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Faster onset of action of formoterol versus salmeterol in patients with chronic obstructive pulmonary disease: A multicenter, randomized study

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a growing public health problem that has increased in recent years. It similarly affects men and women, especially those who smoke. The goals of COPD pharmacotherapy are to improve lung function, reduce symptoms, prevent exacerbations, and improve patients' health status. Bronchodilators are the foundation of treatment for COPD, and the long-acting β_2-agonists formoterol and salmeterol are both indicated for regular use by patients with stable COPD.

Objective: A clinical study was conducted to compare the onset of bronchodilator effects following treatment with formoterol 12 μg administered twice-daily (BID) or salmeterol 50 μg BID. The trial also assessed whether the bronchodilator effects of treatment resulted in significant differences in clinical response.

Methods: This was a randomized, multicenter, open-label, parallel-group study of formoterol 12 μg BID versus salmeterol 50 μg BID, both administered for 28 days. Patients were current or previous smokers aged ≥40 years, with a diagnosis of stable COPD. The primary efficacy variable was change from baseline in forced expiratory volume in 1 s (FEV_1) 5 min after drug administration on day 28. Secondary efficacy variables included changes from baseline in the 6-min walk test (6MWT) and rescue medication use. The primary variable was assessed by analysis of covariance, with baseline FEV_1 as the covariate.

Results: A total of 270 patients were randomized to formoterol 12 μg BID ($n = 137$) or salmeterol 50 μg BID ($n = 133$). In the intent-to-treat population the least square (LS) mean change from baseline in FEV_1 at 5 min postdose on day 28 was 0.13 L in the formoterol group compared with 0.07 L in the salmeterol group ($P = 0.022$). At 30 min postdose on day 28, the LS mean change from baseline in FEV_1 was 0.17 L in the formoterol group compared with 0.07 L in the salmeterol group ($P < 0.001$). Similar changes were reported at 60 min postdose (0.19 L for the formoterol group versus 0.13 L for the salmeterol group, $P = 0.069$). Patients in the formoterol group walked longer distances in the 6MWT and used less rescue medication compared with patients in the salmeterol group, although the differences were not statistically significant.

Conclusions: Significantly greater improvements from baseline in FEV_1 were observed at 5 and 30 min postdose with formoterol 12 μg compared with salmeterol 50 μg after 28 days of treatment. Numeric improvements in the 6MWT and rescue medication use were also observed with formoterol.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common condition that equally affects men and women globally, with a high and continually increasing mortality [1,2]. The disease is thought to be relatively underdiagnosed, with a prevalence of approximately 8%. This includes approximately 10% of individuals older than 40 years [1,2]. COPD is characterized by progressive development of airflow limitation that is not fully reversible [1,2].

Bronchodilators of the β_2-adrenergic agonist and anticholinergic classes are the foundation of pharmacologic therapy in the management of COPD [3–8]. These drugs treat the reversible component of airway obstruction by reducing the smooth muscle

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tone in the walls of airways. This decreases airway resistance, subsequently improving ventilation and reducing hyperinflation, making it easier for patients to breathe [3–8]. Clinically, bronchodilators induce long-term improvements in symptoms, exercise capacity, and airflow limitation. Patients often experience symptom improvements with a single test dose of a bronchodilator even without demonstrable spirometric improvement.

During the past few years, numerous COPD treatment guidelines have been developed by a joint task force of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [9], the National Center for Clinical Excellence (NICE) [10], and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [11]. The GOLD guidelines recommend the use of long-acting β_2-adrenergic agonists (LABAs) and anticholinergic agents, either alone or in combination, for the treatment of moderate to very severe COPD [11].

Two currently available LABAs for the treatment of COPD are formoterol and salmeterol, which have demonstrated efficacy in patients with COPD when administered twice-daily (BID) [4,7,8,12–24]. In clinical studies, formoterol has demonstrated a more rapid onset of action than salmeterol, as measured by forced expiratory volume in 1 s (FEV_1) [19,22,23]. This rapid onset of action may represent a significant benefit for subjects with COPD, especially those with nighttime or early morning symptoms due to reversible bronchospasm. Most of the previous studies that compared formoterol and salmeterol in patients with COPD [12,16,18,19,21,24] either were single-dose studies or involved relatively small study populations. Moreover, the reported relationship between improvements in FEV_1 and clinical improvements with LABA therapy in patients with COPD is not well characterized.

