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Research Submission

Efficacy of ADAM Zolmitriptan for the Acute Treatment of Difficult-to-Treat Migraine Headaches

Stewart J. Tepper, MD; David W. Dodick, MD; Peter C. Schmidt, MD, MSc; Donald J. Kellerman, PharmD

Objective.—To understand the efficacy of zolmitriptan applied with Adhesive Dermally Applied Microarray (ADAM) in treating types of migraine (those with severe headache pain, the presence of nausea, treatment ≥2 hours after migraine onset, or migraine present upon awakening) that are historically considered to be less responsive to oral medications.

Background.—ADAM is an investigational system for intracutaneous drug administration. In a pivotal Phase 2b/3 study (ZOTRIP, N = 321 in the modified intention-to-treat population), ADAM zolmitriptan 3.8 mg provided superior pain freedom and freedom from patients' usual most bothersome associated symptom (MBS), compared with placebo at 2 hours post-dose. We undertook a post hoc analysis of data from the ZOTRIP trial to examine these same outcomes in subsets of patients whose migraine characteristics have been associated with poorer outcomes when treated with oral medications.

Methods.—The ZOTRIP trial was a multicenter, randomized, double-blind, placebo-controlled, parallel group Phase 2b/3 study conducted at 36 sites in the United States. Presented here are post hoc subgroup analyses of patients with nausea (n = 110) or severe pain (n = 72) at baseline, those whose treatment was delayed 2 or more hours after onset (n = 75), and those who awoke with migraine (n = 80). The Cochran–Mantel–Haenszel test was used to assess whether patients in the ADAM zolmitriptan 3.8 mg group had superior treatment outcomes compared with placebo.

Results.—In patients with nausea, 2-hour pain freedom was achieved in 44% (26/59) in the ADAM zolmitriptan 3.8 mg group and 14% (7/51) in the placebo group (P = .005) (odds ratio = 5.11, 95% CI: 1.96–13.30), and 2-hour MBS freedom was achieved in 68% (40/59) in the active treatment group and 45% (23/51) of those receiving placebo (P = .009) (odds ratio = 2.86, 95% CI: 1.28–6.43). For those with severe pain, corresponding pain-free values were 26% (10/39) and 15% (5/33) (P = .249) (odds ratio = 2.14, 95% CI: 0.60–7.62), and MBS-free values were 64% (25/39) and 42% (14/33) (P = .038) (odds ratio = 2.86, 95% CI: 1.05–7.79). Among participants who awoke with migraine, 44% (16/36) and 16% (7/44) were pain-free in the ADAM zolmitriptan 3.8 mg and placebo groups, respectively (P = .006) (odds ratio = 4.29, 95% CI: 1.50–12.31), and 72% (26/36) vs 39% (17/44) were MBS-free, respectively (P = .003) (odds ratio = 4.40, 95% CI: 1.61–12.05). In those whose treatment was delayed ≥2 hours, pain freedom in the active treatment group and placebo group were 33% (12/36) and 10% (4/39), respectively (P = .017) (odds ratio = 4.33, 95% CI: 1.24–15.10), and MBS freedom was achieved in 69% (25/36) and 41% (16/39), respectively, in the delayed treatment group (P = .014) (odds ratio = 3.37, 95% CI: 1.27–8.95). No significant effects (overall interaction P = .353) were observed in logistical regression models of treatment by subgroup interaction.

Conclusion.—Severe pain, delayed treatment, awakening with a headache, and the presence of nausea are factors that predict a poorer response to acute migraine treatment. In these post hoc analyses of subgroups of patients with each of these characteristics in the ZOTRIP trial, participants receiving ADAM zolmitriptan 3.8 mg displayed nearly uniformly better headache responses (2-hour headache freedom and 2-hour MBS freedom) compared with those who received placebo.

From the Department of Neurology, Geisel School of Medicine at Dartmouth, Hanover, NH, USA (S.J. Tepper); Department of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA (S.J. Tepper); Department of Neurology, The Mayo Clinic, Phoenix, AZ, USA (D.W. Dodick); Zosano Pharma, Fremont, CA, USA (P.C. Schmidt and D.J. Kellerman).

