

Efficacy and Safety for the Combination of Levosalbutamol, Ambroxol and Guaifenesin for the Symptomatic Treatment of Productive Cough: Phase IV Clinical Trial

Dr. Mayuresh Dilip Kiran^{*1}, Lalit Jeevan Pawaskar², Shaheen Naseem Sheikh³

¹Vice President, Medical Services, ²Executive, Pharmacovigilance, ³Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd



Corresponding Author –

Dr. Mayuresh Kiran

Centaur Pharmaceuticals Pvt. Ltd.,

Centaur House, Near Grand Hyatt, Vakola, Santacruz (East), Mumbai - 400055

Email: mayuresh_kiran@rediffmail.com

Abstract

Background: Cough is one of the most common symptom that most of the Doctors faces while practising in paediatric population. Cough can be productive or unproductive. Productive cough can be treated with the combination of bronchodilator, expectorant and mucolytics. The main objective of the Phase IV clinical trial conducted was to test the efficacy and safety for the combination of Levosalbutamol (bronchodilator), Ambroxol Hydrochloride (mucolytic agent) and Guaifenesin (expectorant) for the treatment of productive cough associated with bronchospasm in conditions such as bronchitis and bronchial asthma as well as all conditions associated with tenacious mucus, wheezing and chest congestion.

Methodology: The trial was conducted with 23 paediatric speciality Doctors on 325 patients out of which 149 patients were of age group 2 to 12 years and 176 were of age below 1 year. Efficacy assessment was done by analysing the cough severity score at all the visits. Safety assessment was done by analysing the adverse events experienced by the patients or observed by the investigators at all the visits. **Results:** At baseline, CSS was 6.624 reduced to 3.744 at day 3 and 1.049 at day 5. One point reduction in Likert type symptom scale from moderate to mild was in just 5 days. Only 12.923 % of patients experienced non-serious adverse events. **Conclusion:** Combination of Levosalbutamol, Ambroxol Hydrochloride and Guaifenesin was safe as well as efficacious for the treatment of productive cough.

Keywords: Levosalbutamol, Ambroxol, Guaifenesin, Cough

Introduction

Cough is one of the most common symptom that paediatricians faces while practising. According to duration of the cough it can be acute or chronic, recidivist, recurrent or persistent. Cough can be productive or unproductive. Productive cough is the cough with respiratory tract secretions and unproductive cough is the cough with no respiratory tract secretions. A productive cough produces phlegm or mucus or sputum.^[1,2] Productive cough leads to expectoration of sputum for the duration of more than 8 weeks.^[3] Productive cough is a symptom which is mostly observed in developing countries. In developing countries incidence of productive cough is about 20 to 30% and in developed countries it is 3 to 4 %.^[4]

According to A Vora et al productive cough can be treated with the combination of bronchodilators, expectorants and mucolytic agents.^[5] This PMS study was conducted to test the safety and

efficacy for the combination of bronchodilators (Levosaltamol), mucolytic agents (Ambroxol Hydrochloride) and expectorant (Guaifenesin) for the treatment of productive cough in the children patients of different age group, including age up to 1 year and 2 to 12 years for the treatment of productive cough associated with bronchospasm in conditions such as bronchitis and bronchial asthma as well as all conditions associated with tenacious mucus, wheezing and chest congestion.

Levosaltamol activates the adenyl cyclase and lowers the intracellular concentration of 3'5'-cyclic AMP (cAMP). Bronchial smooth muscles in the airways gets relaxed because of increased concentration of cAMP by reducing intracellular calcium level and prevents concentration of hyper-responsive airways. Increased concentration of cAMP also inhibits the release of eosinophils and inflammatory mediators from mast cells. Levosaltamol interacts with β_2 adrenoreceptors and has anti-edematous, bronchodilator and bronchoprotective properties and inhibits activation of

eosinophils and mast cells. Levosalbutamol has approximately 100 and 2 times greater binding affinity for β_2 adrenergic receptor than S Salbutamol and racemic salbutamol respectively.^[6]

Ambroxol hydrochloride is a mucolytic agent, it also increases bronchial secretion and reduces the viscosity of tenacious sputum and it expedites the removal of it by coughing. Ambroxol hydrochloride also upturns the clearance of mucociliary secretions.^[7,8]

Guaifenesin is an expectorant which increases the amount of output of bronchial secretions and sputum by reducing the viscosity of the secretions. It reduces the surface tension and adhesiveness of sputum. The improved flow of bronchial secretions endorses ciliary action which changes an unproductive, dry cough to less frequent and more productive. By reducing the adhesiveness and viscosity of sputum, It increases the efficacy of cough reflex, ciliary actions and mucociliary removal for accumulated bronchial secretions from the lower and upper airway.^[9]

Methodology

This was a Phase IV Clinical trial conducted with 23 Paediatric speciality investigators from different cities all across the India. The clinical trial was started in May 2017 and completed in October 2017. Total 380 patients were recruited for the study out of which 325 patients completed and 54 patients were lost to follow-up. Out of 325 patients 149 patients were of age group 2 to 12 years and 176 patients were of age group up to 1 year.

