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ORIGINAL RESEARCH

Phloroglucinol-Derived Medications are Effective in Reducing Pain and Spasms of Urinary and Biliary Tracts: Results of Phase 3 Multicentre, Open-Label, Randomized, Comparative Studies of Clinical Effectiveness and Safety

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ABSTRACT

Introduction: Pain and spasms of urinary and biliary tracts are conditions causing poor quality of life. Treatment with analgesic drugs such as non-steroidal anti-inflammatory drugs and modulators of the parasympathetic system are not always tolerated, and often additional therapeutic options are necessary. The present analysis aimed to evaluate the pharmacokinetics and effectiveness of oral and parenteral preparations based on phloroglucinol in reducing pain and spasms associated with renal or biliary colic in phase 3, multicentre, open-label, randomized, comparative studies on clinical effectiveness and safety.

Methods: Pharmacokinetic and pharmacodynamic studies were carried out. Four phase 3 multicentre, open-label, randomized, comparative studies were conducted to evaluate the clinical effectiveness and safety in patients with pain and spasms of urinary or biliary tracts. Eligible patients randomly received either phloroglucinol orally or via intramuscular (IM)/intravenous (IV) administration and reference drug, dexketoprofen for urinary spasms and pain, the non-steroidal anti-inflammatory drug metamizole or scopolamine-based reference drug for biliary colic. The primary outcomes were symptoms and observed frequency of spasms, while the secondary outcome was the duration of improvement or the time between the drug administration and the recurrence of symptoms. Comparison of groups by quantitative characteristics was performed using the *T*-test for independent samples or the Mann–Whitney test. Intragroup comparisons were performed using the Wilcoxon test, or the *T*-test for linked samples. Qualitative signs were analysed using the Pearson's χ^2 test and Fisher's exact test.

Results: The pharmacokinetic studies showed that (i) most of the phloroglucinol (> 80% for IV and per os formulations) was eliminated in the first 6 h after dosing, (ii) the drug was eliminated in urine as unchanged phloroglucinol (1,3,5-trihydroxybenzene) in a small proportion (< 3% of the dose) and (iii) a considerable amount of the drug was detected after enzymatic deconjugation with β-glucoronidase/arylsulfatase from *Helix pomatia*. As for the pharmacokinetic study, a total of 364

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patients were enrolled, divided in four studies: two designed to test the effectiveness of oral and IM/IV preparations in biliary colic and two in urinary colic. Baseline characteristics between groups were similar. Phloroglucinol oral or IV/IM showed an effectiveness comparable to the reference drug in reducing pain and spasms associated with both urinary and biliary colic. There was no difference between all groups by survival analysis.
Conclusion: Oral and parenteral preparations based on phloroglucinol are as effective in reducing pain and spasms associated with renal or biliary colic as current therapeutic options. Therefore, phloroglucinol may be considered as useful to treat pain and spasms associated with urinary and biliary colic.

Keywords: Phloroglucinol; Pain; Spasm; Urinary colic; Biliary colic

Key Summary Points

Pain and spasms of urinary and biliary tracts are conditions causing poor quality of life. Treatment with analgesic drugs such as non-steroidal anti-inflammatory drugs and modulators of the parasympathetic system are not always tolerated, and additional therapeutic options are necessary.

We analysed four phase 3 multicentre, open-label, randomized, comparative studies of clinical effectiveness and safety in patients with pain and spasms of urinary or biliary tracts.

Oral and parenteral preparations based on phloroglucinol are as effective in reducing pain and spasms associated with renal or biliary colic as current therapeutic options.

INTRODUCTION

Gallstones and kidney stones are very common disorders. Some of the most common complications of both these disorders are episodes of colic, one of the most severe kinds of pain. Up to 12% of the population will have a urinary stone during their lifetime and the recurrence rate approaches 50% [1]. The lifetime risk of developing an acute attack of renal colic is estimated at 1–10% [2]. Others report that the prevalence of renal colic varies significantly from 5% to 15% according to the geographical distribution of the disease [3]. In the case of biliary colic, the cystic duct or Hartmann's pouch is obstructed by a stone. A patient with silent gallstones has an estimated risk of 1–4% per year of developing the specific clinical symptoms [4].

These conditions can cause severe pain described as one of the worst pains a human being can experience and demand immediate relief [5, 6]. A number of drug classes have been recommended to treat these terrible visceral pains. The most studied and recommended are dipyrone, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. Muscle relaxants such as papaverine and anticholinergics have also been tried alone or in combination with the other drugs but have a lesser effect [7].

A systematic review comparing the efficacy, tolerability and safety of NSAIDs and opioids in acute renal colic, including 20 trials in a total of 1613 patients, showed that whilst both pharmacological classes produced important reductions in pain scores, overall NSAIDs were more effective, as patients on NSAID treatment were less likely to require rescue medication (RR 0.75, 95% CI 0.61–0.93). Moreover, opioid therapy was associated with a higher incidence of adverse events (AEs), especially vomiting [8]. Thus, opioids should be given as first-line agents only to patients with contraindications for NSAIDs, such as impaired renal function and/or

a history of gastrointestinal (GI) bleeding [9–14].

NSAIDs are also far from ideal, as they potentially interfere with the renal autoregulatory response to obstruction by decreasing renal blood flow, have detrimental effects on both renal and cardiac function in patients in whom such functions are impaired and are frequently associated with gastrointestinal intolerance. Moreover, not all NSAIDs are available in formulations for parenteral use and the oral route is inadequate for a condition in which prompt analgesia is essential. Alternative treatment is therefore sought [15].

Some agents have been used to reduce ureteral peristalsis, thus reducing colic and facilitating stone passage, but have not gained widespread acceptance. These include intranasal desmopressin, aminophylline, nifedipine and methylprednisolone [16]. There are anecdotal reports of nitroglycerin use for biliary colic pain [17]. Ceruletide, a decapeptide analogue of the hormone CCK, causes relaxation of the cystic duct and sphincter of Oddi and was found to be effective in biliary and renal colic pain relief [18]. Despite the several therapeutic options available, these drugs are not always tolerated and additional therapeutic options are necessary.

Phloroglucinol (1,3,5-trihydroxybenzene) (Fig. 1) is an effective, well-tolerated antispasmodic agent, widely known in the world, registered for the therapy of renal and biliary colic [19, 20]. Moreover, according to the data produced during clinical studies, a fixed combination of phloroglucinol and its methylated derivative 1,3,5-trimethoxybenzene has an antispasmodic effect. In fact, they have inhibitory activity against the catechol-*O*-methyltransferase (COMT) enzyme, which actively participates in the catabolism of catecholamines in smooth muscle cells. Inhibition of catabolism of catecholamines increases the sympathetic tone of the smooth muscle tissue, which causes an antispasmodic reaction [21]. The drug is considered effective in reducing contractions of smooth muscles and relieving pain caused by spasms of smooth muscles. Antispasmodic effects are more pronounced in spasmodic muscles than in smooth muscles in a normal physiological state. Thus, phloroglucinol dihydrate, in terms of phloroglucinol, and its combination with 1,3,5-trimethoxybenzene is recommended for pain and spasmodic phenomena of the biliary and urinary tract.

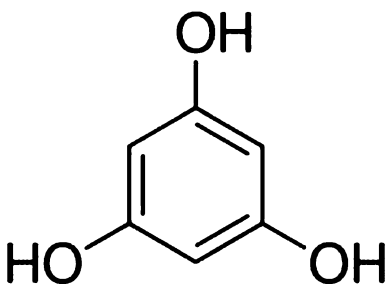


Fig. 1 Chemical structure of phloroglucinol

A solution of phloroglucinol dihydrate for IV and IM administration and tablets containing phloroglucinol and 1,3,5-trimethoxybenzene for oral administration are antispasmodic preparations needed to control pain caused by acute and chronic disorders of the bile excretory system and urinary tract, associated with increased intraluminal pressure.

In the present analysis we report the results of four phase 3 multicentre, open-label, randomized, comparative studies of clinical effectiveness and safety in patients with pain and spasms of urinary or biliary tracts. Eligible patients randomly received either phloroglucinol orally or IM/IV and reference drug, dexketoprofen for urinary spasms and pain, or the non-steroidal anti-inflammatory drug metamizole or scopolamine-based reference drug for biliary colic. The primary outcomes were symptoms and observed frequency of spasms, while the secondary outcome was the duration of improvement or the time between the drug administration and the recurrence of symptoms as before treatment.

In addition, phloroglucinol and 1,3,5-trimethoxybenzene are formulated in different dose(s) of active drugs in relation to different routes of administration. These compounds have been on the market for many years for the management of urinary and biliary tract pain related to muscle spasm. Although the efficacy and safety of this medication is well

documented thanks to the clinical experience, no controlled clinical studies have been recently published to determine its pharmacokinetics (PK) and metabolic profile. For this reason a new PK study was performed.

