Brillia Health Cough Control

Clinical Summary

Table of Contents

2. Synopsis:

Sponsor/Company: Santonika

Active ingredient: Lapine morphine immune globulin– 0.006g*, Lapine histamine immune globulin– 0.006g* and Lapine bradykinin immune globulin – 0.006g*

*mixture of water-ethanol dilutions 100^{12}, 100^{30} and 100^{50} of the active substance used for the saturation of isomalt, respectively.

Study title: Multicenter, randomized, open-label, comparative, parallel-group, clinical trial to assess both the efficacy and safety of Brillia Health Cough Control in the treatment of cough caused by acute respiratory viral infections.

Phase: IV

Principal investigators:

1. Selkova Eugenia Petrovna, Dr. habil. med., Professor
2. Ivleva Alla Yakovlevna, Dr. habil. med., Professor
3. Petrov Dmitry Victorovich, PhD
4. Ilkovich Mikhail Mikhailovich, Dr. habil. med., Professor
5. Akopov Andrei Leonidovich, Dr. habil. med., Professor
6. Trofimov Vasily Ivanovich, Dr. habil. med., Professor
7. Sivkova Elena Borisovna, Chief Physician, PhD
8. Chizhov Danila Aleksandrovich, Head of Clinical Trials Unit, general physician

Study period: First subject enrolled on March 28th, 2011. Last subject completed on December 12th, 2012.

Objectives:

1. Evaluate the clinical efficacy of Brillia Health Cough Control in the treatment of cough
2. Compare the antitussive efficacy of Brillia Health Cough Control and Codelac®
3. Assess the effects of Brillia Health Cough Control on the quality of life of patients with cough

Efficacy criteria:

Primary endpoints:

1. Time to resolution of cough in groups
2. Decrease in the severity of the cough during participation in the trial

Secondary endpoints:

1. Changes in the number of cough episodes throughout the participation
2. Percentage of patients with resolved cough once completing participation
3. The total score of the QoL questionnaire on Day 0 and Day 7
4. The total score of the QoS questionnaire on Day 0, Day 2, Day 4 and Day 7.
5. CGI-EI mean score in groups

Methods:

Design: a multicenter, randomized, open-label, comparative, parallel-group trial.

The study enrolled adult subjects of both sexes aged ≥18 years with a clinical diagnosis of ARVI and non-productive cough caused by acute pharyngitis, laryngitis, laryngotracheitis, tracheitis, tracheobronchitis or bronchitis. The duration of cough varied between 12 hours and 7 days.

After signing of the informed consent form at Visit 1 (Day 0), patients' eligibility was assessed by performing baseline examination, including collecting a patient's history, vital function evaluation, physical examination, URI symptom scoring, documentation of concomitant therapy, filling out the Quality of Life (SF-36) and Quality of Sleep questionnaires, laboratory testing (CBC, urinalysis, blood biochemistry); all women of child-bearing age were to take a pregnancy test.

After determination of eligibility, the subjects were enrolled in the study and randomized into one of the two groups: group 1 received Brillia Health Cough Control as per the selected dosing regimen; group 2 was treated with Codelac®, 1 tablet 3 times a day. The treatment period for both groups was 7 days. Each patient received a patient diary and instructions on filling out the diary, including daytime and nocturnal cough severity scales, cough character and daily and nocturnal cough episodes.

Patients were to perform three visits to a physician (Day 2, Day 4±1 and Day 7±1), with assessment of cough severity, documentation of ARVI symptoms and concomitant therapy, safety assessment, monitoring of a patient's diary, records of drug return and compliance evaluation. A patient had been observed for a total of 7 days (screening - day 1, treatment period - up to 7 days), with daily records made for cough episodes, its severity and time to resolution of cough. At Visit 4 (Day 7±1), physicians were to rate changes in AEs and their severity by the end of the treatment using the CGI scale, assess compliance, re-fill the QoL and QoS questionnaires, and perform laboratory tests (CBC, urinalysis, biochemistry).

Number of patients:

A total of 143 patients were included and randomized into parallel groups: Brillia Health Cough Control (n=73) and Codelac (n=70). One patient in the Brillia Health Cough Control group and three patients in the Codelac group were withdrawn from the study. The number of per-protocol subjects was n=139, with n=72 in the Brillia Health Cough Control group and n=67 in the Codelac group.

Diagnosis and inclusion criteria:

1. Patients with a clinical diagnosis of ARVI with non-productive cough caused by acute pharyngitis, laryngitis, laryngotracheitis, tracheitis, tracheobronchitis or bronchitis. The duration of the cough varied between 12 hours and seven days.
2. Outpatients of both sexes, aged ≥18 years
3. Availability of signed informed consent to participate in the study

Exclusion criteria:

1. Patients with productive cough
2. Subjects aged <18 years
3. Suspected invasive bacterial infection, including suspected pneumonia
4. History of obstructive pulmonary disease, bronchial asthma
5. Acute respiratory failure
6. Oncological diseases

7. Patient's need for mucoactive drugs at inclusion
8. CNS diseases
9. Exacerbated or decompensated chronic diseases affecting a patient's ability to participate in the clinical trial
10. Use of medications listed in the "Prohibited concomitant treatment" within 15 days prior to enrollment.
11. Allergy to/intolerance of any constituent of the medications used in the treatment.
12. Pregnancy, breast-feeding, unwillingness to use contraception during the study.
13. Consumption of narcotics, alcohol > 2 alcohol units per day, mental diseases.
14. Patients who, from the investigator's point of view, will fail to follow the procedures of the trial or adhere to the dosing regimen of the medicines under study.
15. Significant abnormalities in the laboratory values that, from the investigator's point of view, will impede participation in the trial.
16. Participation in other clinical studies within 1 month prior to enrollment in the current trial.
17. Patients related to the research staff of the clinical trial site who are directly involved in the trial or are the immediate family member of the researcher. The immediate family members include husband/wife, parents, children or brothers (or sisters), regardless of whether they are natural or adopted.

Study drug, dose, route of administration and batch No.:

Brillia Health Cough Control, tablets containing Lapine morphine immune globulin– 0.006 g*, Lapine histamine immune globulin– 0.006 g*, affinity purified antibodies to bradykinin - 0.006 g*

**mixture of water-ethanol dilutions 100^{12}, 100^{30}, 100^{50} of the active substance used for the saturation of isomalt*

Excipients: isomalt, sodium saccharin, sodium cyclamate, anhydrous citric acid, magnesium stearate.

The following Brillia Health Cough Control dosing regimen was used during the study: 2 tablets 3 times a day for the first 3 days, followed by 1 tablet 3 times a day for 4 days. The drug is administered outside of meals, a tablet is held in mouth until complete dissolution.

The study used the product with lot number K010211.

Comparitive therapy:

Codelac®, tablets.

Composition per tablet: codeine 8 mg, sodium hydrocarbonate 200 mg, liquorice root 200 mg, thermopsis lanceolata herb 20 mg.

Excipients: potato starch, microcrystalline cellulose, talc.

The following dosing regimen was used during the study: 1 tablet 3 times daily for 7 days.

Concomitant treatment:

In the course of the trial, patients could receive medications against acute respiratory viral infections as per the applicable standards: antipyretics, antivirals, vitamins, decongestant nasal drops, detoxication therapy and

antibacterials, if required (in case of bacterial complications), excluding antitussives (except for Codelac®) and other prohibited concomitant medications.

Prohibited concomitant treatment:

For 15 days prior to enrollment and during the study (after signing an informed consent form and initiation of screening) subjects were not allowed to receive any medications that might affect the severity of cough, including:

1. Cough and cold preparations (ATC R05, R05C Expectorants and R06D Cough suppressants), except for Codelac® prescribed within the trial.
2. Drug products that irritate or suppress the cough center in the CNS or produce such side effects, as described in the instruction.
3. Drugs known to have caused allergic reactions.
4. Antiemetics.
5. ACE inhibitors, β blockers, bronchodilators.
6. Antihistamine drugs.

Treatment and follow-up period: The treatment and follow-up period was 7 days

Safety criteria:

1. Occurrence, nature, duration and other characteristics of adverse events during treatment and causal relationship with the study drug.
2. Changes in laboratory parameters (complete blood analysis, urinalysis, biochemistry).

Statistical methods:

Sample size calculations were based on the non-inferiority model, with the following hypotheses used: 1) null hypothesis: $Ec-Et\geq\delta$; 2) alternative hypothesis: $Et>Ec-\delta$, where Ec – the effect of the control drug (comparator drug); Et – the effect of the test drug; δ – clinical equivalence taken as 10% of the effect of the control.

The total number of patients enrolled in the trial was n=156, randomized in two groups, n=130. Low dropout rates gave the opportunity to stop recruitment when 143 subjects were allocated in two groups, n=73 in the Brillia Health Cough Control group and n=70 in the Codelac group. The data on the treatment outcome in 139 subjects from the PP population were used in the efficacy analysis. The data obtained from 143 subjects in the ITT sample were used in the safety analysis.

The study data were analyzed using the SAS-9.3 software. The following elements of descriptive statistics were calculated: the mean, standard deviation, number of observations – for quantitative variables; incident rates and proportions of subjects with a certain characteristic– for qualitative variables. Parametric statistics were used for continuous and interval variables and non-parametric statistics for frequency analysis of categorical variables.

Efficacy and safety:

Efficacy results:

The study results demonstrate that Brillia Health Cough Control is an effective product for the treatment of cough in subjects with acute infectious and inflammatory respiratory tract diseases. Antitussive effects of the drug product were characterized by reduced duration of cough. The antitussive effect of Brillia Health Cough Control was comparable to that of Codelac® in terms of cough duration ($p<0.025$). The average time to resolution of cough (daytime and nocturnal) was 7.2±1.0 days (versus 7.0±1.1 in the Codelac® group), which was as good as its therapeutic effects in the previous trials).

The efficacy of Brillia Health Cough Control was evidenced by a significant reduction in cough severity scores in the initial few days after treatment onset. As a result of the 7-day treatment, the severity score reduced by 3.1±09 (versus 3.1±1.0 in the Codelac group; $p<0.05$), totaling 0.2±0.5 in both groups at the end of the administration period.

The cough suppressant action of Brillia Health Cough Control was supported by changes in daily cough scores, which were consistently improving throughout the treatment period (with an average daily reduction of 10.7±14.5 vs. 8.4±11.0 in the Codelac® group).

The frequent non-productive/dry cough affecting daily activities and sleep quality in 44% of patients was fully resolved in 76% of subjects; the other participants continued to demonstrate occasional residual cough.

Positive changes in subjects with cough caused by acute respiratory infection improved the quality of life and sleep. The SF-36 survey demonstrated improved physical and mental health (by 10% on average) after 7 days of Brillia Health Cough Control therapy. The improvement of sleep quality within a week and total QoL score achieved due to Brillia Health Cough Control were comparable to the outcome of Codelac® treatment ($p<0.025$).

At the end of the administration period, the investigators assessed the therapeutic effect of Brillia Health Cough Control as “Marked” (vast improvement). The mean total score (3.7±0.5) indicated either remission or significant improvement of patients by the end of the observation period. Occasional adverse effects related to the therapy that did not exert any significant effects on the functional potential of subjects were found. The Clinical Global Impression Scale-Efficacy Indices (CGI-EI) in the groups of Brillia Health Cough Control and Codelac® were comparable - 3.7±0.5 ($p<0.025$).

Safety results:

The monitoring of adverse events and laboratory values indicated the safety of Brillia Health Cough Control. Treatment with Brillia Health Cough Control was not associated with any serious adverse events. One AE (moderate eosinophilia), from the investigator’s point of view, had an unlikely causal relationship with the therapy.

Conclusions:

1. Brillia Health Cough Control is effective for the treatment of subjects with cough caused by acute infectious and inflammatory respiratory tract diseases: ARVI, acute pharyngitis, laryngitis, laryngotracheitis, tracheitis, bronchitis.

2. Therapeutic effect of Brillia Health Cough Control manifests in effective elimination of daytime and nocturnal cough. The antitussive activity of Brillia Health Cough Control indicated by time to resolution of daytime and nocturnal cough is comparable to that of combination product Codelac®.
3. The severity of daytime and nocturnal cough begins to decrease as soon as on the first day after Brillia Health Cough Control administration, with its reduction observed throughout the whole treatment period. By the end of the 7-day administration, cough severity reduced by almost 100% and was comparable to that in the Codelac® group. Minor residual coughing (occasional cough for short periods during the day) continued in 25% of participants.
4. By targeting various cough reflex mediators, Brillia Health Cough Control ingredients enable achieving an antitussive effect in the early days after URI onset (in dry, irritative cough interfering with daily activities), and a protussive effect at later points of treatment.
5. Brillia Health Cough Control exhibits antitussive effect, promotes resolution of cough and infectious respiratory tract inflammation without secondary bacterial complications.
6. Positive changes in subjects with cough after Brillia Health Cough Control therapy improve their quality of life manifested as increased SF-36 physical and mental health summary scales.
7. After 7-day Brillia Health Cough Control therapy, either complete cough resolution or a significant relief in cough severity and incidence improves nocturnal sleep, resulting in positive changes in the quality of sleep.
8. According to the physicians, Brillia Health Cough Control and Codelac® (CGI-EI) show similar clinical efficacy in the treatment of cough.
9. The monitoring of adverse events and laboratory values indicate the safety of Brillia Health Cough Control in the treatment of patients with cough induced by acute infectious and inflammatory diseases of the respiratory tract.
10. Brillia Health Cough Control was not associated with respiratory depression or drug dependence and it produced no narcotic nor hypnotic effects.
11. No adverse interactions were reported with the use of Brillia Health Cough Control in conjunction with therapy for co-morbidities.
12. Compliance in the Brillia Health Cough Control group was significantly higher as compared to the Codelac® group.

Date of report: February 2013

3. Abbreviations

ACE inhibitor – angiotensin-converting-enzyme inhibitor

CRF – Case Report Form

AE – adverse event

UL – urinalysis

ARVI – acute respiratory viral infection

SAE – serious adverse event

FZ – Federal Law

CNS – central nervous system

RR – respiratory rate

HR – heart rate

ANOVA – analysis of variance

CGI – Clinical Global Impression Scale

GCP – Good Clinical Practice

H1, H2 and H3 receptors – histamine receptors (H1, H2, H3)

ITT – Intention-to-treat (all subjects who started treatment). This sample consists of all subjects who signed the informed consent and received at least one dose of the study drug.

mITT – Modified intention-to-treat. This sample consists of all subjects who received at least one dose of treatment and attended at least one visit after treatment initiation with no serious deviations from the protocol.

PP – Per Protocol (all subjects complying with the protocol requirements). This sample includes all subjects who completed the therapy as per the study protocol, without any missing visits and major protocol deviations.

SF-36 – Short Form-36 Health Survey

4. Ethical aspects:

The study was carried out in accordance with Federal Law No. 61-FZ "On Medicinal Product Circulation" of 12.04.2010, GOST R 52379-2005 "Good Clinical Practice" (approved by Decree of Federal Technical Regulation and Metrology Agency No. 232-st. dated September 27, 2005 effective as of 01.04.2006), Guideline for Good Clinical Practice, E6 (R1), Current Step 4 version dated 10 June 1996, and the Declaration of Helsinki of the World Medical Association.

Prior to enrollment, all subjects were provided with the study-related information and signed the informed consent form being one of the inclusion criteria of the study.

5. Principal investigators and administrative structure of the study:

Principal investigators are presented below.

Principal investigators:

- Selkova Eugenia Petrovna, Dr. habil. med., Professor
- Ivleva Alla Yakovlevna, Dr. habil. med., Professor
- Petrov Dmitry Victorovich, PhD
- Ilkovich Mikhail Mikhailovich, Dr. habil. med., Professor
- Akopov Andrei Leonidovich, Dr. habil. med., Professor

- Trofimov Vasily Ivanovich, Dr. habil. med., Professor
- Sivkova Elena Borisovna, Chief Physician, PhD
- Chizhov Danila Aleksandrovich, Head of Clinical Trials Unit, general physician

A total of 143 patients were allocated into parallel groups: Brillia Health Cough Control (n=73) and Codelac (n=70); 139 patients completed the trial as per the study protocol.

6. Introduction

Cough (tussis) is voluntary or involuntary forced exhalation; an important element of the pulmonary clearance; a defensive physiological reflex that eliminates mucus, dust and smoke particles from the respiratory tract [6, 11]. Cough is initiated via the vagus nerve by the irritation of cough receptors which are mainly found in the laryngeal mucosa, vocal cords, carina and branching points of large airways. The cough center is located in the medulla.

