# Brillia Health Cold-Flu Recovery

## Clinical Summary

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**2. Synopsis**

**Company**: Santonika

**Drug name:** Brillia Health Cold-Flu Recovery

**Active ingredient:** Lapine interferon gamma immune globulin — 0.006g*, Lapine histamine immune globulin — 0.006g* and Lapine CD4 immune globulin — 0.006g*

*applied onto lactose monohydrate as a mixture of three active water-alcohol dilutions of the substance, diluted by $100^{12}$, $100^{30}$ and $100^{50}$ times, respectively.

**Study Title:** Multicenter, open-label, comparative, randomized, clinical parallel-group study of both the efficacy and safety of Brillia Health Cold-Flu Recovery in the treatment of influenza.

**Phase:** IV

**Principal investigators:**

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**Study period:** First subject enrolled on February 28, 2011. Last subject terminated on April 21, 2014.

**Study objectives:**

1. To evaluate the clinical efficacy of Brillia Health Cold-Flu Recovery in the treatment of influenza
2. To evaluate the safety of Brillia Health Cold-Flu Recovery in the treatment of influenza
3. To compare efficacy of Brillia Health Cold-Flu Recovery and Oseltamivir in the treatment of influenza

**Safety parameters:**

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

**Efficacy criteria:**

Primary criterion:

1. Proportion of subjects with normalized body temperature (≤ 37°C) by the end of day 1, 2, 3, 4, 5 of therapy.

Secondary criterion:

1. Proportion of subjects having their clinical manifestations eliminated by day 7 of the follow-up
2. Terms of influenza symptom elimination in groups
3. Intensity of clinical manifestations of influenza (body temperature, intoxication signs, catarrhal symptoms in scores) on days 1, 3 and 7 of the follow-up
4. Changes in the number of intakes of antipyretic drugs on days 2, 3, 4 and 5 of therapy
5. Changes in the total score of the quality of life questionnaire by the end of the treatment as compared to baseline (Day 7 vs. Day 1)
6. Proportion of subjects with exacerbation of the disease (development of complications requiring antibiotics and hospitalization).

**Methodology:**

**Design:** multicenter, open-label, comparative, randomized parallel-group study.

The study enrolled subjects aged 18-60 years old with influenza seeking medical advice within the first 24 hours after the disease onset, having fever ≥37.8°C and at least one systemic and one respiratory symptom. After signing informed consent to participate in the clinical study at visit 1 (Day 1), examination was performed including collection of history data, evaluation of vital signs, objective examination and nasal swab for express diagnostics of influenza (detection of virus antigens using immune test).

After determination of compliance with inclusion/non-inclusion criteria, the subjects were enrolled into the study and randomized into two groups: group 1 received Brillia Health Cold-Flu Recovery using a 5-day therapeutic scheme while group 2 received Oseltamivir (Tamiflu®), also for 5 days.

At Visit 1 concomitant therapy was recorded, the EQ5D quality of life questionnaire was filled, health condition was evaluated using visual analogue scale (VAS), laboratory tests (biochemistry, complete blood analysis, urinalysis) and pregnancy tests (for females of childbearing potential only) were performed. The subject was given a diary in which they were to note morning and evening axillary temperature, administration (if applicable) and the intake of antipyretic drugs.

The subject was followed for 7 days (screening - day 1, study therapy - 5 days, follow-up - 2 days). During the treatment and follow-up, the subjects made an additional 2 visits to the investigator, or the investigator made 2 visits to the subjects, i.e. Visit 2 (Day 3±1) and Visit 3 (7±1). At these visits, the doctor collected complaints, recorded objective examination data, evaluated therapeutic safety, monitored the prescribed and concomitant therapy and checked the subject's diary. Furthermore, at Visit 3, compliance, quality of life and health status (EQ5D and VAS) were evaluated, laboratory tests (biochemistry, complete blood analysis, urinalysis) were performed and the doctor filled a clinical global impression scale (CGI-EI).

During the study, antipyretic drugs and other symptomatic drugs for the treatment of influenza and concomitant diseases were allowed except for the drugs specified in the section forbidden concomitant treatment.

**Diagnosis and inclusion criteria:**

1. Age between 18 and 70 years old, inclusively.
2. Subjects with body temperature >37.8°C at the visit with at least one catarrhal symptom (cough, rhinitis, sore throat) and one intoxication symptom (myalgia, chills, malaise, weakness, headache) during seasonal morbidity.
3. Diagnosis of influenza verified by express diagnostics (presence of influenza virus antigens in nasal epithelium verified using QuickVue immunological test).
4. Possibility to initiate therapy within 24 hours from the first symptoms of influenza.
5. Availability of signed informed consent to participate in the study.

**Non-inclusion criteria:**

1. Age under 18 or over 60 years old.

2. Suspected invasive bacterial infection or severe disease requiring antibacterial drugs such as sulfanylamides.
3. Vaccination against influenza prior to epidemiological season.
4. Polyvalent allergy in past medical history.
5. Allergy to/intolerance of any ingredient in the composition of the drugs used in the treatment.
6. Exacerbated or decompensated chronic disease affecting subject eligibility.
7. Chronic renal failure.
8. Use of medications listed in section (Forbidden Concomitant Treatment) within 15 months prior to enrollment.
9. Pregnancy, breast-feeding, unwillingness to use contraception during the study.
10. Use of drugs or alcohol (> 2 alcohol units daily), mental diseases.
11. Subjects unlikely, by the investigator's judgement, to comply with the observation requirements during the trial or treatment regiments under the study.
12. Participation in other clinical studies within one month prior to enrollment in the present trial.
13. Subjects being members of study center personnel directly involved in the study, or those in close familial relationship with the investigator. Close familial relationships refer to spouses, parents, children, brothers/sisters, regardless of whether these are birth or adopted relatives.

**Exclusion criteria:**

1. Participant's failure or decline to comply with the protocol requirements.
2. Necessity for prescribing medications not permitted during the study.
3. Occurrence of AEs requiring immediate discontinuation of treatment.
4. Subject's willingness to withdraw early due to therapeutic inefficacy or for any other reason.
5. Subjects lost for follow-up/ failure to collect sufficient data for the assessment of study objectives and endpoints.
6. Any cases not covered by the protocol when further participation is deemed by the investigator as harmful to the subject.
7. Serious deviations from the protocol (see section Protocol Deviation).
8. Ineligible subjects erroneously enrolled into the study.
9. Pregnancy.

**Study, drug, dose and route of Administration, batch No.:**

**Brillia Health Cold-Flu Recovery**, orodispersible tablets.

Active substances: Lapine interferon gamma immune globulin – 0.006 g*, Lapine histamine immune globulin – 0.006 g*, affinity purified antibodies to CD4 - 0.006 g*

* applied onto lactose monohydrate as a mixture of three active water-alcohol dilutions of the substance - diluted

by $100^{12}$, $100^{30}$, $100^{50}$ times, respectively.

Excipients: lactose monohydrate, 0.267 g; microcrystalline cellulose, 0.03 g; magnesium stearate, 0.003 g.

Dosing regimen: Oral use. 1 tablet per intake. Within the first 8 tablets (1 tablet every 30 min in the first 2 hours, then additional 3 intakes with equal intervals), from day 2 to day 5 - 3 times daily.

The drug may be administered regardless of stomach fullness; the tablet should be held in mouth until completely dissolved.

The study used the drug batches **К221210/ К11181213**.

**Reference therapy: Oseltamivir** (**Tamiflu®):** 75mg twice daily after meal for 5 days.

**Basic therapy:** Throughout the study the subjects may receive therapy for influenza based on the treatment standards including antipyretics (at body temperature elevation > 38°C), vitamins, expectorants, mucolytics, vasoconstrictive nasal drops, where applicable - detoxication therapy except for antiviral, antihistamine, immunomodulating and other drugs regarded as forbidden.

**Forbidden concomitant treatment:**

15 days prior to enrollment and during the study (after signing informed consent form and screening initiation) the following drugs were not allowed:

1. Antiviral drugs (except for Brillia Health Cold-Flu Recovery and Oseltamivir Tamiflu®) prescribed during the study).
2. Interferon drugs and interferon inducers.
3. Antihistamine drugs.
4. Antibacterial drugs including sulfanylamide drugs.
5. Drugs known to previously cause allergic reactions to the subject.

**Treatment and follow-up duration:** In total, the subjects were followed in the study for seven days (screening – day 1, study therapy – 5 days, follow-up – 2 days).

**Statistical methods:**

**Evaluation of sample size** was carried out based on non-inferiority design (no clinically relevant superiority of reference drug Oseltamivir over test drug Brillia Health Cold-Flu Recovery).

1) Null hypothesis (H0): $Ef_{compare} - Ef_{test} \geq \delta$ (effect of reference drug is significantly superior to that of test drug).

2) Alternative hypothesis (H0): $Ef_{compare} - Ef_{test} < \delta$ (effect of test drug is insignificantly different from the one of reference drug or superior to it).

3) To test this pair of hypotheses, two-tailed z-test for proportion difference (z-test) or similar non-parametric statistical methods were used.

4) Clinically relevant difference “δ” was taken as 20% (i.e. Brillia Health Cold-Flu Recovery effect was supposed to be comparable to that of Oseltamivir if test drug effect is different from the one of the control drug by less than

20%). The range of clinical indiscernibility for comparison of temperature parameters was taken as 0.2° C; to evaluate the symptoms by 4-score scale – 0.5 scores; in other cases – 0.2 vs. the relevant value of reference drug being default value in statistical software SAS.

5) Power of statistical criteria "P=(1−β)" was taken as 80% (probability of correct rejection of null hypothesis is equal to 0.8).

6) Probability of type I error "α" < 5% was allowed (probability of erroneous acceptance of alternative hypothesis – < 0.05).

7) Statistical criteria used were two-sided due to lacking aposterior information on the effective superiority of one drug over the other.

8) Calculation of total sample size was based on the assumptions concerning expected effects on the first principal criterion declared in the protocol.

Based on the assumed effect, the minimum required sample size was 148 subjects and given the potential 10% withdrawal, 163 subjects should be enrolled.

Data treatment and all statistical calculations per protocol were made using statistical software SAS-9.3.

To compare the proportion of subjects, frequency analysis with Z-statistics were performed using the Wald method. Comparison of mean values were made using modified unpaired Student's test with plotting confidence intervals for the difference of mean values and calculation of significance of its difference from pre-established delta (margin). The Adaptive Holm method was used for multiple comparisons to monitor type I errors. Description of the results presents method-adjusted *p*-value (type I error).

According to ICH recommendations, to evaluate efficacy of the drug within the clinical non-inferiority study, ITT- and PP-analyses based on the results of Full analysis set and Per Protocol set, respectively, were performed.

**Number of subjects:**

In total, 161 subjects with verified influenza were enrolled and randomized (all the subjects enrolled, or *Total set*) including 81 – Brillia Health Cold-Flu Recovery group and 80 – Oseltamivir group. Number of subjects in *Total set* coincided with the number of "enrolled and randomized subjects receiving at least one dose of the study drug", this sample (n=161) was used to evaluate safety of study therapy (*Safety population*). Monitoring revealed that 4 subjects were enrolled erroneously, since they did not meet inclusion/non-inclusion criteria including 3 from the Brillia Health Cold-Flu Recovery group (due to administration of forbidden drugs on the day preceding enrollment) and 1 from the Oseltamivir group (ineligible subject); 1 subject from Oseltamivir group could not provide all data used for evaluation of the study endpoints. Except for these 5 subjects, all other (n=156) subjects comprised the *Full analysis set*; based on the results of therapy in this sample (n=78 in each group) *Intention to treat* [ITT] efficacy analysis was carried out.

Furthermore, 8 subjects had major deviations from the protocol including 3 from the Brillia Health Cold-Flu Recovery group, 5 from the Oseltamivir group; one subject from the Oseltamivir group required the drugs

forbidden for use. Therefore, the data from these 9 subjects were not included into the final (*Per Protocol* [PP]) efficacy analysis; PP sample included 147 subjects including 75 from the Brillia Health Cold-Flu Recovery group and 72 from the Oseltamivir group.

**Efficacy and safety assessment results:**

Therapeutic efficacy is presented by the results of ITT- and PP-analyses, the results being similar (results of PP-analysis are given in square brackets).

Subjects of both groups were comparable in terms of clinical and demographic characteristics. Average age of the study subjects was 34.7±12.1 years old, females − 65%, males - 35%. All subjects had pyretic fever and intoxication signs typical of influenza. Mean body temperature on day 1 was 38.2±0.4$^0$C [38.3±0.4$^0$C] in the Brillia Health Cold-Flu Recovery group and 38.3±0.4$^0$C [38.3±0.4$^0$C] in the Oseltamivir group; severity of intoxication signs − 18.8±6.2 [19.0±6.7] and 18.6±6.2 [18.6±6.3], respectively; respiratory symptoms were less pronounced (6 scores in both groups on average).

More than 30% of subjects had various concomitant diseases (majority ≥2) receiving antihypertensive drugs (ACE inhibitors, angiotensin receptor antagonists, beta-adrenoblockers, calcium channel blockers), diuretics, bronchodilators, statins, drugs for the treatment of thyroid diseases, etc. The subjects received allowed symptomatic drugs as required, i.e. antipyretics, decongestants, secretolytics and expectorants.