METHODS

Phloroglucinol and 1,3,5-Trimethoxybenzene Pharmacokinetics

The PK of phloroglucinol was previously investigated in a preliminary study on healthy adult volunteers [22], which provided information useful for setting up the present study. This study was carried out according to current GCP standards and thoroughly investigated the main PK parameters of phloroglucinol and of phloroglucinol + 1,3,5-trimethoxybenzene (IV and oral route respectively) after administration in healthy volunteers.

Sixteen subjects were recruited in a single-dose, single-centre, open-label, randomized, crossover, PK study. Eligibility criteria were non-obese adults (18 kg/m^2≤ BMI ≤ 30 kg/m^2) of both genders, 18–45 years old inclusive. The volunteers received one vial containing phloroglucinol 40 mg/4 mL and two tablets equivalent to 160 mg of phloroglucinol plus 160 mg of 1,3,5-trimethoxybenzene according to a randomization list and crossover design in two subsequent periods. The two administrations were separated by a washout of at least 5 days.

Blood sampling was carried out for 12 h, at the following time points: 0, 5, 10, 15, 30 min and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 h after IV administration; and 0, 15, 30 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 and 12 h after oral administration.

Urine was collected pre-dose and 0–6 h and 6–12 h post dose. The concentration data were used to calculate the main PK parameters.

The primary variables were $AUC_{0-\infty}$, V_d and $t_{1/2}$ of phloroglucinol after single IV administration; C_{max}, T_{max} and $AUC_{0-\infty}$ of phloroglucinol after single p.o. administration; C_{max}, T_{max}, $AUC_{0-\infty}$ and $t_{1/2}$ (if feasible) of trimethylphloroglucinol after single p.o. administration. The secondary variables were AUC_{0-t}, Cl, mean residence time (MRT) and

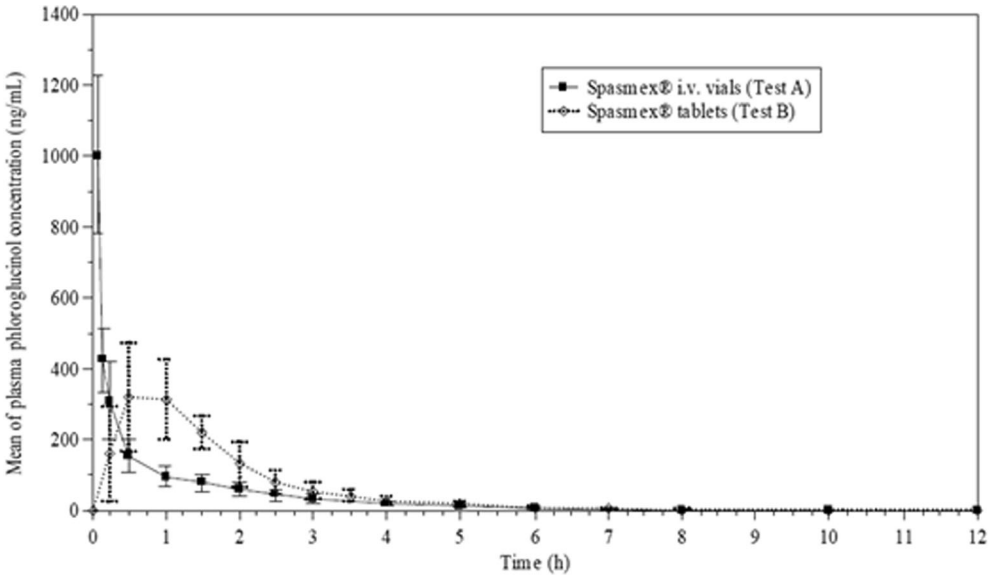


Fig. 2 Mean (± SD) phloroglucinol plasma concentrations (ng/mL) vs. time profiles after single administration of 40 mg phloroglucinol and 1,3,5-trimethoxybenzene IV solution (test A) and after single oral administration of 160 mg (2 tablets) phloroglucinol and 1,3,5-trimethoxybenzene oral formulation (test B). Linear scale

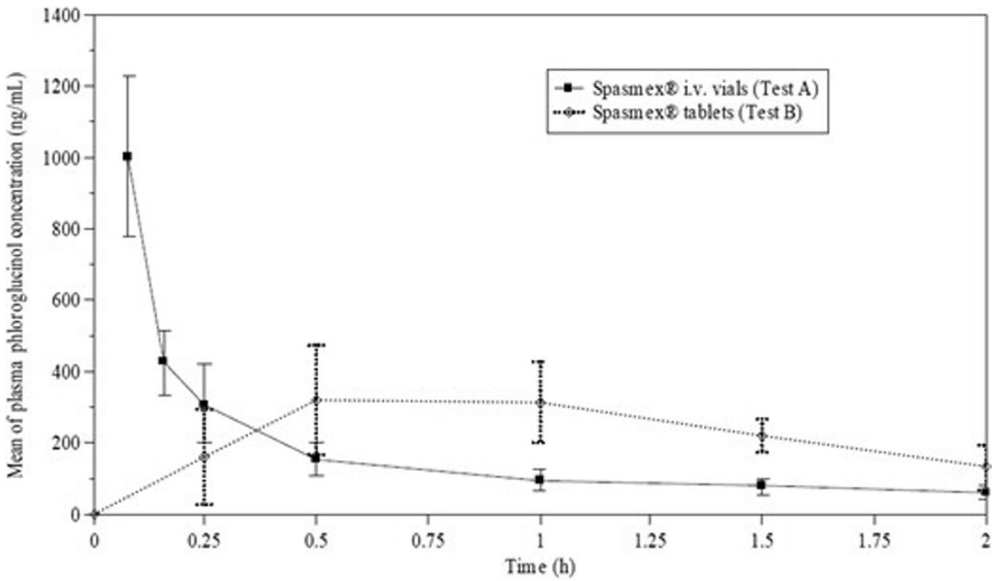


Fig. 3 Mean (± SD) phloroglucinol plasma concentration (ng/mL) up to 2 h post-dose after single administration of 40 mg phloroglucinol and 1,3,5-trimethoxybenzene IV solution (test A) and after single oral administration of 160 mg (2 tablets) phloroglucinol and 1,3,5-trimethoxybenzene oral formulation (test B). Magnified linear scale

Fabs after single dose administration of both formulations. The concentrations of phloroglucinol and trimethylphloroglucinol were determined using a fully validated liquid chromatography/mass spectrometry method. Thus, the study was in compliance with the Note for guidance on the investigation of bioavailability and bioequivalence CPMP/EWP/QWP/1401/98, July 2001, which was in force when it was designed.

A single dose of 40 mg of phloroglucinol was administered to the subjects by IV injection (test A, phloroglucinol IV solution), or a single dose of 160 mg was orally administered (test B, 80 mg of phloroglucinol and 80 mg of 1,3,5-trimethoxybenzene oral formulation, two tablets). The mean dose of phloroglucinol (normalized for the body weight of each subject) was 0.58 ± 0.11 mg/kg BW for test A and 2.33 ± 0.44 mg/kg BW for test B. Figures 2 and 3 show phloroglucinol plasma concentrations (mean + SD) up to 12 h after administration of test A and test B (Fig. 2) and up to 2 h post-dose (magnified scale, Fig. 3). As expected, phloroglucinol concentrations were not detected in any subject at predose of both crossover periods. Following intravenous administration of test A, plasma concentrations of phloroglucinol, extrapolated for time 0, averaged 1607.20 ± 375.23 ng/mL (C_0). Afterwards an apparent monoexponential decay was observed, and the elimination phase could be clearly defined.

The calculated half-life ($t_{1/2}$) was 1.28 ± 0.18 h with an MRT of 1.53 ± 0.22 h. At the last sampling time (12 h post-dose), phloroglucinol was no longer detected in plasma of any subject. The area under the plasma concentration curve up to the last detectable concentration (AUC_{0-t}) was 385.41 ± 104.34 ng/mL × h, while the area under the curve extrapolated to infinity ($AUC_{0-\infty}$) was only slightly greater and amounted to 398.79 ± 104.51 ng/mL × h. Values of total body clearance (Cl/BW) and apparent volume of distribution (V_d/BW) were on average 0.22 ± 0.11 L/h/kg and 0.39 ± 0.16 L/kg. Following the oral administration of test B, at the first sampling time (0.25 h) phloroglucinol was detectable in the

