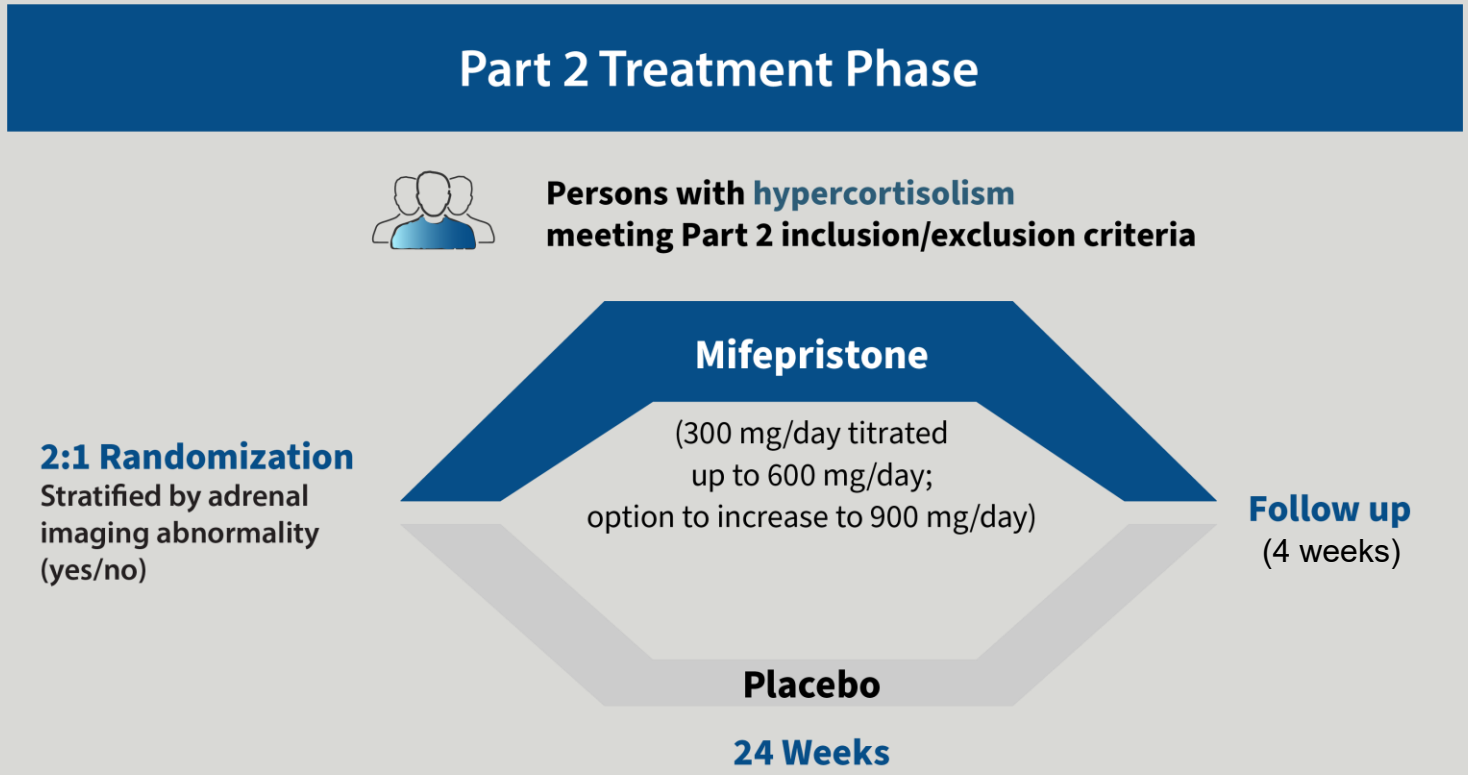
CATALYST
Study of Hypercortisolism in Patients with Difficult-to-Control Type 2 Diabetes