Cough frequency and severity depends on the intensity of an irritant, its location in the respiratory system and excitability of cough receptors. Inflammation of the respiratory mucosa induced by acute respiratory viral infection is one of the common causes of irritation of cough receptors. Painful, “barking” cough may develop with hoarseness and aphonia and observed when inflammation involves the pharynx. A vicious circle of coughing contributes to the genesis of cough.

There are two different aspects of cough [6]: on the one hand, it can have a useful physiological purpose to clear the respiratory tract, but, on the other hand, it can also wear down patients with chronic respiratory diseases by interfering with sleep and meals. Persistent and distressing dry cough adversely affects subjective quality of life. Such cough is usually non-productive. Cough in acute conditions requires active treatment, so healthcare practitioners are to seek ways to achieve its complete resolution. The physician shall adequately prescribe antitussives or protussives to manage cough [6, 9, 12, 14].

Upper and lower respiratory illnesses accompanying distressing, non-productive cough are managed by cough suppressants that improve the subjective health of a patient and minimize the risk of complications [6, 9, 12, 13, 15, 18, 22].

Codeine (methylmorphine) and other morphine-like compounds are classified as centrally acting medicinal products. Several codeine-based cough suppressants have been authorized for use. One of them is Codelac®, a combination drug product containing, apart from codeine, sodium hydrocarbonate, liquorice root and thermopsis lanceolata herb. In addition to antitussive effects, Codelac® enhances the secretory function of the bronchial glands, stimulates ciliary motion, tones up bronchial smooth muscles, produces ganglioplegic, anti-inflammatory and antispasmodic effects, reduces sputum viscosity and accelerates exudation of mucus. Unfortunately, this drug product has a number of side effects since the antitussive action of codeine is not selective: it inhibits the respiratory center leading to depressed ventilation; it can also cause drowsiness, coprostasis, headache, and ocular motor dysfunction.

In 2010, Brillia Health Cough Control, a combination drug against cough containing antibodies to morphine (anti-M), to histamine (anti-H) and to bradykinin (anti-B), was approved. In experimental studies, antibodies to morphine (anti-M) have been found to target the central pathway of the cough reflex that is located in the medulla [3, 7, 13, 15]. Anti-H modulate the activity of H1, H2 and H3 receptors, promoting reduction in peripheral vasopermeability, smooth muscle spasms in the bronchi, production of mucus in the respiratory tract, and histamine release from mast cells and basophils in the mucosa and submucosa of the respiratory tract [1, 3, 8, 20, 21]. Anti-B inhibit cough induced by capsaicin and citric acid in test animals [2, 4, 7]. The components of the drug product affect various pathways of the cough reflex by exerting complex effects on the cough center, afferent nerve fibers in the airways, edema and inflammation in the respiratory tract [7, 8, 17, 20, 21]. Brillia Health Cough Control is neither an expectorant nor mucolytic agent, however, it facilitates clearance of mucus through its antispasmodic and decongestant action. The drug product can be used to manage both non-productive and productive cough due to its combination effects.

A number of non-clinical studies revealed that Brillia Health Cough Control did not show any acute or chronic toxicity, allergenicity, cytogenetic effects, reproductive toxicity (including embryotoxicity and teratogenicity) or toxic effects on immature animals.

This trial evaluated the efficacy and safety of Brillia Health Cough Control in the treatment of cough induced by acute respiratory infections in adults, as compared to Codelac®.

7. Study objectives, primary and secondary efficacy criteria and safety criteria

The objectives of this trial were to assess the clinical efficacy and safety of Brillia Health Cough Control in the treatment of cough, effects of Brillia Health Cough Control on the quality of life of patients with cough, and to compare the antitussive action of Brillia Health Cough Control and Codelac®.

Primary Efficacy Endpoints:

1. Time to resolution of cough in groups.
2. Decrease in the cough severity during the participation in the trial.

Secondary efficacy endpoints:

1. Changes in the number of cough episodes throughout the participation.
2. Percentage of patients with resolved cough at ending the participation.
3. The total score of the QoL questionnaire on Day 0, Day 7.
4. The total score of the QoS questionnaire on Day 0, Day 2, Day 4, Day 7.
5. CGI-EI mean score in groups.

Safety criteria:

1. Presence and nature of adverse events during the therapy, their association with the drug administration and other features.
2. Changes in laboratory parameters (complete blood analysis, urinalysis, biochemistry).

8. Study design

Design: a multicenter, randomized, open-label, comparative, parallel-group trial.

The study enrolled adult subjects of both sexes aged ≥18 years with a clinical diagnosis of ARVI and non-productive cough caused by acute pharyngitis, laryngitis, laryngotracheitis, tracheitis, tracheobronchitis or bronchitis. The duration of cough varied between 12 hours and 7 days.

After the signing of the informed consent form at Visit 1 (Day 0), patients' eligibility was assessed by performing baseline examination, including collecting a patient's history, vital function evaluation, physical examination, URI symptom scoring, daytime and nocturnal cough rating (Annex 1), documentation of concomitant therapy, filling out the Quality of Life (SF-36) and Quality of Sleep surveys (Annex 2 and 3) and laboratory testing (CBC, urinalysis, blood biochemistry); all women of child-bearing age were to take a pregnancy test.

After determination of eligibility, the subjects were enrolled in the study and randomized into one of the two groups: group 1 received Brillia Health Cough Control as per the selected dosing regimen for 7 days; group 2 was treated with Codelac®, 1 tablet 3 times a day for 7 days. Each patient received a patient diary and instructions on filling out the diary, including daytime and nocturnal cough severity scales, cough character, and daily and nocturnal cough episodes.

Patients were to perform three visits to a physician (Day 2, Day 4±1 and Day 7±1), with assessment of cough severity, documentation of ARVI symptoms and concomitant therapy, safety assessment, monitoring of a patient's diary, records of drug return and compliance evaluation. A patient had been observed for a total of 7 days (screening - day 1, treatment period - up to 7 days), with daily records made for cough episodes, its severity and time to resolution of cough. At Visit 4 (Day 7±1), physicians were to rate changes in AEs and their severity by the end of the treatment using the CGI-EI scale (Annex 4), assess compliance, re-fill the QoL and QoS questionnaires, and perform laboratory tests (CBC, urinalysis, biochemistry).

Table 1: Trial flow chart

Procedure/visit	Visit 1 (Day 0)	Visit 2 (Day 2)	Visit 3 (Day 4±1)	Visit 4 (Day 7±1)
Singing ICF	+			
Objective examination	+	+	+	+
Pregnancy test	+			
Body temperature measurement	+	+	+	+
Collection of medical history data	+			
Recording ARVI symptoms	+	+	+	+
Eligibility assessment	+			

Information on concomitant medicines	+	+	+	+
Randomization and prescription of study therapy	+			
Laboratory tests	+			+
Dispensing of the study drug	+			
Drug accountability and return, assessment of compliance		+	+	+
Distribution of diaries	+			
Return and inspection of diaries for adequate filling		+	+	+
Filling quality of life questionnaire (SF-36)	+			+
Filling quality of sleep questionnaire	+			+
Evaluation of therapeutic safety		+	+	+
Filling CGI-EI scale by the investigator				+

Information on each subject was recorded in the case report form, which included data on inclusion/exclusion and withdrawal criteria, disease clinical signs, laboratory values, type of treatment administered, changes in clinical parameters at different study points, and occurrence of adverse events.

9. Screening, randomization, blinding and early withdrawal

9.1 Inclusion criteria

1. Patients with a clinical diagnosis of ARVI with non-productive cough caused by acute pharyngitis, laryngitis, laryngotracheitis, tracheitis, tracheobronchitis or bronchitis. The duration of cough varied between 12 hours and 7 days.
2. Outpatients of both sexes aged ≥ 18 years.
3. Availability of signed informed consent to participate in the study.

9.2 Exclusion criteria

1. Patients with productive cough.
2. Subjects aged <18 years.
3. Suspected invasive bacterial infection, including suspected pneumonia.
4. History of obstructive pulmonary diseases, bronchial asthma.
5. Acute respiratory failure.
6. Oncological diseases.
7. Patient’s need for mucoactive drugs at inclusion.
8. CNS diseases.
9. Exacerbated or decompensated chronic diseases affecting a patient's ability to participate in the clinical trial.

10. Use of medications listed in "Prohibited concomitant treatment" within 15 days prior to enrollment;
11. Allergy to/intolerance of any constituent of the medications used in the treatment.
12. Pregnancy, breast-feeding, unwillingness to use contraception during the study.
13. Consumption of narcotics, alcohol > 2 alcohol units per day, mental diseases.
14. Patients who, from the investigator's point of view, will fail to follow the procedures of the trial or adhere to the dosing regimen of the medicines under study.
15. Significant abnormalities in the laboratory values that, from the investigator's point of view, will impede participation in the trial.
16. Participation in other clinical studies within 1 month prior to enrollment in the current trial.
17. Patients related to the research staff of the clinical trial site who are directly involved in the trial or are the immediate family member of the researcher. The immediate family members include husband/wife, parents, children or brothers (or sisters), regardless of whether they are natural or adopted.

9.3 Screening

After signing of the informed consent form, patients were subject to general examination, including an interview with a patient, collecting a patient's history, documentation of demographic data and concomitant therapy, objective physical examination (pulse, RR and BP measurements), determining patient's eligibility, daytime and nocturnal cough severity rating. At screening, a patient was to fill out the quality of life (SF-36) and quality of sleep surveys.

9.4 Randomization

By the end of screening and enrollment, eligible subjects were randomized into two groups.

Group 1 (Brillia Health Cough Control group) was treated with Brillia Health Cough Control according to the following regimen: 2 tablets 3 times a day for the first 3 days, followed by 1 tablet 3 times a day for 4 days. The drug product is administered without a meal; the tablet should be held in mouth until complete dissolution.

Group 2 (Codelac® group) received Codelac®, 1 tablet 3 times a day.

To observe confidentiality, each subject was assigned with an identification number consisting of a two-digit number of the clinical site, a three-digit screening number of the subject assigned in chronological order, a three-digit randomization number of the subject. The code of the subject was indicated in the documents designed for use outside of the clinical site (CRF, SAE reports, etc.). The code of the subject was entered into CRF and relevant forms and was not subject to changes during the study.

This clinical trial used an ongoing list randomization method.

The investigator assigned the smallest randomization number to the patient after he/she had been deemed eligible for the trial. The patient, investigator and study monitor were informed about the prescribed treatment (Brillia Health Cough Control or Codelac®).

9.5 Withdrawal (early termination) criteria

As per the study protocol, the duration of patient participation in the trial was 7 days, study therapy period - up to 7 days.

Cough resolution before Visit 4 (Day 7±1) was regarded as an ***early withdrawal criterion***, and therefore, from the investigator's point of view, further cough suppressant therapy was not required. In case of early withdrawal, the patient continued with other per-protocol procedures.

Every patient could choose to leave the trial at any time and for any reason without being judged regarding their medical care. After exclusion of the patient from the trial for any reason he/she still had access to the permitted and effective therapeutic methods.

In addition, patients could be withdrawn from the study therapy and trial in the following situations:

1. The necessity to use medications not permitted in the study.
2. A complication requiring hospitalization.
3. An adverse event requiring discontinuation of the investigational product.
4. Failure or refusal of the patient to follow the protocol.
5. Patient's decision to withdraw early for lack of efficacy or other reasons.
6. Patients lost to follow-up (inability to collect sufficient data to evaluate study endpoints).
7. Cases not stipulated in the protocol where the investigator decides that further participation may harm the patient.
8. Significant deviations from the protocol (see 'Protocol deviations').
9. Erroneous inclusion of an ineligible patient in the trial.
10. Pregnancy.

If a patient had received at least one dose of the study drug (Brillia Health Cough Control or Codelac®) before withdrawal, he/she followed the procedures of Visit 4 (Day 7) to assess the safety of the study treatment.

9.5.1 Protocol deviations

In general, any protocol deviation was only permitted in emergency situations or after the prior consent from the Sponsor, with approval from the Ethics Board.

Serious deviations degraded the quality of data collected for analysis. A patient with a serious protocol deviation was to be excluded from the final efficacy analysis, i.e. from mITT and PP populations.

Serious protocol deviations: enrollment of ineligible (not meeting inclusion criteria/ meeting one or more exclusion criteria) subjects, use of medications/interventions not permitted during the study, missing visit windows by more than 1 day and an increase/decrease in the dose intensity tested by ≥15%.

Minor protocol deviations could reduce data validity for analysis; however, it was performed taking such deviations into account. Minor protocol deviations: minor errors in patient diaries or other study documents; other non-serious deviations.

One serious protocol deviation (≥15% increase in the dose intensity of the test drug) was found during the data analysis. The patient with a serious protocol deviation was excluded from the final efficacy analysis.

10. Study product

10.1 Description of the drug

Brillia Health Cough Control contains Lapine morphine immune globulin– 0.006 g*, Lapine histamine immune globulin– 0.006 g*, affinity purified antibodies to bradykinin – 0.006 g*

Excipients: isomalt, sodium saccharin, sodium cyclamate, anhydrous citric acid, magnesium stearate.

* *mixture of water-ethanol dilutions 100^{12}, 100^{30}, 100^{50} of active substance used for saturation of isomalt.*

The drug product is available as white to almost white, flat, cylinder-shaped, bevel-edged tablets scored on one side. The tablets are embossed BRILLIA HEALTH COUGH CONTROL on one flat side.

A patient received a package of 2 polymer bottles with tamper-evident caps; each bottle contained 40 tablets of Brillia Health Cough Control. The trial used Brillia Health Cough Control lot K010211.

Dosing regimen

The Brillia Health Cough Control dosing regimen was as follows: 2 tablets 3 times a day for the first 3 days, followed by 1 tablet 3 times a day for 4 days. The drug product is administered without a meal; the tablet should be held in mouth until complete dissolution. The treatment period was 7 days.

10.3 Prior and concomitant therapy

In the course of the trial, patients in both groups could receive medications against acute respiratory viral infections as per the applicable standards: antipyretics, antivirals, vitamins, decongestant nasal drops, detoxication therapy and antibacterials, if required (in case of bacterial complications), excluding antitussives (except for Codelac®) and other prohibited concomitant medications.

For 15 days prior to enrollment and during the study (after signing informed consent form and initiation of screening) subjects were not allowed to receive any medications that might affect cough intensity:

1. Cough and cold preparations (ATC R05, R05C Expectorants and R06D Cough suppressants), except for Codelac® prescribed within the trial.
2. Drug products that irritate or suppress the cough center in the CNS or produce such side effects, as described in the instructions.
3. Drugs known to have caused allergic reactions.
4. Antiemetics.
5. ACE inhibitors, β blockers, bronchodilators.
6. Antihistamine drugs.

11. Data quality assurance

All clinical activities performed as described in this report comply with European GCP guidelines.

Study monitoring was performed by the Sponsor’s authorized representatives who monitored the study course and made regular visits to the clinical sites from the initiation until the end of the clinical study. These visits included verification of completed CRFs against the original medical records.

The monitor was provided with access to the baseline data (outpatient charts, clinical laboratory test results, subject diaries, questionnaires, study drug dispensing logs) and reviewed the planned and ongoing procedures and observations.

12. Statistical model and methods

Data treatment and all statistical calculations under the protocol were made using SAS-9.3 statistical software. The following elements of descriptive statistics were calculated: the mean, standard deviation, number of observations – for quantitative variables; incident rates and proportions of subjects with a certain characteristic– for qualitative variables. Parametric statistics were used for continuous and interval variables and non-parametric statistics for frequency analysis of categorical variables.

The frequency analysis was carried out using the χ^2 test, Fisher's exact test (if one of the frequencies was <5) or Cochran-Mantel-Haenszel test.

This comparative trial was based on the non-inferiority design (the test drug is as effective as the comparator drug), with the following hypotheses:

1) null hypothesis: $Ec-Et\geq\delta$;

2) alternative hypothesis: $Et>Ec-\delta$,

where Ec – the effect of the control drug (comparator drug); Et – the effect of the test drug; δ – clinical equivalence.

The non-inferiority model implies that the clinical equivalence margin (δ) is to be estimated. In this trial, δ=10% of the effect of the control drug (Codelac®) was used.