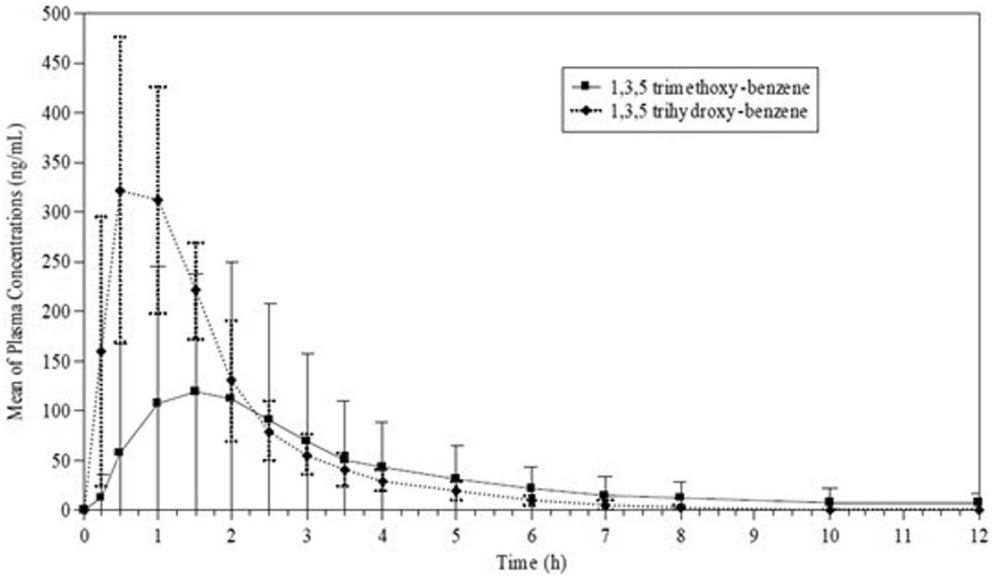


Fig. 4 Mean (± SD) plasma 1,3,5-trimethoxybenzene and phloroglucinol (1,3,5-trihydroxybenzene) concentration (ng/mL) vs. time profiles after single oral administration of two phloroglucinol and 1,3,5-trimethoxybenzene tablets (test B). Linear scale

plasma of all the subjects, except for subject no. 14. In this case the first detectable drug concentration was found at the second sampling time (0.5 h). C_{max} was reached in 0.75 ± 0.37 h (T_{max}) and corresponded to 384.25 ± 125.14 ng/mL. Median T_{max} was 0.50 h with a range between 0.50 and 1.50 h. Calculated $t_{1/2}$ was 1.31 ± 0.17 h and MRT was 1.77 ± 0.25 h. At the last sampling time (12 h post-dose) phloroglucinol was no longer detected in plasma of any subject. AUC_{0-t} mean value was 631.65 ± 146.74 ng/mL × h, while $AUC_{0-\infty}$ was only slightly greater than AUC_{0-t} and amounted to 644.75 ± 146.86 ng/mL × h. Absolute phloroglucinol oral bioavailability (F_{abs}), calculated on the basis of dose-normalized AUC_{0-t} and $AUC_{0-\infty}$ p.o./IV ratios, was 0.42 ± 0.09 and 0.42 ± 0.08, respectively. Values of total body clearance (Cl/F/BW) and apparent volume of distribution (V_d/F/BW) not computing the actual bioavailability (F) were 3.70 ± 0.67 L/h/kg and 7.01 ± 1.62 L/kg.

1,3,5-Trimethoxybenzene and phloroglucinol plasma profiles after administration of test B are shown in the Fig. 4, depicting mean (± SD) plasma concentrations up to 12 h post-dose. As expected, 1,3,5-trimethoxybenzene levels were not detected at pre-dose in any subject. At the first sampling time (0.25 h) 1,3,5-trimethoxybenzene was detectable in plasma of 6 out of the 16 administered subjects (i.e. subjects N. 3, 6, 8, 9, 12, 16). For subjects N. 1, 2, 5, 7, 11, 14, 15 (7/16 subjects) the first detectable drug concentration was found at the second sampling time (0.5 h) and for the remaining two subjects (subjects nos. 10 and 13) at the third (1 h). For subject no. 4, detectable levels of 1,3,5-trimethoxybenzene were not observed at any sampling time.

Peak plasma concentration (C_{max}) of 1,3,5-trimethoxybenzene amounted to 172.29 ± 167.57 ng/mL and was reached in 1.47 ± 0.40 h (T_{max}). Median T_{max} was 1.50 h (range 1.00–2.50 h). After the peak an apparent monoexponential decay was observed. Elimination phase could be clearly defined, and the calculated half-life ($t_{1/2}$) was 3.63 ± 1.84 h and MRT was 4.40 ± 1.14 h.

AUC_{0-t} was 460.68 ± 458.71 ng/mL × h, while $AUC_{0-\infty}$ amounted to 572.82 ± 562.36 ng/mL × h.

Cl/F/BW and V_d/F/BW were respectively 11.66 ± 14.19 L/h/kg and 36.60 ± 25.70 L/kg.

Table 1 Plasma phloroglucinol (1,3,5-trihydroxybenzene) PK parameters

Treatment	1,3,5-Trihydroxybenzene							
	C_0 (ng/mL)	AUC_{0-t} (ng/mL x h)	$AUC_{0-\infty}$ (ng/mL × h)	$t_{1/2}$ (h)	MRT (h)	Cl/BW (L/h × kg)	V_D/BW (L/kg)	
Test A—i.v. 40 mg	1607.20 ± 375.23 (23.35)	385.41 ± 104.34 (27.07)	398.79 ± 104.51 (26.21)	1.28 ± 0.18 (14.23)	1.53 ± 0.22 (14.35)	0.22 ± 0.11 (49.69)	0.39 ± 0.16 (41.01)	
	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng/mL × h)	$AUC_{0-\infty}$ (ng/mL × h)	$t_{1/2}$ (h)	MRT (h)	Cl/F/BW (L/h × kg)	V_D/F/BW (L/kg)
Test B—p.o. 160 mg	384.25 ± 125.14 (32.57)	0.75 ± 0.37 (48.96)	631.65 ± 146.74 (23.23)	644.75 ± 146.86 (22.78)	1.31 ± 0.17 (12.63)	1.77 ± 0.25 (13.95)	3.70 ± 0.67 (18.15)	7.01 ± 1.62 (23.10)

Data are presented as mean ± SD (CV%)
$N = 16$

Plasma phloroglucinol (1,3,5-trihydroxybenzene) PK parameters are summarized as mean (± SD) in the Table 1.

Absolute bioavailability (F_{abs}) for the oral route was 0.42 ± 0.09 based on dose normalized AUC_{0-t} and 0.42 ± 0.08 based on dose normalized $AUC_{0-\infty}$. Only a few data were available in the literature on the metabolism and excretion of phloroglucinol indicating that this compound is eliminated after glucuronidation and/or sulfo-conjugation [13]. In this study, an exploratory investigation on the metabolism of this compound in urine was also performed. Urinary phloroglucinol (1,3,5-trihydroxybenzene) mean (± SD) concentration and amount of excretion in the first 6 h after administration are summarized in Table 2.

From these data it can be concluded that (i) most of the drug (> 80% for both formulations) was eliminated in the first 6 h after dosing, (ii) the drug was eliminated in urine as unchanged phloroglucinol (1,3,5-trihydroxybenzene) in a small proportion (< 3% of the dose) and (iii) a considerable amount of the drug was detected after enzymatic deconjugation with β-glucoronidase/arylsulfatase from *Helix pomatia*.

Plasma 1,3,5-trimethoxybenzenePK parameters are summarized in Table 3.

Comparing these data with those of 1,3,5-trihydroxybenzene, it is evident that the bioavailability of 1,3,5-trimethoxybenzene is on average lower both in terms of rate (i.e. lower C_{max}, later T_{max}) and extent of absorption (smaller AUC_{0-t}). Moreover, 1,3,5-trimethoxybenzene plasma concentrations and derived PK parameters showed a much higher inter-subject variability, data which suggest the occurrence of individual differences in the compound metabolism. For example, one subject showed no detectable levels of in 1,3,5-trimethoxybenzene plasma but did show the presence of its derivatives in urine, indicating a fast biotransformation of the parent compound (see below). The metabolism of 1,3,5-trimethoxybenzene appears to follow the predicted demethylation pathways giving rise to the putative metabolites 3,5-dimethoxyphenol and 5-methoxyresorcinol, while the formation of phloroglucinol seems to be negligible if any.

Table 2 Urinary phloroglucinol (1,3,5-trimethoxybenzene) concentration and elimination in the 0–6 h post-dose time interval

Treatment	1,3,5-Trihydroxybenzene		
	Concentration (ng/mL)	Elimination (mg)	Elimination (%)
Test A—i.v. (40 mg) No deconjugation	1740.88 ± 1528.76 (87.82)	1.12 ± 0.49 (44.07)	2.79 ± 1.23 (44.07)
Test A—i.v. (40 mg) After deconjugation	43,881.25 ± 23,656.13 (53.91)	30.78 ± 7.03 (22.85)	76.94 ± 17.58 (22.85)
Test B—p.o. (160 mg) No deconjugation	2076.88 ± 1705.63 (82.12)	1.33 ± 0.63 (47.15)	0.83 ± 0.39 (47.15)
Test B—p.o. (160 mg) After deconjugation	136,041.67 ± 64,117.61 (47.13)	128.90 ± 30.79 (23.89)	80.57 ± 19.24 (23.89)

Data are presented as mean ± SD (CV%)

Pharmacokinetic results indicate that 3,5-dimethoxyphenol is the major metabolite, while 5-methoxyresorcinol is quantitatively minor. Phase II metabolism with glucuronic acid and/or sulfate conjugation allows urinary elimination of the resulting hydrophilic products.