**Efficacy assessment results:**

Percentage of subjects with normal morning body temperature in the Brillia Health Cold-Flu Recovery group was 19 [19]% on day 2 (vs. 10 [10]% in Oseltamivir group) and 100 [100]% by the end of therapy (vs. 92 [92]% in Oseltamivir group; significant comparability using Wald analysis: $p<0.001$ [$p<0.001$]). Evening temperature by the end of day 4 was ≤37.0$^0$C in 68 [68]% subjects from Brillia Health Cold-Flu Recovery group (vs. 69 [72]% − from Oseltamivir group; $p=0.009$ [$p=0.03$]); by the end of day 5 body temperature was normalized in most subjects (85 [84]% vs.86 [88]%, respectively; $p=0.001$ [$p=0.004$]).

On day 7 of the follow-up, the symptoms of influenza including headache and other types of pain (muscle, joint, eye pain) were absent in 99 [100]% subjects in the Brillia Health Cold-Flu Recovery group and 100 [100]% in the Oseltamivir group; asthenic manifestations (weakness, sweatiness, malaise, drowsiness) − in 82 [83]%, 87 [88]%, 90 [91]%, 96 [96]% and 74 [75]%, 86 [86]%, 91 [92]%, 97 [99]% subjects, respectively. All intoxication symptoms were eliminated on day 7 in 60 [61]% subjects in the Brillia Health Cold-Flu Recovery group and 64 [64]% subjects in the Oseltamivir group (significant comparability using Wald analysis: $Z=1.9$[2.0]; $p=0.028$ [0.22]); catarrhal symptoms − in 83 [83]% and 77 [76]% subjects, respectively ($Z=3.9$ [2.0]; $p<0.001$ [0.021]). Proportion of "full convalescents" was 45 [47]% in the Brillia Health Cold-Flu Recovery group and [49]% in the Oseltamivir group ($Z=1.7$ [2.0]; $p=0.044$ [0.021]). Most clinical symptoms of influenza lasted for approximately 3 days and were not significantly different in the two groups.

Average duration of fever was 2.1±1.5 [2.1±1.4] days in subjects from the Brillia Health Cold-Flu

Recovery group and 2.3±1.6 [2.3±1.6] days − from the Oseltamivir group, intoxication signs − 2.7±2.2 [2.6±2.2] and 2.4±2.1 [2.4±2.1] days, respiratory catarrhal symptoms - 2.8±2.5 [2.7±2.5] and 2.6±2.6 [2.6±2.6] days, average duration of all influenza symptoms − 2.7±2.3 [2.6±2.3] and 2.5±2.2 [2.5±2.2] days, respectively. By day 3 of Brillia Health Cold-Flu Recovery therapy, average body temperature was 37.0±0.5$^0$C (ITT and PP-populations), remaining consistently below 37.0$^0$C in the next days of the follow-up. Body temperature reduction on day 3 as compared to the baseline values was comparable in both groups (ITT-analysis: $\Delta^0$=0.01; 95% CI < 0.14; t=−2.5; p=0.007; PP-analysis: $\Delta^0$=0.005; 95% CI < 0.14; t=−2.4; p=0.008). Severity of intoxication and respiratory syndromes tended to reduce along with fever. Total score of severity of intoxication signs on day 3 of therapy reduced two-fold − from 18.8±6.6 [19.0±6.7] (vs. 18.6±6.2 [18.6±6.3] in the Oseltamivir group) to 9.2±5.0 [9.2±5.1] (vs. 7.7±4.4 [7.8±4.3] respectively), by the end of therapy - to 2.4±2.9 [2.3±2.7] (vs. 2.0±2.5 [1.9±2.3] in the Oseltamivir group).

Mild catarrhal respiratory events (6.1±3.7 [6.1±3.7] and 5.9±3.7 [5.9±3.6] scores at the disease onset typical for influenza) were almost absent by the end of the study (1.3±1.5 [1.3±1.5] and 1.4±1.9 [1.4±1.8] scores in the group, respectively). Statistical analysis of parameters of influenza symptoms on days 3 and 7 of the follow-up evidenced comparability of the results of therapy between the two drugs.

Frequency of dosing of antipyretics on day 1 of the study (day 1 from influenza onset) was 0.65±0.48 [0.65±0.48] on average per one subject in the Brillia Health Cold-Flu Recovery group and 0.69±0.46 [0.72±0.45] − in the Oseltamivir group. In the next 2 days necessity of antipyretics was significantly reduced, being 0.19±0.40 [0.19±0.39] and 0.15±0.36 [0.15±0.36], respectively, on day 3 (significant comparability using Wald analysis: p=0.0044 [p=0.0043]).

Total average EQ5D score in the Brillia Health Cold-Flu Recovery group within 7 days modified almost two-fold being 5.4±0.8 [5.3±0.9] vs. baseline 9.4±1.9 [9.6±1.9] (Δ1-7=−4. [−4.3]) reflecting positive changes in quality of life of the study subjects. Similar parameters in the reference group were 5.5±0.9 [5.4±0.8] and 9.2±2.3 [9.4±2.2] scores, respectively (Δ1-7=−3.7 [−4.0]).

VAS results showed more than two-fold improvement in subjective evaluation of health status (in scores) in both groups (modification of baseline 42.1±18.4 [41.6±18.2] to 87.7±10.6 [87.7±10.6] by the end of therapy; Δ1-7=+45.6 [+46.1] and from 46.7±15.1 [46.2±15.4] to 87.8±11.4 [88.0±10.6]; Δ1-7=+41.1 [+41.8], respectively).

According to statistical analysis, positive changes in total EQ5D scores and health status scale were significantly comparable in both groups.

The Brillia Health Cold-Flu Recovery group did not show cases of aggravated disease including complications requiring antibiotics or hospitalization; all subjects who completed the study were at convalescence period or had evident (significant) improvement. In the Oseltamivir group 2 subjects had

secondary bacterial complications, including community-acquired pneumonia in one subject and acute maxillary sinusitis (highmoritis) in the other subject; both received antibiotic drugs.

The doctors evaluated the clinical effect of Brillia Health Cold-Flu Recovery as expressed since the drug administration resulted in recovery/significant improvement in all subjects. Average total score of "therapeutic efficacy" domain of CGI-EI scale was 3.5±0.5 [3.5±0.5] and was non-inferior to the efficacy of the Oseltamivir (3.7±0.5 [3.7±0.5] scores; $p<0.0001$ [$p<0.0001$]); average total score of Brillia Health Cold-Flu Recovery and Oseltamivir side effects were low (1.1±0.3 [1.1±0.3] and 1.1±0.4 [1.1±0.3], respectively), while the efficacy index was high (3.3±0.7 [3.4±0.7] and 3.5±0.8 [3.6±0.7] scores, respectively) and comparable between both groups ($p<0.0001$ [$p<0.0001$]).

**Safety assessment results**

Brillia Health Cold-Flu Recovery did not exert negative effects on vital signs of the subjects. Baseline tachycardia (average HR > 90 bpm) typical for an acute period of an infectious disease was eliminated throughout therapy and HR was within normal range during convalescence (on day 7 of the follow-up) in all study subjects (ITT and PP analysis findings).

In total, 15 AEs in 11 subjects were revealed in the Brillia Health Cold-Flu Recovery group, 16 AEs in 15 subjects in the Oseltamivir group. All AEs in Brillia Health Cold-Flu Recovery were mild, without definite (significant) association with the study therapy and in most cases (n=13) were modifications in laboratory tests revealed at repeated examination of the subjects. 6 AEs in Oseltamivir were moderate and 10 - mild. No cases of serious AEs or AEs with causal relationship with Brillia Health Cold-Flu Recovery have been revealed.

No data on Brillia Health Cold-Flu Recovery interactions with medicinal products used as concomitant therapy have been obtained including antipyretics and non-steroidal anti-inflammatory drugs, expectorants, broncholytics, antihypertensive drugs (ACE inhibitors, angiotensin receptor antagonists, beta-adrenolytics, calcium channel antagonists), diuretics, statins, drugs for the treatment of thyroid diseases. Co-administration of these drugs with Brillia Health Cold-Flu Recovery did not result in pharmacological incompatibility reactions, antagonistic or synergistic effect.

**Conclusions:**

1. Brillia Health Cold-Flu Recovery is an effective and safe drug for the treatment of influenza, its therapeutic efficacy is comparable with that of Oseltamivir (Tamiflu®).
2. Intensity and duration of fever, i.e. the main clinical marker of viremia and activity of infectious and inflammatory processes against Brillia Health Cold-Flu Recovery therapy were not different from those in the Oseltamivir group thus indirectly confirming similar antiviral efficacy of both drugs.
3. Brillia Health Cold-Flu Recovery;s effect initiated rapidly and after 3-day therapy most subjects had body temperature below $37.0^0$C. Average duration of fever period in subjects with influenza was about two days.

4. Along with fever, rapid and expressed therapeutic effect of Brillia Health Cold-Flu Recovery on the most marked influenza intoxication signs was observed, i.e. Headache and other types of pain (muscle, joint), asthenic and neurovegetative disorders (weakness, malaise, insomnia). Severity of intoxication syndrome on day 3 of therapy reduced two-fold.
5. Five-day course of Brillia Health Cold-Flu Recovery therapy demonstrated effects comparable to that of Oseltamivir, both in terms of individual symptoms and total clinical manifestations of influenza, while the terms of their elimination was less than 3 days. Percentage of "full convalescents" by the end of therapeutic course was significantly comparable between the groups.
6. The effect of Brillia Health Cold-Flu Recovery on influenza infection and its main manifestation, i.e. pyretic fever, resulted in rapid reduction of dosing frequency of antipyretic drugs required predominantly within the first day of therapy.
7. Brillia Health Cold-Flu Recovery administration ensuring adequate antiviral response prevented secondary bacterial complications typical of influenza.
8. Improved quality of life with Brillia Health Cold-Flu Recovery therapy was confirmed by significant positive changes in the total score of EQ5D and the objective health status scale.
9. Brillia Health Cold-Flu Recovery did not affect vital functions of the subjects and did not cause serious adverse effects. All adverse events recorded during the study were mild and were not definitely (significantly) associated with Brillia Health Cold-Flu Recovery.
10. No data demonstrating Brillia Health Cold-Flu Recovery interacting with medicinal products used as concomitant therapy have been obtained including antipyretics and non-steroidal anti-inflammatory drugs, expectorants, broncholytics, antihypertensive drugs (ACE inhibitors, angiotensin receptor antagonists, beta-adrenolytics, calcium channel antagonists), diuretics, statins, drugs for the treatment of thyroid diseases.
11. High total score of therapeutic activity against low adverse event frequency yielded efficacy indexes close to maximum ones (CGI-IE) comparable between Brillia Health Cold-Flu Recovery and Oseltamivir groups.
12. All subjects were 100% compliant and completed the study with convalescence or significant improvement of influenza.

**Date of report:** September 2014

**3. List of abbreviations**

BP – blood pressure ALT – alanine aminotransferase Anti-CD4 – antibodies to CD4

Anti-IFNγ – antibodies to interferon-gamma Anti-H – antibodies to histamine

ACE – angiotensin-converting enzyme AST – aspartate aminotransferase

VAS – visual analogue scale

WHO – World Health Organization GOST – RF State Standard

DBP – diastolic blood pressure CRF – case report form IFN – interferon

ADR – adverse drug reaction AE – adverse event

ARI – acute respiratory infection

SBP – systolic blood pressure SAE – serious adverse event BSR – blood sedimentation rate

FZ – Federal Law

HR – heart rate RR – respiration rate

CD – lymphocyte clusters of differentiation

CGI – Clinical Global Impression Scale

EMEA – European Medicines Agency (Agency involved in evaluation of medicines for their compliance with European Pharmacopeia requirements)

EQ5D – EUROQUAL (European Quality of Life Questionnaire)

FDA − Food and Drug Administration

GCP – Good Clinical Practice

ICH − International Conference on Harmonization (The International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)

IFN-γ – interferon-γ

ITT – Intention to treat (enrolled and randomized subjects intending to receive treatment, i.e. who received at least one dose of the study drug)

LLT − Lower-Level Terms (MedDRA).

MedDRA − Medical Dictionary for Regulatory Activities

PP – Per protocol (subjects who completed the study per protocol/fulfilled all protocol requirements)

SOC − System Organ Class (MedDRA)

Th – T-helper lymphocytes

**4. Ethical aspects**

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

**5. Principal investigators and administrative structure of the study**

**Principal investigators:**

1. Selkova Eugenia Petrovna, MD
2. Kostinov Mikhail Petrovich, MD, professor
3. Chukayeva Irina Ivanovna, MD, professor
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5. Fedorov Sergei Pavlovich, MD (test facility was not initiated)
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11. Chernogorova Marina Viktorovna, MD
12. Oseshnyuk Rodion Alexandrovich, MD (test facility was not initiated)
13. Chizhov Danila Alexandrovich
14. Barabashkina Anna Vladimirovna, MD
15. Alpenidze Diana Nodariyevna, MD

In total, 161 subjects with an Influenza diagnosis verified by rapid test (ITT, or *Total set*) including 81 in the Brillia Health Cold-Flu Recovery group and 80 in the Oseltamivir group were enrolled. The first subject was enrolled on February 28, 2011; the last subject terminated on April 21, 2014. *Full analysis set* included the data from 156 subjects; this sample (n=78 in each group) was used for *Intention to treat* [ITT] efficacy analysis. Final (*Per Protocol* [PP]) efficacy analysis included the data from 147 subjects including 75 – Brillia Health Cold-Flu Recovery group and 72 – Oseltamivir group.

