

Phase II randomized glioma study to evaluate efficacy and satisfaction of rolapitant plus ondansetron in preventing chemoradiation-induced nausea and vomiting

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Abstract

Background. Nausea and vomiting remain feared cancer treatment-related side effects. Antiemetic guideline trials exclude malignant glioma patients. In patients receiving radiation with concurrent temozolomide, chemoradiation-induced nausea; vomiting (cRINV) rates are 35% and 26%, respectively, which reduce quality of life, treatment adherence, and cancer control.

Methods. This randomized phase-II open-label trial, evaluated efficacy, patient preference, and satisfaction of ondansetron (short-acting 5HT3-RA; 3 h-half-life) monotherapy versus rolapitant (long-acting NK1-RA; 180 h-half-life) plus ondansetron in preventing cRINV during 6 weeks of temozolomide (75 mg/m²/day × 42 day) with radiation. Fifty-three eligible patients were randomized to Sequence-A (ondansetron-8 mg days: 1–42, day 22 rolapitant-180 mg) or Sequence-B (rolapitant day 1 plus daily ondansetron). *Primary endpoint* was percentage achieving cRINV-complete response (no vomiting/antiemetic rescue) during the *first 2 weeks* of radiation. *Secondary endpoints:* cRIN/cRIV rates, preference/satisfaction for rolapitant/ondansetron, toxicity, and adherence.

Results. Forty-eight (Sequence-A: 25; Sequence-B: 23) initiated chemoradiation. Mean age = 53, 58% male, 73% Karnofsky performance status (KPS) > 90%, and 73% glioblastoma. During first 2 weeks of radiation, cRINV-CR was 57% with ondansetron and 74% receiving rolapitant/ondansetron ($P = .27$). Patient-reported 6-week cRINV-CR was 55% for both arms. First 2-week cRIN rates (38% Sequence-A; 32% Sequence-B) were more than cRIV rates (19% Sequence-A; 0% Sequence-B). Patients receiving ondansetron alone vomited more during the first 2 weeks and overall (26%) than with rolapitant/ondansetron (11%). Among 35 completers, 20% preferred rolapitant/ondansetron, 60% preferred ondansetron, and 20% had no preference ($P = .0004$). Adverse-events attributable to antiemetics were grade 1–2.

Conclusions. No difference was found in cRINV-CRs between the first 2-week treatments or overall satisfaction. Although not a positive study, less vomiting occurred with rolapitant/ondansetron. While patients prefer ondansetron monotherapy, most perceived better effectiveness with rolapitant/ondansetron.

Key Points

- There was no difference found among patients receiving ondansetron alone versus rolapitant plus ondansetron in preventing chemoradiation-induced nausea and vomiting in the first 2-week of radiation with concomitant temozolomide.

- The addition of an oral NK1-RA to a 5HT3-RA during standard of care radiation and temozolomide in glioma patients may result in less vomiting compared with a 5HT3-RA alone.
- While patients preferred ondansetron monotherapy to prevent nausea and vomiting during standard of care chemoradiation, most perceived better effectiveness with rolapitant plus ondansetron.

Importance of the Study

This randomized phase-II open-label trial addresses a significant gap in the management of chemoradiation-induced nausea and vomiting in patients with high-grade gliomas. The study compares the efficacy and patient satisfaction between ondansetron monotherapy and a combination of rolapitant and ondansetron. No difference was found between patients receiving ondansetron alone versus rolapitant plus ondansetron in preventing chemoradiation-induced nausea and vomiting during the first 2-week of radiation with concomitant temozolomide. Although not a positive study,

less vomiting occurred with rolapitant/ondansetron. While patients prefer ondansetron monotherapy, most perceived better effectiveness with rolapitant/ondansetron. The high rates of nausea continue to be concerning in the glioma population receiving standard chemoradiation. Considering the high prevalence of nausea and vomiting among patients undergoing chemoradiation for glioblastoma, this research is timely and clinically relevant. Low-dose olanzapine may be an effective antiemetic to explore in a future prospective, randomized trial in patients with gliomas.

Brain tumors are rare and account for approximately 1–2% of all cancer diagnoses.¹ Individuals who are newly diagnosed with glioblastoma are faced with an incurable, aggressive disease that is associated with significant morbidity/mortality and a poor 5-year survival rate of 6.8%.¹ Despite advancement in malignant glioma (MG) treatment, the expected median survival remains low at 13–16 months for individuals receiving upfront standard treatment with surgery and chemoradiation.^{2–4} Thus, supportive care to improve quality of life (QoL) symptoms is paramount. Standard treatment consisting of temozolomide (75 mg/m²/d) with concurrent radiation, followed by adjuvant 5-day temozolomide (150–200 mg/m²/d every 28 days) is associated with chemoradiation-induced nausea and vomiting (cRINV) rates of 35% and 26%, respectively.^{5,6} These cRINV rates result in reduced QoL, treatment adherence, and potentially cancer control.^{7,8} Our goal was to develop a *steroid-sparing* cRINV regimen that would ameliorate nausea/vomiting in an orphan disease that is often excluded from antiemetic guideline trials due to brain pathology, glioma treatment drug interactions (ie, aprepitant) and steroid use.⁷

Nausea and vomiting remain the most feared side effects and persist in 10–40% of individuals receiving cancer chemotherapy despite prophylactic guideline antiemetics.^{8–10} Over the past 4 decades, significant progress has been made in preventing nausea/vomiting among patients undergoing cancer therapy due to our knowledge of emesis pathophysiology and to the development of modern-day antiemetics that directly target emetic pathways.⁹ It is vital that oncology providers become familiar with current available antiemetic prophylaxis agents that are supported by updated evidence-based guideline antiemetics (National Comprehensive Cancer Network [NCCN]; MASCC/European Society for Medical Oncology [ESMO]; American Society of Clinical Oncology [ASCO]) as these recommendations

are key to preventing up to ~80–90% chemotherapy and radiation-induced nausea/vomiting.^{11–13} Despite effective guidelines, a barrier to control nausea and vomiting is the lack of guideline adherence.^{9,14} Guideline knowledge alone does not change practice. In our hands, implementation of an educational session, risk-assessment tools, and standardize computerized guideline antiemetic order sets was determined to increase adherence and control rates.^{8,9,15}

