Abstract: CT142
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Reducing nausea and vomiting while maintaining the full potential for efficacy with spevatamig, a CLDN18.2xCD47 bispecific antibody

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Background

Introduction

Claudin 18.2 (CLDN18.2) is a cancer target expressed on several gastrointestinal (GI) carcinomas. CLDN18.2 is also expressed on gastric mucosa, which is thought to be the reason CLDN18.2-targeting agents cause nausea and/or vomiting (N/V). Spevatamig is a novel IgG1-based bispecific antibody with a native IgG structure (Figure 1). Unlike many CLDN18.2-targeting agents that usually have two anti-CLDN18.2 arms, spevatamig has only one anti-CLDN18.2 arm. This allows it to have weaker binding to gastric mucosa, potentially causing less N/V. In addition, spevatamig has one anti-CD47 arm. CD47 is highly expressed on gastric, pancreatic, and biliary tract tumor cells but not on gastric mucosa. Spevatamig, through its bispecific design and resulting high binding to tumor cells, provides the potential to maintain efficacy while limiting on-target, off-tumor GI toxicity (Figure 1). **As of March 2026, more than 160 patients globally have been dosed with spevatamig collectively in monotherapy and combination therapy settings**.

Design of spevatamig with a two-step approach[1]

Step 1: Optimize anti-CD47 mAb

Table 1: Mapping the CD47 biology using three distinct molecules to de-risk clinical development

	PT248	PT240	PT246
Cancer cell binding	High	High	Low
Red blood cell (RBC) binding	High	Low	Low
In vivo efficacy	Complete tumor regression	Complete tumor regression	Nearly complete tumor regression
Hematological tox in monkeys	Severe	Borderline severe	Moderate

- Three distinct anti-CD47 mAbs were used to build empirical correlation between efficacy and risk of hematological toxicity
- PT240 was selected as the **optimized anti-CD47 mAb**
- Spevatamig was constructed using one anti-CD47 arm from PT240 and one anti-CLDN18.2 arm

Step 2: Construct a native IgG1-like bsAb using the anti-CD47 arm from PT240 and one anti-CLDN18.2 arm

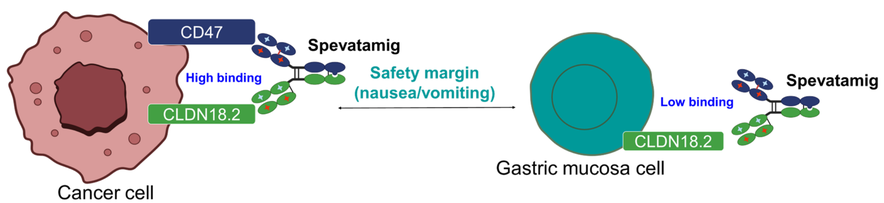

Figure 1: Spevatamig's optimized, bispecific design mitigates high grade nausea and vomiting events and improves tolerability.

Spevatamig was constructed with PACbody and SPECpair

- **PACbody** is a native IgG-like bispecific antibody platform invented by Phanes Therapeutics, Inc.
- **SPECpair** is a technology platform invented by Phanes Therapeutics, Inc.; it enables manufacturing of native IgG-like bispecific antibodies with the mAb manufacturing process

Results

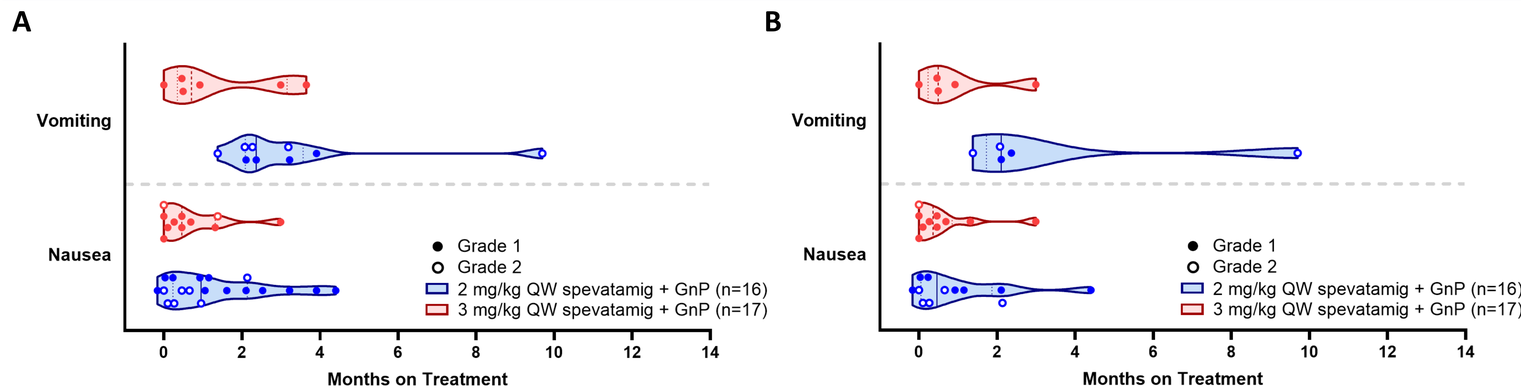

Figure 2: All incidences of N/V events (A) and first N/V incidence (B) per patient treated with spevatamig plus GnP at dose levels chosen for further development. All events were Grade 1 or 2.

Table 2: Dose modifications and discontinuations in patients with 1L PDAC treated with spevatamig plus GnP

	2 mg/kg QW spevatamig + GnP (n=16)	3 mg/kg QW spevatamig + GnP (n=17)*
Patients with ≥ 1 dose reduction of spevatamig	1 (6%)	1 (6%)
Patients with discontinuation due to AE	2 (13%)	1 (6%)
Patients with discontinuation due to N/V	0 (0%)	0 (0%)
Patients with discontinuation due to treatment-related AE	1 (6%)	1 (6%)
Patients with discontinuation due to treatment-related N/V	0 (0%)	0 (0%)

*Enrollment ongoing

- No Grade ≥ 3 N/V events were reported among patients in dose levels chosen for further development of spevatamig in combination with GnP[1].
- From available safety data, there is no apparent increase in N/V rates in patients dosing at 3 mg/kg QW spevatamig plus GnP compared to 2 mg/kg QW (Figure 2).
- While the majority of patients did experience nausea and/or vomiting while on treatment, no patients permanently discontinued spevatamig treatment due to N/V (Table 2).

Conclusions

- Spevatamig's bispecific design targeting CLDN18.2 and CD47 appears to reduce the risk of high-grade N/V associated with CLDN18.2-targeting agents[2], which has enabled its combination with GnP at potentially efficacious doses.
- No Grade ≥ 3 N/V was observed at target dose levels in combination with GnP, suggesting spevatamig does not increase vomiting risk compared to GnP alone[3].
- While incidence of nausea appears higher than in pivotal studies of GnP alone[3], all nausea events for patients dosed with spevatamig plus GnP were effectively managed with no N/V related dose reductions or treatment discontinuations.
- The safety profiles of the 2 mg/kg QW and 3 mg/kg QW spevatamig dose levels in combination with GnP are conducive for further development.

References

1. Saeed et al., J Clin Oncol 2026;44(709).
2. Türeci et al., Ann Oncol 2019; 30(9):1487-95.
3. Wainberg et al., Lancet 2023; 402:1272-1281.