Inclusion and Exclusion criteria

Patients with confirmed diagnosis of productive cough associated with bronchospasm in conditions such as bronchial asthma and bronchitis as well as all conditions associated with tenacious mucus, chest and wheezing congestion were enrolled in the study. Patients of both the genders (male as well as female) having age up to 12 years and weight up to 48 Kg were recruited for the study. Finally the patients who were ready to strictly follow and adhere to the protocol and sign informed consent form (ICF) were recruited for the study.

Patients having hypersensitivity to any individual study drug of the study drug combination or to any of the excipient present in the dosage form and patients suffering from hepatic or renal dysfunction and patients who cannot adhere to the protocol i.e. mentally ill and patients with psychological problem were excluded.

Sample Size

The minimum sample size was decided to be kept 300 patients and by considering the loss of approximately 80 patients total 380 patients were recruited for the study out of which 54 patients were lost to follow-up and the total study was completed with 325 patients.

Study Intervention

A study drug combination of Levosalbutamol, Ambroxol Hydrochloride and Guaifenesin was used for the phase IV clinical trial. Different dose combination in different dosage forms were used for the infants and children. For infants of age up to 1 year, the combination of Levosalbutamol 0.25 mg, Ambroxol 7.5 mg,

Guaifenesin 12.5 mg and mentholated flavoured syrupy base quantity sufficient per ml was given in the form of oral drops dosage form and for children of age more than 2 years and up to 12 years the combination of Levosalbutamol sulphate equivalent to Levosalbutamol 1 mg, Ambroxol hydrochloride 30 mg, Guaifenesin 50 mg and Mentholated flavoured syrupy base quantity sufficient per 5 ml was given in the syrup dosage form.

Guardians of the patients recruited of age up to 1 year in the study were given 10 ml free physician sample of study drug combination drops. Guardians of children patients of age 2 to 12 years recruited in the study were given 2 bottles of 50 ml free physician sample of study drug combination syrup. Guardians will be advised to give it to the patients in the dose as per the following table for the clinical trial duration of 5 days.

Table 1: Dose of study drug combination syrup and oral drops to be given to the patients of different age group

Age	Body weight	dose	Dosage form of study drug combination
Up to 1 years	Up to 11.8 kg	2.5 ml tid	Oral Drops
2 - 5 years	2 – 21 kg	5 ml tid	Syrup
6 – 12 years	18 – 48 kg	10 ml tid	Syrup

Study procedure

The trial was conducted for the duration of 5 days. Patients who were suffering from productive cough associated with bronchospasm in conditions such as bronchitis and bronchial asthma as well as all the conditions associated with tenacious mucus, wheezing and chest congestion who met with the inclusion and exclusion criteria were recruited for the phase IV clinical trial. A detailed medical history was obtained and also physical examination was conducted for each patient recruited for the study by the investigators.

The study was conducted in 2 groups of patients, in 1st group, patients of age up to 1 year and in 2nd group the patients recruited were of age 2 to 12 years. For both groups of patients, the investigators selected were of paediatric speciality from all over the India. Patients of group 1 and group 2 were treated with the study drug combination, oral drops and syrup as per the table 1 for the clinical trial duration of 5 days.

All the guardians of the patients recruited for the study were instructed to maintain a diary of all the adverse events occurring during the study period. Three visits were planned for all the patients, the first visit was baseline visit (V1) on day 1 in which physical examination was done before treating the patient with the study drug combination. The second visit was reevaluation visit (V2) on day 3 and third visit (V3) was on day 5. Efficacy assessment was done with the help of cough severity scale and cough severity score (CSS) was recorded at all the visits. And for the assessment of safety the adverse events experienced by the patient or observed by the clinical trial investigator i.e. Dr was recorded. Investigators were asked to discontinue the study drug in case of severe adverse event and with discretion, clinical experience in case of mild or moderate adverse events. All the efficacy parameters and adverse events experienced by the patient or observed by the investigator were recorded in the case record form by the investigator, collected at the end of the trial and analysed.