While the emetogenicity of an anticancer regimen has been determined to be the primary risk factor, accurately defining emetic risk associated with various antineoplastic agents/regimens continues to be a challenge, as data on emesis in various anticancer trials “are usually highly heterogeneous (different tumor types, advanced versus nonadvanced disease, systemic treatment naive or previously treated, used alone or in combination with other agents, different antiemetic prophylaxis if given or not reported, different reporting systems such as Common Terminology Criteria of AEs [CTCAE] all grades versus only grade 3–4) (p. 2).”¹¹ Oral anticancer agents, such as temozolomide, provide additional challenges as they are used in extended regimens of daily dosing rather than the single bolus intravenous administration of these agents that define level of emetic risk or the proportion of patients experiencing emesis in the absence of effective antiemetic prophylaxis (high [$>90\%$]; moderate [30%–90%]; low [10%–30%]; minimal [$<10\%$]).¹¹ As temozolomide is typically administered not as a single intravenous dose but over a 5-day period or continuously over prolonged time periods, traditional concepts of acute and delayed nausea and vomiting lose their relevance in these settings.

Although it has been demonstrated repeatedly that chemotherapy-induced acute vomiting (occurring <24 h post-chemotherapy) is better controlled than delayed vomiting (occurring >24 –120 h post-chemotherapy),

this concept may not apply to metronomic daily oral temozolomide or 5-day adjuvant temozolomide.⁹ It is also well known that nausea is more difficult to control than vomiting,⁹ perhaps because nausea is a more subjective outcome and is not accurately measured in trials.¹⁶ Nevertheless, nausea has a greater effect on QoL.¹⁶ This fact holds true in patients with MG receiving a combination of chemotherapy and radiation which increases the chemotherapy-induced nausea and vomiting (CINV) risk. In an effort to ameliorate this risk, we previously conducted a trial with palonosetron, a second-generation long-acting 5-hydroxytryptamine-3 receptor-antagonist (5HT3-RA), to prevent delayed cRINV in individuals with MG receiving standard 6 weeks of daily temozolomide with radiation. Palonosetron safely prevented acute and delayed nausea/vomiting with an overall cRINV-complete response rate (CR; no vomiting or antiemetic rescue) of 67–79%.¹⁷ The percentage of patients *without* nausea was less than the percentage *without* vomiting and there was no impact of the regimen on QoL.¹⁷ A small glioma study ($N=21$) by Matshua and colleagues also demonstrated that patients receiving the combination of palonosetron, aprepitant, and with chemoradiation had an overall CR of 76%.¹⁸ Though the long-acting *intravenous* antiemetic, palonosetron, may improve nausea/vomiting associated with temozolomide/radiation, the overall goal with modern-day antiemetics, such as a long-acting substance-P, neurokinin-1, receptor-antagonists (NK1-RA; rolapitant), is to prevent 100% of vomiting and particularly nausea in order to improve overall QoL.¹⁹ Therefore, to more specifically address nausea prevention, we conducted a randomized phase-II open-label trial, to assess the efficacy, patient preference, and satisfaction associated with a more convenient *oral, steroid-sparing*, and prophylactic regimen. This trial compared standard ondansetron (short-acting 5HT3-RA; 3 h-half-life) monotherapy versus a one-time oral dose of rolapitant (long-acting NK1-RA; 180 h-half-life, with limited drug interactions) plus ondansetron in preventing cRINV during standard radiation with concurrent temozolomide.

The *primary objective* of this study was to compare the efficacy of standard antiemetic ondansetron monotherapy versus rolapitant plus ondansetron *during the first 2 weeks* of a standard 6-week course of radiation with concomitant multiday, metronomic temozolomide. Secondary objectives were as follows: (a) assess whether MG patients receiving chemoradiation prefer and/or were more satisfied with ondansetron monotherapy versus rolapitant/ondansetron for the prevention of cRINV; (b) compare efficacy of ondansetron monotherapy versus rolapitant/ondansetron in the prevention of nausea and vomiting outcomes, separately; (c) assess the safety of ondansetron monotherapy versus rolapitant plus ondansetron during chemoradiation; and (d) determine adherence with each antiemetic regimen.

Methods

Study Design

This prospective, open-label, phase-II, randomized, and single institution trial was conducted from November 2017 to June 2022 among adult MG patients scheduled to

receive standard radiation (administered in daily fractions of 1.8–2 Gy given 5 days a week for 6 weeks for a total of 54–60 Gy) and concurrent temozolomide (75 mg/m²/d × 42 days). As shown in [Figure 1](#), once a patient signed informed consent and was determined to be eligible, a permuted block randomization with an allocation ratio of 1:1 was used to assign patients to receive either *Sequence-A*: standard oral ondansetron 8 mg days 1–21 alone followed by a single dose of rolapitant (day 22) plus daily ondansetron for 3 weeks or *Sequence-B*: a single dose of oral rolapitant 180 mg on day 1 plus daily ondansetron for 3 weeks followed by 3 weeks of daily ondansetron alone with radiation and temozolomide. Antiemetic doses were administered 30 min prior to temozolomide in both sequences. Though the primary CR rate endpoint focused on treatment during the first 2 weeks of radiation and temozolomide to prevent confounding, a crossover design was implemented so that patients would experience both modes of treatment, and be equipped to make a comparative assessment of preference, a key secondary outcome. The study was approved by the Institutional Review Board and was reviewed annually for safety by our institution's Protocol Review and Monitoring System.

Inclusion and Exclusion Criteria

Eligible individuals included adult (>18 years) patients with a newly diagnosed histologically confirmed MG (since the trial began in 2017, high-grade MG was based on the 2016 World Health Organization [WHO] classification and defined as Grade 3/Grade 4 tumors including Grade 3 anaplastic astrocytoma, anaplastic oligodendroglioma and Grade 4 glioblastomas),²⁰ who had a Karnofsky Performance Status $\geq 60\%$ and were scheduled to receive standard radiation with concurrent temozolomide. Patients taking higher than physiological doses of corticosteroids had to remain on a stable dose, 1 week prior to initiating antiemetics and remain on a stable steroid dose thereafter, if clinically possible. Males/childbearing females had to use acceptable birth control methods during and until 90 days after the final rolapitant dose. Laboratory requirements included: hematocrit $> 29\%$, absolute neutrophil count (ANC) > 1000 cells/mm³, platelets > 100000 cells/mm³; serum creatinine < 1.4 mg/dL, bilirubin < 1.5 times upper limit of normal; and aspartate aminotransferase ≤ 2.5 × upper limit of normal range. Patients were excluded if they had a positive pregnancy test, had taken/were taking certain investigational drugs, or had prior rolapitant use. Patients were ineligible if they used antiemetics within 48 h or had ongoing vomiting/retching/nausea within 24 h prior to study initiation. Patients were also excluded if they were taking medications that might interact with rolapitant.

