Efficacy and Safety of On-Demand Vonoprazan versus Placebo in the Treatment of Heartburn in Symptomatic Nonerosive Reflux Disease (NERD) Patients: A Phase 2 Randomized Controlled Trial

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Introduction:
Current treatment for NERD is daily acid-suppressive therapy; however, on-demand treatment is an attractive option for long-term management. Vonoprazan, a potassium-competitive acid blocker, rapidly and profoundly suppresses gastric acid. The aim of this study was to evaluate the efficacy and safety of vonoprazan vs placebo for on-demand treatment of symptomatic NERD.

Methods:
This Phase 2, double-blind, placebo-controlled study (NCT04799158) enrolled NERD patients (normal endoscopy, heartburn episodes for ≥6 months, heartburn on ≥4/7 consecutive days) into a 4-week run-in period of once-daily vonoprazan 20mg. Patients without heartburn in the last 7 days of the run-in period were randomized 1:1:1:1 to receive vonoprazan 10mg, 20mg, 40mg, or placebo on-demand for 6 weeks. Patients were asked to take no more than one dose of study drug for 24h after a heartburn episode and to take no rescue antacids ≤3h after taking study drug. Patients recorded heartburn symptoms, drug and antacid use in an electronic diary. The primary endpoint was the % of evaluable heartburn episodes with complete and sustained relief (within 3h and with no further heartburn reported for 24h after taking study drug) during the on-demand treatment period. The onset of complete and sustained relief was evaluated within 30min and 1, 1.5, 2, and 3h after study drug.

Results:
Of 458 patients entering the run-in period, 207 (females: 125; mean age: 54y) were eligible and randomized to treatment. For the primary endpoint, in the vonoprazan 10, 20, and 40mg groups, 56.0% (201/359), 60.6% (198/327) and 70.0% (226/323) of heartburn episodes met the criteria for complete and sustained relief, respectively, vs 27.3% (101/370) for placebo ($P<$ 0.0001 for each vonoprazan treatment vs placebo) (Table 1). Significant differences in complete and sustained relief occurred as early as 1h after study drug for all vonoprazan doses. In the on-demand period, 21.3% of patients receiving placebo reported a treatment-emergent adverse event (TEAE) vs 16.3%, 18.4%, and 16.7% of those on vonoprazan 10, 20, and 40mg, respectively. No TEAE was reported by >1 patient per group. No serious TEAEs were reported.

Discussion:
The results suggest that on-demand vonoprazan treatment for the relief of episodic heartburn in NERD patients is efficacious and well-tolerated. On-demand vonoprazan treatment may offer NERD patients an attractive alternative to daily heartburn therapy.

Data Table:

Endpoint	Vonoprazan 10 mg n=52	Vonoprazan 20 mg n=52	Vonoprazan 40 mg n=51	Placebo n=52
Heartburn episodes with complete and sustained relief within 3 hours[a]				
n/N evaluable episodes[b] (%)	201/359 (56.0)	198/327 (60.6)	226/323 (70.0)	101/370 (27.3)
P-value (vs placebo)	< 0.0001	< 0.0001	< 0.0001	-
Timing of complete and sustained relief[a], n/N evaluable episodes[b] (%)				
Within 30 minutes	31/359 (8.6)	17/327 (5.2)	9/323 (2.8)	21/370 (5.7)
P-value (vs placebo)	0.15	0.87	0.09	-
Within 1 hour	101/359 (28.1)	63/327 (19.3)	74/323 (22.9)	44/370 (11.9)
P-value (vs placebo)	< 0.0001	0.0083	0.0002	-
Within 1.5 hours	151/359 (42.1)	103/327 (31.5)	139/323 (43.0)	67/370 (18.1)
P-value (vs placebo)	< 0.0001	< 0.0001	< 0.0001	-
Within 2 hours	182/359 (50.7)	151/327 (46.2)	187/323 (57.9)	81/370 (21.9)
P-value (vs placebo)	< 0.0001	< 0.0001	< 0.0001	-

Table: Table 1. Comparison of Efficacy Endpoint Results Between the Different Vonoprazan Doses and Placebo.

(a) Complete and sustained relief is defined as complete relief with no antacid taken within the indicated time frame after taking study drug and no further heartburn reported for 24 hours after taking study drug.

(b) An evaluable heartburn episode is defined as any for which study drug was taken and for which the subject completed ≥1 entry in the heartburn episode diary.

Disclosures:

Ronnie Fass: Adcock-Ingram – Speaker. AstraZeneca – Speaker. Celexio – Advisor or Review Panel Member. Dexcel – Advisor or Review Panel Member. Eisai – Speaker. GERDcare – Advisor or Review Panel Member. GI Supply – Speaker. Ginger Health – Stock Options. Johnson & Johnson – Speaker. Medicamenta – Speaker. Medtronic – Advisor or Review Panel Member. Phathom Pharmaceuticals – Advisory Committee/Board Member, Consultant. Salix – Grant/Research Support. Takeda Pharmaceuticals – Advisory Committee/Board Member, Speakers Bureau.
Michael Vaezi: Bayer – Consultant. Diversatek – Consultant, Grant/Research Support, Intellectual Property/Patents. Ironwood – Consultant. ISOThrive – Consultant. Legal – Consultation in litigation relating to acid-suppressive agents. Phathom Pharmaceuticals – Consultant. Sanofi – Consultant.
Prateek Sharma: Bausch – Consultant. Boston Scientific Corporation – Consultant. CDx Labs – Consultant. Cosmo Pharmaceuticals – Grant/Research Support. Covidien LP – Consultant, Grant/Research Support. Docbot – Grant/Research Support. Erbe USA, Inc. – Grant/Research Support. Exact Sciences – Consultant. Fujifilm Holdings America Corporation – Grant/Research Support. Fujifilm Medical Systems USA, Inc. – Consultant. Ironwood Pharmaceuticals – Grant/Research Support. Lucid – Consultant. Lumendi – Consultant. Medtronic – Consultant, Grant/Research Support. Medtronic USA, Inc. – Grant/Research Support. Olympus – Consultant, Grant/Research Support. Phathom Pharmaceuticals – Consultant. Samsung Bioepis – Consultant. Takeda Pharmaceuticals – Consultant.

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