Amisulpride Provides Significant Nausea Reduction in Patients with Established Postoperative Nausea and Vomiting: Pooled Results from Two Phase III Trials

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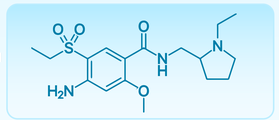
Background

- Epidemiologic data on nausea alone are sparse[1]
- The majority of patients (75-80%) with postoperative nausea and vomiting (PONV) present with postoperative nausea alone rather than vomiting (PONv)[2,3]
- PONv is often more resistant to pharmacologic interventions, both prophylactic and therapeutic, than PONV[4]
- PONV, especially nausea, is believed to be under-reported[2]
- Nausea likely has both peripheral and central components[1]
- PONv may contribute to substantial patient burden/increased resource utilization (delayed discharge, unanticipated hospital admissions)[5,6,7]

Amisulpride

- Selective dopamine D_2/D_3 receptor antagonist approved in 2020 for prevention and rescue treatment of PONV[8]
- Approved as an oral antipsychotic for almost 40 years in Europe and elsewhere with an established safety profile[7]
  - PONV IV doses are much lower (< 1/10th) than antipsychotic doses[8]
- Only FDA-approved antiemetic for rescue treatment of PONV[8]
- Safety and efficacy established in:
  - Prophylaxis[9,10]
  - Treatment of PONV in patients with no prior prophylaxis[11]
  - Rescue therapy in patients who failed antiemetic prophylaxis from other pharmacologic classes[3]



Study Hypothesis

A single 10 mg dose of intravenous (IV) amisulpride significantly improved nausea measurements, including patient-reported nausea, compared to placebo following surgery for patients who received and failed prophylaxis and for patients who did not receive any prophylaxis.

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MG and LB are employees of Eagle Pharmaceuticals and hold company stock, and SA is a consultant for Eagle Pharmaceuticals.

Methods

Post hoc analysis of two randomized, multicenter, double-blind, placebo-controlled, parallel-group, phase III studies, Study 1 (N=1988)[8] and Study 2 (N=2285)[3]

- **Study 1:** patients at low-to-moderate risk of PONV without prior prophylaxis
- **Study 2:** patients at moderate or high risk of PONV who failed prophylaxis
- Primary endpoint was complete response (CR): No emetic episodes (vomiting or retching) or administration of antiemetic rescue medication for 24 hours after study drug dosing
- Nausea was assessed at the time of the PONV event (baseline) and at 5, 15 and 30 minutes and 2 hours after dosing and at any time the patient spontaneously reported nausea up to 24 hours after dosing
  - Utilized a self-reported 11-point verbal scale, where 0 represented no nausea and 10 the worst nausea possible
- Nausea secondary endpoints included:
  - **Incidence of significant nausea**, defined as verbal scale score ≥ 4
  - **Use of rescue medication,** a surrogate measure for nausea
  - **Evolution of nausea score**, calculated as the area under the curve (AUC) of nausea scores against time, over the first 3 hours after study drug administration
    - Serves as a measure of the burden of nausea
    - Larger evolution score of nausea signifies larger burden of nausea
- Patients were randomized to receive a single IV dose of amisulpride (5 mg or 10 mg) or placebo after experiencing PONV in the first 24 hours following wound closure.

Study Schema

Screening
N=4974
- Study 1 n=1988
- Study 2 n=2285

1:1:1 Randomization
Modified Intent-to-Treat (mITT) Population*
N=1270
(Study 1: n=560)
(Study 2: n=702)

Placebo N=416
(Study 1: n=181; Study 2: n=235)

10 mg amisulpride IV N=418
(Study 1: n=188; Study 2: n=230)

5 mg[a] amisulpride IV N=428
(Study 1: n=191; Study 2: n=237)

* mITT population: All subjects who signed informed consent form and received a dose of amisulpride or placebo study medication
[a]5 mg dose was not significantly superior to placebo in Study 2. Only data on 10 mg dose (approved dose for rescue treatment) are presented in this poster.