Outcomes

The *primary study outcome* was measured by the overall cRINV-CR rate (where CR is defined as no emesis; no rescue antiemetic), among MG patients *during the first 2 weeks* of a standard 6-week course of radiation with concomitant multiday temozolomide. Secondary outcomes were (a) patient's preference and/or satisfaction with

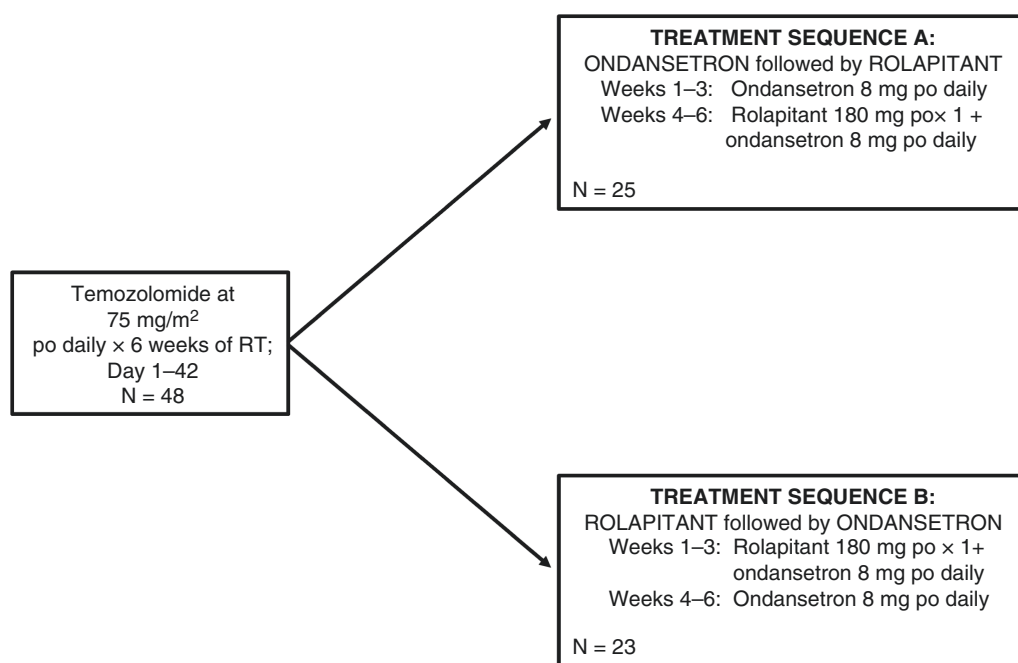


Figure 1. Study schema: phase 2 randomized study to evaluate cRINV efficacy and satisfaction. Abbreviation: cRINV, radiation-induced nausea and vomiting.

ondansetron monotherapy versus rolapitant/ondansetron; (b) chemoradiation-induced nausea (cRIN) and vomiting (cRIV) rates of each antiemetic regimen; (c) safety outcomes using the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) evaluated during ondansetron monotherapy versus rolapitant plus ondansetron during chemoradiation; and (d) adherence for each antiemetic regimen.

Outcome Measurements

Nausea and vomiting trials have often emphasized the importance of patient-reported outcomes for accurate measurement of cRINV endpoints, especially nausea, a subjective outcome.^{7,9,16,17} While safety was assessed using the Common Toxicity Criteria nausea/vomiting grades, this evaluation was conducted by nonpatient trial coordinators/providers and thus, may not be an accurate measure of the patient's nausea and vomiting experience.⁹ As such, the primary cRINV-CR outcome was measured using the MAT validated, *patient-reported*, modified Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool (MAT).^{21,22} Complete response rate was defined as the proportion of patients with *no* emetic episode or use of rescue medication while receiving radiation and concomitant temozolomide. Using the MAT, the cRINV-CR rate associated with standard ondansetron alone and with rolapitant/ondansetron was determined during the first 2 weeks (primary outcome) and throughout the 6 weeks of chemoradiation. Telephone nurse assessment and follow-ups occurred to review the MAT tool daily diary assessment and to collect any missing MAT data. Separate

chemoradiation-induced nausea and vomiting frequency rates were determined using the MAT; cRIN and cRIV were defined as the percentage of patients who *did* experience nausea or had an emetic episode, respectively during the first 2 weeks and overall. At the end of week 3, individuals were asked to fill out a validated Treatment "Satisfaction" Questionnaire for Medication (TSQM-9)^{23–25} that was modified for antiemetics. Individuals were asked at the end of week 6 to choose which antiemetic regimen (ondansetron versus ondansetron/rolapitant) they "preferred" with an additional question (Supplementary Material 1a). Adherence was defined as the percentage of patients who completed each 21-day period of a 42-day treatment. Safety was evaluated by the CTCAE, version 4.0.²⁶

Statistical Analysis

The study was originally designed to enroll 170 MG patients with the expectation that 160 patients would be randomized to receive one of two antiemetic treatment sequences, A or B, for the prevention of nausea and vomiting associated with radiation and concomitant temozolomide. The primary outcome focused on the cRINV-CR rate during the first 2 weeks of radiation/temozolomide. We expected 152 of the 160 randomized patients to provide an assessment of their experience during the first 2 weeks of treatment with the first regimen. With 152 patients, there is 80% power to detect an increase in the CR rate from 75% with ondansetron to 90% with the combination of ondansetron and rolapitant ($\alpha = 0.05$; one-tailed) with a chi-square test. A formal interim analysis was planned after 80 patients had been randomized

(ie, 40 patients randomized to each treatment sequence). In January 2022, the study's funding source requested the termination of study due to low accrual resulting from temporary/required study closure during the COVID-pandemic. Hence, the study was terminated after further accrual and randomization of 53 patients. A chi-square test compared the CR rate during the first 2 weeks of treatment with either ondansetron alone (Sequence-A) or one day of rolapitant with daily ondansetron (Sequence-B). Chi-square tests, including Fisher's exact test, were used to compare arms with respect to cRIN and cRIV. A binomial test assessed whether the proportion of patients who preferred antiemetic treatment with rolapitant was 50%; the effect of antiemetic treatment order on preference was assessed via the Fisher's exact test. A *t*-test using the Satterthwaite method for unequal variances and pooled method for equal variances was used to compare arms with respect to TSQM-9 treatment satisfaction during the first 3 weeks of treatment. Fisher's exact test compared the treatment adherence during the first period and second period within the 2 treatment sequences. All analyses were conducted with SAS (version 9.4).

