Potent Reduction of Apolipoprotein B and Low-Density Lipoprotein Cholesterol by Short-Term Administration of an Antisense Inhibitor of Apolipoprotein B

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Background—Apolipoprotein B (apoB) is an important structural component of low-density lipoprotein cholesterol (LDL-C) and plays a key role in LDL-C transport and removal. Reduction in apoB synthesis is expected to reduce circulating LDL-C, a proven risk factor of cardiovascular disease. In the present study, we describe the outcome of the first-in-humans study on the safety and efficacy of an antisense oligonucleotide inhibitor of apoB.

Methods and Results—This study was a double-blind, randomized, placebo-controlled, dose-escalation investigation conducted at a single site in 36 volunteers with mild dyslipidemia. The study utilized an initial single dose of 50 to 400 mg of ISIS 301012, a 20-mer oligonucleotide, followed by a 4-week multiple-dosing regimen with the same assigned dose. Safety was assessed by the incidence, severity, and relationship of adverse events to dose. Efficacy was determined by changes in serum apoB and LDL-C relative to baseline and placebo. The most common adverse event was erythema at the injection site (21 of 29 subjects). ApoB was reduced by a maximum of 50% ($P_{<0.002}$) from baseline in the 200-mg cohort. This decrease in apoB coincided with a maximum 35% reduction of LDL-C ($P_{<0.001}$). LDL-C and apoB remained significantly below baseline ($P_{<0.05}$) up to 3 months after the last dose.

Conclusions—Administration of an antisense oligonucleotide to human apoB resulted in a significant, prolonged, and dose-dependent reduction in apoB and LDL-C. Although injection-site reactions were common, adherence to protocol was unaffected. (Circulation. 2006;114:1729-1735.)

Key Words: lipoproteins ▪ apolipoproteins ▪ cholesterol ▪ lipids ▪ inhibitors ▪ trials

Low-density lipoprotein cholesterol (LDL-C) is a proven risk factor for atherogenesis and constitutes the primary target of lipid-lowering therapy. The role of LDL-C in atherogenesis is based on information from basic research, animal studies, epidemiological surveys, hereditary dyslipidemia, and, most importantly, intervention studies that use cardiovascular mortality and morbidity as primary end points. A log-linear relationship exists between LDL-C and cardiovascular event rates, even at lower LDL-C levels. As a result, target LDL-C levels represent the core of cardiovascular disease treatment guidelines.1

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The mainstay of LDL-C management is statin-based therapy, and statins are the most widely prescribed drug class in the world. Statins, however, do not provide the entire solution. Even with statin therapy, the majority of cardiovascular events are not prevented. Although statin trials in tens of thousands of patients have shown positive results with regard to cardiovascular event rates, the overall reduction has only been 30% in spite of LDL-C reductions up to 40%.2–7 As a result, a significant medical need persists. This need has directed the search for other LDL-C-lowering strategies that represent novel mechanisms of action, show potent LDL-C lowering, and can be effectively combined with statins.

Apolipoprotein B (apoB), produced in the liver, constitutes an essential structural and receptor-binding component of all atherogenic lipoproteins, including LDL-C and its metabolic precursors, intermediate-density lipoprotein and very-low-density lipoprotein (VLDL).8 ApoB may be highly predictive of cardiovascular risk in certain populations.9

High apoB levels indicate abundant atherogenic particles, which suggests a medical need for additional apoB-lowering strategies that may be effectively combined with statins. Direct inhibition of apoB production may be an attractive therapeutic strategy.10,11 Studies in a variety of animal models have previously shown that antisense-mediated reduction of apoB messenger RNA leads to reduced levels of apoB and LDL-C.12,13
ISIS 301012 (ISIS Pharmaceuticals, Carlsbad, Calif) is a 20-mer oligonucleotide, complementary to the coding region for human apoB mRNA. This antisense oligonucleotide is a second-generation antisense inhibitor, characterized by greater potency, longer half-life, and reduced potential for nonspecific side effects than earlier chemistries. In the present study, we describe a significant apoB-lowering effect of this antisense inhibitor of apoB for the first time in humans.

Methods

Subject Criteria

Study subjects were healthy volunteers from 18 to 65 years of age with fasting cholesterol <300 mg/dL and no concomitant medical illness or laboratory abnormalities. The study was approved by the local institutional Ethics Committee. All subjects gave informed consent. The study was performed in compliance with the standards of Good Clinical Practice and the Declaration of Helsinki (October 2000).

