Sildenafil Citrate for Treatment of Erectile Dysfunction in Men With Type 1 Diabetes

Results of a randomized controlled trial

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OBJECTIVE — In the 5–10% of diabetic men with type 1 diabetes, erectile dysfunction (ED) may be a particularly common and unwanted complication. This is the first study focusing exclusively on the effects of sildenafil in men with type 1 diabetes and ED.

RESEARCH DESIGN AND METHODS — A total of 188 patients were entered into a double-blind, placebo-controlled, parallel-group, flexible-dose study and were randomized to receive sildenafil (25–100 mg; $n = 95$) or placebo ($n = 93$) for 12 weeks. Efficacy was evaluated using questions three (Q3; achieving an erection) and four (Q4; maintaining an erection) from the International Index of Erectile Function (IIEF), a global efficacy question (GEQ; "Did treatment improve your erections?"), and a patient event log of sexual activity.

RESULTS — Improvements in mean scores from baseline to end-of-treatment for IIEF Q3 (35.7 vs. 19.9%) and Q4 (68.4 vs. 26.5%) were significant in patients receiving sildenafil compared with those receiving placebo ($P = 0.0001$). Moreover, the percent of improved erections (GEQ, 66.6 vs. 28.6%) and successful intercourse attempts (63 vs. 33%) was significantly increased with sildenafil compared with placebo. Improvements in sexual function were seen irrespective of the degree of ED severity. Adverse events were generally mild to moderate in severity, with headache (20 vs. 8%), flushing (18 vs. 3%), and dyspepsia (8 vs. 1%) reported more often in the sildenafil than in placebo-treated patients.

CONCLUSIONS — Treatment with sildenafil for ED was effective, resulting in an increased percentage of successful attempts at intercourse, and was well tolerated among men with type 1 diabetes.

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According to the World Health Organization, the number of adults with diabetes was ~135 million in 1995, which corresponds to a worldwide prevalence of 4% (1). It is estimated that 5–10% of diagnosed cases are type 1 diabetes (2).

A common complication of diabetes is erectile dysfunction (ED), with an estimated prevalence of 20–85% (ranging from mild to complete ED) (3), which occurs at an earlier age than in nondiabetic men. In the Massachusetts Male Aging Study (4), men with treated diabetes had a 28% age-adjusted prevalence of complete ED (no erections), almost three times higher than the prevalence of complete ED observed in the entire sample of men (10%).

Several studies have shown an increased risk of ED in men with diabetes; however, most information refers to the total male diabetic population, and few studies have presented data specifically for type 1 diabetes (5–8). Although the prevalence of ED in the total diabetic population increases with age, smoking, and poor metabolic control, one study reported that men with elevated BMI and type 1 diabetes showed a significantly higher risk of ED than men with elevated BMI and type 2 diabetes (7). The same study also showed that the age-adjusted prevalence of ED was higher in men with type 1 diabetes (51%) than with type 2 diabetes (37%).

Although the etiology of ED in patients with diabetes is often complex and can be caused by several mechanisms, organic vasculogenic factors appear to be the most frequent cause of ED in men with diabetes (9), with some studies citing an incidence of up to 87% (10). Within vasculogenic ED, the most common etiology is arterial insufficiency, found more frequently in men with type 1 diabetes (73%) than with type 2 diabetes (61%) (11). Moreover, in men with type 1 diabetes, the severity of arterial insufficiency correlated with the presence of smoking, hypertension, and coronary artery disease, although only those with the latter disease showed a statistically significant reduction in penile blood flow compared with men who had type 2 diabetes (11).

Treatment options for men with ED have advanced significantly during the

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Abbreviations: ED, erectile dysfunction; EF, erectile function; GEQ, Global Efficacy Question; IIEF, International Index of Erectile Function.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

past 10–15 years, and a number of approaches have been used for men with diabetes (12–14). However, efficacy and/or long-term satisfaction with most of these treatment options have been suboptimal. Sildenafil citrate (Viagra; Pfizer, New York) has in past studies demonstrated efficacy in men with diabetes (2,7,8,15,16); the aim of this study was to assess its efficacy exclusively in men with type 1 diabetes and ED.