One of the efficacy measures described for Codelac in the available literature is time to resolution of cough. According to the published results of a placebo-controlled study [5], total cough duration in patients with acute respiratory infections was 7.5 days in the Codelac group. The other parameters used in the efficacy analysis were evaluated on the basis of the efficacy data obtained for Codelac in this trial.

13. Subjects' basic characteristics

Fig. 13.1 shows a diagram of patient flow in the clinical trial.

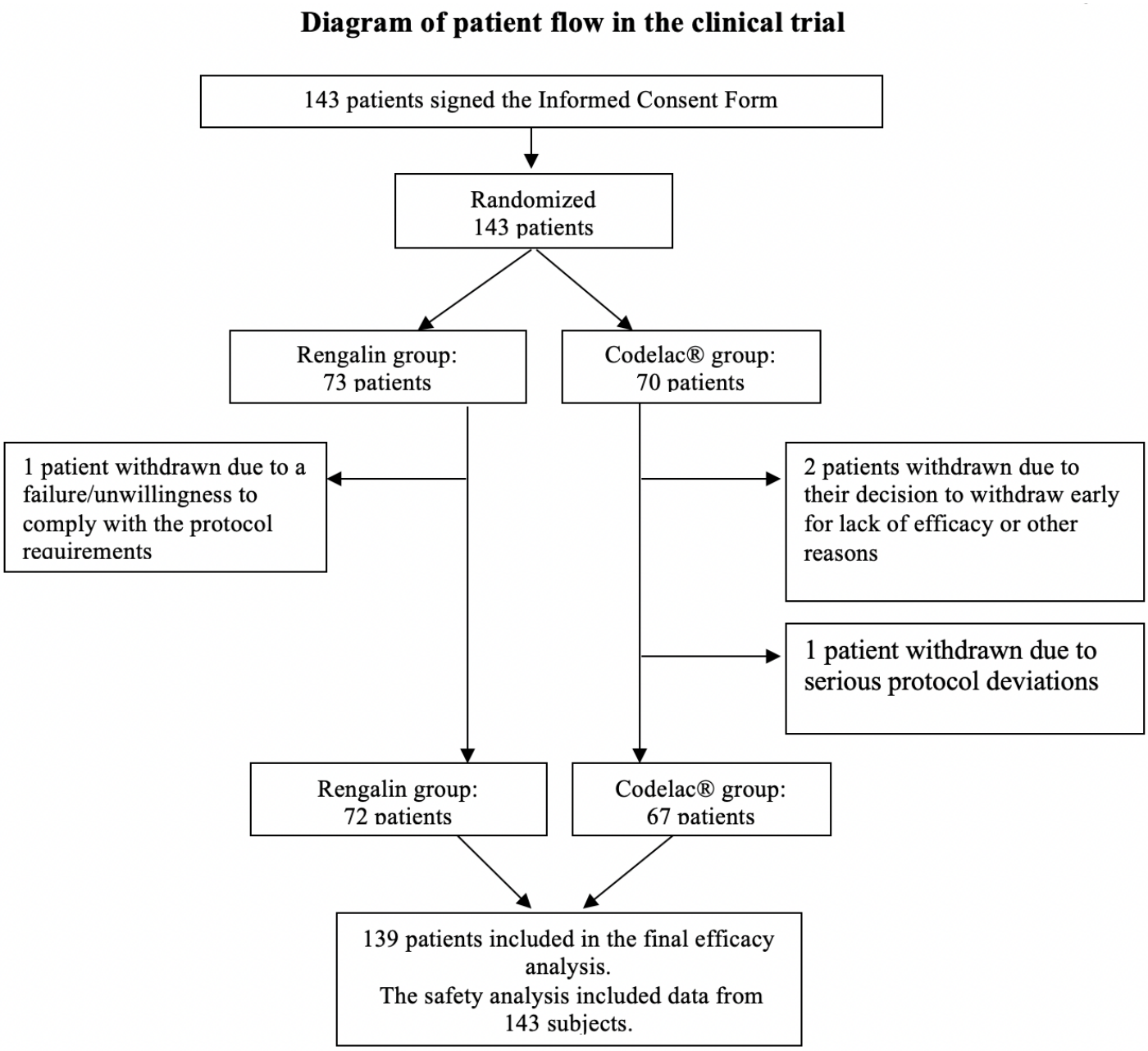

Figure 3: Diagram of patient flow in the clinical trial

A total of 143 subjects were enrolled and randomized in two groups: n=73 in group 1 treated with Brillia Health Cough Control (Brillia Health Cough Control group), n=70 in group 2 receiving Codelac® (Codelac group).

Four patients dropped out from the trial: n=1 in the Brillia Health Cough Control group (a failure/unwillingness to comply with the protocol requirements) and n=3 in the Codelac group (n=2 - a participant's decision to withdraw early for lack of efficacy or other reasons; n=1 - serious protocol deviations). The number of Per-Protocol (PP) subjects was n=139, with n=72 in the Brillia Health Cough Control group and n=67 in the Codelac group. The data from these subjects (n=139) were used in the final efficacy analysis. The

safety analysis used the data from 143 patients who had signed the informed consent form and received at least one dose of the study drug (ITT population).

13.2 Demographic and clinical characteristics of the subjects

The average age of the study subjects was 42.4±14.9 years (Table 13.2.1), with the age limits varying between 18 years (minimum) and 74 years (maximum). Age and anthropometric characteristics of the participants were similar between the groups (Brillia Health Cough Control anf Codelac®). Most trial participants were women (68%). The frequency analysis of the gender-related distribution of patients did not show any differences between the groups.

Table 13.2.1: Demographic and anthropometric data

Parameter		**Group**		**Total**
		Brillia Health Cough Control	**Codelac®**	
Number of patients, n		73	70	143
Average age (min-max), years		43.1±14.7 (18-74)	41.7±14.9 (18-73)	42.4±14.8 (18-74)
Average weight (min-max), kg		71.1±14.6 (43-110)	71.1±13.6 (45-98)	71.1±14.1 (43-110)
Average height (min-max), cm		166.6±7.7 (150-184)	168.6±9.1 (153-190)	167.6±8.4 (150-190)
Gender, n (%)	Males	21 (29%)	25 (36%)	46 (32%)
	Females	52 (71%)	45 (64%)	97 (68%)

The main clinical and laboratory characteristics (patient history, co-morbidities, physical data, vital signs and laboratory values) were comparable between the two groups (Tables 13.2.2-13.2.4).

About one third of the participants (31%) had co-morbidities (Table 13.2.2); the most common condition was essential (primary) hypertension recorded in 7% of patients (10 out of 143). The incidence of diseases of the digestive, musculoskeletal, genitourinary and endocrine systems was almost identical between the two groups (1-4%).

Table 13.2.2: Comorbidities in the study subjects

Disease	**Group**	
	Brillia Health Cough Control (n=73)	**Codelac®** (n=70)

Essential (primary) hypertension, n (%)	3 (4%)	7 (10%)
Ischemic heart disease, n (%)	–	1 (1%)
Mitral valve prolapse, n (%)	–	2 (3%)
Chronic gastritis, n (%)	5 (7%)	2 (3%)
Chronic gastroduodenitis, n (%)	–	3 (4%)
Duodenal ulcer, n (%)	1 (1%)	3 (4%)
Chronic pancreatitis, n (%)	1 (1%)	–
Chronic cholecystitis, n (%)	2 (3%)	1 (1%)
Chronic hepatitis C, n (%)	1 (1%)	–
Fatty liver, n (%)	–	1 (1%)
Chronic cerebral ischemia/hypertensive encephalopathy, n (%)	1 (1%)	1 (1%)
Vestibular disorder, n (%)	2 (3%)	1 (1%)
Spinal osteochondrosis, n (%)	3 (4%)	3 (4%)
Kyphoscoliosis, thoracic region, n (%)	1 (1%)	–
Cervicalgia, n (%)	–	1 (1%)
Diabetes mellitus, n (%)	–	1 (1%)
Nontoxic multinodular goiter, n (%)	1 (1%)	2 (3%)
Obesity, n (%)	1 (1%)	–
Urolithiasis, n (%)	3 (4%)	–
Nephroptosis, n (%)	0	2 (3%)
Chronic cystitis, n (%)	1 (1%)	–
Chronic prostatitis, n (%)	–	1 (1%)
Endometriosis, n (%)	–	2 (3%)
Peritoneal adhesions, n (%)	1 (1%)	–
Atopic dermatitis, n (%)	1 (1%)	–
Allergic rhinitis, n (%)	–	1 (1%)
Chronic tonsillitis, n (%)	–	2 (3%)
Myopia, n (%)	2 (3%)	1 (1%)
Flat foot, n (%)	1 (1%)	2 (3%)
Umbilical hernia, n (%)	–	1 (1%)
Mycosis, n (%)	1 (1%)	–
TOTAL	23 (32%)	21 (30%)

Table 13.2.3 shows tha data from the objective examination by physician and laboratory values obtained on day 1. The vital signs (HR, RR, BP) were within the age-related normal limits and were comparable between the groups.

All patients enrolled had dry (non-productive) cough induced by ARVI, however daily cough frequency at baseline varied significantly as seen from the mean number of coughs recorded by patients prior to antitussive therapy (Table 13.2.3). Cough severity scoring using the cough severity scale (Annex 1) demonstrated comparable values for daytime and nocturnal cough.

The laboratory values (CBC, biochemistry, urinalysis) obtained prior to therapy were within the normal range.

Table 13.2.3: Clinical and laboratory parameters

Parameter	Group	
	Brillia Health Cough Control	**Codelac®**
Vital indices		
HR, bpm	81.3±6.3	81.4±6.6
RR, breaths/min	18.8±3.6	18.0±3.0
Systolic BP, mm Hg	122.4±9.8	123.8±10.4
Diastolic BP, mm Hg	74.9±4.9	75.4±5.8
Cough		
Number of cough episodes during the day, abs	13.6±16.0	10.6±12.1
Daytime cough severity score	3.3±0.9	3.2±0.9
Nocturnal cough severity score	2.3±0.9	2.0±1.1
Maximum cough score during the day	3.3±0.8	3.3±0.9
Complete blood count		
RBC, 10^{12}/L	4.5±0.4	4.5±0.4
Hemoglobin, g/l	138.3±13.3	136.7±12.5
HCT, %	40.9±3.9	40.8±3.5
WBC, 10^9/L	7.0±1.5	7.5±2
Stabs, 10^9/L	5.2±12.5	7.1±15.7
Segmented, %	58.2±10.3	58.1±11.5
Eosinophils, %	2.5±1.5	2.6±1.9
Basophils, %	0.3±0.5	0.3±0.7

Lymphocytes, %,	30.5±9.5	29.2±9.9
Monocytes, %	5.9±2.3	6.5±2.7
Platelets, 10^9/L	269.6±67	262.7±52
ESR, mm/h	11.4±6.8	10.8±6.6
Blood biochemistry		
Glucose, mmol/L	4.9±0.9	4.9±1.1
Toral bilirubin, µmol/L	14.3±4.4	15.1±5.1
ALT, units/L	26±15.4	23.8±10.4
AST, units/L	29.7±21.4	26.9±16
Creatinine, µmol/L	83.7±15.9	84.2±13.5
Urinalysis		
Specific gravity	1021.3±6.1	1020.5±6.8
Pathological constituents	No	No
Abnormal sediment microscopy	No	No

The medicinal products given as a concomitant therapy to patients for their acute respiratory infection or co-morbidities are listed in Table 13.3.3. The common drug products for ARVIs were antivirals (ingavirin, arbidol, kagocel), local antiseptics (bioparox, hexoral, octenisept, miramistin, lysobact) and irrigation medications (Aqua Maris, Quixx) for lavage of the upper respiratory tract. Only one subject in the Codelac® group received antibiotic therapy (azithromycin).

All patients with essential hypertension were treated with antihypertensive medications (calcium channel blockers, angiotensin receptor antagonists or their combinations, diuretics). Some patients in both groups received preparations for endocrine and gastrointestinal conditions.

Table 13.2.4: Concomitant therapy of the study subjects

Product	**INN**	**Brillia Health Cough Control** (n=73)	**Codelac®** (n=70)
Aqua Maris	Sea water	1 (1%)	1 (1%)
Avamys	Fluticasone furoate	1 (1%)	–
Amlodipine	Amlodipine	–	1 (1%)
Amlotop	Amlodipine	1 (1%)	–
Anaferon	No	–	1 (1%)
Aprovel	Irbesartan	1 (1%)	–
Arbidol	Umifenovir	1 (1%)	4 (6%)

Arifon	Indapamide	1 (1%)	–
Ascorbic acid	Ascorbic acid	5 (7%)	5 (7%)
Ascorutin	Ascorbic acid + Rutoside	–	1 (1%)
Bioparox	Fusafungine	–	1 (1%)
Verapamil	Verapamil	1 (1%)	1 (1%)
Hexoral	Hexetidinum	1 (1%)	1 (1%)
Glibomet	Glibenclamide+Metformin	–	1 (1%)
Zitrolid forte	Azithromycin	–	1 (1%)
Ingavirin	Imidazolyl ethanamide pentandioic acid	1 (1%)	–
Kagocel	No	3 (4%)	2 (3%)
Canephron	Gentianaceae+Apiaceae+Lamiaceae	–	1 (1%)
Complivit	Multivitamins+Minerals	1 (1%)	–
Corinfar	Nifedipine	–	1 (1%)
Lysobact	Lysozyme + Pyridoxine	–	1 (1%)
Lozap plus	Losartan	–	1 (1%)
Maalox	Algeldrate+Magnesium hydroxide	–	1 (1%)
Relief	Shark liver oil +Phenylephrine	1 (1%)	–
Miramistin	Miramistin	3 (4%)	5 (7%)
Norvasc	Amlodipine	–	1 (1%)
Normodipine	Amlodipine	–	1 (1%)
Octenisept	octenidine dihydrochloride+ phenoxyethanol	2 (3%)	1 (1%)
Otrivin	Xylometazoline	–	1 (1%)
Quixx solution	Sea water	1 (1%)	–
Sunpras	Pantoprazole	–	1 (1%)
Exforge	Amlodipine+Valsartan	–	1 (1%)
	TOTAL	**25 (34%)**	**37 (53%)**

The data on cigarette smoking and alcohol consumption by patients were almost similar between the groups (Table 13.2.5). 16% of patients in both groups were identified as smokers at enrollment. The average values for smoking time, number of cigarettes and alcohol consumption per week were practically identical.

Table 13.2.5: Nicotine and alcohol consumption by patients

		Brillia Health Cough Control (n=73)	Codelac® (n=70)	Total (n=143)
Number of smokers, n		12 (16%)	11 (16%)	23 (16%)
Smoking history, years (min-max)		16.3±12.5 (0-35)	23.7±11.8 (5-40)	19.7±12.5 (0-40)
Average number of cigarettes per day, n		44.9±36.2 (0-140)	51.5±40.1 (2-140)	48.0±37.3 (0-140)
Alcohol consumption	No	56 (77%)	53 (76%)	109 (76%)
	Once a week or less	17 (23%)	13 (18%)	30 (21%)
	Once a day to once a week	0	4 (6%)	4 (3%)
	Every day	0	0	0
Average volume of alcohol taken for the time period expressed as 96° ethanol, ml		360.7±362.8 (100-1000)	418.8±365.5 (100-1000)	391.7±359.1 (100-1000)

All sexually active patients of reproductive age used adequate contraceptive methods during the trial and within 30 days of ending the participation in the trial (Table 13.2.6).

Table 13.2.6: Data on contraceptive methods during the study

Parameter		Brillia Health Cough Control	Codelac®	Total
Females				
Number of female participants, n		52	45	97
Number of female subjects of childbearing potential, n (%)		32 (62%)	28 (62%)	60 (62%)
Number of female subjects who used adequate contraception methods during the trial and 30 days after the last dose, n (%)		32 (100%)	28 (100%)	60 (100%)
Contraception method used, n (%)	Condoms with spermicide	22 (69%)	18 (64%)	40 (67%)

	Oral and hormonal contraceptives	1 (3%)	0	1 (1%)
	Intrauterine devices	4 (12%)	5 (18%)	9 (15%)
Abstinence, n (%)		5 (16%)	5 (18%)	10 (17%)
Pregnancy test results, n (%)	Positive	0	0	0
	Negative	32 (100%)	28 (100%)	60 (100%)
Number of female subjects in menopause > 1 year, n (%)		20 (38%)	17 (38%)	37 (38%)
Males				
Number of male participants		21	25	46
Number of female subjects who used adequate contraception methods during the trial and 30 days after the last dose, n (%)		21 (100%)	25 (100%)	46 (100%)

Treatment compliance in the Brillia Health Cough Control group (100.5±4.1%) was significantly higher than that in the Codelac® group (98.1±3.9%), despite almost 100% compliance in the comparator group (t-test: $t=-3.41$; $p=0.0009$; Mann-Whitney test: $U=-3.76$; $p=0.0002$).

