Treatment of Unruptured Cerebral Aneurysms with the Mineralocorticoid Receptor Blocker Eplerenone—Pilot Study

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Background: Currently there are no pharmacological therapies for patients with unruptured cerebral aneurysms. Elsewhere we showed that the mineralocorticoid receptor antagonist eplerenone prevented the formation of cerebral aneurysms in our ovariectomized hypertensive aneurysm rat model. The current pilot study evaluated whether it can be used to prevent the growth and rupture of cerebral aneurysms in hypertensive patients. *Methods:* Between August 2011 and May 2014, we enrolled 82 patients with 90 aneurysms in an open-label uncontrolled clinical trial. All provided prior informed consent for inclusion in this study, and all were treated with eplerenone (25-100 mg/d). The primary end points of our study were the rupture and enlargement of the cerebral aneurysms. *Results:* Of the 82 patients, 80 (88 unruptured aneurysms) were followed for a mean of 21.3 months (153.4 aneurysm-years); 12 patients (15.0%) permanently discontinued taking the drug. One month after the start of eplerenone administration and throughout the follow-up period, eplerenone kept the blood pressure within the normal range. Most notably, no aneurysms smaller than 9 mm ruptured or enlarged. However, of 2 large thrombosed aneurysms, 1 enlarged and the other ruptured. The overall annual rupture rate was .65%; it was 13.16% for aneurysms larger than 10 mm; the overall annual rate for reaching the primary end points was 1.30%. *Conclusion:* Our observations suggest that eplerenone may help to prevent the growth and rupture of unruptured cerebral aneurysms smaller than 9 mm. To assess its

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potential long-term clinical benefits, large clinical trials are needed. **Key Words:** Mineralocorticoid receptor blocker—eplerenone—hypertension—unruptured cerebral aneurysms.

Introduction

Subarachnoid hemorrhage (SAH) due to the rupture of cerebral aneurysms carries a high mortality risk.[1] Advances in imaging techniques have led to the incidental discovery of unruptured cerebral aneurysms. Indications for surgical treatment depend on the patient's life expectancy and the size and site of the aneurysms. The mortality and morbidity rates after the clipping and coiling of unruptured aneurysms are not negligible. Therefore, pharmacological means to prevent aneurysmal growth and rupture are an attractive option, especially in patients with a high surgical risk.

Based on epidemiological data that show a high incidence of cerebral aneurysms and SAH in postmenopausal women, we established a cerebral aneurysm model in female rats subjected to estrogen deficiency, hypertension, and hemodynamic stress.[2] In this model, pharmacological treatment with 17β-estradiol, antihypertensive drugs, or a phosphodiesterase 4 inhibitor reduced the incidence of cerebral aneurysms via their antioxidative and anti-inflammatory effects.[3-6] The mineralocorticoid receptor eplerenone effectively, and blood pressure (BP) independently, prevented the formation of cerebral aneurysm in our model rats.[4] We also found that in eplerenone-untreated model rats, the expression of CD68, monocyte chemoattractant protein-1, and matrix metalloproteinase-9 increased. Eplerenone abrogated these adverse changes.

To obtain knowledge on the potential effectiveness of eplerenone for the prevention of human aneurysmal growth and rupture, we performed a pilot study and recorded the clinical course of hypertensive, eplerenone-treated patients with unruptured cerebral aneurysms.

Methods

Patient Recruitment

Investigators at the 11 participating hospitals obtained the approval of their local institutional review boards before joining the study. Table 1 is a list of the institutions, investigators, and cases. All patients gave their written informed consent before enrollment. Our inclusion criteria were as follows: (1) They had at least 1 previously or newly diagnosed unruptured aneurysm whose diameter was 2 mm or larger in the maximum external diameter in any direction without referable clinical symptoms or signs. Aneurysm discovery was by angiography, magnetic resonance imaging, magnetic resonance angiography, or computed tomography angiography studies performed for reasons other than a suspicion of an index aneurysm. (2) They have no included unruptured aneurysms that had been treated by surgical clipping or endovascular coiling. (3) They have hypertension, defined as a systolic BP of 140 mm Hg or higher or a diastolic BP of 90 mm Hg or higher, or use antihypertensive medication. (4) They are aged between 40 and 84 years. (5) They have a modified Rankin Scale of ≤2.

