Comparison of Efficacy and Safety of *Vitex negundo* 600 mg (Ascof® Forte) Capsules with *Vitex negundo* 600 mg (Ascof® Forte) Tablets in the Treatment of Acute Uncomplicated Cough among Filipino Adults in Cavite

Clinical Trial Phase 3b

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ABSTRACT

Objectives. *Vitex negundo* is an endemic shrub in the Philippines which has been clinically tested for the symptomatic treatment of cough in syrup and tablet formats. However, the effectiveness and safety of the capsule have not been formally documented in a clinical trial setting. Therefore, in compliance with the Philippine FDA directive, this study compared the efficacy and safety of the capsule and tablet formats after three days of treatment among Filipinos with acute uncomplicated cough.

Methods. This is a Phase 3b randomized, open-label, parallel-group non-inferiority study with 335 subjects using improvement based on Global Rating of Change Scale scores as primary efficacy endpoint and several secondary endpoints. Descriptive and inferential analyses were performed. The Farrington-Manning Method of Z-test with -10% non-inferiority margin was used for the primary outcome. Appropriate inferential tests were used for the secondary outcomes.

Results. Of 335 enrolled subjects, 170 were randomized to the capsule group and 165 to the tablet group with comparable baseline characteristics. The proportion of success based on the Global Rating of Change Scale rated by patients was 95.71% and 91.19% for the capsule and tablet groups, respectively. Based on doctors' ratings, they were 96.93% and 94.34%, respectively. In addition, the Farrington-Manning Method of Z-test revealed the capsule was not inferior to the tablet based on patients' and doctors' ratings (90% Confidence Intervals: -0.0086 to 0.0988 and -0.0228 to 0.0747, respectively). The intention-to-treat analysis also showed non-inferiority, indicating robust results. Significant and similar improvements in cough severity and quality of life were observed in both groups based on Cough Severity Diary scores and Leicester Cough Questionnaire for acute cough, respectively. There were also improvements in the Forced Expiratory Volume at 1 second [FEV_1] (capsule group) and Peak Expiratory Flow Rate [PEFR] (both groups), but these were not clinically significant. The safety profiles were also comparable (p= 0.4437) with 1.23% and 2.52% incidence of adverse events, respectively, all of which were mild and assessed as not related to the drug.

Conclusion. In terms of efficacy, Ascof® Forte capsule was non-inferior to Ascof® Forte tablet in treating acute uncomplicated cough among Filipinos based on Global Rating of Change Scale scores as rated by patients and doctors. Both treatments showed significant and similar improvements in cough severity and quality of life. They were also comparable in safety with few adverse events in both groups, all mild and assessed unrelated to drug intake.

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INTRODUCTION

Vitex negundo is a shrub that is endemic in the Philippines. Known locally as Lagundi, it has been clinically tested to effectively treat cough due to colds, flu, bronchial asthma, chronic bronchitis, and pharyngitis.

The tablet and capsule formulations of *Vitex negundo* are registered as drugs indicated for the treatment of mild to moderate cough due to common colds and flu and mild to moderate acute bronchitis and for mild to moderate bronchospasm with obstructive airway disease such as asthma and chronic bronchitis.[1,2]

Vitex negundo has been available in the Philippines in tablet and syrup formulations. In clinical trials involving Filipino children and adults, Lagundi has been found effective at doses of 15 mg/kg and 45 mg/kg in reducing cough frequency and severity. Based on the patients' global assessment of efficacy, 84% of patients rated the treatment after four days as successful.[3] In addition, a double-blind, randomized controlled trial compared the mucolytic effect of *Vitex negundo* syrup with ambroxol (a mucolytic) and placebo in pediatric patients. Results showed that Lagundi significantly improved the liquefaction of phlegm compared to ambroxol and placebo at day 3 and day 5, and both Lagundi and ambroxol have significantly better liquefaction of phlegm compared to placebo (p-values <0.05).[4]

While a capsule formulation of *Vitex negundo* has been introduced in the market, there has been no formal documentation of its parity with the tablet formulation. Therefore, this study has addressed the need to establish that the capsule formulation is non-inferior to the tablet formulation in treating acute cough. Consequently, it is a non-inferiority study conducted in the Philippines in compliance with the Philippine FDA directive to establish parity of Ascof® Forte capsule with Ascof® Forte tablet formulation in terms of efficacy and safety, and thereby to provide clear clinical evidence of its therapeutic benefit for people suffering from acute uncomplicated cough.

