Original Article

Multi-Institutional, Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Efficacy of a Mucoadhesive Hydrogel (MuGard) in Mitigating Oral Mucositis Symptoms in Patients Being Treated With Chemoradiation Therapy for Cancers of the Head and Neck

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BACKGROUND: The objective of this trial was to determine how a mucoadhesive hydrogel (MuGard), a marketed medical device, would fare when tested with the strictness of a conventional multi-institutional, double-blind, randomized, placebo-controlled study format. **METHODS:** A total of 120 subjects planned to receive chemoradiation therapy (CRT) for treatment of head and neck cancers were randomized to receive either MuGard or sham control rinse (SC) during CRT. Subjects completed the validated Oral Mucositis Daily Questionnaire. Weight, opiate use, and World Health Organization (WHO) oral mucositis (OM) scores were recorded. Subjects who dosed at least once daily during the first 2.5 weeks of CRT were included in the efficacy analysis. **RESULTS:** Of 120 subjects enrolled, 78 (SC, N = 41; MuGard, N = 37) were eligible for efficacy analysis. Both cohorts were similar in demographics, baseline characteristics, primary tumor type, and planned CRT regimen. MuGard effectively mitigated OM symptoms as reflected by area under the curve of daily patient-reported oral soreness ($P = .034$) and WHO scores on the last day of radiation therapy ($P = .038$). MuGard was also associated with nonsignificant trends related to therapeutic benefit including opioid use duration, and OM scores (WHO criteria) at CRT week 4. Rinse compliance was identical between cohorts. No significant adverse events were reported, and the adverse event incidence was similar between cohorts. **CONCLUSIONS:** Testing MuGard, a rinse marketed as a device, in a standard clinical trial format demonstrated its superiority to SC in mitigating OM symptoms, delaying OM progression, and its safety and tolerability. ***Cancer* 2014;120:1433–40.**

KEYWORDS: mucositis, mucoadhesive gel, head and neck cancer, chemoradiation.

INTRODUCTION

Oral mucositis (OM) is a common, painful, debilitating side effect of chemoradiation therapy (CRT).[1,2] Severe OM is also associated with adverse quality of life, weight loss, increased opioid use, gastrostomy-dependent feeding, greater numbers of emergency room and unplanned office visits, and hospitalizations.[3,4] OM's incremental cost in the head and neck cancer (HNC) population is about $18,000.[5]

OM treatment options for patients with HNC are sparse.[6] A number of agents have US Food and Drug Administration marketing allowances as medical devices including GelClair, Episil, Mucotrol, Caphosol, and MuGard, but

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evaluation of medical devices is markedly less rigorous than is typical for biologics or drugs. In addition, the use of "magic mouthwashes" is relatively common. Typically, the composition of such agents is largely based on institutional folklore and objective assessments of their efficacy is marginal.[7] In a comparative trial, the efficacy of a magic mouthwash formulation was no better than a control solution.[8]

MuGard is a proprietary viscous liquid mucoadhesive hydrogel (MAH) formulation. Results of open-labeled trials suggested that it created a palliative barrier over injured mucosa and reduced objective mucositis scores compared with historical data.[9,10] As is the case of other OM devices, data from a multi-institutional controlled clinical trial were lacking. The objective of the present investigation was to assess MuGard's efficacy as an intervention for OM induced by standard CRT used for the treatment of HNC. The study replicated OM trials used to evaluate drugs or biologics and included a multi-institutional, double-blind, randomized, placebo-controlled design. In this way, we sought to establish a more rigorous standard for the assessment and clinical adoption of devices intended for OM.

MATERIALS AND METHODS

Patients

Institutional review boards of participating sites (n = 22) approved the study. Planned enrollment was 120 adults (≥ 18 years) having Karnofsky performance scores > 80% with recently diagnosed, pathologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, or related site, planned to receive a conventional course of external beam irradiation (single daily fractions of 2.0-2.2 Gy) with a cumulative dose of between 50 Gy and 72 Gy. Concomitant cisplatin was administered weekly or triweekly. The radiation field included at least 2 mucosal sites within the oral cavity (buccal mucosa, floor of mouth, lateral or ventral tongue, or soft palate).

Study Medication

MuGard and sham-control (SC) were supplied by Access Pharmaceuticals. The SC consisted of flavored saline bicarbonate rinse indistinguishable in appearance from MuGard and identically bottled and labeled.