14. Efficacy analysis

The efficacy of the therapy was assessed using the data recorded by a patient (cough severity scale [19], number of coughs [14, 16, 18], SF-36 Health Survey and quality of sleep survey) and examinations by a physician during the visits (cough characteristics, continuation/withdrawal of the antitussive therapy based on the parameters assessed, analysis of the outcome and CGI-EI).

14.1 Time to resolution of cough

The total cough duration in patients in the Brillia Health Cough Control group was 7.2±1.0 days vs. 7.0±1.1 days in the Codelac group (Table 14.1.1). In most patients, daytime cough persisted for a longer period than night-time cough (Table 14.1.2; fig. 14.1.1). The mean daytime cough duration was 7.1±1.1 days in the Brillia Health Cough Control group vs. 6.9±1.1 days in the Codelac group. The mean nocturnal cough duration was 5.4±1.7 and 5.0±1.8 days, respectively.

Table 14.1.1: Total cough duration

Statistical data	Brillia Health Cough Control		Codelac®	
M±SD	7.2±1.0		7.0±1.1	
95% CI Mean	7.0	7.5	6.7	7.2
Diff C-T	−0.28±1.07			
95% CI_{diff}	−0.64÷0.08			
δ	±0.70			
p	<0.025			

Note. M – mean value; SD – standard deviation; Diff – difference between the effects of the two drugs; C – control drug (or comparator drug, Codelac®);

T – test (or study) drug (Brillia Health Cough Control); CI – confidence interval.

Table 14.1.1: Daytime and nocturnal cough duration

Group	**Cough duration**, days	
	Daytime	Nocturnal
Brillia Health Cough Control (n=72)	7.1±1.1	5.4±1.7
Codelac (n=67)	6.9±1.1	5.0±1.8

The antitussive efficacy of Brillia Health Cough Control manifested by the time to resolution of both daytime and nocturnal cough was comparable to that of Codelac®. The statistical analysis demonstrated that the time to resolution of cough in patients in the Brillia Health Cough Control group was within δ=10% of the values in the Codelac® group (Diff C-T=−0.28; 95% CI_{diff}=−0.64÷0.08; δ=±0.70; CI_{diff}>−0.70; p<0.025), indicating clinical comparability (non-inferiority) of the study drug (Brillia Health Cough Control) with the comparator drug (Codelac®).

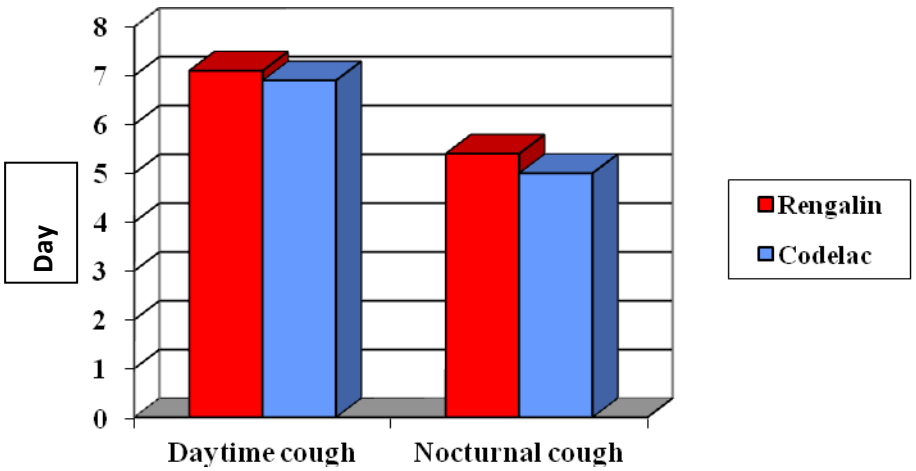

Figure 14.1.1: Time to resolution of daytime and nocturnal cough

The antitussive efficacy of Codelac® in this trial was as good as the published outcomes of the previous clinical studies on its therapeutic efficacy [5, 12, 24].

Thus, Brillia Health Cough Control can be regarded as effective in the treatment of cough induced by acute respiratory viral diseases in adults, based on the time to resolution of cough.

14.2 Decrease in the cough severity during the participation in the trial

Cough severity recorded by patients in the diaries every day for 8 days of the participation using the CSS [19] could vary from single episodes of cough (1 - minimum score) to distressing daytime and nocturnal cough (5 - maximum score). Absolute and relative changes in the daytime and nocturnal cough severity were estimated; daily maximum cough severity and its reduction due to therapy were rated.

14.2.1 Changes in absolute values obtained for daytime cough severity

In the Brillia Health Cough Control group, the cough severity score at baseline was 3.3±0.8, i.e. frequent daytime cough that interfered (4) or did not interfere (3) with daily activities of a patient (Table 14.2.1; fig. 14.2.1). The mean score in the Codelac group was 3.3±0.9, indicating similar daytime cough severity at baseline.

Table 14.2.1: Absolute values obtained for daytime cough severity (score)

Group		**Brillia Health Cough Control**	**Codelac®**
Day	1	3.3±0.9	3.2±0.9
	2	3.1±0.7	3.0±0.6
	3	2.7±0.7	2.7±0.8
	4	2.4±0.7	2.4±0.7
	5	2.0±0.9	1.9±0.8
	6	1.5±0.8	1.4±0.7
	7	1.0±0.8	0.8±0.8
	8	0.2±0.5	0.2±0.5

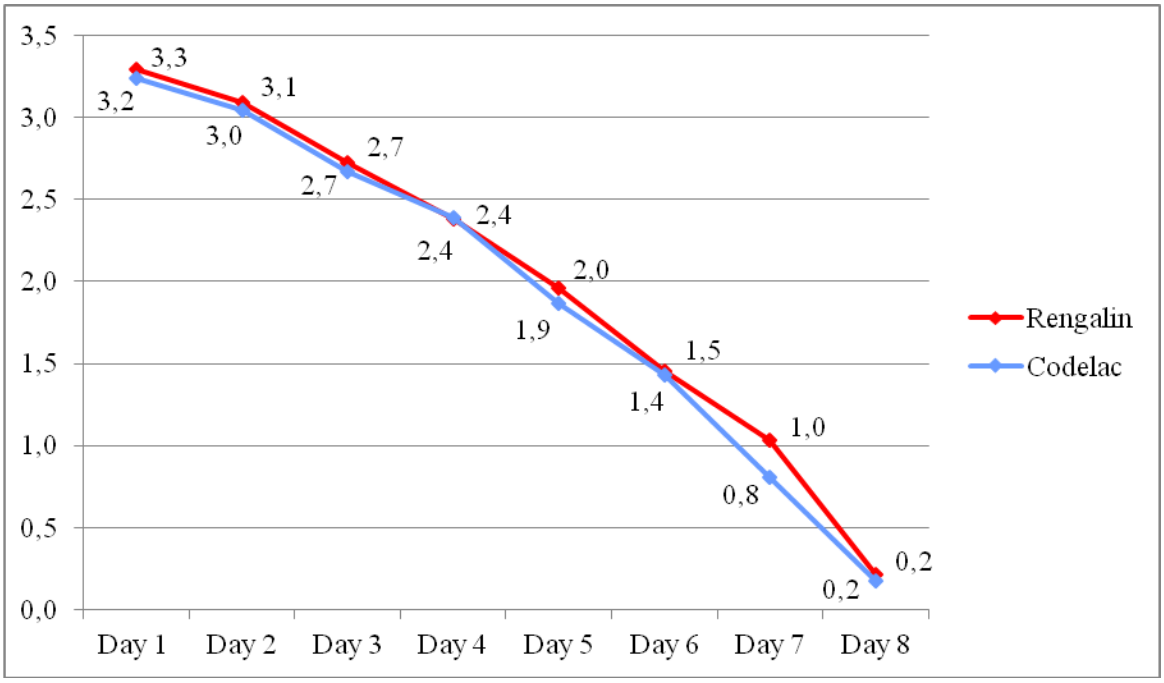

Figure 14.2.1: Changes in absolute values obtained for daytime cough severity (score)

Cough severity began to reduce as soon as on the first days after Brillia Health Cough Control administration (Table 14.2.1, fig. 14.2.1). On day 3 of therapy, the mean score decreased to 2.8±0.6, i.e. occasional cough for short periods not interfering with daily activities was observed. The mean daytime cough score declined to 1.5±0.8 beginning on day 6 of the observation period (day 5 of therapy). This suggested the presence of a single episode of cough or occasional cough for 2-3 short periods a day in some patients. After 7 days, the cough severity score was 0.2±0.5, showing either resolved or residual cough.

Similar changes in the daytime cough severity were found in the Codelac® group (Table 14.2.1, fig. 14.2.1).

14.2.2 Changes in relative values obtained for daytime cough severity

We carried out a statistical analysis of relative changes in cough severity to objectively assess the test values (Table 14.2.2; fig. 14.2.2).

Table 14.2.2: Relative values obtained for daytime cough severity

Group		**Brillia Health Cough Control**	**Codelac®**
Day	1	0.0±0.0	0.0±0.0
	2	−0.2±0.7	−0.2±0.9
	3	−0.6±0.9	−0.6±0.9
	4	−0.9±0.9	−0.8±1.0
	5	−1.3±1.0	−1.4±1.1
	6	−1.8±1.0	−1.8±1.0
	7	−2.3±1.0	−2.4±1.2

	8	−3.1±0.9	−3.1±1.0

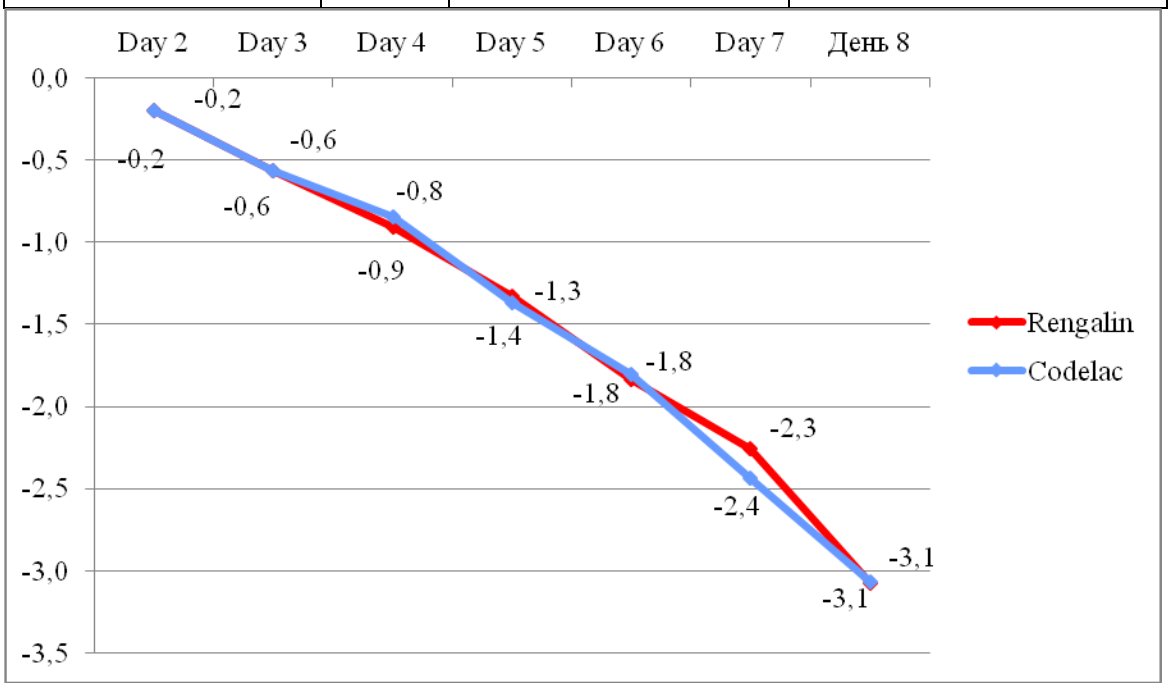

Figure 14.2.2: Changes in relative values obtained for daytime cough severity (score)

The results obtained demonstrated comparable antitussive efficacy of the test drug and comparator drug. In the Brillia Health Cough Control group, daytime cough severity gradually reduced starting on the first day of treatment. As a result, the cough score declined by –3.1±0.9 after seven days. In the Codelac group, this value was –3.1±1.0.

14.2.3 Changes in absolute values obtained for nocturnal cough severity

In the Brillia Health Cough Control group, the mean nocturnal cough score at baseline was 2.3±0.9, i.e. patients woke up at night either once (2) or several times (3) due to cough. In the Codelac group, this value was slightly lower, 2.0±1.1.

Table 14.2.3: Absolute values obtained for nocturnal cough severity (score)

Group		**Brillia Health Cough Control**	**Codelac®**
Night	1	2.3±0.9	2.0±1.1
	2	2.1±0.8	1.9±1.1
	3	1.6±0.9	1.4±1.0
	4	1.3±0.7	1.1±0.9
	5	0.7±0.8	0.5±0.8
	6	0.4±0.7	0.3±0.6
	7	0.1±0.4	0.1±0.4
	8	0.1±0.3	0.0±0.3

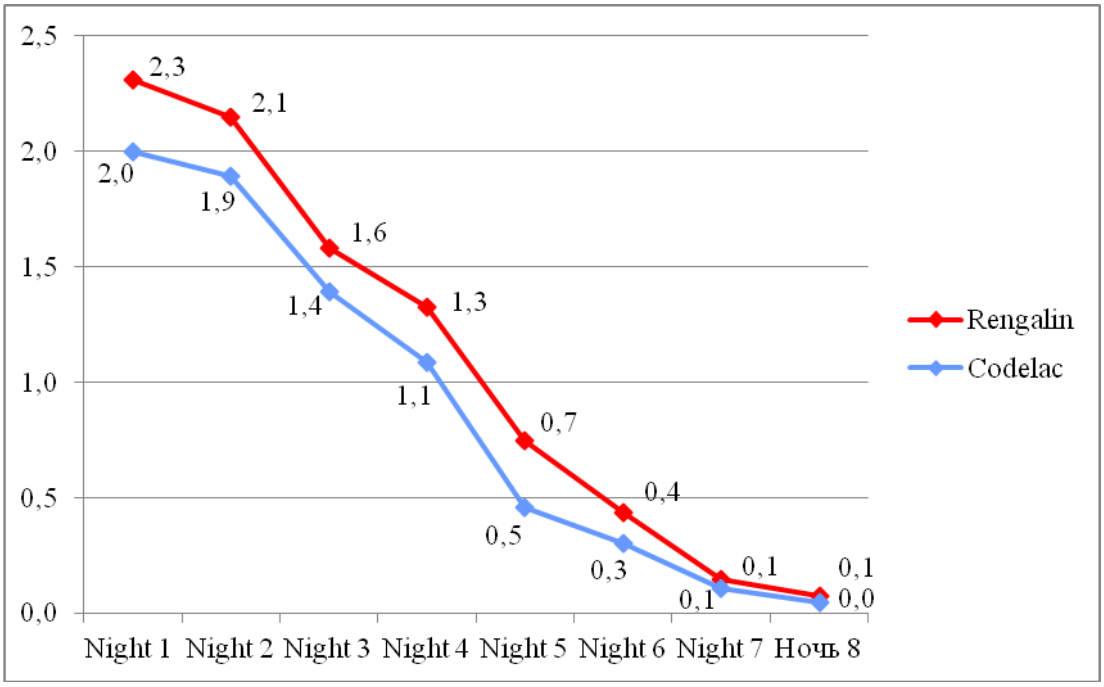

Figure 14.2.3: Changes in absolute values obtained for nocturnal cough severity

Brillia Health Cough Control was found to improve cough throughout the treatment period. The mean cough severity score declined to 1.6±0.9 by the third night, being indicative of either "Coughing when falling asleep or waking up" or "Waking up once due to cough". By the end of the treatment, cough severity was rated as minimal (0.1±0.3), i.e only occasional night-time cough was observed. Absolute cough values obtained in the Codelac group for nocturnal cough showed similar changes as compared to the outcome in the Brillia Health Cough Control group (Table 14.2.3, fig. 14.2.3).