METHODS

Study design

This non-inferiority study was a Phase 3b randomized, open-label, parallel-group study in adult Filipino subjects with acute uncomplicated cough, defined as cough of less than 14 days duration with no fever, chest pain, or difficulty of breathing. The primary objective was to determine and compare the efficacy of *Vitex negundo* 600 mg capsules with *Vitex negundo* 600 mg tablets given three times a day for three days to treat acute uncomplicated cough among Filipinos aged 18 to 55 years. A secondary objective was to evaluate the safety and tolerability of the above medications under the same conditions. This Phase 3b clinical trial aimed to determine if the Ascof® Forte capsule formulation was non-inferior to the Ascof® Forte tablet formulation based on the Global Rating of Change Scale scores. A non-inferiority design was chosen to establish if the capsule formulation is at least as good as the tablet formulation in terms of efficacy with a non-inferiority margin set at minus ten percent (-10%). This was based on a meta-analysis of three randomized clinical trials that compared the percentage of patients based on the patient's global impression of improved severity of cough after eight days of treatment with Lagundi syrup or placebo.[5] Pooled results showed a response rate of 94.8% in the Lagundi group compared with 50% in the placebo group for a difference of 44.87%. We sought to retain about 75% of the treatment effect (i.e., around 33.65%) in setting the non-inferiority limit or a difference of around -11.21%. For simplicity, the more conservative -10% difference was selected as the non-inferiority margin. Setting at least 75% retention of treatment effect as the non-inferiority margin is more stringent than the 50% retention implicitly recommended by a draft US FDA Guideline.[6]

The details of the test drugs employed were as follows: Ascof® Forte 600 mg capsule manufactured by Pascual Laboratories, Inc. with Batch No. 331GOI; and for the tablet formulation: Ascof® Forte 600 mg tablet manufactured by Pascual Laboratories, Inc. with Batch No. 124GWB.

The study was conducted from January to February 2018. Subjects were randomized to receive either Ascof® Forte tablets or capsules. Treatment allocation was randomized using a randomization plan generator. Twelve tablets or capsules were dispensed with instruction to take the drug three times a day for three days, with the extra three provided allowance for possible losses. The assigned drug was taken orally with a glass of water three times a day for three days.

On the day of the first scheduled dose of the study drugs (Visit 1), subjects who gave signed informed consent to participate in the study were screened for eligibility and subsequently enrolled. Participants were asked to maximally blow through Vitalograph asma-1 three times with the highest values of Forced Expiratory Volume in 1 second (FEV_1) and Peak Expiratory Flow Rate (PEFR) recorded in the Case Report Form. Participants were then asked to complete baseline measurements, including Cough Severity Diary (CSD) and Leicester Cough Questionnaire for acute cough (LCQ-acute).

After completion of the three-day treatment period, participants repeated the assessments with the addition of the Global Rating of Change Scale scoring. All rating methods used Visual Analog Scales. Tablet and capsule counts of the study drugs were conducted on the last visit to assess compliance with the treatment regimen. Each participant was asked to complete a Study Diary that contained volunteer name, study visit dates, and time of intake of study medications on days 1 to 3. The importance of taking the medications on schedule was emphasized during enrollment.

Safety assessments focused on adverse events experienced by the participants after enrollment and were checked during the final assessment at Visit 2. On adverse

events, the attending physician completed the Adverse Event page in the Case Report Form. In addition, they entered the type of adverse event, severity, onset, treatment, if any, and a causality assessment. No radiographic nor serological examinations were planned as treatment guidelines did not recommend these for acute uncomplicated cough.

The Protocol and Informed Consent Form were reviewed and approved by the Ethics Review Board of University of the East Ramon Magsaysay Memorial Medical Center, Inc. (UERMMMCI).

Study participants

Males and females aged 18 to 55 years living in Cavite and diagnosed with acute uncomplicated cough were included in the study. The five sites that participated were: Gentri Medical Center and Hospital, Pagamutan ng Dasmariñas, Imus City Health Office, Carmona Municipal Health Office, and Silang Rural Health Unit. The study doctors were physicians from the participating City Health Offices. They underwent Good Clinical Practice and Study Protocol training before study initiation. All study procedures were discussed during the training, including the use of the questionnaires and the peak flow meters.