RESEARCH DESIGN AND METHODS

Study design

This was a double-blind, randomized, placebo-controlled, multicenter, parallel-group, flexible-dose study that included 188 patients with type 1 diabetes and ED. Following a 4-week run-in period, during which baseline data on sexual function were collected, patients were randomized to sildenafil (50 mg) or matching placebo and entered a 12-week double-blind treatment period with follow-up visits after 2, 4, 8, and 12 weeks of treatment. Dosage adjustments to 100 or 25 mg sildenafil or matching placebo were made according to efficacy and tolerability.

Inclusion criteria

This study included male patients of age 18 years or older with a clinical diagnosis of ED of more than 6 months' duration and in a stable relationship with a female partner of more than 6 months' duration. Patients had a clinical diagnosis of type 1 diabetes of at least 1 year's duration as defined by the National Diabetes Data Group (17) and had required insulin within 1 month of diagnosis. Diabetes had to be generally stable for 6 months before study entry, with HbA_{1c} levels $<11\%$.

Major exclusion criteria

Patients with genital anatomical deformities; a major psychiatric disorder; a history of alcoholism or substance abuse; ED as a result of spinal cord injury; a history of myocardial infarction, stroke, heart failure, or unstable angina within the past 6 months; or a history of hypotension or who were taking nitrates were excluded. Also excluded were patients who exhibited one of the following: HbA_{1c} levels $\geq 11\%$, recurrent hypoglycemic episodes, severe autonomic neuropathy, diabetes secondary to pancreatic damage, Cushing's syndrome, or acromegaly.

Table 1—*Demographics of study subjects*

	Placebo	Sildenafil
n	93	95
Mean age (years)	47.8 (27–66)	46.8 (25–69)
Mean weight (kg)	76.6 (53–139)	79.7 (56–118)
Ethnicity (%)		
White	91.4	95.8
Black	2.2	0
Asian	6.5	4.2
Country (%)		
Argentina	14.0	18.9
Australia	34.4	32.6
Brazil	4.3	5.3
Canada	11.8	9.5
Italy	12.9	10.5
Spain	3.2	4.2
Thailand	4.3	4.2
Turkey	15.1	14.7
Smoking status (%)		
Ex-smoker	32.3	36.8
Never smoked	25.8	40.0
Smoker	41.9	23.2
ED etiology (%)		
Organic	65.6	78.9
Mixed	33.3	21.1
Psychogenic	1.1	0
Mean time since diagnosis of ED (years)	5.8 (0.7–26.8)	4.9 (0.6–18.7)
Mean treatment duration (days)	77.1 (1–134)	82.4 (15–141)
Previous ED treatment (%)		
Total	20.4	28.4
Intracavernosal injections	14.0	18.9
Intraurethral alprostadil	0	2.1
Vacuum pump	2.1	2.1
Sildenafil	4.3	3.1
Number of doses taken per month	10.65 ± 5.9	11.48 ± 6.1
Last dose taken (%)		
50 mg	—	28.4
100 mg	—	71.6
Mean time since diagnosis of diabetes (years)	20.9 (2.1–56.3)	19.9 (1.1–48.1)
Baseline HbA_{1c} levels (%)	8.6 (5.9–12.9)	8.5 (5.6–10.9)
Diabetes treatment (%)		
Insulin	100	100
Oral antidiabetic	2.1	3.2
Concomitant cardiovascular disease (%)	38.7	33.6
Hypertension	33.3	29.5
Peripheral vascular disease	5.3	1.0
Other	0	3.1

Data are *n* (range), %, or mean ± SD.

Randomization and blinding

A randomization list was generated using random permuted blocks via a computer algorithm and a pseudo-random number generator. The list indicated, for each bottle number, the drug assigned to the corresponding study medication bottle. The patient was assigned a screening number at visit one (screening) and, if eligible for participation, was then assigned a randomization number at visit two (baseline). The investigator was provided a sealed copy of the randomization codes

