Adrenal adenomas are usually diagnosed in older patients for whom systolic HTN is most severe, uncontrolled hypertension (mean SBP >130 mmHg based on 24-h ABPM) will be used, AUC of the SBP profile will be chosen as another primary endpoint. The mean change in AUC will be calculated by the trapezoidal rule.

As a result, relacorilant may potentially be more effective in immediately treating hypertension in this patient population.

Approximately 130 patients 18–80 years old will be recruited and assigned to either the GRADE (GRADIENT) or placebo (BL) group. The GRADE study design is shown in Figure 3.

### KEY INCLUSION CRITERIA: GRADIENT VS GRACE

- Lack of cortisol suppression (>1.8 μg/dL serum cortisol on at least 2 occasions on at least 2 days)
- Suspected or proven adrenal and/or hyperplasia
- Fasting plasma glucose ≥140 and <200 mg/dL on 2-h oGTT
- Dyslipidemia and/or DM; BMI ≥30
- Actively controlled HTN with mean SBP ≥135 to ≤170 mmHg or mean DBP ≥85 mmHg
- Urinary free cortisol >ULN

- Relacorilant arm
  - Fasted: 100 mg BID (morning and evening)
  - Informed consent
  - Diabetes mellitus (DM): Impaired glucose tolerance (IGT): Glucose ≥140 and <200 mg/dL on 2-h oGTT
  - Informed consent
  - Diabetes mellitus (DM): Uncontrolled, clinically significant hypo- or hyperglycemia
  - Informed consent

- Placebo arm
  - Placebo: 100 mg BID (morning and evening)
  - Informed consent
  - Diabetes mellitus (DM): Impaired glucose tolerance (IGT): Glucose ≥140 and <200 mg/dL on 2-h oGTT
  - Informed consent

### SUMMARY

- GRADE will be the first international, multicenter, randomized, double-blind, placebo-controlled Phase 3 study to test a new class of adrenal cortisol-modulating medications. It uses a novel mechanism of action to reduce the unphysiologic levels of cortisol.
- GRADE will be assessed for safety and efficacy in patients with autonomous cortisol secretion due to cortisol-secreting adrenal adenomas or hyperplasia.
- GRADE will be an open-label, randomized, double-blind, placebo-controlled Phase 3 study to test a new class of adrenal cortisol-modulating medications. It uses a novel mechanism of action to reduce the unphysiologic levels of cortisol.
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