



# Pharmacokinetics of Ambroxol Sustained Release (Mucosolvan<sup>®</sup> Retard) Compared with Other Formulations in Healthy Volunteers

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## ABSTRACT

**Introduction:** Ambroxol is used in the treatment of acute and chronic respiratory conditions characterized by abnormal mucus secretion and impaired mucus transport and is available in a variety of formulations. This study aimed to compare the steady-state (SS) pharmacokinetic characteristics of extended-release (ER) 75-mg retard capsules with two immediate-release (IR) formulations (60-mg effervescent tablets and 30-mg tablets) over a 24-h period.

**Methods:** An open-label, randomized, three-period, six-sequence crossover study was conducted in healthy volunteers aged 18–45 years who had a normal body mass index. The test (ER 75-mg

retard capsule once daily) and reference treatments (half of IR 60-mg effervescent tablet twice daily or 30-mg IR tablet twice daily) were administered on days 1–5 of each treatment period. Meals were standardized and concomitant therapy was prohibited. Blood samples for pharmacokinetic assessment were collected on day 5 (SS) of each treatment period. The co-primary endpoints were exposure ( $AUC_{SS\ 0-24}$ ) and maximum plasma level ( $C_{max\ SS}$ ).

**Results:** Twenty-four participants received ambroxol (male  $n = 13$ , 54.2%; mean  $\pm$  standard deviation [SD] age  $25.0 \pm 6.4$  years) and 23 completed the study. ER retard capsules provided similar  $AUC_{SS\ 0-24}$  compared to IR tablets (geometric means ratio [GMR] 110.7%; 90% confidence interval [CI] 99.8%, 122.7%) and effervescent tablets (GMR 106.9%; 90% CI 100.3%, 114.0%). ER retard capsules provided similar  $C_{max\ SS}$  compared to IR tablets (GMR 84.7%, 90% CI 77.0%, 93.3%), and lower  $C_{max\ SS}$  compared to effervescent tablets (GMR 80.9%, 90% CI 73.9%, 88.6%). Time to  $C_{max\ SS}$  ( $t_{max\ SS}$ ) was longer with ER retard capsules (6.0 h) than with IR tablets (2.0 h) or effervescent tablets (1.0 h).

**Conclusions:** ER ambroxol 75-mg retard capsules given once daily showed a similar pharmacokinetic profile to IR ambroxol formulations and therefore can be used instead of these in the treatment of respiratory conditions.

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## PLAIN LANGUAGE SUMMARY

Ambroxol is used to relieve the symptoms of respiratory conditions in which abnormal mucus secretion is a problem, including the common cold, acute and chronic bronchitis, and chronic obstructive pulmonary disease. Different formulations of ambroxol are available, including tablets and effervescent tablets that release the drug as soon as they are digested, but need to be taken twice a day, or extended release (retard) capsules that release the drug slowly over 24 h and can be taken once a day. This randomized, three-period, six-sequence crossover study in 24 healthy volunteers compared the pharmacokinetics of three formulations of ambroxol: tablets, effervescent tablets, and retard capsules. The amount of drug in the bloodstream over 24 h was similar with all three formulations, but (as expected) the time to reach peak plasma concentration was longer with the retard capsules than both forms of tablet. These results show that people who take ambroxol for respiratory conditions will receive the same amount of ambroxol whether they take retard capsules, standard tablets, or effervescent tablets.

**Keywords:** Ambroxol; Extended release; Retard capsule; Immediate release; Pharmacokinetic; Safety; Steady state; Tablet

### Key Summary Points

#### *Why Carry Out This Study?*

Ambroxol is used to relieve the symptoms of respiratory conditions in which abnormal mucus secretion is a problem, including the common cold, acute and chronic bronchitis, and chronic obstructive pulmonary disease.

Different formulations of ambroxol are available, including immediate-release (IR) tablets, effervescent tablets, and extended release (retard) capsules.

Studies comparing the pharmacokinetics of these formulations were conducted 30 years ago and did not conform to current Good Clinical Practice guidelines.

#### *What was Learned from the Study?*

This study used current GCP standards to compare the steady-state pharmacokinetics of ambroxol retard capsules with those of IR tablets and effervescent tablets in healthy volunteers.

24-h plasma exposure was similar with the three ambroxol formulations.

## INTRODUCTION

Abnormal mucus secretion and impaired mucus transport are common in respiratory diseases such as the common cold, acute and chronic bronchitis, chronic obstructive pulmonary disease (COPD), and cystic fibrosis [1]. Abnormal airway mucus secretion often leads to complications, including bacterial colonization, repeated chest infections, and exacerbations, which are associated with increased morbidity and mortality [1].