Study Design

This was a double-blind, placebo-controlled, 2-arm parallel study in which subjects were randomized 1:1 to receive SC or MuGard. Subjects were asked to rinse with 5 mL of study material for a full minute and expectorate, with a target dosing frequency of 4 times per day beginning on the first day of radiation and continuing until the last day of radiation therapy (LDRT). Subjects were advised to refrain from eating or drinking for 1 hour after dosing.

Investigators could provide supportive therapy as needed including analgesics, antiemetics, antifungal therapy, hydration, or other treatment. Agents suggested to modify OM risk or course were excluded including amifostine, benzydamine, cevimeline, glutamine rinse, topical GM-CSF, interleukin-11, chlorhexidine, hydrogen peroxide, diphenhydramine, paliferim, pilocarpine, steroid rinses, sucralfate, and various oral rinse medical devices.

At baseline and then daily beginning on the first day of radiation until the LDRT subjects completed the Oral Mucositis Daily Questionnaire (OMDQ), a validated patient-reported instrument.[11,12] On the first visit during week 4 of radiation and on the LDRT the oral cavity was examined and OM severity scored by a trained evaluator using WHO criteria. Safety data (AEs) were recorded on days of radiation.

Patients received a physical examination, assessment of performance score, height and weight measurements, and a quality of life (QoL) assessment weekly. Twice weekly, concomitant medication use, gastrostomy placement, and/or use and study rinse reconciliation were performed and subjects were given new test material.

Efficacy Endpoints

The study's primary endpoint was a reduction in mouth and throat soreness (MTS) associated with OM as defined by area under the curve (AUC) of the OMDQ MTS question 2 (Q2) score. Q2 is a 5-point categorical scale in which patients grade MTS from 0 (no soreness) to 4 (extreme soreness)[3] which is a component of the OMDQ in that it tracks very well with objective (WHO score and opioid use) and subjective measurement of OM severity.[3,13]

Secondary endpoints included delay to onset of OMDQ score of > 2 (previously described to align with severe mucositis)[3,13] and time to OM resolution. Health and resource use endpoints were opioid use, gastrostomy placement and feedings, subjects' ability to eat, radiation treatment breaks, unplanned office and emergency room visits and changes in body weight during CRT.

Analysis Populations

Safety was evaluated in all subjects who used study rinse (Safety Population). Efficacy parameters were assessed for subjects who documented daily study medication use during the first 2.5 weeks following the start of radiation therapy (Efficacy Population). Efficacy assessment was deliberately restricted to this population as this was a postmarketing

study in which we sought to determine objectively if subjects who used the rinse benefited. The minimum dosing duration was based on the well-established course of OM which identifies 30 Gy as the cumulative dose typically associated with the onset of ulcerative mucositis.[14]

Randomization and Statistical Methods

A stratified block randomization (1:1) with a block size of 4 was provided by an independent statistician and participants were assigned to either the MuGard or SC arms by an isolated employee of the CRO that managed this study. Interim analyses of the data were conducted following accrual of 40 and 70 patients. Sample size was determined based on an alpha of 0.05 and an 80% power approximately based on a standard deviations noted in an earlier mucositis trial in which efficacy was demonstrated.[13] The original accrual target of 80 patients was increased to 120 patients prior to the second interim analysis.

Descriptive statistical methods were used to analyze study results. The primary efficacy endpoint, comparison of the AUC of OMDQ MTS Q2 for the 2 cohorts, was evaluated by analysis of variance (ANOVA) with factors for treatment and initial OMDQ MTS score. A Wilcoxon-Gehan test was used to assess the effect of treatment on delay of MTS Question $2 > 2$. Fisher's exact test was used in comparing the numbers of patients in each cohort in comparisons of weight loss, opioid use, WHO scores, frequency of emergency room or office visits, gastrostomy feeding, or unplanned breaks in treatment.

The statistical analyses were conducted with the SAS System, version 9.1.3. All analyses were subject to formal verification procedures. P values < 0.05 were considered to be statistically significant.

RESULTS

Study Population

A total of 120 subjects were enrolled in the Safety Population and were equally distributed between treatment arms. The 78 subjects who met the Efficacy Population criteria (SC, n = 41; MuGard, n = 37) were accrued at 18 study sites (range, 1-10 subjects per site; mean, 4.2 subjects per site).