Results

Patient Characteristics

Seventy-seven patients were screened, 20 were ineligible, and 4 withdrew consent. Of the 53 randomized patients, 5 did not start protocol treatment due to consent withdrawal (1 each in Sequence-A and -B) or were ineligible before treatment began (2 in Sequence-A, 1 in Sequence-B) due to not taking a stable steroid dose or taking an antiemetic 24 h within start of treatment. Thus, 48 randomized patients (25 in Sequence-A: ondansetron, 23 in Sequence-B: rolapitant plus ondansetron) were evaluated for the primary outcome (Figure 2). Demographic data are presented in Table 1. Patients were 58% male, 96% white, and 73% had a KPS > 90%. A majority (93%) of individuals had a glioblastoma (Grade-4) with a mean age of 53 (\pm SD: 13.82). Molecular data is described in Table 1. While this trial began prior to the 2021 WHO classification, there was no significant difference in the MGMT and IDH results by sequence ($P = .154$ for MGMT; $P = .260$ for IDH using exact chi-square test). High rates of relevant cRINV risk factors for both groups included 77% with low alcohol use (<5 days/week), and 83% who were nonsmokers. More patients denied alcohol use in Sequence-A (48%) versus B (26%), whereas more patients drank some alcohol (<5 days/week) in Sequence-B (48%) versus A (32%). The majority of patients adhered to temozolomide treatment guidelines through 30 days. After 30 days, adherence slowly decreased in both sequences. Five patients did not complete the treatment as scheduled (8.33% Sequence-A and 13.64% Sequence-B). Additionally, 3 patients (Sequence-A) completed the treatment as scheduled at 40 days due to dose schedule changes. Overall, there was no significant difference in temozolomide adherence between treatment sequences.

All evaluable patients completed radiation without disease progression. Forty-six (Sequence-A: 24 Sequence-B:

22, 2-missing) completed temozolomide as prescribed during study participation; 7 stopped temozolomide early (A/B: 3/3 for thrombocytopenia; A:1 for ondansetron intolerance). There was no difference in the number of patients who took steroids for radiation-induced cerebral swelling (Sequence-A: 8/25–32%; Sequence-B: 10/23–43%; $P = .4119$) over 6 weeks. Additionally, there was no difference in the average number of days (Sequence-A: 30.13 [SD = 16.23]; Sequence-B: 32.14 [SD = 0.54]; $P = .7776$), nor the average daily dexamethasone dose (Sequence-A: 2.33 mg [SD = 2.61 mg]; Sequence-B: 2.33 mg [SD = 2.61 mg]; $P = .8476$).

Outcomes

Outcomes from patient-completed validated MATs are presented in Table 2. Despite diligent follow-up to capture data, MAT responses were missing in 17% of patients. Hence, available MAT responses were supplemented by built-in nursing (telephone) assessments for the cRINV-CR response rate (no vomit or use of rescue antiemetic). The primary cRINV-CR outcome based on the *valid* MAT assessments during the first 2 weeks was 57% for ondansetron alone and 74% for rolapitant/ondansetron ($P = .27$); (Table 2). When incorporating the nursing follow-up query asking about the primary cRINV-CR outcome, 4 additional patient responses were added to each arm and the cRINV-CR rate during the first 2 weeks was 60% for patients receiving standard ondansetron alone and 65% for those receiving rolapitant/ondansetron ($P = .71$). Patient-reported 6-week overall cRINV-CR was 55% for both arms. No patient vomited in the rolapitant/ondansetron group during the first 2 weeks compared to the ondansetron group (19%) based on the patient-reported MAT tool responses (Table 2). With nurse follow-up questions, patients receiving ondansetron alone still vomited more during the *first 2 weeks* (20%) than with rolapitant/ondansetron (4%); (Table 2). As demonstrated in Table 2, the overall 6-week cRIN rates (53% Sequence-A; B) were more than cRIV rates (26% Sequence-A; 11% Sequence-B). Exploratory data suggest that lower vomiting rates occurred in patients receiving rolapitant/ondansetron versus ondansetron first in the first 2 weeks of radiation (0% versus 19%); (Table 2). Overall, patients who received rolapitant/ondansetron during the first 3-week period followed by ondansetron alone for the second 3-week period versus the opposite sequence had less vomiting (11% versus 26%); (Table 2). The time to first emesis during the first 3 weeks of treatment was significantly delayed (>21 days) in patients receiving rolapitant/ondansetron compared to those receiving ondansetron (<10 days); ($P < .0469$). We also conducted additional analysis that demonstrated no significant difference in nausea and vomiting as recorded by MAT and/or nurse notes between patients with IDH mutant or wildtype or with patients with a MGMT methylated and unmethylated status.