Concomitant therapy

No Pharmacological intervention including any drug or drug combination other than study drug combination was allowed to take during the clinical trial duration of 5 days. Non-Pharmacological interventions like drinking of hot water at regular intervals or steam inhalation were allowed and encouraged during the study period.

Efficacy Assessment

The primary assessment was done by evaluating the reduction in CSS of all the symptoms related to cough on an eleven point scale. CSS is recorded with the help of cough severity scale which is an 11 point scale in which 0 is no symptoms and 10 means maximum symptoms. CSS scale was further extrapolated to Likert-type symptom severity scale where 0 on CSS scale means no symptoms, 1 to 3 means mild symptoms, 4-6 means moderate symptoms and 7-10 means severe symptoms.

In primary efficacy assessment decrease in mean CSS of all the patients at each visit, percentage decrease in CSS at visit 2 and 3 as compared to baseline was calculated. In secondary efficacy assessment percentage of patients having CSS of mild, moderate and severe intensity was calculated and presented graphically.

Safety assessment

Throughout the clinical study, investigators asked patients for any adverse events and if found then it was noted in the case report form (CRF) during each post-dose visit. Noted adverse events were classified into 2 categories as serious or non-serious adverse events. Adverse events were classified as drug related or nondrug related adverse events by using Naranjo’s scale of probability. Adverse events observed were followed up and treated if necessary by the investigators till their resolution.

Regulatory and Ethical matters

The study drug combination is currently available in India and classified under schedule H drugs i.e. it can be sold only in the presence of a prescription of a registered medical practitioner. All the patients recruited in the study have read informed consent form and signed the same. Clinical trial protocol, ICF, CRF, undertaking by the investigators form, ethical committee certificates were collected before initiating the clinical study.

Results

Total 380 patients were recruited at 23 centers across India, 325 patients completed the study. Demographic characteristics are mentioned in the table 2.

Table 2: Demographic characteristics of the patients recruited in the clinical trial

Mean age of patients (years)	2.89 years
No. of males patients	189
No. of females patients	136

Efficacy analysis

At baseline i.e. visit 1 the mean CSS score was 6.624 which was reduced to 3.744 after initiating the treatment with the study drug combination at visit 2 i.e. at day 3 and it was further reduced to 1.049 at visit 3 i.e. at day 5. Mean CSS at all the visits is presented graphically at figure 1.

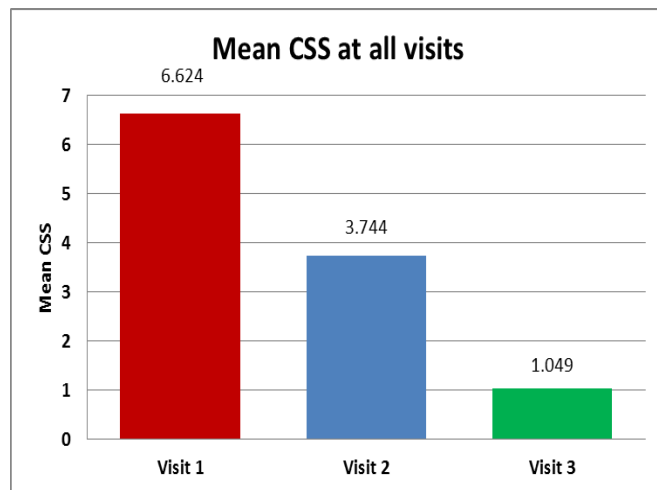


Figure 1: Mean CSS score at all the visits

As compared to baseline at visit 2 and visit 3 there was reduction of 43.478 % and 84.183 % at visit 2 and visit 3 respectively. Percentage decrease in mean CSS at visit 2 and 3 is presented graphically in figure 2.

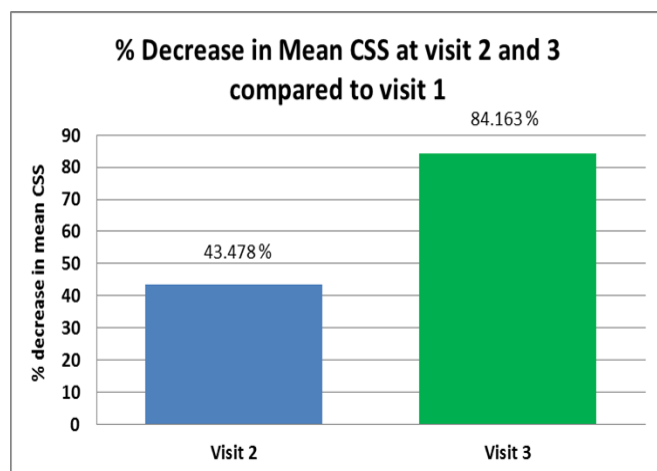


Figure 2: Percentage decrease in mean CSS at visit 2 and visit 3 as compared to baseline