In the Efficacy Population, there was no difference between study arms in the proportion of eligible subjects (SC 83%, MuGard 78%), the number of weeks on study or weeks on study medication (Table 1).

Efficacy Demographics and Baseline Characteristics

Subject demographics and baseline characteristics were similar between study arms. Slightly more males (90%) were randomized to the SC versus MuGard (78%) arm. SC subjects were slightly heavier (89.7 kg) at baseline compared to those in the MuGard arm (81.5 kg) possibly due to the sex distribution noted. Performance scores were equivalent. No differences in baseline WHO mucositis scores were seen. Study cohorts were the same with respect to tumor staging, planned cumulative radiation dose, and type of radiation planned (IMRT: SC = 93%, MuGard = 89%).

Primary tumor sites were similar between cohorts. The vast majority of subjects presented with cancers of the oral cavity and oropharynx. The number of subjects with non-oral or oropharyngeal primary sites was equivalent.

Efficacy Analyses

For the study's primary endpoint, MuGard effectively attenuated the AUC for daily mean MTS scores versus SC (Table 2). Whereas the mean AUC for OMDQ Q2 was 86.1 for SC, it was 68.0 for MuGard-treated individuals ($P = .034$, ANOVA). LS Mean AUC for the MuGard cohort (86.5) was superior to SC (103.3; $P = .046$, ANOVA).

The study yielded several results that although not statistically significant (NS) suggested that MuGard might provide additional clinical benefit. MuGard appeared to delay the onset of significant MTS (Table 3). Whereas the median cumulative radiation dose to an MTS Q2 score > 2 was 28 Gy among SC subjects, it was 40 Gy among MuGard-treated subjects (NS). Similarly, time to first occurrence of MTS Q2 scores of > 2 was 19 days for SC versus 28 days MuGard (NS). MuGard did not affect time to resolution of patient-reported MTS.

Another NS result implied that MuGard use was coupled with reduced duration of opioid use versus SC. SC subjects used opioids longer (median 16.0 days) compared to subjects receiving MuGard (6.0 days). This trend was unaffected by the route of opioid administration (Table 4). Likewise, the duration of topical or oral opioid use was 50% less than SC in MuGard-treated subjects. And whereas the overall use of parenteral opioid among study subjects was low (SC = 12%; MuGard = 22%), for subjects using this form of opioid, the median duration for SC-treated individuals was 21 days versus 3.5 days for MuGard subjects (NS).

Clinician-assessed OM evaluations were performed at radiation week 4 and on LDRT (Table 5). Although WHO scores trended in favor of MuGard at week 4 when ulcerative mucositis (WHO grades 2, 3, or 4) occurred in 43% of MuGard-treated subjects versus 61% of SC-treated subjects (NS) and severe (grades 3, 4) mucositis occurred in 16% of MuGard- versus 24% SC-treated

TABLE 1. Demographics and Baseline Characteristics of the Efficacy Population

Characteristic	Sham-Control (N = 41)	MuGard (N = 37)
Age at informed consent (years)		
Median (Min, Max)	58 (38,73)	58 (38,81)
Sex		
Male	37 (90%)	29 (78%)
Female	4 (10%)	8 (22%)
Race		
White	38 (93%)	36 (97%)
Black/African American	2 (5%)	1 (3%)
Asian	1 (2%)	0
Ethnicity		
Hispanic	1 (2%)	1 (3%)
Non-Hispanic	40 (98%)	36 (97%)
Weight (kg)		
Mean (SD)	89.7 (18.91)	81.5 (14.44)
Median	89.3	84.8
Min, Max	51.4, 133.9	47.5, 116.0
Oral mucositis score–WHO Scale		
Grade 0	35 (85%)	32 (86%)
Grade 1	1 (2%)	1 (3%)
>Grade 1	0	0
Missing	5 (12%)	4 (11%)
Location/site of primary tumor		
Oral cavity	16	16
Oropharynx	25	16
Hypopharynx	2	0
Nasopharynx	1	1
Salivary glands	1	0
Larynx	3	3
Unknown primary	1	5
AJCC Stage		
I	1 (2%)	0
II	0	2 (5%)
III	8 (20%)	8 (22%)
IVA	31 (76%)	20 (54%)
IVB	1 (2%)	3 (8%)
IVC	0	0
Missing	0	4 (11%)
Type of radiation therapy planned		
External beam	3 (7%)	3 (8%)
Intensity-modulated radiotherapy	38 (93%)	33 (89%)
Missing	0	1 (3%)
Cumulative radiation dose planned (Gy)		
Mean (SD)	65.7 (13.16)	63.9 (14.26)
Median	70.0	70.0

Abbreviations: AJCC, American Joint Committee on Cancer; SD, standard deviation; WHO, World Health Organization.