Treatment Phase Study Design

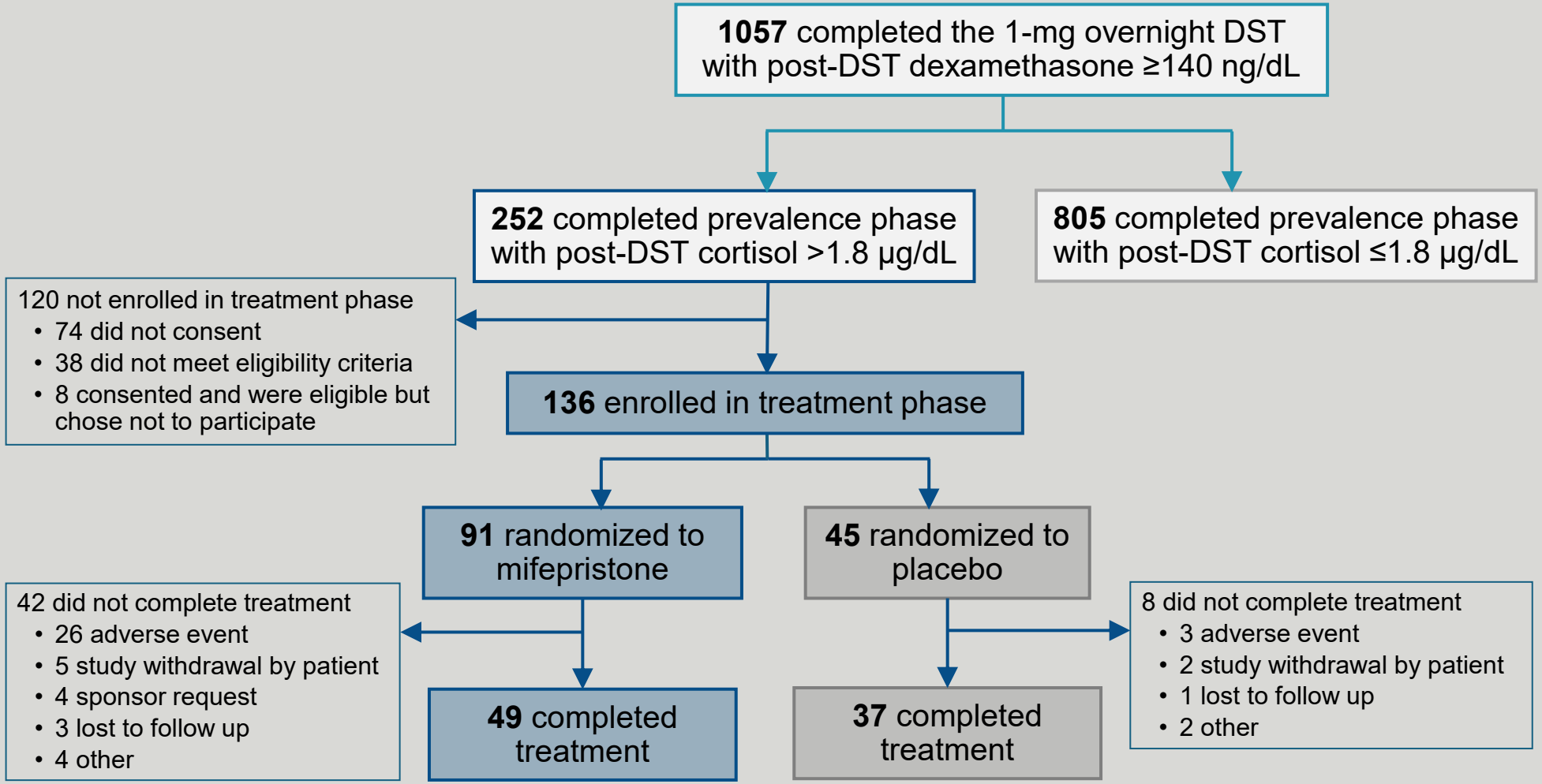


Primary Endpoint

- Change in HbA1c from baseline to week 24 in participants treated with mifepristone versus placebo

CT, computed tomography; HbA1c, hemoglobin A1c. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.

CATALYST | Participant Flow



Reasons for not completing treatment due to sponsor request included not meeting inclusion/exclusion criteria (n=2), life events preventing the participant from continuing in the study (n=1), and adverse event (n=1; worsening fatigue and elevated thyroid stimulating hormone). 4 participants did not meet all inclusion criteria but were enrolled in the treatment phase.

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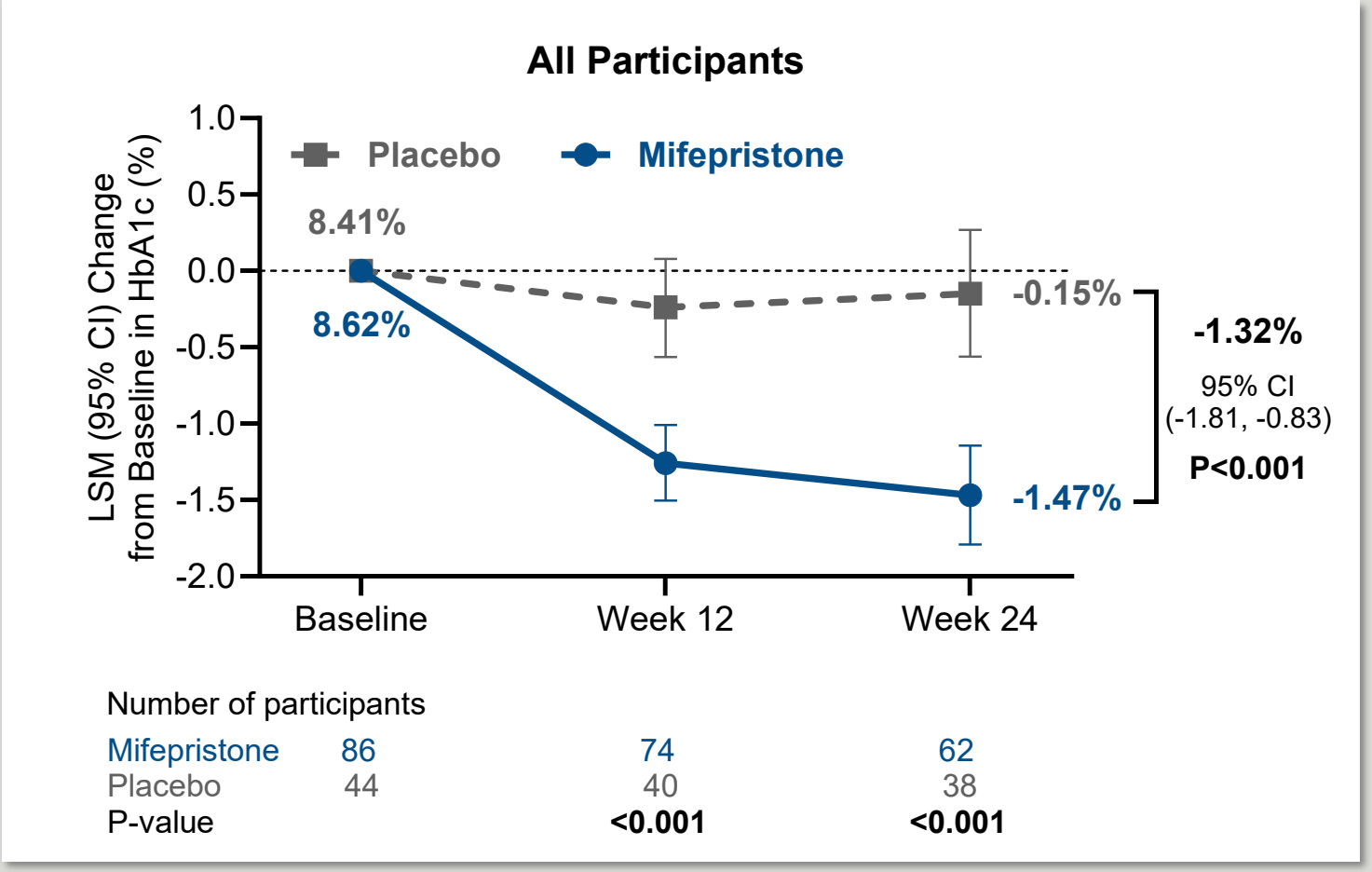
Demographics and Baseline Characteristics