14.2.4 Changes in relative values obtained for nocturnal cough severity

Comparability of antitussive effects observed in both groups was supported by reduced nocturnal cough severity (Table 14.2.4; fig. 14.2.4).

Table 14.2.4: Changes in relative values obtained for nocturnal cough severity (score)

Group		**Brillia Health Cough Control**	**Codelac®**
Night	1	0.0±0.0	0.0±0.0
	2	−0.2±0.5	−0.1±0.8
	3	−0.7±0.8	−0.6±0.9
	4	−1.0±0.8	−0.9±0.8
	5	−1.6±1.9	−1.5±1.0
	6	−1.9±1.0	−1.7±1.1
	7	−2.2±1.0	−1.9±1.2
	8	−2.2±0.9	−2.0±1.2

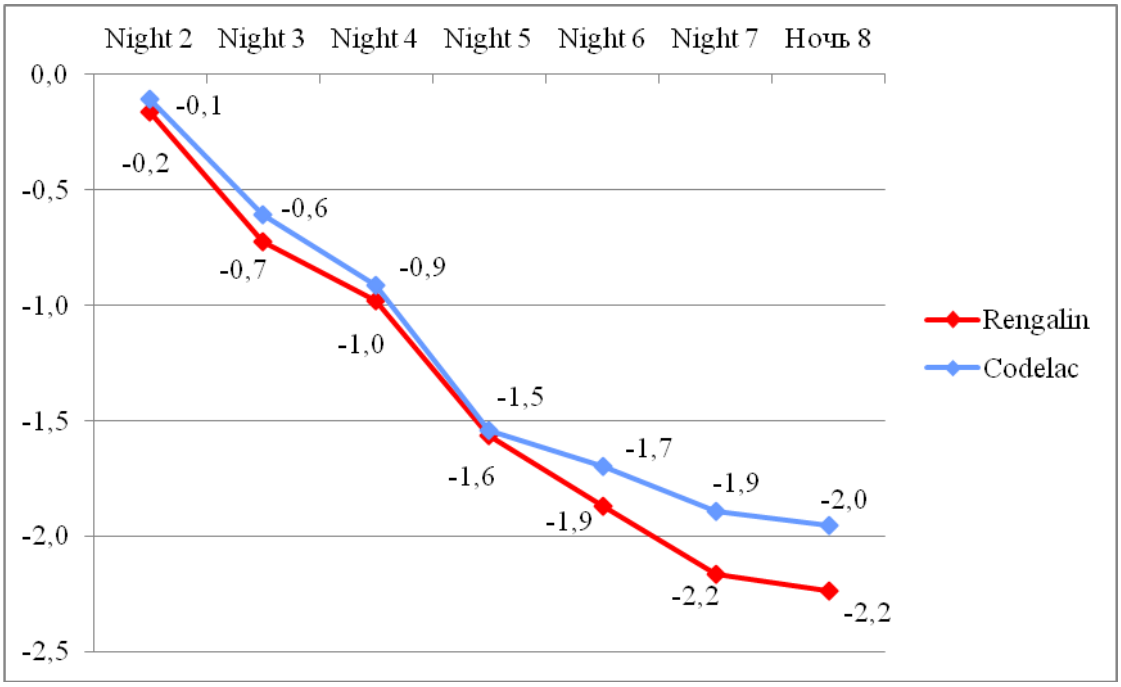

Figure 14.2.4: Changes in relative values obtained for nocturnal cough severity

The most pronounced reduction in the cough severity score associated with Brillia Health Cough Control administration was recorded on the first three days: –1.0±0.8, being comparable to that in the Codelac group (–0.9±0.8). Over the following days, therapeutic efficacy of Brillia Health Cough Control was further enhanced and resulted in a decline in the nocturnal cough score by –2.2±0.9, being comparable to the effects of Codelac (–2.0±1.2).

14.2.5 Decrease in the cough severity during the participation in the trial

Changes in cough severity throughout the treatment and observation period were analyzed by estimating the absolute (Table 14.2.5.1; fig. 14.2.5.1) and relative (Table 14.2.5.2; 14.2.5.3; fig. 14.2.5.2) scores of mean maximum cough severity during the day.

Table 14.2.5.1: Maximum cough severity score during the day

Group		**Brillia Health Cough Control**	**Codelac®**
Day	1	3.3±0.8	3.3±0.9
	2	3.1±0.7	3.1±0.6
	3	2.8±0.6	2.7±0.7
	4	2.4±0.7	2.4±0.7
	5	2.0±0.9	1.9±0.8
	6	1.5±0.8	1.4±0.7
	7	1.1±0.8	0.8±0.8
	8	0.2±0.5	0.2±0.5

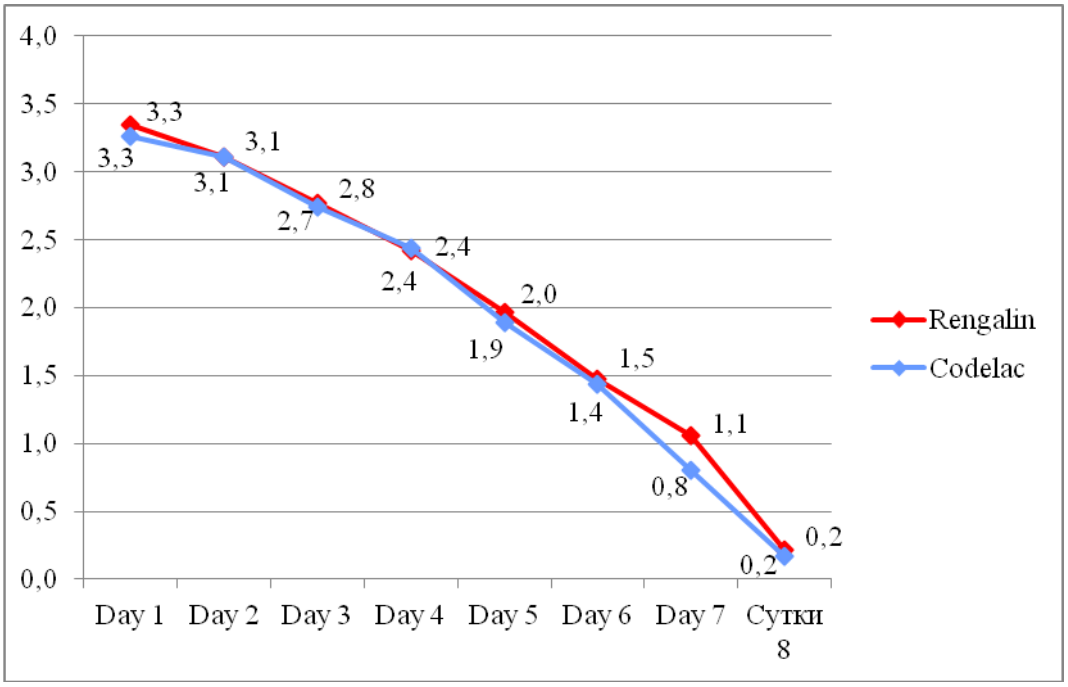

Figure 14.2.5.1: Changes in absolute values obtained for maximum daily cough severity (score)

Only several patients experienced severe nocturnal cough. Most subjects had severe daytime cough. Therefore, maximum daily severity values were close to absolute and relative values obtained for daytime cough.

The maximum cough severity at baseline was comparable between the Brillia Health Cough Control and Codelac® groups (3.3±0.8 and 3.3±0.9, respectively). Brillia Health Cough Control therapy resulted in cough resolution, with the average severity score of 0.2±0.5, as self-assessed by patients, indicating no residual cough within 24 hours by the end of the 7-day therapy. Similar values were registered in the Codelac® group (Table 14.2.5.1, fig. 14.2.5.1).

The analysis of relative changes in the maximum daily cough severity demonstrated similar changes in the cough scores during the day (Table 14.2.5.2, fig. 14.2.5.2).

Table 14.2.5.2: Relative values of the maximum daily cough (score)

Group		**Brillia Health Cough Control**	**Codelac®**
Day	1	0.0±0.0	0.0±0.0
	2	−0.2±0.7	−0.2±0.8
	3	−0.6±0.9	−0.5±0.9
	4	−0.9±0.9	−0.8±1.0
	5	−1.4±1.0	−1.4±1.1
	6	−1.9±1.0	−1.8±1.0
	7	−2.3±1.0	−2.5±1.2
	8	−3.1±0.9	−3.1±1.0

Table 14.2.5.3: Reduction in cough severity by the end of the treatment

Statistical data	Brillia Health Cough Control		Codelac®	
M±SD	3.1±0.9		−3.1±1.0	
95% CI Mean	−3.3	−2.9	−3.3	−2.9
Diff C-T	−0.02±0.91			
90% CI_{diff}	−0.28÷0.32			
δ	±0.31			
p	<0.05			

Note. M – mean value; SD – standard deviation; Diff – difference between the effects of the two drugs; C – control drug (or comparator drug, Codelac®);

T – test (or study) drug (Brillia Health Cough Control); CI – confidence interval.

A total reduction in the maximum cough score was −3.1±0.8 in the Brillia Health Cough Control group vs. −3.1±1.0 in the Codelac® group (Table 14.2.5.3). A reduction in the cough severity in the Brillia Health Cough Control group was within δ=10% of the values obtained in the Codelac® group (Diff C-T=−0.02; 90% CIdiff=−0.28÷0.32; δ=±0.31; CIdiff>−0.31; p<0.05), further suggesting comparable efficacy of the two cough suppressants.

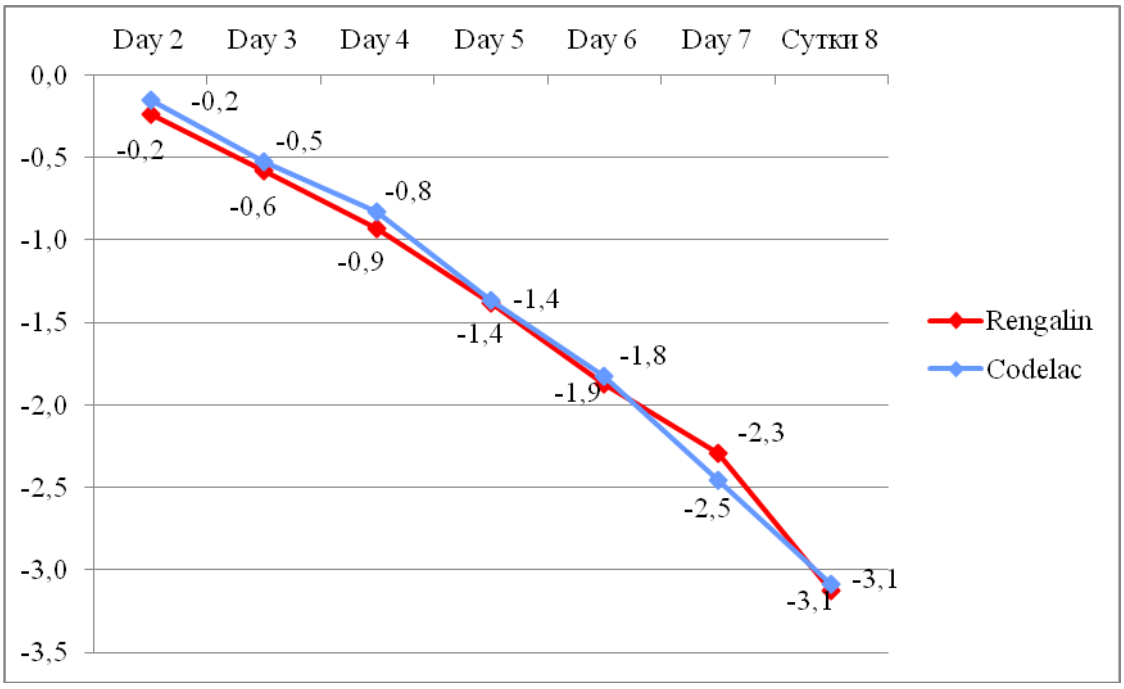

Figure 14.2.5.2: Changes in relative values obtained for maximum daily coughs severity (score)

The evaluation of primary endpoints demonstrated clinical efficacy of Brillia Health Cough Control in the treatment of cough induced by acute respiratory viral diseases. Antitussive effects of the drug product were

primarily manifested by reduced duration of distressing dry cough. Time to resolution of cough achieved with Brillia Health Cough Control was comparable to that of Codelac® [5, 12, 24], a well-known product containing codeine that inhibits the cough center [6, 10, 17]. Besides, the therapeutic efficacy of Brillia Health Cough Control was characterized by a pronounced reduction in cough severity in patients with an acute infectious and inflammatory process in the respiratory tract within 7 days of the treatment. All patients recovered from ARVI without any secondary bacterial complications.

14.3 Changes in the number of cough episodes throughout the participation in the study

One of the secondary endpoints of Brillia Health Cough Control efficacy was changes in cough episodes during the day as self-estimated by a patient throughout the treatment period.

In both groups, the number of coughs varied a lot, from occasional to 10 and >100 coughs, since the baseline cough severity demonstrated significant variations at enrollment. The mean number of cough episodes at baseline was 13.6±16.0 in the Brillia Health Cough Control group and 10.6±12.1 in the Codelac group (Table 14.3.1; fig. 14.3.1). The number of coughs reduced to 3.7±8.0 in the Brillia Health Cough Control group and to 2.7±6.3 in the Codelac group (Table 14.3.2; fig. 14.3.2). A total reduction in the mean absolute values was -10.7±14.5 in the Brillia Health Cough Control group vs. -8.4±11.0 in the Codelac group.

Table 14.1.3: Number of coughs during treatment

Group		**Brillia Health Cough Control**	**Codelac®**
Day	1	13.6±16.0	10.6±12.1
	3	8.4±9.4	6.8±7.7
	5	9.1±15.7	7.3±14.6
	7	5.5±12.8	3.1±6.1
	8	3.7±8.0	2.7±6.3

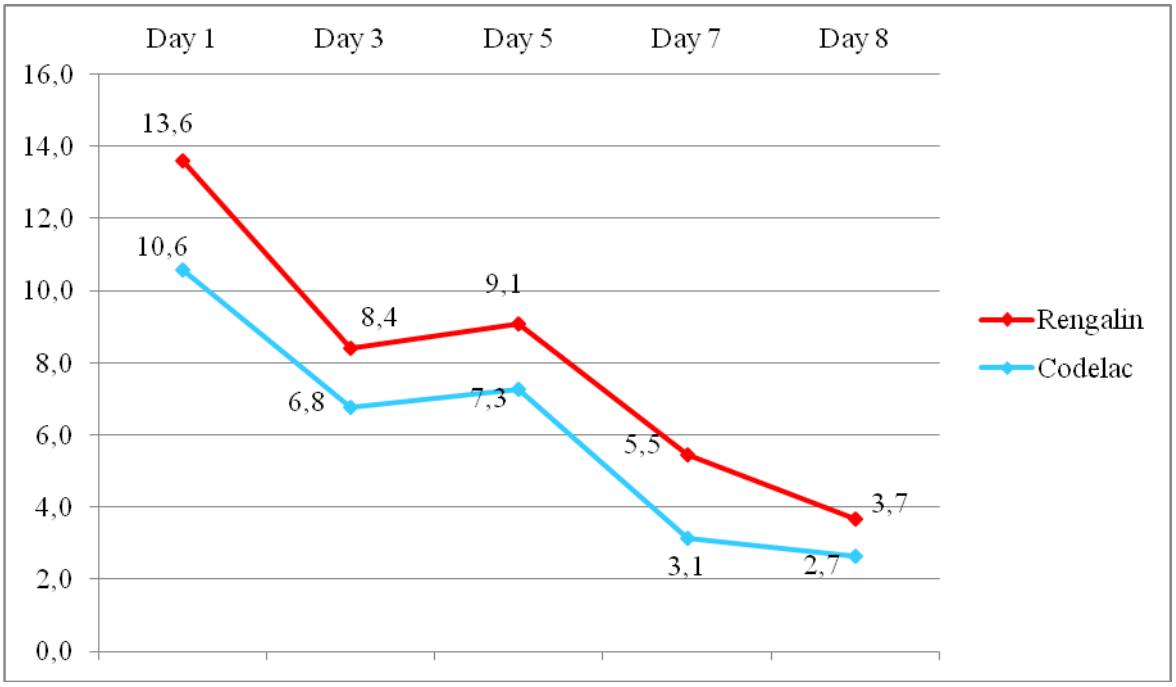

Figure 14.3.1: Changes in the number of coughs

Table 14.3.2: Changes in the number of coughs by the end of treatment as compared to baseline

Statistical data	**Brillia Health Cough Control**		**Codelac®**	
M±SD	-10.7±14.5		-8.4±11.0	
95% CI Mean	-15.7	-5.7	-12.9	-4.0
Diff C-T	2.26±13.12			
95% CI_{diff}	−4.53÷9.06			
δ	±0.84			

Note. M – mean value; SD – standard deviation; Diff – difference between the effects of the two drugs; C – control drug (or comparator drug, Codelac®);

T – test (or study) drug (Brillia Health Cough Control); CI – confidence interval.

