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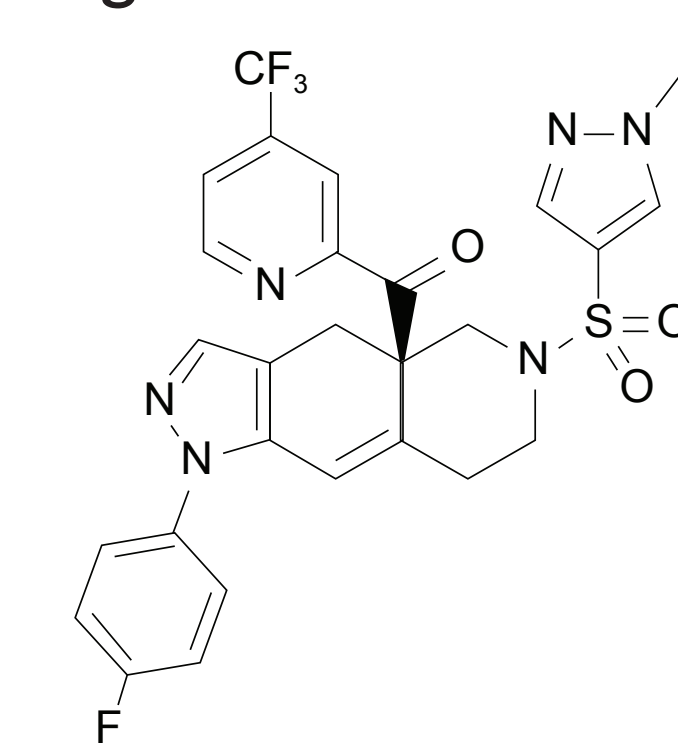
SUMMARY AND CONCLUSIONS

- Relacorilant is in development for the treatment of endogenous hypercortisolism and has demonstrated improvements in hypertension, hyperglycemia, and other manifestations of cortisol excess in the phase 3 GRACE study
- Efficacy was observed without reported cases of relacorilant-induced hypokalemia, adrenal insufficiency, vaginal bleeding associated with endometrial hypertrophy, or QT interval prolongation¹
- In the open-label phase of GRACE, pituitary tumor volume decreased or remained unchanged following relacorilant treatment for 87% of patients with Cushing Disease
- One patient with a macroadenoma had complete resolution with no visible residual tumor by magnetic resonance imaging after relacorilant treatment

BACKGROUND AND OBJECTIVE

- Relacorilant is an oral, investigational selective glucocorticoid receptor (GR) modulator (Figure 1) designed to modulate excess cortisol activity at the GR to treat the manifestations of endogenous hypercortisolism^{2,3}
 - Structurally different from the nonselective GR antagonist mifepristone^{2,3}
 - Highly selective for the GR, with no activity at the progesterone, mineralocorticoid, or androgen receptors^{2,3}
 - Avoids unwanted off-target progesterone receptor effects (eg, endometrial hypertrophy, vaginal bleeding)^{1,4-6}