Using the proportion of success at Day 4 in patients given Ascof® Forte tablet formulation in a previous study which was 84%, assuming a power of 80% and a 5% level of significance and allowing for a -10% margin of difference, at least 93 patients per group were needed to determine non-inferiority if the proportion of success in the Ascof® Forte capsule group was assumed to be 80%. With a β equal to 0.2, the power is equal to 1- β or 80%. This is an acceptable power in drug trials and reflects the ability of the study to detect a difference when there is a true difference. However, the FDA suggested enrollment of at least 150 subjects per group to increase the likelihood of acceptability of the study size to other regulatory agencies, should the submission be decided by the sponsor later, citing different regulatory requirements across countries and ongoing discussion among ASEAN member countries on this requirement. Considering the calculated sample size of 93 patients per group, enrolling at least 150 subjects per group would have adequate power to detect the primary outcome.

Targeting a sample size of at least 150 per group or 300 for both groups, the proposed five sites were to enroll around 60 patients each. However, considering attrition and differences in enrollment rates, each site was allowed to register anywhere from 60 to 70 patients. In addition, a 10% allocation for drop-outs was provided, bringing the total target sample size to 330. Recruitment was stopped on the day when the target number was reached.

Exclusion criteria were: any evidence or history of clinically significant diseases which may put the subject at risk because of participation in the trial such as cardiovascular, liver, or renal disease; recorded vital signs outside of normally defined limits; acute chest pain; history of hypersensitivity to *Vitex negundo*; treatment with corticosteroids, beta-2 agonists, expectorants, theophylline, antitussives, anesthetics, acetylsalicylic acid, or other non-steroidal anti-inflammatory drugs, leukotriene inhibitors, angiotensin-converting enzyme inhibitors, antiviral drugs or antibiotics, antihistamines, immunosuppressants, isoprenaline, atropine, sodium cromoglicate or herbal drugs against common colds, flu, and acute bronchitis within three days before inclusion into the study; drug or alcohol abuse in the opinion of the investigator; pregnant or lactating women; current smoker; patients needing immediate evaluation/management for conditions other than acute cough.

Grounds for discontinuation or withdrawal of a patient from the study included: significant study intervention non-compliance; occurrence of any clinical adverse event, laboratory abnormality, or other medical condition or situation such that continued participation in the study would not be in the best interest of the participant; disease progression which requires discontinuation of the study intervention; and development of an exclusion criterion by the patient (either newly developed or not previously recognized) that precludes further study participation.

Participants were free to withdraw from the study at any time upon request without necessarily giving a reason for it and without penalty. However, a participant was considered lost to follow-up if he or she failed to return on Day 4 or Day 5 and could not be contacted by the study site staff.

Primary and secondary outcome measures

The primary outcome measure was Global Rating of Change Scale (GRCS) scores. It is often used in assessing whether a drug is effective or not. The patient was asked to determine if his condition worsened or improved using an 11-point visual analog scale. GRCS offers a flexible, quick, and simple method of charting self-assessed clinical progress in research and clinical setting.[7] This instrument had the advantage of clinical relevance, adequate reproducibility, and sensitivity to change and is intuitively easy to understand by the patient and the administering personnel. A score of +2 is considered a treatment success.

The efficacy-related secondary outcome measures used in the study were Cough Severity Diary (CSD) score, Leicester Cough Questionnaire for acute cough (LCQ-acute) for quality of life, Forced Expiratory Volume at 1 second (FEV_1), and the Peak Expiratory Flow Rate (PEFR).

In assessing the severity of cough, we should consider the frequency of coughing and evaluate the severity and impact of cough intensity. A CSD score is a brief tool comprised of 7 items selected based on feedback from patients themselves.[8]

The LCQ-acute is a 19-item questionnaire comprising three domains: physical, psychological, and social. It is a brief, easy-to-use scoring system.[9,10] It was developed using a patient-rated importance scale, also known as the clinimetric method. It is well-validated with excellent internal reliability, repeatability, and responsiveness.

FEV_1 and the PEFR are objective parameters that measure lung function and indicate airway caliber, which may or may not be affected by coughing.

The secondary outcome of safety was assessed, as in other clinical trials, based on the type, severity, frequency, and causality assessment of adverse events in both groups.

Statistical methods

For descriptive statistics, categorical data were presented as frequency distributions with percentages. Continuous data were presented as measures of central tendency (mean and median) and variation (standard deviation and range). For inferential tests, an α of 0.05 and a β of 0.20 were used.