TABLE 2. Area Under the Curve for MTS Question 2 by Treatment: Efficacy Population

	Sham-Control (N = 41)	MuGard (N = 37)	*P* (ANOVA)
N	41	37	
Mean (SD)	86.1 (34.30)	68.0 (39.74)	.034
Median	80.0	59.5	
Min, Max	31.5, 154.0	2.0, 155.5	
LS Means (SEM)	103.3 (10.31)	86.5 (10.47)	.046

Abbreviations: ANOVA, analysis of variance; MTS, mouth and throat soreness; SEM, standard error of the mean; SD, standard deviation.

subjects (NS). On the LDRT, a statistically significant benefit ($P = .038$, Fisher's exact test) was seen for MuGard in ulcerative mucositis frequency (SC = 68%; MuGard = 43%). The trend noted for severe OM was consistent (NS), SC = 44% versus MuGard = 27%.

MuGard-treated subjects trended toward less weight loss than control subjects (NS) (Table 6). At the end of the study, mean weight loss in the MuGard cohort was half (52%) that in the sham cohort.

There were no relevant differences with respect to frequency of emergency room or office visits, gastrostomy feeding, or unplanned breaks in treatment, or patient-reported QoL.

Safety

No difference was observed in unanticipated AEs between study cohorts in either the Safety or Efficacy populations (SC = 12% versus MuGard = 8%) (Table 7). There were no cases in which MuGard was discontinued because of an AE, but 2 SC subjects stopped study medication use because of nausea or vomiting.

DISCUSSION

MuGard is an oral rinse product for the management of OM that is regulated as a medical device. The rigor of OM clinical trials required for assessment of drugs or biologics has not been extended to medical devices which can be marketed with minimal or no supportive clinical data. In the current environment in which evidence-based decision making is a mandate, we believed that it was highly desirable to define medical device efficacy more rigorously using a multi-institutional, randomized, double-blind, placebo-controlled approach that characterizes typical drug trials. The primary efficacy endpoints of this trial were based on a symptom-dependent, patient-reported measurement for OM: MTS scored by criteria delineated by OMDQ Q2. Endpoint selection was based on 3 considerations: the OMDQ was validated in a variety of patient populations[11]; OMDQ Q2 scores correlate well with objective and functional measures of OM[3,11,13,15]; combining OMDQ self-assessment with objective measures of mucositis provided an opportunity to assess MuGard's overall clinical benefit.

Saline-bicarbonate rinse was selected as the SC rinse because it is safe and physically resembles MuGard. A preservative in SC imparted a slight "medicinal" flavor similar to that in MuGard. Because saline-bicarbonate rinse is a treatment for OM symptom amelioration recommended by the National Cancer Institute,[16] it is probably not a true sham or placebo. Possibly, control subjects

TABLE 3. Delay to Onset, Time to First Occurrence, and Time to Resolution of MTS Question 2 Score > 2 by Treatment: Efficacy Population

	Sham-Control (N = 41)	MuGard (N = 37)	*P*[a]
Delay to Onset MTS Q2 > 2 (K-M Estimated RT-Dose Gy)			
N (N censored)	41 (12)	37 (12)	
Median (95% CI)	28.0 (22.0, 48.0)	40.0 (26.0, 54.0)	
Mean (SE)	34.8 (2.88)	41.6 (3.21)	.297
Time to First Occurrence of MTS Q2 > 2 (K-M Estimated Days)			
N (N censored)	41 (12)	37 (12)	
Median (95% CI)	19.0 (14.0, 31.0)	28.0 (16.0, 41.0)	
Mean (SE)	24.1 (2.20)	27.6 (2.18)	.322
Time to Resolution of MTS Q2 > 2 (K-M Estimated Days)			
N (N censored)	41 (34)	37 (31)	
Median (95% CI)	5.0 (1.0, 11.0)	5.5 (1.0, 15.0)	
Mean (SE)	8.0 (3.38)	5.8 (2.10)	.651

[a] Wilcoxon-Gehan test.
Abbreviations: CI, confidence interval; K-M, Kaplan-Meier; MTS, mouth and throat soreness; RT, radiotherapy; SE, standard error.