Study Drug

ISIS 301012 is a 20-nucleotide phosphorothioate oligonucleotide composed of five 2'-O-(2-methoxyethyl) modified ribonucleosides (2'-MOE) at the 3' and 5' ends with ten 2'-deoxynucleosides in between. The sequence of ISIS 301012 is 5'-GGCTCAGTCGTT-GGACC-3', where the italicized bases are 2'-MOE modified ribonucleosides, and all cytosines are methylated at the C5 position. ISIS 301012 was provided in sterile, unpreserved, buffered saline (250 mg/mL, pH 7.9) by Isis Pharmaceuticals.

Study Design

The study was designed as a placebo-controlled, double-blind, dose-escalation study with a final randomization ratio of 4:1 for active drug to placebo (Figure 1). The randomization list was prepared by the study center. All subjects, monitors, and site personnel related to the study, except for the pharmacist who prepared the study drug, were blinded throughout the study. Study end points included the safety and tolerability of ISIS 301012, drug pharmacokinetics, and efficacy. The study consisted of a single, subcutaneous dose of 50, 100, 200, or 400 mg of ISIS 301012, followed by a 4-week observation period (Figure 2). Subjects then entered the multiple-dose phase of the study at the same assigned dose. The multiple-dose phase was characterized by 3 alternate-day intravenous infusions of antisense designed to reach ~70% of hepatic tissue steady state levels in the first week (internal communication, ISIS study No. 301012-AS02PK). Thereafter, 3 weekly subcutaneous doses at the same assigned dose, ranging from 50 to 400 mg of drug, were administered. Subjects were followed up for a maximum of 12 weeks or until total cholesterol levels had returned to ≥90% of baseline, whichever occurred first.

Safety Monitoring

The safety and tolerability of ISIS 301012 were assessed by determining the incidence, severity, and dose relationship of adverse events.
events and changes in laboratory evaluations. Laboratory evaluations included routine hematology, blood chemistries, coagulation parameters, complement split products C5a and Bb, and urinalysis. Blood pressure and heart rate were monitored at intervals before and after dosing. In the multiple-dose portion of the study, dosing of a given cohort commenced only after the single-dose component of the next-highest dose was completed without clinically significant adverse effects.

**Pharmacokinetic Analysis**

Pharmacokinetic properties were assessed after the single- and multiple-dose administration periods by noncompartmental methods. Plasma concentrations were measured at PPD Development (Richmond, Va). Terminal elimination half-life was estimated from first order input and biexponential elimination equations from 3 days to 3 months after the final dose. Trough area under the curve was calculated from day 25 to day 55 with the linear trapezoidal rule.

**Lipid and Lipoprotein Analysis**

Fasting blood samples were analyzed for apoB, total cholesterol, VLDL, LDL-C, high-density lipoprotein (HDL), and triglycerides at baseline, followed by analysis on days 1, 8, 15, 22, and 25 and every 2 weeks thereafter. ApoB levels were determined by an immunoturbidimetric method (MDS PharmaServices, Belfast, Ireland). Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were measured with standard enzyme-based colorimetric assays (MDS PharmaServices; and LipoScience, Raleigh, NC). Lipoprotein subclass concentrations were determined by nuclear magnetic resonance spectroscopy (LipoScience).

**Statistical Analysis**

Descriptive statistics for apoB and LDL-C data are presented as dose versus time. Baseline was defined as the observation before first dose for each subject. Percent change from baseline for each of the dose groups was compared with the pooled placebo group with a nonparametric repeated-measurements method of analysis. Correlation coefficients were determined with a descriptive linear regression model. Software used for the analyses was SAS version 8.2 (SAS Institute, Cary, NC). The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

**Subject Demographics**

A total of 36 subjects were enrolled in the study, 18 men and 18 women who ranged in age from 30 to 64 years. Fasting total cholesterol levels at baseline ranged from 174 to 290 mg/dL with a mean of 219 (±27) mg/dL. LDL-C levels at baseline ranged from 91 to 173 mg/dL with a mean of 128 (±22) mg/dL. Demographics and baseline lipid characteristics of the study subjects are summarized in Table 1.

**Safety and Tolerability**

No drug-related serious adverse events were reported in the study. Injection-site reactions were the most common adverse event (Table 2), occurring in 21 (72%) of 29 subjects who received ISIS 301012. These reactions were typically described as areas of mild, painless erythema that presented within 24 hours of subcutaneous injection and resolved spontaneously after a median of 5 days.