Ambroxol has mucokinetic, mucociliary, anti-inflammatory, anti-oxidant, and local anesthetic effects [1–3]. It also stimulates surfactant production [1–3]. Ambroxol is approved for use as secretolytic therapy and as pain relief in acute sore throat, as well as for the prophylaxis and treatment of infant respiratory distress syndrome and postoperative bronchopulmonary complications [4].

Ambroxol is available in a variety of over-the-counter and prescription formulations. Immediate-release (IR) oral formulations of ambroxol include tablets, soft pastilles, granules, syrup, and oral solution. The half-life of ambroxol is approximately 10 h; therefore, IR formulations require twice-daily administration [3]. Extended-release (ER) formulations of ambroxol have been developed in order to reduce the frequency of administration to once daily. Other potential advantages of ER formulations include sustained blood levels,

attenuation of adverse effects, and improved treatment compliance [5]. A preliminary study conducted in 1990 showed that ER ambroxol 75-mg retard capsules and IR ambroxol 30-mg tablets were bioequivalent in terms of exposure (see online supplement). However, plasma levels of ambroxol were more evenly distributed over time with the ER than with the IR formulation. Another study that compared ER retard capsules with the standard ER formulation also showed that plasma levels with ER retard capsules were more stable, while bioavailability was similar [6]. As the preliminary study was not conducted under the Good Clinical Practice guidelines, more rigorous pharmacokinetic studies are required to establish bioequivalence between different ER and IR ambroxol formulations.

In this pharmacokinetic study, administration of ambroxol ER 75-mg retard capsules once daily, ambroxol IR 60-mg effervescent tablets half a tablet twice daily and ambroxol 30-mg IR tablets twice daily were compared in healthy volunteers. The objective of the study was to assess the peak exposure and relative bioavailability of the ER formulation compared to IR formulations over a 24-h period at steady state.

## METHODS

### Study design and participants

This was an open-label, randomized, three-period, six-sequence crossover study that was conducted in 2014 at the St. Petersburg State Medical University named after I. P. Pavlov (ClinicalTrials.gov registration number: NCT02036775). The Williams design was used, whereby patients were randomly assigned in equal numbers to one of six sequences (four patients per sequence) using a pseudorandom number generator and a supplied seed number, thus ensuring that allocation was both reproducible and non-predictable. The study consisted of a screening period, three treatment periods separated by wash-out periods, and a follow-up period (Fig. 1). The maximum duration of the screening period was 14 days; each treatment period was 6 days long; and each wash-out period was also 6 days long. The end-

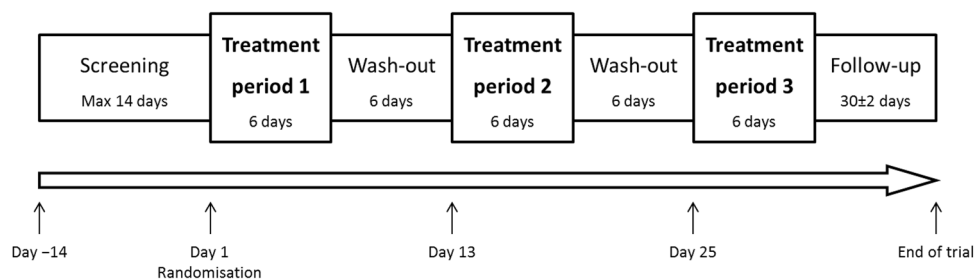
of-study evaluation was conducted  $30 \pm 2$  days after the last study procedure.

The elimination half-life of ambroxol is 8–12 h [1]. A 5-day period (120 h) would include approximately 10–15 times the elimination half-life of ambroxol. Therefore, it was assumed that steady state would be reached by day 5.

Males or females aged 18–45 years with a body mass index (BMI) of  $18.5 < 25.0 \text{ kg/m}^2$  who were judged by the investigator to be in good health and who agreed to use effective contraception for the duration of the study, were included. Exclusion criteria were hypersensitivity to ambroxol hydrochloride or other constituents of study drugs; pregnancy or breastfeeding; and other conditions that could affect the conduct or results of the study (see Supplementary appendix for complete list of exclusion criteria). All participants provided written informed consent prior to entering the trial. The study protocol, participant information leaflet and informed consent form were reviewed and approved by the Ethics Committee of St. Petersburg State Medical University prior to study initiation. The study was conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines and local regulatory requirements.