Address all correspondence to P.C. Schmidt, Zosano Pharma, 34790 Ardentech Court, Fremont, CA 94555, USA, email: PSchmidt@zosanopharma.com

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Abbreviations: ADAM Adhesive Dermally Applied Microarray, CI confidence interval, MBS most bothersome symptom, OR odds ratio

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INTRODUCTION

Despite the well-established effectiveness of triptans in the acute treatment of migraine, they elicit a headache response in only 40–70% of patients in clinical trials, and the frequency of achieving complete pain freedom is considerably lower.[1-3] A number of factors are known to contribute to suboptimal acute treatment response. Multiple studies on large numbers of migraine sufferers have found that severe headache pain and nausea are important predictors of response.[4-6]

Early treatment initiation is also a significant predictor of enhanced therapeutic outcome.[7-13] Early treatment can prevent pain from progressing to moderate or severe and lessen the chances of central sensitization. The clinical consequence of central sensitization, allodynia, is itself an independent risk factor for migraine progression.[14] However, early treatment is not always an option, especially in those with rapid pain escalation as well as in the 48% of headaches that develop during sleep ("morning migraine").[15] These are often less responsive to acute treatment with oral therapies.[15-20]

For all migraine headaches, and particularly for these difficult-to-treat headaches, medication should have a fast onset. Guidance from the American Headache Society suggests for migraine headaches that reach maximal intensity rapidly and those associated with nausea and vomiting, non-oral formulations, such as intranasal or injectable treatments, may be more effective,[21] likely due to avoidance (or reduction, in the case of intranasal formulations) of the need for gastrointestinal absorption.

Adhesive Dermally Applied Microarray (ADAM) is a small adhesive device for intracutaneous drug delivery, which allows for rapid absorption. In a study evaluating the pharmacokinetics of zolmitriptan delivered with ADAM, the median t_{max} in serum was less than 20 minutes, comparable to subcutaneous sumatriptan. Absorption was considerably faster

Conflict of Interest: Within the last 12 months, David W. Dodick reports personal fees from Amgen, Alder, Allergan, Autonomic Technologies, Biohaven, Eli Lilly, eNeura, Foresight Capital, Neurolief, Zosano, WL Gore, Vedanta Associates, Promius Pharma, Nocira, Novartis, electroCore, Teva, Ipsen, Impel, Satsuma, Charleston Laboratories, and Theranica. Compensation for activities related to data safety monitoring committee from Axsome. Compensation related to CME content development: Healthlogix, Medicom Worldwide, Medlogix Communications, MedNet, Miller Medical Communications, PeerView Operation Services America, Web MD/Medscape, American Academy of Neurology, American Headache Society, PeerView Institute for Medical Education, Chameleon Communications, Academy for Continued Healthcare Learning, Universal Meeting Management, Haymarket Medical Education, Global Scientific Communications, UpToDate, and Meeting LogiX. Royalties from editorial or book publishing: Oxford University Press, Cambridge University Press, Wiley Blackwell, Sage, and Wolters Kluwer Health. Consulting use agreement through employer: NeuroAssessment Systems and Myndshft. Holds equity in: Aural Analytics, Healint, Theranica, and Second Opinion/Mobile Health. Board of Directors position: King-Devick Technologies, Ontologics, and Epien. He holds the following Patent 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis (no compensation). Stewart J. Tepper serves as a consultant and/or on the Advisory Board for Acorda Therapeutics, Alder Biopharmaceuticals, Alexsa, Allergan, Alphasights, Amgen, Autonomic Technologies, Inc., Avanir Pharmaceuticals, Axsome, Biovision, Charleston Laboratories, DeepBench, Dr. Reddy's, electroCore, Eli Lilly, eNeura, Gerson Lehman Group, GSK, Guidepoint Global, Kimberly-Clark, Magellan Rx Management, Neurolief, Nordic BioTech, Pfizer, Scion Neurostim, Slingshot Insights, Supernus, Teva Pharmaceutical Industries, and Zosano Pharma. Received stock options from Autonomic Technologies, Inc., and receives royalties from University of Mississippi Press and Springer. Receives salary compensation from Dartmouth-Hitchcock Medical Center and the American Headache Society. Peter C. Schmidt and Donald J. Kellerman are employees of Zosano Pharma.