Phase 3 Study Design

The studies described in the present manuscript are four phase 3 open-label, randomized, parallel-group comparative studies with use of standard schemes and doses of phloroglucinol, as solution for IV and IM administration, and phloroglucinol + 1,3,5-trimethoxybenzene, as tablets.

The studies were conducted in accordance with the principles set forth in the Helsinki Declaration of the World Medical Association (adopted at the 18th WMA Assembly in Helsinki in June 1964, the latest version was adopted at the 60th Assembly in Fortaleza in 2013) and the principles of Good Clinical Practice (GOST R 52,379–2005 "Good Clinical Practice", Order No. 200-n dated 04/01/2016). The research protocol was approved by the Ministry of Health of the Russian Federation No. 506 of 09/14/2015, No. 3 of 11/01/2017, No. 29 of 23/01/2017. Informed consent was obtained from all participants prior to study participation.

Drug treatment scheme of the four phase 3 studies	
1. Phloroglucinol IV/IM vs metamizole sodium	Biliary spasms
2. Phloroglucinol + 1,3,5-trimethoxybenzene vs scopolamine butylbromide	Biliary spasms
3. Phloroglucinol IV/IM + dexketoprofen vs dexketoprofen	Urinary tract spasms
4. Phloroglucinol + 1,3,5-trimethoxybenzene + dexketoprofen vs dexketoprofen	Urinary tract spasms

Phloroglucinol Solution for IV and IM Administration vs Metamizole Sodium in Biliary Spasms

This study is a phase 3, open-label, randomized, parallel-group comparative study with use of standard schemes and doses of phloroglucinol, a solution for IV and IM administration, versus basic therapy with the metamizole-based drug in 102 patients with diagnosed acute biliary colic.

Table 3 Plasma 1,3,5-trimethoxybenzene mean (± SD) PK parameters

Treatment	1,3,5-Trimethoxybenzene							
	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng/mL × h)	$AUC_{0-\infty}$ [b] (ng/mL × h)	$t_{1/2}$ [a] (h)	MRT[a] (h)	Cl/F/BW[a] (L/h × kg)	$V_d/F/BW$ (L/kg)[a]
Test B—p.o. 160 mg	172.29 ± 167.57 (97.26)	1.47 ± 0.40 (27.23)	460.68 ± 458.71 (99.57)	572.82 ± 562.36 (98.17)	3.63 ± 1.84 (50.77)	4.40 ± 1.14 (25.90)	11.66 ± 14.19 (121.67)	36.60 ± 25.70 (70.22)

Data are presented as mean ± SD (CV%). $N = 15$ unless otherwise specified
[a] $N = 12$
[b] $N = 14$

Phloroglucinol + 1,3,5-Trimethoxybenzene vs Scopolamine-Based Drug in Biliary Spasms

This study is a phase 3, open-label, randomized, parallel-group comparative study with use of standard schemes and doses of phloroglucinol + 1,3,5-trimethoxybenzene tablets versus basic therapy with the scopolamine-based drug coated tablets in 90 patients with diagnosed acute biliary colic.

Phloroglucinol Solution for IV and IM Administration vs Dexketoprofen in Urinary Colic

This study is a phase 3, open-label, randomized, parallel-group comparative study with use of standard schemes and doses of phloroglucinol, a solution for I/V and I/M administration plus the dexketoprofen-based versus basic therapy with dexketoprofen in 86 patients with diagnosed acute renal colic.

Phloroglucinol + 1,3,5-Trimethoxybenzene vs Dexketoprofen in Urinary Colic

This study is a phase 3, open-label, randomized, parallel-group comparative study with use of standard schemes and doses of phloroglucinol + 1,3,5-trimethoxybenzene tablets plus the dexketoprofen-based drug versus basic therapy with dexketoprofen in 86 patients with diagnosed acute renal colic.

Study Population

The studies included a total of 364 patients, women and men over the age of 18 years with diagnosed acute biliary colic with cholelithiasis or with spasm in dyskinesia of the gallbladder and the documented diagnosis, or with diagnosed acute renal colic or pain and spasms in the urinary tract, and the documented diagnosis, as well as signed informed consent for the participation of the patient in the clinical study.

The exclusion criteria included pregnant or lactating women, patients who were allergic to antispasmodics and NSAIDs in history and who were affected by infectious diseases, such as HIV, syphilis, hepatitis B and hepatitis C.

Study Intervention

The total duration of the studies was 5–7 days. Throughout the study, each patient was examined three times: visit 1 (V1), V2 and V3.

All the necessary information about the past medical history and the present diseases at the time of the study onset and the demographic data were recorded in the card of each patient. At the first screening visit, a detailed anamnesis regarding previous kidney and bladder diseases, as well as pharmacotherapy (including therapies with prohibited drugs by the study criteria), was carried out.

Complete clinical examination, including the assessment of vital signs (VAS), was performed at the screening and final visits. Before the treatment, patients completed the VAS form. At the end, the final evaluation of the efficiency and safety of ongoing pharmacotherapy was performed.

Method of Administration

Phloroglucinol Solution for IV and IM Administration

The study involved patients with diagnosed acute renal colic or pain and spasmodic phenomena in urinary tracts, who received a solution of phloroglucinol, in a single intravenous dose of 40 mg (ampoule 4 ml) with a possible repeated administration after 30 min (one ampoule) against the background of basic therapy with the drug dexketoprofen, a solution for IV and IM administration, at a dose of 25 mg two times a day.

Similarly, a second study recruited patients with acute biliary pain with gallstones or with spastic conditions associated with diseases of the biliary tract or spasm caused by dyskinesia of biliary ducts, who were randomized either in a study group that received a solution of phloroglucinol, in a single intravenous dose of 40 mg (ampoule 4 ml) with a possible repeated administration after 30 min (one ampoule), or in a control group who received metamizolein, in a single intravenous dose of 500 mg. Supportive therapy is indicated intramuscularly, two injections of the study drug per day up to 5/7 days.

Phloroglucinol + 1,3,5-Trimethoxybenzene Tablets

The two studies implied oral therapy with the spasmolytic drug phloroglucinol + 1,3,5-trimethoxybenzene, as tablets, which was prescribed to patients after relief of acute biliary or renal colic at a dose of 160 mg three times in day. Besides phloroglucinol + 1,3,5-trimethoxybenzene, patients with diagnosed acute renal colic received also the basic therapy with dexketoprofen at a dose of 25 mg two times a day.

In case of cholelithiasis or spasm in dyskinesia of the gallbladder, the reference group received scopolamine, coated tablets, at a dose of 10–20 mg three times a day. Instead, in case of pain and spasms in the urinary tract, the reference group was administered with a dexketoprofen solution, at a dosage of 25 mg two times a day.

Randomization

All eligible patients were randomized to two treatment groups, in a ratio of 1:1. Patients of both groups were comparable in all clinical and laboratory parameters, which could otherwise influence the outcome of the disease.

Study Outcomes

The primary and secondary outcomes were determined and are summarized in Table 4.

Safety data were analysed in all patients who received at least one dose of the test medication. Occurrence of adverse events was recorded after the patient signed the informed consent form and throughout the study, and before the expiration of 30 days after the last administration of the drug. The safety analysis of the medication was carried out on the basis of the following: (i) assessment of vital indicators, (ii) assessment of adverse events/serious adverse events relative to the study medications, (iii) assessment of the severity of the pain syndrome according to the VAS and VRS scores of spasms

Table 4 Primary and secondary efficiency criteria of the four studies

Phloroglucinol solution for IV and IM administration in biliary tract	Primary efficiency criteria
	Complete relief from pain, according to the patient's subjective evaluation of their condition by the following rating scales: VAS and VRS after the first or repeated injection on the first day of treatment
	Secondary efficiency criteria
	Onset of painkilling effect, according to the patient's evaluation of their pain by a VAS and VRS every 15 min for 60 min after administration of the study drug
	Absence of occurrence of repeated pain episodes or spastic phenomena during the follow-up period
	Need for repeated injections of the drug
	Elimination of spasm and improvement in gallbladder outflow and motor function of the gallbladder and ducts—according to ultrasound or CT* or plain film*
Phloroglucinol solution for IV and IM administration in urinary tract	Primary efficiency criteria
	Difference between the two groups in the intensity of pain (PID) according to the subjective assessment by the patient of the pain syndrome by the VAS in millimetres. A significant difference between the groups is a difference of 13 mm or more on the VAS at 30 min after intravenous injection on the first day of the study and at 60 min after intramuscular injection on the second and consecutive days of the study
	Secondary efficiency criteria
	Assessment by the patient of relief from the pain syndrome according to the VRS in points, after 30 and 60 min (the first day of the study) and 60 min (the second and consecutive days of the study) after injection of the drugs, for a preliminary evaluation of the therapy efficiency, as an additional measure of pain assessment; to decide whether to increase repeated injections (the first day of study) or to exclude the patient from the study in the absence of the therapy efficiency. Any improvement on the VRS at least by 1 point will be considered a positive response to therapy
	Assessment of pain intensity on the VAS in millimetres, in comparison with the baseline at 30 min after injection on the first day of the study or at 60 min after injection on the second and consecutive days of the study, to calculate PID. Reduction of pain intensity on the VAS 60 min after the first injection to assess the stability of the effect on the first day of the study
	Absence of recurrent colic during follow-up during the entire study period
	Elimination of spasm and recovery of urine passage—according to ultrasound examination of kidneys and bladder, a plain film of the urinary tract* or CT of the urinary tract*
	Discharge of concernment

