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Research Submission

A Double-Blind Placebo-Controlled Pilot Study of Sublingual Feverfew and Ginger (LipiGesic™M) in the Treatment of Migraine

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Background.—Therapeutic needs of migraineurs vary considerably from patient to patient and even attack to attack. Some attacks require high-end therapy, while other attacks have treatment needs that are less immediate. While triptans are considered the "gold standard" of migraine therapy, they do have limitations and many patients are seeking other therapeutic alternatives. In 2005, an open-label study of feverfew/ginger suggested efficacy for attacks of migraine treated early during the mild headache phase of the attack.

Methods/Materials.—In this multi-center pilot study, 60 patients treated 221 attacks of migraine with sublingual feverfew/ginger or placebo. All subjects met International Headache Society criteria for migraine with or without aura, experiencing 2-6 attacks of migraine per month within the previous 3 months. Subjects had <15 headache days per month and were not experiencing medication overuse headache. Inclusion required that subjects were able to identify a period of mild headache in at least 75% of attacks. Subjects were required to be able to distinguish migraine from non-migraine headache. Subjects were randomized 3:1 to receive either sublingual feverfew/ginger or a matching placebo and were instructed but not required to treat with study medication at the earliest recognition of migraine.

Results.—Sixty subjects treated 208 evaluable attacks of migraine over a 1-month period; 45 subjects treated 163 attacks with sublingual feverfew/ginger and 15 subjects treated 58 attacks with a sublingual placebo preparation. Evaluable diaries were completed for 151 attacks of migraine in the population using feverfew/ginger and 57 attacks for those attacks treated with placebo. At 2 hours, 32% of subjects receiving active medication and 16% of subjects receiving placebo were pain-free ($P = .02$). At 2 hours, 63% of subjects receiving feverfew/ginger found pain relief (pain-free or mild headache) vs 39% for placebo ($P = .002$). Pain level differences on a 4-point pain scale for those receiving feverfew/ginger vs placebo were –0.24 vs –0.04 respectively ($P = .006$). Feverfew/ginger was generally well tolerated with oral numbness and nausea being the most frequently occurring adverse event.

Conclusion.—Sublingual feverfew/ginger appears safe and effective as a first-line abortive treatment for a population of migraineurs who frequently experience mild headache prior to the onset of moderate to severe headache.

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Conflict of Interest: Dr. Roger Cady has served as a consultant for GlaxoSmithKline, Merck, Ortho-McNeil and received research grants from Allergan, Endo Pharmaceuticals, GlaxoSmithKline, Merck, PuraMed Bioscience and Wyeth. Dr. Jerome Goldstein has served as a consultant and/or served on advisory boards for multiple pharmaceutical companies. Dr. Robert Nett has served as a consultant and/or served on advisory boards for multiple pharmaceutical companies. Mr. Russell Mitchell is Chairman/CEO and stockholder in PuraMed BioScience, Inc. Ms. M.E. Beach and Ms. Rebecca Browning have nothing to disclose.

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Key words: acute migraine, feverfew, ginger, herbal migraine treatment, over-the-counter

Abbreviations: DISC Disability in Strategies of Care Study, PPMQ-R Revised Patient Perception of Migraine Questionnaire

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Migraine is a complex neurobiological disease characterized by episodic periods of disabling physiological dysfunction typically recurring over decades of an individual's lifetime. While the most obvious symptom associated with migraine is headache, it is only one of numerous disruptions that can be observed during an attack. Other commonly occurring symptoms include nausea, photophobia, phonophobia, autonomic nasal symptoms, muscle pain, and cognitive disruption. The impact of migraine accumulates over decades of time and can vary from one attack to another with some attacks requiring bed rest while others produce only mild or limited disability.

Treatment needs for migraine vary considerably from patient to patient and indeed, from attack to attack for the same patient. Pharmacologically, many over-the-counter and prescription products are effective treatment in acute migraine.[1] Commonly employed acute treatments approved for migraine can be classified as over-the-counter products, such as acetaminophen/aspirin/caffeine combination products and non-steroidal anti-inflammatory medications,[2] and prescription products, such as triptans and non-steroidal anti-inflammatories.[3] Various opioid and butalbital containing analgesics are also commonly prescribed, but most do not have Food and Drug Administration approval for migraine and are generally avoided by physicians because of their propensity to produce medication overuse headache.[4,5] In meta-analysis of clinical trials, the efficacy of any specific oral medication rarely exceeds 65% for pain relief of migraine with moderate to severe headache or 40% for pain freedom at 2 hours.[6] In addition, recurrence of migraine, adverse events, cost, and quantity limits placed on prescription medications further limit the utility of currently available migraine treatments. Thus, there remains a need for affordable effective treatments for migraine sufferers.