TABLE 4. Comparison of Opioid Use Between Study Groups in the Efficacy Population

	Sham-Control (N = 41)	MuGard (N = 37)	*P*[a]
Subjects who received opioid analgesia	31/41 (76%)	26/37 (70%)	.619
Opioid analgesia (no. of days required)			
N	41	37	
Mean (SD)	17.0 (15.68)	13.3 (15.38)	.305
Median	16.0	6.0	
Min, Max	0.0, 50.0	0.0, 53.0	
Topical			
N	8	3	
Mean (SD)	7.4 (6.78)	13.3 (17.90)	
Median	6.5	3.0	
Min, Max	1.0, 19.0	3.0, 34.0	
Opioid-Oral			
N	24	24	
Mean (SD)	23.2 (15.75)	18.6 (15.63)	.421
Median	27.5	12.5	
Min, Max	2.0, 50.0	2.0, 53.0	
Opioid-transdermal, intramuscular, or intravenous			
N	5	8	
Mean (SD)	16.2 (10.83)	7.0 (7.52)	.123
Median	21.0	3.5	
Min, Max	1.0, 27.0	1.0 (20.0)	

[a] Fisher's exact test.
Abbreviation: SD, standard deviation.

TABLE 5. Subjects With Ulcerative or Severe Oral Mucositis (OM) at Week 4, Visit 1 and at the End of Radiation Therapy (RT) by Treatment: Efficacy Population

	Sham-Control (N = 41)	MuGard (N = 37)	*P*[a]
Subjects with ulcerative OM at week 4, visit 1	25 (61%)	16 (43%)	.173
Subjects with severe OM at week 4, visit 1	10 (24%)	6 (16%)	.413
Subjects with ulcerative OM at end of RT	28 (68%)	16 (43%)	.038
Subjects with severe OM at end of RT	18 (44%)	10 (27%)	.159

[a] Fisher's exact test.

derived some benefit from its use thereby providing a bias against MuGard. The finding that the percent of ulcerative or severe mucositis among SC subjects was less than typically reported substantiates its possible benefit.

Despite greater opioid use by control subjects, MuGard was superior to SC in ameliorating the onset and course of symptomatically significant OM as reflected by the statistically significant difference in AUC ($P = .036$;

ANOVA analysis) between MuGard and sham cohorts, the study's primary endpoint.

In addition, MuGard use was associated with other favorable outcomes compared to control. Although these failed to reach statistical significance, the consistency of signals trending in the same direction are noteworthy. Whereas 50% of the patients using SC noted MTS scores ≥ 2 within 15 days of the start of radiation, that frequency of OM was not seen in the MuGard arm until day 37 (NS). Of the 24 subjects in each study cohort requiring oral opioid analgesics, those treated with MuGard used narcotics for a median 12.5 days compared to 27.5 days for control subjects (NS). Subjects treated with MuGard were better able to maintain baseline weights than controls. Consistent with prior studies[17] mean weight loss in the SC cohort was 9.14%. In contrast, mean weight loss in the MuGard cohort was 5.28%.

Clinician-WHO assessments of OM scored midway through radiation and the LDRT trended in favor of MuGard. At LDRT, this trend reached statistical significance. The reason for this finding is unclear as MuGard's formulation does not include known biologically active components. MuGard likely forms a thin, temporary protective hydrogel layer over the mucosa. Conceivably, MuGard might entrap mucins, which have been identified as having a protective role in chemotherapy-induced mucosal injury.[18,19] Additional studies are needed to test this hypothesis.

Although all subjects were included in the safety analysis (an intent-to-treat population), the efficacy analysis was limited to the small number of subjects who complied with using study medication at least once a day in

TABLE 6. Change From Baseline in Subject Body Weight by Treatment: Efficacy Population

	Sham-Control (N = 41)	MuGard (N = 37)	P[a]
Baseline			
N	40	36	
Mean (SD)	89.3 (18.0)	80.4 (14.5)	
Median	88.0	81.9	
Min, Max	63.1, 132.0	45.1, 114.0	
Week 7			
N	35	29	
Mean (SD)	83.1 (17.1)	77.1 (20.7)	
Median	82.1	78.9	
Min, Max	54.1, 125.6	43.3, 160.0	
Change from baseline to week 7			
N	34	29	.379
Mean (SD)	−8.2 (4.44)	−4.3 (16.7)	
Median	−7.7	−7.9	
Min, Max	−19.0, −1.4	−14.0, 80.2	

[a] Fisher's exact test.
Abbreviation: SD, standard deviation.