Secondary Outcomes

As shown in Table 3, 20% of patients preferred rolapitant/ondansetron compared to either ondansetron alone or had

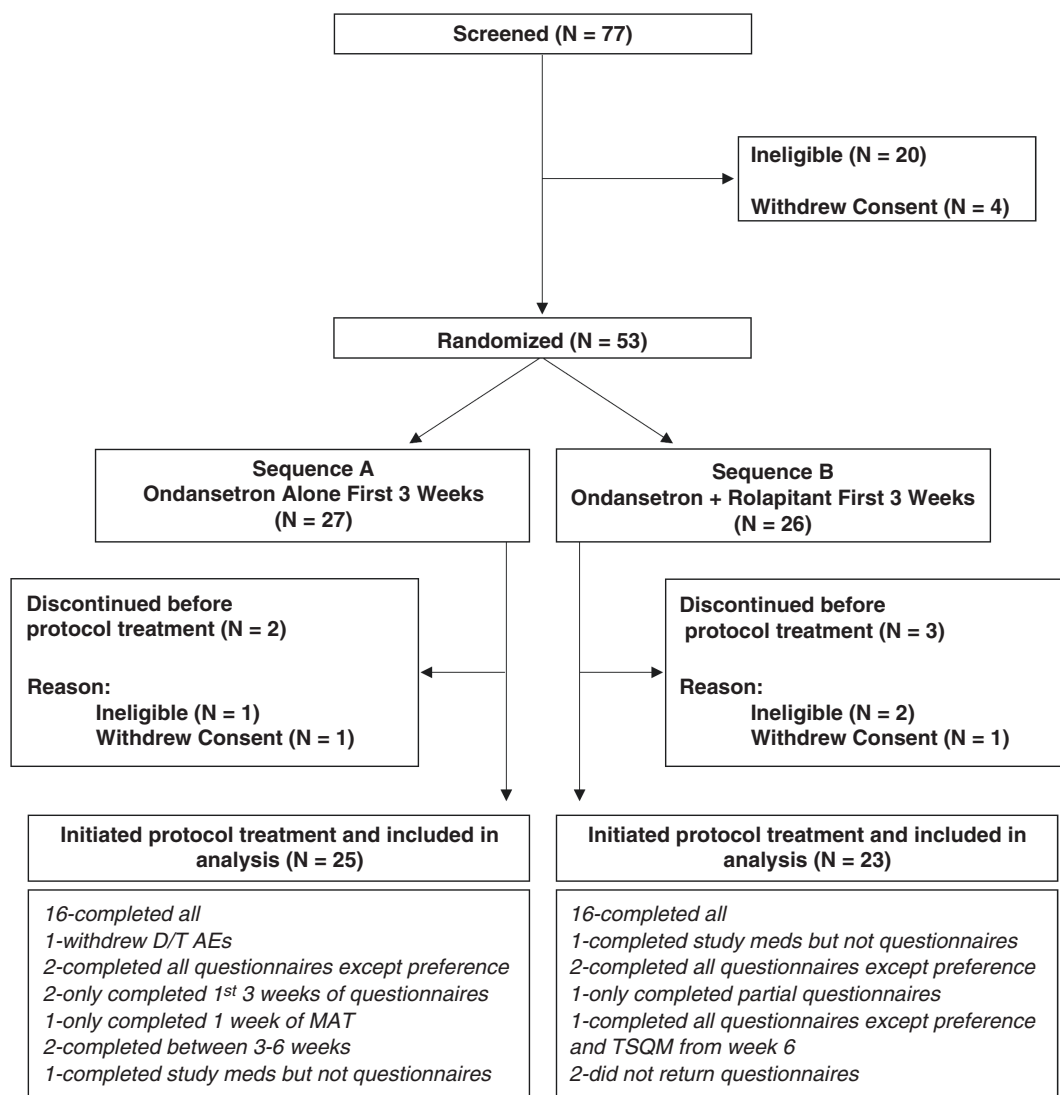


Figure 2. Consort flow diagram: patient disposition.

no preference (80%; 60% preferred ondansetron alone, 20% had no preference), ($P = .0004$); (Table 3). Within the crossover design, the effect of order might have influenced patient preference. As such, analyses were conducted that showed no evidence that the antiemetic order affected preference ($P = .5207$). There was no difference in overall satisfaction between regimens ($P = .0781$), nor convenience ($P = .054$); yet, perceived effectiveness was significantly greater among those receiving rolapitant/ondansetron ($P < .041$); (Table 3). There was >90% adherence to antiemetic treatments and 100% in those who took rolapitant/ondansetron first (Table 4).

Safety

Rolapitant/ondansetron is a safe regimen with only grade 1–2 adverse events (AE) that were attributable (possibly, probably, or definitely related) to rolapitant

and ondansetron (fatigue: 13%; constipation: 26%) and ondansetron (fatigue: 4%; constipation: 40%); All grade 3–4 toxicities were unassociated with antiemetics and related to chemoradiation treatment (eg, hematological toxicity); no grade 5 toxicities noted (Supplementary Material 1b–g).

Discussion

Chemoradiation Guideline Antiemetics for MG

Unfortunately, RINV affects 50–80% of all patients and there is a lack of recent robust trials that establish the cRINV guidelines specifically for the glioma population.²⁷ According to guidelines and systematic reviews, cranial radiation alone has been determined to have a low-emetogenic risk potential and requires only rescue steroids.^{11,27} When brain radiation is given in combination

Table 1. Patient Characteristics

Patient characteristics	Treatment sequence				Totals	
	A—Ondansetron alone first 3-week period		B—Rolapitant and ondansetron first 3-week period		N	%
	N	%	N	%		
Number of patients	25	100.00	23	100.00	48	100.00
Gender						
Female	11	44.00	9	39.13	20	41.67
Male	14	56.00	14	60.87	28	58.33
Ethnicity						
Not Hispanic or Latino	24	96.00	21	91.30	45	93.75
Unknown	1	4.00	2	8.7	3	6.25
Race						
White	24	96.00	22	95.65	46	95.83
Unknown	1	4.00	1	4.35	2	5.17
Age at consent						
18–55 y	11	44.00	13	56.52	24	50.00
55+ y	14	56.00	10	43.48	24	50.00
Mean (standard deviation)	52.56 (13.99)		52.78 (13.95)		52.67 (13.82)	
KPS						
100–90	19	76.00	16	69.57	35	72.92
70–80	6	24.00	7	30.43	13	27.08
Histology						
Glioblastoma	19	76.00	16	69.57	35	72.92
Grade 3 astrocytoma	6	24.00	7	30.43	13	27.08
MGMT						
Methylated	9	36.000	7	30.43	16	33.33
Unmethylated	14	56.00	9	39.13	23	47.92
Missing	2	8.00	7	30.43	9	18.75
IDH						
Wildtype	17	68.00	14	60.86	31	64.58
Mutant	8	32.00	6	26.09	14	29.17
Indeterminate/missing	0	0.00	3	14.04	3	18.75
History of motion sickness						
Yes	1	4.00	1	4.35	2	4.17
No	21	84.00	18	78.26	40	83.33
Unknown	3	12.00	4	17.39	7	14.39
History of pregnancy-related nausea/vomiting						
Yes	3	12.00	4	17.39	7	14.58
No	19	76.00	15	63.22	34	65.22
Unknown	3	12.00	4	17.39	7	14.39
History of chemo-related nausea/vomiting						
Yes	0	0.00	1	4.35	1	2.08
No	22	88.0	18	78.26	40	83.33
Unknown	3	12.00	4	17.39	7	14.39
History of other nausea/vomiting						
Yes	0	0.00	0	0.00	0	0.00
No	22	88.0	18	79.26	40	83.33
Unknown	3	12.00	5	21.74	8	16.67

