Improvements in Health-Related Quality of Life with Sumatriptan Treatment for Migraine

Priti Jhingran, PhD; Roger K. Cady, MD; John Rubino, MD; David Miller, PhD; Robert B. Grice; and Donna L. Gutterman, PharmD

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Background. The debilitating effects of migraine might be reduced in patients using an effective migraine medication. The serotonin ($5HT_1$) receptor agonist sumatriptan has been shown in clinical trials to alleviate headache and associated symptoms in the majority of patients treated.

Methods. Three hundred forty-four (344) patients with migraine were allowed to treat an unlimited number of migraine attacks for up to 24 months with subcutaneous sumatriptan (6 mg). Open-label oral sumatriptan (100 mg) could be used between 1 hour and 24 hours after the initial injection for treatment of recurrent or persistent headache. On four occasions during the treatment period, patients completed the Medical Outcomes Study Short Form-36 Health Survey, a general health status instrument; the Migraine-Specific Quality of Life Questionnaire, a disease-specific instrument; and a series of questions designed to measure the impact of migraine on productivity and disability.

Results. Treatment with sumatriptan was associated with significant ($P<.05$) improvements relative to baseline in three of the Short Form-36 Health Survey quality-of-life dimensions (Bodily Pain, General Health Perceptions, and Social Functioning) and three of the Migraine-Specific Quality of Life Questionnaire dimensions (Role Function–Restrictive, Role Function–Preventive, and Emotional Function). Significant ($P<.05$) improvements in patient-rated productivity and reductions in patient-rated disability also occurred during the trial.

Conclusions. Patients using sumatriptan to treat migraines for up to 24 months experienced improvements in disability and productivity as well as in health-related quality of life as measured either by a general health status instrument or a disease-specific instrument.

Key words. Sumatriptan; health-related quality of life; migraine; headache. (*J Fam Pract 1996; 42:36-42*)

General and family physicians in the United States are visited over 9 million times a year by patients complaining of headache.[1] Occurring in 4 of every 100 Americans,[2] migraines may exact substantial personal and socioeconomic costs. Data from the National Health Interview Survey show that in 1989 10 million migraineurs in the United States spent over 3 million days per month bedridden due to migraine.[2] Employed men with migraine had an estimated 2.7 million days per year of restricted activity, while employed women with migraine had an estimated 18.8 million days per year of restricted activity. The results of another survey[3] of 648 patients meeting the International Headache Society diagnostic criteria for migraine showed that more than 90% of respondents had visited a clinic for the treatment of migraine during the year before the survey, and more than 50% had visited an emergency room. It was estimated that health care services related to migraine for these 648 patients cost $529,199 in 1 year.

These data reflect the large socioeconomic cost of acute migraine attacks, which may restrict or prohibit patients' usual activities and cause them to seek palliative medical treatment. The impact of migraine on the individual sufferer extends well beyond the pain and disability

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From Glaxo Research Institute, Research Triangle Park (P.J., D.M., R.B.G., D.L.G.), and Raleigh (J.R.), North Carolina; and Clinvest, Inc, Springfield, Missouri (R.K.C.). Requests for reprints should be addressed to Priti Jhingran, PhD, Glaxo Wellcome, Inc., 5 Moore Dr, Research Triangle Park, NC 27709.

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Table 1. Information About the Short Form-36 Health Survey and Interpretation of High and Low Scores

Concepts	No. of Items*	Meaning of Scores	
		Low Score	High Score
Physical Functioning	10	Limited a lot in performing all physical activities, including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role Function–Physical†	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health
Social Functioning	2	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems
Bodily Pain	2	Very severe and extremely limiting pain	No pain or limitations due to pain
General Mental Health	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time
Role Function–Emotional‡	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional problems
Vitality	4	Feels tired and worn out all of the time	Feels full of pep and energy all of the time
General Health Perceptions	5	Believes personal health is poor and likely to get worse	Believes personal health is excellent

**One of the 36 items is not included in the eight dimensions.*
†Role limitations due to physical problems.
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associated with the acute attack. Migraineurs' health-related quality of life has been shown to be impaired during intervals between migraine attacks.[1,4,5] In cases in which migraine is uncontrolled or unpredictable, the inability of the patient to anticipate or prevent migraine-induced interruptions in normal daily activities may contribute to this quality-of-life impairment.