	Mifepristone (n=91)	Placebo (n=45)	Completed Prevalence Phase with Post-DST Cortisol >1.8 µg/dL but Did Not Enroll in Treatment Phase (n=118)
Age, years, mean (SD)	62.9 (8.9)	63.8 (11.5)	64.3 (9.5)
Male, n (%)	54 (59.3%)	29 (64.4%)	60 (50.8%)
Race, n (%)			
White	71 (78.0%)	39 (86.7%)	79 (66.9%)
Black or African American	16 (17.6%)	5 (11.1%)	34 (28.8%)
Other[a]	4 (4.4%)	1 (2.2%)	5 (4.2%)
Ethnicity, n (%)			
Hispanic or Latino	5 (5.5%)	4 (8.9%)	12 (10.2%)
Not Hispanic or Latino	85 (93.4%)	41 (91.1%)	106 (89.8%)
Abnormal adrenal CT scan, n (%)	25 (27.5%)	13 (28.9%)	N/A[c]
Body weight, kg, mean (SD)	99.7 (23.21)	97.4 (23.43)	95.4 (24.2)
Waist circumference, cm, mean (SD)	114.0 (17.45)	115.3 (18.24)	112.8 (17.4)
Body mass index, kg/m^2, mean (SD)	33.1 (7.31)	33.7 (8.21)	32.8 (7.9)
HbA1c, %, mean (SD)	8.62 (1.27)	8.41 (1.08)	8.82 (0.97)
Systolic blood pressure, mmHg, mean (SD)	125.0 (15.98)	125.4 (14.78)	128.3 (16.5)
Diastolic blood pressure, mmHg, mean (SD)	74.1 (9.12)	73.3 (9.44)	74.3 (9.5)

[a]Race category "Other" includes Asian, multiple, and other. [b]The main reasons why participants with hypercortisolism did not enroll in the treatment phase were participant did not consent (n=74), not meeting eligibility criteria for the treatment phase (n=38), and participant decision (n=8). [c]Not all participants completed the CT scan. CT, computed tomography; HbA1c, hemoglobin A1c; SD, standard deviation.

Primary Endpoint: Statistically Significant Reduction in HbA1c



Of the 91 participants randomized to mifepristone, 65 (71%) received 600 mg and of those, 28 (31%) received 900 mg mifepristone during the study

CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; LSM, least-squares mean; SUs, sulfonylureas. P-value for LSM difference between mifepristone and placebo shown.

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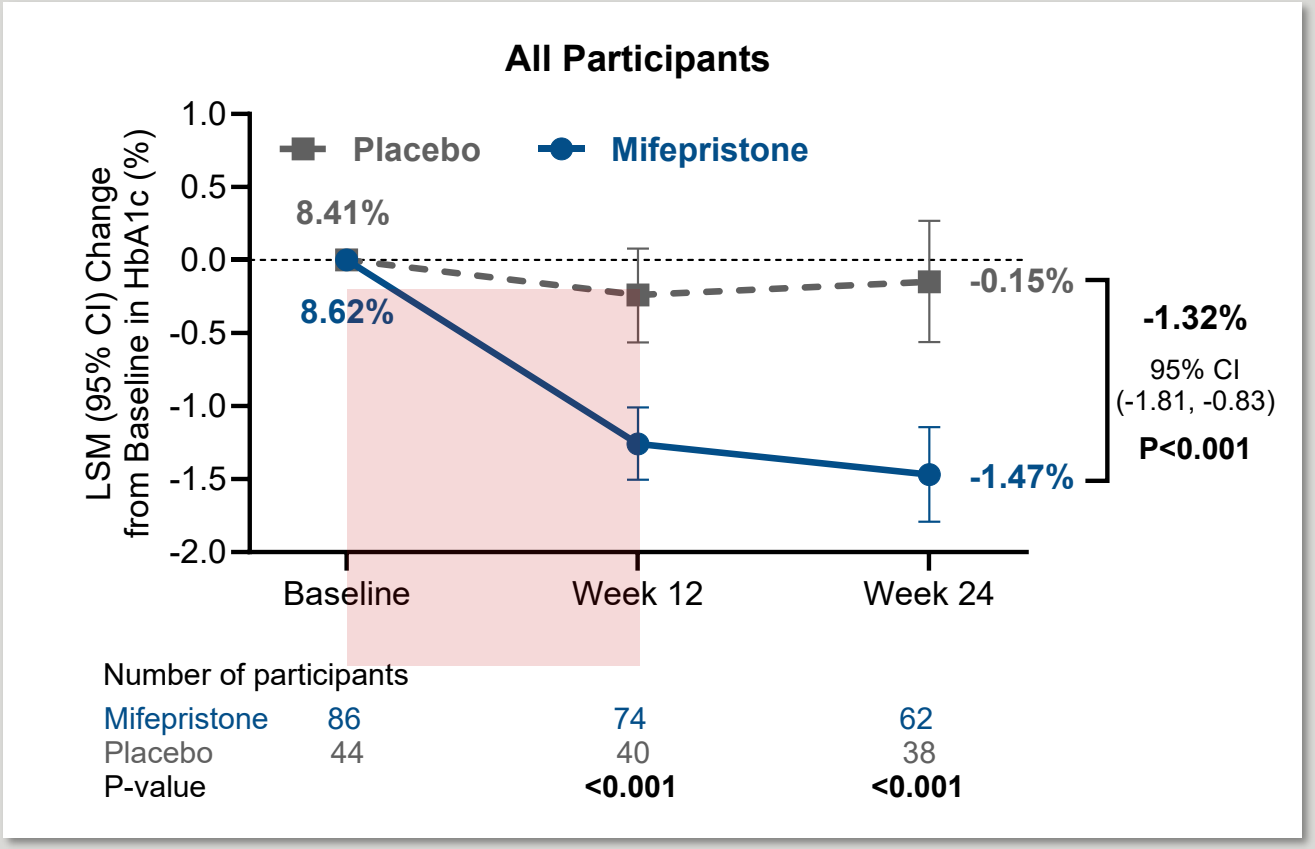
Treatment Phase

