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Fluticasone/Formoterol dry powder versus Budesonide/Formoterol in adults and adolescents with uncontrolled or partly controlled asthma

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Summary

This 12-week study compared the efficacy and safety of a fixed combination of fluticasone propionate plus formoterol (FL/F) 250/12 µgb.i.d. administered via a dry powder inhaler (DPI) to a combination of budesonide plus formoterol (BD/F) 400/12 µgb.i.d. After a 2-week run-in period (in which all patients were treated exclusively with budesonide plus formoterol), patients aged 12–65 years of age (N = 98) with uncontrolled asthma were randomized into an actively controlled, open-labelled, parallel-group study. The primary objective was to demonstrate non-inferiority, measured by morning peak expiratory flow (mPEF). The non-inferiority was demonstrated. A statistically significant improvement from baseline was observed in both groups in terms of lung function, asthma control, and the use of rescue medication. FL/F demonstrated a statistical superiority to BD/F in terms of lung function (FEV_1) (p = 0.01) and for asthma control (p = 0.02). Non-significant between-group differences were observed with regards to exacerbation rates and adverse events.

In uncontrolled or partly controlled asthma patients, the use of a combination of fluticasone propionate plus formoterol via DPI for 12-weeks was non-inferior and showed improvements in FEV1 and asthma control when compared to a combination of budesonide plus formoterol.

Keywords: *Asthma control questionnaire; Forced expiratory volume in 1s; Single inhaler; Non-inferiority; Morning peak expiratory flow.*

Introduction

Asthma is a worldwide disease associated with a growing burden in terms of morbidity, lower quality of life, and healthcare costs[1]. The goal of therapy in asthma is to achieve and maintain clinical control by reducing the patient's exposure to factors that exacerbate asthma and by using medications for the purposes of relief and control. For patients with uncontrolled asthma treated with inhaled corticosteroids (ICS) alone, international guidelines recommend a combination of inhaled corticosteroids (ICS) and long-acting b2-agonists

(LABA)[1]. The use of an ICS/ LABA combination in 1 inhaler may be more effective due to convenience and ease of use by improving patient compliance and long-term control[2,3].

Fluticasone propionate is an inhaled corticosteroid with high potency in vitro[4], high topical anti-inflammatory activity[5], and a rapidly induced protective effect[6]. Fluticasone propionate has been shown to be effective in adults and children with regards to treating chronic asthma[7]. Formoterol is a LABA with a very quick onset of action[8]. It has been used as a maintenance therapy and as a relief medication in combination with an ICS[9]. The FL/F combination in a single, pressurized, metered dose inhaler has been compared with the single agent treatment of either propionate fluticasone or formoterol and with combination of either fluticasone/salmeterol or budesonide/formoterol, which to the majority concluded similar efficacy and safety[10-17]. In patients with severe asthma, the combination of FL/F showed similar efficacy and similar patient tolerance[10] as compared to single agents. In patients with mild-to-moderate asthma, the FL/F combination showed superior efficacy compared to either single agent fluticasone, formoterol, or placebo[13]. FL/F in a single aerosol inhaler was also compared with fluticasone propionate plus salmeterol, resulting in similar efficacy and a faster onset of action[11]. FL/F was also compared with budesonide plus formoterol and again, showed comparable efficacy[12].

Chronic asthma control remains suboptimal despite the continued development of improved treatments for asthma, particularly in India[18,19]. The consequences of suboptimal asthma control include a poor quality of life, frequent and urgent health care visits, an increase in the risk of asthma exacerbations, and increased mortality[20]. Alternative treatment options, with different combinations and formulations, may provide more flexibility with regards to adjusting to a patient's clinical severity and device preferences. This flexibility in treatment has the potential to increase compliance and effectiveness of therapy[21,22]. The

rationale behind combining fluticasone propionate and formoterol (FL/F) is to provide the benefits of a high-potency anti-inflammatory agent with the fast onset of action of a β-2 agonist in a new formulation (dry powder) using a single inhaler. Previous studies using metered dose inhaler showed similar efficacy between FL/F and others combinations. This study is to evaluate the fixed combination of FL/F administered via a dry powder inhaler. It was designed in order to demonstrate the non-inferiority of the fixed combination of FL/F in comparison with the fixed combination of budesonide/formoterol (BUD/F) in the treatment of uncontrolled and partly controlled asthma patients. The BUD/F combination was selected for comparison because it contains the same LABA, i.e. formoterol.