CSS scale was further extrapolated to Likert-type symptom severity scale. At visit 1; 170, 134 and 21 patients were of severe, moderate and mild intensity of CSS respectively. At visit 2; 3, 192 and 126 patients were of severe, moderate and mild intensity of CSS and 4 patients were having no symptoms. At visit 3; 21 and 176 patients were of moderate and mild intensity of CSS. And at visit 2 and visit 3; 4 and 128 patients respectively had 0 CSS. All the patients having different CSS at visit 1, 2 and 3 is presented graphically in figure 3.

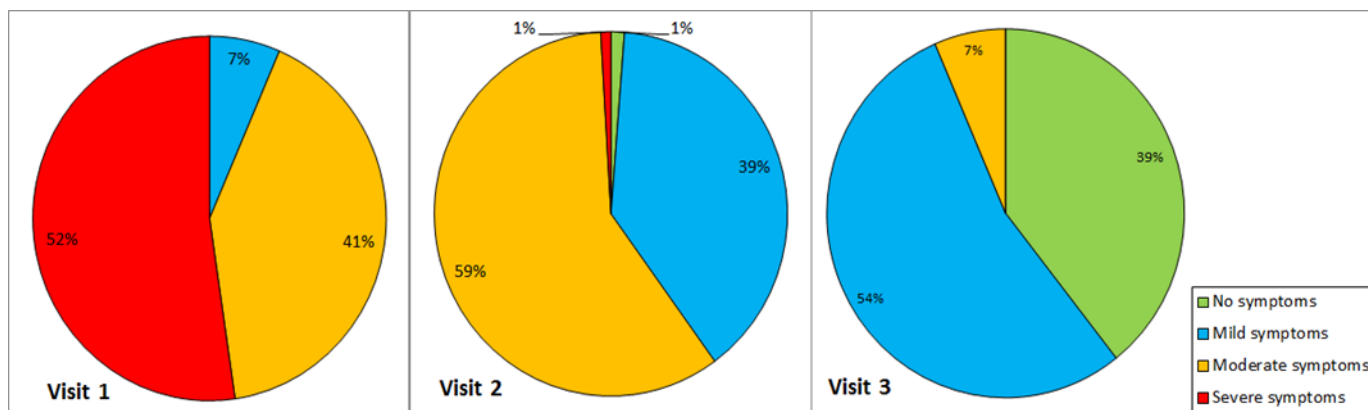


Figure 3: Patients having none, mild, moderate and severe CSS at visit 1, 2 and 3

Safety analysis

The overall incidences of reported study drug combination related adverse events were seen in 61 patients. The list of adverse events with the number of episodes is mentioned in Table 3.

Table 3: Adverse events, no. of episodes, no. of patients and percentage of patients experienced from total population

Adverse Events	No. of episodes	No. of patients	% of patients
Dizziness	54	31	9.538 %
Nausea	21	10	3.076 %
Heartburn	38	23	7.076 %
Diarrhea	32	15	4.615 %
Total	145	61	12.923 %

Discussion

According to A Vora et al productive cough can be treated by the combination of bronchodilators, expectorants and mucolytics.^[5] This PMS study was conducted to test the efficacy as well as safety for the combination of Levosalbutamol, Ambroxol and Ambroxol Hydrochloride for the treatment of productive cough associated with bronchospasm in conditions such as bronchitis and bronchial asthma as well as all conditions associated with tenacious mucus, wheezing and chest congestion in patients of age up to 12 years.

At baseline mean CSS score was 6.624 and after initiating the treatment the mean CSS was reduced to 3.744 at visit 2 which was further reduced to 1.049 at visit 3. At visit 2 the mean CSS score was reduced by 43.478 % which was further reduced to 84.163 % at visit 3 as compared to baseline. So the study drug combination was efficacious in reducing the CSS within 5 days. When the CSS score was extrapolated to likert scale then it was found that at visit 1, 170 patients were having severe symptoms of productive cough, 134 patients were having moderate symptoms and 21 were having mild symptoms. At visit 2 the number of patients having severe symptoms of productive cough were reduced to 3 which was 170 in number at baseline and the number of patients having moderate and mild symptoms were 192 and 126 respectively. At visit 2, 4 patients were completely cured from the productive cough symptom. At visit 3, no patient was having severe symptoms of productive cough, only 21 patients of moderate symptoms, 176 patients of mild symptoms and 128 patients were completely got symptomatic relief from productive cough. So at visit 3 total 39.38 % of patients got total symptomatic relief from the productive cough and 54.15 % of patients were having mild symptoms.