Figure 1. Relacorilant



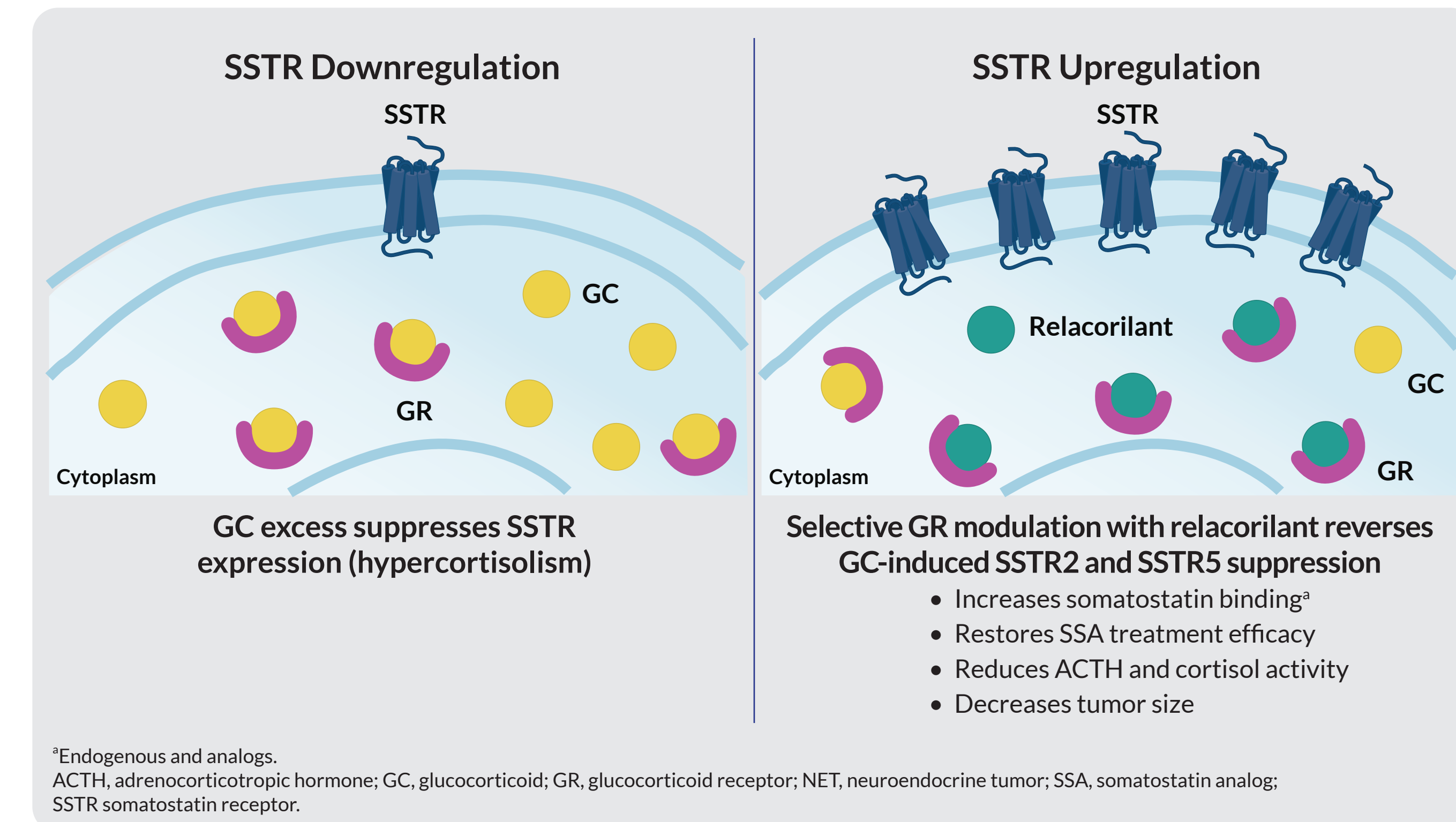
Phase 3 GRACE Results

- The phase 3 GRACE study (NCT03697109) investigated relacorilant treatment for the signs and symptoms of excess cortisol in individuals with endogenous hypercortisolism who had uncontrolled hypertension, hyperglycemia, or both^{1,7}
- GRACE achieved its primary endpoint of loss of hypertension control during the randomized-withdrawal (RW) phase (odds ratio 0.17 for relacorilant vs placebo; $P=0.02$)^{1,7}
 - Relacorilant treatment was associated with improvements in hypertension, hyperglycemia, and other manifestations of cortisol excess
 - The improvements occurred without reported cases of relacorilant-associated hypokalemia, adrenal insufficiency, vaginal bleeding associated with endometrial hypertrophy, or QT prolongation

Relacorilant Effects on Pituitary Tumors

- Case reports in patients with Cushing Disease (CD) due to pituitary macroadenomas and research using pituitary neuroendocrine tumor (PitNET) organoid models have suggested that GR modulation with relacorilant induces previously suppressed somatostatin receptor type 5 (SSTR5) and, to a lesser extent, SSTR2 expression in adrenocorticotropic (ACTH)-secreting PitNETs, resulting in tumor-specific antiproliferative and antiproliferative effects, including tumor shrinkage (Figure 2)^{8,9}
 - SSTR2 and SSTR5 upregulation are thought to sensitize tumors to the antitumor and ACTH-suppressive effects of somatostatin and its analogs^{8,9}
 - In PitNET organoids, relacorilant resulted in tumor cell apoptosis and did not significantly increase ACTH expression⁹
- The objective of this analysis was to assess the effect of relacorilant on pituitary tumors in patients with CD participating in the GRACE study