The detrimental effects of migraine on health-related quality of life might be reduced in patients using an effective migraine medication. The serotonin ($5HT_1$) receptor agonist sumatriptan has been shown to alleviate headache and associated symptoms, such as nausea, vomiting, photophobia, and phonophobia, in the majority of patients in clinical trials.[6–9] This study was conducted to determine whether the long-term use of sumatriptan for the treatment of migraine is associated with an improvement in patients' health-related quality of life. The effects of migraine and sumatriptan treatment on disability and productivity also were assessed.

Health-related quality of life was measured with a general health status instrument, the Short Form-36 Health Survey,[10,11] and a disease-specific survey instrument, the Migraine-Specific Quality of Life Questionnaire (© 1992, Glaxo Wellcome Inc).[12] Whereas a general health status instrument facilitates comparisons across study populations and disease states, a disease-specific instrument is more sensitive to changes in health-related quality of life within the context of a clinical intervention.

The Short Form-36 Health Survey, a valid, reliable general health status questionnaire widely used in medical practice and clinical trials, measures eight aspects of health-related quality of life: Physical Functioning, Role Function–Physical, Social Functioning, Bodily Pain, General Mental Health, Role Function–Emotional, Vitality, and General Health Perceptions. In the Short Form-36 Health Survey, scores on the eight health dimensions yield a composite health profile (Table 1). Patients with chronic conditions, such as migraine, may show impairment on one or more of these dimensions of quality of life.[10,13,14]

The Migraine-Specific Quality of Life Questionnaire, a 16-item disease-specific instrument, assesses aspects of health believed to be particularly affected by migraine. Three dimensions are measured: Role Function–Restrictive (degree to which performance of normal activities is restricted by migraine); Role Function–Preventive (degree to which performance of normal activities is prevented by migraine); and Emotional Function (emotional and psychological effects of migraine). Typical questions address, for example, migraine-associated difficulties in attending social activities (a Role Function–Restrictive item) or the degree to which migraine creates burdens for others (an Emotional Function item). The Migraine-Specific Quality of Life Questionnaire has shown evidence of reliability and validity in a health maintenance organization migraine patient population.[12]

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In addition to the two health-related quality-of-life surveys, patients answered a series of questions measuring the impact of migraine and sumatriptan treatment on productivity and disability and on global quality of life. Productivity items included the number of work days missed due to migraine in the past 4 weeks. Disability items included patient-rated disability due to migraine and the number of days in bed due to migraine in the past 4 weeks.

Methods

Adult migraineurs at least 18 years of age were eligible for this study if they gave written informed consent. Patients were required to have at least a 6-month history of migraine, as diagnosed by the investigator. Patients with a history suggestive of ischemic heart disease or Raynaud's syndrome, diastolic blood pressure greater than 95 mm Hg at screening, or systolic blood pressure greater than 160 mm Hg at screening were excluded. At treatment, patients with chronic tension-type headache or cluster headache, as diagnosed by the investigator, were excluded. Women with a positive urine pregnancy test were also excluded.

In general, patients were referred for the study by general or family physicians or by headache specialists. Some patients had participated in a placebo-controlled clinical trial evaluating the effects of oral sumatriptan (100 mg) for headache recurring after treatment with subcutaneous sumatriptan (6 mg).[15] These patients were given the option to enroll in the present study as long as they met the eligibility criteria described above. In addition to referring patients who had participated in a previous sumatriptan trial, the physicians conducting the present study had the option to enroll up to 15 additional patients per site.

The protocol for this open-label study was approved by institutional review boards for the 12 study sites. Patients could treat an unlimited number of migraine attacks in the clinic for up to 24 months with subcutaneous sumatriptan (6 mg). Oral sumatriptan (100 mg) could be used in the clinic or at home for treatment of significantly worsening existing headache, continuation of mild headache, or recurrence of headache between 1 and 24 hours after initial subcutaneous treatment.