Primary Endpoint: Statistically Significant Reduction in HbA1c Despite Medication Reductions / Discontinuation



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Discontinuations/Dose-reductions in Glucose-lowering Medications by Week 12

n/N[a] (%)	Mifepristone	Placebo
Long-acting insulin	32/65 (49.2%)	3/23 (13.0%)
Fast-acting insulin	10/33 (30.3%)	2/19 (10.5%)
Sulfonylureas	4/18 (22.2%)	2/19 (10.5%)
GLP-1 RAs	4/33 (12.1%)	0/19
Tirzepatide	2/19 (10.5%)	0/3
Metformin	1/67 (1.5%)	0/33
SGLT2 inhibitors	0/56	1/27 (3.7%)
Total	**53**	**8**

CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; LSM, least-squares mean; SUs, sulfonylureas. P-value for LSM difference between mifepristone and placebo shown. Dose decreases and discontinuations combined for insulin, SUs, GLP-1 RAs, and tirzepatide; discontinuations only for metformin and SGLT2 inhibitors.
[a]N indicates the number of participants taking a medication from the class at baseline.

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HbA1c: Subgroup Analyses Support the Primary Endpoint

HbA1c (%)	Mifepristone	Placebo	Difference from Placebo	P-value
Participants who completed 24 weeks of treatment				
Baseline, mean (SD) [n]	8.82 (1.33) [47]	8.42 (1.02) [36]	—	—
Change from baseline to week 24, LSM (95% CI) [n]	**-1.69** (-2.09, -1.30) [47]	-0.13 (-0.58, 0.32) [36]	**-1.56** (-2.12, -1.00)	**<0.001**
Participants who received 3 tablets (900 mg mifepristone)				
Baseline, mean (SD) [n]	9.10 (1.35) [24]	8.62 (1.09) [25]	—	—
Change from baseline to week 24, LSM (95% CI) [n]	**-2.01** (-2.63, -1.39) [23]	-0.16 (-0.76, 0.45) [25]	**-1.85** (-2.67, -1.04)	**<0.001**

Analyses conducted to assess the robustness of the primary endpoint (tested in the intent-to-treat population). Analysis in participants who received 3 tablets includes those who received 3 tablets for at least consecutive 28 days. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect. CI, confidence interval; HbA1c, hemoglobin A1c; LSM, least-squares mean; SD, standard deviation.

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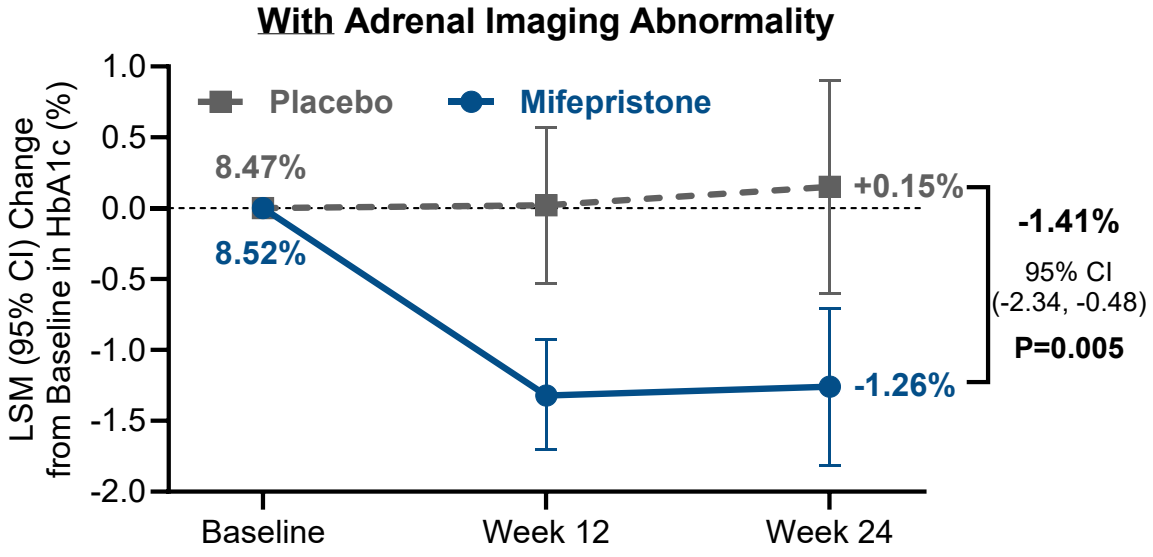
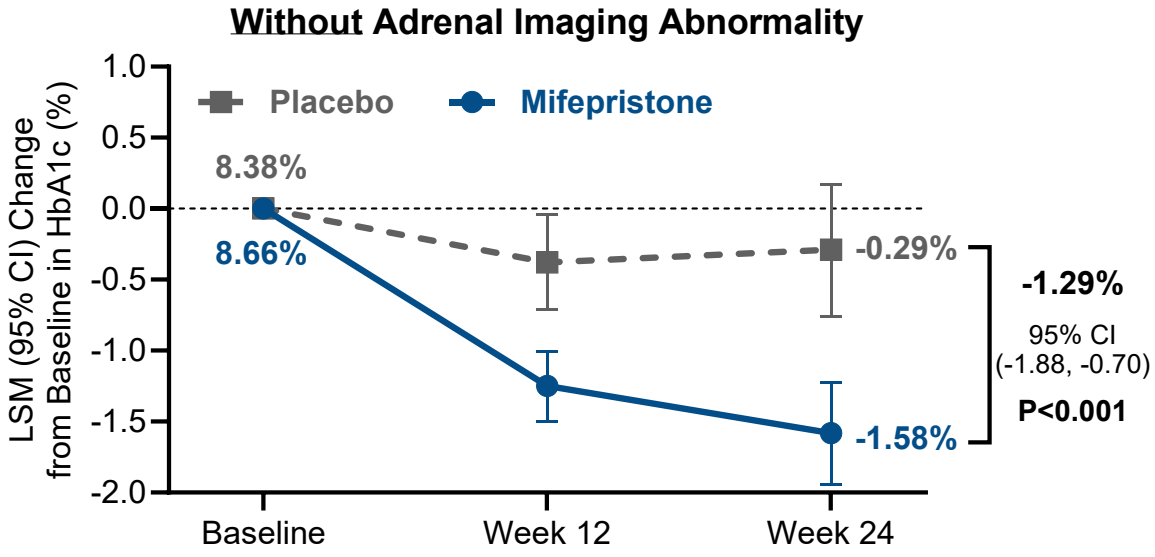
Treatment Phase