### Procedures

Participants received the test treatment (ambroxol ER 75-mg retard capsules once daily) or one of the reference treatments (half an ambroxol IR 60-mg effervescent tablet twice daily [for a total daily dose of 60 mg] or ambroxol 30-mg IR tablets twice daily) on days 1–5 of each treatment period. Study drugs were administered either during the stay at study site or during study site visits. Participants were required to stay at the study site on two occasions during each treatment period: from the evening before the start of the period until 30 min after morning drug administration on day 1, and from the evening on day 4 until the last procedure on day 6. Morning visits were scheduled for participants who received ambroxol ER capsules. Morning and evening



**Fig. 1** Study design

visits were scheduled for participants who received ambroxol effervescent tablets and ambroxol tablets.

During days 1–4 of each treatment period, the morning drug dose (one ambroxol ER 75-mg retard capsule, one half ambroxol IR 60-mg effervescent tablet, one ambroxol IR 30-mg tablet) was taken immediately after a standardized breakfast with 200 ml of water. Participants were not allowed to lie down for 2 h following administration and water and meals were not permitted for 1 h. On day 5, when the assessment of steady-state pharmacokinetics was conducted, study drugs were administered in the same way after an overnight fast of  $\geq 10$  h. Standardized meals were served at 4, 8, and 12 h after morning drug administration. The evening drug dose (one half ambroxol 60-mg effervescent tablet, one ambroxol 30-mg tablet) was administered 12 h after the morning dose after the standardized supper, with 200 ml of water.

No concomitant drugs were permitted, except for symptomatic therapy in case of adverse events. Participants were required to refrain from smoking, alcohol, and strenuous exercise for 24 h prior to drug administration and during the treatment periods. Methylxanthine-containing drinks or food (coffee, tea, cola, energy drinks, chocolate, etc.) were not permitted during the 24 h before drug administration on day 5 of each treatment period. Fruit juices were not permitted during the 3 days before drug administration and grapefruit juice was prohibited for the duration of the study.

Plasma levels of ambroxol hydrochloride were determined by means of a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) assay. LLOQ was established in

order to be able to quantify 5% of expected (individual)  $C_{\max}$ -levels (below 1.5 ng/ml). Blood for pharmacokinetic assessments was collected before the morning drug administration on days 1, 3, 4, and 5 of each treatment period. No blood was collected on day 2. In addition, for patients receiving ambroxol ER 75-mg retard capsules, blood was collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7.5, 9, 10.5, 12, 14, 17, and 20 h after morning drug administration on day 5 (steady state). For patients receiving ambroxol 60-mg effervescent tablets or ambroxol 30-mg tablets, blood was collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7.5, 9, 10.5, 12, 12.25, 12.5, 12.75, 13, 13.5, 14, 15, 16, 17, and 20 h after the morning drug administration on day 5 (steady state). On day 6, blood was collected at 24 h after morning drug administration on the previous day (day 5).

## Endpoints

Primary pharmacokinetic endpoints included area under the plasma concentration–time curve over a 24-h period ( $AUC_{SS\ 0-24}$ ) and maximum plasma concentration ( $C_{\max\ SS}$ ) at steady state, without adjustment for dose. Secondary pharmacokinetic endpoints included steady-state  $AUC_{SS\ 0-24}$  normalized to a daily dose of 60 mg ( $AUC_{SS\ 0-24\ norm}$ ); rate of absorption (calculated as  $C_{\max\ SS}/AUC_{SS\ 0-24}$ ); minimum plasma concentration ( $C_{\min\ SS}$ ); average plasma concentration ( $C_{av\ SS}$ ); time to  $C_{\max\ SS}$  ( $t_{\max\ SS}$ ); peak-to-trough fluctuation ( $PTF_{SS}$ ); calculated as  $C_{\max\ SS} - C_{\min\ SS}$ ; peak-trough swing ( $PTS_{SS}$ ); time when plasma concentration exceeded  $C_{av}$  ( $t_{C>C_{av\ SS}}$ ); and time when plasma concentrations exceeded 75% of  $C_{\max\ SS}$  ( $t_{C>75\%C_{\max\ SS}}$ ).

Safety assessments included adverse events (AEs), vital signs, electrocardiogram (ECG), and laboratory tests.

### Statistics

The following descriptive statistics were calculated for plasma concentrations as well as for all primary and secondary pharmacokinetic parameters: number of participants, arithmetic mean, standard deviation (SD), minimum, median, maximum, and arithmetic coefficient of variation.

