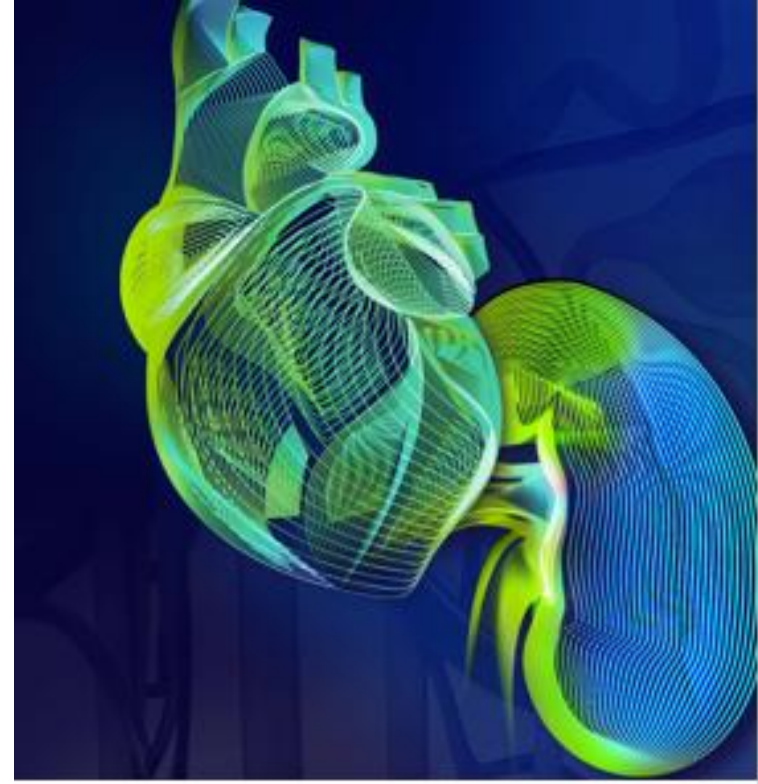


# A Physiology-Guided Strategy to Address Metabolic Acidosis in Chronic Kidney Disease: Rationale and Design of the REVIVE Study

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## INTRODUCTION

- Metabolic acidosis is a common complication of chronic kidney disease (CKD), affecting 15-50% of patients depending upon CKD stage
- Metabolic acidosis contributes to CKD progression, sarcopenia, osteopenia, and reduced quality of life, yet remains under-recognized and under-treated
- Current management includes alkali treatment which is limited by tolerability, sodium/potassium load, high pill burden, and poor adherence
- Veverimer is a non-absorbed polymer that binds hydrochloric acid (HCl) in the stomach, thereby increasing serum bicarbonate concentration (SBC) without counterion exposure<sup>1</sup>
- Prior studies with veverimer demonstrated improvements in SBC, although variability in response suggested that gastric physiologic factors may influence treatment efficacy<sup>2,3</sup>

## AIM

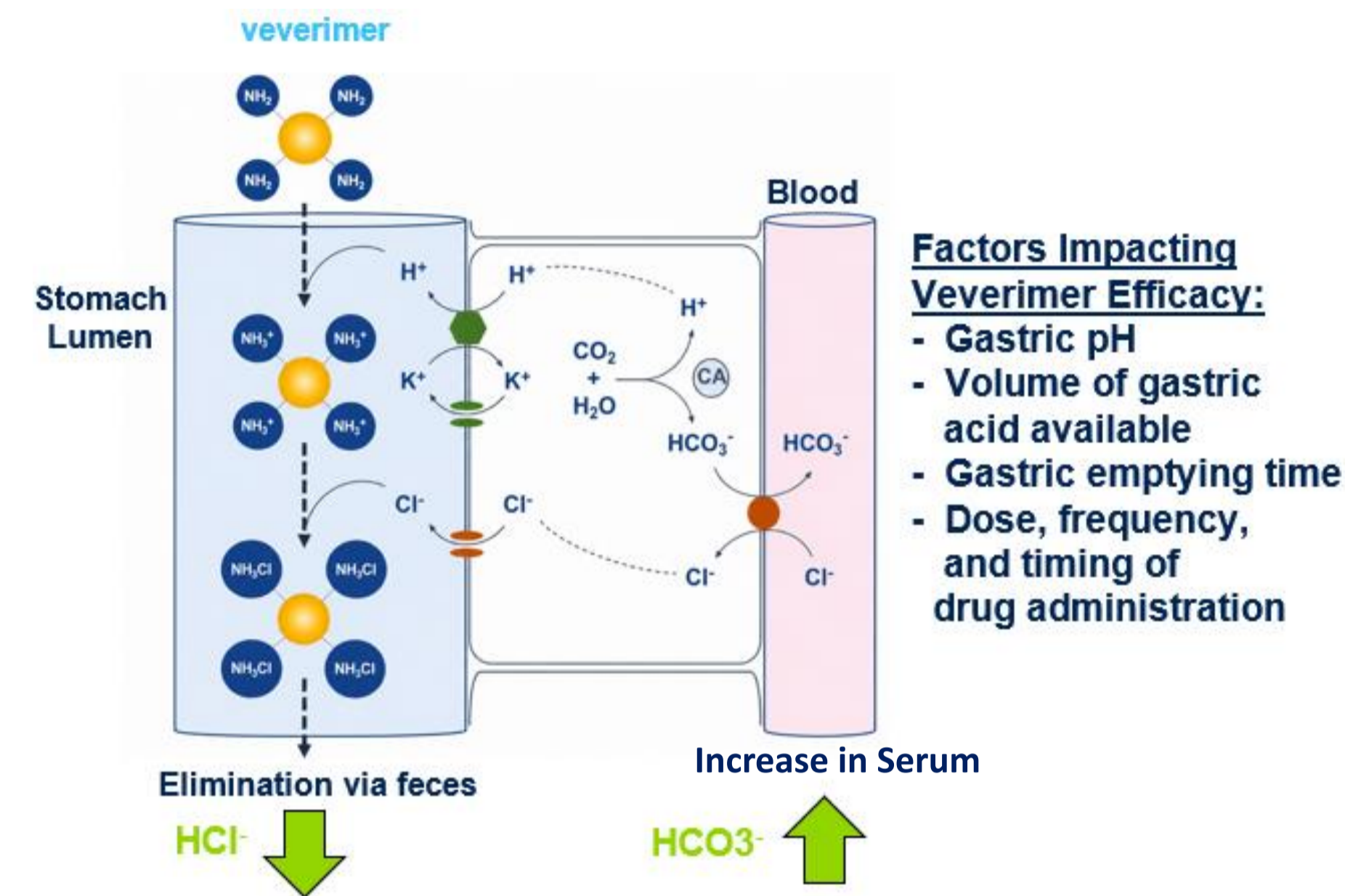
- Identify gastrointestinal physiologic factors that may influence treatment efficacy of veverimer