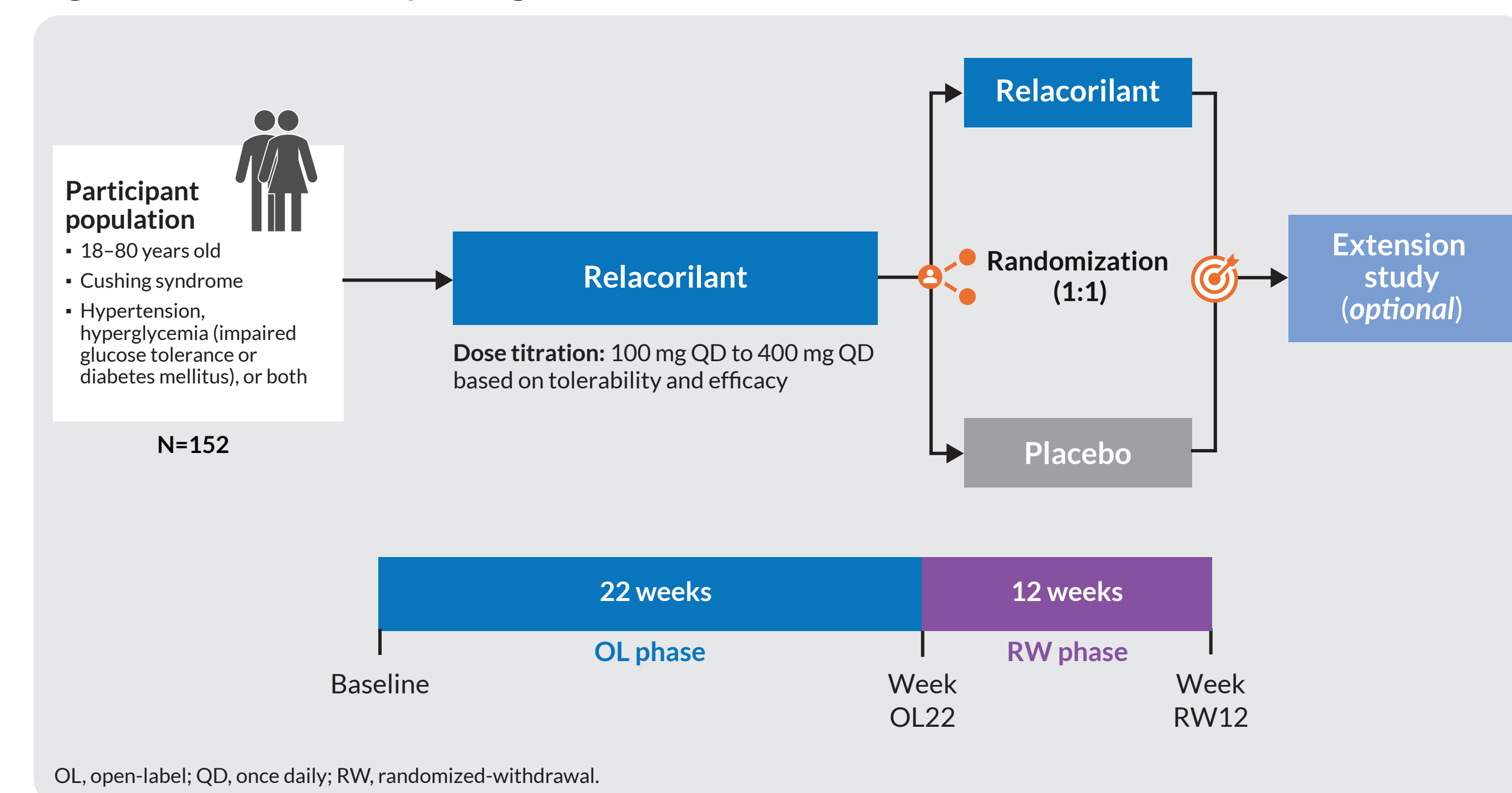
Figure 2. Proposed Effects of Glucocorticoids and GR Modulation With Relacorilant on SSTR Regulation in ACTH-Secreting NETs^{8,9}



METHODS

- GRACE was a 2-part study (Figure 3):
 - In the initial open-label (OL) phase, adults with endogenous hypercortisolism and hypertension, hyperglycemia, or both were treated with relacorilant 100 mg to 400 mg once daily
 - In the double-blind RW phase, study participants who completed the OL phase and met the prespecified response criteria were then randomized to continue relacorilant treatment or be switched to placebo