**6. Introduction**

Influenza is characterized by high contagiousness, epidemic aggressiveness and mutagenicity of virus, severity of pathological process and dangerous complications. Annual seasonal influenza epidemics create serious load on healthcare services and result in serious harm to the economies of other countries. According to the World Health Organization (WHO), annual influenza epidemics account for approximately 3-5 million cases of severe diseases and 250,000-500,000 lethal cases globally [40].

Currently, A(H1N1) and A(H3N2) influenza A subtypes and B type are circulating among humans. Development and distribution of new hazardous porcine and avian flu subtypes (H5N1, H5N8, H7N9, H9N2) has

been noted which are capable of inducing extremely aggressive disease. Thus, about 200 cases of the disease have been revealed in Indonesia within several years, most of them being lethal [40]. In China, 458 cases of avian influenza A(H7N9) cases have been reported in 2013-2014 among humans, 175 of them being lethal, at that not all the ill subjects had been in contact with live birds [15].

Based on FluNet (a global tool for influenza virological surveillance covering National Influenza Centers and other national laboratories of 45 countries) as of the end of November, 2014, the main cause of influenza morbidity is virus A (82.5%) including A(H3N2) – 97.0%; A(H1N1)pdm09 – 2.9% and 1 A(H5) – 0.1; among B subtypes causing the disease in 17.5% cases - B-Yamagata (94.4%) is most commonly isolated currently [41]. Mutations result in modified virulence and resistance of the virus to the available anti-flu drugs. The data concerning unsuccessful therapy with Oseltamivir in subjects carrying pandemic virus A(H1N1)pdm09 in developed countries [19, 20, 26, 27, 35] have been published.

Therefore, the drugs capable of affecting the proper universal mechanisms of antiviral defense of a macroorganism are vital, allowing to surpass drug resistance and cope with viral infection. These drugs include the release-active drug Brillia Health Cold-Flu Recovery, containing antibodies to interferon-gamma (anti-IFNγ), CD4 (anti-CD4) and histamine (anti-H). Efficacy of the drug associated with specific release activity is mediated by the manufacturing technique [18]. Combination of active components influences various links of antiviral defense due to induction of endogenous interferon and its effect on its receptors, regulation of activity of CD4+ cells including antigen-presenting (macrophages and dendrite cells) and T-helpers (Th1 and Th2) playing a vital role in antiviral immune response [20, 25, 37, 38, 39]. Nonspecific antiviral activity of the first two components is supplemented by the effects of anti-H affecting the intensity of respiratory inflammation. Combination of anti-IFN-γ+anti-CD4+anti-H allows to use Brillia Health Cold-Flu Recovery as a universal antiviral, pathogenetic and symptomatic drug for the treatment of influenza and other acute respiratory viral infections (ARVI).

A number of experimental studies designed to investigate specific activity and toxicity demonstrated that combined application of the components of the complex drug Brillia Health Cold-Flu Recovery was associated with reinforced antiviral activity of the drug components. Standard models demonstrated antiviral effects against influenza A viruses (A/Aichi/2/68 (H3N2); H3N8, Equi2/Miami/1/63, ATCC VR317); vesicular stomatitis virus, respiratory syncytial virus, rhinovirus, etc. [31-33, 36-38].

Numerous clinical studies of Brillia Health Cold-Flu Recovery verified its efficacy and safety in the treatment of influenza and other ARVI [1, 4-14, 16]. Brillia Health Cold-Flu Recovery used according to the therapeutic scheme demonstrated to normalize increased body temperature, intoxication and catarrhal symptoms significantly faster as compared to Placebo. Brillia Health Cold-Flu Recovery prevented bacterial complications requiring antibiotic therapy. The studies demonstrated a high safety profile of Brillia Health Cold-Flu Recovery in subjects with acute respiratory infections when it was used according to the therapeutic scheme for five days.

The current clinical study evaluated efficacy and safety of Brillia Health Cold-Flu Recovery in the treatment of influenza in adult subjects. Comparison of the therapeutic activity of the drug with Oseltamivir

(Tamiflu®) was carried out.

**7. Objectives, primary and secondary efficacy criteria and safety Criteria**

**Study objectives:**

1. To evaluate the clinical efficacy of Brillia Health Cold-Flu Recovery in the treatment of influenza.
2. To evaluate the safety of Brillia Health Cold-Flu Recovery in the treatment of influenza.
3. To compare efficacy of Brillia Health Cold-Flu Recovery and Oseltamivir in the treatment of influenza.

**Safety criteria:**

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

**Primary efficacy criterion:**

1. Proportion of subjects with normalized body temperature (≤ 37.0ºC) by the end of day 1, 2, 3, 4, 5 of therapy.

**Secondary efficacy criteria:**

1. Proportion of subjects having their clinical manifestations eliminated by day 7 of the follow-up.
2. Terms of influenza symptom elimination in groups.
3. Intensity of clinical manifestations of influenza (body temperature, intoxication signs, catarrhal symptoms in scores) on days 1, 3 and 7 of the follow-up.
4. Changes in the number of intakes of antipyretic drugs on days 2, 3, 4 and 5 of therapy.
5. Changes in total score of quality of life questionnaire by the end of therapy vs. baseline (Day 7 vs. Day 1).
6. Proportion of subjects with exacerbation of the disease (development of complications requiring antibiotics and hospitalization).

**8. Study design**

Study design - multicenter, open-label, comparative, randomized, parallel-group study.

The study enrolled outpatient subjects of both genders aged 18-60 years old with diagnosis of influenza verified by rapid test (isolation of influenza virus antigens in nasal swabs using immunological test) seeking medical advice during seasonal morbidity within 24 hours of the manifestation of the first symptom. The study enrolled only the subjects with axillary temperatures (measured by electronic thermometer) above 37.802

C at the time of examination. In addition to fever, the subject was to have at least one catarrhal symptom (cough, rhinitis, sore throat) and one general symptom (myalgia, chill/sweatiness, malaise, weakness, headache).

The first visit was made at the clinical site or at the subject's home. The subject signed an information sheet (informed consent form) to participate in the clinical study. Based on the screening results (past medical history, thermometry, objective examination, rapid influenza diagnostics) the physician determined the eligibility of the subject. Quality of life questionnaires EUROQUAL (EQ5D) and health status visual analogue scale (VAS) were filled, laboratory tests were performed (complete blood analysis, urinalysis, biochemistry) and females of childbearing potential underwent pregnancy tests.

If the subject met the inclusion criteria and did not satisfy any non-inclusion criteria at visit 1 (Day 1), the subject was enrolled into the study and randomized into one of the two groups: group 1 received Brillia Health Cold-Flu Recovery using therapeutic scheme for 5 days; group 2 – oseltamivir (Tamiflu®) - also for 5 days.

The subject at visit 1 was given a diary in which he was to note axillary temperature in the morning and in the evening, administration of antipyretic drugs as indicated; the subject was instructed on the diary filling.
The subject was examined for 7±1 days (screening – 1 day, treatment - 1-5 days, follow-up - up to 2 days). In total the subjects/physicians made 3 visits (days 1, 3 and 7) during the treatment and follow-up period. At visits 2 and 3 the investigator performed objective examination, monitored the prescribed and concomitant therapy, evaluated therapeutic safety and checked the subject's diary. Furthermore, at visit 3 compliance was evaluated, quality of life EQ5D and VAS questionnaires were repeatedly filled, samples were collected for repeated laboratory tests (complete blood analysis, urinalysis, biochemistry) and the physician filled a clinical global impression scale (CGI-EI).

Administration of symptomatic therapy and therapy of concomitant diseases was allowed during the study except for the drugs specified in the section forbidden concomitant treatment.

**Schedule of Study Procedures**

| **Procedure/visit** | Visit 1 | Visit 2 | Visit 3 |
|---|---|---|---|
| Singing ICF | + | | |
| Objective examination | + | + | + |
| Pregnancy test | + | | |
| Collection of the past medical history | + | | |
| Recording influenza symptoms | + | + | + |
| Inclusion/exclusion criteria | + | | |
| Recording concomitant therapy | + | + | + |
| Randomization and prescription of study therapy | + | | |
| Laboratory tests | + | | + |
| Collection of nasal smears and isolation of influenza agent antigens | + | | |
| Drug issue | + | | |
| Accounting and return of the drug, compliance | | | + |
| Diary issue | + | | |
| Return and evaluation of correctness diary filling | | + | + |

| | | | |
|---|---|---|---|
| Filling quality of life questionnaire (EQ5D) | + | | + |
| Evaluation of therapeutic safety | | + | + |
| Filling CGI-EI scale by the investigator | | | + |

**9. Screening, randomization, blinding and early withdrawal**

**9.1 Inclusion criteria**

1. Age between 18 and 60 years old inclusively.
2. Subjects with body temperature >37.8°C at the visit and at least one catarrhal symptom (cough, rhinitis, sore throat) and one intoxication symptom (myalgia, chill/sweatiness, malaise, weakness, headache) during seasonal morbidity.
3. Diagnosis of influenza verified by rapid diagnostics (isolation of influenza antigens in nasal epithelium verified by immunological test QuichVue).
4. Possibility to initiate therapy within 24 hours from the first symptoms of influenza.
5. Availability of signed informed consent to participate in the study.

**9.2 Non-inclusion criteria**

1. Age under 18 or over 60 years old.
2. Suspected invasive bacterial infection or severe disease requiring antibacterial drugs (including sulfanylamides).
3. Vaccination against influenza prior to epidemiological season.
4. Polyvalent allergy in the past medical history.
5. Allergy/intolerability of any of the study drug components.
6. Exacerbation or decompensation of chronic diseases affecting the subject's ability to participate in the clinical study.
7. Chronic renal failure.
8. Administration of drugs specified in the section "Forbidden concomitant therapy" for 15 days prior to enrollment.
9. Pregnancy, breast-feeding, unwillingness to use contraception during the study.
10. Consumption of narcotics, alcohol > 2 alcohol units per day, mental diseases.
11. Subjects who, according to the investigator, shall not follow the requirements during the study or follow the dosing regimen.
12. Participation in other clinical studies within 1 month prior to enrollment in the present trial.
13. The subject belongs to the study personnel of the site directly involved in the study or a close relative of the investigator. Close relatives include spouses, parents, children or brothers (sisters) regardless of whether they are biological or adopted.

**9.3 Screening and enrollment**

After signing the informed consent their eligibility was verified taking into account all inclusion/non-inclusion criteria.

Visit 1 included a general clinical examination, rapid diagnostics of influenza and laboratory examination.

1. General clinical examination:

- questioning;
- collection of the past medical history;
- recording demographic data;
- objective examination including evaluation of clinical manifestations of influenza - axillary temperature in degrees C, intoxication symptoms and catarrhal symptoms in scores 0-3 (Appendix 1).

Measurement of body temperature was taken in the armpit using an electronic thermometer provided by the study sponsor for each subject.

Recording clinical manifestations of influenza at objective examination by the physician included evaluation of intoxication signs (headache, chill, sweatiness, weakness, malaise, muscle pain, joint pain, eye pain, photophobia and somnolence) and catarrhal symptoms (nasal congestion, nasal discharge, sneezing, sore throat, cough).

Results of objective examination were recorded in source documentation. The list of influenza symptoms and evaluation of their severity are included into CRF (Appendix 1).

Based on intensity of each symptom (no symptom - 0 scores; mild - 1 score; moderate - 2 scores, severe - 3 scores) at subsequent statistical data treatment, total influenza severity score was calculated (see Appendix 1).

2. Rapid influenza diagnostics.

To verify influenza, immunological method of rapid diagnostics of influenza A and B - isolation of influenza antigens in nasal epithelium was carried out. Rapid diagnostics of influenza was performed to enroll the subject into the study.

3. Laboratory examination.

- Complete blood analysis: hemoglobin, erythrocytes, packed cell volume, platelets, leukocyte count and leukogram, BSR.
- Biochemistry: ALT, AST, creatinine, bilirubin.
- Urinalysis: Relative urine density, color, cellular composition, protein, glucose, ketone bodies, salts and other parameters.

Laboratory tests were performed to evaluate therapeutic safety.

In the case of a home visit, blood was sampled using a vacutainer with subsequent transportation to local laboratory in a thermal container.

**9.4 Randomization**

By the end of screening and enrollment at Visit 1, the subjects were randomized into two groups.

Group 1 (n=81; Brillia Health Cold-Flu Recovery) received the test drug using the following scheme on day 1 of therapy - 8 doses (in the first 2 hours - 1 tablet every 30 minutes, then additional 3 times with equal intervals), from day 2 to day 5 − 1 tablet 3 times daily. The drug was administered without a meal, the tablet was held in the mouth until complete dissolution.

Group 2 (n=80; Oseltamivir) received Oseltamivir (Tamiflu®) at 75 mg twice daily after meal for 5 days.

To maintain confidentiality, each subject was assigned to an identification number consisting of a two-digit number of the clinical site, three-digit screening number of the subject assigned in chronological order and 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.