Exclusion Criteria and Study End Points

We imposed 6 exclusion criteria: (1) a history of mycotic, traumatic, vasculitic, or previously treated aneurysms; (2) severe coexisting or terminal systemic disease such as

Table 1. *List of participating institutions, investigators, and cases*

Study center	Entry case number	Valid case number	Local investigators
Anan Kyoei Hospital	3	2	D. Ebisudani, K. Bando
Kitajima Taoka Hospital	3	3	Y. Murayama
Kyoritsu Hospital	3	3	S. Yoshijima
Mizunomiyako Kinen Hospital	1	1	I. Sasaki
Yoshinogawa Medical Center	1	1	N. Asano, K. Hara
Taoka Hospital	7	7	S. Manabe
Tezuka Hospital	3	3	T. Soga
Tokusima Prefectural Central Hospital	1	1	H. Hondo
Tokushima Prefecture Naruto Hospital	2	2	M. Agawa
Tokushima Red Cross Hospital	6	6	K. Sato
Tokushima University Graduate School	52	51	S. Nagahiro

malignant neoplasms, or cardiac or liver failure; (3) serum potassium concentration > 5.0 mmol/L; and (4) creatinine clearance < 50 mL/min.

Patients who met all inclusion criteria and harbored unruptured aneurysms were registered from August 2011 to May 2014. They had undergone no prior surgical or endovascular interventions to address the included aneurysms and followed at 1, 3, 6, and 12 months postregistration and every 6 or 12 months thereafter. All patients had a history of hypertension and were treated with eplerenone (25-100 mg/d).

The primary end points were the enlargement or rupture of the cerebral aneurysms. Enlargement was recorded for aneurysms when the aneurysmal diameter increased by 2 mm or more, or a bleb developed in the course of observation. The aneurysmal size was measured on T1- or T2-weighted images of thrombosed aneurysms. The secondary end points were fatal/nonfatal cerebrovascular events and all-cause mortality.

BP and Adverse Event Monitoring

BP measurements were taken with a validated mercury sphygmomanometer with the patients in the sitting position. The mean of 2 measurements that provided a stable value (difference in the values < 5 mm Hg) was calculated and recorded. BP measurements were obtained before and 1, 3, 6, and 12 months after the start of the eplerenone treatment. Adverse events and concurrent medications were recorded at each visit.

Statistical Analysis

Analyses were performed with SPSS version 11 software. Differences in the response to eplerenone were assessed with the paired *t*-test. All measurements are presented as the mean ± standard deviation for parametric and as the median (interquartile range) for nonparametric variables. Inter-rater agreement for the identification of aneurysmal enlargement was assessed with kappa (κ) statistics.

The follow-up duration was expressed using the aneurysm-years method. The average annual risk of rupture associated with unruptured aneurysms was calculated by dividing the number of first-rupture events or enlargement by the number of aneurysm-years of the follow-up duration.

Results

Patient Characteristics

For this open-label uncontrolled clinical trial, we were able to obtain neither the total number of patients seen at the 11 participating institutions in the course of our study period from August 2011 to May 2014 nor the number of patients who would have satisfied our inclusion criteria. We enrolled 82 patients (90 aneurysms) who gave their consent for inclusion in our study and satisfied both our inclusion and exclusion criteria; 2 patients were excluded from further analysis because data obtained at 2 hospitals were inadequate. Consequently, 80 patients (88 unruptured aneurysms) were included and followed for a mean of 21.3 months (153.4 aneurysm-years). Data on the patients and aneurysms are shown in Tables 2 and 3. The mean patient age was 68 ± 10 years; 74% of the patients were women, 9% had a family history of SAH, and in 78 of the 80 patients (98%), unruptured aneurysms were discovered incidentally. The mean aneurysmal diameter was 4.6 ± 2.6 mm, 50% were 3-4 mm in diameter, 39% were at the middle cerebral artery, 20% were at the internal carotid artery, and 19% were at the anterior communicating artery; 2 aneurysms were thrombosed. All 80 patients were diagnosed with hypertension and were treated with eplerenone (25-100 mg/d). We addressed 1 aneurysm by neck clipping 128 days after registration because the patient demanded surgery to prevent its rupture.