The Farrington-Manning Method of Z-test for testing significance of difference in the proportions of success in the two treatment groups was used with a non-inferiority margin set at -10%.

The baseline scores in Cough Severity Diary scoring and Leicester Cough Questionnaire scoring were compared to the final scores. The significance of the differences within groups was tested using Wilcoxon signed ranks test. Comparison of baseline to end-study changes between the groups was performed using the Wilcoxon-Mann-Whitney test.

Airway treatment responses were measured using Forced Expiratory Volume in one second (FEV_1) and Peak Expiratory Flow Rate (PEFR). In addition, the difference in the changes from baseline to end-study values were compared using an independent t-test.

Safety was assessed using the frequency of adverse events compared between groups using Fisher's Exact Test.

RESULTS

Study population

A total of 338 patients were screened, of which 335 were eligible for randomization. One hundred and seventy patients were randomized to Ascof® Forte capsule and 165 to Ascof® Forte tablet (Table 1). The mean ages of the capsule and tablet groups were 33.2 and 33.3 years, respectively. The p-value of 0.9238 indicates that there was no significant difference in mean age between the two groups. In addition, the sex and marital status distributions were similar with p-values of 0.8574 and 0.6596, respectively. This indicates that the two groups were comparable as to age, sex, and marital status.

Of the 170 patients randomized to the capsule group, six were lost to follow-up, and one was withdrawn, leaving 163 patients. The withdrawal of one patient was before the second visit, and due to a protocol violation, particularly non-compliance with the dosing instructions, taking two capsules every night instead of one. Of the 165 randomized to the tablet group, six were lost to follow-up leaving 159 patients.

Efficacy results

Treatment success, the primary outcome, was based on the Global Rating of Change scores given by patients and doctors. The mean rating of 3.5 by the patients in both groups was similar. The mean rating of 3.7 by doctors was also identical for both groups. The proportion of success assessed by patients was 95.71% and 91.19% in the capsule group and tablet group, respectively. Furthermore, the proportion of success assessed by doctors was 96.93% and 94.34% in the capsule group and tablet group, respectively. (Table 2).

The proportion difference assessed by patients was 4.51% in favor of the capsule group and 2.59% in favor of the capsule group as evaluated by doctors (Table 3). Thus, the Farrington-Manning Method of the Z-test for testing significance of the difference in proportions confirmed that the proportion of success in the capsule group was not lower by 10% compared to the tablet group; it was, in fact, numerically higher as assessed by patients and doctors, although not statistically significant.

The lower boundary of the 90% confidence interval of the proportion difference as evaluated by the patients

Table 1. Subject Demographics by Treatment Group; Cavite 2018 (N=335)

Characteristic	Statistic	Ascof Capsule (N=170)	Ascof Tablet (N=165)	Overall (N=335)	p-value
Age (years)					0.9238
	Mean (SD)	33.2 (11.71)	33.3 (11.32)	33.2 (11.50)	
	Median	31.0	31.0	31.0	
	Range	18-55	18-55	18-55	
Gender					0.8574
Male	n (%)	81 (47.65)	77 (46.67)	158 (47.16)	
Female	n (%)	89 (52.35)	88 (53.33)	177 (52.84)	
Marital Status					0.6596
Single	n (%)	116 (68.24)	115 (69.70)	231 (68.96)	
Married	n (%)	49 (28.82)	44 (26.67)	93 (27.76)	
Widow/Widower	n (%)	4 (2.35)	6 (3.64)	10 (2.99)	
Separated	n (%)	1 (0.59)		1 (0.30)	

Legend: SD – Standard Deviation; p<0.05 considered statistically significant

Table 2. Primary Efficacy by Treatment Group; Cavite 2018 (N=322)

Characteristic	Statistic	Ascof Capsule (N=163)	Ascof Tablet (N=159)	Overall (N=322)
Global Rating of Change Scale				
Rating (Patient)	Mean (SD)	3.5 (1.01)	3.5 (1.25)	3.5 (1.13)
	Median	4.0	4.0	4.0
	Range	0-5	-1-5	-1-5
Rating (Doctor)	Mean (SD)	3.7 (0.95)	3.7 (1.19)	3.7 (1.08)
	Median	4.0	4.0	4.0
	Range	0-5	-1-5	-1-5
Rating (Patient)				
> +2	n (%)	156 (95.71%)	145 (91.19%)	301 (93.46%)
< +2	n (%)	7 (4.29%)	14 (8.81%)	21 (6.52%)
Rating (Doctor)				
> +2	n (%)	158 (96.93%)	150 (94.34%)	308 (95.65%)
< +2	n (%)	5 (3.07%)	9 (5.66%)	14 (4.35%)