The present study was designed to compare the onset of action of formoterol versus salmeterol in patients with COPD and examine the relationship between onset of action and clinical response over 28 days of treatment. Safety and tolerability profiles of treatments were also reviewed.

2. Methods

We conducted a randomized, multicenter, open-label, parallel-group trial. This study was conducted in compliance with the human experimentation guidelines of the United States Department of Health and Human Services and the Helsinki Declaration. Written informed consent was obtained from each patient before any study-related procedures were performed.

3. Study design

This was a 28-day study that compared the onset of action and clinical effects of formoterol and salmeterol. At the first visit (screening), information on patients' disease characteristics, COPD history, previous therapy, and concomitant medications was collected. At the second visit (baseline), assessments of lung function were performed and patients were randomized in a 1:1 ratio to receive either formoterol 12 μg BID administered via a dry powder inhaler or salmeterol 50 μg BID administered via a metered-dose inhaler. The planned study period was the time between baseline and the last follow-up visit, which was conducted 28 days after the first dose of study treatment. Adherence to treatment was assessed by reviewing medication counts.

4. Patients

Patients enrolled in the study were ≥40 years of age; were current or previous smokers (>10 pack-years); and had a diagnosis of COPD according to the ATS guidelines, with a prebronchodilator $FEV_1 > 35\%$ of predicted normal, an $FEV_1 \leq 70\%$ of forced vital capacity within the last 6 months, and use of salmeterol 50 μg BID for at least 4 weeks before screening. Patients were also physically able to perform the 6-min walk test (6MWT). Patients included in the study had to demonstrate proper inhaler technique.

Patients were excluded if they were diagnosed with a respiratory tract infection within 1 month of their second visit; required hospitalization or emergency department treatment for COPD exacerbation; were currently on oxygen therapy; presented with clinically significant abnormal electrocardiogram; or were being treated with oral steroids, theophylline, or β-blockers 1 month before enrollment. Patients were also ineligible if they had been diagnosed with significant renal or hepatic disease, acute sinusitis, or sleep apnea; had known sensitivity to either of the study drug(s) or the class of study drug(s); had severe medical condition(s) prohibiting participation; had used any other investigational medications in the 30 days before enrollment; were diagnosed with asthma, unless secondary to COPD; or were currently prescribed formoterol. Also excluded were women of childbearing potential who were not using adequate contraception and women who were breast-feeding.

5. Efficacy assessments

Efficacy analysis was based on the intent-to-treat (ITT) population, which included all subjects who used at least 1 dose of study treatment and had at least 1 postbaseline efficacy measurement. The primary efficacy variable was the change from baseline in FEV_1 5 min postdose on day 28. Secondary efficacy measurements included change from baseline in FEV_1 at 30 and 60 min postdose on day 28, changes from baseline in distance walked in the 6MWT on day 28, and changes in Borg scores for perception of breathlessness (10-point scale, in which 0 = nothing at all and 10 = maximal) after the 6MWT. Two 6MWTs were done at both the baseline and final visits, with at least 1 h between the 2 tests. In addition, mean change in morning peak expiratory flow (PEF) predose over the last 7 days before day 28 and mean daily number of puffs of rescue medication over the last 7 days before day 28 were also measured.

6. Safety assessments

The safety population included all subjects who received at least 1 dose of study treatment. Safety assessments included monitoring of vital signs and recording of adverse events (AEs). Treatment-emergent AEs were defined as either a new illness with onset on or after day 1 or exacerbation of a preexisting condition after the start of treatment. Vital signs were assessed at screening, baseline, and the last study visit.