## METHODS

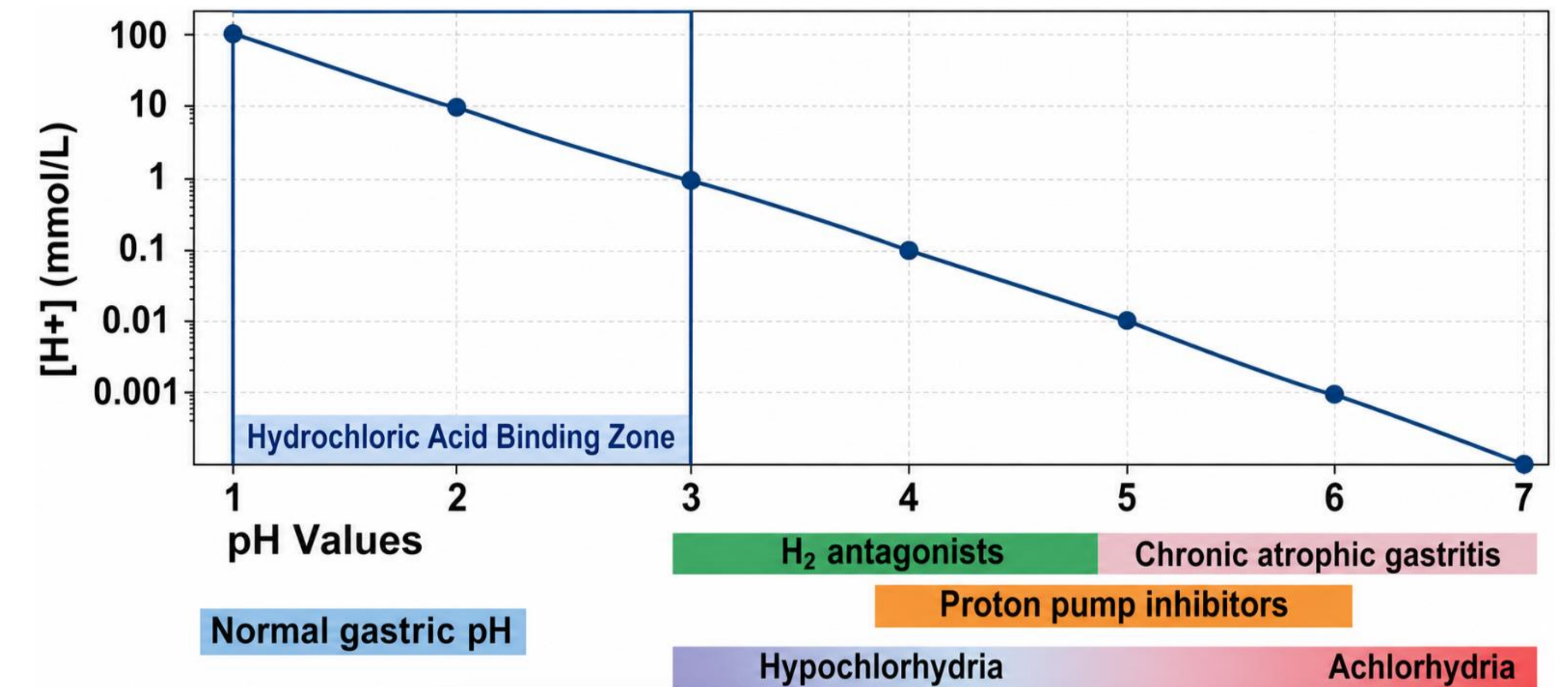
- We performed translational analyses incorporating prior non-clinical and clinical trial data, gastric physiology, and pharmacologic modeling to identify determinants of veverimer's efficacy
- Evaluated factors included: HCl concentrations at various gastric pH levels, gastric acid volume, gastric emptying time, meal composition, dosing frequency, and impact of medications/ medical conditions known to reduce gastric acid secretion