Patients completed the Short Form-36 Health Survey, the Migraine-Specific Quality of Life Questionnaire, and the productivity/disability questionnaires on four occasions: at baseline and on visits 1, 2, and 3. These occasions were separated by 6 months ± 1 month. Patients completed the questionnaires in the clinic without assistance. In answering the survey questions, patients were required to recall the past 4 weeks. Safety evaluations, including adverse event assessments and clinical laboratory tests, were also performed at each clinic visit.

Intent-to-treat analyses, including patients who completed all four visits as well as those who missed one or more visits, were performed on the study data. Last observation carried forward was used as the imputation method. For any missing value on the health-related quality of life and productivity/disability measures, the last observation for that patient was carried forward if it was possible for the patient to complete that visit before the study closing date.

Each of the eight Short Form-36 Health Survey dimensions and the three Migraine-Specific Quality of Life Questionnaire dimensions were scored separately and transformed to a scale ranging from 0 (least favorable score) to 100 (most favorable score). Repeated-measures analyses of variance with visits as the repeated factor were performed on the Short Form-36 Health Survey and the Migraine-Specific Quality of Life Questionnaire data. Separate repeated-measures models were developed for each of the eight dimensions of the Short Form-36 Health Survey and each of the three dimensions of the Migraine-Specific Quality of Life Questionnaire. When appropriate, contrast statements were used to produce pairwise comparisons between baseline scores and scores from visits 1, 2, or 3. Pairwise comparisons were performed only after the repeated-measures models were rejected. P values $<.05$ were considered statistically significant.

Linear regression analyses were used to produce adjusted scores for both the Short Form-36 Health Survey (scores adjusted for age; sex; race; baseline scores; and selected comorbidities, including arthritis, chronic obstructive pulmonary disease, back pain, hypertension, gastrointestinal distress, clinical depression, and urinary tract infection) and the Migraine-Specific Quality of Life Questionnaire (scores adjusted for age, sex, race, and baseline scores). Because adjusted scores did not differ from unadjusted scores, the repeated-measures analyses of variance were performed on unadjusted scores.

Data from the productivity/disability questionnaire were analyzed for differences between scores at visit 3 and baseline using paired t tests for continuous variables, eg, days in bed, and Wilcoxon sign rank tests for categorical variables, eg, pain severity.

Results

Patient Characteristics

Three hundred forty-four patients enrolled in the study and were administered the health-related quality-of-life

Table 2. Short Form-36 Health Survey Scores in Patients Treating Migraine Attacks with Sumatriptan over 24 Months

		Quality of Life Score			
		Baseline Visit	Visit 1	Visit 2	Visit 3
Significance of Improvement	N*	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Significantly improved					
Bodily Pain†‡	301	49.8 (23.3)	53.6 (21.1)	54.7 (21.0)	55.5 (21.3)
General Health†	299	72.1 (18.3)	71.7 (18.9)	73.1 (18.3)	73.3 (18.9)
Social Functioning†§	295	74.4 (20.8)	75.4 (20.8)	76.9 (20.1)	77.4 (20.0)
Not significantly improved					
Physical Functioning	303	88.9 (15.3)	87.8 (15.1)	88.1 (15.1)	87.6 (16.1)
Role Function–Physical ‖	253	56.0 (42.5)	53.0 (44.1)	55.5 (43.7)	58.1 (43.6)
Vitality	299	57.4 (19.7)	56.7 (20.5)	58.1 (19.6)	57.8 (20.3)
Role Function–Emotional¶	297	81.5 (32.9)	80.5 (35.0)	82.6 (32.2)	81.6 (33.4)
Mental Health	299	73.8 (15.6)	73.6 (16.1)	73.4 (15.7)	75.0 (15.0)

**Includes patients who completed all four visits as well as those who missed one or more visits. For any missing scores, last observation carried forward was used as the imputation method.*
†P <.05 for differences among visits.
‡P<.05 for baseline visit score vs scores for visits 1, 2, and 3.
§P <.05 for baseline visit score vs scores for visits 2 and 3.
‖Role limitations due to physical problems.
¶Role limitations due to emotional problems.
SD denotes standard deviation.

surveys at the baseline visit. One hundred seventy-six of the patients elected to enroll in the present study after they had completed a previous sumatriptan study[15]; 168 of the patients had not been involved in that previous study.