Material and methods
Study design

This randomized, open, parallel-group study was conducted over 12 weeks (with an additional 2-week run-in period) in Hi-Tech Medical College and Hospital, Bhubaneswar. Odisha. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice, and approved by the institutional ethics committee on human research at the institution. All patients were provided with written informed consent. The study was conducted from August 2016 to March 2017. The patients who quailed for the study based on the inclusion and exclusion criteria (as described below) started a 2-week run-in period in which all patients were treated with budesonide plus formoterolat a dose of 400/12 mg twice daily. At the same time, they received PIKO-1 peak flow meters, rescue medication (salbutamol), and diaries for data collection. All other asthma medication was discontinued. Patients who had satisfactory compliance (<8 missed doses during the run-in period), had a predicted post-bronchodilator FEV of >60%, and had uncontrolled or partially controlled asthma, were randomized to receive the same dose of budesonide plus formoterol used in the run-in

period or 250 mg of fluticasone propionate plus 12 mg formoterol twice daily. The daily dose of 500 mg of propionate fluticasone used in thisstudy is equivalent of 800 mg of budesonide[1]. Lung function assessments, reviews of patient's diaries and safety records were evaluated at weeks 4, 8 and 12. At each visit, patients completed a lung function test before receiving their morning dose.

Study patients

Males and females aged between 12 and 65 years, with a diagnosis of asthma for ≥3 months prior to screening, a body mass index between 19 and 30 kg/m2, and currently receiving treatment with a combination therapy of a LABA and an ICS (800 mg budesonide or equivalent) for ≥30 days were included in the study. Patients were required to have partially controlled (patients with at least one of the following characteristic: daytime symptoms twice/week; need for reliever treatment twice/week; any limitation of activities; any nocturnal symptoms; or lung function less than 80% of predicted value) or uncontrolled asthma[1] and to have a post-bronchodilator FEV >60% of predicted value in order to be eligible for randomization. Exclusion criteria were defined as any of the following: current or ex-smokers (>10 pack-years); pregnant or lactating women; severe asthma exacerbation during the run-in period; 3 or more courses of oral corticosteroids in the previous 6 months; hospitalization due to asthma in the previous 6 months; any course of oral corticosteroids 30 days prior to screening; concomitant lung disease; treatment with anti-cholinergics, antihistamines, leukotriene receptor antagonists, beta blockers, tricyclic antidepressant, methylxanthines, ritonavir, or ketoconazole in the previous 2 weeks.

Protocol outcome measures

The primary endpoint for the determination of efficacy of study treatments was the mean change in morning PEF. Patients used diaries in order to document morning and evening PEF, document answers to questions of the Asthma Control Questionnaire (ACQ-7 validated in India and allowed for use in this study)[23,24], and to keep record of salbutamol and other medication use. Diaries were collected at each study visit. Patients performed a measured morning and evening PEF by using a portable PIKO-1 peak flow meter (nSpire Health Inc). All measurements were documented in diaries and the highest of the 3results was automatically recorded in a calendar. The patients underwent spirometry (in accordance with the Indian Thoracic Society[25]) at screening and at each of the study visits. Reference ranges were calculated based on statistics formulated from the Indian population[26,27]. Patients recorded their use of rescue medication as the number of puffs of salbutamol taken in each 24-h period. At week 12, investigators rated each patient's response to therapy compared with their baseline in a 5-point scale from 1 (much improved) to 5 (much worse). Medication use was measured by the assessment of used blister packs (for FL/F) and by a dose counter (for BD/F). Daily data collection included the morning and evening PEF and asthma control days. For PEF analysis, however, it was used the average of 2 weeks run in period and 2 weeks period before follow-up visits. To the asthma control analysis, it was also measured the average of the Asthma Control Questionnaire score during the 2-week baseline and at 2 weeks before follow-up visits.

Safety assessments

Adverse events were reported throughout the study period. A physical examination (including an oropharyngeal examination and vital signs measurements) was performed at the pre-randomization visit and at each subsequent visit (day 1, weeks 4, 8, and 12). Clinical laboratorial tests (complete blood count, serum glucose, serum potassium) and a 12-lead ECG were performed at baseline and at the end of the study.