The study group was chosen randomly using random number generation based on the study group ratio 1:1. Prior to the study, a randomization sheet was made specifying randomization numbers. The study therapy (Brillia Health Cold-Flu Recovery and Oseltamivir) was indicated opposite to each number. Block randomization with block size 10 was used.

Each subject may be randomized only once during the study. Packs with the drug issued to withdrawn subjects were not used anymore. A special interactive system was used for randomization ensuring correct distribution of the subjects by groups and correct prescription of the study therapy.

The test drug (Brillia Health Cold-Flu Recovery) was supplied in boxes, packs and vials specifying randomization number generated by the interactive system.

CRF was filled for each subject reflecting inclusion and non-inclusion criteria, clinical signs of the disease including score rating of the symptoms of the disease by influenza symptom scale (Appendix 1), quality of life EQ5D questionnaire (Appendix 2), laboratory parameters, therapy, changes in clinical parameters and adverse effects.

**9.5 Exclusion (early withdrawal) criteria**

The subject was able to terminate the study early in the following cases:

1. Inability or refusal of the subject to follow the protocol.
2. Necessity of the drugs not allowed within the study.
3. AEs requiring drug discontinuation.
4. Subject’s wish to terminate the study due to therapeutic inefficacy or for any other reason.

5. Inability to collect all data for the subjects used for evaluation of the study endpoints.
6. Cases not stipulated by the protocol where the investigator deems that further participation of the subject will be hazardous for him.
7. Major protocol deviation (see Protocol deviations).
8. Erroneous enrollment of non-eligible subject.
9. Pregnancy.

**9.5.1 Protocol deviations**

Generally, any protocol deviation may be only accepted in the case that it is made for safety reasons and for the sake of the subject, in case of force-majeure events and after written confirmation from the Sponsor and provided notification of the Ethics committee. Any protocol deviation was clearly described in the source documentation.

Major protocol deviations resulting in invalidity of the data for analysis were as follows:

1. Enrollment of the subject not meeting inclusion criteria / having one or more non-inclusion criteria; such subjects were 4 including 3 from Brillia Health Cold-Flu Recovery group (administration of forbidden drugs within the day preceding enrollment) and 1 - from Oseltamivir group (ineligible subject);
2. Inability to collect all data used for evaluation of the study endpoints (1 subject from Oseltamivir group);
3. Administration of forbidden drugs and treatment methods during the study (9 subjects in total, including 3 - from Brillia Health Cold-Flu Recovery group and 6 - from Oseltamivir group);
4. Deviation from the next visit date by more than 1 day;
5. Increase or decrease in the study drug dosing by ≥ 25%;

The subjects not meeting inclusion/non-inclusion criteria (3 − Brillia Health Cold-Flu Recovery and 1 - Oseltamivir) and the subject from which all data used for evaluation of the study endpoints could not be collected (1 subject from Oseltamivir group) were not included into *Full Analysis Set*, their data were not used in ITT-analysis (non-ITT, n=5). In total 14 subjects were with major protocol deviations, their data was excluded from PP analysis (non-PP, n=14).

Minor protocol deviations could reduce data validity for analysis, however, it was performed taking such deviations into account. Minor protocol deviations: minor errors when filling the study-related documents; other deviations not referring to major ones.

**10. Test drug**

**10.1 Description of the drug**

**Brillia Health Cold-Flu Recovery,** orodispersible tablets containing Lapine interferon gamma immune globulin – 0.006 g*, Lapine histamine immune globulin – 0.006 g*, affinity purified antibodies to CD4 - 0.006 g*

* applied onto lactose monohydrate as a mixture of three active water-alcohol dilutions of the substance - diluted by $100^{12}$, $100^{30}$, $100^{50}$ times, respectively.

Excipients: lactose monohydrate 0.267 g, microcrystalline cellulose 0.03 g, magnesium stearate 0.003 g.

The drug should be taken without meals. 1 tablet per intake.

The tablet should be held in mouth until complete dissolution.

The drug is manufactured in the form of flat-cylinder shape, scored white to off-white tablets with a smooth homogeneous surface.

The drug was supplied to the sites in vials (with tamper-evident cap) containing 30 tablets. The vials had a label specifying the name, logo and contact information of the manufacturer, name of the drug, formulation and number of tablets per vial, recommended storage conditions, batch No. and shelf life, "For use in clinical studies only", dosing scheme, randomization No. of the subject. Brillia Health Cold-Flu Recovery batches **К221210/ К11181213** were used.

Reference group comprised of the subjects receiving placebo.

**10.2 Treatment scheme**

Brillia Health Cold-Flu Recovery was prescribed using the following scheme: on day 1 of therapy – 8 tablets (in the first 2 hours - 1 tablet every 30 minutes, then additional 3 times with equal intervals), from day 2 to day 5 − the drug should be administered 3 times daily.

The first dose of the drug was administered in the presence of the investigator.

Treatment period - 5 days.

**10.3 Previous and concomitant therapy**

Subjects of both groups could receive symptomatic therapy of influenza based on the routine treatment standard including antipyretics as indicated (at body temperature increase > $38^0$C), vitamins, expectorants, mucolytics, vasoconstrictive nasal drops as indicated - detoxification therapy.

Other drugs not included on the list of forbidden ones could be used.

15 days prior to screening and throughout the study (after signing information sheet (informed consent form) and screening onset) the following drugs were not allowed:

1. Antiviral drugs except for Brillia Health Cold-Flu Recovery and Oseltamivir (Tamiflu®) prescribed within the study.
2. Interferon drugs and interferon inducers.
3. Antihistamine drugs.
4. Antibacterial drugs including sulfanylamide drugs.

5. Drugs previously causing allergic reactions in the subject

**11. Statistical methods**

Data treatment and all statistical calculations under the protocol were made using statistical software SAS-9.3[1].

**11.1 Evaluation of sample size**

Evaluation of sample size for efficacy analysis was performed using non-inferiority design (absence of clinically relevant superiority of reference drug Oseltamivir over test drug Brillia Health Cold-Flu Recovery).

1) Null hypothesis (H0): $Ef_{compare} - Ef_{test} \geq \delta$ (effect of reference drug is significantly superior than the one of test drug) where $Ef_{compare}$ – reference drug efficacy parameter, $Ef_{test}$ – test drug efficacy parameter, $\delta$ – clinical insignificance range.

2) Alternative hypothesis (HA): $Ef_{compare} - Ef_{test} < \delta$ (effect of test drug is insignificantly different from the one of reference drug or whatever superior), at that such inequality should be made for the whole confidence interval used to assess the difference in $Ef_{compare} - Ef_{test}$ [23, 24].

3) To test this hypothesis, two-tailed z-test was used for the difference of proportions (z-test) or similar methods of nonparametric statistics.

4) Value of clinically relevant difference "δ" was taken as 20% (i.e. Brillia Health Cold-Flu Recovery effect was supposed to be comparable to that of Oseltamivir, if the effect of test drug is difference from the one of reference drug by more than 20%). δ value in this study, i.e. the value of clinical insignificance range was equal to:

a. for comparison of temperature parameters – 0.2° C;

b. for evaluation of symptoms using 4-score scale – 0.5 scores;

c. in other cases - 0.2 from the relevant value of reference drug being default value in statistical software SAS.

5) Power of statistical criteria "$P=(1-\beta)$" was taken as equal to 80% (probability of correct rejection of null hypothesis is equal to 0.8).

6) Probability of type 1 error "α" was admitted < 5% (probability of erroneous acceptance of alternative hypothesis – < 0.05).

7) Utilized statistical criteria were two-sided due to the absence of aposterior information on superiority of the effect of one drug over the other.

8) Calculation of total sample was based on assumption of expected effects on the first main efficacy criterion declared in the present protocol.

Based on the fact that the estimated proportion of subjects with decreased body temperature to 37.0ºC after one day of therapy with Oseltamivir is 81% (John J. et al., 2000) [30], to ensure one-sided evaluation of proportion

difference at 95% level of confidence (5% level of significance), each group should include at least 74 subjects, i.e. at least 148 subjects should sign informed consent.

Taking into account potential withdrawal after signing informed consent and about 10% subjects during the treatment, 163 subjects in total should be enrolled.

**11.2 Peculiarities of statistical analysis**

1. Statistical treatment of data in equivalence design included two principal methods:

   a. To compare proportions of the subjects, frequency analysis was used with calculating Z-statistics using the Wald method;

   b. Comparison of mean values was made using modified two-sample Student's test plotting confidence intervals for the differences of mean values and calculation of significance of differences from the pre-established margin.

2. In all cases where multiple comparisons were made, the adaptive Holman method was used to control type I error. In all cases, adjusted p-value (type I error) is presented in the description of the results.
3. According to ICH recommendations for the drug efficacy analysis evaluated in the non-inferiority clinical study, both types of analysis (ITT and PP) should be used, since Full analysis set data (in such studies) is not generally conservative and its role should be considered with great attention [34]. Given these recommendations, the results of statistical analysis (ITT and PP) in the report are described for two samples (Full analysis set and Per Protocol set) simultaneously except for the figures based on a more relevant design of comparability of the PP sample.
4. Missing temperature values were replaced with average ones throughout the whole set (Brillia Health Cold-Flu Recovery+Oseltamivir) within the day or time of the day analyzed.
5. Missing values, except for body temperature, were replaced with similar values recorded at the previous visit or on the day preceding the day of treatment (LOCF).
6. If such value was the very first and no preceding data was available, it was replaced by the average one throughout the whole set (Brillia Health Cold-Flu Recovery+Oseltamivir) including body temperature values within the day or time of the day analyzed.
7. Intensity of fever in scores as a symptom was determined using the following scheme:

   a) 0 score – temperature $\leq$ 37.0°C;

   b) 1 score – temperature > 37.0°C and up to 37.9 inclusively;

   c) 2 scores - temperature > 38.0°C and up to 38.9 inclusively;

   d) 3 scores - temperature $\geq$ 39.0°C.

8. Duration of the symptom was determined by the investigator who recorded presence/absence of the symptom at objective examination of the subject on days 1, 3 and 7 of the follow-up. Since there were

three visits in total, maximum duration was 7 days if the symptom was still observed at visit 3. Duration was 3 days if the symptom was present at visit 2 (day 3 of the follow-up) but absent at visit 3; one - if noted at visit 1 (day 1 of the follow-up) and absent at visit 2; null duration was determined as no symptom, both at visit 1 and subsequent visits.

**11.3 Data presentation**

All variables are presented as descriptive statistics. Numerical data is presented as mean values, median, standard deviation, 25% and 75% quartiles and maximum and minimum values. Extreme values (outliers) were analyzed additionally. The data was grouped by study groups and follow-up terms. Ordinary and nominal data is presented as frequency tables individually by study groups and follow-up terms.

**12. Data quality assurance**

All clinical procedures performed according to the report are in accordance with Good Clinical Practice in the European GCP Guidelines.

Study monitoring was performed by authorized sponsor's representative who monitored the study course and made regular visits to the clinical sites from the initiation until the end of the clinical study. During the visits to the clinical sites data verification between medical records and filled CRFs were performed.

The investigators provided the authorized sponsor's representative with access to baseline data (case histories, results of clinical and laboratory studies, subjects' diaries, questionnaires, study drug distribution log) coordinating the plans and course of the current follow-ups.

**13. Main characteristics of subject samples**

In total 161 subjects with an Influenza diagnosis verified by rapid test (ITT, or *Total set*) including 81 in Brillia Health Cold-Flu Recovery group and 80 – in Oseltamivir group were enrolled.

The number of the subjects from the total set coincided with the number of "enrolled and randomized subjects receiving at least one dose of the study drug", this sample was used to evaluate safety of the study therapy (*Safety population*).

Out of all subjects enrolled, 4 subjects were included erroneously including 3 - Brillia Health Cold-Flu Recovery group (due to administration of forbidden drugs the day preceding enrollment) and 1− Oseltamir group ("ineligible subject"); 1 subject from the Oseltamivir group did not allow the collection of all data used for evaluation of the study endpoints. Except for these 5 subjects, all other (n=156) comprised a *Full analysis set*; based on therapy results in this set (n=78 in each group) *Intention to treat* [ITT] efficacy analysis was carried out.

Monitoring revealed that 8 subjects had major deviations from the protocol including 3 - from the Brillia Health Cold-Flu Recovery group, 5 - from the Oseltamivir group; one subject from the Oseltamivir group required the drugs forbidden for use. Therefore, the data from these 9 subjects was not included into final efficacy analysis (*Per Protocol* [PP]); PP-analysis set was comprised by 147 subjects including 75 – Brillia Health Cold-Flu Recovery group and 72 – Oseltamivir group.

Scheme of enrollment/exclusion (movement) of the subjects during the clinical study is presented below in Figure 13.

161 subjects with a diagnosis of influenza verified by a rapid diagnostic test were enrolled and randomized.

**Randomization**

Brillia Health Cold-Flu Recovery: n=81

Oseltamivir n=80

**Study termination**

Brillia Health Cold-Flu Recovery:

Excluded due to erroneous inclusion, Non-ITT n=3

Excluded due to major protocol deviations, Non-PP n=3

Oseltamivir:

Excluded due to erroneous inclusion, Non-ITT n=2

Excluded due to major protocol deviations, Non-PP n=6

**Analysis:**

Brillia Health Cold-Flu Recovery:

Analyzed intention-to-treat n=78

Analyzed per-protocol n=75

Oseltamivir:

Analyzed intention-to-treat n=78

Analyzed per-protocol n=72

**Fig.13. Subject movement within the study**

### 13.1 Demographic and anthropometric parameters

Average age of the study subjects was 34.7±12.1 years, the range of age variations was from minimum 18 years to maximum 59 years old. Both groups (Brillia Health Cold-Flu Recovery and Oseltamivir) were not significantly different in terms of age. Most subjects were females (see Table 13.1.1).