This study compares the efficacy of a unique lipid-based formulation of a sublingual homeopathic product of feverfew and ginger (LipiGesic™M, PuraMed BioScience, Inc., Schofield, WI, USA) vs a matching peppermint-flavored sublingual placebo as abortive treatment for acute episodic migraine. An earlier open-label study had reported efficacy for a water-based formulation of a feverfew/ginger product in treatment of acute migraine.[7] The present study explores utilization of a lipid-based formulation of feverfew/ginger at the onset of migraine. This early intervention strategy considers that well-tolerated effective early interventions that have no interactions with other pharmacological interventions could be a useful addition as an initial therapy for many individuals with migraine.

Primary Objective.—To assess the efficacy of sublingually administered preparation of feverfew/ginger in providing relief of headache and associated symptoms in acute migraine when administered early in the process of migraine.

Secondary Objectives.—

1. Evaluate persistent or recurrent headache 2-24 hours following treatment
2. Assess adverse events
3. Compare Patient Perception of Migraine Questionnaire scores between active therapy and placebo

MATERIALS AND METHODS

This double-blind, placebo-controlled, randomized study was approved by an independent investigational review board and conducted at 3 headache centers in the USA. A total of 60 subjects were enrolled in the study and 59 provided data for analysis; 1 subject withdrew because of pregnancy. All subjects aged 12-60, met criteria for International Headache Society migraine with or without aura and had a history of migraine for greater than 1 year. Attack frequency was between 2-6 attacks per month over the previous 3 months and subjects reported that at least 75% of attacks began with mild headache and that they could differentiate migraine from non-migraine

headache. All women of childbearing potential were requested to use a reliable method of birth control throughout the study period and were stabilized on dosages of current medications including migraine preventives for at least 90 days and continued on these medications throughout the 1-month study period.

Exclusion criteria included any medical condition that, in the opinion of the investigator, could confound the results of the study and subjects with 15 or more headache days per month or utilizing medications to treat acute migraine 15 or more days per month over the previous 3 months. Women who were pregnant or breastfeeding, and subjects taking anticoagulants, or with a known sensitivity to any component of the active study product were also excluded.

All subjects signed an informed consent or in the case of minors an assent with legal parent or guardian signing informed consent before screening.

Study Design.—The study was conducted at 3 investigational sites and consisted of 2 study visits: screening and exit visits conducted 1 month apart. Subjects were asked to treat all migraine attacks over a 1-month period regardless of the intensity of headache at the time of treatment. They were encouraged to initiate treatment when the headache of migraine was mild in intensity but with the understanding that the attacks would, in the subject's experience, become more disabling if left untreated.

At the screening visit and following written informed consent, all subjects provided a medical, medication, and migraine history. A physical and neurological exam and pregnancy test (if appropriate) were performed. Vital signs were recorded and the Revised Patient Perception of Migraine Questionnaire (PPMQ-R) was completed.

A randomization plan was created using an online randomization generator (http://www.randomization.com). The plan randomized each subject to either the active feverfew/ginger or a matching placebo group at a ratio of 3 to 1 by using the method of randomly permuted blocks. The sublingual matching placebo mimicked the peppermint-like taste of the active feverfew/ginger treatment. The plan was based on number of subjects per block and number of blocks. The investigator and research coordinator were blinded to the randomization.

Subjects were encouraged but not required to treat all migraines at the onset of mild pain through the 1-month study period. Subjects were instructed to treat with sequential administrations of 2 unit dose applicators according to provided written instructions.

The liquid from 1 unit dose applicator is applied sublingually, held under the tongue for 60 seconds, and then swallowed. The second unit dose applicator is administered in an identical manner following the first unit dose by 5 minutes. If any headache pain persists at 1 hour, a second treatment of 2 unit doses could be administered. A Headache Diary documenting onset of headache pain and presence of migraine-associated symptoms, time of treatment with study medication, symptoms at 1 and 2 hours following treatment, time of relief, recurrence of symptoms within 24 hours post-treatment, and adverse events were recorded. Additional rescue medication could be utilized 2 hours after the first treatment with study medication. The subject's standard medication, or any medication of their choice, was allowed as rescue following confirmation by the investigator. Subjects were instructed to be headache-free for 24 hours before recording the onset of another migraine attack. The majority of subjects did not use rescue medication.

At Visit 2, subjects returned the completed Headache Diaries. Adverse events were documented and the PPMQ-R was completed as a comparison of study medication with their usual pre-study treatment (Table 1).