Table 2. *Clinical characteristics of the 80 enrolled patients*

Characteristics	Unruptured aneurysms
Number of patients	80
Number of aneurysms	88
Number of multiple aneurysm cases	8 (10%)
Age	68 ± 10
Women	59 (74%)
Family history of subarachnoid hemorrhage	7 (9%)
Aneurysm detection	
Screening	15 (19%)
Headache or dizziness	44 (55%)
Associated with investigation for stroke or brain tumor	11 (14%)
Subarachnoid hemorrhage	2 (2%)
Other	8 (10%)
Former or current smoking	23 (29%)
Medical and social history	
Hypertension	80 (100%)
Diabetes mellitus	11 (14%)
Dyslipidemia	26 (33%)
Ischemic stroke	10 (13%)

Effect of Eplerenone on the Growth and Rupture of Aneurysms and the Study End Points

Eighty patients (88 unruptured aneurysms) were followed for a mean of 21.3 months (153.4 aneurysm-years). The annual rate of rupture and primary endpoint events (aneurysmal rupture and enlargement) based on the aneurysm size are shown in Table 4. Importantly, the annual rate of primary events was 0% for the eplerenone-treated aneurysms smaller than 9 mm. However,

Table 3. *Characteristics of the 88 aneurysms*

Characteristics	Unruptured aneurysms
Aneurysm size	
diameter, mm (mean ± SD)	4.6 ± 2.6
Distribution	n (%)
2-3 mm	18 (20%)
3-4 mm	44 (50%)
5-6 mm	16 (18%)
7-9 mm	4 (5%)
10-24 mm	6 (7%)
Location	
MCA	34 (39%)
AcomA	17 (19%)
Distal ACA	1 (1%)
ICA	18 (20%)
IC-PC	10 (11%)
BA	5 (6%)
VA	1 (1%)
Others	2 (2%)
Other features	
Thrombosed	2 (2%)
Daughter sac	13 (15%)

Abbreviations: ACA, anterior cerebral artery; AcomA, anterior communication artery; BA, basilar artery; ICA, internal carotid artery; IC-PC, internal carotid-posterior communicating artery; MCA, middle cerebral artery; VA, vertebral artery.

1 thrombosed 15-mm middle cerebral artery aneurysm in a 77-year-old woman ruptured 13.5 months after registration during the 153.4 aneurysm-years of follow-up (Fig 1, A). Another thrombosed 15.8-mm aneurysm was found in a 50-year-old woman (Fig 1, B). It was located at the basilar artery-superior cerebellar artery and was enlarged 27 months postregistration. The overall annual risk for rupture was .65%; it was 13.16% for aneurysms larger than 10 mm. The overall annual rate for reaching the primary end points was 1.30%. Inter-rater agreement for the determination of growth was good ($\kappa = .65$).

Two patients developed ischemic stroke as secondary endpoints.

Effects on the Systolic and Diastolic BP

The systolic and diastolic BP before eplerenone administration was 144 ± 11 and 82 ± 10 mm Hg, respectively (Fig 2). At all examined time points, starting 1 month after the initiation of eplerenone therapy, the BP was significantly lower than the baseline value and remained normalized throughout the study period.

Safety of Eplerenone

Adverse events are listed in Table 5. In the course of our study, 12 patients (15%) permanently stopped taking the drug (mean interval between registration and the last dose, 191 days). Adverse events occurred in 16 of the 80 study subjects (20%); 4 (5%) developed hypotension and 3 (4%) hyperkalemia, defined as a serum potassium concentration ≥ 5.0 mmol/L). In 2 patients with hyperkalemia we transiently stopped eplerenone until it resolved. There were no serious adverse events attributable to the administration of eplerenone.

Discussion

As our previous study had shown that eplerenone effectively prevented the formation of aneurysms in our rat model,[4] in the current pilot study we examined its potential for use in patients with unruptured cerebral aneurysms. The drug is approved to treat hypertension in humans.

We found that in eplerenone-treated patients, the annual rupture rate and the rate of primary end-point events (aneurysmal rupture and enlargement) was 0% in patients whose aneurysms were smaller than 9 mm in diameter; these rates were 13.16% and 26.32% when the aneurysm size was 10 mm or larger. The overall annual rate of rupture and of primary end-point events for the 88 unruptured cerebral aneurysms treated with eplerenone was .65% and 1.30%, respectively. Therefore, our uncontrolled, open-label study suggests that the drug may help to prevent the rupture and growth of human cerebral aneurysms smaller than 9 mm but not of aneurysms larger than 10 mm.

