Tesamorelin — Basic Review Questions
Modes of Action and Clinical Relevance

Question 1 — Receptor and signaling mechanism
What receptor does tesamorelin act on, and what is the immediate intracellular signaling cascade it triggers?

Response: Tesamorelin binds with high affinity to the growth hormone-releasing hormone receptor (GHRHR), a G protein-coupled receptor on somatotroph cells in the anterior pituitary. Binding activates adenylate cyclase, which raises cyclic AMP (cAMP). The increased cAMP activates protein kinase A (PKA), stimulating GH gene transcription and protein synthesis, which results in pulsatile GH release that mimics normal physiological secretion.

Question 2 — Structural modification
What structural change distinguishes tesamorelin from native GHRH, and why is it clinically important?

Response: Tesamorelin is a stabilized synthetic version of native GHRH(1-44)NH2 with a trans-3-hexanoic acid group added at the N-terminal end. This modification dramatically enhances stability against dipeptidyl peptidase-4 (DPP-4) degradation, extending the half-life from roughly 5 minutes (native GHRH) to about 26-38 minutes, while preserving the biological activity and receptor-binding capacity of endogenous GHRH.

Question 3 — Tesamorelin vs. exogenous growth hormone
How does tesamorelin's effect on the GH axis differ mechanistically from administering exogenous growth hormone, and why does this matter?

Response: Tesamorelin works through the hypothalamic-pituitary axis rather than bypassing it, so it produces pulsatile, physiological GH release and preserves the natural somatostatin/IGF-1 negative feedback loop. Exogenous GH instead produces continuous, supraphysiologic levels and suppresses feedback. Because feedback stays intact with tesamorelin, IGF-1 remains within age-adjusted normal limits, glucose homeostasis is preserved (less insulin resistance), and there is lower theoretical malignancy risk — advantages not seen with exogenous GH.

Question 4 — Visceral fat selectivity
What is meant by tesamorelin's "VAT selectivity," and why is this clinically advantageous?

Response: Tesamorelin preferentially reduces visceral adipose tissue (VAT) — the metabolically active, pro-inflammatory fat depot linked to cardiovascular risk, insulin resistance, and fatty liver disease — while sparing subcutaneous fat. Mechanistically this involves activation of hormone-sensitive lipase in visceral adipocytes. The clinical

advantage is targeting the harmful fat depot without the gaunt or "wasted" appearance that can accompany general lipolysis from exogenous GH or some other agents.

Question 5 — Glucose safety
What does the clinical evidence show about tesamorelin's effect on glucose control, including in patients with type 2 diabetes?

Response: Because it preserves physiological feedback, tesamorelin does not generally cause the insulin resistance associated with exogenous GH. In a 12-week RCT in type 2 diabetic patients (Clemmons et al., PLoS One 2017, N=53), it produced no significant change in HbA1c, insulin response, or fasting glucose, and no patient discontinued for loss of glycemic control; total and non-HDL cholesterol actually decreased. That said, the guide still advises monitoring HbA1c and fasting glucose, since transient glucose increases can occur early in therapy.

Question 6 — Defining and maintaining clinical response
What VAT-reduction threshold defines a clinical responder, and what happens to the benefit if therapy is stopped?

Response: A reduction of at least 8% in VAT at 26 weeks defines clinical response and predicts sustained metabolic benefit; responders show significantly greater improvements in triglycerides, adiponectin, and glucose homeostasis than non-responders. The benefit is not permanent — upon discontinuation, VAT reaccumulates, so ongoing therapy is generally required to maintain the effect. In non-HIV patients, addressing upstream drivers of visceral adiposity (diet, stress, immune factors) may influence how durable the response is.