Analysis.—Descriptive statistics were used to establish the mean and standard deviation for each of the primary and secondary endpoints. A 2-way analysis of variance (ANOVA) was conducted to measure the significance of the responses comparing the active and placebo groups.

Missing diary data for 6 attacks in the active group were managed by carrying the last observation forward for pain scores. Incomplete diary data were dropped from the analysis for 7 attacks, 6 in the active group and 1 in the placebo group (see Table 2).

Demographics.—There were 60 subjects, 46 female and 14 male, enrolled in the study. The mean age was 40.6 years with a range of 13 to 60. Only 5 subjects

Table 1.—Study Flow Chart

Procedure	Pre-Study	Visit 1/Day 0	Visit 2/Day 30
Participate in webcast (investigator and coordinator)	×		
Informed consent		×	
Medical/migraine/medication history		×	
Physical/neurological exam		×	
Urine pregnancy test (if appropriate)		×	
Vital signs		×	
Administer Patient Perception of Migraine Questionnaire (PPMQ-R)		×	×
Dispense study medication with instructions		×	
Instruct/dispense Headache Diaries		×	
Collect/review Headache Diaries			×
Update medical, migraine, medication history			×
Adverse events monitoring			×
Drug accountability			×

were minors; 86.7% were Caucasians. One subject withdrew because of pregnancy (see Table 3).

RESULTS

At time of treatment, the average severity of headache was 1.41 on a scale of 0-3 for those receiving active treatment and 1.67 for those receiving placebo. This represents a modest randomization imbalance and was a significant difference between groups ($P = .01$). At 2 hours post-treatment, the active group exhibited a significant drop in headache severity compared to the placebo group where at 2 hours post-dose, there was a 0.03 increase in headache intensity score (see Table 4).

Of all subjects treating across the range of headache severity (1-3) with sublingual feverfew/ginger, 32% reported being pain-free at 2 hours post-dose compared to 16% utilizing placebo ($P = .02$). At 2 hours post-dose, the percentage of attacks that was rated as no pain or mild pain was 64% for sublingual feverfew/ginger compared to 39% for placebo ($P = .003$) (see Table 5).

At 2 hours post-dose, there was a statistically significant difference in associated migraine symptoms and headache characteristics between active and placebo groups. This included statistical superiority for feverfew/ginger over placebo in eliminating the pulsating character of the headache ($P = .007$), the worsening of headache with activity (0.015), and

Table 2.—Study Profile

	All	LipiGesic™	Placebo
# Subjects	60	45	15
# Migraines	221	163	58
# Migraines where subjects reported pain level at treatment	208	151	57
# Migraines treated at mild	134	110	24
# Migraines treated at mild and reported 2-hour pain	127	104	23

Table 3.—Demographics

Demographics	Overall (n = 60)
Gender	
Female	n = 46 (76.7%)
Male	n = 14 (23.3%)
Age (years)	
Mean	40.6
SD	13.6
Range (Min, Max)	13-60
Ethnicity	
Caucasian	n = 52 (86.7%)
African American	n = 3 (5.0%)
Native American	n = 2 (3.3%)
Indian	n = 2 (3.3%)
Filipino	n = 1 (1.7%)

Ratio of active to placebo is 3:1.

Table 4.—Treated vs Placebo Pain Levels

	LipiGesic™	Placebo
Pain level at treatment	1.41096	1.66667
Pain level 2 hours after treatment	1.17123	1.70175
Mean difference	–0.2397	0.03509
Two-tailed probability	0.0126*	0.8051

*P value ≤ .05.
Where 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain.
Two hours after treatment.
221 total migraines treated (163 TX, 58 PL).
203 of migraines treated answered questions about 2-hour pain (146 TX, 57 PL).
TX = treatment; PL = placebo.

the presence of light sensitivity (0.001), sound sensitivity (0.003), and nausea (P = .002) (see Table 6).

Sublingual feverfew/ginger was well tolerated in this study. Adverse events were mild, similar to the placebo group with the exception of oral numbness (see Table 7).

Recurrence of headache, defined as a headache that at 2 hours post-treatment was rated as 0, progressed to an intensity score of 2 or 3 from 2 to 24 hours post-treatment was not statistically analyzable, because there were only 9 attacks in the placebo group that were pain-free at 2 hours post-dose. Of the 47 attacks that became pain-free at 2 hours in the active group, the recurrence rate was 20.4%, meaning return of moderate to severe migraine pain or use of rescue medication within 22 hours of becoming pain-free.