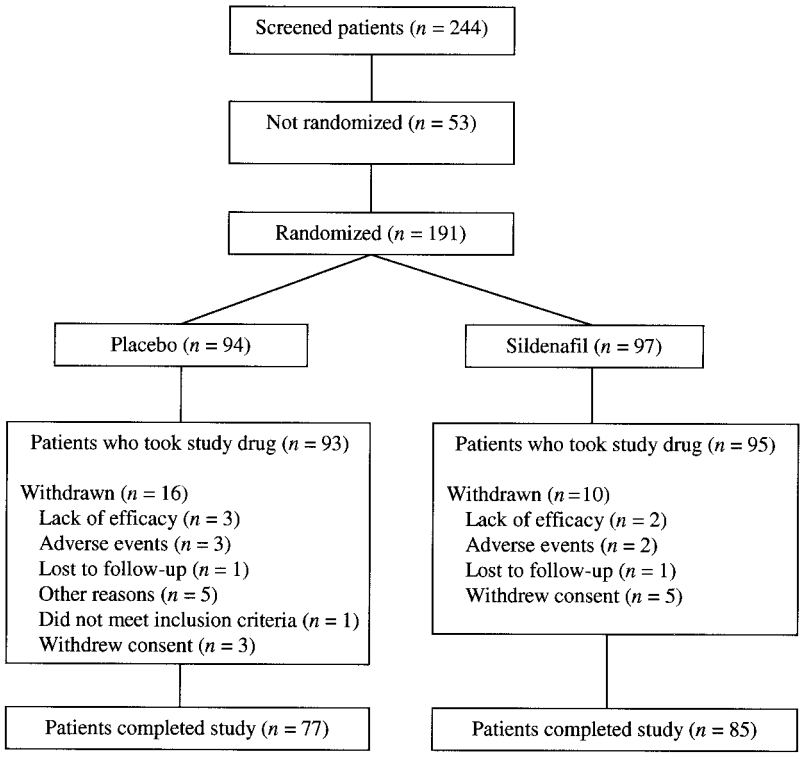

Figure 1—*Flow diagram of patient disposition.*

and was instructed to break the treatment code only in the event of an emergency.

Study drug

Sildenafil and placebo, identical in packaging and appearance, were to be taken as needed ~1 h before anticipated sexual activity, not more than once daily. Patients were instructed not to consume more than two units of alcohol before sexual activity (one unit of alcohol equals one glass of wine, one half-pint of beer, or one measure of spirits). All patients started at a 50-mg dose of sildenafil (n = 95) or matching placebo (n = 93), with the option of adjusting the dosage to 100 or 25 mg, based on efficacy and tolerability.

Study evaluations

Primary efficacy assessment

The primary efficacy assessment consisted of responses to question three (Q3; achieving an erection) and question four (Q4; maintaining an erection) from the International Index of Erectile Function (IIEF) (18). These were recorded at weeks 0 and 12. Answers were scored from 1 (almost never/never) to 5 (almost always/always), with 0 indicating no sexual activity.

Secondary efficacy assessment

The secondary efficacy assessments were as follows:

1. Global Efficacy Question (GEQ): At week 12, this question asked, "Has the treatment you have been taking over the past 4 weeks improved your erections?"

2. IIEF domains: The IIEF consists of 15 questions grouped into five different domains:

Erectile Function: Questions 1–5 and 15 (score range, 1–30)

Intercourse Satisfaction: Questions 6–8 (score range, 0–15)

Orgasmic Function: Questions 9 and 10 (score range, 0–10)

Sexual Desire: Questions 11 and 12 (score range, 2–10)

Overall Satisfaction: Questions 13 and 14 (score range, 2–10).

3. Event Log of Erectile Function: Recorded from pretreatment 4-week run-in period through week 12 of treatment; completed by patients each time they engaged in sexual activity. This asked about response to study drug and success of intercourse attempts. Intercourse success rates were derived from these event log entries.

Stratification of efficacy results

Primary and secondary efficacy results were stratified by patients' *1*) ED severity, which was categorized as mild/moderate or severe based on erectile function (EF) domain scores of 11–25 or ≤10, respectively, from the IIEF; *2*) level of metabolic control, defined as baseline HbA_{1c} levels of <8% (adequate) or ≥8% (poor); *3*) smoking status, defined as current smokers, ex-smokers, or those who never smoked; and *4*) presence of cardiovascular complications, defined as a history of hypertension, ischemic heart disease, or peripheral vascular disease.