**Table 13.1.1: Demographic and anthropometric parameters**

| Parameter | Group | | Statistics |
|---|---|---|---|
| | | | |
| Brillia Health Cold-Flu | Oseltamivir | Total | |

| | | | | |
|---|---|---|---|---|
| Age, years | | | | |
| Total Set [81/80] | | | | |
| ITT [78/78] | 34.5±11.6 | 34.9±12.6 | 34.7±12.1 | t=0.2; p=0.84 |
| PP [75/72] | 34.2±11.7 | 35.0±12.7 | 34.6±12.2 | t=0.41; p=0.68 |
| Non-ITT+Non-PP | 34.4±11.7 | 35.5±12.5 | 34.9±12.1 | t=0.58; p=0.56 |
| [6/8] | 36.3±11.6 | 29.1±11.8 | 29.1±11.8 | t=−1.14; p=0.28 |
| Weight, kg | | | | |
| Total Set [81/80] | | | | |
| ITT [78/78] | 72.1±12.8 | 72.4±14.5 | 72.3±13.6 | t=0.16; p=0.88 |
| PP [75/72] | 72.2±13.0 | 72.4±14.7 | 72.3±13.8 | t=0.08; p=0.94 |
| Non-ITT+Non-PP | 72.2±13.3 | 73.3±14.8 | 72.7±14.0 | t=0.44; p=0.66 t=-1.32; p=0.21 |
| [6/8] | 70.2±3.8 | 65.0±8.9 | 67.2±7.4 | |
| Height, cm | | | | |
| Total Set [81/80] | | | | |
| ITT [78/78] | 169.7±6.9 | 168.9±7.0 | 169.3±7.0 | t=-0.76; p=0.45 t=-0.94; p=0.35 t=-0.84; p=0.40 t=0; p=1.0 |
| PP [75/72] | 169.7±6.9 | 168.7±7.0 | 169.2±6.9 | |
| Non-ITT+Non-PP | 169.6±6.9 | 168.6±7.0 | 169.1±6.9 | |
| [6/8] | 171.0±7.6 | 171.0±7.8 | 171.0±7.4 | |
| Gender, n (%) | | | | |
| Total Set [81/80] | | | | |
| Males | 32 (40) | 25 (31) | 57 (35) | $\chi^2$=1.2; p=0.27 |
| Females | 49 (60) | 55 (69) | 104 (65) | |
| ITT [78/78] | | 24 (31) | 55 (35) | $\chi^2$=1.4; p=0.24 |
| Males | 31 (40) | | | |
| Females | 47 (60) | 54 (69) | 101 (65) | |
| PP [75/72] | | 23 (32) | 53 (36) | $\chi^2$=1.03; p=0.31 |
| Males | 30 (40) | | | |
| Females | 45 (60) | 49 (68) | 94 (64) | |
| Non-ITT+Non-PP | | | | |
| [6/8] | | | | |
| Males | 2 (33) | 2 (25) | 4 (29) | p=1.0 |
| Females | 4 (67) | 6 (75) | 10 (71) | |

*Note*. ITT – set for ITT-analysis; PP – set for PP-analysis.

Hereinafter square brackets in tables specify the number of the subjects (n) in two groups [Brillia Health Cold-Flu Recovery/Oseltamivir]; mean values are presented as Mean±SD.

Continuous data were analyzed using Student's test, categorical data - using chi-square test and exact Fisher's test.

Statistical analysis comparing demographic and anthropometric parameters using Student's test demonstrated that the subjects of Brillia Health Cold-Flu Recovery group were not significantly different from Oseltamivir group in terms of average age, weight and height (ITT and PP sets). Frequency analysis ($\chi 2$ test and exact Fisher's test) did not reveal relevant differences in terms of gender between Brillia Health Cold-Flu Recovery and Oseltamivir groups (Table 13.1.1). Anthropometric and demographic characteristics of the subjects excluded from ITT-analysis (Non-ITT) and PP-analysis (Non-PP) were within the values of the subjects whose data were included into both efficacy analyses (ITT and PP).

**13.2 Clinical manifestations of influenza**

Acute onset of the disease, increased body temperature up to febrile values, prevailing intoxication syndrome over catarrhal within the first day of the disease typical for influenza symptom complexes [2, 3] were noted in most of the subjects enrolled. Clinical diagnosis of influenza was verified in all subjects by immunological rapid diagnostics.

All subjects were enrolled within the first 24 hours from the first symptoms of influenza. Mean body temperature on day 1 for ITT subjects was 38.2±0.4$^0$C in Brillia Health Cold-Flu Recovery group and 38.3±0.4$^0$C in Oseltamivir group; for PP − 38.3±0.4$^0$C in each group (Table 13.1.2).

**Table 13.1.2: Severity of clinical symptoms of influenza at enrollment**

| Parameter | Group | | Statistics |
|---|---|---|---|
| | Brillia Health Cold-Flu Recovery | Oseltamivir | |
| Body temperature, $^0$C | | | |
| Total Set [81/80] | 38.2±0.4 | 38.3±0.4 | t=0.36; p=0.72 |
| ITT [78/78] | 38.2±0.4 | 38.3±0.4 | t=0.38; p=0.70 |
| PP [75/72] | 38.3±0.4 | 38.3±0.4 | t=0.37; p=0.71 |
| Non-ITT+Non-PP [6/8] | 37.9±0.2 | 38.0±0.4 | t=0.27; p=0.79 |
| Clinical intoxication signs (average total score by 10 symptoms) | | | |
| Total Set [81/80] | 18.7±6.5 | 18.5±6.2 | t=-0.18; p=0.86 |
| ITT [78/78] | 18.8±6.6 | 18.6±6.2 | t=-0.19; p=0.85 |
| PP [75/72] | 19.0±6.7 | 18.6±6.3 | t=-0.33; p=0.74 |
| Non-ITT+Non-PP [6/8] | 14.3±1.5 | 16.9±4.3 | t=1.55; p=0.15 |
| Clinical manifestations of catarrhal symptoms (average total score by 5 symptoms) | | | |
| Total Set [81/80] | 6.0±3.7 | 5.9±3.7 | t=-0.27; p=0.79 |
| ITT [78/78] | 6.1±3.7 | 5.9±3.7 | t=-0.35; p=0.73 |
| PP [75/72] | 6.1±3.7 | 5.9±3.6 | t=-0.37; p=0.71 |
| Non-ITT+Non-PP [6/8] | 4.3±2.3 | 5.3±4.9 | t=0.42; p=0.68 |

*Note.* The results were presented as Mean ± SD; the data were analyzed using Student's test.

Intoxication signs were observed in all subjects, most of them complained of moderate or intensive (severe) headache, chill, weakness, muscle pain and malaise. Mean severity of intoxication signs according to examination findings at visit 1 was approximately 19 scores: 18.8±6.2 in Brillia Health Cold-Flu Recovery group and 18.6±6.2 in Oseltamivir group (ITT); 19.0±6.7 and 18.6±6.3, respectively (PP). Respiratory syndrome was more commonly observed with moderate symptoms with nasal congestion and sore throat prevailing. Intensity of respiratory symptoms was also almost identical in both groups being 6 scores on average.

Statistical analysis using Student's test indicated that both groups did not have significant differences in terms of baseline fever and other clinical manifestations of influenza (ITT and PP analysis data) (Table 13.1.2). Intensity of clinical manifestations of the disease (intoxication and catarrhal symptoms in subjects excluded from ITT and PP analyses (Non-ITT +Non-PP) was slightly lower associated with a milder baseline administration of forbidden anti-influenza drugs within the preceding day; that is why the subjects were considered to be "erroneously enrolled into the study" or "having major protocol deviations" and were excluded from ITT and PP analyses. However, due to a small number in Non-ITT +Non-PP sets in each group (Brillia Health Cold-Flu Recovery [n=6] and Oseltamivir [n=8], statistical analysis of their values to compare them with ITT and PP has low power, therefore it has not been presented.

**13.3 Concomitant diseases and therapy of the study subjects**

More than 30% of study subjects had various concomitant diseases. A vast majority of them had from 1 to 4 clinical diagnoses, single subjects had > 5 chronic diseases (Table 13.1.3).

**Table 13.3.1: Distribution of subjects by the number of concomitant diseases**

| Number of concomitant diseases | Total Set | | ITT | | PP | | Non-ITT + Non-PP | |
|---|---|---|---|---|---|---|---|---|
| | Brillia Health Cold-Flu Recovery (N=81) | Oseltamivir (N=80) | Brillia Health Cold-Flu Recovery (N=78) | Oseltamivir (N=78) | Brillia Health Cold-Flu Recovery (N=75) | Oseltamivir (N=72) | Brillia Health Cold-Flu Recovery (N=6) | Oseltamivir (N=8) |
| 1 disease | 13 (50) | 12 (41) | 12 (50) | 12 (44) | 12 (50) | 12 (44) | 1 (50) | 0 |
| 2 diseases | 4 (15) | 6 (21) | 3 (13) | 5 (19) | 3 (13) | 5 (19) | 1 (50) | 1 (50) |
| 3 diseases | 2 (8) | 3 (10) | 2 (8) | 2 (7) | 2 (8) | 2 (7) | 0 | 1 (50) |
| 4 diseases | 3 (12) | 4 (14) | 3 (13) | 4 (15) | 3 (13) | 4 (15) | 0 | 0 |
| 5 diseases | 0 | 1 (3) | 0 | 1 (4) | 0 | 1 (4) | 0 | 0 |
| 6 diseases | 1 (4) | 1 (3) | 1 (4) | 1 (4) | 1 (4) | 1 (4) | 0 | 0 |
| 7 diseases | 0 | 1 (3) | 0 | 1 (4) | 0 | 1 (4) | 0 | 0 |
| 8 diseases | 1 (4) | 0 | 1 (4) | 0 | 1 (4) | 0 | 0 | 0 |
| 9 diseases | 1 (4) | 0 | 1 (4) | 0 | 1 (4) | 0 | 0 | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 10 diseases | 1 (4) | 0 | 1 (4) | 0 | 1 (4) | 0 | 0 | 0 |
| 15 diseases | 0 | 1 (3) | 0 | 1 (4) | 0 | 1 (4) | 0 | 0 |
| Total | 26 (32) | 29 (36) | 24 (31) | 27 (36) | 24 (32) | 27 (38) | 2 (33) | 2 (25) |

*Note.* The data are presented as n (%).

The most common (*Total set* data) were gastrointestinal disorders (> 20%) – chronic gastritis and gastroduodenitis, duodenal ulcer, pancreatic diseases, petaobiliary diseases (Table 13.3.2). Hematopoietic disorders were recorded in 15% study subjects; > 10% had endocrine diseases, digestive disorders or metabolic disorders. In 12% of cases the subjects had a history of musculoskeletal diseases, namely spinal pathologies (osteochondrosis), joint diseases (gonarthrosis), foot disorders (flat-foot), pain syndrome in various spinal regions (cervicobrachialgia, lumboischialgia, thoracalgia). Urinary tract diseases (pyelonephritis, urolithiasis, etc.) were found in 8% of subjects, respiratory diseases - in 4%. Neoplasms (liver hemangioma, uterine fibroid) were previously diagnosed in 7% of subjects in the Brillia Health Cold-Flu Recovery group and in single subjects in the Oseltamivir group. 3% of the subjects had underwent gynecological and gastrointestinal surgery. Eye, skin and skin appendage diseases were rare.

Frequency analysis ($\chi 2$ test and exact Fisher's test) demonstrated that Brillia Health Cold-Flu Recovery and Oseltamivir groups (ITT and PP) were not significantly different in terms of the number of subjects with concomitant diseases and conditions. A full list of concomitant pathologies is presented in Table 13.3.2.