Evaluation of subjects' responses on the Patient Perception of Migraine Questionnaire (PPMQ-R) revealed statistical superiority for feverfew/ginger over placebo in total score (efficacy + functionality + ease of use) (P = .30), efficacy (P = .04), and functionality (P = .02) (see Table 8).

DISCUSSION

This study supports the efficacy of lipid-based sublingual feverfew/ginger in the acute treatment of migraine when administered early in the migraine attack. Evidence for efficacy is demonstrated by statistically significant differences in headache scores and reductions in disabling features of the headache (pulsating and pain increased with activity) as well as associated migraine symptoms of nausea, photophobia, and phonophobia. The lipid-based sublingual feverfew/ginger was well tolerated. Feverfew/ginger is believed to be compatible with other acute abortive treatments for migraine and represents a unique acute treatment option for migraine.

Migraine is a highly prevalent disease and the treatment needs of the migraine population are complex and incompletely understood. It is estimated that 50% of people with migraine are managing migraine outside of medical supervision and the advantages of prescriptive intervention.[8] Even when migraine sufferers choose to report migraine as a medical condition, they often lapse from care. In fact, the growth of triptans, often heralded as a medical breakthrough for abortive treatment, has not expanded for several years despite being recommended as first-line therapy for moderate to severe migraine by the US Consortium Acute Treatment Guidelines.[9]

Acute treatment needs for a migraineur typically span over decades. With time, treatment needs may change or specific therapies may be inappropriate based on medical risk factors or co-morbidities. Scientific explorations of clinical response to abortive treatments have to date largely focused on the response of a specific intervention in comparison to placebo over relatively few migraine attacks. Further efforts and guidelines have been directed at simplifying acute intervention strategies into such efforts as early intervention or stratified care. Yet, many people

Table 5.—No Pain or Mild Pain at 2 Hours Post-Dose

	No Pain at 2 Hours	Mild Pain at 2 Hours	No Pain or Mild Pain at 2 Hours
LipiGesic™	47 (32.19%)	46 (31.51%)	93 (63.70%)
Placebo	9 (15.79%)	13 (22.81%)	22 (38.60%)
Two-tailed probability	0.0227*	0.2346	0.0026

*P value ≤ .05.
221 total migraines treated (163 TX, 58 PL).
203 of migraines treated answered questions about 2-hour pain (146 TX, 57 PL).
TX = treatment; PL = placebo.

Table 6.—Migraine Associated Symptoms at 2 Hours Post-Treatment

	Presence at Onset					Presence at 2 Hours				
	Active (n = 163)		Placebo (n = 58)			Active (n = 163)		Placebo (n = 58)		
	n	%	n	%	Prob > ChiSq	n	%	n	%	Prob > ChiSq
Pulsating	72	44.2	37	63.8	0.0099*	51	31.3	30	51.7	0.0067*
One-sided	73	44.8	26	44.8	0.9956	52	31.9	25	43.1	0.1352
Worsens with activity	59	36.2	23	39.7	0.6405	49	30.1	28	48.3	0.0147*
Light sensitivity	80	49.1	33	56.9	0.3057	57	35.0	35	60.3	0.0009*
Sound sensitivity	54	33.1	26	44.8	0.1145	41	25.2	27	46.6	0.0032*
Nausea	19	11.7	14	24.1	0.0197*	20	12.3	18	31.0	0.0020*
Vomiting	1	0.6	0	0	0.4346	1	0.6	0	0	0.4334

*P value ≤ .05.
n = attacks.
Prob = probability; ChiSq = chi-square.

with migraine concoct complex treatment algorithms that include neither of these treatment strategies even after being recommended by the healthcare professional.

Several studies have explored patient treatment behaviors. The Disability in Strategies of Care (DISC) study demonstrated that better outcomes occurred when patients with disabling migraines (determined by Migraine Disability Assessment [MIDAS]) were stratified to zolmitriptan as their initial treatment vs treatment strategies of stepped-within-attack care at 2 hours post-dose. Yet, interestingly for a secondary end point, greater numerically superior patient efficacy and comparable satisfaction was reported at 4 hours for those using a stepped-within-attack administration beginning with metoclopramide and aspirin and followed 2 hours later with zolmitriptan if complete relief had not been achieved with the initial medication.[10] While the DISC study was not designed as a comparison of triptan vs non-triptan, the authors did comment that stepped-within-attack care may be appropriate care for those patients usually responding to non-specific treatments, given the cautionary note that it may delay relief and functional restoration. In addition, studies of early intervention demonstrate greater efficacy for oral triptans when administered during the mild headache of migraine, yet nearly half of patients fail or cannot successfully employ this strategy.[11,12] Together, these studies suggest many patients are seeking and could utilize novel acute treatment strategies and perhaps desire greater autonomy in defining treatment needs.