Similar HbA1c Reductions in Participants With and Without Adrenal Imaging Abnormalities



Number of participants

Mifepristone	25	22	19
Placebo	13	11	11
P-value		**<0.001**	**0.005**



Number of participants

Mifepristone	61	52	43
Placebo	31	29	27
P-value		**<0.001**	**<0.001**

First randomized, placebo-controlled study to show that hypercortisolism without an adrenal imaging abnormality responds to cortisol-directed pharmacological treatment

CI, confidence interval; CT, computed tomography; HbA1c, hemoglobin A1c; LSM, least-squares mean. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.

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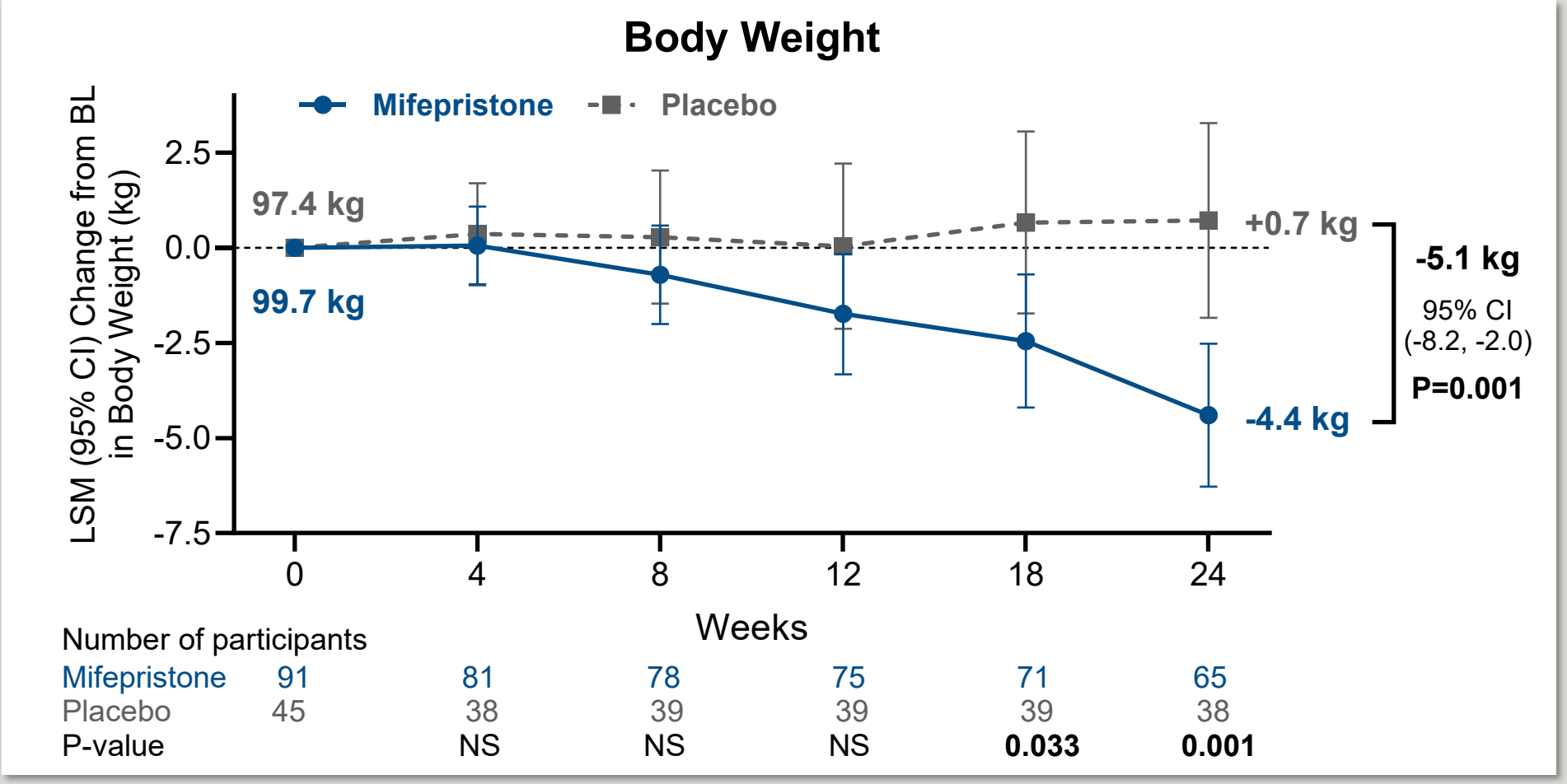
Treatment Phase

Body Weight Loss With Mifepristone



By week 24, participants taking mifepristone had a 3.6% reduction in body weight compared to an increase of 0.3% in those taking placebo

BL, baseline; CI, confidence interval; LSM, least-squares mean; NS, not significant. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.