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than for oral zolmitriptan, with higher exposure in the first 2 hours.[22] In a pivotal Phase 2b/3 randomized, double-blind, placebo-controlled study (ZOTRIP), ADAM zolmitriptan 3.8 mg met both co-primary endpoints of superior pain freedom and freedom from patients' usual other most bothersome symptom (MBS), compared with placebo at 2 hours post-dose.[23] The frequency of achievement of pain relief as well as lack of recurrence were also superior in the ADAM zolmitriptan 3.8 mg treatment group vs placebo.[23,24]

As ADAM zolmitriptan displays pharmacodynamic properties that may be desirable for use in difficult-to-treat headaches, we have undertaken a post hoc analysis of data from the ZOTRIP trial to examine efficacy in subsets of patients whose headaches had characteristics suggesting potential refractoriness to treatment.

The objective of this post hoc analysis of study data was to determine whether severe headache pain, the presence of nausea, treatment ≥2 hours after migraine onset, or awaking with migraine impacted the efficacy of ADAM zolmitriptan on the co-primary endpoints of the ZOTRIP trial.

METHODS

Post hoc subgroup analyses were performed using data from a multicenter, randomized, double-blind, placebo-controlled, parallel group Phase 2b/3 study conducted at 36 sites in the United States. The protocol was approved by the Quorum Review Institutional Review Board (Seattle, WA). All participants gave written informed consent prior to any study procedures being performed. Detailed methods have been previously reported.[23] Eligible patients had experienced 2 to 8 migraine headaches (with or without aura) during a 28-day run-in period. On the first day of the run-in period, patients declared their MBS other than pain (nausea [with or without vomiting], photophobia, or phonophobia), that is most bothersome most of the time with their migraine headaches. Patients were randomly assigned in a 1:1:1:1 ratio, stratified by MBS, to receive ADAM zolmitriptan 1, 1.9, 3.8 mg, or placebo to treat 1 moderate or severe headache. Symptoms were recorded using an e-diary.

In accordance with the co-primary endpoints in the ZOTRIP trial, which were selected based on recently issued guidance by the US Food and Drug Administration,[25] we analyzed pain freedom and MBS freedom at 2 hours post-dose in patients whose migraine headaches might be characterized as more difficult to treat. Specifically, we evaluated those with severe pain at the time of treatment, those whose headaches were associated with nausea at the time of treatment, headaches treated ≥2 hours after onset, and headaches present upon awakening in the morning. Data are only reported here for the ADAM zolmitriptan 3.8 mg dose, which showed a significant treatment effect vs placebo for the co-primary endpoints of pain freedom and MBS freedom at 2 hours post-dose.

Statistical Analysis.—In the original ZOTRIP trial, sample size (n = 360) was determined by estimating that 15% of patients receiving placebo and 35% of those receiving active treatment would achieve freedom from each co-primary endpoint, pain or MBS, at 2 hours post-dose. A stratified chi-square test was used to estimate the number needed to detect this treatment difference with 80% statistical power and 5% 2-sided significance level. Allowing for 15% dropout rate, this equated to approximately 90 subjects per group.

Analysis of each subgroup was performed via the Cochran–Mantel–Haenszel test stratified by MBS. Last observation carried forward was used to impute missing data. Subgroup by treatment interactions were formally assessed using logistic regression on the full sample with the categorical effects of treatment, MBS, subgroup, and subgroup by treatment interaction. All statistical tests were 2-sided and tested at a significance level of .05. No adjustments to *P* values were made for the multiple post hoc analyses performed.

All authors had full access to all study data. Analyses were performed using Statistical Analysis System (SAS®) software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 365 patients were randomized; 321 were treated and had at least 1 post-treatment symptom assessment (mITT population). Patient demographics and baseline characteristics as well as primary study results were reported previously.[23] Of the 321 treated,

77 received placebo, and 82 were treated with ADAM zolmitriptan 3.8 mg. The incidences of migraine headaches in each of the analyzed subgroups (severe pain at the time of treatment, nausea at the time of treatment, treatment ≥2 hours after onset, and headaches present upon awakening in the morning) are presented in Table 1.

No significant effects (all $P > .200$) were observed in logistical regression models of treatment by subgroup interaction, suggesting that none of the subgroups modify the effect of ADAM zolmitriptan 3.8 mg compared to placebo (overall interaction $P = .353$). The following results further support this finding.