Statistics

A sample size of 180 patients and a standard deviation (SD) of 45 L/min were required in order to provide a power of 80% with respect to non-inferiority. Non-inferiority was concluded if the lower limit of the 97.5% confidence interval (CI)

for the treatment difference (fluticasone/ formoterol vs budesonide/formoterol) was ≥ -20 L/min.

Efficacy and safety were based on the intention-to-treat (ITT) population, defined as patients who had taken at least 1 dose of the study medication and provided some post baseline efficacy data. A per-protocol population (PP) analysis was also reported. The reasons for early discontinuation included lack of compliance, patient request, adverse effects, or pre-defined reasons for discontinuation.

The Student's t test was used for comparing baseline variables between the groups, absolute means related to lung function, asthma control scores, and measurements of rescue medication. The number of patients with asthma exacerbations was analyzed using Chi-square test. Changes in lung function from baseline were measured via analysis of covariance with the fixed effect of treatment and the baseline as a covariate. Changes in laboratory analysis from baseline were compared using the Student's t test (parametric) or

Manne-Whitney test (non-parametric) according to the statistical distribution.

Descriptive statistics included:- counts and percentages for categorical variables; means and standard deviations for normally distribution variables; and medians, including variables defined by first and third quartiles, that were not normally distributed on the original or log-transformed scales (Graphpad Prism software, version 8, was used for these analyses).

Results

Overall, 137 patients were enrolled and 98 patients were randomized and entered the treatment period (48 patients were randomly assigned to the FL/F arm and 50 to the BD/F arm). Patient flow and baseline characteristics are shown in Fig. 1 and Table 1. In the fluticasone/formoterol and budesonide/formoterol groups, 42 and 43 patients completed the study and were included in the per-protocol (PP) analysis, respectively. The treatment groups of the ITT population were comparable in terms of their demographical and baseline characteristics (Table 1).
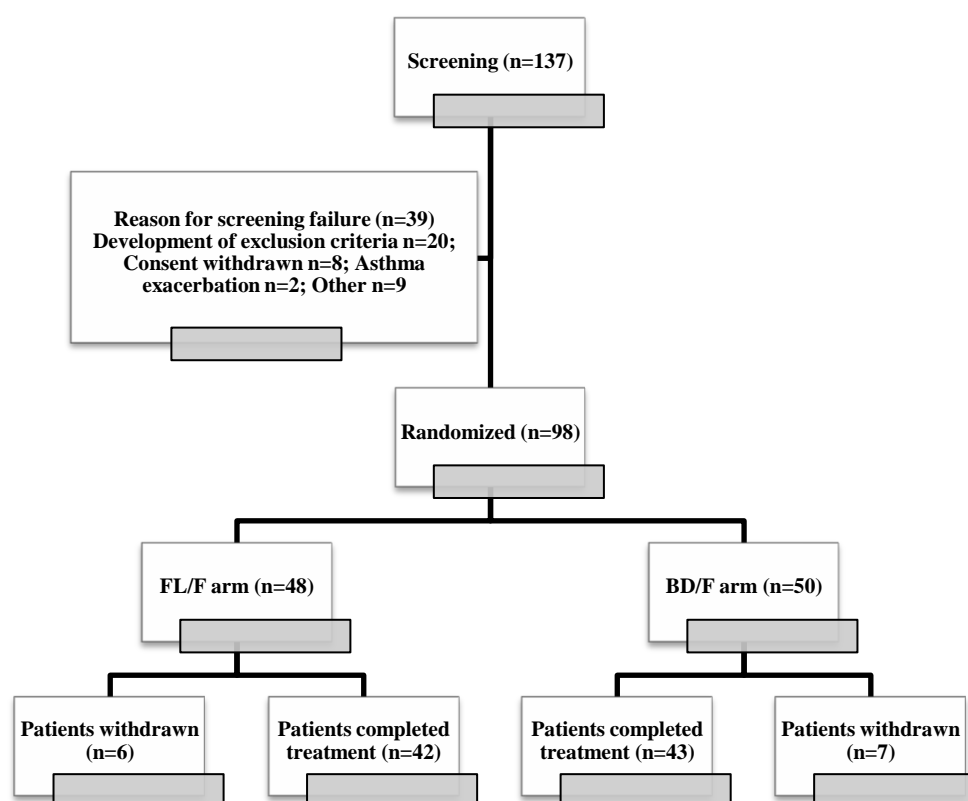
Figure 1: Flow of patients. BD/F: budesonide/formoterol; FL/F: Fluticasone propionate/formoterol