Changes in the number of coughs by the end of therapy in the Brillia Health Cough Control group were similar to those in the Codelac® group, however, the statistical methods could not provide sufficient data to confirm clinical comparability of the products due to major variations (Diff C-T=2.26; 95% CIdiff=-4.53÷9.06; δ=±0.84; CIdiff<-0.84; δ is within CIdiff).

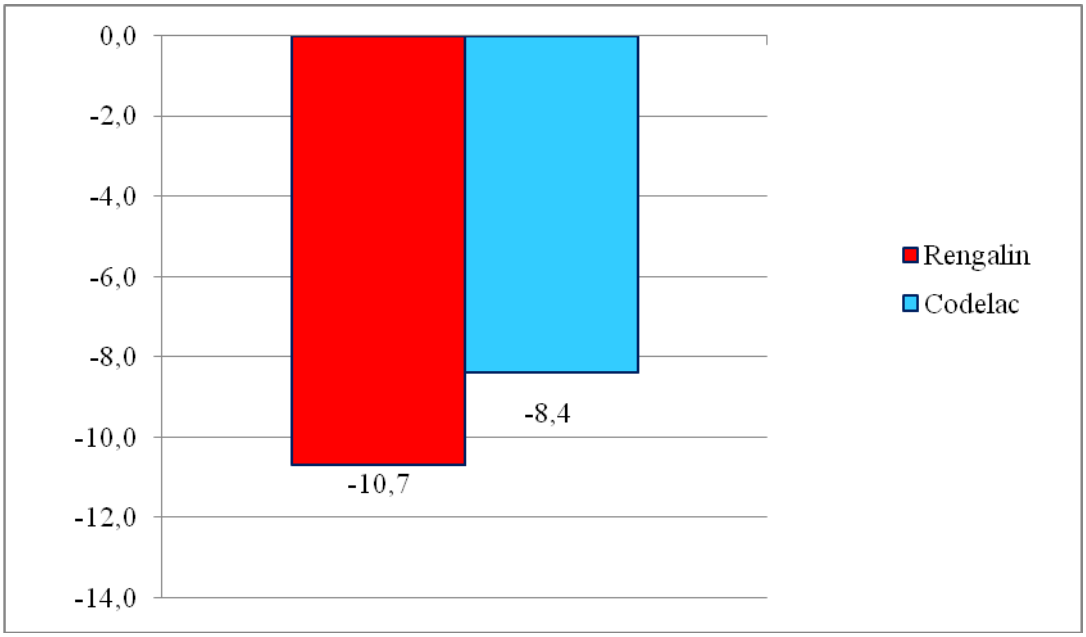

Figure 14.3.2: Changes in the number of coughs by the end of treatment as compared to baseline

14.4 Percentage of patients with resolved cough at following the completion of the study

Another efficacy endpoint is body weight of patients who demonstrated resolution of cough during the observation period and thus stopped the study therapy early.

The percentage of patients with resolved daytime and nocturnal cough due to therapy and general improvement was 76% and 89% in the Brillia Health Cough Control and Codelac group, respectively. The percentage of patients with resolved nocturnal cough, but persistent daytime cough, was 92% and 98%, accordingly.

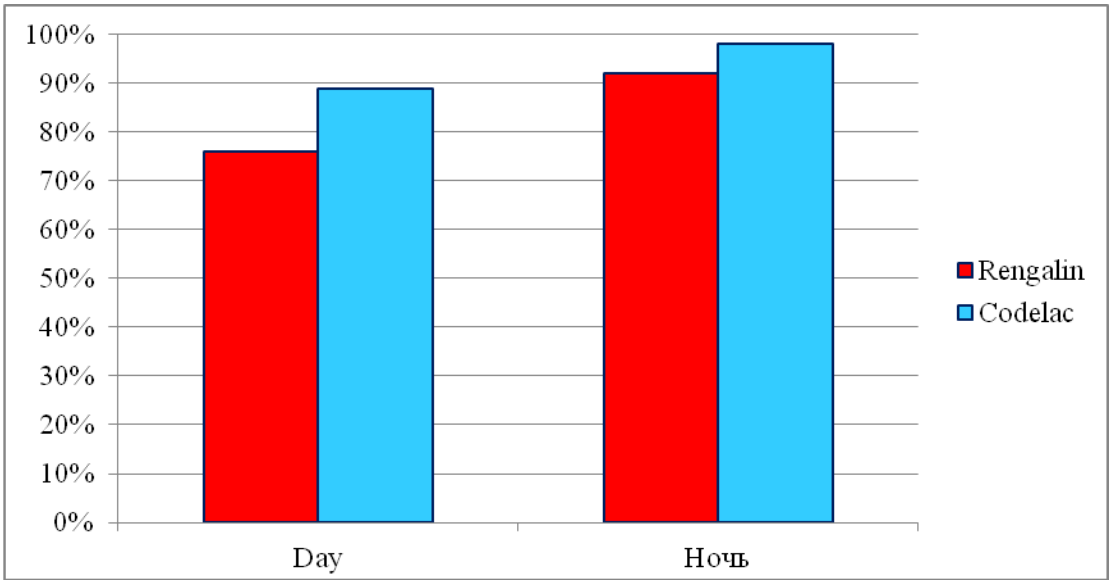

Figure 14.4.1: Percentage of patients with resolved cough by the end of treatment

Figure 14.4.2 shows the percentages of patients with different cough severities during the observation and treatment period. Most subjects in the Brillia Health Cough Control group (87%) had a cough score of 3 or 4 at baseline, which interfered with daily activities in 42% of patients. In the Codelac® group, these values were slightly lower – 78% and 37%, respectively. Further changes in the percentage of patients with different cough

severity were almost identical in both groups. Brillia Health Cough Control and Codelac® were withdrawn early in 29% and 46% of patients, respectively, due to successful treatment. By the end of therapy, the cough severity score of 1 to 2 was recorded in 24% of subjects in the Brillia Health Cough Control group and in 10% of subjects in the Codelac group for daytime cough and in 6% and 2% of patients for nocturnal cough, accordingly (Fig. 14.4.1).

Thus, the analysis of the secondary endpoints describing the antitussive efficacy of Brillia Health Cough Control also revealed its therapeutic efficacy. Acute, dry (non-productive) and frequent cough induced by acute respiratory infection interfered with daily activities of many patients and became resolved in the majority of the subjects, with only residual daytime cough present in some of them.

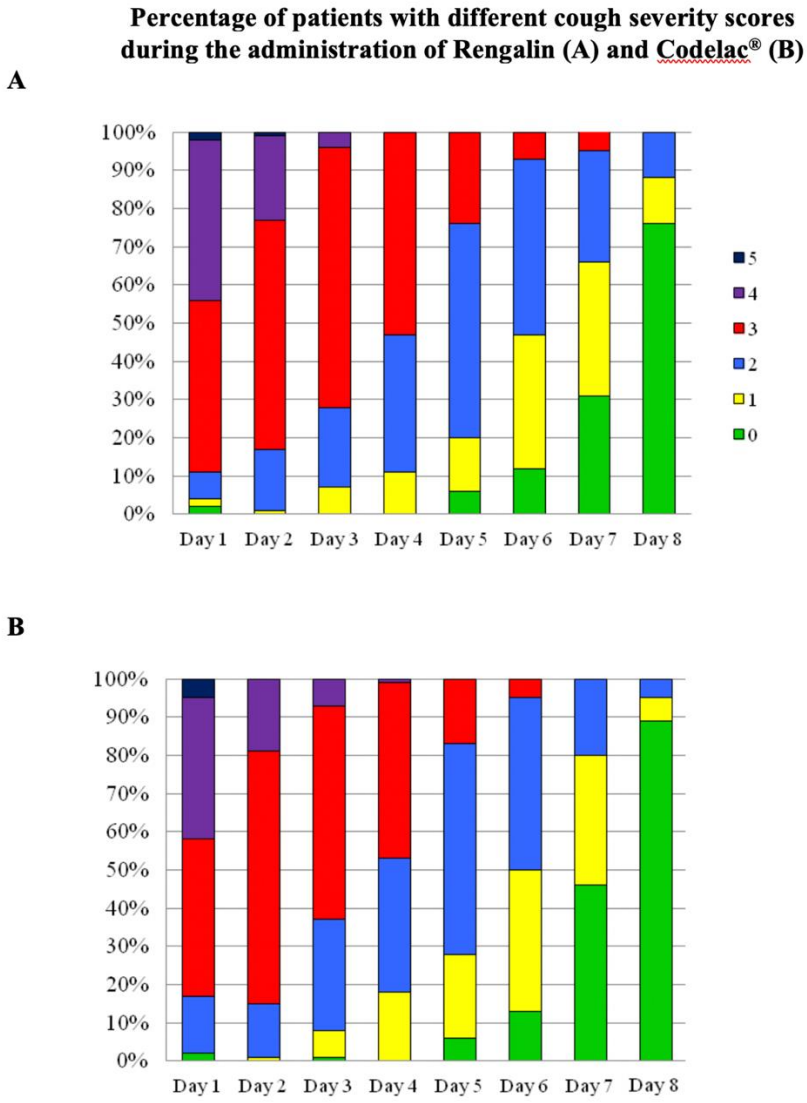

Figure 14.4.2: Percentage of patients with different cough severity scores during the administration of Brillia Health Cough Control (A) and Codelac® (B)

14.5 Physical and mental health parameters throughout the course of observation (QoL Survey)

The quality of life of patients with cough was estimated with the SF-36 questionnaire used to assess the physical and emotional health of patients with an acute condition.

The mean total score for physical health in the Brillia Health Cough Control group was 47.1±6.8 prior to treatment. This value increased to 50.4±5.5 after 7 days of therapy. In the comparator group, these values were 48.2±6.8 and 51.6±4.8, respectively (Fig. 14.5.1).

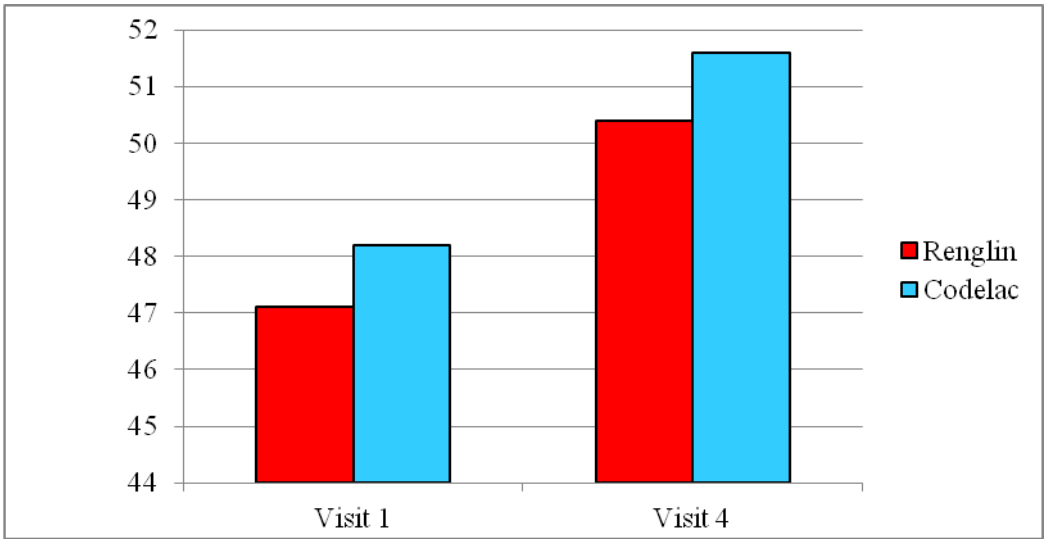

Figure 14.5.1: SF-36 Total Score for Physical Health (SF-36 score)

Mental health also improved in both groups due to treatment: 41.4±8.1 to 44.1±5.9 in the Brillia Health Cough Control group and 42.8±8.5 to 45.1±7.1 in the Codelac® group (fig. 14.5.2).

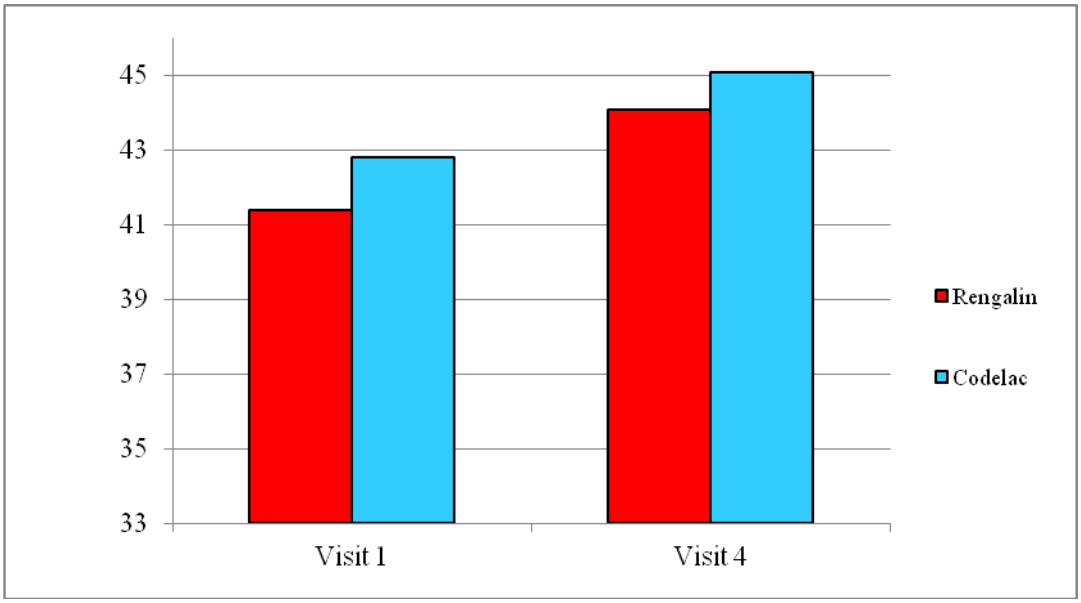

Figure 14.5.2: SF-36 Total Score for Mental Health

In general, physical health improved by 1.08 in both groups; mental health, by 1.09 in the course of Brillia Health Cough Control treatment (vs. 1.08 in the comparator group) (Table 14.5.3, fig. 14.5.3).

Table 14.5.3: Relative changes in physical and mental health scores due to treatment

Statistical data	Physical health				Emotional health			
	Brillia Health Cough Control		Codelac®		Brillia Health Cough Control		Codelac®	
M±SD	1.1±0.1		1.1±0.1		1.1±0.2		1.1±0.2	
95% CI Mean	1.1	1.1	1.1	1.1	1.1	1.1	1.0	1.1
Diff C-T	0.0±0.13				−0.01±0.18			
95% CI_{diff}	−0.04÷0.04				−0.07÷0.05			
δ	±0.11				±0.11			
p	<0.025				<0.025			

Note. M – mean value; SD – standard deviation; Diff – difference between the effects of the two drugs; C – control drug (or comparator drug, Codelac®);
T – test (or study) drug (Brillia Health Cough Control); CI – confidence interval.