Table 4 continued

Phloroglucinol + 1,3,5-trimethoxybenzene tablets in biliary tract	Primary efficiency criteria
	Relief from the pain syndrome according to the patient's assessment of their condition on the VAS and digital rating scale of the pain assessment prior to taking the drug and 1 h after taking the drug, during the entire treatment period
	Secondary efficiency criteria
	Elimination of spasm and improvement in gallbladder outflow and motor function of the gallbladder and ducts
	According to ultrasound* or CT* of the ducts and gallbladder
Phloroglucinol + 1,3,5-trimethoxybenzene tablets in urinary tract	Primary efficiency criteria
	Difference between the two groups in the intensity of pain (PID) according to the subjective assessment by the patient of the pain syndrome by the VAS in millimetres. A significant difference between the groups is a difference of 13 mm or more on the VAS, 60 min after the intake of the drugs
	Secondary efficiency criteria
	Assessment by the patient of relief from the pain syndrome according to the VRS in points, 60 min after taking the drugs, for a preliminary evaluation of the therapy efficiency, as an additional measure of pain assessment; to decide whether to increase the dose of the drug or to exclude the patient from the study in the absence of the therapy efficiency. Any improvement on the VRS at least by 1 point will be considered a positive response to therapy
	Elimination of spasm and recovery of urine passage according to ultrasound examination of kidneys and bladder (compulsory method), a plain film of the urinary tract* or CT of the urinary tract*
	Discharge of concernment

CT computed tomography, *PID* pain intensity difference, *VAS* visual analogue scale, *VRS* verbal rating scale
*Optional method, as determined by the clinical investigator

and pain in the urinary tract. The following indicators used to assess the risk factors associated with the medications under study: (i) the total number of adverse events and serious adverse events in each patient; (ii) number of patients with adverse events and serious adverse events that occurred during the study; (iii) number of patients who discontinued the study early because of adverse events/serious adverse events.

Statistical Methods

The statistical analysis was carried out using the programs Statsoft Statistica Professional 13 and Microsoft Excel 2016. For quantitative characteristics, the conformity to the law of the normal distribution according to the Shapiro–Wilk criterion was previously estimated. Parametric criteria were used when testing statistical hypotheses for indicators with normal distribution, while nonparametric criteria were used for parameters whose distribution was different from the normal. Comparison of groups by

Table 5 Demographic characteristics of patients with pain and spasms in urinary and biliary tract subdivided into study groups (group A) versus control groups (group B)

	Phloroglucinol IV and IM vs metamizole, solution for injection		Phloroglucinol IV and IM vs dexketoprofen IV and IM		Phloroglucinol vs scopolamine 10 mg		Phloroglucinol tablets 160 mg		Phloroglucinol tablets 160 mg vs dexketoprofen IV and IM	
	Group A ($n = 51$)	**Group B ($n = 51$)**	**Group A ($n = 43$)**	**Group B ($n = 43$)**	**Group A ($n = 45$)**	**Group B ($n = 45$)**	**Group A ($n = 43$)**	**Group B ($n = 43$)**	**Group A ($n = 43$)**	**Group B ($n = 43$)**
Enrolled patients	102		86		90		86			
Male sex, %	31.37	37.25	32.56	41.86	31.11	40.00	58.14	53.49		
Age	46.76 ± 14.53	52.65 ± 13.47	48,00	47,00	57	60	52.00	41.00		
Weight (kg)	75.56 ± 12.52	78.44 ± 12.95	73,22 ± 11,86	77,37 ± 13,22	78.87 ± 11.97	81.80 ± 13.32	83.50	80.40		
Height (cm)	166	168	168,00	172,00	169	167	173.00	172.00		

quantitative characteristics was performed using the *T*-test for independent samples or the Mann–Whitney test. Intragroup comparisons were performed using the Wilcoxon test, or the *T*-test for linked samples. Qualitative signs were analysed using the Pearson's χ^2 test and Fisher's exact test. For intragroup multiple comparisons nonparametric analysis of variance of repeated measures (Friedman test) was used. The differences at $p < 0.05$ were considered statistically significant. All parameters were measured in duplicate.

RESULTS

Results of Clinical Studies

Baseline Data

Demographic data and baseline characteristics are summarized in Table 5. A statistical analysis of socio-demographic and anthropometric indicators (gender, age, weight, height) was performed. Since the groups of patients who took at least one test drug tablet (safety population), patients included in the study (intention to treat, ITT), and patients who completed the study under the protocol (per protocol, PP) are identical, the analysis of the indices was similar for all the patient groups.

Outcomes

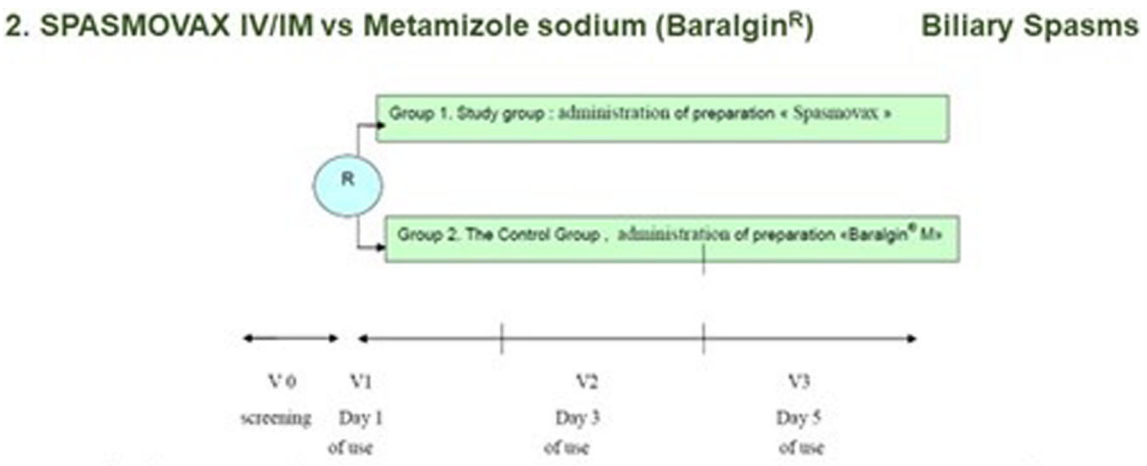
Phloroglucinol Solution for IV and IM Administration

Primary and Secondary Efficiency The evaluation of the effectiveness of the therapy was performed according to the criteria described in Table 4.

The primary and secondary outcomes are summarized as follows.

Phloroglucinol Solution for IV and IM Administration in Biliary Tract Figure 5 summarizes the results obtained in the phase 3 clinical study of phloroglucinol vs metamizole.

The assessment of the therapy efficacy, according to patients' subjective evaluation, was performed during day 1 of treatment of



	Pain relief on the VAS scale		Preparation							
			Spasmovax				Baralgin M			
			Days 4-5, 60 minutes after intake preparation							
			Day 4 intake 1	Day 4 intake 2	Day 5 intake 1	Day 5 intake 2	Day 4 intake 1	Day 4 intake 2	Day 5 intake 1	Day 5 intake 2
1 injection	Success	Abs.	20	15	10	4	21	13	5	6
		%	86,96%	93,75%	83,33%	66,67 %	91,30%	100,00%	62,50%	85,71%
	Failure	Abs.	3	1	2	2	2	0	3	1
		%	13,04%	6,25%	16,67%	33,33 %	8,70%	0,00%	37,50%	14,29%
	Intergroup differences (p)		a – Fisher's exact test, b – Pearson's test χ2				p=1,000 0[a]	p=1,000 [a]	p=0,347 3[a]	p=0,559 4[a]

Fig. 5 Main results obtained in phase 3 clinical study phloroglucinol vs metamizole

colic attack with intravenous administration of the drugs.