Table 1. Continued

Patient characteristics	Treatment sequence				Totals	
	A—Ondansetron alone first 3-week period		B—Rolapitant and ondansetron first 3-week period		N	%
	N	%	N	%		
Alcohol use						
Never	12	48.00	6	26.09	18	37.50
<5 days/week	8	32.00	11	47.83	19	39.58
5–7 days/week	2	8.00	2	8.70	4	8.33
Unknown	3	12.00	4	17.39	7	14.39
Smoking history						
Never	15	60.00	12	52.17	27	56.25
Former	6	24.00	7	30.43	13	27.08
Current	1	4.00	0	0.00	1	2.08
Unknown	3	12.00	4	17.4	7	14.58

with multiday chemotherapy, the guideline antiemetic regimen should be chosen based on the emetogenic risk of the chemotherapy. Therefore, standard radiation and concomitant metronomic temozolomide that is administered to patients with MG remain in a low-risk category (<30% chance of N, V).²⁷ According to the MASCC and American Society of Oncology RINV guidelines, patients are either to receive prophylaxis with a 5HT3-RA, and/or prophylaxis and rescue with dexamethasone (specifically with cranial radiation).²⁷ For CINV prophylaxis with the low-risk metronomic temozolomide all guidelines at the time of the study recommended to administer 5HT3-RA or dexamethasone with the National Comprehensive Cancer Network (NCCN) additionally recommending a dopamine receptor antagonist (DRA) as an option.^{13,28–30} The 5HT3-RAs may provide more efficacy for rescue therapy than DRA plus dexamethasone.³¹ Additionally, a systematic review of randomized trials indicated that “5HT3-RA is superior to placebo and other antiemetics for prevention of (radiation-induced) vomiting, but little benefit was identified for nausea prevention” (p. 408).^{31,32} Suboptimal nausea control was noted in our previous cRINV trial utilizing a long-acting intravenous 5HT3-RA (palonosetron) which demonstrated similar acute/delayed CINV-CR rates but the percentage of those *without* nausea was less than those *without* vomiting.

While steroid-use is often effective in preventing cRINV and is often included in antiemetic guidelines,^{11,12} it is important for MG treatment to limit steroids due to untoward side effects. Within this steroid-sparing trial that added the long-acting *oral* NK1-RA, rolapitant, to the guideline antiemetic ondansetron for a low-emetic chemoradiation regimen, we continue to see that the cRINV-CR (no emesis or use of rescue medication) rate is suboptimal (60% for ondansetron and 65% for rolapitant/ondansetron). Even *with the use* of guideline-directed ondansetron alone, the chemoradiation-induced vomiting rate was suboptimal for the first 2 weeks (19–20%). The nausea rate, which primarily affects QoL, was even more concerning at ~40%. While

one must be cautious due to the small study sample size, when adding rolapitant to daily ondansetron the nausea rate associated with rolapitant/ondansetron remained (31–39%) for the first 2 weeks yet, there was a trend to lower vomiting rates (0–4%). It is also interesting to note that administering rolapitant/ondansetron in the sequence first may have prevented later vomiting and reduced overall vomiting (11% with rolapitant/ondansetron administered first versus 26% with administration of ondansetron monotherapy first). The time to first emesis during the first 3 weeks of treatment was significantly delayed (>21 days) in patients receiving rolapitant/ondansetron first compared to those receiving ondansetron (<10 days); ($P < .0469$). Longer acting rolapitant has a 7-day half-life and is recommended to repeat dosing every 14 days. The pharmacokinetics suggests repeating a rolapitant dose in 3 weeks for a higher rate of emesis control to further reduce cRIV.³³ However, it is also well known that a previous episode of vomiting is a risk factor for causing subsequent episodes; thus, preventing cRIV early may prevent overall cRINV.^{8,10,12} The older small study ($N = 18$) by Matsuda and colleagues stated that concomitant temozolomide with radiation is a unique regimen and questioned whether standard guideline antiemetics (short-acting 5HT3-RA *with steroids*) are effective. Even with the additional steroids with a short-acting 5HT3-RA their concluded *incidence rates* of all CTC grade nausea (89%), moderate/severe (grade 2, 3) nausea and emetic episodes (39% each) were suboptimal outcomes.³⁴ As stated earlier, the Matsuda study measures the CTC incidence rates as outcomes which do not capture the patient CINV-CR, MAT reported experience as measured in our trial and which is the standard for nausea and vomiting trials. Yet, our study had 78% (15/32) of all grade nausea, only 3, grade 1 vomiting, and no grade 3–5 nausea/vomiting attributable to temozolomide or radiation ([Supplementary Material 1b–g](#)). In addition, their study defined delayed vomiting atypically after day 21 (delayed vomiting is typically applied to the day after chemotherapy