Table 1 Baseline characteristics of the 196 patients			
	FL/F	BD/F	p Value
Female sex– no. (%)	74 (76.4)	72 (72.6)	0.54
Age– years	33.5 ±14.0	35.7± 17.5	0.66
Asian race–no. (%)	66 (67.0)	72 (71.7)	0.34
Duration of asthma– years	23.8±13.4	22.4 ± 14.3	0.41
Weight (kg)	68.2 ± 14.8	65.9 ± 15.2	0.28
Ex-smoker– no. (%)	14 (14.4)	10 (10.1)	0.35
Morning PEF – L/min	355.6 ± 115.5	345.1 ± 124.2	0.54
Evening PEF – L/min	362.5 ± 121	351.4 ±123.5	0.53
FEV1–L	2.51 ± 0.71	2.50±0.77	0.95
FEV1%–% predicted	85.5 ±18.6	85.2 ± 17.6	0.90
ACQ-7 score[a]	0.93 ± 0.69	0.87± 0.64	0.52

FL/F: Fluticasone propionate/formoterol group; BD/F: Budesonide/formoterol group; PEF: Peak expiratory flow; FEV1: forced expiratory volume in 1 s; ACQ: Asthma Control Questionnaire.
Data expressed as mean ± SD.
[a] Scores on the Asthma Control Questionnaire range from 0 to 6, with a higher score indicating worse asthma control; the minimal important difference (MID) is 0.5.

The majority of patients were Asian (69.3%) and female (74.4%). The average age was 35.2 years, with 19.8% adolescents aged between 12 and 18 years. The mean baseline FEV before bronchodilation was 2.50 ± 0.74 L (85.4± 17% of the predicted value). There were no differences in terms of demographical and baseline characteristics in the treatment groups of the PP population. Patient compliance was greater in the FL/F group than the BD/F group (mean percentage of administered drug 92.8 ± 9.8% in FL/F versus 87.1±12.8 in BD/F).

Primary outcome

For both treatment groups, average morning PEF was automatically recorded by peak flow meter and increased significantly by week 12 (both p < 0.05) (Fig. 2). Non- inferiority was achieved in the ITT and PP analysis with respect to morning PEF as the lower limit of the CI for the treatment differences (–12.6 L/min in the ITT population) was > of 20 L/min for the morning PEF, as recorded using peak flow meter. There was no significant difference in the change from baseline between treatment groups (Table 2).

Secondary outcomes

The mean FEV1 values for the FL/F group at baseline, week 4, week 8, and week 12 were 2.52 L, 2.66 L, 2.71 L, and 2.67 L, respectively. For the BD/F group the mean FEV1 values at baseline, week 4, week 8, and week 12 were 2.51 L, 2.50 L, 2.49 L, and 2.53 L, respectively. An increase from the baseline FEV1 was observed in the FL/F treatment group at weeks 4, 8, and 12 and were statistically significant (all with p < 0.01). There was no statistically significant change from the baseline during any period of evaluation in the BD/F group. In addition, the increase in the mean FEV1 from baseline to week 12 was significantly greater in patients receiving FL/F than in patients receiving BUD/F (Table 2).

We observed in both groups a statistically significant improvement in the ACQ7 score from baseline (mean values at baseline and at the end of the study were 0.93 to 0.64 in the FL/F group, respectively; and 0.87 to 0.73 in the BD/F group, respectively; p < 0.01 for both groups). In the FL/F group, A statistically significant difference was observed in the ACQ7 score from baseline to week 12 (p = 0.02) (Table 2). With regards to rescue salbutamol use, the FL/F group showed less use over the time of the study (mean values at baseline and at the end of the study were, 1.1 and 0.57 puffs/day, respectively; p < 0.01). The BD/F group failed to show a statistically significant reduction in rescue salbutamol use (mean values at baseline and at the end of the study were 0.71 and 0.60 puffs/ day, respectively; p = 0.058). There were no statistically significant differences from baseline

to the end of the study in terms of the evening PEF. In the ITT population, there were no statistically significant differences between treatment groups when considering either the change in the evening PEF or the use of rescue salbutamol from baseline to week 12 ($p = 0.19$, $p = 0.29$; respectively) (Table 2).