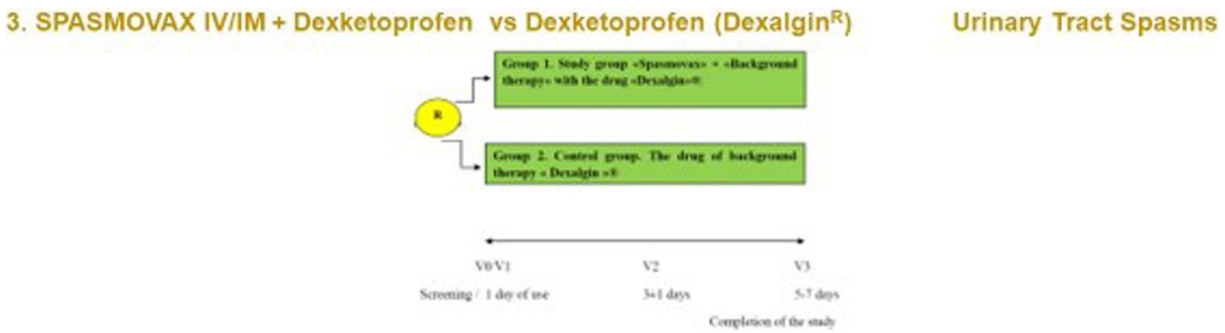
The manifestation of efficacy according to the VAS and VRS was observed from day 0/1, intake 1, after 30 min. Non-inferiority of the study medication on day 1 for the rate of arresting the colic attack according to pain assessment on VAS and VRS was confirmed at all stages of the study, except for the initial 15 min after the drug administration on day 0/1, because that was the minimum time needed for the medicine to act.

Starting from day 2 of treatment, subjects received the maintenance therapy consisting in an intramuscular injection of the two drugs two times per day for 4 days (maximum eight intakes). Most patients received the treatment, including the maintenance therapy for 4 days.

On the basis of the statistical results, it was shown that after 2 days of therapy with phloroglucinol, a stable effect was achieved in four patients and the pain episodes were completely arrested; after 3 days of treatment with phloroglucinol, a stable effect in pain episode relief was achieved in five patients, and in two patients receiving treatment with metamizole.

Primary efficiency:

- Complete cessation of pain by VAS in comparison with the initial period and the cessation of pain by VRS after drug administration during the observation period (60 min) on the first day of treatment from one or repeated injection of the drug: non-inferiority of the study drug on the first day of the study evaluated by pain scales. VAS and VRS were confirmed for the entire period of observation, except the first 15 min after



Complete pain relief according to the VAS scale		Preparation											
		Spasmovax solution + Dexalgin						Dexalgin					
		Day 3 intake 1	Day 3 intake 2	Day 4 intake 1	Day 4 intake 2	Day 5 intake 1	Day 5 intake 2	Day 3 intake 1	Day 3 intake 2	Day 4 intake 1	Day 4 intake 2	Day 5 intake 1	Day 5 intake 2
No	Abs.	39	38	26	21	15	10	43	42	38	29	27	17
	%	90.70%	88.37%	60.47%	48.84%	34.88%	24.39%	100.00%	97.67%	88.37%	67.44%	62.79%	42.50%
Yes	Abs.	4	5	17	22	28	31	0	1	5	14	16	23
	%	9.30%	11.63%	39.53%	51.16%	65.12%	75.61%	0.00%	2.33%	11.63%	32.56%	37.21%	57.50%
Intergroup differences (p)		[a] - Fisher's exact test [b] - Pearson's test $\chi 2$						0.1162[a]	0.2020[a]	0.0058[a]	0.0804[b]	0.0096[b]	0.0839[b]

Fig. 6 Main results obtained in phase 3 clinical study phloroglucinol + dexketoprofen vs dexketoprofen

the administration of drugs required for the medications to act.

Secondary efficiency:

- Onset of painkilling effect, according to the patient's subjective evaluation of the pain by VAS and VRS every 15 min for 60 min after administration of the study drug: in most cases, time of complete relief from pain during intravenous administration in the first day of study occurs at 60 min of observation after the injection, both with the test and the comparison drug.
- Absence of occurrence of repeated pain episodes or spastic phenomena during the follow-up period: repeated seizures and spasticity (VAS $\geq$ 50 mm) were detected only on day 2 in the study group. Pain of its lesser intensity was not considered as a repeated seizure but was also terminated with the administration of maintenance therapy in accordance with the study protocol.
- Need for repeated injections of the drug: complete relief from pain on the first day of the study takes place in the majority of cases after repeated intravenous injection.
- Elimination of spasm and improvement of the bile outflow and motor function of the gallbladder and ducts by ultrasound, CT or plain film (the last two are optional methods in the study, based on the decision of the study doctor): the ultrasound of the gallbladder assessed at screening and at the final visit showed dynamics in the studied parameter manifested in the improvement of the bile outflow and motor function of the gallbladder and ducts, elimination of spasm both in patients of the metamizole group and patients of the phloroglucinol study group.

Phloroglucinol Solution for IV and IM Administration in Urinary Tract Figure 6 summarizes the results obtained in the phase 3 clinical

study of phloroglucinol + dexketoprofen vs dexketoprofen.

The study of efficacy and safety of phloroglucinol solution for IV and IM administration in basic therapy using standard schemes and doses of dexketoprofen was conducted with patients suffering from urinary tract pain and spasms, based on four clinical sites.

During the treatment period (up to 7 days), the patients received phloroglucinol, depending on the randomization scheme against the background of the basic therapy with dexketoprofen, twice a day, versus only basic therapy with dexketoprofen, twice a day, according to the open scheme.

The efficacy of the treatment was evaluated on the basis of patients' subjective self-assessment using the VAS, the primary efficacy criterion, and VRS, the secondary efficacy criterion. Each patient performed the self-assessment during the entire treatment period—up to 7 days, before and after each drug intake (maximum 14 administrations). Most patients were treated for 5 days.

According to the statistical results, it was revealed that the combination therapy of phloroglucinol + dexketoprofen showed higher efficacy compared with the basic therapy, considering the superiority margin set in the protocol.

Evaluation of the therapy safety was conducted from the moment of intake of the first dose of the studied drugs to the end of the patient follow-up. Safety parameters included assessment of vital signs, adverse events/serious adverse events for the study drugs, severity of pain syndrome on the VAS and VRS for spasms and pain in the urinary tract. Adverse events, as well as cases of pregnancy, were not revealed.

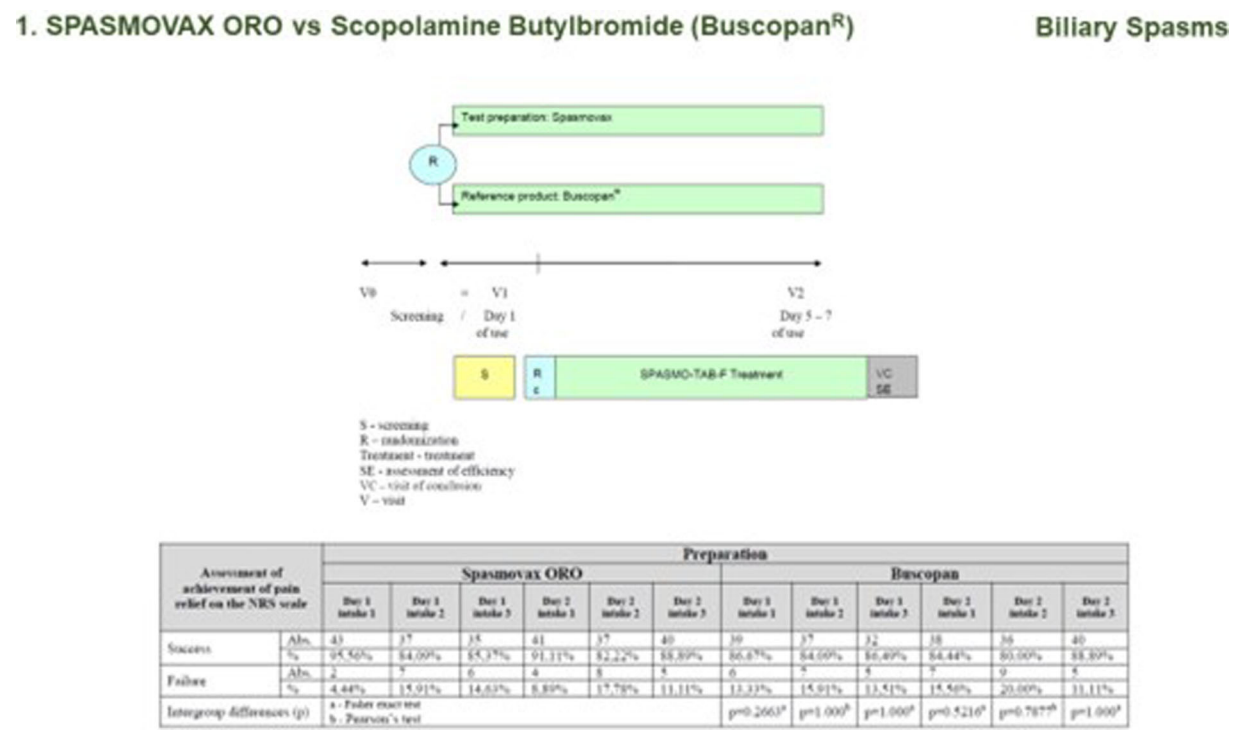
In the study, there were no significant deviations in the indicators of laboratory, instrumental methods of examination, as well as data of physical examination and vital functions, which the investigators would consider as significant.