Selected Baseline Characteristics (mITT Population)

	Studies 1 and 2	
	Amisulpride 10 mg N=418	Placebo N=416
	Number (%) of Patients	
Female	353 (84.4)	348 (83.7)
History of PONV or Motion Sickness	167 (40.0)	182 (43.8)
Non-Smoker	355 (84.9)	339 (81.5)
Expected to Receive Post-operative Opioids	399 (95.5)	399 (95.9)
Number of PONV Risk Factors:		
≤2	87 (20.8)	91 (21.9)
3	213 (51.0)	195 (46 .9)
4	118 (28.2)	130 (31.3)

Results

Efficacy Results in First 24 Hours After Treatment (Pooled Treatment)

Patients Randomized	Amisulpride 10 mg (n=418)	Placebo (n=416)	Treatment Difference %	95% CI[b]	*P* value[c]
Complete Response at 24 hrs: 1° endpoint	155 (37.1%)	106 (25.5%)	11.6	5.4, 17.8	<0.001
Complete Response at 2 hrs: 2° endpoint	265 (63.4%)	195 (46.9%)	16.5	12.6, 25.8	<0.001
Incidence of Significant Nausea (0-24 hrs)*	219 (52.4%)	254 (61.1%)	-8.7	-15.4, -2.0	0.006
Use of rescue medication, (0-24 hrs)*	246 (58.9%)	298 (71.6%)	-12.8	-19.2, -6.4	<0.001

*Nausea secondary endpoints (post hoc analyses)
CI = confidence interval; mITT=modified intent-to-treat.
a. Percentages are based on the number of patients with a non-missing response (n) in each treatment group (N)
b. CIs for the difference in proportions: normal approximation
c. Based on Pearson X^2 test (one-sided) unless otherwise specified; one-sided significance level of 2.5%

Evolution of Nausea Scores (secondary endpoint, post hoc analysis)

Time (min)	Amisulpride 10 mg (n=403) Mean (SD)	Placebo (N=404) Mean (SD)	H-L Estimate of Median Difference	95% CI	*P* value[a]
0-60*	2550 (2039)	3110 (2169)	-498.0	-778.6, -243.8	<0.001
0-120*	4376 (4094)	5489 (4355)	-927.7	-1500.0, -438.8	<0.001
0-180*	6018 (6115)	7599 (6368)	-1383.3	-2100.8, -695.7	<0.001

*From rescue treatment drug administration, measured on an 11-point verbal rating scale, ranging from 0 (no nausea at all) to 10 (worst nausea imaginable)
CI = confidence interval; H-L= Hodges-Lehmann; mITT=modified intent-to-treat
a. Mann Whitney test (one-sided); one-sided significance level of 2.5%

*Evolution of nausea score, calculated as the area under the curve (AUC) of nausea scores against time, over the first 3 hours after study drug administration
- May serve as a measure of the burden of nausea
- Larger evolution score of nausea signifies larger burden of nausea

Results (cont.)

Table 2: Treatment- Emergent Adverse Events Occurring in ≥ 5% in Either Treatment Group

TEAE	Amisulpride 10 mg (n=418)	Placebo (n=416)
	Patients, n (%)	Patients, n (%)
Nausea*	45 (10.8)	49 (11.8)
Flatulence	30 (7.2)	39 (9.4)
Constipation	24 (5.7)	33 (7.9)
Vomiting*	15 (3.6)	23 (5.5)
Headache	15 (3.6)	22 (5.3)
Infusion site pain	25 (6.0)	17 (4.1)

*Nausea and vomiting occurring more than 24 hours after study drug dosing

Conclusions

- PONV/PONv remain under-reported and represent a significant burden to both patients and health systems
- A single dose of IV amisulpride 10 mg was safe and effective for treatment of nausea across multiple measures, including
  - ✓ Significant nausea
  - ✓ Use of rescue medication
  - ✓ Evolution of nausea (burden of nausea) over time
- The AE profile was comparable between the placebo and 10 mg amisulpride groups
- One of the few analyses to report on PONv

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