Bioequivalence assessment was conducted on the basis of two-sided 90% confidence intervals (CIs) for the ratio of the geometric means (GMR) of test/reference of  $AUC_{SS\ 0-24norm}$  and  $C_{max\ SS}$ . The protocol-specified bioequivalence assessment was based on the 2008 Russian Federation guideline, which states that bioequivalence is established when the 90% CIs for the GMR of  $AUC_{SS\ 0-24norm}$  are within the 80–125% range and the 90% CIs for the GMR of  $C_{max\ SS}$  are within the 75–133% range. A post hoc bioequivalence assessment was based on the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines, which specify the 80–125% range for both  $AUC_{SS\ 0-24norm}$  and  $C_{max\ SS}$  [7, 8]. An ANOVA statistical model on the logarithmic scale, which included effects for ‘sequence’, ‘participants nested within sequences’, ‘period’, and ‘treatment’, was used. CIs were calculated based on the residual error from this model. The primary pharmacokinetic parameters were obtained by non-compartmental analysis using WinNonlin software (Certara; Princeton, NJ, USA).

The sample size for this study was determined based on  $AUC_{SS\ 0-24norm}$ . Assuming a within-participant coefficient of variation of 15% and a GMR of  $AUC_{SS\ 0-24norm}$  of 1.03, a sample of 18 participants would provide 95% power to establish bioequivalence. Up to six participants were expected to discontinue. Therefore, 24 participants would need to be recruited. The calculation had been performed as described in Russian national guidelines on bioequivalence studies using software PASS 2008 (NCSS, LCC, Kaysville, UT, USA).

## RESULTS

A total of 24 participants entered the study and received at least one of the investigational drugs. Of these, 23 participants (95.8%) completed the study. One participant (4.2%) withdrew consent during the second treatment period after completing the first treatment period with ambroxol effervescent tablets.

Thirteen participants (54.2%) were male and 11 (45.8%) were female (Table 1). The mean

**Table 1** Participant demographic and baseline characteristics

	<i>N</i> = 24
Age, years, mean ± SD	25.0 ± 6.4
Height, cm, mean ± SD	177.0 ± 11.1
Weight, kg, mean ± SD	68.6 ± 12.9
BMI, kg/m <sup>2</sup> , mean ± SD	21.7 ± 1.8
Sex, <i>n</i> (%)	
Male	13 (54.2%)
Female	11 (45.8%)
Race, <i>n</i> (%)	
Caucasian	24 (100.0%)
Alcohol use, <i>n</i> (%)	
Yes	14 (58.3%)
No	10 (41.7%)
Tobacco use, <i>n</i> (%)	
Ex-tobacco user	1 (4.2%)
Non-tobacco user	15 (62.5%)
Current tobacco user	8 (33.3%)
Medical history, <i>n</i> (%)	
Pneumonia	1 (4.2%)
Appendectomy	2 (8.3%)
Septoplasty	1 (4.2%)
Concomitant medications, <i>n</i> (%)	
Pyrazolones	1 (4.2%)

*BMI* body mass index, *SD* standard deviation

(SD) age was 25.0 (6.4) years. A total of three participants had a relevant medical history and one participant used concomitant therapies (Table 1).

### Pharmacokinetics

The two IR ambroxol formulations, 60-mg effervescent tablets (half tablet twice daily) and 30-mg tablets (twice daily), showed similar steady-state plasma concentration–time profiles (Fig. 2). These profiles were each characterized by the presence of two relatively sharp peaks, followed by a steep decline. The co-primary pharmacokinetic endpoint of mean  $\pm$  SD  $AUC_{SS\ 0-24}$  was  $1147 \pm 333.4\ \text{ng} \times \text{h/ml}$  for effervescent tablets and  $1115 \pm 348.4\ \text{ng} \times \text{h/ml}$  for tablets. For effervescent tablets, the co-primary pharmacokinetic endpoint of mean  $\pm$  SD  $C_{\max\ SS}$  was  $96.4 \pm 31.9\ \text{ng/ml}$  after a median (range)  $t_{\max\ SS}$  of 1.0 (0.8–3.0) hours. For tablets, the mean  $\pm$  SD  $C_{\max\ SS}$  was  $92.9 \pm 30.6\ \text{ng/ml}$  after a median (range)  $t_{\max\ SS}$  of 2.0 (0.8–3.0) hours (Table 2).

On the other hand, the steady-state plasma concentration–time profile of the 75-mg ER ambroxol retard capsules (once daily) was

characterized by a gradual increase to a single peak, followed by a gradual decline over the rest of the 24-h period (Fig. 2). The co-primary pharmacokinetic endpoints of mean  $\pm$  SD  $AUC_{SS\ 0-24}$  and  $C_{\max\ SS}$  were  $1228 \pm 356.6\ \text{ng} \times \text{h/ml}$  and  $76.1 \pm 21.1\ \text{ng/ml}$ , respectively. The latter was reached after a median (range)  $t_{\max\ SS}$  of 6.0 (2.0–12.0) hours. In contrast to  $AUC_{SS\ 0-24}$ , the mean  $\pm$  SD  $AUC_{SS\ 0-24\ \text{norm}}$  was lower with ambroxol ER retard capsules ( $982.7 \pm 285.3\ \text{ng} \times \text{h/ml}$ ) than with the two IR tablet formulations (Table 2).