**Table 13.3.2: Concomitant diseases of the study subjects**

| System/organs | Disease | Total Set | | ITT | | PP | | Non-ITT + Non-PP | |
|---|---|---|---|---|---|---|---|---|---|
| | | Brillia Health Cold-Flu Recovery (N=81) | Oseltamivir (N=80) | Brillia Health Cold-Flu Recovery (N=78) | Oseltamivir (N=78) | Brillia Health Cold-Flu Recovery (N=75) | Oseltamivir (N=72) | Brillia Health Cold-Flu Recovery (N=6) | Oseltamivir (N=8) |
| Skin and subcutaneous tissue disorders | Smooth skin mycosis | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Onychodystrophy | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | **Total:** | **2(2)** | **0** | **2(3)** | **0** | **2(3)** | **0** | **0** | **0** |
| Musculoskeletal diseases | Osteochondrosis | 2 (2) | 1 (1) | 2 (3) | 1 (1) | 2 (3) | 1 (1) | 0 | 0 |
| | Thoracic scoliosis | 3 (4) | 2 (3) | 3 (4) | 1 (1) | 3 (4) | 1 (1) | 0 | 1(13) |
| | Gonarthrosis | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Intervertebral disk hernia | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Degenerative dystrophic changes | 0 | 2 (3) | 0 | 2 (3) | 0 | 2 (3) | 0 | 0 |
| | Flat foot | 1 (1) | 2 (3) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 1 (13) |
| | Chronic cervichobrachalgia | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Chronic lumboischialgia | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Chronic lumbalgia | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Chronic throacalgia | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Total: | **8 (10)** | **11 (14)** | **8 (10)** | **9 (12)** | **8 (10)** | **9 (13)** | 0 | **2 (25)0** |
| Respiratory disorders | Chronic tonsillitis | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |
| | Chronic pharyngitis | 2 (2) | 0 | 2 (3) | 0 | 2 (3) | 0 | 0 | **0** |
| | Chronic highmoritis | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Chronic sinusitis | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Total: | **3 (4)** | **3 (4)** | **3 (4)** | **3 (4)** | **3 (4)** | **3 (4)** | 0 | 0 |
| Hematopoietic diseases | Arterial hypertension | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |
| | Vegetovascular dystonia | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Congenital heart disorder | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Mitral valve prolapse | 1 (1) | 2 (3) | 1 (1) | 2 (3) | 1 (1) | 2 (3) | 0 | 0 |
| | High ventricular septal defect | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Essential hypertension | 3 (4) | 7 (9) | 3 (4) | 7 (9) | 3 (4) | 7 (10) | 0 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cardiosclerosis | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Initial manifestations of cerebrovascular insufficiency | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Neurocirculatory hypertonic-type dystonia | 1 (1) | 0 | 0 | 0 | 0 | 0 | 1(17) | 0 |
| | Cardiac-type neurocirculatory dystonia | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Thrombophlebitis | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Lower limb varicosis | 2(2) | 1 (1) | 2(3) | 1 (1) | 2(3) | 1 (1) | 0 | 0 |
| | Chronic hemorrhoids | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Total: | **13 (16)** | **14 (18)** | **12 (16)** | **14 (19)** | **12 (16)** | **14 (19)** | **1 (17)** | 0 |
| Gastrointestinal disorders | Chronic gastritis | 4 (5) | 6 (8) | 4 (5) | 6 (8) | 4 (5) | 6 (8) | 0 | 0 |
| | Chronic gastroduodenitis | 3 (4) | 4 (5) | 3 (4) | 4 (5) | 3 (4) | 4 (6) | 0 | 0 |
| | Duodenal ulcer | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Chronic pancreatitis | 2(2) | 1(1) | 2(3) | 1(1) | 2(3) | 1(1) | 0 | 0 |
| | Pancreatic polycystosis | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Biliary dyskinesia | 1 (1) | 2(3) | 1 (1) | 2(3) | 1 (1) | 2(3) | 0 | 0 |
| | Chronic cholecystitis | 2(2) | 5(6) | 2(3) | 5(7) | 2(3) | 5(7) | 0 | 0 |
| | Cholelithiasis | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Hepatic steatosis | 3 (4) | 1 (1) | 3 (4) | 1 (1) | 3 (4) | 1 (1) | 0 | 0 |
| | Total: | **16 (20)** | **21 (26)** | **16 (20)** | **21 (28)** | **16 (21)** | **21 (29)** | **0** | **0** |
| Urinary disorders | Chronic pyelonephritis | 0 | 3 (4) | 0 | 3 (11) | 0 | 3 (4) | 0 | 0 |
| | Urolithiasis | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |
| | Diffuse fibrous-cystous mastopathy | 3 (4) | 0 | 3 (4) | 0 | 3 (4) | 0 | 0 | 0 |
| | Chronic prostatitis | 2 (2) | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 0 | 0 |
| | Endometriosis | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Total: | **6 (7)** | **7 (9)** | **6 (7)** | **7 (9)** | **6 (8)** | **7 (10)** | **0** | **0** |
| Eye diseases | Myopia | 1 (1) | 2 (3) | 1 (1) | 2 (3) | 1 (1) | 2 (3) | 0 | 0 |
| | Glaucoma | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Total: | **2(2)** | **2 (3)** | **2 (3)** | **2 (3)** | **2 (3)** | **2 (3)** | 0 | 0 |
| Endocrine, nutrition and metabolic diseases | Autoimmune thyroiditis | 1 (1) | 2 (3) | 0 | 1 (1) | 0 | 1 (1) | 1 (17) | 1 (13) |
| | Hypothyroidism | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Drug-induced eurthyroidism | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Euthyroidism | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Diffuse-nodular goiter | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |
| | Non-toxic multinodular goiter | 4(5) | 1 (1) | 4(5) | 1 (1) | 4(5) | 1 (1) | 0 | 0 |
| | Dyslipidemia | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Obesity | 2 (2) | 5 (6) | 2 (3) | 5 (7) | 2 (3) | 5 (7) | 0 | 0 |
| | Total: | **9 (11)** | **12 (15)** | **8 (10)** | **11 (15)** | **8 (11)** | **11 (15)** | **1 (17)** | **1 (13)** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Infectious diseases | Delayed sequelae of lung tuberculosis | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| Neoplasms | Liver hemangioma | 2 (2) | 0 | 2 (3) | 0 | 2 (3) | 0 | 0 | 0 |
| | Uterine fibroid | 6 (7) | 2 (3) | 5 (6) | 1 (1) | 5 (7) | 1 (1) | 1 (17) | 1 (13) |
| | Total: | **8 (10)** | **2 (3)** | **7 (9)** | **1 (1)** | **7 (9)** | **1 (1)** | **1 (17)** | **1 (13)** |
| Other | Appendectomy | 1(1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Resection of anterior rectal wall | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Pelvic adhesive process | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Condition after endometriod cyst | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Total hysterectomy | 0 | 1 (1) | 0 | 0 | 0 | 0 | 0 | 1 (13) |
| | Total: | **1 (1)** | **4 (5)** | **1 (1)** | **3 (4)** | **1 (1)** | **3 (4)** | **0** | **1 (13)** |
| | **Total concomitant diseases** | **68 (84)** | **76 (95)** | **65 (83)** | **71 (96)** | **65 (87)** | **71 (95)** | **3 (50)** | **5 (63)** |

*Note.* The results are presented as n (%)

Most study subjects (> 90%) received various drugs (Table 13.3.3) for symptomatic therapy and for the treatment of background chronic pathology. Most commonly the subjects received no more than 4 drugs, single subjects in both groups received 5 and more drugs.

**Table 13.3.3: Distribution of subjects in terms of concomitant therapy**

| Amount of drug per one subject | **Total Set** | | **ITT** | | **PP** | | **Non-ITT + Non-PP** | |
|---|---|---|---|---|---|---|---|---|
| | Brillia (n=81) | Oseltamivir (n=80) | Brillia (n=78) | Oseltamivir (n=78) | Brillia (n=75) | Oseltamivir (n=72) | Brillia (N=6) | Oseltamivir (n=8) |
| 1 drug | 24 (31) | 27 (35) | 24 (32) | 26 (35) | 23 (31) | 23 (32) | 1 (20) | 5 (62) |
| 2 drugs | 16 (21) | 17 (22) | 15 (20) | 17 (23) | 16 (21) | 17 (24) | 1 (20) | 0 |
| 3 drugs | 21 (27) | 10 (13) | 20 (27) | 9 (12) | 20 (27) | 10 (14) | 2 (40) | 1 (13) |
| 4 drugs | 12 (16) | 13 (17) | 11 (15) | 13 (17) | 12 (16) | 11 (15) | 1 (20) | 2 (25) |
| 5 drugs | 2 (3) | 7 (9) | 2 (3) | 7 (9) | 2 (3) | 7 (10) | 0 | 0 |
| 6 drugs | 0 | 3 (4) | 0 | 3 (4) | 0 | 3 (4) | 0 | 0 |
| 7 drugs | 2 (3) | 0 | 2 (3) | 0 | 2 (3) | 0 | 0 | 0 |
| Total | 77 (95) | 77 (96) | 74 (95) | 75 (96) | 75 (96) | 71 (96) | 5 (83) | 8 (100) |

*Note.* The results are presented as n (%).

About 90% took antipyretic drugs on the first day, many of them used vasoconstrictor nasal drops and sprays, topical antiseptic solutions and lozenges, antitussive drugs, vitamin drugs, predominantly containing ascorbic acid. Some of them received bronchodilators.

Antihypertensive drugs of various classes (ACE inhibitors, angiotensin receptor antagonists, beta-adrenoblockers, calcium channel blockers) and diuretics were continuously administered by 4% subjects in Brillia Health Cold-Flu Recovery group and 10% in Oseltamivir group. Single subjects received statins, drugs for the treatment of thyroid diseases and drugs normalizing intestinal flora. Full list of medicinal products used by the subjects during the study is presented in Table 13.3.4.

Frequency test ($\chi^2$ square test and exact Fisher's test) did not reveal differences between the groups in terms of concomitant drug dosing frequency (ITT and PP analysis). Data on concomitant diseases and drugs administered by the subjects excluded from efficacy analysis (Non-ITT+Non-PP) are presented in Tables 13.3.3 and 13.3.4; they are not described due to a low number of the subjects in subgroups.