7. Statistical methods

Primary and secondary efficacy variables were analyzed using analysis of covariance. In addition, 95% confidence intervals for the difference in least squares (LS) means between the 2 treatments were reported. If the assumption of normality was not satisfied, a Wilcoxon Rank-sum test was used to compare the 2 treatment groups. A correlation coefficient was computed to examine the relationship between treatment effects on FEV_1 5 min postdose and distance walked in the 6MWT. Adverse events were summarized for each treatment group. All statistical analyses were performed using SAS procedures version 8.1. Statistical significance was declared when $P \leq 0.05$. It was determined that a total of 300 patients, with an overall dropout rate of approximately 10%, would provide 90% power to detect a significant difference between treatments of 0.12 L (±0.3 L) at a 2-sided significance level of $P \leq 0.05$.

8. Results

8.1. Patient disposition and demographics

A total of 270 patients were randomized, 137 to formoterol and 133 to salmeterol. The majority of randomized patients, 131 (96%) in the formoterol group and 122 (92%) in the salmeterol group, completed the study (Fig. 1). The ITT population consisted of 135 patients in the formoterol group and 131 patients in the salmeterol group. Baseline demographics were similar between the 2 treatment groups (Table 1). The majority of patients took the study treatment as scheduled, with a mean compliance rate of 99.8% for the formoterol group and 99.1% for the salmeterol group.

Table 1
Demographics and disease characteristics (intent-to-treat population).

	Formoterol 12 μg ($n = 135$)	Salmeterol 50 μg ($n = 131$)
Race, *n* (%)		
White	127 (94.1)	123 (93.9)
Nonwhite	8 (5.9)	8 (6.1)
Sex, *n* (%)		
Women	48 (35.6)	46 (35.1)
Men	87 (64.4)	85 (64.9)
Mean (SD) age, y	65.8 (9.0)	65.4 (9.1)
Mean (SD) weight, kg	82.7 (18.1)	81.2 (18.4)
Mean (SD) disease duration, y	17.74 (12.3)	18.79 (12.9)
Mean (SD) baseline FEV_1, L/min	1.5 (0.5)	1.5 (0.6)

FEV_1 = forced expiratory volume in 1 s; SD = standard deviation.

8.2. Efficacy

Changes from baseline in FEV_1 at 5 min postdose on day 28 favored treatment with formoterol over treatment with salmeterol ($P = 0.022$; Fig. 2). Changes from baseline in FEV_1 on day 28 showed a greater response to formoterol than to salmeterol at 30 and 60 min postdose ($P < 0.001$, $P = 0.069$; Fig. 2).

Other treatment effects were numerically superior in patients treated with formoterol versus salmeterol. Patients in the formoterol group walked longer distances in the 6MWT (Table 2) and used less rescue medication compared with patients in the salmeterol group, although the differences were not statistically significant. The weekly average of PEF at predose and 5 min postdose, as well as, the Borg dyspnea scale after the 6MWT showed no significant treatment differences in the ITT population. In addition, no strong correlations were observed between treatment effects on FEV_1 5 min postdose and in distance walked in the 6MWT.

8.3. Safety

The mean number of treatment days was similar between the formoterol and salmeterol groups (28.0 and 27.7, respectively). Treatment-emergent AEs were generally mild-to-moderate in both groups, with 25.5% reported in the formoterol group and 17.3% reported in the salmeterol group ($P = 0.105$). AEs reported in ≥1% of the safety population for either treatment group are shown in Table 3. Overall, the reported AEs caused few discontinuations (4 patients in the formoterol group and 3 patients in the salmeterol group). Treatment-associated treatment-emergent AEs were observed in 5.8% of patients in the formoterol group and 1.5% of patients in the salmeterol group ($P = 0.103$).

One patient in the formoterol group reported severe pneumonia, and there were 3 reports of severe AEs (chest pain, malignant lung neoplasm, and exacerbated dyspnea) in the salmeterol group. None of these severe AEs were considered by investigators to be treatment related. Headache was the most common AE (3.6%) in the formoterol group. Bronchitis and upper respiratory tract infection were the most commonly experienced AEs (2.3% each) in the salmeterol group.