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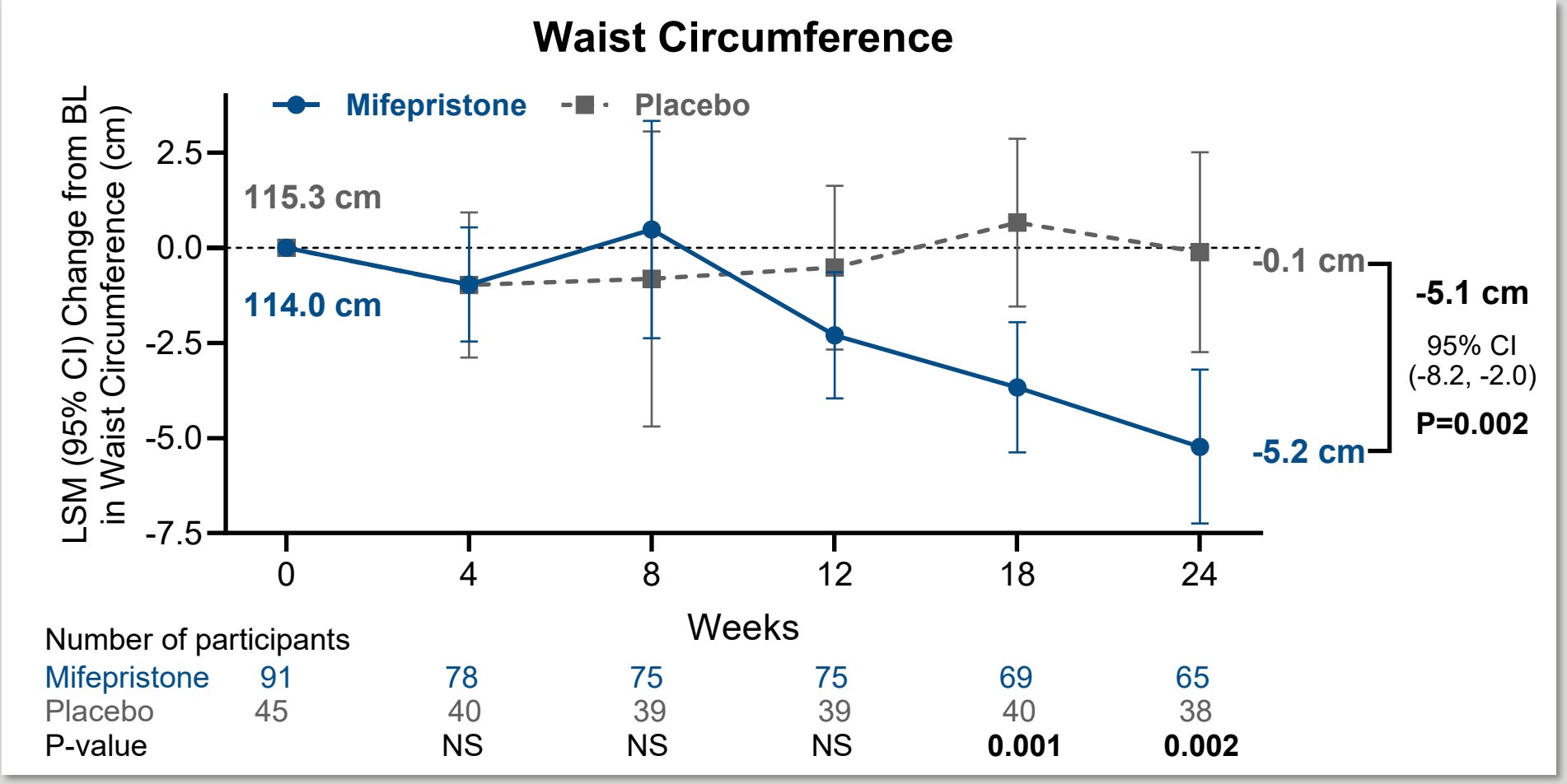
Treatment Phase

Waist Circumference Decreased With Mifepristone



Waist circumference decreased along with body weight, suggesting loss of primarily visceral fat mass

BL, baseline; CI, confidence interval; LSM, least-squares mean; NS, not significant. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.

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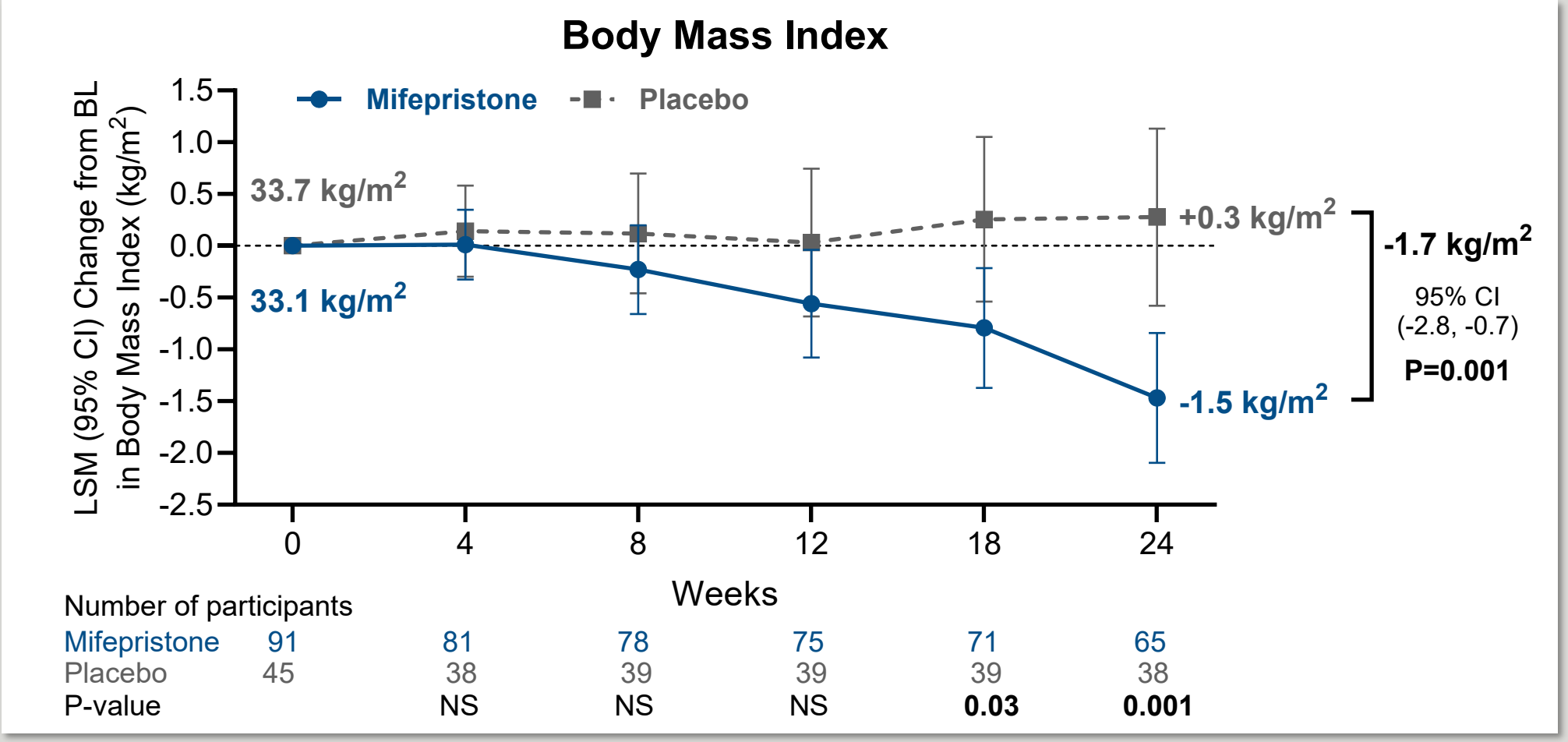
Body Mass Index Decreased With Mifepristone