Table 7.—Reported Adverse Events

	# Patients with Event	
Event	Active	Placebo
Asthma diagnosis	1	0
Back pain twinges	0	1
Body aches	1	0
Diarrhea	0	4
Gagging	3	0
Heartburn	1	0
Loss of libido	0	1
Nausea	10	3
Oral numbness	6	0
Pregnancy	0	1
Sinus infection	1	0
Stomach cramp	3	0
Stomach flu	1	0
Tastes terrible	1	0
Vomiting	3	0
Vomiting sensation	0	1

n = events.

Table 8.—Patient Perception of Migraine Questionnaire (PPMQ-R)

	Treatment (n = 44)		Placebo (n = 15)		Mean Difference	ANOVA
	Mean	SD	Mean	SD	TX–PL	*P* Value
Efficacy	51.34	29.65	31.81	33.15	19.53	.0368*
Functionality	54.65	31.44	31.16	54.65	23.49	.0177*
Ease of use	66.27	30.00	57.31	24.95	8.96	.3033
Cost	23.40	27.65	24.98	31.51	–1.58	.8547
Bothersomeness	95.57	8.33	96.50	4.61	–0.93	.6829
Total score	57.59	25.42	40.05	26.34	17.53	.0259*

*P value ≤ .05.
Treatment vs placebo for end of study questions.
Scores range from 0 to 100. Higher scores represent better satisfaction.
PL = placebo; TX = treatment.

Other common patient-reported reasons for reluctance to use prescription abortive medications for acute migraine are adverse events and safety concerns.[13] This appears counter-intuitive as, from a medical perspective, migraine abortives are described as safe and well tolerated. Patient behavior may suggest otherwise. In addition, many patients report hesitancy to take a medicine unless they are certain they really need it.[14] From this perspective, it appears many patients desire an effective, non-prescription medication to use as a first-line treatment for at least some attacks of migraine with the flexibility to rescue with another medication if required.

From the patient's perspective, treatment of acute migraine has many more layers of complexity than addressed in clinical guidelines. For example, patients often understand a spectrum of migraine that requires different and unique treatment interventions.[15] There are, of course, prescription quantity limits put on many patients regardless of their treatment need. Adding to treatment complexities are adverse events experienced and interpreted by patients differently than by their healthcare provider. As a consequence, there exists an "adherence gap" between what providers think patients need for treatment and what patients seek from treatment.

This is apparent when one recognizes that triptans, while considered the "gold standard" of migraine treatment, are not increasing in utilization by the migraine population.[16,17] Reality dictates that patients are seeking more than triptans alone provide. Understanding this "adherence gap" represents the distance between evidence-based medicine and patient-centered care.

Numerous efforts designed to ascertain this adherence gap suggest no single treatment is effective for all migraines and that patients seek to match resources for treatment with available acute therapies. For example, if one was prescribed a specific triptan and advised to treat all migraine attacks early, yet could not afford the number of tablets per month required to accomplish this, the patient must devise an alternative treatment plan. Future studies need to be conducted to more completely understand the treatment dynamics of the migraine population.

This study explores a treatment that, when provided early in the migraine process, has statistically significant efficacy compared to placebo. The treatment is well tolerated with adverse events comparable to placebo except for oral numbing and nausea. Further, there is no reason to assume that feverfew/ginger as first-line therapy would preclude rescue with any current migraine abortive, thus suggesting little disadvantage for a person with reasonable opportunity to respond to acute treatment with feverfew/ginger.

Several limitations to this study need to be considered. It is a relatively small study and the random-

ization rate was 3:1, which may have biased subjects based on the increased likelihood of receiving active treatment. Additionally, although both the active product and placebo were flavored, the numbness that may be associated with ginger may have introduced bias for any study participant aware of this potential distinction between active product and placebo. This study explores an intervention that is homeopathic suggesting that there is no clear scientific or allopathic explanation of its mechanism of action. However, recent studies suggest that there may be an inhibitory effect on nitric oxide.[18]

However, given the study limitations, a lipid-based formulation of sublingual feverfew/ginger appears effective in treating acute migraine. Just how a product such as this can be used in the armamentarium of a migraineur remains to be seen but undoubtedly, there is an important potential role for such a product. Clearly, larger more comprehensive studies are warranted.

CONCLUSION

Sublingual feverfew/ginger appears safe and effective as a first-line abortive treatment for a population of migraineurs who frequently experience mild headache prior to the onset of moderate to severe headache. It appears to be well tolerated and has no known contraindications with other acute treatments for migraine.

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