Four (14%) of the 29 treated subjects had elevated alanine aminotransferase (ALT) levels related to the study drug. These elevations were asymptomatic and were not associated with elevated bilirubin or prothrombin time prolongation. One of these 4 subjects had transaminase elevations >3 times the upper limit of normal. This subject was asymptomatic; other measures of liver function were normal, and ALT returned to normal within a 2-week period. Treated subjects who completed the study (n=26) showed a direct correlation between maximum ALT and maximum apoB reduction (r=0.58, P=0.002).

No abnormal changes in vital signs, ECGs, or urinalyses were observed, and there was no evidence of steatorrhea. No unanticipated safety issues or unexpected drug intolerabilities were otherwise encountered.

**Pharmacokinetic Profile of the Multiple-Dose Phase**

Plasma pharmacokinetics revealed dose-dependent maximum plasma concentrations that ranged from 4.8 to 21.5 μg/mL (50 to 200 mg) at the end of the 2-hour intravenous infusion. Maximum plasma concentration after subcutaneous administration was also dose-dependent but lower than the equivalent intravenous doses, ranging from 1.0 to 2.7 μg/mL. Intravenous and subcutaneous routes of administration showed a similar plasma area under the curve. The terminal elimination half-life ranged from 23 (±1) days in the 50-mg group to 31 (±11) days in the 200-mg group.

**Efficacy Outcome**

Administration of ISIS 301012 resulted in a dose-dependent, prolonged reduction of apoB (Figure 3A; Table 3). The 200-mg dose group (n=8) showed a maximum apoB change from baseline of 50% (P=0.002), 72 hours after the last dose.

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**TABLE 1. Subject Demographics and Baseline Lipid Characteristics***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=7)</th>
<th>50 mg (n=8)</th>
<th>100 mg (n=8)</th>
<th>200 mg (n=9)</th>
<th>400 mg (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>3:4</td>
<td>4:4</td>
<td>6:2</td>
<td>3:6</td>
<td>2:2</td>
</tr>
<tr>
<td>Age, y</td>
<td>57±3</td>
<td>45±11</td>
<td>48±9</td>
<td>58±6</td>
<td>51±9</td>
</tr>
<tr>
<td>ApoB</td>
<td>102±22</td>
<td>101±20</td>
<td>105±22</td>
<td>101±17</td>
<td>113±27</td>
</tr>
<tr>
<td>LDL-C</td>
<td>131±27</td>
<td>126±24</td>
<td>131±24</td>
<td>123±16</td>
<td>133±23</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>51±19</td>
<td>59±18</td>
<td>49±11</td>
<td>53±13</td>
<td>59±17</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>216±33</td>
<td>221±33</td>
<td>218±24</td>
<td>210±18</td>
<td>239±30</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>104±90</td>
<td>95±29</td>
<td>105±47</td>
<td>103±44</td>
<td>127±57</td>
</tr>
</tbody>
</table>

M:F indicates male:female.

*Data are presented as mean±SD. Lipid and lipoprotein values are presented in mg/dL.
Concomitant with a reduction in apoB, a prolonged and dose-dependent reduction of LDL-C was also observed (Figure 3B; Table 3). The maximum percent reduction of LDL-C in the 200 mg cohort was 35% ($P<0.001$). ApoB and LDL-C levels remained below baseline for 90 days after treatment in 6 of 8 subjects of the 200-mg cohort. There was direct correlation between exposure to drug (by plasma trough area under the curve) and percentage of reduction in apoB and LDL-C ($r=0.67$, $P=0.0002$) at the end of the treatment period (day 25).

Total cholesterol showed a maximum reduction of 27% in the 200-mg dose group ($P=0.002$) and 40% in the 400-mg group. Dose-dependent but variable reductions in total triglycerides and VLDL were also observed, with maximum reductions of 27% and 30% in the 200-mg dose group and

### Table 2. Adverse Events Considered Related to Study Medication by Dosage

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=7)</th>
<th>50 mg (n=8)</th>
<th>100 mg (n=8)</th>
<th>200 mg (n=9)</th>
<th>400 mg (n=4)</th>
<th>All Treated (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site reaction</td>
<td>0</td>
<td>5 (62)</td>
<td>4 (50)</td>
<td>8 (89)</td>
<td>4 (100)</td>
<td>21 (72)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
<td>7 (78)</td>
<td>0</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (11)</td>
<td>2 (50)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (14)</td>
<td>1 (12)</td>
<td>1 (12)</td>
<td>3 (33)</td>
<td>0</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1 (12)</td>
<td>1 (12)</td>
<td>1 (11)</td>
<td>2 (50)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Muscle fatigue</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (75)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (22)</td>
<td>2 (50)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (75)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (11)</td>
<td>2 (50)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

$AE$ indicates adverse event. Values are n (%).

