Drug Corner

Safety & Efficacy of a Fixed Dose Combination of Paracetamol (125 mg), Phenylephrine (2.5 mg) and Chlorpheniramine Maleate (1mg) [Flucold Drops] in the Treatment of Common Cold and Flu Syndrome in Children : Postmarketing Surveillance Study

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Background :The common cold and flu syndrome primarily affects the upper respiratory tract, along with a low fever and some systemic symptoms such as sore throat, cough, nasal decongestion, headache, and so on. Several clinical studies have shown that combining analgesics, antihistaminics, and decongestants provides better symptom relief in the common cold. The current post-marketing surveillance study was designed to look into the safety and efficacy of commercially available Flucold Drops in the Indian population.

Methodology :A current prospective, single arm, multicenter, post-marketing clinical study included 224 subjects, 220 of whom completed the study. All patients were given Flucold Drops for three days and then monitored for the next six days. During the study, the incidence of adverse events (AE) and serious adverse events (SAE) was assessed. The efficacy of the Flucold Drops was evaluated using VAS score changes from the beginning to the end of the treatment. The product's safety was also evaluated using blood biomarkers such as haemoglobin, platelet count, SGOT, SGPT, and creatinine level.

Results : Results show the reduction in symptomatic score of common cold and flu syndrome observed after 2rd follow-up visit (0.202±0.325 to 0.139±0.231). During the study, no intervention-related adverse events were observed. Furthermore, no Serious Adverse Events (SAE) were observed in the study or follow-up period. The study found no changes in the levels of blood biomarkers (haemoglobin, platelets, SGOT, SGPT, and creatinine).

Conclusions : Flucold Drops are safe and effective in the treatment of common cold and flu syndrome in Children and infants.

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***Key words* : Flucold Drops is a fixed dose combination of paracetamol (125 mg), phenylephrine (2.5 mg) and chlorpheniramine maleate (1mg), SGOT, SGPT, Flu syndrome, Congestion, Haemoglobin.**

The common cold and flu are an acute viral infection occur in the upper respiratory tract which involves the nose, sinuses, pharynx and larynx. The virus is propagated by when person comes in contact with secretions from an infected patient and virus[1]. The period require for incubation varies but it is two days for rhinovirus[2]. Symptoms of common clod and flu are associated with infected mucosa usually peak within 1 to 3 days and remain for at least 7 to 10 days however they persist for 3 to 5 weeks[1,3-5]. They consist of rhinitis, sore throat, malaise and cough[1,4]. The severity and variety of symptoms will differ within individuals and with several infective agents. For example, fever is observed commonly in children but rare and comparatively mild in adult[1]. The common cold occurrence decline with age[5-7]. In terms of infection frequency, children under two years of age have about 6 infections a year, adult 2 to 3 and old age people about one every year[5-9]. Factors such as stress and poor sleep pattern elevated the risk of common cold and flu in adults whereas attendance at day care center increases risk in preschool children[10-12].

Because of its high prevalence, particularly among children, the common cold imposes a significant economic and social burden[13,14]. Symptoms of the common cold in children usually peak shortly after the onset of illness[15]. The duration of the symptoms is approximately 7-10 days, but it can range from 2-14 days[16]. The common cold can be difficult to diagnose and treat in young children and infants who are unable to communicate their symptoms.

Treatment of cold and flu in children involves use of conventional medicines such as antipyretics, cough suppressants and decongestant. These agents expected to rapidly improve the comfort of ill child,

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cough and antiviral medicines. Symptomatic treatment of common cold and flu have been evaluated by meta-analysis and found that use of monotherapy is not efficient in enhancement of symptoms in children and adult[17]. In another meta-analysis, investigators evaluated the use of nasal decongestant in 286 subjects and no beneficial effect in nasal decongestion[18,19]. Effectiveness of combination comprised of antihistamine-decongestant-analgesic in reducing duration of symptom of common cold was evaluated in children and adult using Cochrane meta-analysis. The results of the study showed that combination provide general benefits in adults however no evidence of effectiveness is available in children[20].

The current study investigated the safety and efficacy of Flucold Drops [Fixed dose combination of paracetamol (125 mg), phenylephrine (2.5 mg), and chlorpheniramine maleate (1mg)] in the treatment of common cold and flu syndrome in children.

Currently, no clinical trial assessed for the efficacy and safety of Flucold Drops (Wallace Pharmaceuticals) in the treatment of common cold and flu syndrome in infants and children. This was the first clinical trial conducted in India designed to assess the adverse events associated with fixed-dose combination.