Table 2 shows the percentages of patients with MBS freedom or pain freedom stratified by pain intensity (moderate or severe). The numbers of patients with MBS freedom were higher in the ADAM zolmitriptan 3.8 mg group compared with the placebo group for both moderate and severe pain. For pain freedom, differences between the groups were significant for those with moderate pain, but not those with severe pain.

Among those with severe pain, pain relief (defined as improvement from moderate to severe headache pain to mild or no pain) was achieved in 69% (27/39) of those treated with ADAM zolmitriptan 3.8 mg and 46% (15/33) of those who received placebo ($P = .026$). Corresponding values for those with moderate pain were 91% (39/43) and 66% (29/44) ($P = .009$). The frequency of pain recurrence following relief is shown in Table 3. Overall, recurrence was lower in the active treatment group at both 24 and 48 hours compared with placebo.

Nausea at the time of treatment was reported in 69% (110/159) of patients (n = 51 in the placebo group and n = 59 in the active treatment group). Among these, more patients in the zolmitriptan 3.8 mg group were pain-free or MBS-free 2 hours post-dose compared with those in the placebo group (Table 4).

The mean time to migraine treatment after patient-estimated headache onset among all groups was 4.96 hours and the median was 1.79 hours. In those who waited for 2 or more hours to treat their migraine (n = 40 in the placebo group and n = 36 in the active treatment group), 2-hour pain freedom and 2-hour MBS freedom were both more frequent in the active treatment group (Table 5).

Fifty-one percent (80/159) of patients overall reported waking up with pain already present at moderate to severe intensity (n = 44 in the placebo group and n = 36 in the zolmitriptan group). In those who awoke with migraine, the frequencies of 2-hour pain

Table 1.—Characteristics of Treated Migraine

n (%)	Placebo n = 77	ADAM Zolmitriptan 3.8 mg n = 82
Severe pain	33 (43)	39 (48)
Nausea	51 (66)	59 (72)
Treatment ≥2 hours	40 (52)	36 (44)
Awoke with migraine	44 (57)	36 (44)

Table 2.—Outcomes in Patients Whose Headache Was Moderate or Severe at the Time of Treatment

	2-Hour Pain-Free[†]				2-Hour MBS-Free[†]			
n (%)	Placebo	ADAM Zolmitriptan 3.8 mg	*P* Value	OR (95% CI)	Placebo	ADAM Zolmitriptan 3.8 mg	*P* Value	OR (95% CI)
Severe pain	5 (15)	10 (26)	.249	2.14 (0.60–7.62)	14 (42.4)	25 (64)	.038	2.86 (1.05–7.79)
Moderate pain	6 (13)	24 (56)	<.001	7.75 (2.69–22.29)	19 (43.2)	31 (72)	.014	3.10 (1.24–7.74)

CI = confidence interval; OR = odds ratio.
[†]Nine (12%) placebo patients and 13 (16%) patients treated with ADAM zolmitriptan 3.8 mg were missing 2-hour outcome data. These data were imputed using LOCF and included in the analyses.

Table 3.—Frequency of Pain Recurrence

		24-Hour				48-Hour			
		Placebo	ADAM Zolmitriptan 3.8 mg	*P* Value	OR (95% CI)	Placebo	ADAM Zolmitriptan 3.8 mg	*P* Value	OR (95% CI)
Overall	n	44	66	.021	0.36 (0.14–0.89)	44	66	.015	0.36 (0.15–0.83)
	Recurrence, n (%)	15 (34)	10 (15)			19 (43)	14 (21)		
Moderate pain	n	29	39	.028	0.27 (0.08–0.92)	29	39	.120	0.43 (0.15–1.24)
	Recurrence, n (%)	10 (34)	5 (12)			12 (41)	9 (23)		
Severe pain	n	15	27	.098	0.27 (0.06–1.33)	15	27	.059	0.23 (0.05–1.11)
	Recurrence, n (%)	5 (33)	5 (19)			7 (47)	5 (19)		
Nausea	n	27	47	.301	0.56 (0.19–1.71)	27	47	.180	0.49 (0.17–1.38)
	Recurrence, n (%)	8 (30)	9 (19)			11 (41)	12 (26)		
No nausea	n	17	19	.020	0.09 (0.01–0.88)	17	19	.027	0.16 (0.03–0.92)
	Recurrence, n (%)	7 (41)	1 (5)			8 (47)	2 (11)		
Treatment ≥2 hours	n	21	28	.218	0.45 (0.12–1.68)	21	28	.611	0.72 (0.21–2.50)
	Recurrence, n (%)	7 (33)	5 (18)			8 (38)	9 (32)		
Treatment <2 hours	n	22	35	.055	0.29 (0.08–1.06)	22	35	.004	0.18 (0.05–0.61)
	Recurrence, n (%)	8 (36)	5 (14)			11 (50)	5 (14)		
Awoke with migraine	n	27	29	.011	0.22 (0.06–0.77)	27	29	.008	0.22 (0.07–0.71)
	Recurrence, n (%)	12 (44)	4 (14)			14 (52)	5 (17)		
Did not awake with migraine	n	17	37		0.99 (0.22–4.37)	17	37		0.82 (0.24–2.76)
	Recurrence, n (%)	3 (18)	6 (16)	.986		5 (29)	9 (24)	.729	