According to The International Study of Unruptured Intracranial Aneurysms, the rupture rate of small cerebral aneurysms in the anterior circulation is very low.[7,8] However, prospective studies on Japanese patients revealed their higher risk for the rupture of cerebral aneurysms.[9-11] As the risk for SAH due to aneurysmal rupture is higher in Japanese and Finnish individuals than in other populations,[12] differences in the ethnic background may play a role. The overall annual rupture rate

Table 4. *Annual primary end-point events (aneurysmal rupture and enlargement) and rupture according to the aneurysmal size*

	Overall (n=88)	≤ 5 mm (n=71)	≤ 9 mm (n=82)	10-24 mm (n=6)
Primary end points	2	1	1	2
Subarachnoid hemorrhage	1	0	0	1
Enlargement of aneurysms	1	0	0	1
Annually risks of rupture	.65%	0%	0%	13.16%
Annual rate of primary end point	1.30%	0%	0%	26.32%

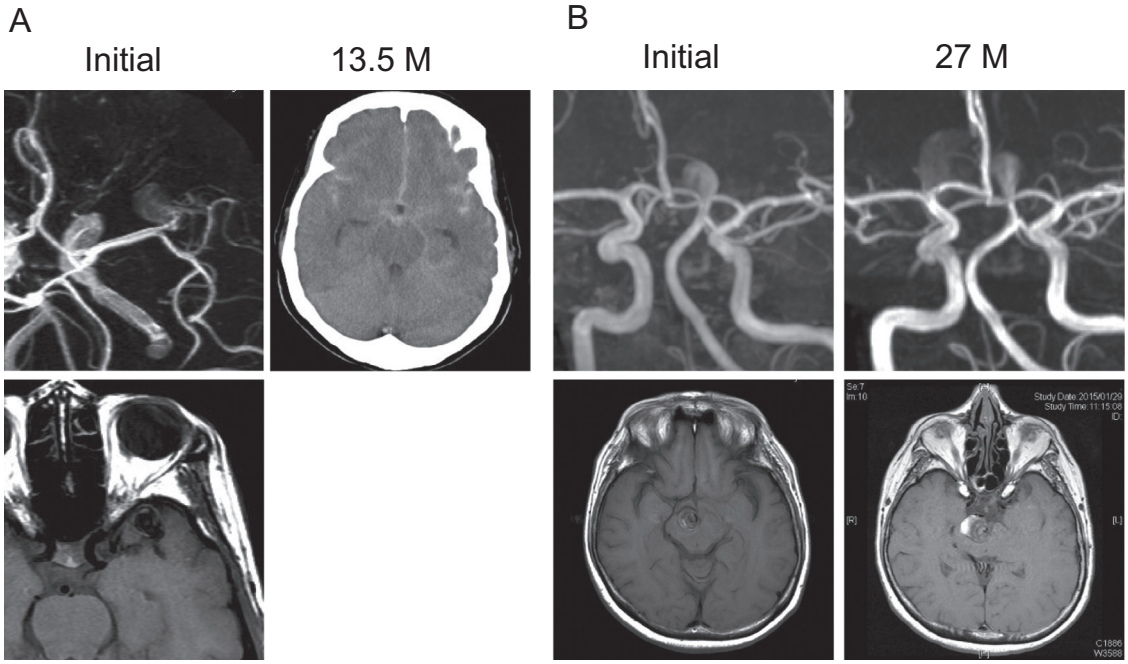

Figure 1. *Ruptured aneurysm and aneurysmal enlargement during follow-up. (A) Case 8. A 77-year-old woman with a 15-mm aneurysm that ruptured in the course of follow-up. Left: Initial MRA and T1-weighted image revealed a thrombosed middle cerebral artery aneurysm. Right: Computed tomography showed subarachnoid hemorrhage 13.5 months postregistration. (B) Case 36. A 50-year-old woman with a 15.8-mm aneurysm at the BA-SCA that enlarged in the course of follow-up. Left: Initial MRA and T1-weighted image revealed a thrombosed aneurysm at BA-SCA. Right: Repeat MRA and T1-weighted images obtained 27 months postregistration showed aneurysm enlargement. Abbreviations: MRA, magnetic resonance angiography; BA-SCA, basilar artery-superior cerebellar artery.*