9. Discussion

This study was designed to evaluate the onset of action of formoterol versus salmeterol in patients with COPD and examine the relationship between onset of action and clinical response over 28

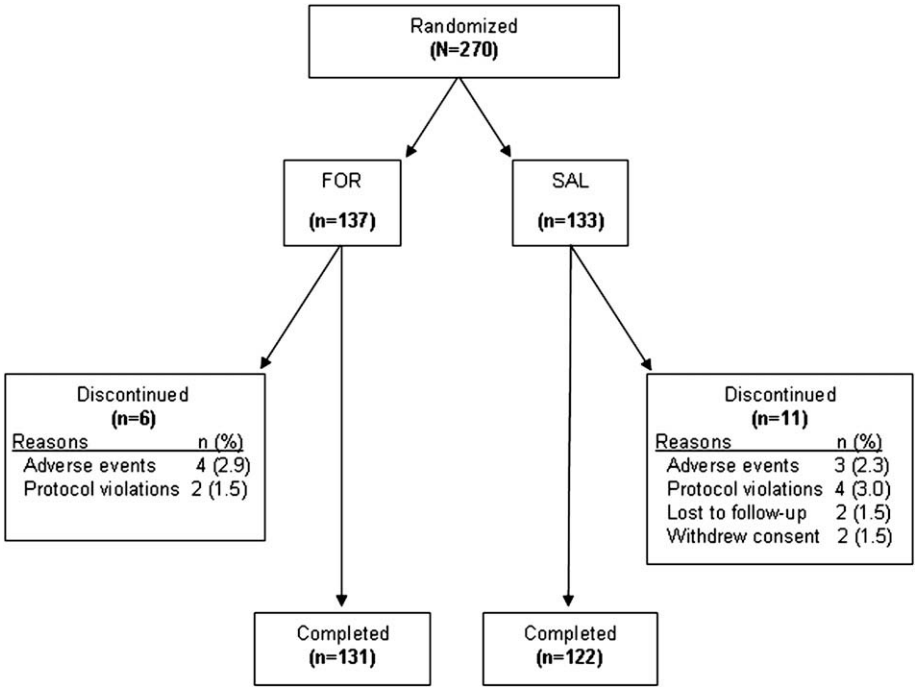

Fig. 1. Patient disposition. FOR = formoterol; SAL = salmeterol.

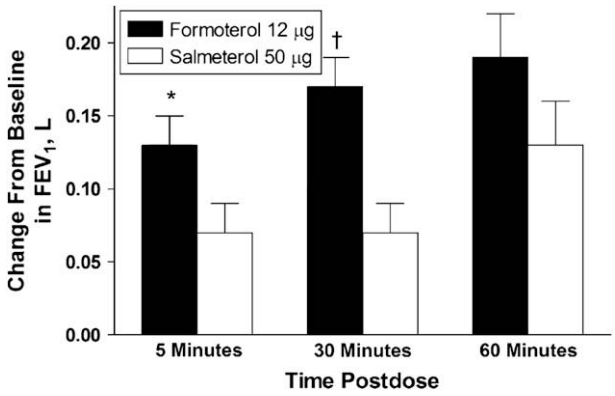

Fig. 2. Changes from baseline in mean FEV_1 (±SE) 5, 30 and 60 min postdose on day 28. FEV_1 = forced expiratory volume in 1 s. $^{*}P = 0.022$, $^{\dagger}P < 0.001$.

days of treatment. Findings from this study indicate that formoterol has a significantly faster onset of action than salmeterol, with differences between treatment effects observed as early as 5 min postinhalation (the earliest performed measurement). This is important because patients with COPD experience progressive and debilitating symptoms, and a rapid onset of action allows patients to feel that their medication is working, which may influence medication adherence. Patients randomized to formoterol demonstrated favorable results in change in FEV_1 from baseline at 5 and 30 min postdose on day 28 ($P = 0.022$, $P < 0.001$). This rapid onset of action is similar to findings in a previous study by Kottakis et al. in which patients treated with formoterol 12 μg demonstrated a faster onset of effect with respect to FEV_1 compared with patients treated with salmeterol 50 μg. In that study of 47 patients aged 42–80 years, the absolute change from baseline ($P = 0.0044$) and percentage change from baseline line in FEV_1 ($P = 0.0021$) for patients taking formoterol 12 μg were found to be superior to changes in FEV_1 for patients taking salmeterol 50 μg [16]. An additional small study ($n = 22$) also reported a faster onset of action when formoterol was compared with salmeterol [21], and similar onset of action was observed when compared with salbutamol (albuterol) [25]. Similar studies have also documented an onset of action of less than 5 min when formoterol was compared with ipratropium in patients with COPD [6]. In addition, changes in FEV_1 from baseline at 30 min postdose on day 28 were also greater with formoterol than with salmeterol, although this change was not statistically significant. This study is significant in that it confirms the findings of Kottakis et al. which used a larger patient population, and also included the 6MWT.