Body mass index decreases were continuing at study end

BL, baseline; BMI, body mass index; CI, confidence interval; LSM, least-squares mean; NS, not significant. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.

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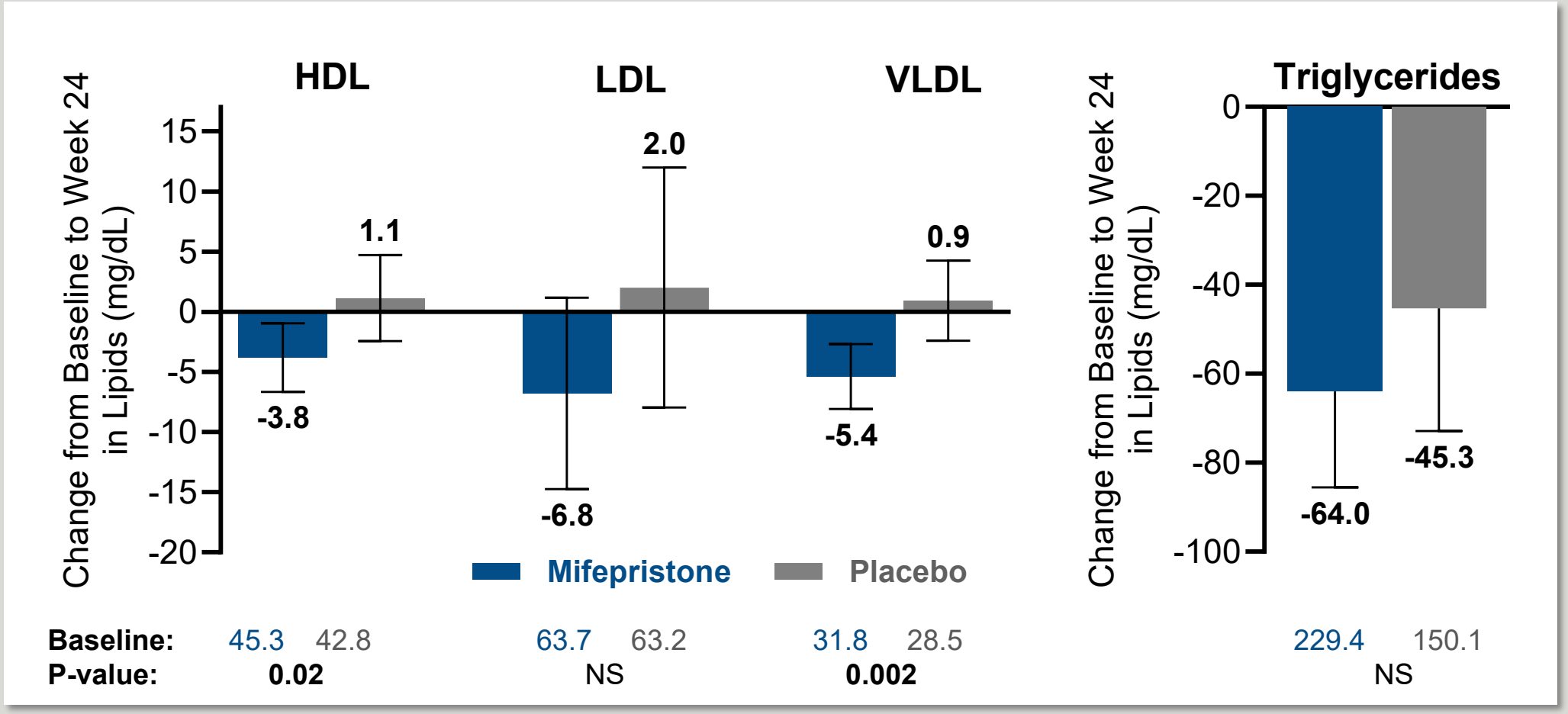
Treatment Phase

Effects of Mifepristone on Lipids



BL, baseline; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSM, least-squares mean; NS, not significant (P>0.05); SD, standard deviation; VLDL, very low-density lipoprotein. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.