Legend: SD – Standard Deviation

Table 3. Non-Inferiority Analysis for the Proportion Difference as assessed by patients and doctors

$H_0: \theta_1 - \theta_2 \leq \bar{O}$ $H_a: \theta_1 - \theta_2 > \bar{O}$
$\bar{O}$ = -0.1 Farrington-Manning Method

	Patient's Score	Doctor's Score
Per Protocol Data Set		
Proportion Difference	0.0451	0.0259
p-value	<0.0001	<0.0001
90% Confidence Limits	-0.0086 to 0.0988	-0.0228 to 0.0747
Modified Intention-to-Treat Data Set		
Proportion Difference	0.0025	-0.0160
p-value	0.0009	0.0025
90% Confidence Limits	-0.0517 to 0.0567	-0.0652 to 0.0331

and doctors did not breach the -10% non-inferiority limit indicating non-inferiority of the capsule compared to the tablet (90% Confidence Intervals: -0.0086 to 0.0988 and -0.0228 to 0.0747, respectively).

A modified intention-to-treat analysis was performed on the primary outcome, including all patients who took at least one dose of the assigned drugs (Table 3). The worst-case scenario was assumed with the dropouts in the capsule group considered treatment failures, and dropouts in the tablet group considered treatment successes. The proportion of success in both treatment groups was then compared based on the assessment of the patients and doctors. Here, the proportion difference assessed by patients was 0.25% in favor of the capsule group, while it was 1.6% in favor of the tablet group as evaluated by doctors. The lower boundary of the 90% confidence interval of the proportion difference as judged by the patients and doctors did not breach the -10% non-inferiority limit indicating that even in the worst-case scenario, the capsule group was still non-inferior to the tablet group (90% Confidence Intervals: -0.0517 to 0.0567 and -0.0652 to 0.0331, respectively).

Figure 1 compares efficacy-related secondary outcomes, including cough severity based on CSD scores, quality of life based on LCQ, FEV_1 and PEFR scores at baseline (Visit 1) and endpoint (Visit 2) and their changes in both groups.

The CSD score showed that the two groups were comparable at baseline and final visit for cough severity. It also showed that both treatments significantly improved cough severity. However, comparing the improvement in both groups showed no significant difference (p = 0.1342).

The LCQ assessed patients' quality of life with acute cough considering three domains: physical, psychological, and social. The scores of both groups at baseline and the final visit were comparable. In addition, the change from baseline to the final visit for both groups was significant, indicating that both treatments improved the patients' quality of life, and the improvement in both groups was comparable (p = 0.1309).

The mean FEV_1 at baseline for the capsule and tablet groups were 2.3 and 2.4 liters, respectively. At the final visit, the mean FEV_1 were 2.4 and 2.4 liters, respectively. The FEV_1 at both visits was comparable between groups; however, the improvement in FEV_1 from baseline to final visit was statistically significant in the capsule group (p = 0.0471) but not in the tablet group (p = 0.0933). Though the capsule group showed statistically significant improvement from baseline to final visit, a comparison of the improvement of FEV_1 from baseline to final visit in both groups did not have adequate evidence of significant difference (p = 0.6360).

The PEFR of the capsule and tablet groups were comparable at baseline and final visit. PEFR showed significant improvement in both groups. Comparing the change in PEFR from baseline to final visit in both groups showed no statistically significant difference (p = 0.4172).