CI = confidence interval; OR = odds ratio.

Table 4.—Outcomes in Patients Who Reported Nausea at Time of treatment

	2-Hour Pain-Free[†]				2-Hour MBS-Free[†]			
n (%)	Placebo	ADAM Zolmitriptan 3.8 mg	*P* Value	OR (95% CI)	Placebo	ADAM Zolmitriptan 3.8 mg	*P* Value	OR (95% CI)
Nausea	7 (14)	26 (44)	<.001	5.11 (1.96–13.30)	23 (45)	40 (68)	.009	2.86 (1.28–6.43)
No nausea	4 (15)	8 (35)	.121	2.8 (0.74–10.60)	10 (39)	16 (70)	.032	3.70 (1.12–12.24)

CI = confidence interval; OR = odds ratio.
[†]Nine (12%) placebo patients and 13 (16%) patients treated with ADAM zolmitriptan 3.8 mg were missing 2-hour outcome data. These data were imputed using LOCF and included in the analyses.

Table 5.—Outcomes in Patients Who Treated Their Headache <2 Hours or ≥2 Hours After Onset

	2-Hour Pain-Free[†]				2-Hour MBS-Free[†]			
n (%)	Placebo[‡]	ADAM Zolmitriptan 3.8 mg[§]	*P* Value	OR (95% CI)	Placebo[‡]	ADAM Zolmitriptan 3.8 mg[§]	*P* Value	OR (95% CI)
< 2 hours	7 (19)	20 (47)	.009	3.63 (1.33–9.92)	17 (47)	28 (65)	.090	2.21 (0.88–5.55)
≥2 hours	4 (10)	12 (33)	.017	4.33 (1.24–15.10)	16 (41)	25 (69)	.014	3.37 (1.27–8.95)

CI = confidence interval; OR = odds ratio.
[†]Nine (12%) placebo patients and 13 (16%) patients treated with ADAM zolmitriptan 3.8 mg were missing 2-hour outcome data. These data were imputed using LOCF and included in the analyses.
[‡]Two patients excluded due to missing patch application times.
[§]Three patients excluded due to missing patch application times.

freedom and 2-hour MBS freedom were both higher in the zolmitriptan 3.8 mg group relative to placebo (Table 6). The frequency of pain recurrence at 24 hours and at 48 hours was also lower in the active treatment group (Table 3).

CONCLUSIONS AND DISCUSSION

Severe pain, delayed treatment, awakening with migraine, and the presence of nausea are established factors that predict a poorer response to acute migraine treatment. In subsets of patients with each of these characteristics in the ZOTRIP trial, participants receiving ADAM zolmitriptan 3.8 mg displayed nearly uniformly better headache responses (2-hour headache freedom and 2-hour MBS freedom) compared with those who received placebo.

