

RESEARCH MONOGRAPH . COMPOUND PROFILE

Larazotide

An eight-residue zonulin receptor antagonist developed by Innovate Biopharmaceuticals (now 9 Meters Biopharma) as the first specific gut tight junction modulator advanced to Phase 3 in celiac disease.

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COMPOUND CLASS	Zonulin antagonist octapeptide and tight junction modulator

ABSTRACT

Larazotide acetate (Gly-Gly-Val-Leu-Val-Gln-Pro-Gly; CAS 258818-34-7; molecular weight 754.86 free peptide) is an eight-residue synthetic peptide developed at the University of Maryland by Alessio Fasano and colleagues as a competitive antagonist at the zonulin receptor. Zonulin (also designated pre-haptoglobin 2) is the human ortholog of the *Vibrio cholerae* zonula occludens toxin (ZOT) and is the only known endogenous regulator of intestinal epithelial tight junction permeability; activation of the zonulin pathway in response to gluten exposure or other triggers produces transient opening of intestinal tight junctions and translocation of luminal antigens into the lamina propria, contributing to celiac disease pathogenesis and a broader leaky-gut phenotype implicated in autoimmune and inflammatory conditions. Larazotide binds the zonulin receptor and blocks ZOT/zonulin-induced tight junction disassembly without directly affecting baseline tight junction integrity. The compound was advanced through Phase 1 and Phase 2 trials in celiac disease and entered Phase 3 (CeDLara) for the residual gluten-cross-contamination phenotype in patients on a gluten-free diet who continue to experience symptoms. The Phase 3 readout in 2022 did not meet the primary endpoint of celiac disease patient-reported outcome, and 9 Meters Biopharma announced discontinuation of the program. Despite the clinical setback in celiac disease, larazotide remains a pharmacologically distinct research tool for tight junction modulation in inflammatory bowel disease, multiple sclerosis, and other indications where intestinal barrier dysfunction is implicated. Oral bioavailability is essentially zero (the peptide acts in the gut lumen and is not absorbed); the

route of administration is per oral as a sustained-release formulation. Adverse events in clinical trials were mild and dominated by gastrointestinal effects.

1. Compound Identification

Larazotide is described as zonulin antagonist octapeptide and tight junction modulator. An eight-residue zonulin receptor antagonist developed by Innovate Biopharmaceuticals (now 9 Meters Biopharma) as the first specific gut tight junction modulator advanced to Phase 3 in celiac disease.

1.1 Class summary

Zonulin antagonist octapeptide and tight junction modulator

1.2 Subtitle

An eight-residue zonulin receptor antagonist developed by Innovate Biopharmaceuticals (now 9 Meters Biopharma) as the first specific gut tight junction modulator advanced to Phase 3 in celiac disease.

2. Abstract

Larazotide acetate (Gly-Gly-Val-Leu-Val-Gln-Pro-Gly; CAS 258818-34-7; molecular weight 754.86 free peptide) is an eight-residue synthetic peptide developed at the University of Maryland by Alessio Fasano and colleagues as a competitive antagonist at the zonulin receptor. Zonulin (also designated pre-haptoglobin 2) is the human ortholog of the *Vibrio cholerae* zonula occludens toxin (ZOT) and is the only known endogenous regulator of intestinal epithelial tight junction permeability; activation of the zonulin pathway in response to gluten exposure or other triggers produces transient opening of intestinal tight junctions and translocation of luminal antigens into the lamina propria, contributing to celiac disease pathogenesis and a broader leaky-gut phenotype implicated in autoimmune and inflammatory conditions. Larazotide binds the zonulin receptor and blocks ZOT/zonulin-induced tight junction disassembly without directly affecting baseline tight junction integrity. The compound was advanced through Phase 1 and Phase 2 trials in celiac disease and entered Phase 3 (CeDLara) for the residual gluten-cross-contamination phenotype in patients on a gluten-free diet who continue to experience symptoms. The Phase 3 readout in 2022 did not meet the primary endpoint of celiac disease patient-reported outcome, and 9 Meters Biopharma announced discontinuation of the program. Despite the clinical setback in celiac disease, larazotide remains a pharmacologically distinct research tool for tight junction modulation in inflammatory bowel disease, multiple sclerosis, and other indications where intestinal barrier dysfunction is implicated. Oral bioavailability is essentially zero (the peptide acts in the gut lumen and is not absorbed); the route of administration is per oral as a sustained-release formulation. Adverse events in clinical trials were mild and dominated by gastrointestinal effects.

3. Mechanism of Action

Competitive antagonism at the zonulin receptor on intestinal epithelium. Blocks ZOT/zonulin-induced tight junction opening without affecting baseline barrier integrity. Acts in gut lumen with negligible systemic absorption.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

5. Reported Research Dose Ranges

Phase 3 dosing 0.5 mg per oral administration three times daily before meals. Earlier phase studies 0.25 to 8 mg per dose.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

9. References

1. Fasano A. Zonulin and its regulation of intestinal barrier function. *Physiol Rev* 2011.
2. Leffler DA, et al. A randomized, double-blind study of larazotide acetate in celiac disease. *Aliment Pharmacol Ther* 2012.
3. Slifer ZM, Blikslager AT. The integral role of tight junction proteins in the repair of injured intestinal epithelium. *Int J Mol Sci* 2020.
4. 9 Meters Biopharma. CeDLara Phase 3 topline results. Press release 2022.

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