Material and Methods

Study Design & Participant :

In a prospective, interventional, multicenter, post marketing study, 224 participants were enrolled.

Study was conducted in accordance with the ICMR guidelines, New Drugs and Clinical Trial Rules 2019 India, & the Declaration of Helsinki (Brazil 2013) & the ICH E6, R2, "Guidance on Good Clinical Practice" (GCP). Furthermore, the trial was approved by Royal Pune Independence Ethics Committee, Prakash Institutional Ethics Committee & SPARSH Hospital Institutional Ethics Committee (ICBio/CR/WPPL/0309/109).

Total 224eligible participants with common flu and cold were treated with Flucold Drops (WALLACE Pharmaceuticals). The total duration of the study for the patient was 9 days (03 days medications with 6 days of follow-up).Study included patients between the age of 6 month to 12 years with recent onset of symptoms not less than 72 hrs such as common cold (with symptoms such as sneezing, rhinorrhea, nasal congestion, headache, discomfort in throat) & flu syndrome (with symptoms such as high-grade fever, headache, chest discomfort, dizziness). Patients with known hypersensitivity, seasonal perennial allergic rhinitis, recent history of influenza vaccination, severely immune compromised patient excluded from the study.

Participant removal or withdrawn criteria :

The investigator has the authority to withdraw a patient from the study for any of the following reasons: the occurrence of an adverse event associated with the administration of the IP, necessitating its cancellation; the emergence of any diseases or conditions during the study that worsen the patient's prognosis and make it impossible for the patient to continue participating in the clinical study; the need for a prohibited concomitant therapy; Patient pregnancy; research protocol violations; inappropriate inclusion of a patient who did not fulfil the inclusion criteria and/or met the applicable exclusion criteria; other serious protocol violations, according to the investigators; The patient withdraws his or her informed consent. Four patients were removed from the study due to absenteeism during the follow up.

Recruitment :

Suitable subjects, who agree to participate in the study were recruited from 3 sites (Jyothi Multispecialty Clinic, MAVEN's Hospital&Basaveshwara Medical College and Hospital Chitradurga. Each site recruited the participants who have voluntarily visited each trial site for enrollment.

Intervention :

After selection of the subjects, all were treated with FLUCOLD drops (consisting of a fixed-dose combination of Paracetamol 125 mg + Phenylephrine HCl 2.5 mg + Chlorpheniramine maleate 1 mg/ml)(Wallace Pharmaceutical Pvt. Ltd.) for three days and follow up of performed for the next 6 days (Fig 1).

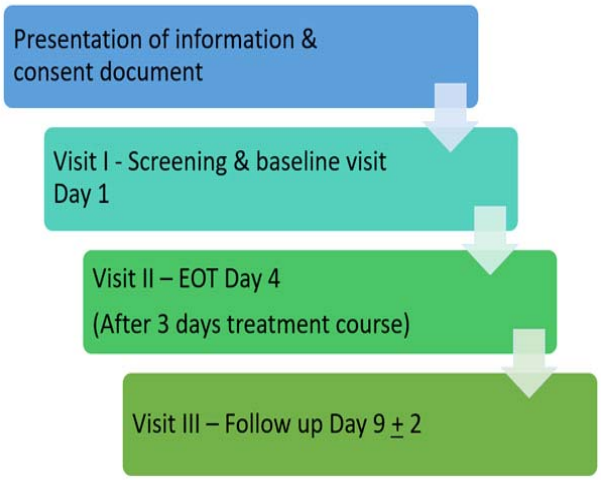

Fig 1 — Study Flow Chart

Outcome Measures :

Primary outcome measure

To evaluate the safety of fixed-dose combination Flucold Drops (Paracetamol 125 mg + Phenylephrine HCl 2.5 mg + Chlorpheniramine maleate 1 mg /ml) from Wallace Pharmaceutical Pvt Ltd in the treatment of common cold and flu syndrome in the children and infants. During the study, Treatment-emergent Adverse Events (TEAE) and serious adverse events were reviewed.

Secondary outcome measures

Subjects were evaluated for secondary outcome which included evaluation of relief from common cold and flu syndrome, significant changes in Visual Analogue Score (VAS) & safety of drops measured in terms of hemoglobin, platelet, SGOT, SGPT & creatinine levels.

Statistical Analysis :

Data analysis was performed using ANOVA & $\div^2$ test &SAS version 9.1 INC, CARY, USA used during the analysis. Efficacy analysis was performed for the per-protocol (PP) population. Primary efficacy was based on PP patients' samples.

Results

During the study, total of 224 patients were enrolled in the study from 3 sites out of which 4patient withdrew from the study (Fig 2).