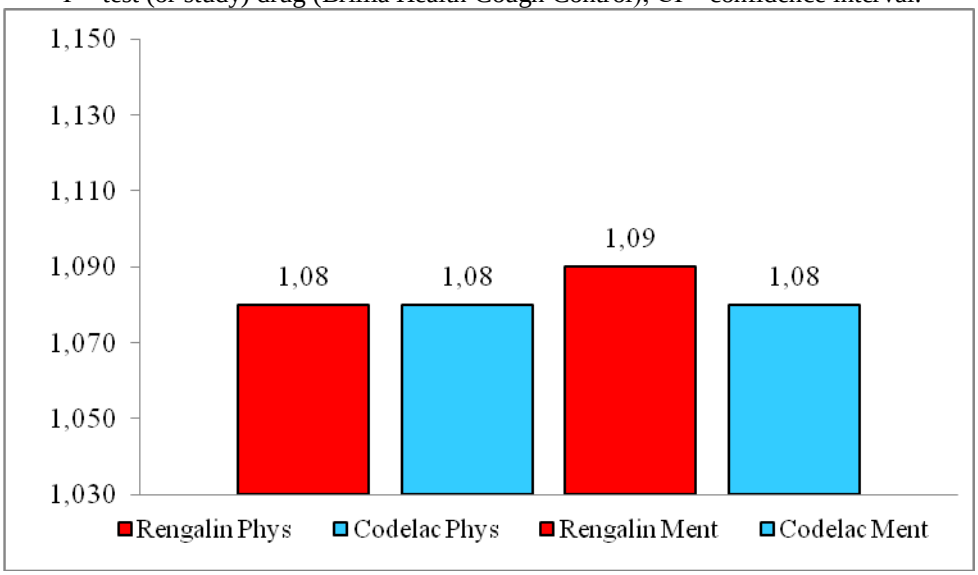

Figure 14.5.3: Relative increase in physical and mental health values by the end of treatment

The statistical analysis demonstrated that changes in the total physical health score due to Brillia Health Cough Control treatment were within δ=10% of those in the Codelac® group (Diff C-T=0.0; 95% CI_{diff}=−0.04÷0.04; δ=±0.11; CI_{diff}<0.11; p<0.025), supporting clinical equivalence (non-inferiority) of the two drug products.

Similar results were obtained in the statistical analysis of the effects of Brillia Health Cough Control on mental health. Changes in mental health values as per SF-36 in the Brillia Health Cough Control group were comparable to the outcome in the Codelac® group (Diff C-T=−0.01; 95% CI_{diff}=−0.07÷0.05; δ=±0.11; CI_{diff}<0.11; p<0.025).

14.6 Treatment-related quality of life changes

Night-time cough was estimated using the sleep quality questionnaire (0 – best score, 20 – worst score) to assess its interference with sleep.

The mean nocturnal cough score at baseline was 10.3±2.5 in the Brillia Health Cough Control group. After 7 days of treatment, the total questionnaire score decreased to 8.4±2.1 showing improved sleep in patients who almost achieved resolution of night-time cough (Fig. 14.6.1). In the comparator group, these values were

comparable (10.3±2.5 and 8.5±1.7, respectively), which was supported by the statistical analysis of the quality of sleep in both groups (Diff C-T=0.01; 95% CI_{diff}=−0.05÷0.08; δ=±0.08; CI_{diff}>−0.08; p<0.025) (Table 14.6.1. and fig. 14.6.2.)

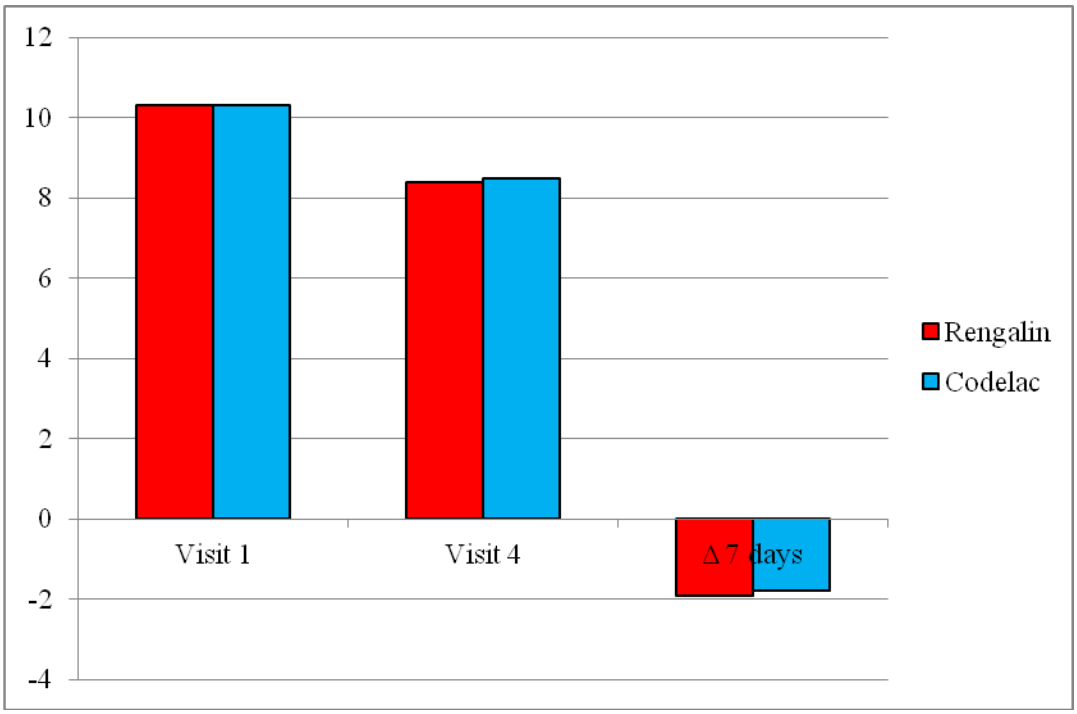

Figure 14.6.1: Changes in the QoS total score due to treatment

Table 14.6.1: Changes in the QoS total score due to treatment

Statistical data	Brillia Health Cough Control		Codelac®	
M±SD	0.8±0.2		0.9±0.2	
95% CI Mean	0.8	0.9	0.8	0.9
Diff C-T	0.01±0.20			
95% CI_{diff}	−0.05÷0.08			
δ	±0.08			
p	<0.025			

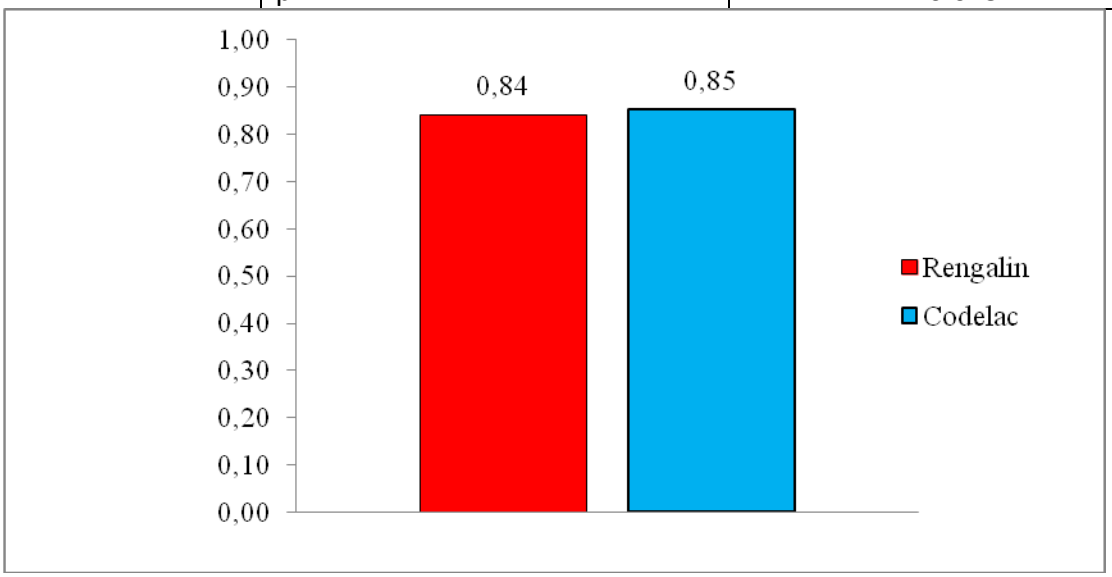

Figure 14.6.2: Changes in the QoS total score due to treatment (Visit 4 vs. Visit 1)

14.7 Therapeutic efficacy index as per CGI-EI

Upon the end of treatment, the therapeutic effect to side effects ratio was rated using the CGI-EI, with a range of scores from 0.25 (minimum) through to 4.0 (maximum). Treatment response ratings as made by a clinician took account of any treatment-related adverse events (Table 14.7.1, fig. 14.7.1).

Table 14.7.1: Therapeutic effects and side effects as per the CGI

Statistical data	Therapeutic effect				Side effects			
	Brillia Health Cough Control		Codelac®		Brillia Health Cough Control		Codelac®	
M±SD	3.7±0.5		3.8±0.5		1.0±0.2		1.0±0.3	
95% CI Mean	3.6	3.8	3.7	3.9	1.0	1.1	1.0	1.1
Diff C-T	0.1±0.51				0.02±0.22			
95% CI_{diff}	-0.08÷0,28				-0.06÷0.09			
δ	±0.38				±0.11			
p	<0.025				<0.025			

Most investigators assessed the therapeutic effect of Brillia Health Cough Control as “Marked” (vast improvement): the mean total score was 3.7±0.5. This demonstrated that Brillia Health Cough Control resulted in either remission or vast improvement in patients by the end of therapy, according to the physician, with antitussive efficacy of Codelac® rated as 3.8±0.5. Therapeutic efficacy of the two drug products was found to be comparable (Diff C-T=0.1; 95% CI_{diff}=−0.08÷0.28; δ=±0.38; CI_{diff}<0.38; p<0.025).

No drug-related adverse events were registered in most subjects throughout 7 days of treatment, as observed by investigators. Occasional side effects without pronounced impact on the functional performance of patients were only found. The mean total values for side effects of Brillia Health Cough Control and Codelac® were comparable - 1.0±0.2 and 1.0±0.3, respectively (Diff C-T=0.02; 95% CI_{diff}=−0.06÷0.09; δ=±0.11; CI_{diff}>-0.11; p<0.025).

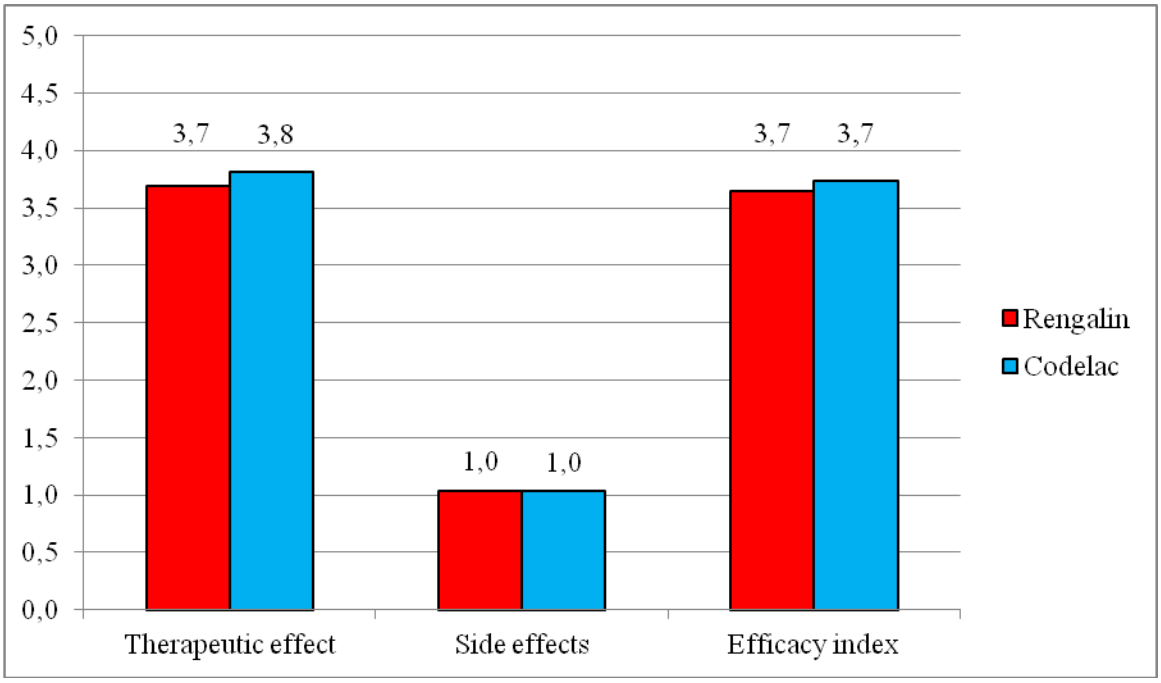

Figure 14.7.1: CGI mean scores by the end of treatment

The total clinical efficacy score was found to be high and comparable in both groups (Table 14.7.2) (Diff C-T=0.08; 95% CI_{diff}=−0.13÷0.29; δ=±0.37; CI_{diff}<0.37; p<0.025).

Table 14.7.2: Therapeutic efficacy index as per CGI

Statistical data	Brillia Health Cough Control		Codelac®	
M±SD	3.7±0.6		3.7±0.6	
95% CI Mean	3.5	3.8	3.6	3.9
Diff C-T	0.08±0.62			
95% CI_{diff}	−0.13÷0.29			
δ	±0.37			
p	<0.025			

15. Safety evaluation

Safety analysis was based on the data obtained from the intention-to-treat population who received at least one dose of the study drug or comparator drug (n=143).

No complaints or impaired physical status due to Brillia Health Cough Control administration were observed (Table 15.1). The drug product did not result in any respiratory depression, addiction or drowsiness. In general, the drug product was well tolerated by patients. No cases of drug incompatibility were reported for Brillia Health Cough Control when co-administered with concomitant medications used against comorbidities.

Table 15.1: Changes in vital signs

	Visit 1	Visit 2	Visit 3	Visit 4
HR, bpm				
Brillia Health Cough Control (n=73)	81.3±6.3	78.8±6.1	75.9±5.7	73.3±9.7

Codelac® (n=70)	81.4±6.6	78.2±6.4	74.9±5.0	73.6±5.2
RR, bpm				
Brillia Health Cough Control (n=73)	18.8±3.6	18.2±3.1	17.6±2.8	17.5±2.7
Codelac® (n=70)	18.0±3.0	17.5±2.5	17.0±2.3	17.0±2.3
Systolic BP, mm Hg				
Brillia Health Cough Control (n=73)	122.4±9.8	120.6±10.1	120.0±9.6	119.8±8.3
Codelac® (n=70)	123.8±10.4	121.4±11.2	122.1±9.8	119.7±8.7
Diastolic BP, mm Hg				
Brillia Health Cough Control (n=73)	74.9±4.9	75.5±5.3	74.6±5.5	74.5±4.8
Codelac® (n=70)	75.4±5.8	75.2±5.9	74.6±5.8	74.3±5.5

The recorded AEs were found in the laboratory tests monitored to evaluate the safety of the therapy. Only one AE - abnormal blood values (eosinophilia) - unlikely related to the study drug, according to investigator, was documented in the Brillia Health Cough Control group. Two cases of elevated ALT levels in the Codelac group were also considered unlikely related to the therapy (Table 15.2; 15.3). No modifications of the study treatment were implemented. The frequency analysis showed no significant differences in the number of patients developing AEs between the Brillia Health Cough Control and the Codelac® groups (Fisher's exact test; p=0.615). Mean laboratory values are given in Tables 15.4 and 15.5.