Statistical evaluation

Each of the primary efficacy variables (IIEF Q3 and Q4) was analyzed using ANCOVA models containing treatment group and the following covariates: country, etiology of ED, smoking status, age, duration of ED, duration of diabetes, and baseline value. Treatment group, country, etiology of ED, and smoking status were categorical variables, whereas age, duration of ED, duration of diabetes, and baseline value were continuous variables that were centered before inclusion into the analysis. Significant results at the 5% level (using two-sided tests) in both analyses were required to demonstrate efficacy over placebo. The GEQ was analyzed using a logistic regression model with terms for treatment group, country, etiology of ED, smoking status, age, duration of ED, and duration of diabetes. The percent of successful intercourse attempts was

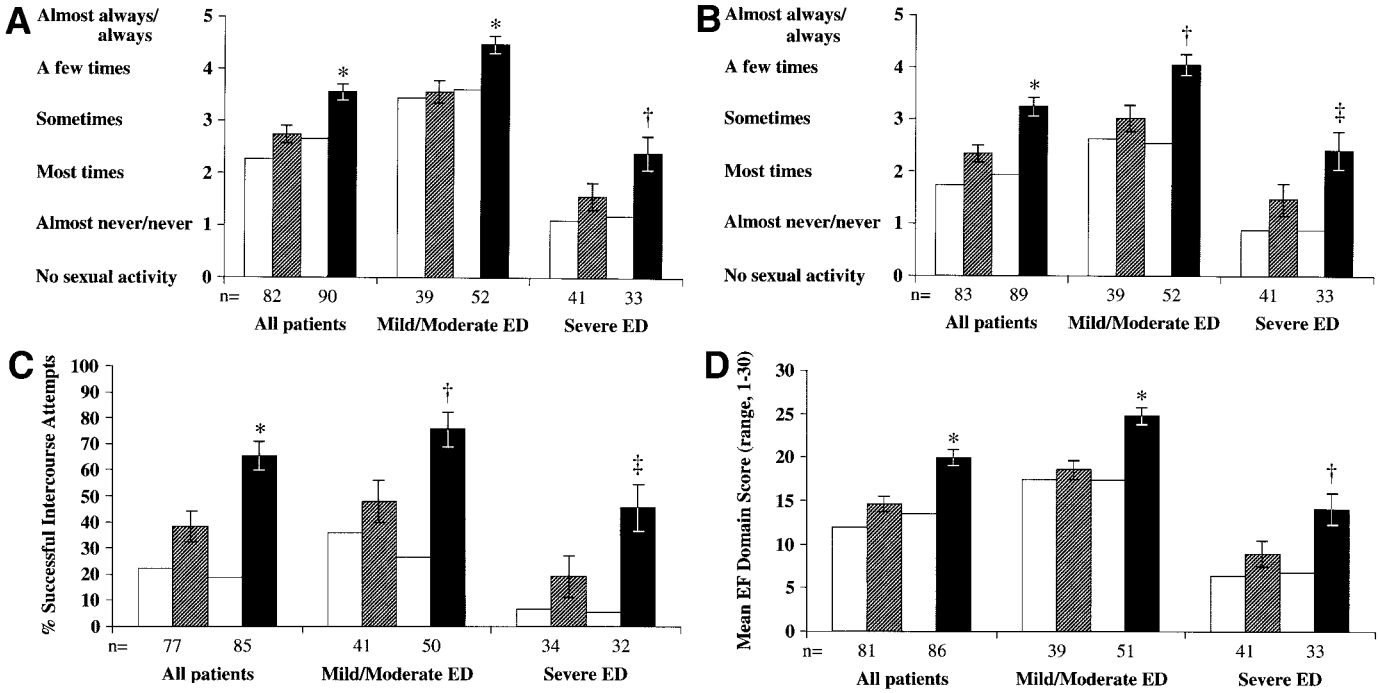

Figure 2—*After 12 weeks of treatment, the mean scores for IIEF Q3* (A; *ability to achieve an erection) and IIEF Q4* (B; *ability to maintain an erection) were significantly improved in patients receiving sildenafil compared with those receiving placebo. Answers were scored from 1 (almost never/never) to 5 (almost always/always), with 0 indicating no sexual activity. The number of successful intercourse attempts (C), as derived from patient-completed event logs, was also significantly greater in patients receiving sildenafil compared with those receiving placebo. Mean scores of the EF domain* (D) *were significantly higher in patients receiving sildenafil compared with the placebo group.* □, *baseline;* ▨, *placebo;* ■, *sildenafil.* A: **P = 0.001; †P < 0.05;* B: **P = 0.001; †P < 0.001; ‡P < 0.05;* C: **P = 0.0001; †P < 0.001; ‡P < 0.005;* D: **P = 0.001; †P < 0.05.*

tested at the 5% significance level and was two-sided.