Primary efficiency:

- Difference between the two groups in the intensity of pain (PID) according to the subjective assessment of patients based on VAS (in millimetres) regarding the pain syndrome: a difference of 13 mm or more on the VAS 30 min after intravenous injection (on the first day of the study) and 60 min after intramuscular injection (on the second and consecutive days of the study) was considered as significant.

Secondary efficiency:

- Pain relief according to VRS: at most stages of the study, the pain relief rates of the study group were higher than the control group ones, which indicates the superiority of the combination therapy with phloroglucinol + dexketoprofen in relation to monotherapy with dexketoprofen. Intergroup differences for this indicator were statistically significant at the following stages of the study: day 1, 60 min after the first/30 min after the second intake; day 3, intake 2; day 4, intake 1; day 5, intake 1. In the study group, the presence of a positive response to therapy according to the VRS at all stages of the study was noted in 100% of patients; in the control group, the frequency of achieving a positive response to therapy did not reach 100% in the following stages of the study: day 1, 30 min after the first intake (97.67%), day 2, intake 2 (97.67%), day 3, intake 1 (97.67%), day 3, intake 2 (97.67%), day 4, intake 1 (97.67%), day 4, intake 2 (97.67%), day 5, intake 1 (95.35%), day 5, intake 2 (94.29%).
- Assessment of pain intensity on the VAS in millimetres, compared to the baseline level: at the initial stages of the study, statistically significant intergroup differences in the indices of the dynamics of pain intensity reduction against the background of the therapy were noted. In the study group, there was a more pronounced decrease in the intensity of pain than in the control group, which indicates the superiority of combination therapy with the use of phloroglucinol + dexketoprofen in relation to therapy with the drug dexketoprofen.
- Absence of repeated pains and spasmodic phenomena during the subsequent period of observation. At several stages of the study,



Assessment of achievement of pain relief on the NRS scale		Preparation											
		Spasmovax ORO						Buscopan					
		Day 1 intake 1	Day 1 intake 2	Day 1 intake 3	Day 2 intake 1	Day 2 intake 2	Day 2 intake 3	Day 1 intake 1	Day 1 intake 2	Day 1 intake 3	Day 2 intake 1	Day 2 intake 2	Day 2 intake 3
Success	Abs.	43	37	35	41	37	40	39	37	32	38	36	40
	%	95.56%	84.09%	85.37%	91.11%	82.22%	88.89%	86.67%	84.09%	80.49%	84.44%	80.00%	88.89%
Failure	Abs.	2	7	6	4	8	5	6	7	8	7	9	5
	%	4.44%	15.91%	14.63%	8.89%	17.78%	11.11%	13.33%	15.91%	19.51%	15.56%	20.00%	11.11%
Intergroup differences (p)	a - Fisher exact test b - Pearson's test							p=0.2663[a]	p=1.000[b]	p=1.000[a]	p=0.5216[a]	p=0.7877[b]	p=1.000[a]

Fig. 7 Schematic protocol of the phase 3 study phloroglucinol + 1,3,5-trimethoxybenzene vs scopolamine in biliary colic

the indices of the absence of repeated pain in the study group were statistically significantly higher than in the control group, which indicates the superiority of the combination therapy using drugs phloroglucinol + dexketoprofen in relation to therapy using only dexketoprofen.

- Results of instrumental examinations (ultrasound, X-ray, CT): statistically significant intergroup differences were absent ($p > 0.05$, Pearson's χ^2 criterion, Fisher's exact test).
- Discharge of concernment: statistically significant intergroup differences were absent. The frequency of discharge of concernment was 16.63% and 30.23% in the study group and the control group, respectively ($p = 0.0616$, Pearson's χ^2 criterion).

Phloroglucinol + 1,3,5-Trimethoxybenzene Tablets

Primary and Secondary Efficiency Regarding the studies on phloroglucinol + 1,3,5-trimethoxybenzene tablets in patients with diagnosed acute biliary and renal colic, the evaluation of the therapy efficacy was performed according to the criteria described in Table 4. The primary and secondary outcomes are following summarized as follows.

Phloroglucinol + 1,3,5-Trimethoxybenzene Tablets in Biliary Tract Figure 7 summarizes the results obtained in the phase 3 clinical study of phloroglucinol + 1,3,5-trimethoxybenzene vs scopolamine in biliary colic.

The study of efficacy and safety of phloroglucinol + 1,3,5-trimethoxybenzene tablets in comparison with a scopolamine-based reference drug was conducted on patients affected by pain and spasms in the bile duct, based on three study sites. During the treatment period (up to 7 days), the patients received the preparation of phloroglucinol + 1,3,5-trimethoxybenzene tablets or scopolamine according to the open scheme three times a day, depending on the randomization scheme. Assessment of the therapy efficiency

was carried out on the basis of subjective assessment of well-being by the patient themself using the scales VAS, NRS and VRS, which was the primary criterion of efficiency. Patients' subjective assessment of therapy efficacy was conducted during the entire treatment period—up to 7 days, before and after each drug intake (maximum 21 intakes). Most patients were treated for 5 days. In most cases, the statistically significant efficacy of the study drugs was achieved. In addition, in most cases, the noninferiority of the test drug towards the reference product was reported, which was the primary criterion of efficiency. The secondary efficiency criteria included CT and ultrasonography of the gallbladder, assessed at the screening and at the final visit. According to the results of the study, in six patients of the phloroglucinol + 1,3,5-trimethoxybenzene group and in three patients of the scopolamine group, the signs of hypertension of the gallbladder were noted at the screening; at the final visit, there were no signs of hypertension in these patients. Thus, it is possible to establish evidence of equivalence of the analysed medications according to the stated criteria.

Primary efficiency:

- Analysis of the indicators on the VAS: in all cases, intragroup dynamics ($p < 0.05$, Wilcoxon test) of the VAS were statistically significant, except for the following cases: (i) day 7, intake 2—for the control group; (ii) day 7, intake 3—for both groups of patients. As most of the patients were treated for 6 days and on day 7 the number of patients was not significant, the calculation data for day 7 cannot be considered significant for interpreting the results of treatment. No statistically significant differences were found in the analysis of the VAS values of the test medication compared to the reference drug, except for day 6, intake1; day 6, intake 3; day 7, intake 1; and day 7, intake 3 scores.
- Analysis of the NRS scores: statistical analysis of the NRS score was performed. In all cases, statistically significant intragroup dynamics ($p < 0.05$, Wilcoxon's test) of the NRS score was observed, except for the following cases: (i) day 7, intake 2—for the control group; (ii) day 7, intake 3—for both groups of patients. In addition, according to the results of post hoc multiple comparisons of the absolute dynamics of the NRS scores with the use of the Friedman test, the statistically significant intragroup differences between the different stages of intake were noted at the stages day 2, intake 3 and day 7, intake 2 when scopolamine was used. In general, in most cases, the noninferiority of the test drug towards the reference product was revealed, except for the indices obtained on day 3, intake 1 and 2; day 6, intake 1 and 3; and day 7, intake 3.
- Analysis of the VRS scores: the statistical analysis of the VRS scores was performed. In all cases, the indices had no statistically significant intergroup differences ($p > 0.05$, Pearson's χ^2 test, Fisher exact test). In general, in most cases, noninferiority of the test preparation towards the reference product was established, except for the indices obtained on day 6, intake 2 and 3 and day 7, all intakes.

Secondary efficiency:

- Elimination of spasm and improvement in gallbladder outflow and motor function of the gallbladder and ducts: according to ultrasound or CT of the ducts and gallbladder. According to the results of the study, there were no changes in internal organs during the radiography and CT in all patients both at the screening stage and at the final visit. When performing ultrasound examination of the abdominal cavity organs in six patients of the phloroglucinol + 1,3,5-trimethoxybenzene group and three patients of the scopolamine group, we noted signs of hypertension of the gallbladder, which are the typical manifestations of spasm and inflammation. These events are expected to disappear by the end of the treatment, i.e. at the end of the study. The signs of hypertension of the gallbladder were absent in 100% of patients in both treatment groups.