Table 2. Chemoradiation-Induced Nausea and Vomiting (cRINV) Rates

cRINV-complete response (CR) rate by treatment Sequence-A (ondansetron) versus B (rolapitant/ondansetron) during first 2 weeks of radiation			
Complete response rate (no vomit; no rescue antiemetic use) during first 2 weeks of TMZ and radiation			
Data source	Treatment sequence		Chi-square test P-value
	Ondansetron alone	Rolapitant and ondansetron	
MAT (MASCC antiemesis tool) ^a	12/21 (57.17%)	14/19 (73.68%)	.2734
MAT supplemented by nurses notes ^a	15/25 (60.00%)	15/23 (65.22%)	.7091
Chemoradiation-induced nausea (cRIN) and vomiting (cRIV) rates during first 2 weeks of radiation			
Nausea	Treatment sequence		Chi-square/Fisher's exact tests P-values
	Ondansetron alone	Rolapitant and ondansetron	
Yes	8/21 (38.10%)	6/19 (31.58%)	Chi-square test .6661
First 2 weeks MATs	10/25 (40.00%)	9/23 (39.13%)	Chi-square test .9509
Vomiting	Treatment sequence		Test P-values
	Ondansetron alone	Rolapitant and ondansetron	
Yes	4/21 (19.05%)	0/19 (0.00%)	Fisher's exact test .1079
First 2 weeks MATs	5/25 (20.00%)	1/23 (4.35%)	Fisher's exact test .1908
Chemoradiation-induced nausea (cRIN) and vomiting (cRIV) rates during 6 weeks of radiation (overall)			
Nausea	Treatment sequence		Chi-square/Fisher's exact tests P-values
	Ondansetron alone (3 weeks) then rolapitant/ondansetron (3 weeks)	Rolapitant/ondansetron (3 weeks) then ondansetron alone (3 weeks)	
Yes	10/19 (52.63%)	10/19 (52.63%)	Chi-square test >.9999
Vomiting	Treatment sequence		Test P-values
	Ondansetron alone (3 weeks) then rolapitant/ondansetron (3 weeks)	Rolapitant/ondansetron (3 weeks) then ondansetron alone (3 weeks)	
Yes	5/19 (26.32%)	2/19 (10.53%)	Fisher's exact test .4048

^aNote: 17% (8/48) of patients did not complete MAT, data also captured by nurses (telephone) notes.

^b17% (8/48) of patients did not complete MAT, data captured by nurses (telephone) notes.

^c20.83% of patients (10/48) did not complete 6 weeks MAT or sufficient antiemetic treatment.

Table 3. Treatment Preference and Satisfaction

Overall treatment preference ^a								
Preference	Frequency						Percent	
Rolapitant/ondansetron	7						20.00	
No preference	7						20.00	
Ondansetron	21						60.00	
Total	35 ^b						100.00	
Treatment satisfaction (TSQM) during the first 3 weeks								
TSQM-9 Scale	Treatment sequence						t-test	
	Ondansetron alone			Rolapitant and ondansetron			Method	Two-sided P-value
	N	Mean	Std dev	N	Mean	Std dev		
Effectiveness score	21	83.60	20.14	19	94.44	11.11	Satterthwaite (unequal)	.0406
Convenience score	21	85.71	15.57	19	94.15	10.05	Pooled (equal)	.0541
Overall satisfaction score	21	81.88	17.69	19	90.94	13.38	Pooled (equal)	.0781

Note: 40 respondents.

^aThe proportion of patients who preferred rolapitant/ondansetron over other treatments was significantly less than 0.5 (binomial test: $P = .0004$).

^bOf the 48 treated patients, 35 responded to the treatment preference, 3 patients (from Sequence-A) withdrew before exposure to rolapitant, 10 (Sequence-A: 5; Sequence-B: 5) patients did not return completed questionnaires or acknowledge a treatment preference.

Table 4. Antiemetic Adherence Between Regimens

Ondansetron adherence by 3 weeks by treatment sequence			
Treatment weeks 1–3	Treatment sequence		Fisher's exact tests
	Sequence-A	Sequence-B	P-values
	Ondansetron alone first	Rolapitant and ondansetron first	
Adhered	Adhered		
Adherence of at least 21 days ^a	21/23 (91.30%)	21/21 (100.00%)	.4894
Treatment weeks 4–6	Rolapitant and ondansetron second		Ondansetron alone second
	Adhered		Adhered
	Adhered		P-values
Adherence of at least 21 days ^b	19/20 (95.00%)	20/21 (95.24%)	>.9999

^aFour patients were not evaluable: 1 patient (Sequence-A: 1) withdrew prior to 19 days, 3 patients (Sequence-A: 1; Sequence-B: 2) have missing ondansetron treatment data.

^bSeven patients were not evaluable, 3 patients (Sequence-A: 3) withdrew prior to 40 days, 2 patients (Sequence-B: 2) have missing ondansetron treatment data, and 2 patients (Sequence-B: 2) completed temozolomide as scheduled at 40 days and stopped ondansetron.

has ended and not with multiday chemotherapy) suggesting a cumulative effect. However, in our study more patients experienced less overall vomiting when they received rolapitant first.

We and ~67% (191/285) of neuro-oncology practitioners suspended enrollment for clinical trials during the COVID-pandemic. In our case, we eventually were required to permanently terminate the study prematurely.³⁵ Given that the final accrual was less than originally planned, inferences for this study will be limited. With the smaller sample size, parameter estimates were estimated less precisely than originally planned. Regardless, we believe that these descriptive data are important to report given the lack of RINV trials, in patients with brain tumors. There was no difference in the primary outcome, cRINV-CR rate,

between antiemetic treatments *during the first 2 weeks*. The lack of statistical significance may be due to low power secondary to decreased accrual/required study suspension during the COVID-pandemic and ultimate study closure. While there was no statistical significant difference noted in cRINV-CR rates between the 2 treatment groups during the first 2 weeks, data suggest vomiting rates are lower in those receiving rolapitant/ondansetron. Although rolapitant in combination with a 5HT3-RA has been shown to significantly ameliorate CINV, the high rates of nausea continue to be concerning in this MG population receiving standard chemoradiation.⁷ Based on current guidelines, chemoradiation treatments are classified as low, moderate, high emetogenic risk based on the anatomical site being irradiated (dose per fraction, total dose, radiation field

size, and radiation technique), emetogenic risk of the chemotherapy, and patient-risk factors.³¹ Additional possible patient-risk factors affecting higher rates of nausea in this trial were low alcohol usage, nonsmoking, and perhaps a younger population (<55 years) in Sequence-B (57%) versus Sequence-A (44%).³⁶ While MG chemoradiation is considered low-risk, a nausea rate of ~40% is suboptimal and does not constitute a “low” risk regimen.