The study participants were 96% white, 2% African-American, and 1% Hispanic. The average age of women and men was 43 years, with a range of 18 to 69 years. Among the men enrolled in the study, 6% were 18 to 30 years old, 39% were 31 to 40 years old, 27% were 41 to 50 years old, 24% were 51 to 60 years old, and 3% were older than 60 years. Among women enrolled in the study, 11% were 18 to 30 years old, 29% were 31 to 40 years old, 41% were 41 to 50 years old, 15% were 51 to 60 years old, and 4% were older than 60 years.

One hundred fifty-one patients withdrew during the course of the study: 63 failed to return following the baseline visit, 7 withdrew due to adverse events, 9 withdrew due to lack of efficacy, and 72 withdrew for other reasons, such as protocol violations. Mean time intervals in months were 6.23 (standard deviation [SD] 0.89) between baseline and visit 1; 6.12 (SD=0.91) between visit 1 and visit 2; 5.33 (SD=1.27) between visit 2 and visit 3; and 16.49 (SD=2.79) between baseline and visit 3. Over the course of the study, 2673 attacks were treated with subcutaneous sumatriptan.

Short Form-36 Health Survey Data

Repeated-measures analyses of variance were statistically significant for three of the eight Short Form-36 Health Survey dimensions (Table 2): Bodily Pain ($P<.001$); General Health Perceptions ($P<.04$); and Social Function ($P<.02$). Pairwise comparisons using contrast statements showed that both Social Function scores at baseline were significantly different from those at visits 2 and 3, and Bodily Pain scores at baseline were significantly different from those at visits 1, 2, and 3. None of the pairwise comparisons for General Health Perceptions was statistically significant.

Migraine-Specific Quality of Life Questionnaire Data

Repeated-measures analyses of variance were statistically significant ($P<.001$) for each of the three Migraine-Specific Quality of Life Questionnaire dimensions (Table 3). Pairwise comparisons revealed that Role–Function Restrictive, Role–Function Preventive, and Emotional Function scores were significantly different from baseline visit scores at visits 1, 2, and 3.

Productivity/Disability Data

At each visit, patients estimated that they had experienced a mean of three migraines in the past 4 weeks (Table 4). There was no difference in the number of attacks experienced in the past 4 weeks between baseline visit and visit 3. The severity of migraines as reported by the patients declined from the baseline visit to visit 3 (Wilcoxon $t=-4869$; $P<.001$).

Asked to rate whether their quality of life had im-

Table 3. Migraine-Specific Quality of Life Questionnaire Scores in Patients Treating Migraine Attacks with Sumatriptan Over 24 Months

		Quality of Life Score			
		Baseline Visit	Visit 1	Visit 2	Visit 3
Dimensions*	N†	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Role Function–Restrictive	241	55.7 (18.3)	59.5 (17.3)	62.3 (16.9)	62.8 (16.6)
Role Function–Preventive	239	54.4 (18.7)	56.9 (17.8)	59.2 (18.1)	60.2 (19.3)
Emotional Function	303	65.6 (22.4)	70.2 (22.3)	73.6 (20.6)	75.5 (20.9)

**For each of these dimensions, P <.05 for differences among visits, and for baseline visit score vs scores for visits 1, 2, and 3.*
†Includes patients who completed all four visits as well as those who missed one or more visits. For any missing scores, last observation carried forward was used as the imputation method.
SD denotes standard deviation.

proved over the past 4 weeks, patients rated their quality of life significantly more favorably at visit 3 than they did at the baseline visit (Wilcoxon $t=8926$; $P<.001$). At visit 3, patients also reported fewer days of work missed due to migraine and fewer days spent in bed compared with the baseline visit (paired $t=2.96$ for days of work missed [$P<.03$]; paired $t=-5.37$ for days in bed [$P<.001$]). Patient-reported disability at visit 3 was also significantly lower than that at the baseline visit (Wilcoxon $t=-3577$; $P<.001$).