The rapid onset of formoterol may be a result of its chemical structure. Formoterol is a moderately lipophilic drug that is absorbed into the lipid bilayer of the cell membrane where it is retained. Upon coalescing with the cell membrane, a portion of the drug is released into the extracellular aqueous phase. This released portion interacts with the β_2-adrenergic receptor on contact, allowing for rapid bronchodilation after inhalation [13]. The rapid bronchodilator effect results in faster enhancement of exertion tolerance [26], which invariably leads to easier breathing and rapid relief of symptoms [15]. This sequence of events is likely to improve user compliance with treatment in real life conditions, although in the present controlled study the compliance rate was similar between treatment groups.

Distance walked in the 6MWT (10 min postdose on day 28) was longer for patients taking formoterol than patients taking salmeterol (Table 2); however, the difference was not statistically significant. Similarly, numerical differences favoring patients taking formoterol suggest that patients on formoterol used less rescue medication than patients taking salmeterol, but the differences did not reach statistical significance. Because patients with COPD tend to live relatively sedentary lifestyles with low activity levels in order to avoid symptoms, the 6MWT was a useful test in evaluating the relevance of the faster action of formoterol in this study. In addition, it is apparent that changes in FEV_1 do not reflect accurate symptomatic improvement in COPD; therefore, in future studies it might be useful to measure the inspiratory capacity (IC). This is thought to correlate more closely with improvements in exercise endurance and dyspnea after bronchodilator therapy [27,28].

The results from this large study focusing solely on the 12-μg dose of formoterol substantiate findings from previous clinical studies demonstrating a more rapid onset of action for formoterol compared with salmeterol [19,22,23].

In conclusion, the onset of action of formoterol was significantly faster than that of salmeterol with differences reaching statistical significance as early as 5 min postdose, the earliest scheduled measurement. In addition, patients administered formoterol consistently experienced significantly greater improvements in FEV_1 postdose than patients taking salmeterol. Numeric differences favoring formoterol treatment were also observed in the 6MWT (total distance walked), as well as in the need to use rescue medication; however, these numerical differences did not reach statistical significance. Both treatments showed good safety and tolerability profiles; there were no significant differences between treatment groups. The most common AEs reported were headache in the formoterol group and bronchitis and upper respiratory tract infection in the salmeterol group.

Table 3
Adverse events in ≥1% of study population.

Adverse event[a]	Formoterol 12 μg ($n = 137$)	Salmeterol 50 μg ($n = 133$)
Bronchitis	2 (1.5)	3 (2.3)
Upper respiratory tract infection	0 (0)	3 (2.3)
Pain	0 (0)	2 (1.5)
Fall	0 (0)	2 (1.5)
Increase in blood pressure	2 (1.5)	0 (0.0)
Diarrhea	2 (1.5)	0 (0.0)
Arthralgia	2 (1.5)	0 (0.0)

[a] *n* (%).

Table 2
Effects of treatment distance walked (feet) during 6MWT.

	Formoterol 12 μg ($n = 135$)	Salmeterol 50 μg ($n = 131$)	95% CI	*P*-value
Baseline (visit 2)[a]	1217.8 (30.7)	1169.0 (30.9)	−21.9 to 119.6	0.175
Change from baseline at predose (visit 4), LS mean (SE)	20.6 (18.4)	20.2 (19.0)	−42.0 to 42.8	0.985
Change from second predose (visit 2) at 10 min postdose (visit 4), LS mean (SE)	59.8 (18.4)	50.4 (19.1)	−32.8 to 51.7	0.660
Change from baseline at 10 min postdose (visit 4), LS mean (SE)	65.2 (17.9)	48.1 (18.6)	−24.0 to 58.3	0.412

LS = least squares; SE = standard error; 6MWT = 6-min walk test.
[a] Baseline is the mean of two 6MWTs at visit 2.