Ethics

Informed written consent was obtained from each patient, and the study was approved by the local ethics committee at each participating center.

RESULTS — The baseline characteristics of men with ED randomized to placebo or sildenafil were largely similar with respect to age, race, ED etiology, duration of ED and diabetes, metabolic control, concomitant illnesses, and previous ED treatment received (Table 1). There were twice as many patients with HbA_{1c} levels ≥8% (n = 125) than with levels <8% (n = 63). Patient disposition during the course of the study is shown in Fig. 1.

Efficacy

After 12 weeks, there were marked improvements in the ability to achieve and maintain an erection, with the mean scores for IIEF Q3 (Fig. 2*A*) and Q4 (Fig. 2*B*) significantly higher (33 and 48%, respectively) in the sildenafil group (3.61 ± 0.48 and 3.25 ± 0.52; $P \leq 0.001$) compared with the placebo group (2.71 ± 0.47 and 2.19 ± 0.5). Patients with mild/moderate ED achieved higher final scores for Q3 and Q4 (4.48 and 4.05) than patients with severe ED (2.39 and 2.41) but also started with approximately three times higher baseline scores. The percent of successful intercourse attempts (Fig. 2*C*) was significantly higher in the sildenafil group ($P < 0.051$), with twice as many patients answering in the affirmative compared with the placebo group, irrespective of ED severity; however, patients with severe ED had fewer overall successful attempts compared with men who had mild/moderate ED. Positive responses to the GEQ ("Has treatment improved your erections?") were higher in the sildenafil group, with 66% of patients with mild/moderate ED responding in the affirmative compared with 29% of patients taking placebo. Patients with severe ED (sildenafil, n = 33; placebo, n = 41) reported a lower percent of improved erections (sildenafil, 30%; placebo, 10%).

After 12 weeks of sildenafil treatment, the EF domain showed on average a 6-point increase in the mean score over placebo, irrespective of the ED severity (Fig. 2*D*). As observed for the other efficacy parameters, men with mild/moderate ED achieved a higher overall score compared with men with severe ED (Fig. 2*D*).

Stratification of efficacy by metabolic control, smoking status, and presence of cardiovascular complications. When efficacy was analyzed for patients (subject numbers variable across efficacy parameters) with baseline HbA_{1c} levels <8% (n = 54–57) or ≥8% (n = 108–117), no significant differences were found in end-of-treatment scores for any of the efficacy parameters, indicating that sildenafil was efficacious even in patients with poorly controlled diabetes. Similarly, sildenafil efficacy was maintained in patients who had never smoked (n = 55–57) or were ex-smokers (n = 55–62) as well as in those currently smoking (n = 53–54), with no statistical differences in end-of-treatment scores between groups. Finally, patients with cardiovascular complications (n = 56–61) did equally well with sildenafil when compared with the overall

Table 2—*Treatment-related adverse events*

	Placebo	Sildenafil
Randomized patients	94	97
Evaluable patients	93	95
Completed study	77	85
Number of AEs	25	67
Patients with AEs	13	34
Patients with serious AEs	1	0
Patients with severe AEs	1	5
Patients discontinued due to AEs	2	1
Patients discontinued due to insufficient clinical response	3	2
Adverse events		
Headache (%)	7.5	20.0
Flushing (%)	3.2	17.9
Dyspepsia (%)	1.1	8.4
Visual disturbances (%)	2.2	2.1

Data are *n* or %, as indicated. AE, adverse events.

patient group ($n = 162–174$) for all efficacy parameters.

Adverse events

The most common treatment-related adverse events included headache, flushing, and dyspepsia; all other adverse events occurred in <5% of patients (Table 2). All events were transient and mild to moderate in nature, and the rate of discontinuations because of these events was low (2.2% and 1.1% for sildenafil and placebo, respectively).