Figure 3. Dose-dependent effect of ISIS 301012 on (A) apoB and (B) LDL cholesterol levels, presented as mean percent change from baseline. Time period ranges from day 1 (first intravenous infusion) to day 83. Arrows indicate dosing days. Baseline is defined by measure before initial treatment of each subject. Bars represent ± SEM.
TABLE 3. ApoB and LDL-C Levels by Mean Percent Change Relative to Baseline*

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Placebo (n=7)</th>
<th>50 mg (n=8)</th>
<th>100 mg (n=8)</th>
<th>200 mg (n=8)</th>
<th>400 mg (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 25</td>
<td>−6.6±16.2</td>
<td>−12.6±12.4</td>
<td>−15.6±12.8</td>
<td>−50.2±17.3</td>
<td>−43.8</td>
</tr>
<tr>
<td>Day 39</td>
<td>2.3±20.9</td>
<td>−13.5±9.0</td>
<td>−22.2±15.0</td>
<td>−38.5±18.0</td>
<td>−49.5</td>
</tr>
<tr>
<td>Day 55</td>
<td>−10.6±29.2</td>
<td>−14.3±13.3</td>
<td>−27.7±14.7</td>
<td>−42.4±14.4</td>
<td>−47.4</td>
</tr>
<tr>
<td>Pt</td>
<td>0.12</td>
<td>0.05</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 25</td>
<td>−5.5±19.1</td>
<td>3.4±16.0</td>
<td>−18.5±11.1</td>
<td>−30.6±15.9</td>
<td>−43.7</td>
</tr>
<tr>
<td>Day 39</td>
<td>−0.8±13.0</td>
<td>−3.7±15.8</td>
<td>−18.6±13.5</td>
<td>−35.2±19.3</td>
<td>−44.2</td>
</tr>
<tr>
<td>Day 55</td>
<td>−1.4±14.7</td>
<td>−5.9±8.2</td>
<td>−20.0±17.4</td>
<td>−33.9±18.5</td>
<td>−40.7</td>
</tr>
<tr>
<td>Pt</td>
<td>0.96</td>
<td>0.06</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD.
†P values correspond to the comparison of each dose group to placebo by analysis of repeated measures.

43% and 60% in the 400-mg group, respectively. No significant changes were observed in HDL cholesterol.

Discussion

The present study is the initial demonstration in humans that antisense inhibition of apoB leads to reductions of up to 50% in apoB and 35% in LDL-C. These findings imply the possibility of apoB and LDL-C reductions in patients that may translate into significant reductions in cardiovascular events.

The LDL-C reductions observed in the present study are in range similar to that in the 80-mg atorvastatin groups in both the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering)\(^\text{17}\) and the TNT (Treating to New Targets)\(^\text{18}\) trials. This suggests a potential role for ISIS 301012 in the clinic.

Double-stranded synthetic small interfering RNAs (siRNAs) are also absorbed by the liver.\(^\text{13,22}\) Although siRNA has demonstrated apoB reduction in animal models, it has not been used in humans for this purpose. Unlike the RNase H–mediated antisense inhibitors that are administered in saline, siRNAs currently require enhanced delivery methods (eg, cholesterol conjugation,\(^\text{13}\) lipid encapsulation,\(^\text{22}\) or hydrodynamics\(^\text{21}\)) to achieve pharmacology. Lack of in vivo efficacy in the absence of such methods has been attributed to degradation by nucleases, insufficient distribution to plasma proteins, and inefficient cellular uptake of these larger and more negatively charged antisense inhibitors.

Second-generation 2'MOE modified antisense inhibitors are more resistant to nuclease activity than the earlier chemistries. This enhanced stability results in slower tissue clearance, as reflected by longer terminal elimination half-lives.\(^\text{19–21}\) In the clinical setting, the terminal elimination half-life for ISIS 301012 was ≈31 days, which translates to a protracted pharmacological effect of 12 weeks in the majority of the subjects in the higher dose groups. This extended duration of action raises the potential for effective yet infrequent dosing.