The mean age of the participants included in the study was 4.711±3.251 years whereas average weight & height was 17.519±8.247 kg & 100.511 ±25.943 cm respectively. The average BMI calculated during the study was found to be at 15.828±2.44 kg/m^2.

Table 1 — *Demographic data of the patient*

Demographics of patient	Values
Age	4.711 ± 3.251
Weight	17.519 ± 8.247
Height	100.511 ± 25943
BMI	15.828 ± 2.440

During the study, no intervention-related adverse events were observed. Furthermore, no treatment related & Serious Adverse Events (SAE) were observed during the study and follow-up period.

During the study, reduction in total symptom score from day 1 to day 4 and during follow up was assessed by using a 4-point scale (0- No symptom, 1-Mild, 2-Moderate, 3-Severe). Study results indicated that use of Flucold Drops in children total symptom score reduced significantly ($p<0.001$) from 0.302 ± 0.325 (visit 1) to 0.000 ± 0.000 (Visit 3) (Fig 3).

Severity of the flu and syndrome was assessed by using change in Visual analogue score (VAS) in children. Treatment with Flucold Drops in children leads to significantly ($p < 0.05$) change in VAS score from 4.532 ± 1.438 (Visit 1) to 0.000 ± 0.000 (Visit 3)(Fig 4).

Flucold Drops tolerability was analysed during the study in each subject& tolerability scale was used during the analysis. During the study, it was observed that no side effects were observed and Flucold Drops was well tolerated in children (Table 2).

Further safety of the product was evaluated by analysing biomarker levels such as haemoglobin, platelet, liver and kidney function test at the end of the study. No effect was exerted by Flucold Drops on haemoglobin (11.950 ± 0.739) and platelet (210.214 ± 119.047) count during the study (Table 3). Liver biomarkers such as SGOT and SGPT levels analysed and found to be at 21.809 ± 5.978 and 22.610 ± 7.321 respectively in children (Table 3). The levels of liver biomarker were not elevated after the intervention indicating the safety of Flucold Drops in subjects. Kidney function was analysed using serum creatinine level and no elevation

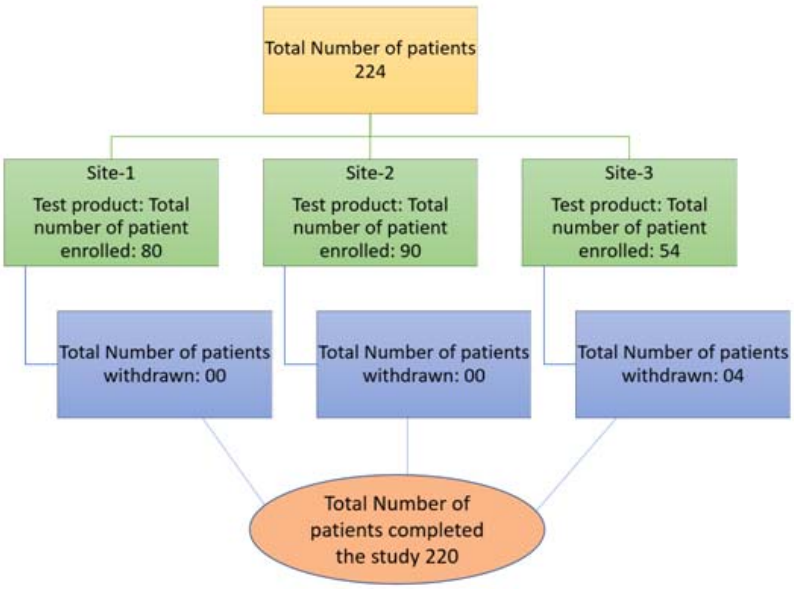

Fig 2 — Deposition of the patient

Table 2 — *Frequency count for FLUCOLD Drops tolerability*

Scale	No. of Subjects
Very good (No Side effects)	220
Good (insignificant side effects which do not cause serious problems to the Patient)	0
Satisfactory (side effects which affect the patient's condition, but do not necessitate discontinuation of the formulation)	0
Unsatisfactory (adverse side effect which significantly affects the patient's condition and necessitates discontinuation of the formulation)	0
Highly unsatisfactory(adverse side effect which necessitates Discontinuation of the formulation and use of additional clinical measures)	0

in creatinine levels (0.603 ± 0.1845) was observed after intervention (Table 3).