of unruptured cerebral aneurysms was .9% in Poland (mean aneurysm size, 3.6 mm), .95% in Japan (mean size, 5.7 mm), 1% in Korea (mean size, 4.5 mm), and 1.2% in Finland (median size, 4 mm).[10,13-15] In our eplerenone-treated patients (mean aneurysmal size, 4.6 mm) it was .65%, and no aneurysms smaller than 9 mm ruptured. In UCAS Japan[10] the annual rupture rate for aneurysms measuring 3-4, 5-6, and 7-9 mm were .36%, .50%, and 1.69%, respectively. On the other hand, the rupture rate of our unruptured aneurysms measuring 10-24 mm (13.16%) was higher than the rupture risk reported by UCAS Japan

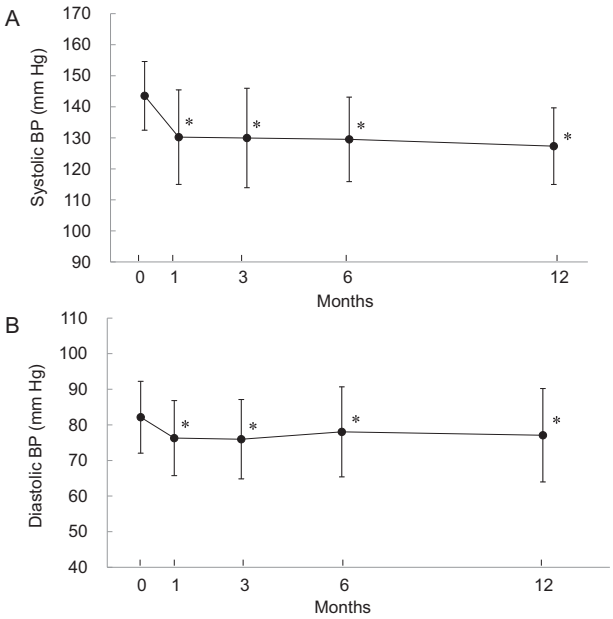

Figure 2. *(A) Systolic and (B) diastolic blood pressure levels at the inception of the study and 1, 3, 6, and 12 months after the start of eplerenone treatment. Each datum represents the mean ± standard deviation. *P < .05 versus baseline.*

Table 5. *Number of patients with adverse events; the data are for all adverse events reported, whether or not they were related to a study end point*

	Adverse event (n, %)	Adverse event leading to study drug withdrawal (n, %)
All events	16 (20)	10 (12.5)
Subarachnoid hemorrhage	1 (1.3)	1 (1.3)
Cerebral infarction	2 (2.5)	0 (.0)
Headache	2 (2.5)	2 (2.5)
Chest pain	1 (1.3)	0 (.0)
Tinnitus	1 (1.3)	1 (1.3)
Seizure	1 (1.3)	1 (1.3)
Hypotension	4 (5.0)	4 (4.9)
Hyperkalemia	3 (3.8)	1 (1.3)
Liver function disorder	1 (1.3)	0 (.0)

(4.37%). These findings suggest that eplerenone does not prevent the rupture of aneurysms larger than 10 mm. The low rupture rate in our series may be ascribable to the small number (n = 4) of aneurysms that measured between 7 and 9 mm in diameter. Nonetheless, as we encountered no ruptures among our eplerenone-treated patients with aneurysms smaller than 5 mm, their rupture risk seemed to be lower than has been reported in the small unruptured intracranial aneurysm verification study (SUAVe study) (.54%)[9] and UCAS Japan (.36%).[10]

Our primary end points included the rupture and enlargement of unruptured aneurysms. In other studies,[9,15] the annual rate of rupture and enlargement of aneurysms smaller than 5 and 7 mm was 2.4% and 7.8%, respectively. Burns et al[16] reported that 10% of unruptured aneurysms with a median diameter of 4.9 mm grew during a median follow-up period of 47 months. Matsumoto et al[11] reported the annual rupture and growth rates were 1.8% and 3.9%, respectively. Our annual rate of primary end-point events was relatively low (1.30% for all aneurysms and 0% for aneurysms smaller than 9 mm), and no aneurysms smaller than 9 mm grew during eplerenone treatment. On the other hand, both large thrombosed aneurysms in our series ruptured or enlarged in the course of follow-up, suggesting that eplerenone does not exert beneficial effects in the presence of such aneurysms.