CONCLUSIONS — Men with diabetes have an approximate threefold higher risk for ED than men without diabetes (4). In the present study, sildenafil (50–100 mg) was an effective oral therapy for men with type 1 diabetes; >66% of patients reported improved erections (compared with 29% in the placebo group), and the number of successful intercourse attempts with sildenafil (63%) was significantly higher compared with placebo (33%). These data are in agreement with an earlier study, where sildenafil was shown to be an effective and well-tolerated treatment in a group of 268 men with ED and concomitant diabetes (type 1 and 2) (2). In this patient group, efficacy of sildenafil was independent of age, duration of ED, and duration of diabetes, and erections were improved in 56% of patients receiving sildenafil compared with 10% of patients taking placebo. Similarly, a recent study in 219 patients exclusively with type 2 diabetes demonstrated that sildenafil was well tolerated and effective in improving ED in this patient group (65% of patients reported improved erections compared with 11% in the placebo group), even in cases with poor glycemic control and chronic complications (16). Thus, the current study demonstrated similar efficacy, although the improvement in the placebo group was larger.

It is well documented that in comparison with other disease-specific populations, the efficacy of sildenafil is lower in men with diabetes. For example, Goldstein et al. (19) reported improved erections in 77–88% of men with broad spectrum ED receiving sildenafil. Similarly, men with spinal cord injury (20) or depression (21) demonstrated high response rates to sildenafil (78 and 69%, respectively). The reason for poorer efficacy in the diabetic population is thought to be the multifactorial nature of the disease. Poor vascular blood supply to the penile arteries as a result of macrovascular disease and atherosclerotic lesions (22), reduced production of nitric oxide and cyclic guanosine monophosphate in the corpus cavernosum as a result of advanced glycosylation product accumulation (23), and impaired neurogenic and endothelium-dependent relaxation of penile arteries (24) all contribute to diabetes-associated ED. Moreover, concomitant medications frequently used in diabetic patients, such as antihypertensive agents (β-blockers, calcium channel antagonists) (25) and lipid-lowering drugs (fibrates, statins) can contribute to a reduced efficacy of sildenafil (26).

Patients with type 1 diabetes are often relatively young and may thus benefit from a well-tolerated treatment regimen. The drop-out rate with sildenafil treatment is low compared with that for other treatments for ED, such as intracavernosal injections, which have a high attrition rate, pain with injection, or nodule formation (27), and penile implants, which may require implant removal because of infection (28). However, because sildenafil does not resolve ED in all patients with diabetes, each patient should be given information on other treatment options that have shown efficacy for this population.

The efficacy and safety of sildenafil have been assessed from more than 11,000 patient-years of observation in controlled clinical trials, many of which focused on and/or included men with diabetes (29). The safety profile of sildenafil in this study of men with ED and type 1 diabetes is in agreement with previous reports in which the most common adverse events associated with use of sildenafil in flexible-dose studies were headache (20%), flushing (18%), dyspepsia (8%), and visual disturbances (2%), all consistent with the known pharmacological effects of the drug (30). These effects were generally transient and mild to moderate in nature, and the rate of discontinuations because of these events was similar for patients receiving placebo (2.2%) or sildenafil (1.1%). All clinical studies conducted so far have shown that the incidence of adverse events and the rate of discontinuations attributed to them are similar in patients with diabetes compared with patients without diabetes (~2%) (31).

Adverse effects on metabolic control are an important consideration when treating patients with diabetes. There is no indication from clinical trial data that sildenafil adversely affects blood glucose levels in patients with diabetes; furthermore, in a previously published study in 21 men with type 1 or 2 diabetes, no clinically significant changes in laboratory test results were observed, suggesting that sildenafil did not impair metabolic control (15).

In summary, ED is known to occur with greater frequency in patients with type 1 diabetes than in the general population (32). It is thus encouraging that treatment with sildenafil was able to improve erections and was well tolerated in men with ED and concomitant diabetes in

this study, irrespective of ED severity, level of metabolic control, smoking status, or the presence of cardiovascular complications. Therefore, unless there is a contraindication to the use of sildenafil, it would be reasonable for sildenafil to be considered the initial therapeutic choice for patients with ED and concomitant type 1 diabetes.

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