While improvements in the FEV_1 in the capsule group (0.1L) and PEFR in both groups (11% in the capsule and 8.5% in the tablet) were statistically significant,

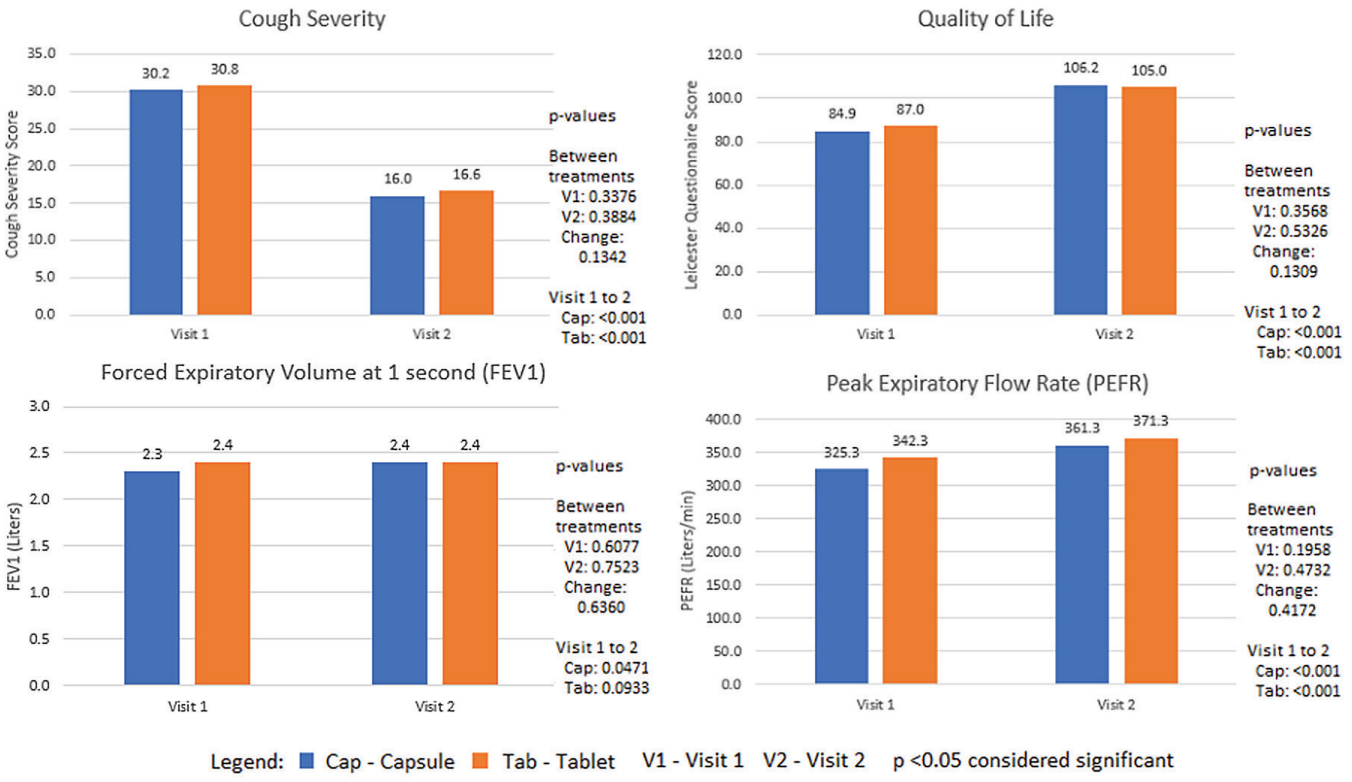

Figure 1. Comparison of efficacy-related secondary outcomes.

these improvements did not reach the threshold to be considered clinically significant. FEV_1 must increase by at least 0.2L, while PEFR must increase by at least 12% to be considered clinically significant.[11,12]

Adverse events

The frequency of adverse events was low at two for the capsule group and five for the tablet group. The incidence rates were 1.23% and 2.52%, respectively, for the duration of the study. The rates were comparable with a p-value of 0.4437 based on Fisher's Exact Test.

Seven mild adverse events were reported, consisting of two in the capsule group (diarrhea and sleepiness) and five in the tablet group (colds, hypertension, dizziness, headache, and itchy throat). The doctors assessed all adverse events as unrelated to the investigational drugs. There was no serious adverse event reported.

DISCUSSION

The mucolytic and bronchodilatory effects of *Vitex negundo* or Lagundi have been shown in clinical studies.[3-5] Although the precise mechanisms have not yet been fully identified, the mucolytic action is believed to be related to flavonoids that naturally bind to polymers and fibrins in the lungs to help dissolve hard sticky mucus.[13,14] At the same time, the bronchodilatory property is partly explained by the presence of anti-eosinophilic activity of the leaves and the presence of papaverine-like phosphodiesterase inhibitors and diltiazem-like calcium channel blockers.[15,16] Overall, this investigation supports the previous studies of the cough relieving action of Lagundi. However, this is the first phase 3 randomized controlled trial to show that the effect of the capsule is comparable to the tablet.