Patient-Reported Outcomes

Navari and colleagues note that nausea is difficult to quantify due to its subjectivity and inconsistent measurement in the literature.¹⁶ In this trial, we were careful to utilize the validated *patient-reported* MAT tool to measure nausea (and vomiting). The MAT completion rate was 83–80%. We have noted this issue in prior RINV studies which is why we focused on a more accurate 2-week primary endpoint to also prevent confounding of prior N/V as a risk-factor. In addition to the importance of accurate patient-reported symptoms, we also wanted to know which regimen patient’s preferred. While 60% of patients preferred ondansetron alone (one daily pill) over the 20% who preferred rolapitant/ondansetron (more pills), patients perceived more effectiveness with rolapitant/ondansetron. Though not significant, there was a trend to more satisfaction and convenience for one oral rolapitant dose lasting for >3 weeks. The long-lasting oral rolapitant dose may also increase adherence especially in glioma patients who have memory challenges, forget to take daily antiemetics or rely on carepartners for medication administration.

A major weakness of this study was that MAT responses were missing in 17% of MG patients. Capturing all MAT survey data is a continual issue possibly due to patient’s fear of reporting nausea/vomiting. Despite diligent follow-up to make certain patient-reported MAT assessments were completed, we have learned the importance of the oncology provider’s role in conducting timely (telehealth) follow-up to collect accurate or missing nausea/vomiting data and more importantly to encourage patients to voice their cRINV symptoms without fear. Patients often do not report symptoms for concern about reducing the *chemotherapy* dose which from the patients’ perspective translates to “less effective” anticancer treatment. Instead, changing the *antiemetic* dose or regimen should be emphasized. Data collected by the oncology nurse were used to supplement available MAT responses for those patients lacking MAT data. We acknowledge that data from nursing notes/interviews were not collected in the same manner as the MAT survey data; hence, some biases may have resulted.

Future Studies

Low-dose olanzapine may be an effective antiemetic to explore in a future prospective, randomized trial in patients with gliomas. Olanzapine has clinically significant antiemetic properties as it blocks multiple neurotransmitters within the central nervous system including dopamine at D1–D4 receptors and various

serotonin-5-HT-type-receptors.³⁷ Recent evidence-based trials that support guidelines have shown that olanzapine can be as effective in reducing nausea with/and in place of NK1-RA plus steroids for prophylaxis in high/moderate risk chemotherapy²⁷ or as a breakthrough antiemetic to treat *refractory* CINV. A retrospective audit by Patil³⁸ suggests “the combination of ondansetron with olanzapine leads to a statistically significant decrease *in the frequency rate* of moderate-to-severe (CINV) in glioma patients and should be explored in a prospective study” (p. 479). This study reported positive nausea/vomiting *frequencies*, however, did not measure the standard CINV-CR outcome (no vomiting or use of rescue medication). Our retrospective analysis found that approximately half of glioma patients with refractory-CINV achieved improved nausea/vomiting control with olanzapine.³⁹ Thus, in order to improve vomiting and high rates of nausea among patients with MG receiving radiation and concurrent, low-dose olanzapine may be an effective antiemetic to explore in a future multicenter randomized trial.

Conclusion

We observed there to be no significant difference in the cRINV-CR rates between ondansetron alone and rolapitant/ondansetron, among patients with MG receiving the first 2 weeks of radiation with concomitant temozolomide. Given that accrual was terminated early, the interpretation of these results is complicated by the fact that the truncated study no longer has the power to detect the clinically important differences in cRINV-CR rates originally hypothesized in the design of the study. Though data provided by this study are very important, we need to label the trial as being “inconclusive” regarding differences between ondansetron alone and rolapitant/ondansetron. Exploratory data suggest vomiting rates are lower and delayed in those receiving rolapitant/ondansetron. Most patients perceived greater effectiveness with rolapitant/ondansetron. Though not statistically significant, there is a *trend* to many perceiving a better convenience and overall satisfaction with the rolapitant/ondansetron combination. The rolapitant/ondansetron combination was safe and was thought to be effective (except for high nausea rates). Further research should be conducted to identify an effective antiemetic regimen in patients with MG with the goal of preventing >70–100% chemoradiation-induced vomiting with a focus on nausea.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Practice* (<https://academic.oup.com/nop/>).

Keywords

antiemesis | emesis | gliomas | nausea | radiation-induced-nausea/vomiting

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Conflict of interest statement

M.L.A. received funding from TerSera to conduct this investigator-initiated Phase II Study. M.L.A. is the Vice-Chair of the MASCC Antiemetic study group and was on the 2023 Antiemetic Guideline Consensus Committee (Chaired the Patient Antiemetic Guideline committee; and was a member of Integrative/Nonpharmacological Antiemetic Guideline committee) without financial compensation. M.L.A. is on the 2023 Society for Neuro-Oncology serving as Board Directors and receives no financial compensation; M.P.P. reports SERVIER Glioma Center of Excellence participation; C.B. reports personal fees from Centers for Disease Control and Prevention, personal fees from Oregon Health & Science University Knight Cancer Institute, outside the submitted work; H.S.F. reports other from Cancer Expert Now, other from Diverse Biotech, other from ISTARI Oncology, outside the submitted work; A.D. reports grants and personal fees from Orbus Therapeutics, grants and personal fees from Midatech Pharma, during the conduct of the study; other from Istari Oncology and Orbus Therapeutics, other from ISTARI Oncology, other from ISTARI Oncology, outside the submitted work; K.B.P. reports grants from Agios, grants from Abbvie, grants from BioMimetix, grants from Novocure, grants from SERVIER, grants from Sapience Therapeutics, during the conduct of the study; other from AnHeart, other from Rigel, other from Telix, other from Sapience Therapeutics, other from SERVIER, outside the submitted work. The other authors declare no conflict of interest.

Authorship statement

M.L.A., K.B.P., M.O.J., M.P.P., and J.E.H.: study concept and design, acquisition of data, analysis and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. E.K.S., C.L., and K.B.: acquisition of data. J.E.H., C.B., and E.S.L.: acquisition of data, analysis and interpretation of data, drafting/revising the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical approval

The study was approved by the Institutional Review Board and was reviewed annually for safety by our institution's Protocol Review and Monitoring System.

Data availability

De-identified data will be made available upon reasonable request.

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