Mild erythema at the site of subcutaneous injections was the most common side effect observed in the present study. This finding has been described in earlier human trials, and although common, it had no impact on adherence to protocol. Investigation into the underlying mechanism and methods of mitigation is in progress.

Elevated serum ALT levels were also observed during the course of study, but these elevations did not produce symptoms and were not accompanied by abnormalities in other liver function tests. The basis of the elevated ALT levels in subjects treated with ISIS 301012 is unknown; however, previous experience with other classes of lipid-lowering agents has suggested that the pharmacology of lipid lowering per se may be associated with hepatic transaminase eleva-
increased in the 3p21 genotype, in which apoB is normal in quantitatively abnormal. Hepatic triglyceride, however, is not increased in the 3p21 genotype, in which apoB is normal in character and only quantitatively reduced.30,31

Similar to the 3p21 familial hypobetalipoproteinemia phenotype, but in contrast to studies on small-molecule inhibitors of the microsomal triglyceride protein transfer protein,32 hepatic steatosis has not been observed in preclinical animal model studies of antisense-mediated reduction of apoB production.12 Assessment of hepatic triglyceride content in humans treated with ISIS 301012 is currently being studied.

Several aspects of the present study merit caution. First, the population in this study may be different from the patient population requiring pharmacological intervention for long-term lipid lowering. Second, although the statistics are convincing, the sample size in the higher dose range is limited. A small sample size can mask side effects or potentially overestimate efficacy or duration of effect. Third, the study used only short-term drug administration, whereas lipid-lowering therapy is, of necessity, always long term. Finally, evaluation of the safety and efficacy of ISIS 301012 in combination with statins requires further studies.

In summary, this is the first study to report potent LDL-C and apoB lowering with antisense inhibition in humans. These data demonstrate the potential use of antisense as a pharmacological agent and warrant further testing in combination with statins and other lipid-lowering agents, as well as in different patient populations.

Sources of Funding

This study was funded by Isis Pharmaceuticals, Inc.

Disclosures

Dr Kastelein has received research support from Isis Pharmaceuticals, Inc, and serves as a consultant/advisory board member for Isis. The remaining authors are employees of and have ownership interest in Isis Pharmaceuticals. Dr Wedel has served as an expert witness for Critical Care Medicine.

Study data were transferred from Isis Pharmaceuticals, Inc, to the Department of Biostatistics at the Harvard School of Public Health for independent analysis by Dr J.L. Wei. There were no discrepancies between analyses and the original interpretation of the results and conclusions. Isis Pharmaceuticals, Inc, was involved in study design and conduct and in the analysis and interpretation of the data. The data were independently analyzed by an academic statistician. The sponsor was permitted to review the manuscript, but the final decision on content was with the corresponding author.

References


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CLINICAL PERSPECTIVE

Low-density lipoprotein cholesterol (LDL-C) levels bear a direct, log-linear relationship to major cardiovascular events, including death. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) reduce circulating LDL-C by upregulating LDL-C receptors, thereby increasing LDL-C clearance. Data from more than 100 000 subjects enrolled in clinical trials utilizing statins have demonstrated unequivocal reduction in both LDL-C and major adverse cardiovascular events. Not surprisingly, statins are now the most widely prescribed medication in the Western world. In spite of these findings, however, a large share of the high-risk population fails to achieve recommended LDL-C target levels. Moreover, individuals with familial hypercholesterolemia frequently fail to meet LDL-C targets while taking the maximum tolerated lipid-lowering therapy. Finally, as many as 8% of the general population may be intolerant of statins, which leaves these individuals with few therapeutic alternatives. This article describes the first-in-humans experience with an antisense mechanism for reducing the production of atherogenic lipoproteins. This “kill the messenger” approach to lipid reduction in healthy volunteers affirms the validity of antisense for lowering circulating apolipoprotein B and LDL-C levels in humans. Additionally, the data set the stage for future work combining 2 complementary approaches to lipid lowering—decreased lipid production as the result of antisense inhibition of apolipoprotein B production and increased clearance of circulating LDL-C by statins—in high-risk patients who fail to meet target goals with their current therapy. Finally, we see the promise of a therapeutic alternative for those subjects who are intolerant of statins.
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