Figure 3. GRACE Study Design



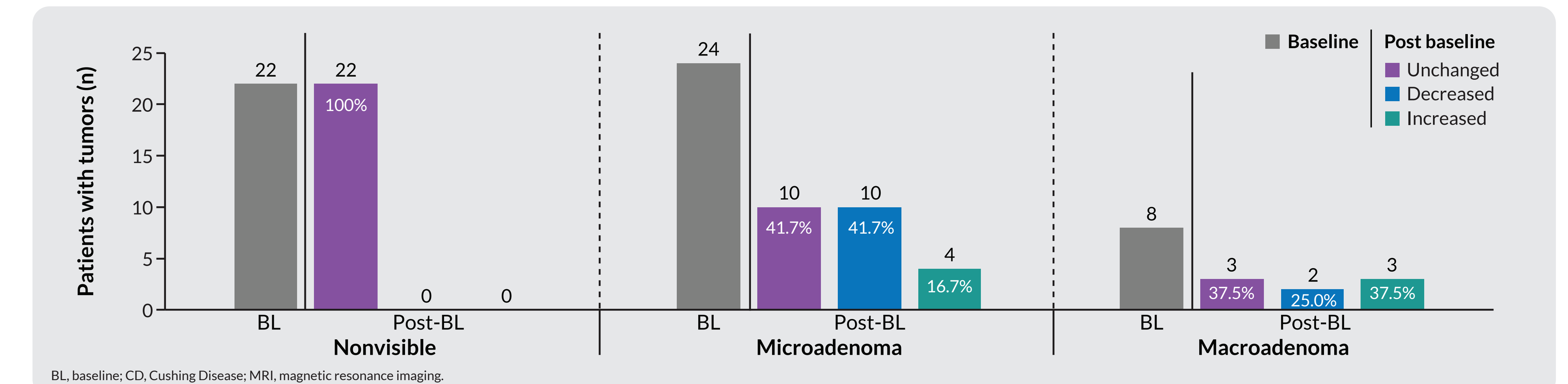
- Participants had ≥ 2 clinical signs and symptoms of hypercortisolism, including bodily characteristics of a Cushingoid appearance, increased body weight or central obesity, proximal muscle weakness, low bone mass, psychiatric symptoms, skin manifestations, and easy bruisability
- Hypercortisolism was defined based on the presence of ≥ 2 of the following:
 - Urinary free cortisol greater than the upper limit of normal (ULN) in ≥ 2 complete 24-hour tests
 - Late-night salivary cortisol $>ULN$ in ≥ 2 tests
 - >1.8 $\mu\text{g/dL}$ serum cortisol on either the 1-mg overnight or 2-mg 48-hour dexamethasone suppression test
- Pituitary magnetic resonance imaging (MRI) was planned to be done at baseline and at the end of the OL phase for patients with pituitary hypercortisolism
 - The MRI protocol included sagittal/coronal 2-dimensional (2D) T1 turbo spin echo (TSE), coronal 2D T2 TSE, and postcontrast sagittal 3-dimensional T1 gradient echo or sagittal/coronal 2D T1 TSE
 - MRI scans were centrally collected and quality controlled at Clario's imaging core laboratory and reviewed by 2 expert neuroradiologists blinded to scan date, visit order, and clinical details
 - Tumor contours were manually delineated on each MRI slice
 - Adjudication was performed by a third reader when volume measurements differed by $\geq 10\%$
- Tumor volume (mm^3) change was defined as a 20% increase or decrease from baseline
- The study was approved by the respective participating institutions' ethics committees

RESULTS

Overall Results for Change in Pituitary Tumor Volume

- In GRACE, 54 patients had CD and evaluable pituitary MRIs at baseline and post baseline
- At baseline, 22 patients (40.7%) had nonvisible tumors, 24 (44.4%) had microadenomas, and 8 (14.8%) had macroadenomas
- Post baseline, all nonvisible tumors remained unchanged, and tumor volume decreased or remained unchanged for 20 patients (83.3%) with microadenomas and 5 patients (62.5%) with macroadenomas (Figure 4)

Figure 4. Change From Baseline in Pituitary Tumor Volume by MRI With Relacorilant in Patients With CD



Results for 2 Patients Who Completed the OL Phase and Experienced Decreased Macroadenoma Volume With Relacorilant Treatment