## Table 13.3.4: Concomitant therapy of the study subjects

| Drug | INN | Total Set | | ITT | | PP | | Non-ITT + Non-PP | |
|---|---|---|---|---|---|---|---|---|---|
| | | Brillia Health Cold-Flu Recovery (N=81) | Oseltamivir (N=80) | Brillia Health Cold-Flu Recovery (N=78) | Oseltamivir (N=78) | Brillia Health Cold-Flu Recovery (N=75) | Oseltamivir (N=72) | Brillia Health Cold-Flu Recovery (N=6) | Oseltamivir (N=8) |
| **Analgesics and antipyretics** | | | | | | | | | |
| **Paracetamol** | Paracetamol | **49 (60)** | 54 (68) | 48 (62) | 53 (72) | 47 (63) | 50 (69) | 2 (33) | 4 (50) |
| **Coldrex** | Paracetamol + Phenylephrine hydrochloride + Caffeine + Terpinhydrate + Ascorbic acid | **2 (2)** | 3 (4) | 2 (3) | 3 (4) | 2 (3) | 3 (4) | 0 | 0 |
| **Non-steroidal anti-inflammatory drugs** | | | | | | | | | |
| Analgin | Metamizole sodium | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |
| Acetylsalicylic acid | Acetylsalicylic acid | 7 (9) | 6 (8) | 7 (9) | 6 (8) | 6 (8) | 4 (6) | 1 (17) | 2 (25) |
| Ibuclin | Ibuprofen + Paracetamol | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Nise | Nimesulide | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| Nimesil | Nimesulide | 0 | 2 (3) | 0 | 2 (3) | 0 | 2 (3) | 0 | 0 |
| Nimesulide | Nimesulide | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Nurofen | Ibuprofen | | 6 (7) | 4 (5) | 5 (6) | 4 (5) | 5 (7) | 4 (6) | 1 (17) |
| Oral contraceptives | Ketoprofen | | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | | Total | **66 (81)** | **73 (91)** | **64 (82)** | **72 (91)** | **62 (81)** | **66 (91)** | **4 (67)** |
| **Decongestants and other topical drugs** | | | | | | | | | |
| Aquamaris | Saline seawater with minerals and elements | 13 (16) | 8 (10) | 13 (17) | 8 (11) | 13 (17) | 8 (11) | 0 | 0 |
| Quixx | Water of Atlantic ocean | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 | 1 (13) |
| Nasivin | Oxymetazoline | 12 (15) | 11 (14) | 10 (13) | 11 (15) | 9 (12) | 11 (15) | 3 (50) | 0 |
| Naphthyzine | Naphazoline | 1 (1) | 3 (4) | 1 (1) | 2 (3) | 1 (1) | 1 (1) | 0 | 2 (25) |
| Otrivin | Xylometazoline | 2(2) | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 0 | 0 |
| Rinofluimucil | Acetylcystein + Tuaminoheptane sulphate | 1 | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |
| Snup | Xylometazoline hydrochloride | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Tyzine | Tetrizoline | 3 (4) | 2 (3) | 3 (4) | 2 (3) | 3 (4) | 2 (3) | 0 | 0 |
| | Total | **33 (41)** | **29 (36)** | **31 (40)** | **28 (38)** | **30 (40)** | **26 (36)** | **3 (50)** | **3 (38)** |
| **Throat remedies** | | | | | | | | | |
| Hexoral | Hexetidine | 8 (10) | 10 (13) | 8 (10) | 10 (14) | 8 (11) | 10 (14) | 0 | 0 |
| Lysobact | Lysozyme hydrochloride + Pyridoxine hydrochloride | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Lugol's solution with glycerol | Iodine + Potassium iodide + Glycerol | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| Rotocan | Calendula flower extract + blue chamomile flowers + Sanguinary herb extract | 2 (2) | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 0 | 0 |
| Strepsils | Dichlorobenzyl alcohol + Amylmethacresol Peppermint oil+Aniseed oil+Levomenthol | 1 (1) | 3 (4) | 0 | 3 (4) | 0 | 3 (4) | 1 (17) | 0 |
| Tantum verde | Benzydamine hydrochloride | 2 (2) | 0 | 2 (3) | 0 | 2 (3) | 0 | 0 | 0 |
| Teraflu lar | Benzaxonium chloride + Lidocaine hydrochloride | 5 (6) | 5 (6) | 3 (4) | 5 (7) | 3 (4) | 5 (7) | 2 (33) | 0 |
| Faringosept | Ambazone monohydrate | 3 (4) | 2 (3) | 3 (4) | 2 (3) | 3 (4) | 2 (3) | 0 | 0 |
| | Total | **23 (28)** | **23 (29)** | **20 (26)** | **23 (31)** | **20 (27)** | **23 (32)** | **3 (50)** | **0** |
| **Antiseptics and disinfectants** | | | | | | | | | |
| Miramistin | Benzyldimethyl [3-(miristoylamino)propyl] ammonia chloride monohydrate | 7 (9) | 2 (3) | 7 (9) | 2 (3) | 7 (9) | 2 (3) | 0 | 0 |
| Octenisept | Octenidine dihydrochloride + Phenoxyethanol | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| Chlorhexidine | Chlorhexidine | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Total: | **8 (10)** | **3 (4)** | **8 (10)** | **3 (4)** | **8 (11)** | **3 (4)** | **0** | **0** |
| **Total antiseptic drugs** | | **31 (38)** | **26 (33)** | **28 (36)** | **26 (35)** | **28 (37)** | **26 (36)** | **3 (50)** | **0** |
| **Antitussive drugs** including | | | | | | | | | |
| **cough and cold remedies** | | | | | | | | | |
| Ambrobene retard | Ambroxol hydrochloride | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 | 1 (13) |
| Ascoryl | Bromhexin + Guaifenesin + Salbutamol | 0 | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| ACC | Acetylcystein | 9 (11) | 8 (10) | 9 (12) | 7 (9) | 9 (12) | 6 (8) | 0 | 2 (25) |
| Bromhexin | Bromhexin | 1 (1) | 5 (6) | 0 | 5 (7) | 0 | 5 (7) | 1 (17) | 0 |
| Codelac | Codeine +Sodium hydrocarbonate + Licorice radix + Thermopsis lanceolata herb | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |
| Lasolvan | Ambroxol hydrochloride | 7(9) | 5 (6) | 7 (9) | 5 (7) | 7 (9) | 5 (7) | 0 | 0 |
| Mucaltin | Althaea Officinalis herb extract | 2 (2) | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 2 (3) | 0 | 0 |
| Tussin plus | Guaifenesin + Dextromethorphan | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| **Antitussive herbal drugs** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Breast tea | Althaea radix+ Farfara leaves + Marjoram herb | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 | 1 (13) |
| Chamomile | Blue chamomile | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Antitussive drugs total | | **21 (26)** | **25 (31)** | **21 (27)** | **24 (32)** | **20 (27)** | **21 (29)** | **1 (17)** | **4 (50)** |
| **Remedies for obstructive respiratory diseases** | | | | | | | | | |
| **Berodual** | Ipratropium bromide + Fenoterol | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| Teopec retard | Theophylline | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Erespal | Fenspiride | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| | Total | **2 (2)** | **1 (1)** | **2 (3)** | **1 (1)** | **2 (3)** | **1 (1)** | **0** | **0** |
| **Saline solutions** | | | | | | | | | |
| Saline solution | Sodium chloride | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| **Antihypertensive drugs** including **ACE inhibitors** | | | | | | | | | |
| Accupro | Quinapril | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Prestarium | Perindopril | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| Hartil | Ramipril | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Enap | Enalapril | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| **Angiotensin II receptor antagonists** | | | | | | | | | |
| Lorista N | Losartan+ Hydrochlorothiazide | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 | 0 |
| **Beta-adrenoblockers** | | | | | | | | | |
| Betaloc | Metoprolol | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Bisoprolol | Bisoprolol | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| **Diuretics** | | | | | | | | | |
| Indapamide MB | Indapamide | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| **Calcium receptor antagonists** | | | | | | | | | |
| Amlodipine | Amlodipine | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| Norvasc | Amlodipine | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| | Total antihypertensive drugs | **3 (4)** | **8 (10)** | **3 (4)** | **8 (11)** | **3 (4)** | **8 (11)** | **0** | **0** |
| **Statins** | | | | | | | | | |
| Simvastatin | Simvastatin | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |
| **Vitamins** | | | | | | | | | |
| Ascorbic acid | Ascorbic acid | 13 (16) | 8 (10) | 13 (17) | 8 (11) | 12 (17) | 8 (12) | 1 (17) | 0 |
| Ascorutin | Ascorbic acid + Rutoside | 0 | 1 (1) | 0 | 0 | 0 | 0 | 0 | 1 (13) |
| Vitamin C | Ascorbic acid | 21 (26) | 23 (29) | 20 (26) | 23 (31) | 20 (28) | 23 (33) | 1 (17) | 0 |
| | **Vitamins total** | **34 (42)** | **32 (40)** | **33 (42)** | **31 (42)** | **32 (43)** | **31 (43)** | **2 (33)** | **1 (13)** |
| **Thyroid disease remedies** | | | | | | | | | |
| Euthyrox | Levothyroxin sodium | 0 | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 |
| **Drugs normalizing intestinal flora** | | | | | | | | | |
| Acipol | Live acidophyllic Lactobacilli + Polysaccaride of kefir fungi | 1 (1) | 0 | 1 (1) | 0 | 1 (1) | 0 | 0 | 0 |

*Note.* The results are presented as n (%).

### 13.4 Data on contraceptive methods during the study

Most (86%) females participating in the study had childbearing potential (Table 13.4.1). The results of pregnancy tests were negative in all female subjects of childbearing potential. All of them, including 90% in the Brillia Health Cold-Flu Recovery group and 82% in the Oseltamivir group used contraception during the study and for 30 days after the study termination. Frequency analysis ($\chi^2$ square test and exact Fisher's test) did not reveal differences between the groups in terms of these parameters (Table 13.1.4).

**Table 13.4.1: Results of pregnancy test and contraception data**

| Parameter | Group | | | Statistics |
|---|---|---|---|---|
| | Brillia Health Cold-Flu Recovery | Oseltamivir | Total | |
| 1. Number of female subjects of childbearing potential | | | | |
| Total Set [81/80] | 44 (90) | 45 (82) | 89 (86) | $\chi^2$=1.8; p=0.18 |
| ITT [78/78] | 42 (89) | 44 (81) | 86 (85) | $\chi^2$=1.68; p=0.20 |
| PP [75/72] | 40 (89) | 40 (82) | 80 (86) | $\chi^2$=1.41; p=0.24 |
| Non-ITT+Non-PP [6/8] | 4 (100) | 5 (83) | 9 (90) | p=1.0 |
| 2. Number of female subjects using adequate contraception method | | | | |
| Total Set [81/80] | 44 (100) | 45 (100) | 89 (100) | |
| ITT [78/78] | 42 (100) | 44 (100) | 86 (100) | |
| PP [75/72] | 40 (100) | 40 (100) | 80 (100) | |
| Non-ITT+Non-PP [6/8] | 4 (100) | 5 (100) | 9 (100) | |
| 3. Contraception method used | | | | |
| Total Set [81/80] | | | | |
| Condoms with spermicide | 33 (75) | 30 (67) | 63 (71) | $\chi^2$=0.88; p=0.83 |
| Intrauterine devices | | | | |
| Abstinence | 7 (16) | 9 (20) | 16 (18) | |
| Condoms with spermicide and abstinence | 3(7)<br>1(2) | 5 (11)<br>1 (2) | 8 (9)<br>2 (2) | |
| ITT [78/78] | | | | |
| Condoms with spermicide | 31 (74) | 30 (68) | 61 (71) | $\chi^2$=0.54; p=0.91 |
| Intrauterine devices | | | | |
| Abstinence | 7 (17) | 8 (18) | 15 (18) | |
| Condoms with spermicide and abstinence | 3 (7)<br>1 (2) | 5 (12)<br>1 (2) | 8 (9)<br>2 (2) | |
| PP [75/72] | | | | |
| Condoms with spermicide | 30 (75) | 27 (67) | 57 (71) | $\chi^2$=0.58; p=0.46 |

| | | | | |
|---|---|---|---|---|
| Intrauterine devices | 6 (15) | 8 (20) | 14 (18) | |
| Abstinence | 3 (7) | 4 (10) | 7 (9) | |
| Condoms with spermicide and abstinence | 1 (3) | 1 (3) | 2 (2) | |
| Non-ITT+Non-PP [6/8] | | | | |
| Condoms with spermicide | 3 (75) | 3(60) | 6 (67) | $\chi^2$=0.9; p=0.64 |
| Intrauterine devices | 1 (25) | 1(20) | 2 (22) | |
| Abstinence | 0 | 1(20) | 1 (11) | |
| Condoms with spermicide and abstinence | 0 | 0 | 0 | |
| 4. Pregnancy test results | | | | |
| Total Set [81/80] | | | | |
| Positive | 0 | 0 | 0 | |
| Negative | 44 (100) | 45 (100) | 89 (100) | |
| ITT [78/78] | | | | |
| Positive | 0 | 0 | 0 | |
| Negative | 42 (100) | 44 (100) | 86 (100) | |
| PP [75/72] | | | | |
| Positive | 0 | 0 | 0 | |
| Negative | 40 (100) | 40 (100) | 80 (100) | |
| Non-ITT+Non-PP [6/8] | | | | |
| Positive | 0 | 0 | 0 | |
| Negative | 4 (100) | 5 (100) | 9 (100) | |
| 5. Number of female subjects who underwent surgery terminating their fertile function | | | | |
| Total Set [81/80] | 0 | 2 (4) | 2 (2) | $\chi^2$=1.85; p=0.17 |
| ITT [78/78] | 0 | 2 (5) | 2 (2) | $\chi^2$=1.7; p=0.19 |
| PP [75/72] | 0 | 1 (3) | 1 (1) | $\chi^2$=0.8; p=0.36 |
| Non-ITT+Non-PP [6/8] | 0 | 1 (17) | 1 (10) | p=0.25 |
| 1. Number of female subjects in menopause > 1 year | | | | |
| Total Set [81/80] | 5 (10) | 11 (20) | 16 (15) | $\chi^2$=2.4; p=0.12 |
| ITT [78/78] | 5 (11) | 11 (20) | 16 (16) | $\chi^2$=1.75; p=0.19 |
| PP [75/72] | 5 (13) | 10 (25) | 15 (19) | $\chi^2$=1.1; p=0.29 |
| Non-ITT+Non-PP [6/8] | 0 | 1 (17) | 1 (10) | p=0.25 |

*Note.* The data are presented as n (%). Parameters 2-6 were calculated in % of the number of females of childbearing potential; the data were analyzed using chi-square test ($\chi^2$-test).

**13.6 Group compliance**

The study results demonstrated a high degree of compliance of the subjects with the therapy prescribed. According to statistical analysis, compliance in Brillia Health Cold-Flu Recovery and Oseltamivir group was not significantly different (Table 13.1.5).

**Table 13.5.1: Compliance in groups**

| Parameter | Group | | | Statistics |
|---|---|---|---|---|
| | Brillia Health Cold-Flu Recovery | Oseltamivir | Total | |
| | ITT [78/78] | 100.9±4.3 | 100.8±4.1 | t=−1.95; p=0.054 |
| | PP [75/72] | 100.0±0.0 | 100.0±0.0 | t=−1.68; p=0.096 |

*Note*. The data are presented as Mean±SD; data were analyzed using Student's test.

## 14. Efficacy evaluation

Efficacy of the study therapy according to the current recommendations is presented based on ITT and PP analysis results.

### 14.1 Proportions of subjects with normalized body temperature (≤37C) by the end of days 1, 2, 3, 4, 5 of therapy

Efficacy of the study therapy by the primary criterion was based on axillary temperature measured by an electronic thermometer twice daily (in the morning and in the evening). Criterion of temperature normalization was considered to be its reduction to 37.0°C and below (without subsequent increase). This study used "stricter", as compared to the current reference values, criterion of normalization of axillary temperature (≤37.0°C and not ≤37.3°C). According to the requirements of the statistical non-inferiority model, **δ** for comparison of temperature values was taken as equal to 20% of the effect of reference drug Oseltamivir (Tamiflu®), i.e. 0.2°C

**Morning body temperature**

According to ITT-analysis, Brillia Health Cold-Flu Recovery's effect started manifesting after the first day of application. in the morning of day 2 body temperature normalized in 15% subjects vs. 8% in Oseltamivir group), in the morning of day 3 normal body temperature was noted in 46% subjects from the Brillia Health Cold-Flu Recovery group and 42% from the Oseltamivir group, on day 4 - 81% and 71%, respectively (Table 14.1.1.). By the end of the treatment course (by day 6) all subjects from test drug group had normal body temperature (vs. 92% in the Oseltamivir group).