Mostafa Yakoot, Amel Salem and Abdel Mohsen Omar conducted the pragmatic, randomized, single blinded, comparative study to determine the efficacy in reducing symptom of cough, sputum and breathlessness. For study both male and female patients were shortlisted of age less than 45 years. Patients having history of smoking, patients diagnosed with acute cerebations and chronic bronchitis were recruited for the study. Total 100 patients were randomized to receive either the combination of Ambroxol (15 mg); Theophylline (50 mg); Guaifenesin (30 mg), per 5 ml syrup or Guaifenesine (100 mg) per 5 ml. In addition patients were received ciprofloxacin 500 mg, twice daily, for 7 days); inhaled or nebulized bronchodilator, salbutamol (two inhaler puffs or 5 mg in 2 mL saline nebulized); and/ or ipratropium 0.5 mg as needed, or up to four times daily or nebulized salbutamol. Breathlessness was measured on a 7-point Likert scale. Severity of cough and sputum clearance was measured using the Modified Questionnaire for Ease of Cough and Sputum Clearance. At the end of one week treatment, all patients were asked to grade their impression of improvement or change in their condition using the Clinical Global Impression of Improvement or Change Scale (CGIC), 11 which is a 7-point rated scale where 0 = not assessed; 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worsened; 6 = much worsened; and 7 = very much worsened. Baseline score for breathlessness for both study combination and Guaifenesin syrup was 4 which was reduced to 2 and 3 at day 3 for combination and single Guaifenesin syrup respectively. At day 7, score for breathlessness was further reduced to 1 and 2 for combination and single Guaifenesin syrup respectively. At baseline the cough score for both the groups was 16 which was reduced to 10 and 13 at day 3 for study combination and Guaifenesin respectively. At day 7 the cough score was further reduced to 8 and 12 for study combination and Guaifenesin respectively. So in the study duration it was found that study drug combination of Ambroxol (15 mg); Theophylline (50 mg); Guaifenesin (30 mg), per 5 mL syrup was more efficacious than Guaifenesin (100 mg) per 5 ml for reducing the breathlessness and cough score.^[8]

Kurli. Sankar et al conducted a parallel, comparative and prospective clinical trial to evaluate and compare the efficacy and adverse events causing by Salbutamol and Levosalbutamol. The study was conducted on total 210 patients and 105 patients in each group. One group was treated with 2mg racemic Salbutamol 3 times a day and second group was treated with 1 mg Levosalbutamol given orally thrice a day. Both the groups were treated for the study duration of 21 days. FEV1 was measured at baseline and after every 7 days as an efficacy evaluation parameter

and results were analysed statistically. At baseline FEV1 and % FEV1 for Salbutamol group was 1.54 and 76.51 % which was increased to 1.58 and 78.4 % at the end of the study and at baseline FEV1 and % FEV1 for Salbutamol group was 1.66 and 75.29 % which was increased to 1.72 and 78.43 % at the end of the study. The adverse events experienced by the patients because of Levosalbutamol were significantly low as compared to Salbutamol. Paired t test was used to compare the FEV1 and % FEV1 value before and after the study period in each group separately. In which T value of FEV1 and %FEV1 was 23.6956 and 23.6332 and P value of FEV1 and %FEV1 was <0.0001 and <0.0001. Improvements in FEV1 and %FEV1 values were statistically significant in Salbutamol and Levosalbutamol group. Finally it was concluded that both the drugs are efficacious but Levosalbutamol was more superior to salbutamol in terms of safety and tolerability.^[10]

Conclusion

Combination of Levosalbutamol 0.25 mg, Ambroxol Hydrochloride 7.5 mg and Guaifenesin 12.5 mg per ml and combination of Levosalbutamol 1 mg, Ambroxol hydrochloride 30 mg and Guaifenesin 50 mg per 5 ml is safe as well as efficacious for the treatment of productive cough associated with bronchospasm in conditions such as bronchitis and bronchial asthma as well as all conditions associated with tenacious mucus, wheezing and chest congestion in the paediatric population of age up to 1 year and of age 2 to 12 years respectively.

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Disclosure

This study was conducted as a part of Pharmacovigilance activity for Kofarest PD Drops and Kofarest LS Syrup of Centaur Pharmaceuticals Pvt. Ltd.

Conflict of Interest - None

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