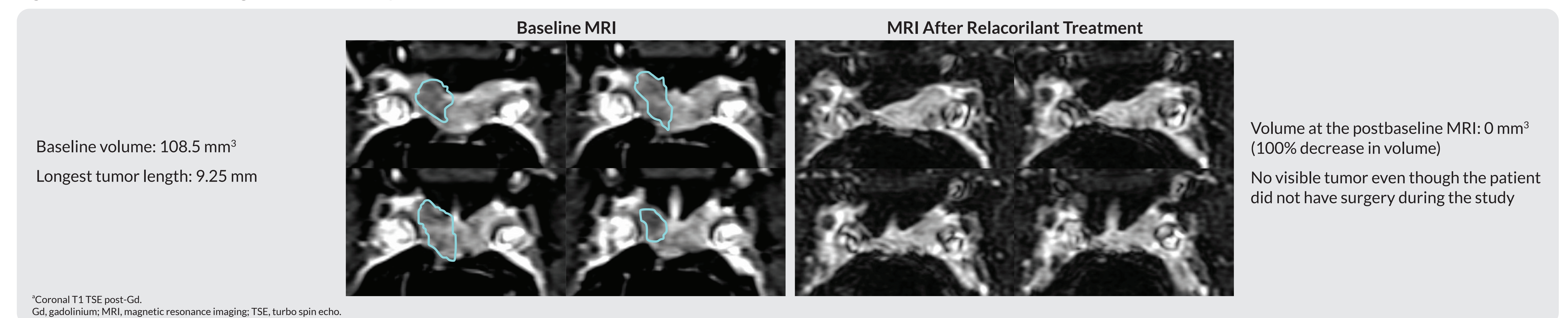
- Patient 1** was a 27-year-old African American woman with a history of pathology-confirmed CD diagnosed in 2017 and persistent disease despite surgery prior to the study (Figure 5)
 - Medical history included hypertension, prediabetes, central hypothyroidism, hyperandrogenism, hidradenitis, anxiety, and depression
 - At the baseline MRI (October 2019), she had a macroadenoma with a volume of 108.5 mm^3 , which decreased over time with relacorilant treatment. At the postbaseline MRI (May 2020), the tumor had completely resolved and was no longer visible

ACTH and Serum Cortisol Values for Patient 1

	Baseline	Week OL10	Week OL22
ACTH, pmol/L	14	7	N/A
Serum cortisol, $\mu\text{g/dL}$	20	10.2	N/A

ACTH, adrenocorticotropic hormone; N/A, not available; OL, open-label.

Figure 5. Patient 1: MRI Images^a of the Pituitary Macroadenoma Before and After Relacorilant Treatment



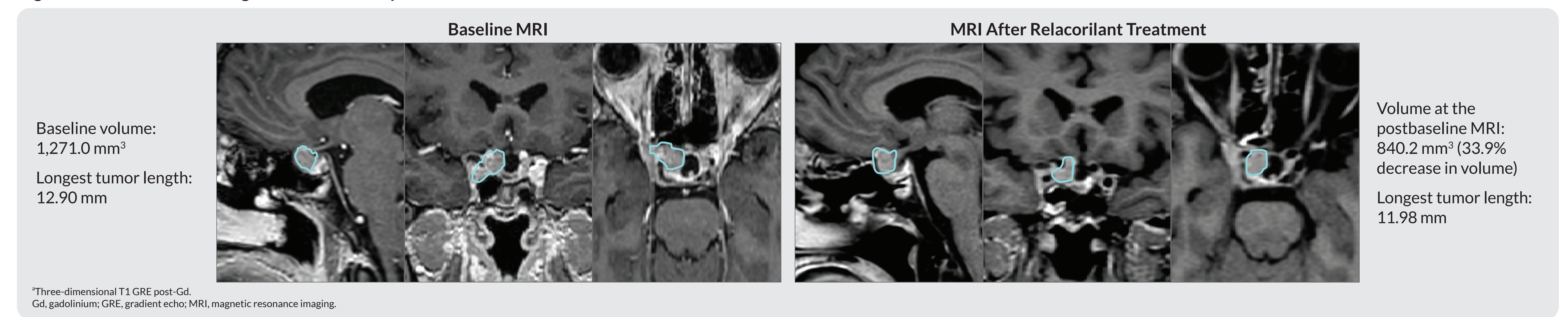
- Patient 2** was a 52-year-old Caucasian man with a history of pathology-confirmed CD diagnosed in 2015 and persistent disease following radiation therapy (Figure 6)
 - Medical history included type 2 diabetes mellitus, hypercholesterolemia, hypokalemia, hypothyroidism, and central hypogonadism
 - At the baseline MRI (June 2020), he had a macroadenoma with a volume of 1,271.0 mm^3 . At the postbaseline MRI (October 2020), tumor volume had decreased by 33.9% to 840.2 mm^3

ACTH and Serum Cortisol Values for Patient 2

	Baseline	Week OL10	Week OL22
ACTH, pmol/L	89	48	34
Serum cortisol, $\mu\text{g/dL}$	25.6	13.3	10.7

ACTH, adrenocorticotropic hormone; OL, open-label.

Figure 6. Patient 2: MRI Images^a of the Pituitary Macroadenoma Before and After Relacorilant Treatment



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