There are many strategies for the measurement and detection of aneurysmal growth.[9,11,16] Others recorded enlargement when the size of unruptured aneurysms measuring less than 5 mm in diameter increased by at least 2 mm,[9] when the transverse measurement of such aneurysms increased by at least 1 mm, or when aneurysms measuring at least 5 mm grew by at least 2 mm.[16] During the 2.8-year period of our study, there were upgrades in imaging machines, software, and protocols, which could have had an impact on aneurysmal size and shape estimates, and we may have underestimated the rate in enlargement. To avoid the measurement error and false-positive diagnosis for the enlarged aneurysms, we diagnosed enlargement only when aneurysmal growth measured at least 2 mm or when we observed the development of a bleb in the course of follow-up lasting for an average 21.3 months (153.4 aneurysm-years). The period was shorter than in other studies (11,660 aneurysm-years,[10] mean follow-up 41.0 months,[9] or 47 months[16]) and may have affected our low annual rate of primary end-point events. In the future trials we must include patients treated with eplerenone and patients receiving a placebo or other antihypertensive drugs. Based on our 1.3% annual rate of primary end-point events (aneurysmal rupture and enlargement) and the 5.7% annual rupture and enlargement rate reported by Matsumoto et al,[11] 546 patients are required to detect a 4.4 difference (1-sided significance level, 5%; power level, 80%) with the statistical analysis system. Assuming that 10% of patients are lost during follow-up, the sample size will be set at 305 in each group and at 610 for the 2 groups combined.

In animal models of cerebral aneurysms, eplerenone, an angiotensin II type 1 receptor blocker, a phosphodiesterase 4 inhibitor, a peroxisome proliferator-activated receptor-γ agonist, statins, 17β-estradiol, an estrogen receptor β agonist, and an estrogen receptor modulator prevented the formation or rupture of cerebral aneurysms.[2-6,17-22] High-dose pravastatin and simvastatin, on the other hand, promoted their growth and rupture in female rats.[23] In humans, aspirin may lower the incidence of aneurysmal SAH.[24] In our rat model, eplerenone prevented the formation of aneurysms independent from BP; it was more effective than other agents we tested, and it prevented the formation of cerebral aneurysms by reducing oxidative stress, inflammation, the activation of the local renin-angiotensin system, and salt intake.[4] Elsewhere we demonstrated that BP normalization with hydralazine reduced the rate of aneurysmal rupture.[18] Based on these earlier findings we performed a pilot study to examine the efficacy of eplerenone in our aneurysm patients. All patients had a history of hypertension, a risk factor for aneurysmal rupture. While eplerenone reduced their systolic and diastolic BP, we were not able to determine whether antihypertensive or pleiotropic effects of eplerenone were related to the low incidence of primary end-point events in patients with aneurysms smaller than 9 mm in diameter. Earlier studies[9-11,13] that analyzed the risk for the rupture or the enlargement of cerebral aneurysms did not report the rate of hypertensive patients on antihypertensive drugs. It is unclear whether their unruptured aneurysms were treated with antihypertensive drugs.

Our pilot study has some limitations. As 20% of the aneurysms were smaller than 3 mm, we cannot deny bias toward underestimating the rate of aneurysmal rupture and enlargement. As all enrolled patients were hypertensive, some patients with unruptured cerebral aneurysms were ineligible for enrollment on the basis of our inclusion criteria. Also, our open-labeled uncontrolled study did not include eplerenone-untreated controls, so we cannot exclude the effect of confounding factors.

This is the first clinical study to validate the use of eplerenone for the management of cerebral aneurysms, and it presents the first clinical findings on the efficacy of this drug. Based on our observations we think that treatment with eplerenone is feasible in patients with unruptured aneurysms smaller than 9 mm.

Conclusions

Based on our pilot study we suggest that patients with unruptured aneurysms smaller than 9 mm may benefit from treatment with eplerenone and that further studies are warranted to confirm its efficacy and safety in a large-scale, multicenter, double-blind trial.

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