For all secondary outcomes, PP analysis showed similar results. At week 12, 78.6% of the patients in the FL/F group and 69.4% of the patients in the BD/F group were rated by investigators as "improved" or "much improved"; this difference between the groups was not statistically significant ($p = 0.29$).

Table 2 Outcome variables in the intention-to-treat population (mean change from baseline)

	FL/F	BD/F	P Value
Morning PEF–L/min			
Baseline (Mean ± SD)	355.6 (115.5)	345.1 (124.2)	
End of study (Mean ± SD)	379.9 (137.3)	356.6 (134.4)	
Change from baseline (Mean ± SD)	24.3 (85.9))	11.5 (92.6	0.32
Evening PEF – L/min			
Baseline (Mean ± SD)	362.5 (121.0)	351.4 (123.5)	
End of study (Mean ± SD)	380.5 (129.7)	355.3 (131.0)	
Change from baseline (Mean ± SD)	18.0 (78.1)	3.9 (73.9)	0.19
Prebroncodilatador FEV_1-L			
Baseline (Mean ± SD)	2.52 (0.71)	2.51 (0.77)	
End of study (Mean ± SD)	2.66 (0.74)	2.52 (0.73)	
Change from baseline (Mean ± SD)	0.14 (0.41)	0.01 (0.27)	0.01
FEV1-percent of predicted value before bronchodilation			
Baseline (Mean ± SD)	85.8 (18.8)	85.3 (17.4)	
End of study (Mean ± SD)	91.2 (19.4)	86.2 (16.6)	
Change from baseline (Mean ± SD)	5.4 (11.1)	0.9 (10.5)	<0.01
Salbutamol rescue use- puffs/day			
Baseline (Mean ± SD)	1.10 (2.57)	0.71 (1.09)	
End of study (Mean ± SD)	0.57 (1.25)	0.61 (1.17)	
Change from baseline (Mean ± SD)	−0.53 (2.46)	−0.08 (0.75)	0.29
ACQ7 score			
Baseline (Mean ± SD)	0.93 (0.69)	0.87 (0.64)	
End of study (Mean ± SD)	0.64 (0.63)	0.73 (0.65)	
Change from baseline (Mean ± SD)	−0.30 (0.48)	−0.14 (0.47)	0.02
Data are presented as mean ± SD. FL/F: Fluticasone propionate/formoterol group; BD/F: Budesonide/formoterol group; PEF: peak expiratory flow; FEV_1: forced expiratory volume in 1 s; ACQ: Asthma Control Questionnaire.			

Tolerability

During the study, 91 non-serious adverse events were reported: 45 among patients receiving fluticasone/formoterol and 48 among patients receiving budesonide/formoterol. The most commonly reported adverse events are listed in Table 3. Oral candidiasis was infrequent, occurring only in 1 patient receiving budesonide/ formoterol. Six patients in each group experienced a severe asthma exacerbation requiring an oral corticosteroid and 1 patient in each treatment group discontinued the study because of adverse events.

Laboratory evaluations showed no statistically significant differences between the treatment

groups. A small increase in aspartate aminotransferase and in alanine aminotransferase (mean 7.7 U/L and 3.8 U/L, respectively) was observed in the FL/F group; however, this was not considered to be clinically significant. Blood pressure and heart rate were stable throughout the study period in both treatment groups with no clinically relevant changes.

Discussion

This is the first study to evaluate and compare the combination of fluticasone propionate plus formoterol administered via a dry powder inhaler to budesonide plus formoterol in uncontrolled asthma patients. The results of the

study show the non-inferiority of fluticasone propionate plus formoterol to budesonide plus formoterol during 12- weeks on the basis of the predefined criteria of morning PEF. Morning PEF, rescue medication use, and asthma control improved in relation to the baseline in both treatment groups. A greater improvement in FEV1 and asthma control was also seen in uncontrolled and partly controlled asthma patients who used FL/F compared to those who used BD/F, with no difference considering need to rescue therapy and PEF measures.