Table 15.2: Incidence of adverse effects

	Brillia Health Cough Control (n=73)	**Codelac®** (n=70)
Number of AEs, abs (%)	1 (1.4%)	2 (2.9%)

Table 15.3: List of adverse effects

Subject ID #	Description	MedDRA code	AE severity	Causal relationship with the treatment
Brillia Health Cough Control				
07-005-025	Eosinophilia	10005506	Moderate	Unlikely related
Codelac®				
07-003-023	ALT increased	10001845	Moderate	Unlikely related
07-029-114	ALT increased	10001845	Moderate	Unlikely related

Table 15.4: Changes in laboratory parameters

Blood test					
		Brillia Health Cough Control		**Codelac**	
Parameter	Units	Visit 1	Visit 4	Visit 1	Visit 4
Blood biochemistry					
Glucose	mmol/l	4.9±0.9	4.9±1	4.9±1.1	4.8±1.1

Total bilirubin	µmol/L	14.3±4.4	15.3±8	15.1±5.1	14.6±4.2
ALT	U/L	26±15.4	23.7±12.3	23.8±10.4	24±15
AST	U/L	29.7±21.4	24.9±6.7	26.9±16	24.2±9.4
Creatinine	µmol/L	83.7±15.9	83.7±14.3	84.2±13.5	84.9±15.2
Complete blood count					
RBC	10^{12}/L	4.5±0.4	4.5±0.3	4.5±0.4	4.6±0.4
Hemoglobin	g/L	138.3±13.3	136.5±11	136.7±12.5	138.6±13.3
HCT	%	40.9±3.9	40.5±2.6	40.8±3.5	41.4±3.7
WBC	10^9/L	7±1.5	7.1±1.7	7.5±2	7±1.8
Stab neutrophils	10^9/L	5.2±12.5	4.7±11.6	7.1±15.7	6.7±15.4
Segmented neutrophils	%	58.2±10.3	56±8.2	58.1±11.5	56.2±12.1
Eosinophils	%	2.5±1.5	2.7±2.6	2.6±1.9	2.4±1.6
Basophils	%	0.3±0.5	0.3±0.5	0.3±0.7	0.2±0.4
Lymphocytes	%	30.5±9.5	32±8	29.2±9.9	31.5±9.7
Monocytes	%	5.9±2.3	6±2.3	6.5±2.7	6.7±2.8
Platelets	10^9/L	269.6±67	267.5±59.4	262.7±52	267.1±51.4
ESR	mm/hr	11.4±6.8	10.2±6.2	10.8±6.6	9.3±6.3

Table 15.5: Abnormal findings in urinalysis

	Brillia Health Cough Control		**Codelac**	
	Visit 1	Visit 4	Visit 1	Visit 4
Specific gravity (M±SD)	1021.3±6.1	1020.3±7.1	1020.5±6.8	1019.5±6.9
Abnormal findings / total patients				
Colour	0/73	0/72	0/70	0/67
Protein	0/73	0/72	0/70	0/67
Glucose	0/73	0/72	0/70	0/67
Ketones	0/73	0/72	0/70	0/67
WBC	0/73	0/72	0/70	0/67
RBC	0/73	0/72	0/70	0/67
Squamous epithelium	0/73	0/72	0/70	0/67
Casts	0/73	0/72	0/70	0/67

16. Conclusion

This multicenter, randomized, open-label clinical trial assessed the efficacy and safety of Brillia Health Cough Control in the treatment of cough caused by acute respiratory infections as compared to the antitussive effects of Codelac®.

The trial enrolled 143 patients aged ≥18 years with non-productive cough resulting from an acute respiratory infection (acute pharyngitis, laryngitis, laryngotracheitis, tracheitis, tracheobronchitis, bronchitis); 139 patients (n=72 in the Brillia Health Cough Control group and n=67 in the Codelac® group) completed the trial as per the protocol. The therapeutic efficacy of Brillia Health Cough Control was estimated by assessing primary (time to resolution of cough, changes in cough severity during the participation) and secondary (changes in the number of coughs, quality of life and quality of sleep, efficacy index) endpoints.

The clinical trial demonstrated that the antitussive efficacy of Brillia Health Cough Control was comparable to that of Codelac®. The average time to resolution of daytime and nocturnal cough was 7.2±1.0 days, being comparable ($p<0.025$) to that achieved with Codelac® (7.0±1.1 days), which was as good as its therapeutic effects in the previous trials [5, 12, 24]).

The antitussive action of Brillia Health Cough Control was manifested by a gradual reduction in cough severity and observed early on the first days. The mean cough score recorded on Day 3 of therapy (2.8±0.6) indicated that most patients experienced occasional cough for short periods that did not interfere with their daily activities and sleep. As a result of the 7-day treatment, the severity score reduced by –3.1±09 (versus –3.1±1.0 in the Codelac group), totaling 0.2±0.5 in both groups. i.e. either resolved or residual cough at the end of the therapy. According to the statistical analysis, a reduction in cough severity was comparable to that observed in the comparator group ($p<0.05$).

Brillia Health Cough Control reduced the daily number of coughs by −10.7±14.5 (vs. −8.4±11.0 in the Codelac® group). The frequent, severe cough affecting daily activities and sleep quality in almost half of the patients was fully resolved in 76% of subjects; the other participants continued to demonstrate occasional cough. All patients recovered from AVRI without any secondary bacterial complications.

Thus, the therapeutic efficacy of Brillia Health Cough Control was manifested by a pronounced (almost 100%) reduction in cough severity in patients with an acute infectious and inflammatory process in the respiratory tract within 7 days of the treatment.

These effects of Brillia Health Cough Control are due to a combined action of the components on various pathogenic pathways of the cough reflex [1-4, 7, 11, 15, 17, 18, 19]. These components allow achieve different therapeutic targets in the treatment of patients with cough induced by acute inflammatory diseases of the respiratory tract. At the first stages of infection and inflammation when the respiratory mucosa is involved (”dry” inflammation with hyperirritation of cough receptors), a patient suffers from acute and distressing cough that can lead to serious complications and produce a “vicious circle” of coughing. In this case, when cough suppressants are usually required to break the cough reflex arc and lower the excitability of receptors [9, 14, 17], the first component of Brillia Health Cough Control - anti-M - exerts its effects on the central pathway of the cough reflex. The other two ingredients of Brillia Health Cough Control are useful at the next stages of respiratory infections, with prevailing exudative and catarrhal processes in the respiratory tract. Anti-H modulates the activity of H1 and H2 receptors, lowering peripheral vasopermeability, excessive production of mucus and histamine release, thus reducing edema and exudation. Anti-B inhibits the synthesis and release of bradykinin, prostaglandins, TNF-α, a number of interleukins and histamines, reduces leukocyte extravasation and pain, promotes relaxation of smooth muscles, and modifies the inflammatory process and development of the cough reflex. Brillia Health Cough Control exerts its antitussive, antispasmodic and decongestant effects and

facilitates expectoration via a combination action of the three components on the central and peripheral pathways of the cough reflex and its cause (inflammation in the respiratory tract), thus promoting early recovery of patients by reducing cough and inflammation.

Positive changes in subjects with cough caused by acute respiratory infection improved the quality of life and sleep. Physical and mental health of the participants improved by 10% on average in both groups, according to the SF-36 results. The QoS values obtained through a week also demonstrated improvements in both groups. The statistical analysis of the total scores obtained with the QoL and QoS surveys showed that the therapeutic efficacy of Brillia Health Cough Control was similar to that of Codelac® ($p<0.025$).

At the end of the administration period, the investigators assessed the therapeutic effect of Brillia Health Cough Control as "Marked" (vast improvement) using the CGI scale. The mean total score (3.7±0.5) indicated either remission or a significant improvement of patients' health by the end of the Brillia Health Cough Control treatment period. Occasional adverse effects related to the therapy were only found in some patients and did not exert any significant effects on the functional potential of subjects. The Clinical Global Impression Scale-Efficacy Indices (CGI-EI) in the groups of Brillia Health Cough Control and Codelac® were comparable - 3.7±0.6 ($p<0.025$).

The monitoring of adverse events and laboratory values indicated the safety of Brillia Health Cough Control. No serious adverse events were registered during the treatment. One AE (moderate blood eosinophilia), from the investigator's point of view, had an unlikely causal relationship with the therapy. Brillia Health Cough Control did not result in any respiratory depression, addiction or drowsiness. No adverse interactions were reported with the use of Brillia Health Cough Control in conjunction with therapy for co-morbidities.

Thus, the study results show that Brillia Health Cough Control is an effective and safe drug product for patients with cough caused by acute respiratory infections. The combination of the components evokes antitussive effects early in the course of disease, that help to manage dry, irritant cough interfering with a patient's daily activities, and protussive effects later, achieving the main therapeutic target, i.e. resolution of cough in most of the subjects.

Conclusions:

1. Brillia Health Cough Control is effective for the treatment of subjects with cough caused by acute infectious and inflammatory respiratory tract diseases: ARVI, acute pharyngitis, laryngitis, laryngotracheitis, tracheitis, bronchitis.
2. The therapeutic effect of Brillia Health Cough Control manifests in effective elimination of diurnal and nocturnal cough. Antitussive activity of Brillia Health Cough Control in terms of complete recovery (diurnal and nocturnal) is comparable to that of combination product Codelac®.

3. The severity of daytime and nocturnal cough begins to decrease as soon as on the first day after Brillia Health Cough Control administration, with its reduction observed throughout the whole treatment period. By the end of the 7-day administration, cough severity reduced by almost 100% and was comparable to that in the Codelac® group. Minor residual coughing (occasional cough for short periods during the day) continued in 25% of participants.
4. By targeting various cough reflex mediators, Brillia Health Cough Control's ingredients enable the achievement of an antitussive effect in the early days after URI onset (in dry, irritative cough interfering with daily activities), and a protussive effect at later points of treatment.
5. Brillia Health Cough Control exhibits an antitussive effect and promotes resolution of cough and infectious respiratory tract inflammation without secondary bacterial complications.
6. Positive changes in subjects with cough after Brillia Health Cough Control therapy improve their quality of life manifested as increased SF-36 physical and mental health summary scales.
7. After 7-day Brillia Health Cough Control therapy, either complete cough resolution or a significant relief in cough severity and incidence improves noctural sleep, resulting in positive changes in the quality of sleep.
8. According to the physicians, Brillia Health Cough Control and Codelac® (CGI-EI) show similar clinical efficacy in the treatment of cough.
9. The monitoring of adverse events and laboratory values indicate the safety of Brillia Health Cough Control in the treatment of patients with cough induced by acute infectious and inflammatory diseases of the respiratory tract.
10. Brillia Health Cough Control was not associated with respiratory depression or drug dependence and it produced no narcotic nor hypnotic effects.
11. No adverse interactions were reported with the use of Brillia Health Cough Control in conjunction with therapy for co-morbidities.
12. Compliance in the Brillia Health Cough Control group was significantly higher as compared to the Codelac® group.

17. References

1. Chuchalin AG, Abrosimov VN. Cough. Second edition, updated and revised. Moscow: Echo, 2012; 128 p.
2. Bolser D.C. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1): 238–249.
3. Bolser D.C., Degennaro F.C. Effect of codeine on the inspiratory and expiratory burst pattern during active cough in cats. Brain Res. 1994; 662: 25-30.
4. Canning B.J. Anatomy and Neurophysiology of the Cough Reflex. ACCP evidence-based clinical practice guidelines. Chest 2006; 129(1): 33-47.
5. Chang C.C., Cheng A.C., Chang A.B. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults (Review). Cochrane Database of Systematic Reviews

2012, Issue 2. The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd. http://www.thecochranelibrary.com
6. Chang C.C., Platter G.M.R., Brightling C.E. et al. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129 (1): 222-273.
7. Diagnosis and management of cough. Executive Summary: ACCP evidence-based clinical practice guidelines. / Irwin R.S., Baumann M.H., Bolser D.C. et al. Chest, 2006;129:1S-23S. 1S-23S.
8. Dicpinigaitis P.V., Colice G.L., Goolsby M.J. et al. Acute cough: a diagnostic and therapeutic challenge. Cough, 2009; 5: 11.
9. ERS guidelines on the assessment of cough. ERS Task Force. Morice A.H., Fontana G.A., Belvisi M.G. et al.; Eur. Respir. J. 2007; 29: 1256-1276.
10. Footitt J, Johnston SL. Cough and viruses in airways disease: mechanisms. Pulm Pharmacol Ther. 2009; 22 (2): 108-13.
11. Guidelines for the management of adult lower respiratory tract infections. European Society of Clinical Microbiology and Infectious Diseases. Woodhead M. et al. Clinical Microbiology and infection, 2011; V. 17; Supplement 6.
12. Hsu J.Y., Stone R.A., Logan-Sinclair R.B. et al. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. Eur. Respire. J. 1994; 7: 1246-1253.
13. Platter M.R., Abouzgheib W. Make The Cough Go Away. Chest, 2006; 129 (5): 1121-1122.
14. Pratter M.R. Cough and the Common Cold: ACCP Evidence-Based Clinical Practice Guidelines. Chest, 2006;129:1S-23S. 59S–62S.
15. Smith S.M., Schroeder K., Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. The Cochrane Library, 2010, Issue 9. The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd. http://www.thecochranelibrary.com

Annex 1

Cough severity scale

The scale is to be filled in by a patient.
Please circle **one** response that comes best to describe the severity of cough you experience: during the **day (9.00 till 21.00)** and **last night (21.00 yesterday till 09.00 today)**.

Daytime	Score
No cough	**0**
Occasional cough for one short period	**1**
Occasional cough for 2-3 short periods	**2**
Frequent cough that does not interfere with daily activities	**3**

Frequent cough that interferes with daily activities	**4**
Severe distressing cough	**5**
Night-time	**Score**
No cough	**0**
Coughing when falling asleep or waking up	**1**
Waking once due to cough	**2**
Frequent waking due to cough	**3**
Frequent cough most of the night	**4**
Severe distressing cough	**5**

Annex 2

SF-36 Survey

1. In general, would you say your health is (choose one option):

Excellent.....1
Very good 2
Good 3
Fair 4
Poor 5

2. *Compared to one year ago*, how would you rate your health in general *now*? (choose one option)

Much better now than one year ago 1

Somewhat better now than one year ago 2
About the same..... 3
Somewhat worse now than one year ago..... 4
Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (choose one option)

	Yes, limited a lot	Yes, limited a little	No, not limited at all
A. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
B. Moderate activities, such as moving a table, pushing a vacuum cleaner, picking mushrooms or berries.	1	2	3
C. Lifting or carrying groceries.	1	2	3
D. Climbing several flights of stairs.	1	2	3
E. Climbing one flight of stairs.	1	2	3
F. Bending, kneeling, or stooping.	1	2	3
G. Walking more than a mile.	1	2	3
H. Walking several blocks.	1	2	3
I. Walking one block.	1	2	3
J. Bathing or dressing yourself.	1	2	3

4. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (choose one option)

	Yes	**No**
A. Cut down the *amount of time* you spent on work or other activities.	1	2
B. *Accomplished less* than you would like.	1	2
C. Were limited in the *kind* of work or other activities.	1	2
D. Had *difficulty* performing the work or other activities (for example, it took extra effort).	1	2

5. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems? (choose one option)

	Yes	No
A. Cut down the *amount of time* you spent on work or other activities.	1	2
B. *Accomplished less* than you would like.	1	2
C. Didn't do work or other	1	2

activities as *carefully* as usual.		

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (choose one option)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

How much bodily pain have you had during the past week? (choose one option)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe……6

8. During the *past week*, how much did *pain* interfere with your normal work (including both work outside the home and housework)? (choose one option)

Not at all 1
A little bit 2
Moderately 3
Quite a bit 4
Extremely 5

9. These questions are about how you feel and how things have been with you *during the past week*. For each question, please give the answer that comes closest to the way you have been feeling (choose one option).

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
A. Did you feel full of pep?	1	2	3	4	5	6
B. Have you been a very nervous person?	1	2	3	4	5	6
C. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
D. Have you felt calm and peaceful?	1	2	3	4	5	6
E. Did you have a lot of energy?	1	2	3	4	5	6
F. Have you felt downhearted and blue?	1	2	3	4	5	6
G. Did you feel worn out?	1	2	3	4	5	6
H. Have you been a happy person?	1	2	3	4	5	6
I. Did you feel tired?	1	2	3	4	5	6

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (choose one option)

All of the time 1
Most of the time 2
Some of the time..... 3
A little of the time……4
None of the time 5

11. How TRUE or FALSE is each of the following statements for you? (choose one option)

	Definitely tr-ue	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Annex 3

QUALITY OF SLEEP SURVEY FOR PATIENTS WITH COUGH

1. In the past 7 days, to what extent has your cough troubled you?
a. Not at all
b. A little
c. Somewhat
d. Much
e. Very much

2. In the past 7 days, how much of the time have you woken up in the middle of the night and had difficulty getting to sleep?
a. None of the time
b. A little of the time
c. Several times
d. A lot of the time
e. All of the time

3. In the past 7 days, how often have you failed to get enough sleep?
a. None of the time
b. A little of the time
c. Several times
d. A lot of the time
e. All of the time

4. In the past 7 days, how often have you found yourself feeling sleepy throughout the day?
a. None of the time
b. A little of the time
c. Several times
d. A lot of the time
e. All of the time

Annex 4

Clinical Global Impression (CGI)

EFFICACY INDEX					
	Side effects	No	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
Therapeutic effect	**4.** Marked Vast improvement. Complete or nearly complete remission of all symptoms	4.00	2.00	1.33	1.00
	3. Moderate Decided improvement. Partial remission of symptoms.	3.00	1.50	1.00	0.75
	2. Minimal Slight improvement which doesn't alter status of care of patient	2.00	1.00	0.67	0.50
	1. Unchanged or worse	1.00	0.50	0.33	0.25