The values for other secondary pharmacokinetic endpoints further illustrated the fact that the ER formulation had a more even plasma concentration–time profile. The mean  $C_{\min\ SS}$ ,  $C_{\text{av}\ SS}$ ,  $t_{C>75\%C_{\text{av}\ SS}}$  and  $t_{C>75\%C_{\max\ SS}}$  were higher, and  $PTF_{SS}$  and  $PTS_{SS}$  were lower, with ambroxol ER retard capsules than with either of the IR formulations (Table 2).

### Bioequivalence

When ER ambroxol retard capsules were compared to ambroxol IR tablets for the two co-primary endpoints, the adjusted GMR of  $AUC_{SS\ 0-24}$  was 110.7% (90% CI 99.8%, 122.7%)

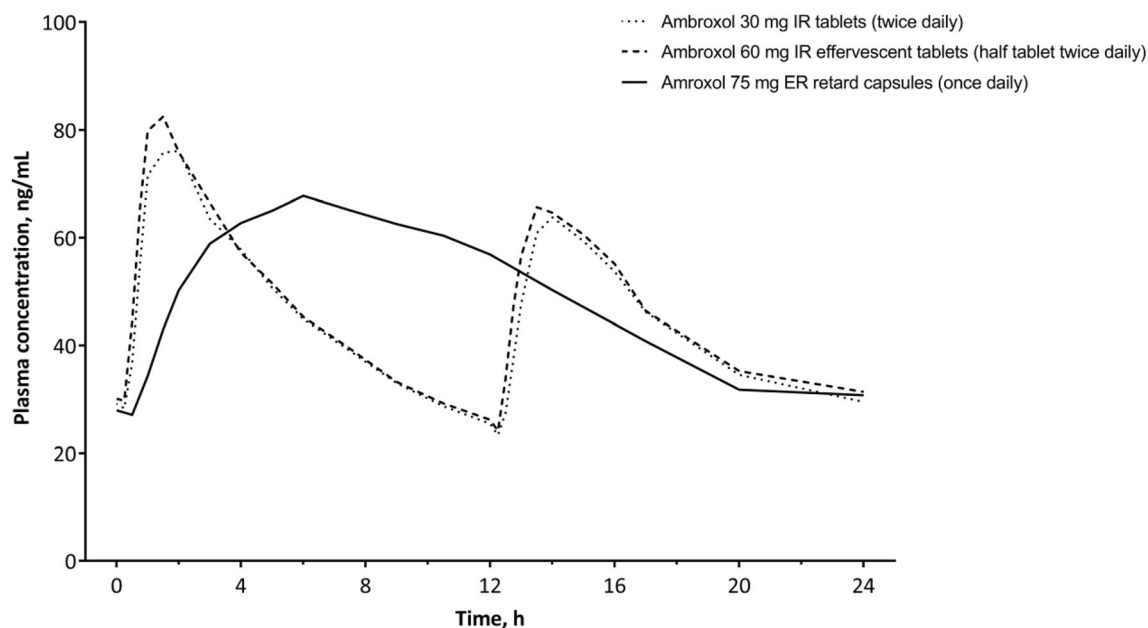


Fig. 2 Mean pharmacokinetic profiles. ER extended release, IR immediate release

**Table 2** Pharmacokinetic parameters ( $n = 23$ )

	Ambroxol ER retard capsule 75 mg	Ambroxol IR effervescent tablet 60 mg	Ambroxol IR tablet 30 mg
$AUC_{SS\ 0-24}$ , ng $\times$ h/ml	1228 $\pm$ 356.6	1147 $\pm$ 333.4	1115 $\pm$ 348.4
$AUC_{SS\ 0-24norm}$ , ng $\times$ h/ml	982.7 $\pm$ 285.3	1147 $\pm$ 333.4	1115 $\pm$ 348.4
$C_{max\ SS}$ , ng/ml	76.1 $\pm$ 21.1	96.4 $\pm$ 31.9	92.9 $\pm$ 30.6
$C_{max\ SS}/AUC_{SS\ 0-24}$ , 1/h	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0
$C_{max\ SS}/AUC_{SS\ 0-24norm}$ , 1/h	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0	0.1 $\pm$ 0.0
$C_{min\ SS}$ , ng/ml	26.7 $\pm$ 10.5	24.1 $\pm$ 8.3	23.2 $\pm$ 9.0
$C_{av\ SS}$ , ng/ml	51.2 $\pm$ 14.9	47.8 $\pm$ 13.9	46.5 $\pm$ 14.5
$t_{max\ SS}$ , h	6.0 (2.0, 12.0)	1.0 (0.8, 3.0)	2.0 (0.8, 3.0)
$PTF_{SS}$	1.0 $\pm$ 0.3	1.5 $\pm$ 0.3	1.5 $\pm$ 0.3
$PTS_{SS}$ , %	205.1 $\pm$ 82.7	317.1 $\pm$ 112.3	326.5 $\pm$ 133.6
$t_{C>75\%C_{av\ SS}}$ , h	10.6 $\pm$ 1.2	8.3 $\pm$ 1.0	7.9 $\pm$ 1.1
$t_{C>75\%C_{max\ SS}}$ , h	8.9 $\pm$ 3.3	2.4 $\pm$ 1.3	2.2 $\pm$ 1.3

Data are arithmetic mean  $\pm$  SD, except  $t_{max}$ , which is median (min, max)

*AUC* area under the curve, *ER* extended release, *IR* immediate release, *PTF* peak-trough fluctuation, *PTS* peak-trough swing, *SD* standard deviation, *SS* steady state