Table 3: Adverse events occurring in patients in either treatment group in the intention-to-treat population.

Adverse event	FL/F	BD/F
Influenza-like symptoms	8 (8.2)	13 (13.2)
Asthma exacerbation	10 (10.3)	12 (12.1)
Headache	11 (11.3)	4 (4)
Upper respiratory tract infection	8 (8.2)	4 (4.0)
Sinusitis	4 (4.1)	3 (3.0)
Cough	1 (1.0)	3 (3.0)
Data are presented as number (%). FL/F: Fluticasone propionate/formoterol group; BD/F: Budesonide/ formoterol group.		

The observed improvement in the pre-bronchodilator FEV1 and asthma control with the fixed combination FL/F may be related to the efficacy of the fluticasone propionate component. Experimental studies have shown that fluticasone propionate shows a higher affinity for the human glucocorticoid receptor[28] than does budesonide and has superior transrepress AP-1 or NF-kB activity[4]. Clinical experience has also shown an increase in lung function after treatment with fluticasone propionate relative to budesonide, as demonstrated by improvements in morning PEF observed in a meta-analysis involving 7 comparative trials[29].

The difference in efficacy observed may be also related to the type of inhaler. Both medications were administrated via a dry powder inhaler. However, therapy compliance[30] and delivery of the drug to the lungs[31] may change with the use of different DPI, and FL/F was administrated using an inhaler with improvements to reduce patients with difficult to handle the inhaler (easier to open the lid and to pierce the capsule, more friendly designed)[32]. In our study, we observed better compliance with the FL/F inhaler which may have contributed to the better results of combining fluticasone and formoterol.

The clinical relevance of these statistical differences is difficult to estimate. Pre-bronchodilator FEV1 is a strong, independent predictor of the risk of asthma exacerbations[29]. However, based on studies of the subjective perception by patients, the minimal increase required in FEV1 for a patient to notice improvement is about 0.23 L (or 10%)[33,34]. Based on this data, the difference observed in our study may not be clinically significant. Likewise, a change of 0.5 in the ACQ has been reported as the cut off for clinical improvement[34].

Therefore, the difference in the ACQ observed in our study may not be clinically significant, either.

During the 3-month study period, the FL/F combination was tolerated just as well as the BUD/F combination. The most common adverse effects in each group (influenza-like symptoms and asthma exacerbations) can probably be attributed to seasonal factors, as suggested by their similar frequency in the 2 groups. There was no evidence of detrimental effects on the cardiovascular system (no changes in ECG tracings). A limitation of the present study is the open label design. However, the results are unlikely to be influenced by investigator bias, by design, or by converting all patients to BUD/F during run-in. It could be argued that these may have encouraged patients to be more motivated in FL/F arm, leading to an inbuilt bias influencing patient's behaviour and adherence. However, a number of precautions were taken to minimize the bias. First, expectation bias was minimized by training all patients to use correctly the inhalation device and by stressing the relevance of the correct use of treatment and compliance

at each visit. Second, to reduce expectation bias of patients and investigators[35] we chose as primary outcome an objective measure. It is impossible to determine whether how switching to a new inhalation device influenced the study results because it may affect adherence in two opposite ways: increasing adherence due to motivation/hope or reducing adherence due to the individual preferences[36]. Finally, we also performed a PP analysis without non- adherent patients and the results were the same.

As a consequence of our study design, we cannot comment on either the rate of asthma exacerbation or long-term safety issues. Longer longitudinal studies, with sufficient statistical power, will be needed in order to evaluate exacerbations and additional safety events.

In conclusion, this study showed the non-inferiority of the combination of FL/F to BD/F in asthmatics not controlled with other ICS/LABA combinations. The data also suggests an improvement in terms of lung function and asthma control after 12-weeks of treatment in patients using the combination FL/F. The findings of this study support the use of fluticasone propionate plus formoterol (as a dry powder combination) as an option in treating uncontrolled asthma patients. Many asthmatic patients still show poor control despite of the use of combination therapy. As an alternative for asthma treatment, this formulation may offer a new option in asthma medication and delivery when considering patient preference and treatment response. Further double blind studies powered to evaluated superiority are required to establish differences between therapies.

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