TABLE 7. Unanticipated Adverse Device Effects by System Organ Classification and Preferred Term: Efficacy Population

System Organ Classification Preferred Term	Sham-Control (N = 41)	MuGard (N = 37)
Any Event	5 (12%)	3 (8%)
Gastrointestinal Disorders	4 (10%)	1 (3%)
Nausea	3 (7%)	0
Vomiting	2 (5%)	1 (3%)
Constipation	1 (2%)	0
Diarrhea	0	1 (3%)
Stomatitis	1 (2%)	0
Blood and Lymphatic System Disorders	0	1 (3%)
Febrile Neutropenia	0	1 (3%)
Metabolism and Nutrition Disorders	0	1 (3%)
Dehydration	0	1 (3%)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (3%)
Hemoptysis	0	1 (3%)
Uncoded	1 (2%)	0

Unanticipated Adverse Device Effects Leading to the Discontinuation of CTM by System Organ Classification and Preferred Term: Efficacy Population

System Organ Classification Preferred Term	Sham-Control (N = 41)	MuGard (N = 37)
Any adverse event leading to discontinuation	2 (5%)	0
Gastrointestinal Disorders	2 (5%)	0
Nausea	1 (2%)	0
Vomiting	1 (2%)	0

the first 2.5 weeks of RT. Although this rate was the same for individuals in either cohort and was the same as had been reported in an earlier multicenter European study,[10] it nonetheless compromised the trial's statistical power. This resulted in positive and consistent efficacy trends for several outcomes, but which lacked statistical significance. A recent report of a single site assessment of MuGard in patients with HNC confirmed that its effectiveness was enhanced with dosing concurrent with the start of CRT.[20]

Accrual to the study was stopped following the finding of statistical significance for the primary endpoint at the second interim analysis. Because the finding was the same as was noted at an earlier analysis, it was concluded that additional accrual into the placebo arm would not alter the study's conclusion and would not be in the interest of subjects assigned to the placebo cohort. This was done understanding that the statistical analyses of other endpoints would be handicapped.

Our definition of full study compliance may have been overly ambitious, because it mandated a final study visit 4 weeks after the LDRT. This requirement impacted the observed low compliance rate (50%) among the Safety Population. Case report forms indicated that early dropout was a consequence of symptomatic subjects believing that they had received SC and not wishing to continue, subjects being overwhelmed by their disease and treatment, or formulation intolerance. Of individuals who terminated early, study medication intolerance was only noted in a small number equally distributed between cohorts. We did not attempt to stratify endpoints by dosing frequency. Despite MuGard's efficacy in attenuating MTS, it was not superior to SC in impacting subjects' ability to swallow, eat, or drink. Nor did MuGard significantly alter gastrostomy reliance, unplanned office visits, emergency room visits, or hospitalizations.

This study represents the first multicenter, randomized, placebo-controlled assessment of a medical device indicated for OM treatment. It is hoped that this study design provides a template for evaluation of other agents in the medical device class and in that way raises the threshold of their clinical use to a level that is similar to pharmaceuticals.

The study results support the addition of MuGard to the armamentarium for the management of oral mucositis in patients being treated with standard radiation therapy protocols for HNC.

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CONFLICT OF INTEREST DISCLOSURES

Drs. Feldman, Finkelstein, Lane, Taylor, Wisbeck, and Yuh have received research funding from Access Pharmaceuticals, Inc. Dr. Allison has received an honorarium from Access Pharmaceuticals, Inc. Dr. Nowotnik was an employee of Access Pharmaceuticals, Inc. when the study was conducted Dr. Sonis is a paid consultant for Clinical Assistance Programs, LLC (the contract research organization that conducted this study), a consultant for Actogenix, Alder, Galera, Synedgen, Pfizer, Piramal, Polymedix, BioAlliance, and is Chief Scientific Officer for Biomodels, LLC. All other authors made no disclosure.

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