and the adjusted GMR of  $C_{max\ SS}$  was 84.7% (90% CI 77.0%, 93.3%) (Table 3). Therefore, based on the protocol-specified acceptance range (80–125% for  $AUC_{SS\ 0-24}$  and 75–133% for  $C_{max\ SS}$ ), ambroxol retard capsules were bioequivalent to tablets in terms of  $C_{max\ SS}$  and  $AUC_{SS\ 0-24}$ . However, based on the acceptance range provided in FDA and EMA guidelines (80%–125% for both  $AUC_{SS\ 0-24}$  and  $C_{max\ SS}$ ) [7, 8], ambroxol retard capsules were equivalent to tablets in terms of  $AUC_{SS\ 0-24}$  only. Bioequivalence was not established based on the secondary endpoint of  $C_{max\ SS}$ .

In the comparison of ambroxol IR effervescent tablets with IR tablets, the adjusted GMR of  $AUC_{SS\ 0-24}$  was 103.4% (90% CI 96.6%, 110.7%) and the adjusted GMR of  $C_{max\ SS}$  was 103.9% (90% CI 95.2%, 113.3%). Therefore, based on both the protocol-specified and post hoc acceptance ranges, ambroxol IR effervescent tablets were bioequivalent to IR tablets in terms of  $C_{max\ SS}$  and  $AUC_{SS\ 0-24}$ .

In the comparison of ambroxol ER retard capsules and IR effervescent tablets, the

adjusted GMR of  $AUC_{SS\ 0-24}$  was 106.9% (90% CI 100.3%, 114.0%) and the adjusted GMR of  $C_{max\ SS}$  was 80.9% (90% CI 73.9%, 88.6%). Therefore, based on both the protocol-specified and post hoc acceptance ranges, ambroxol ER retard capsules were bioequivalent to IR effervescent tablets in terms of  $AUC_{SS\ 0-24}$  but not  $C_{max\ SS}$ . The adjusted GMR of  $AUC_{SS\ 0-24norm}$  (85.6%, 90% CI 80.2%, 91.2%) also fell within the bioequivalence range.

### Safety

Two participants (8.3%) reported AEs. One participant had a mild drug-related headache during treatment with ambroxol ER retard capsules. This participant received concomitant medication for headache. Another participant had a mild increase in ALT and AST after treatment with ambroxol IR effervescent tablets, which was possibly attributable to diet violation.