Assessment of the presence of a positive response to therapy on the VRS scale		Preparations											
		Spasmovax ORO + Dexalgin						Dexalgin					
		Day 1 intake 1	Day 1 intake 2	Day 1 intake 3	Day 2 intake 1	Day 2 intake 2	Day 2 intake 3	Day 1 intake 1	Day 1 intake 2	Day 1 intake 3	Day 2 intake 1	Day 2 intake 2	Day 2 intake 3
Yes	Abs.	43	43	25	40	39	36	43	39	0	42	38	0
	%	100.00%	100.00%	100.00%	97.56%	100.00%	100.00%	100.00%	90.70%	0%	97.67%	92.68%	0
No	Abs.	0	0	0	1	0	0	0	4	0	1	3	0
	%	0.00%	0.00%	0.00%	2.44%	0.00%	0.00%	0.00%	9.30%	0.00%	2.33%	7.32%	0.00%
Intergroup differences (p)		Fisher's exact test						-	0.1162	-	1.0000	0.2410	-

Assessment of the presence of a positive response to therapy on the VRS scale		Preparations											
		Spasmovax ORO + Dexalgin						Dexalgin					
		Day 3 intake 1	Day 3 intake 2	Day 3 intake 3	Day 4 intake 1	Day 4 intake 2	Day 4 intake 3	Day 3 intake 1	Day 3 intake 2	Day 3 intake 3	Day 4 intake 1	Day 4 intake 2	Day 4 intake 3
Yes	Abs.	39	42	33	40	40	31	43	35	0	39	35	5
	%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	89.74%	0%	97.50%	89.74%	0%
No	Abs.	0	0	0	0	0	0	0	4	0	1	4	0
	%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	10.26%	0.00%	2.50%	10.26%	0.00%
Intergroup differences (p)		Fisher's exact test						-	0.0494	-	1.0000	0.0547	-

Fig. 8 Schematic protocol of the phase 3 study phloroglucinol + 1,3,5-trimethoxybenzene + dexketoprofen vs dexketoprofen in urinary tract

Phloroglucinol + 1,3,5-Trimethoxybenzene Tablets in Urinary Tract Figure 8 summarizes the results obtained in the phase 3 clinical study of phloroglucinol + 1,3,5-trimethoxybenzene + dexketoprofen vs dexketoprofen in the urinary tract.

The study of efficacy and safety of phloroglucinol + 1,3,5-trimethoxybenzene and of dexketoprofen was conducted with the participation of patients in the presence of pain and spasms in the urinary tract, based on six clinical sites.

During the treatment period (up to 7 days), the patients received phloroglucinol + 1,3,5-trimethoxybenzene tablets three times a day against the background of the basic therapy with dexketoprofen, twice a day, or basic therapy only (dexketoprofen, twice a day).

The efficacy of the therapy was evaluated on the basis of subjective self-assessment by the patient using the VAS, the primary efficiency criterion, and VRS, the secondary efficiency criterion. The efficacy of the therapy was evaluated by the patients during the entire treatment period, up to 7 days, before and after each drug intake (maximum 21 administrations).

Most patients were treated for 5 days.

According to the statistical results, it was revealed that the combination therapy of phloroglucinol + 1,3,5-trimethoxybenzene + dexketoprofen showed higher efficacy compared with the basic therapy, taking into account the superiority margin set in the protocol. One of the secondary efficacy criteria (ultrasound examination of the kidneys and bladder) also showed a tendency to superior therapy in the phloroglucinol + 1,3,5-trimethoxybenzene + dexketoprofen group.

Primary efficiency:

- Analysis of the indicators on the VAS: the pain scores on the VAS on day 1 after first intake were 6.42 ± 6.78 mm and 19.70 ± 12.49 mm in the treatment group and the comparison group, respectively. The difference in the average values of the pain indices between the study groups was − 13.28 mm, which exceeds the boundary

of clinically significant differences and enables one to state the superiority of therapy including phloroglucinol and dexketoprofen in comparison with the monotherapy with dexketoprofen. Differences between the compared groups for the indicator under consideration are statistically significant ($p = 0.000$, the Mann–Whitney test).

Secondary efficiency:

- Pain relief according to VRS: achievement of a positive response to therapy, according to VRS data, on day 1 after the first intake was noted in 100% of patients in both groups.
- Elimination of spasm and recovery of urine passage: on the basis of the results of ultrasound of the kidneys and bladder at the stage of visit 2, the treatment group was characterized by a lower frequency of pathology detection: 67.44% in the treatment group and 79.07% in the comparison group; however, the intergroup differences by the considered indicator are statistically insignificant ($p = 0.2232$, Pearson's χ^2 criterion).

According to the statistical results, the combination therapy of phloroglucinol + dexketoprofen showed higher efficacy compared with the control group therapy, considering the superiority set in the protocol. One of the secondary efficiency criteria (ultrasound of the kidneys and bladder) also showed a tendency to superiority of the phloroglucinol + dexketoprofen treatment.

During the study, two adverse events were registered in two patients. These adverse events included sickness and bitter taste in mouth of mild severity. Therefore, the tolerability of the tablet preparations was satisfactory. In the study, there were no significant deviations in the indicators of laboratory, instrumental methods of examination, as well as data of physical examination and vital functions, which the investigator would consider significant.

DISCUSSION

In this analysis, we report for the first time the pharmacokinetic results of two formulations of phloroglucinol and results obtained in four phase 3 open-label, randomized, comparative studies of clinical effectiveness and safety that aimed to demonstrate the effectiveness of oral and parenteral preparations based on phloroglucinol in reducing pain and spasms associated with renal or biliary colic.

Pain and spasms of urinary and biliary tracts are conditions causing poor quality of life. Treatment with analgesic drugs such as nonsteroidal anti-inflammatory drugs and modulators of the parasympathetic system are not always tolerated, and additional therapeutic options are necessary. The present analysis shows the effectiveness of phloroglucinol in reducing pain and spasms associated with urinary and biliary colic. More interestingly, the effect was present when the drug was given orally or IV/IM and was comparable to the reference drugs without serious adverse effects (AEs) registered.

Phloroglucinol is a musculotropic antispasmodic drug. It is frequently prescribed in many European countries but, on the basis of current literature, there are few randomized controlled trials on the effectiveness of phloroglucinol-based drugs on the relief of abdominal pain [20]. Here we demonstrate that phloroglucinol is as effective as the reference drugs both in IV/IM and oral routes, thus justifying its use for urinary and biliary spasms.

As for pharmacokinetic studies we demonstrated that (i) most of the phloroglucinol (> 80% for i.v. and per os formulations) was eliminated in the first 6 h after dosing, (ii) the drug was eliminated in urine as unchanged phloroglucinol (1,3,5-trihydroxybenzene) in a small proportion (< 3% of the dose) and (iii) a considerable amount of the drug was detected after enzymatic deconjugation with β-glucoronidase/arylsulfatase from *Helix pomatia*.

In summary, we can state the equivalence of the drugs under study. Safety parameters included assessment of vital signs, adverse events/serious adverse events, severity of pain

syndrome on the scales VAS, NRS and VRS for biliary colic. From the first intake of the studied drugs to the end of the patient follow-up, two adverse events were detected in two patients. Data from all patients who were randomized and took at least one dose of the study drugs were considered for the analysis of safety and tolerability. The severity was regarded as "mild", the connection with the test drug was marked as "possible", and all the AEs were resolved independently. Serious adverse events, as well as cases of pregnancy, were not revealed. Thus, we can state a comparable safety profile of the medications under study.

LIMITATIONS

The main limitations of the studies are the small number of subjects included and the open-label design and some methods of data collection that are susceptible to bias.

CONCLUSIONS

Results provided in the present paper showed that oral and parenteral preparations based on phloroglucinol have excellent pharmacokinetics properties and are as effective in reducing pain and spasms associated with renal or biliary colic as other current therapeutic options.

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Compliance with Ethics Guidelines. The studies were conducted in accordance with the principles set forth in the Helsinki Declaration of the World Medical Association (adopted at the 18th WMA Assembly in Helsinki in June 1964, the latest version was adopted at the 60th Assembly in Fortaleza in 2013) and the principles of Good Clinical Practice (GOST R 52,379–2005 "Good Clinical Practice", Order No. 200-n dated 04/01/2016). The research protocol was approved by the Ministry of Health of the Russian Federation No. 506 of 09/14/2015, No. 3 of 11/01/2017, No. 29 of 23/01/2017. Link: https://grls.rosminzdrav.ru/CiPermitionReg.aspx?PermYear=0&Qualifier=&CiPhase=&CiType=&Status=&DateInc=&NumInc=&DateBeg=&DateEnd=&Protocol=%d0%a1%d0%bf%d0%b0%d0%b7%d0%bc%d0%be%d0%b2%d0%b0%d0%ba%d1%81&RegNm=&Statement=&ProtoId=&idCIStatementCh=&RangeOfApp=&Torg=%d1%81%d0%bf%d0%b0%d0%b7%d0%bc%d0%be%d0%b2%d0%b0%d0%ba%d1%81&LFDos=&Producer=&Recearcher=&sponsorCountry=&MedBaseCount=&PatientCount=&OrgDocOut=2&NotInReg=0&All=0&PageSize=10&order=numperm&orderType=desc&pagenum=1. Informed consent was obtained from all participants prior to study participation.

Data Availability. The datasets generated during and/or analysed during the current study are not publicly available because they are Scharper's internal data on file.

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