Conflicts of interest

Dr. Cote has served as a consultant and has participated in Speaker's Bureaus for Boehringer-Ingelheim, Pfizer, Dey Pharmaceutical, and GlaxoSmithKline. Dr. Pearle has received research grants from Schering-Plough. Dr. Sharafkhaneh has served as a consultant and has participated in Speaker's Bureaus for Boehringer-Ingelheim, Pfizer, Dey Pharmaceutical, and GlaxoSmithKline. Dr. Spangenthal serves on Speaker's Bureaus for Pfizer, Novartis, Sepracor, and Boehringer-Ingelheim.

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Appendix A. Complete list of study sites and investigators

Pulmonary and Critical Care Division New England Medical Center, Boston, MA (John Unterborn, MD); Rocky Mtn Center for Clinical Research, Wheat Ridge, CO (Robert Lapidus, MD); San Ramon, CA (Narenda Malani, MD); Complete Family Care, Northglen, CO (Larry Doehring, MD); Colorado Pulmonary Associates, PC, Denver, CO (Timothy Clark, MD); Healthcare Research Consultants, Tulsa, OK (Joseph E. Schelbar, MD); California Research, Fullerton, CA (James L. Pearle, MD); Vermont Lung Center, Colchester, VT (Anne Dixon, MD); So. California Institute for Respiratory Diseases, Los Angeles, CA (Robert N. Wolfe, MD, FCCP); Victor Marchione, LLC, Jersey City, NJ (Victor Marchione, MD); Institute of Healthcare Assessment, Inc., San Diego, CA (Shari A. Brazinsky, MD); Lung Diagnostics, San Antonio, TX (Charles P. Andrews, MD); Charlotte Lung and Health Center, Charlotte, NC (Selwyn Spangenthal, MD); Abingdon Internal Medicine, Abingdon, VA (Emory H. Robinette, MD); Crawford Long Hospital, Atlanta, GA (Kenneth Leeper, MD); University of Maryland School of Medicine, Baltimore, MD (Pamela J. Amelung, MD); Lanes and Mangas, MD, PA, Miami Beach, FL (Jose R. Garrigo, MD); VA Medical Center, Pulmonary Section, Ann Arbor, MI (Jeffrey L. Curtis, MD); Respiratory Consultants of Houston, Houston, TX (Kim Bloom, MD); VA Medical Center #222P, Indianapolis, IN (Mark Farber, MD); Bay Pines Veterans Hospital, St. Petersburg, FL (Claudia Cote, MD); Louis Stokes Cleveland Dept. of Veterans Affairs Medical Center, Cleveland, OH (Kingman P. Strohl, MD); Diagnostic Clinic, Largo, FL (Francis J. Averill, MD); Pulmonary Medical Research of NY, Bay Shore, NY (Jay Enden, MD); Biomedical Research Foundation of Southern Arizona, Tucson, AZ (Sammy C. Campbell, MD); VAMC, Oklahoma City, OK (David C. Levin, MD); Bernstein Clinical Research Center, Inc., Cincinnati, OH (Jonathan Bernstein, MD); Pulmonary & Critical Care, Summit Medical Center, Oakland, CA (Jerrold A. Kram, MD); Pulmonary & Allergy Associates, Springfield, NJ (Robert Sussman, MD); Graves-Gilbert Clinic, Bowling Green, KY (J. Randall Hansbrough, MD); Falmouth Hospital, Falmouth, MA (Mir Shuttari, MD); California Allergy & Asthma Medical Group, Los Angeles, CA (Sheldon Spector, MD); Houston Veterans Affairs Medical Center, Houston, TX (Amir Sharafkhaneh, MD); MediSphere Medical Research Center, LLC, Evansville, IN (Steven K. Elliott, MD); The Asthma Allergy Clinic, Shreveport, LA (Peter Boggs, MD); Radiant Research, Inc., Mogadore, OH (Dennis C. McCluskey, MD); Medical Pulmonary Associates, Tamarac, FL (Douglas E. Weiner, MD); Radiant Research Alexian Brothers, Elk Grove Village, IL (Edward J. Diamond, MD).

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