## RESULTS

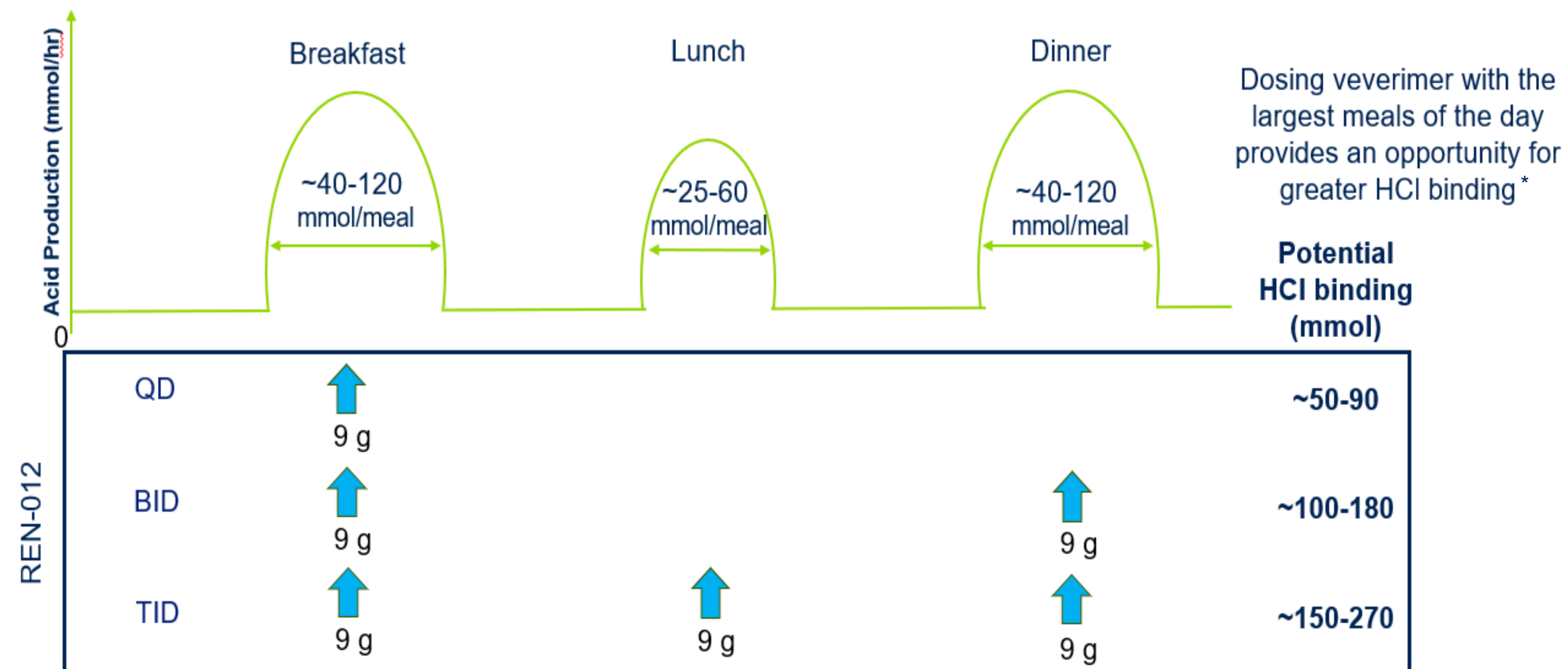
### A. Veverimer MOA and Gastric HCl Binding



### B. Increased Gastric pH by Certain Medications or Medical Conditions Will Reduce HCl Availability



### C. Increased Dose Frequency and Administration with Larger Meals May Improve Veverimer Efficacy



\* Protein and fat contents of large meals will stimulate gastric acid production and prolong emptying time., respectively, thus increasing HCl availability and exposure time

## CONCLUSIONS

- Management of metabolic acidosis in patients with CKD can be achieved with alkali supplementation, or acid-removal (e.g., HCl binding with veverimer)
- Alignment of the therapeutic mechanism of veverimer with gastric physiology is important for successful clinical outcomes
- Translational analyses has identified gastric pH, meal content, gastric emptying time, and dosing frequency as modifiable determinants of veverimer efficacy
- A Phase 3 study of veverimer which prospectively integrates these principles into the protocol has been initiated in 2026.