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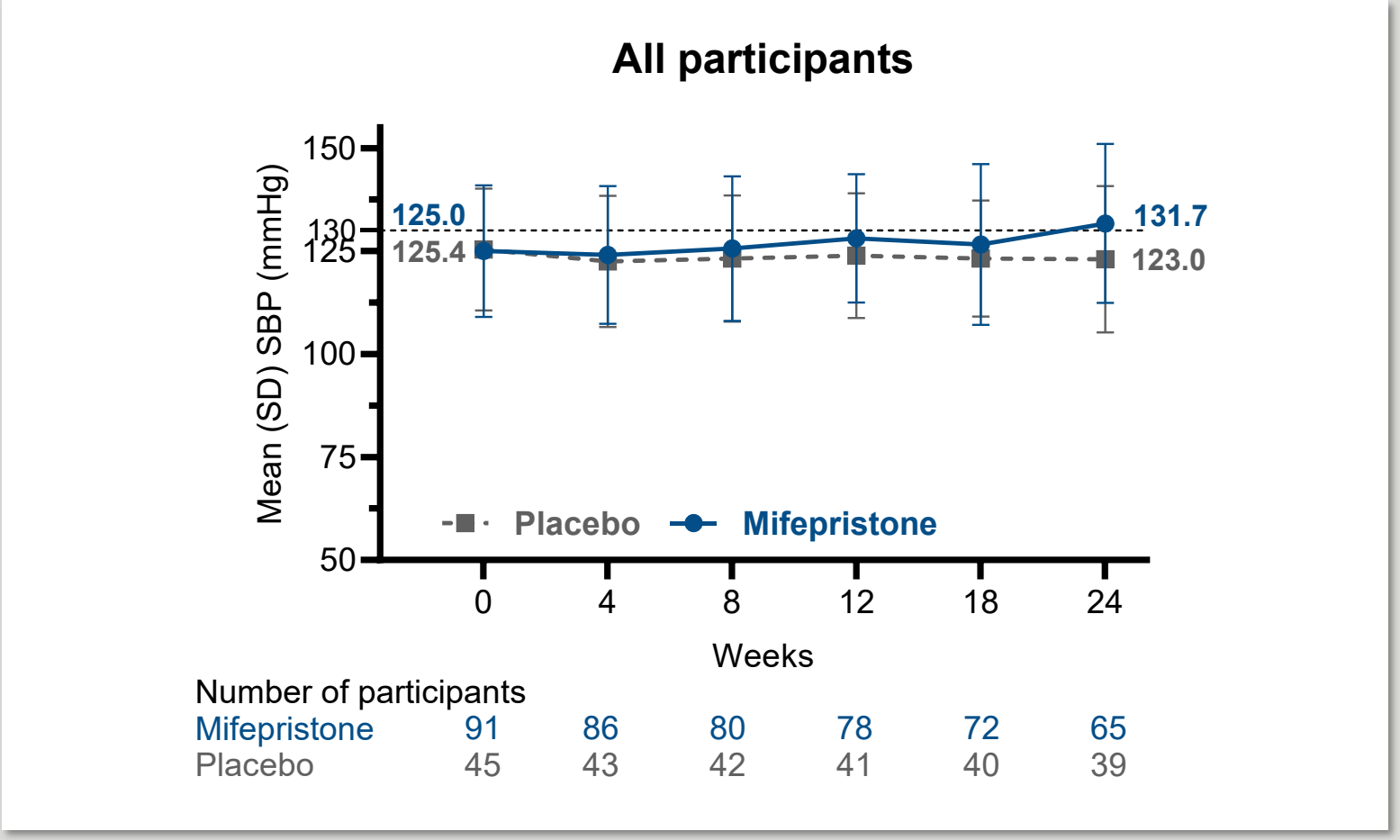
Effect of Mifepristone on Blood Pressure



SBP remained near target in the overall population and no changes from baseline were observed in participants with baseline SBP ≥130 mmHg

SBP, systolic blood pressure; SD, standard deviation.

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Treatment-emergent Adverse Events Reported in >10% of Participants

Preferred Term, n (%)	Mifepristone (n=91)	Placebo (N=43)
At least one TEAE event	86 (94.5%)	36 (83.7%)
At least one treatment-related AE	56 (61.5%)	14 (32.6%)
TEAEs leading to treatment discontinuation	26 (28.6%)	1 (2.3%)
Serious TEAE	29 (31.9%)	2 (4.7%)
Most common TEAEs		
Hypokalemia	27 (29.7%)	0
Fatigue	19 (20.9%)	7 (16.3%)
Nausea	19 (20.9%)	5 (11.6%)
Vomiting	14 (15.4%)	3 (7.0%)
Peripheral edema	14 (15.4%)	1 (2.3%)
Headache	11 (12.1%)	5 (11.6%)
Diarrhea	10 (11.0%)	3 (7.0%)
Dizziness	10 (11.0%)	3 (7.0%)

Overall TEAEs were mostly mild-to-moderate in severity; no grade 4 TEAEs observed

TEAEs were manageable and consistent with mifepristone's known safety profile

TEAE, treatment-emergent adverse event.

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Hypokalemia, a known side-effect of mifepristone, was the most common adverse event

Due to overstimulation of the mineralocorticoid receptor

TEAE, treatment-emergent adverse event.

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Many of the most common TEAEs were consistent with glucocorticoid withdrawal, which can occur with any treatment for hypercortisolism, surgical or pharmacological

TEAE, treatment-emergent adverse event.

Summary and Conclusions

- In a cohort with difficult-to-control type 2 diabetes and hypercortisolism, mifepristone resulted in **clinically & statistically significant improvements in HbA1c** and other comorbidities
  - Comparable reductions in HbA1c were observed in participants with and without adrenal imaging abnormalities
- **Adverse events were consistent with mifepristone's known safety profile**
  - The most common adverse events were consistent with glucocorticoid withdrawal syndrome
  - Hypokalemia may be addressed by proactive initiation of a potassium-sparing diuretic, eg, spironolactone, in clinical practice (as opposed to a double-blind trial)

Key takeaway

In individuals with inadequately controlled type 2 diabetes and hypercortisolism, cortisol-directed medical therapy with mifepristone significantly reduced HbA1c

HbA1c, hemoglobin A1c.

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