Table 3 — *Biomarkers of systemic safety after FLUCOLD treatment*

Demographics of patient	Values
Haemoglobin	11.950 ± 0.739
Platelet count	210.214 ± 119.047
SGOT	21.809 ± 5.978
SGPT	22.610 ± 7.312
Creatinine	0.603 ± 0.1845

Discussion

In a current prospective, multicentre, single arm, post-marketing surveillance study efficacy and safety of Flucold Drops was analysed in Children. The study results revealed that Flucold Drops is effective in reducing symptoms of cold and flu syndrome from baseline in children within 3 visits. The mean score changes from 0.302 ± 0.325 to 0.00 ± 0.00 during the retreatment. Biomarker evaluation demonstrated that Flucold Drops have no effect on liver and kidney function parameters of the subject. No major changes were observed in haemoglobin (11.950 ± 0.739) and platelet count (210.214 ± 119.047) after administration of Flucold Drops. Liver and kidney function test parameters indicate that Flucold Drops are safe to use in infants and children. During the study no treatment emergent adverse events (TAEs) and Serious Adverse Events (SAEs) was reported during the study demonstrate that Flucold Drops are safe in the children.

Currently no study available on effectiveness and safety of paracetamol, phenylephrine and chlorpheniramine combination in children with common cold and flu symptom.However different studies conducted on adult shows that combination of chlorpheniramine maleate, paracetamol, and phenylephrine is effective in the treatment of common cold and flu symptoms.

The effectiveness and safety of chlorpheniramine maleate, paracetamol, and phenylephrine combination evaluated by Picon et al in 146 subjects. Study findings revealed that after treatment with fixed dose combination for 10 days reduced symptom score from 14.09 to 3.54 and no adverse effects observed in the subjects[21]. The results of the study are in line with current study.

Similarly, a phase IV open labelled multicentre study was conducted in 159 patient and found that mean TSS reduced from 6.62 (Day 1) to 0.69 (Day 5). Mist patient included in the study had more than 50% reduction in total symptom score at visit 3 and 58.49% patient had complete relief from symptom[22].

Eccles et al. suggested the combination of products to treat the symptoms of the common cold and flu. When used as directed, multi-ingredient combination products for multi-symptom relief are formulated to

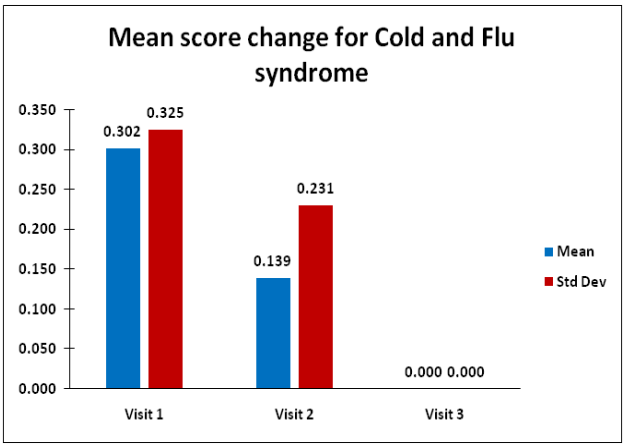

Fig 3 — Mean score change for cold and flu syndrome after Flucold Drops

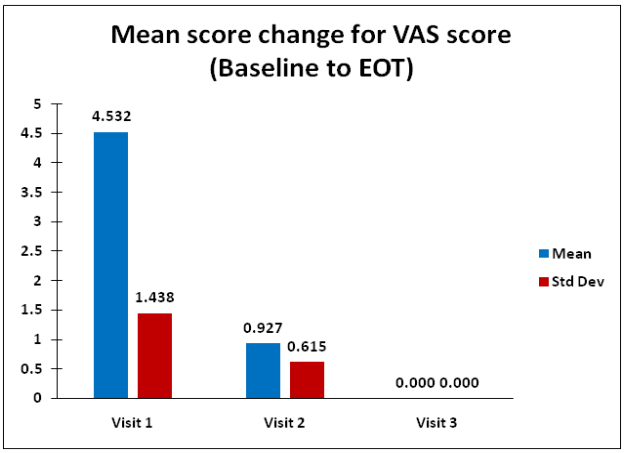

Fig 4 — Significant changes in VAS score from baseline to EOT

safely, simply, and simultaneously treat multiple symptoms. As a result, the rationale for the formulation for common cold and flu is practical, logical, and reasonable. There is no evidence that multi-symptom relief medications are inherently less safe than single-active ingredient medications. When used as directed, multi-symptom relief combination products containing several active ingredients provide a safe, effective, cost-effective, and convenient way of treating the multiple symptoms of the common cold and flu[23].