The single exception was patients with severe pain at the time of treatment. In this subset, MBS freedom was more frequent in the ADAM zolmitriptan group than in the placebo group ($P = .038$), whereas pain freedom at 2 hours post-dose did not reach significance vs placebo ($P = .249$). However, the sample size in this group is low, and the percentage of patients (26%) who achieved 2-hour pain freedom was not dissimilar to what has previously been reported (30%) in a meta-analysis of 2657 patients with severe pain and treated with sumatriptan 100 mg.[4] Notably, other studies that have examined the effect of headache severity on triptan efficacy have evaluated the relative treatment effect in those with mild and moderate/severe pain intensity.[4,7,8,10,26] All participants in the ZOTRIP trial were required to have moderate/severe

Table 6.—Outcomes in Patients Who Did or Did Not Awaken With Migraine

	2-Hour Pain-Free[†]				2-Hour MBS-Free[†]			
n (%)	Placebo	ADAM Zolmitriptan 3.8 mg	*P* Value	OR (95% CI)	Placebo	ADAM Zolmitriptan 3.8 mg	*P* Value	OR (95% CI)
Awoke with migraine	7 (16)	16 (44)	.006	4.29 (1.50–12.31)	17 (39)	26 (72)	.003	4.40 (1.61–12.05)
Did not awake with migraine	4 (12)	18 (39)	.008	5.13 (1.46–18.00)	16 (49)	30 (65)	.114	2.17 (0.84–5.63)

CI = confidence interval; OR = odds ratio.
[†]Nine (12%) placebo patients and 13 (16%) patients treated with ADAM zolmitriptan 3.8 mg were missing 2-hour outcome data. These data were imputed using LOCF and included in the analyses.

pain, and in aggregate, a clear treatment effect was observed for 2-hour pain freedom.

Migraine headaches peak in intensity within 60 minutes of onset 60–80% of the time,[27] and it is not always possible to treat before headache pain becomes severe. Studies evaluating treatment efficacy as a function of time from onset have often used 1 hour as a cutoff for early vs delayed treatment.[7,8,10,12] In the analysis from the ZOTRIP trial presented here, patients who delayed treatment 2 hours or more after headache onset still responded following ADAM zolmitriptan administration with higher rates of 2-hour pain freedom and 2-hour MBS freedom compared with placebo. Similarly, a significant treatment effect was observed in those who awoke with a migraine headache. The rapid absorption profile of ADAM zolmitriptan[22] may contribute to its ability to provide pain and MBS freedom in patients even when treatment is delayed.

Migraine-associated nausea is a substantial barrier to, and consequence of, taking oral acute therapies.[27,28] ADAM zolmitriptan 3.8 mg was also more effective than placebo in patients who experienced nausea at the time of treatment. Intracutaneous administration may therefore provide an additional advantage in these patients by bypassing the need for swallowing or inhaling medication.

As noted above, these analyses were not prespecified, and adjustment was not made for multiple subgroup analyses to control for overall type I error, thus *P* values cannot formally be cited as significant or nonsignificant. For this reason, it is useful to evaluate numerical differences. Every endpoint for every subset was numerically superior in the ADAM zolmitriptan arm than the placebo arm.

Thus, the efficacy results seen in this trial suggest that ADAM zolmitriptan may be more effective than other routes of administration of triptans, particularly oral. The reasons for the improved efficacy are still speculative, but others have reported that efficacy is likely related to the rate of drug absorption.[15] Fast intracutaneous absorption accomplished with ADAM may facilitate rapidly delivering zolmitriptan to the 5-HT_{1B} and 5-HT_{1D} receptors.[29]

The ZOTRIP trial was not designed nor powered to assess treatment efficacy in the subsets of patients examined in these post hoc subgroup analyses. The sample sizes in the subsets were relatively small, which should be taken into consideration in interpreting the results. The fact that treatment effects were seen for the primary endpoints of the study for nearly all the subsets, and the uniform numerical differences in favor of the ADAM zolmitriptan in every subset analysis of each of the endpoints assessed, are noteworthy and suggest that ADAM zolmitriptan 3.8 mg may be an effective alternative for the types of migraine headache that have historically been difficult to treat.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Stewart J. Tepper, Donald J. Kellerman, Peter C. Schmidt

(b) Acquisition of Data

Donald J. Kellerman, Peter C. Schmidt

(c) Analysis and Interpretation of Data

Stewart J. Tepper, David W. Dodick, Donald J. Kellerman, Peter C. Schmidt

Category 2

(a) Drafting the Manuscript

Stewart J. Tepper, David W. Dodick, Donald J. Kellerman, Peter C. Schmidt

(b) Revising It for Intellectual Content

Stewart J. Tepper, David W. Dodick, Donald J. Kellerman, Peter C. Schmidt

Category 3

(a) Final Approval of the Completed Manuscript

Stewart J. Tepper, David W. Dodick, Donald J. Kellerman, Peter C. Schmidt

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