In this study, the primary efficacy endpoint was cough improvement after three days of treatment as measured by the GRCS score, rated both by the patient and the doctor. Both per-protocol and modified intention-to-treat analyses revealed that the capsule format was non-inferior to the tablet format. The intention-to-treat analysis assumed that all patients lost to follow-up in the capsule group were treatment failures while all lost to follow-up in the tablet group were treatment successes. The consistent results of the intention-to-treat and per-protocol analyses on the primary efficacy endpoint revealed robust results on the comparability of the two formulations.

The capsule and tablet formulations also showed statistically significant improvements in cough severity and quality of life of the patients after three days of treatment with comparable improvements in both groups. This further supported the clinical significance of the cough improvement based on GRCS scores showing that such improvement correlated with measurable improvements in cough severity and quality of life and helped further define the benefits experienced by patients on Lagundi treatment.

Meanwhile, the improvements in FEV_1 (capsule group) and PEFR (both groups), although statistically significant, were not shown to be clinically significant based on current literature.[11,12] As these measures indicate airway caliber; it was expected that changes would be more pronounced for patients who have cough associated with bronchospasm, such as asthma, compared to patients who have acute cough in general, which were represented in this study. To validate this, research specific to patients with cough associated with bronchospasm would be needed.

On potential biases, selection bias and recall bias were unlikely as randomization indicated similar characteristics of the two groups at baseline, and the period between the two visits was short (3 days). However, since the formats of the drugs being compared were different (capsules vs. tablets), blinding could not be performed, and hence assessment bias by the patients and the doctors may have come into play. While this was mitigated by training of the study doctors/assessors and the appropriate scales, this could not be excluded and may be bidirectional depending on their preference.

The safety profiles were also comparable, both with a low incidence of adverse events, which were all mild and assessed by the study doctors as not related to the drug.

Overall, the study showed that the Lagundi capsule was not inferior to the Lagundi tablet for acute uncomplicated cough in terms of efficacy and safety. While studies have shown that such similarity could be achieved between tablet and capsule formulations of synthetic drugs, this study revealed the same could also be achieved for herbal medicine, particularly Lagundi.[17-19]

Considering the similarity of tablet and capsule in efficacy and safety, either may be taken to relieve acute uncomplicated cough with the choice left to the patient's preference. There are characteristics of a capsule that may be perceived as advantageous by patients over the tablet. Some patients found gelatin capsules easier to swallow than regular uncoated tablets, and capsules being tasteless may also facilitate easier administration.[20,21] A few participants noted the capsules were odorless and tasteless, and some remarked that the capsules were easy to ingest.

From the clinical standpoint, once a clinician had decided to treat an acute uncomplicated cough with Lagundi, it is recommended that they weigh in the findings of this study and the patient's preference in choosing the format to prescribe. From a regulatory standpoint, since herbal medicines have multiple active components, which makes bioequivalence studies hardly feasible, the alternative approach of doing one phase 3 trial instead to substantiate similarity in efficacy and safety could be considered as an alternative pragmatic approach to showing the therapeutic equivalence of different formats of herbal medicines. Future efficacy and safety studies on herbal medicines for acute uncomplicated cough may also consider adopting the parameters used in this study to compare their effects with that of the products used in this study.

CONCLUSION

In terms of efficacy, Ascof® Forte capsule was non-inferior to Ascof® Forte tablet in treating acute uncomplicated cough among Filipinos based on Global Rating of Change Scale scores as rated by patients and doctors. Further, both treatments showed significant and similar improvements in cough severity and quality of life-based on Cough Severity Diary scores and Leicester Cough Questionnaire scores, respectively. They were also comparable in safety with few adverse events in both groups, all mild and assessed unrelated to drug intake.

Statement of Authorship

All authors participated in the data collection and analysis and approved the final version submitted.

Author Disclosure

Dr. Rita Grace Alvero, Clinical Director and Dr. Josefino Alvero, President and COO of Pharmalytics Corporation reports personal fees from Pascual Laboratories, Inc., during the conduct of the study, and Dr. Geraldo Balaccua, Medical and Regulatory Affairs Director of Pascual Laboratories, Inc. reports fees from Pascual Laboratories, Inc., outside the submitted work.

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