Table 3 Analysis of bioequivalence based on the ANOVA statistical model

	Ambroxol ER retard capsule 75 mg	Ambroxol IR tablet 30 mg	Ambroxol IR effervescent tablet 60 mg	Ambroxol IR tablet 30 mg	Ambroxol ER retard capsule 75 mg	Ambroxol IR effervescent tablet 60 mg
<i>Primary endpoints</i>						
<b>AUC<sub>SS</sub> 0–24, ng × h/l</b>						
Adjusted geometric mean	1184.7	1070.4	1108.8	1072.4	1184.7	1107.9
Adjusted GMR, %	110.7		103.4		106.9	
90% CI	99.8, 122.7		96.5, 110.7		100.3, 114.0	
Within-participant CV, %	20.4		13.5		12.7	
<b>C<sub>max</sub> ss, nmol/l</b>						
Adjusted geometric mean	73.7	87.0	90.8	87.4	73.5	90.9
Adjusted GMR, %	84.7		103.9		80.9	
90% CI	77.0, 93.3		95.2, 113.3		73.9, 88.6	
Within-participant gCV, %	19.0		17.2		18.0	
<i>Secondary endpoints</i>						
<b>AUC<sub>SS</sub> 0–24norm, nmol × h/l</b>						
Adjusted geometric mean	947.7	1070.4	1108.8	1072.4	947.8	1107.9
Adjusted GMR, %	88.5		103.4		85.6	
90% CI	79.9, 98.2		96.5, 110.7		80.2, 91.2	
Within-participant gCV, %	20.4		13.5		12.7	
<b>C<sub>max</sub> ss/AUC<sub>SS</sub> 0–24</b>						
Adjusted GMR, %	76.6		100.5		75.7	
90% CI	71.1, 82.4		94.7, 106.6		69.9, 81.9	
Within-participant gCV, %	14.6		11.7		15.6	



Table 3 continued

	Ambroxol ER retard capsule 75 mg	Ambroxol IR tablet 30 mg	Ambroxol IR effervescent tablet 60 mg	Ambroxol IR tablet 30 mg	Ambroxol ER retard capsule 75 mg	Ambroxol IR effervescent tablet 60 mg
$C_{max\ SS}/AUC_{SS\ 0-24norm}$			100.5		94.6	
Adjusted GMR, %	95.7				87.4, 102.4	
90% CI	88.9, 103.0		94.7, 106.6			
Within-participant gCV, %	14.6		11.7		15.6	

*AUC* area under the curve, *CI* confidence interval, *CV* coefficient of variation, *ER* extended release, *GMR* geometric mean ratio, *IR* immediate release, *SS* steady state

There were no clinically relevant findings with respect to laboratory parameters, vital signs, ECG, or physical examination. There were three new episodes of incomplete right bundle branch block and one new episode of sinus bradycardia on ECG which were assessed as not clinically significant by the investigator.

## DISCUSSION

A preliminary study (see Supplementary material), which was conducted in Germany in 12 healthy volunteers and which also used the three-period cross-over design, established that the ambroxol ER formulation was equivalent to ambroxol 30-mg IR tablets in terms of exposure. In the present paper, we describe the results of a pharmacokinetic study that was conducted in healthy volunteers to determine the pharmacokinetic characteristics and relative bioavailability of an ER formulation of ambroxol (75-mg retard capsules once daily) compared to two IR formulations (60-mg effervescent tablets, half a tablet twice daily, and 30-mg tablets twice daily).

This study used two sets of criteria to establish bioequivalence, those recommended by the Russian guidelines and those recommended by the FDA and EMA guidelines. The acceptance range for exposure was the same in all guidelines (80–125%), while the acceptance range for maximum plasma concentration was broader in the Russian guidelines (75–133%) than in the FDA and EMA guidelines (80–125%) [7, 8]. Based on exposure, all ambroxol formulations were considered to be bioequivalent. In addition, based on maximum concentration, IR effervescent tablets were bioequivalent to IR tablets, while ER retard capsules were not bioequivalent to IR effervescent tablets, regardless of which guidelines were applied. Lastly, ER retard capsules reached a  $C_{max\ SS}$  that was bioequivalent to IR tablets based on the Russian, but not the FDA and EMA, guidelines.

In both the preliminary study (Supplementary material) and the present study, ambroxol ER retard capsules demonstrated a pharmacokinetic profile that was characterized by more consistent plasma concentrations over the 24-h

period than was the case with IR formulations. In particular,  $t_{C>75\%C_{av\ SS}}$  was 10.6 h with ER retard capsule, 8.3 h with IR effervescent tablets and 7.9 h with IR tablets. An even greater difference was observed in  $t_{C>75\%C_{max\ SS}}$ , which was 8.9 h with the ER retard capsule, 2.4 h with IR effervescent tablets, and 2.2 h with IR tablets. These findings show that the ER retard formulation produces therapeutically relevant levels of ambroxol over a longer period of time compared to IR effervescent tablets or IR tablets and thus being suitable for once daily treatment regimen. However, the relative bioavailability was lower with the ER than with the IR formulations. Therefore, the use of a higher loading dose in the ER formulation (75 mg once daily) relative to IR formulations (30 mg twice daily) is justified.