Discussion

The results of this study demonstrate that treatment o migraine attacks with open-label sumatriptan (6 mg sub cutaneously for initial attacks and oral 100 mg for recur rent headache or as rescue medication for persistent head ache) may be associated with an improvement in health related quality of life, as measured by either a general or disease-specific instrument. The Short Form-36 Healt Survey dimensions of Bodily Pain, General Health Per

Table 4. Responses to Selected Questions About Disability and Productivity from Patients Treating Migraine Attacks with Sumatriptan Over 24 Months

	Patient Responses			
Questionnaire Items	Baseline Visit	Visit 1	Visit 2	Visit 3
No. of attacks, mean (SD)	3.5 (3.4)	3.3 (3.5)	3.2 (3.2)	3.4 (3.6)
No. of work days missed, mean (SD)	2.5 (3.9)	2.0 (2.8)	1.7 (1.9)	1.4 (1.8)
No. of days in bed, mean (SD)	2.3 (2.6)	1.6 (2.0)	1.3 (1.6)	1.3 (1.7)
Severity, n (%)				
Did not have migraine	13 (4)	30 (9)	26 (8)	36 (11)
No problem at all	0 (0)	0 (0)	1 (<1)	2 (<1)
Mild	21 (6)	28 (8)	37 (11)	34 (11)
Moderate	59 (17)	71 (21)	72 (22)	59 (19)
Moderately severe	111 (33)	105 (31)	100 (30)	106 (34)
Severe	88 (26)	79 (23)	73 (22)	61 (19)
Very severe	48 (14)	25 (7)	24 (7)	18 (6)
Change in quality of life, n (%)				
Have not taken medication	155 (47)	38 (11)	39 (12)	26 (8)
Much worse	0 (0)	0 (0)	0 (0)	0 (0)
Moderately worse	4 (1)	0 (0)	0 (0)	0 (0)
Slightly worse	1 (<1)	2 (<1)	2 (<1)	2 (<1)
Not changed	33 (10)	55 (16)	46 (14)	37 (12)
Slightly improved	40 (12)	65 (19)	60 (18)	52 (16)
Moderately improved	38 (12)	81 (24)	72 (22)	77 (24)
Greatly improved	56 (17)	96 (29)	108 (33)	123 (39)
Disability due to migraine, n (%)				
Not at all	23 (7)	36 (11)	41 (12)	58 (19)
A little of the time	101 (30)	130 (39)	126 (38)	112 (37)
Some of the time	139 (42)	116 (34)	124 (38)	101 (33)
A good bit of the time	40 (12)	31 (9)	25 (8)	24 (8)
Most of the time	29 (9)	21 (6)	11 (3)	9 (3)
All of the time	3 (<1)	4 (1)	3 (<1)	2 (<1)

SD denotes standard deviation
NOTE: Numbers include patients who completed all four visits as well as those who missed one or more visits. For any missing scores, last observation carried forward was used as the imputation method. Percentages may not total 100 because of rounding.

ceptions, and Social Function improved relative to baseline scores in patients using sumatriptan to treat migraine. Although scores on the Role Function–Physical and Role Function–Emotional dimensions also improved relative to baseline scores, these changes were not statistically significant. These two dimensions, containing items with dichotomous response options, may lack the sensitivity to detect small changes in health-related quality of life.

Unlike some of the Short Form-36 Health Survey dimensions, the Migraine-Specific Quality of Life Questionnaire was sensitive to the effects of sumatriptan on aspects of health that are believed to be primarily affected by migraine. Migraine-Specific Quality of Life Questionnaire scores in all three migraine-specific dimensions (Role–Function Restrictive, Role–Function Preventive, and Emotional Function) were more favorable than baseline scores. These results suggest that sumatriptan treatment may alleviate the impairment in normal role functioning and reduce the emotional burden that migraines impose.