Our study results showed that symptoms of common cold and flu syndrome were resolved mostly on the second visit and no drug-related side effects were observed during the treatment and follow-up in children and infants.

Conclusion :

After 5 days of treatment with FLUCOLDdrops, substantialdevelopment in symptomatic relief of common cold and flu syndrome was observed in children and infants. Our study demonstrated that fixed dose combination of Paracetamol 125 mg, Phenylephrine 2.5 mg, Chlorpheniramine maleate 1mg per ml, provides optimum symptomatic relief and is safe for use in the symptomatic management of common cold and flu.

References

1 Heikkinen T, Järvinen A — The common cold. Lancet 2003; 361: 51-9.
2 Lessler J, Reich NG, Brookmeyer R — Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect Dis* 2009; **9:** 291-300.
3 Lober B. The common cold. *J Gen Intern Med* 1996; **11:** 229-36.
4 Arruda E, Pitkäranta A, Witek TJ Jr — Frequency and natural history of rhinovirus infections in adults during autumn. *J Clin Microbiol* 1997; **35:** 2864-8.
5 Leder K, Sinclair MI, Mitakakis TZ — A community-based study of respiratory episodes in Melbourne, Australia. *Aust N Z J Public Health* 2003; **27:** 399-404.
6 Monto AS, Sullivan KM — Acute respiratory illness in the community. Frequency of illness and the agents involved. *Epidemiol Infect* 1993; **110:** 145-60.
7 Monto AS — Epidemiology of viral respiratory infections. *Am J Med* 2002; **112(Suppl 6A):** 4S–12S.
8 Nicholson KG, Kent J, Hammersley V — Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ* 1997; **315:** 1060-4.
9 Kvaerner KJ, Nafstad P, Jaakkola JJ — Upper respiratory morbidity in preschool children: a cross-sectional study. *Arch Otolaryngol Head Neck Surg* 2000; **126:** 1201–6
10 Cohen S, Tyrrell DA, Smith AP — Psychological stress and susceptibility to the common cold. *N Engl J Med* 1991; **325:** 606-12.
11 Cohen S, Doyle WJ, Alper CM — Sleep habits and susceptibility to the common cold. *Arch Intern Med* 2009; **169:** 62-7.
12 Ball TM, Holberg CJ, Aldous MB — Influence of attendance at day care on the common cold from birth through 13 years of age. *Arch Pediatr Adolesc Med* 2002; **156:** 121-6.
13 Fendrick AM, Monto AS, Nightengale B, Sarnes M — The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch Intern Med* 2003; **163(4):** 487-94
14 Eccles R — Understanding the symptoms of the common cold and influenza. *Lancet Infect Dis* 2005; **5(11):** 718-25.
15 Pappas DE, Hendley JO, Hayden FG, Winther B — Symptom profile of common colds in school-aged children. *Pediatr Infect Dis J* 2008; **27(1):** 8-11.
16 Tilston NL, Eames KT, Paolotti D, Ealden T, Edmunds WJ — Internet-based surveillance of Influenza-like-illness in the UK during the 2009 H1N1 influenza pandemic. *BMC Public Health* 2010; **10:** 650.
17 Sutter AI, Lemiengre M, Kumar AA, Lesslar O, Skrt A — Oral antihistamine-decongestant-analgesic combinations for the common cold. *Cochrane Database Syst Rev* 2012; 2 CD004976.
18 Simasek M, Blandino DA — Treatment of the common cold. *Am Fam Physician* 2007; **75(4):** 515-20
19 Taverner D, Latte J, Draper M — Nasal decongestants for the common cold. *Cochrane Database Syst Rev* 2004; (3): CD001953.
20 Taverner D, Latte J, Draper M — Nasal decongestants for the common cold. *Cochrane Database Syst Rev* 2004; **(3):** CD001953
21 Picon PD, Costa MB, da VeigaPicon R, Fendt LC, Suksteris ML, Saccilotto IC, *et al* — Symptomatic treatment of the common cold with a fixed-dose combination of paracetamol, chlorphenamine and phenylephrine: a randomized, placebo-controlled trial. *BMC Infect Dis* 2013; **13:** 556
22 Kiran MD — Efficacy and safety of a fixed dose combination of paracetamol, chlorpheniramine maleate and phenylephrine in treatment of common cold: a phase IV, open-labelled, multi-centric study. *Int J Basic Clin Pharmacol* 2019; **8(1):** 34-8.
23 Eccles R, Fietze I, Rose UB — Rationale for Treatment of Common Cold and Flu with MultiIngredient Combination Products for Multi-Symptom Relief in Adults. *Open J Resp Dise* 2014; **4:** 73-82.