Our results are further supported by those of two two-period, two-sequence crossover studies that compared the bioavailability of the 75-mg ER retard capsule (test) and the standard ER (reference) formulation of ambroxol in healthy volunteers [6]. In the first study (focus on pharmaceutical rational), the pharmacokinetic characteristics of the two different retard ambroxol formulations were evaluated after a single dose in 12 participants. This study showed that the extent of exposure to ambroxol was similar with the two preparations (mean  $\pm$  SD  $AUC_{0-24}$  was  $1026 \pm 314$  ng  $\times$  h/ml for the test and  $1048 \pm 321$  ng  $\times$  h/ml for the reference preparation). However, statistically significant differences in the mean plasma concentration of ambroxol were observed, as the concentration was lower with the test than with the reference formulation from 0 to approximately 12 h after administration, and higher with the test than with the reference formulation from 12 to 24 h after administration ( $p < 0.05$ ). In the second study, the pharmacokinetics of the two ambroxol formulations was assessed in eight participants over the course of 5 days of once daily administration. The mean plasma concentration of ambroxol was higher with the test than with the reference formulation at 24, 48, 72, and 96 h after the first administration ( $p < 0.05$ ). This study found no significant differences in the mean  $AUC_{0-24}$ ,  $C_{max}$  and  $t_{max}$  of ambroxol with the test and the

reference formulation, while mean  $\pm$  SD  $C_{ss}$  was significantly higher with the test ( $39 \pm 16$  ng/ml) than with the reference formulation ( $25 \pm 9$  ng/ml,  $p < 0.05$ ). The results of these studies show that the retard formulation has the same bioavailability as the standard ER ambroxol preparation, but a different plasma concentration–time profile. Compared to the standard ER formulation, the ER retard capsule produced lower plasma concentrations during the first 12 h after administration and higher concentrations thereafter [6].

Ambroxol ER retard capsules were shown to be effective in the treatment of chronic respiratory conditions in several randomized, placebo-controlled, and real-world studies [9–12]. In patients with chronic bronchitis, ER ambroxol was associated with a significantly higher proportion of patients who had no exacerbations (45.5 vs. 14.4%) [9], and with significant improvement in lung function and subjective symptoms of disease compared to placebo [10]. In patients with COPD, the difference between ER ambroxol and placebo in the proportion of patients with no exacerbations was significant only in the subset of patients with more severe symptoms at baseline (63 vs. 38%,  $p = 0.038$ ) [11]. ER ambroxol decreased the incidence of exacerbations and the length of antibiotic therapy and improved respiratory signs and symptoms in an observational study conducted in 5635 patients with chronic respiratory diseases [12].

A study conducted in 941 individuals who purchased one of four over-the-counter ambroxol formulations (IR soft pastilles, adult and pediatric syrups and ER retard capsules) compared customer profiles and treatment responses using the modified Bronchitis Severity Scale (BSS) [13]. Participants who purchased ER capsules were older (mean age 41.2 years) than those who purchased other ambroxol formulations (adult syrup 39.3 years, pediatric syrup 12.8 years, pastilles 38.2 years). Baseline BSS was higher in participants who purchased ER capsules and adult syrup (10.0 and 10.1, respectively) than in those who purchased pediatric syrup and pastilles (8.7 and 8.8, respectively). The highest percent improvement in BSS score was observed with pediatric syrup

(62%), followed by ER capsules and pastilles (59%) and adult syrup (55%). Most participants who used pastilles (45.2%) and pediatric syrup (43.4%) reported improvement in symptoms 15–30 min after taking ambroxol, while most participants who used ER capsules (47.8%) and adult syrup (42.1%) reported improvement after 30–60 min. As the  $t_{\max}$  is 1.0–2.5 h for IR ambroxol and 6.5 h for ER ambroxol, time to onset of symptom relief was likely influenced by local effects of the pastille and syrup formulations, as well as the placebo effect [13]. The results of this study of treatment responses in individuals who purchased over-the-counter ambroxol formulations provide real-world evidence to support the use of ER ambroxol in the treatment of acute respiratory conditions.

The present study was performed in healthy volunteers. Therefore, a limitation of this study is the possibility that the pharmacokinetics of the three ambroxol formulations studied would be somewhat different in individuals of different age groups and ethnicities, as well as those with medical conditions.

## CONCLUSIONS

The results of the pharmacokinetic study described in this paper show that ambroxol 75-mg ER capsules represent a valid alternative to IR formulations and are interchangeable with them.

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**Compliance with Ethics Guidelines.** All participants provided written informed consent prior to entering the trial. The study protocol, participant information leaflet and informed consent form were reviewed and approved by the Ethics Committee of St. Petersburg State Medical University prior to study initiation. The study was conducted in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines and local regulatory requirements.

**Data Availability.** Qualified researchers may request access to patient-level data and related study documents including the clinical

study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at <https://www.clinicalstudydatarequest.com>.

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