Migraineurs' responses to the productivity- and disability-related questions at the baseline visit show that migraine substantially reduced their productivity and restricted their normal daily activities. It is plausible that migraine-associated restriction or prohibition of normal daily activities or the threat of such restriction or prohibition contributes substantially to the impairment of quality of life in migraineurs. That improvements in patient-reported productivity and reductions in disability over the course of the study were accompanied by improvements in health-related quality of life, measured with either the Short Form-36 Health Survey or the Migraine-Specific Quality of Life Questionnaire, supports this contention. With repeated use of sumatriptan to treat migraine, patients' health-related quality of life improved. They reported significantly less time missed from work or other activities, significantly fewer days spent in bed due to migraine, and significantly fewer activity interruptions.

Because multiple testing is a concern when series of tests are performed within an instrument, the Bonferroni method was applied post hoc to control for multiplicity. Adjusting for multiplicity did not greatly affect the findings. When adjusted for multiple testing, improvements on Social Function and General Health Perceptions dimensions of the Short Form-36 Health Survey no longer achieved statistical significance. Neither the Migraine-Specific Quality of Life Questionnaire results nor the disability and productivity results changed when adjusted for multiple testing.

The finding that treatment-associated changes in health-related quality of life were detected with the Short Form-36 Health Survey suggests that the impact of sumatriptan treatment on health-related quality of life may be substantial. However, because this study did not include a placebo control group, the effects of drug treatment on health-related quality of life cannot be distinguished from the effects of participating in a clinical trial. The extent to which the improvements in health-related quality of life, productivity, and disability are due to internal validity threats such as measurement, maturation, and regression toward the mean are not known. Future parallel-group studies will enable stronger, more specific conclusions to be drawn with respect to the effects of sumatriptan on health-related quality of life. To gain further long-term data on patients participating in this study, patients were given an opportunity at the termination of the study to roll over into another 24-month investigation. Approximately 132 patients entered this open-label study extension, the results of which will be available next year.

In spite of the limitations associated with the open-label, single-group design, the pattern of use of sumatriptan in this study probably more closely resembles patients' actual use of the drug than the pattern of use in a controlled clinical trial. Because the study was designed to determine the long-term effects of sumatriptan, it was impractical and possibly unethical to conduct this study as a double-blind, placebo-controlled investigation.

The improvement in health-related quality of life associated with the use of sumatriptan is consistent with the drug's high degree of clinical efficacy. Sumatriptan (subcutaneous 6 mg or oral 100 mg) has been shown in a number of studies to alleviate headache and associated symptoms such as nausea, vomiting, photophobia, and phonophobia in up to 80% of patients.[6–9] Similarly high efficacy rates were observed in the current study: the efficacy of sumatriptan did not diminish with repeated administration for up to 24 months.[16]

Somewhat surprisingly, patients reported that headache severity diminished as the number of attacks treated with sumatriptan during the trial increased. Possibly, patients' survey responses were influenced by their increasing confidence in their ability to control their migraines pharmacologically as the trial progressed. Patients may have learned by the end of the trial that they could control their pain, and this knowledge may have been accompanied by a decrease in perceived severity relative to baseline visit levels.

Most patients in this study were long-term migraine sufferers who may have been experienced patients and who may have used a variety of medication types during their migraine histories. Most patients were referred for the study by general or family physicians or by headache specialists, and many had participated in a previous sumatriptan clinical trial. Although the sample is probably representative of the population of migraineurs that re-

ceives treatment, the representativeness of the sample to the general migraine population, including those who do not seek treatment, is unknown.

The improvements in health-related quality of life, disability, and productivity occurring in these patients are not surprising, given the effectiveness of sumatriptan in the treatment of acute migraine. The findings of this study suggest that migraineurs' confidence in the ability of sumatriptan to stop a migraine attack allows them to continue their normal activities of daily life. Family physicians interested in improving the clinical symptoms as well as reducing the humanistic cost of migraine will find these results important. A skillful intervention by a physician who understands both the clinical and the psychosocial implications of migraine and its treatment will help improve the standard of care provided to migraine patients.

The degree to which treatment with sumatriptan is responsible for improvement in health-related quality of life will be explored in other studies. In this study, the treatment of migraines for up to 24 months with sumatriptan was associated with improvement in health-related quality of life (as measured with a general and a disease-specific instrument) and in productivity and the length of disability. This study provides promising data that will serve as a firm foundation for future work.

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