**Table 14.1.1: Proportions of subjects with normalized body temperature**

| | *ITT-analysis* | | | *PP-analysis* | | |
|---|---|---|---|---|---|---|
| **Day of therapy** | **Brillia Health Cold-Flu Recovery** (n=78) | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health Cold-Flu Recovery** (n=75) | **Oseltamivir** (n=72) | **Statistics** |
| **1** | 0 (0) | 1 (1) | Δ=−1%; Z=15.7; p<0.001 | 0 (0) | 1(1) | Δ=−1% Z=12.5; p<0.001 |
| **2** | 15 (19) | 8 (10) | Δ=9%; | 14 (19) | 7 (10) | Δ=9% |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | Z=4.9; p<0.001 | | | Z=4.8; p<0.001 |
| **3** | 36 (46) | 33 (42) | Δ=4%; Z=2.8; p=0.002 | 35 (47) | 31 (43) | Δ=4% Z=2.7; p=0.003 |
| **4** | 63 (81) | 55 (71) | Δ=10%; Z=4.2; p<0.001 | 60 (80) | 54 (75) | Δ=5% Z=3.4; p<0.001 |
| **5** | 74 (95) | 65 (83) | Δ=12%; Z=6.2; p<0.001 | 71 (95) | 60 (83) | Δ=12% Z=5.9; p<0.001 |
| **6** | 78 (100) | 72 (92) | Δ=8%; Z=8.8; p<0.001 | 75 (100) | 66 (92) | Δ=8% Z=8.3; p<0.001 |
| **7** | 77 (99) | 78 (100) | Δ=−1%; Z=13.7; p<0.001 | 74 (99) | 72 (100) | Δ=−1% Z=13.1; p<0.001 |
| **8** | 78 (100) | 78 (100) | Δ=0%; Z=13.7; p<0.001 | 75 (100) | 72 (100) | Δ=0% p<0.001 |

*Note.* The data are presented as n (%). "Statistics" column contains the data of frequency analysis (Wald method).

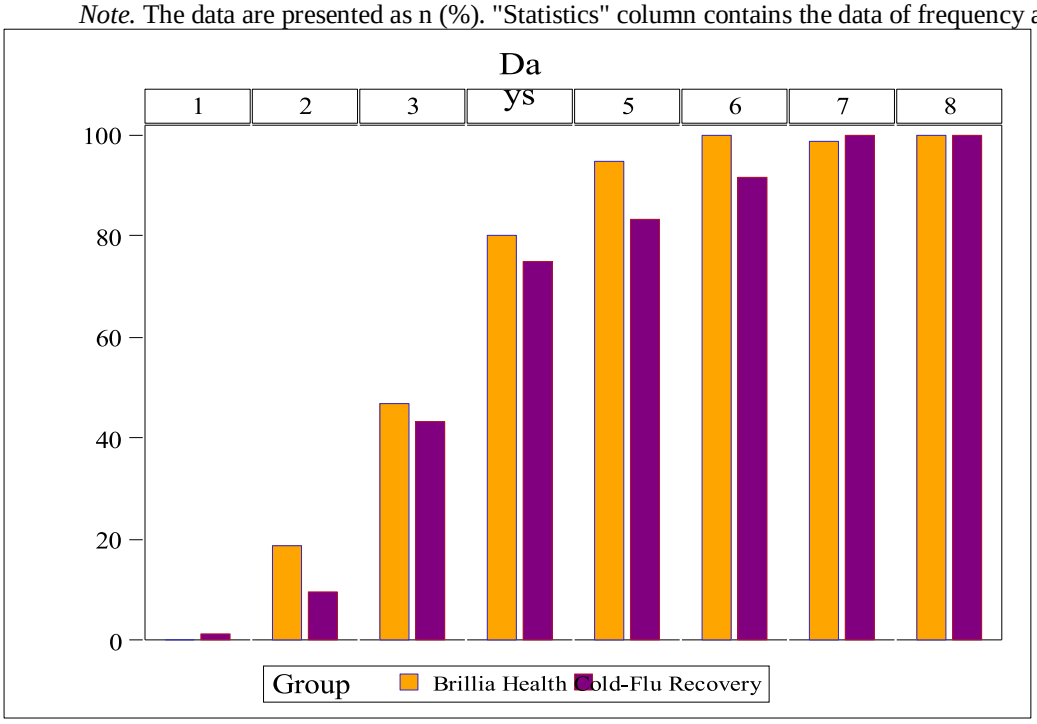


**Figure 14.1.1. Proportions of subjects with normalized morning body temperature (PP-analysis)**

PP-analysis evidenced a similar speed of normalization of body temperature in both groups. on day 2 – 19% and 10%, on day 3 − 47% and 43%, on day 4 − 80% and 75% subjects from the Brillia Health Cold-Flu Recovery and Oseltamivir groups, respectively; by the morning of day 5 all subjects from Brillia Health Cold-Flu Recovery group and 92% from the Oseltamivir group had normal temperature (Table 14.1.1; fig. 14.1.1).

Frequency analysis (Wald method) for each of 8 pairs of morning temperature measurements (ITT and PP sets) demonstrated significant result evidencing comparable therapeutic effects of Brillia Health Cold-Flu Recovery and Oseltamivir (Table 14.1.1).

**Evening body temperature**

According to ITT analysis, evening body temperature in the Brillia Health Cold-Flu Recovery group was normalized in 41% subjects on day 3, in 68% - on day 4 and in vast majority of subjects (85%) - by the end of day 5 (Table 14.1.2; fig. 14.1.2). Parameters in the Oseltamivir group were approximately the same: 42%, 69% and 86%, respectively.

**Table 14.1.2: Proportions of subjects with normalized evening body temperature**

| | *ITT-analysis* | | | *PP-analysis* | | |
|---|---|---|---|---|---|---|
| **Day of therapy** | **Brillia Health Cold-Flu Recovery** (n=78) | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health Cold-Flu Recovery** (n=75) | **Oseltamivir** (n=72) | **Statistics** |
| **1** | 3 (4) | | Δ=3%; Z=8.4; p<0.001 | 3 (4) | 1 (1) | Δ=3% Z=8.0; p<0.001 |
| **2** | 11 (14) | 12 (15) | Δ=−1%; Z=3.1; p=0.001 | 11 (15) | 11 (15) | Δ=0% Z=3.1; p=0.001 |
| **3** | 32 (41) | 33 (42) | Δ=−1%; Z=2.2; p=0.014 | 31 (41) | 31 (43) | Δ=−2% Z=2.1; p=0.019 |
| **4** | 53 (68) | 54 (69) | Δ=−1%; Z=2.3; p=0.009 | 51 (68) | 52 (72) | Δ=−4% Z=1.9; p=0.028 |
| **5** | 66 (85) | 67 (86) | Δ=−1%; Z=3.1; p=0.001 | 63 (84) | 63 (88) | Δ=−4% Z=2.6; p=0.004 |
| **6** | 73 (94) | 75 (96) | Δ=−2%; Z=4.6; p<0.001 | 70 (93) | 69 (96) | Δ=−3% Z=4.3; p<0.001 |
| **7** | 78 (100) | 76 (97) | Δ=3%; Z=11.9; p<0.001 | 75 (100) | 70 (97) | Δ=3% Z=11.1; p<0.001 |
| **8** | 78 (100) | 78 (100) | Δ=0%; Z=11.9; p<0.001 | 75 (100) | 72 (100) | Δ=0% Z=11.1; p<0.001 |

*Note.* The data are presented as n (%). “Statistics” column contains the data of frequency analysis (Wald method).

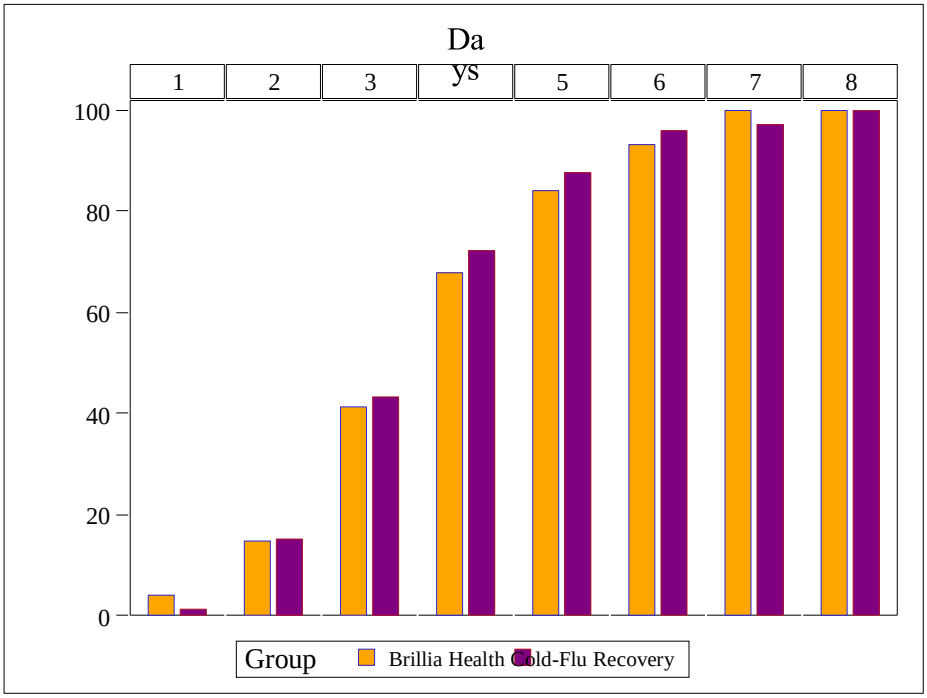

**Figure 14.1.2. Proportions of subjects with normalized evening body temperature (PP-analysis)**

According to PP-analysis, proportions of the subjects with normal temperature values by the end of day 3-5 of therapy were insignificantly different from the same in ITT-set: 41%; 68% and 84% vs. 43%, 72% and 88% in two groups, respectively:

Frequency analysis (Wald method) for each of 8 pairs of evening temperature measurements (ITT and PP sets) demonstrated significant results evidencing comparable values in both groups (Table 14.1.2).

Therefore, analysis of the study results by the primary criterion in ITT and PP populations demonstrated therapeutic efficacy of Brillia Health Cold-Flu Recovery in the treatment of influenza which was significantly comparable to the effects of reference antiviral drug Oseltamivir. Brillia Health Cold-Flu Recovery exerted effects similar to that of Oseltamivir on febrile reaction, i.e. the marker of infections process activity in influenza. More than two thirds of subjects with influenza by the end of day 4 and majority of subjects by the end of day 5 had body temperature $\leq 37.0^0$C.

**14.2 Proportions of subjects with clinical manifestations of influenza eliminated by day 7 of follow-up**

Secondary criteria used for the investigation and comparison of Brillia Health Cold-Flu Recovery efficacy in the treatment of influenza were numerous. The first included evaluation of the proportion of the subjects with no clinical symptoms of the disease (fever, intoxication and respiratory symptoms) observed on day of the study (Visit 3). Severity of influenza symptoms were evaluated by the investigator in scores from 0 to 3, where 0 - no symptom, 1 score - mild, 2 scores - moderate, 3 scores - severe. According to the requirements of the statistical non-inferiority model (necessity of the target level of clinical insignificance δ), δ value for evaluation of the symptoms using 4-point scale was taken as 0.5 scores.

A five-day course of Brillia Health Cold-Flu Recovery therapy demonstrated clinical effect comparable to that of Oseltamivir, both in terms of individual symptoms and in overall clinical symptoms of influenza. As shown in Table 14.2.1, day 7 of the follow-up was characterized by normal body temperature in all subjects and absence of intoxication and respiratory symptoms in most subjects of both groups (ITT and PP sets).

**Table 14.2.1: Proportions of the subjects with no clinical symptoms of influenza on day 7 of the follow-up**

| | ***ITT-analysis*** | | | ***PP-analysis*** | | |
|---|---|---|---|---|---|---|
| **Day of therapy** | **Brillia Health Cold-Flu Recovery** (n=78) | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health Cold-Flu Recovery** (n=75) | **Oseltamivir** (n=72) | **Statistics** |
| **1 Temperature** | 78 (100) | 78 (100) | p<0.0001 | 75 (100) | 72 (100) | p<0.001 |
| **Intoxication signs** | | | | | | |
| **2 Headache** | 77 (99) | 75 (96) | Z=8.4; p<0.001 | 75 (100) | 70 (97) | Z=11.1; p<0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **3 Chill** | 78 (100) | 78 (100) | p<0.0001 | 75 (100) | 72 (100) | p<0.001 |
| **4 Sweatiness** | 68 (87) | 67 (86) | Z=3.7; p<0.001 | 65 (88) | 62 (86) | Z=3.4; p<0.001 |
| **5 Weakness** | 64 (82) | 58 (74) | Z=4.0; p<0.001 | 62 (83) | 54 (75) | Z=3.9; p<0.001 |
| **6 Malaise** | 70 (90) | 71 (91) | Z=3.7; p<0.001 | 68 (91) | 66 (92) | Z=3.8; p<0.001 |
| **7 Muscle pain** | 77 (99) | 78 (100) | Z=13.7; p<0.001 | 75 (100) | 72 (100) | p<0.001 |
| **8 Join pain** | 78 (100) | 78 (100) | p<0.0001 | 75 (100) | 72 (100) | p<0.001 |
| **9 Eye pain** | 77 (99) | 78 (100) | Z=13.7; p<0.001 | 75 (100) | 72 (100) | p<0.001 |
| **10 Photophobia** | 77 (99) | 78 (100) | Z=13.7; | 74 (99 | 72 (100) | Z=13.1; p<0.001 |
| **11 Somnolence** | 75 (96) | 76 (97) | Z=6.2; p<0.001 | 72 (96) | 71 (99) | Z=6.0; p<0.001 |
| **All intoxication symptoms** | **47 (60)** | **50 (64)** | **Z=1.9; p=0.028** | **46 (61)** | **46 (64)** | **Z=2.0; p=0.022** |
| **Catarrhal symptoms** | | | | | | |
| **12 Nasal congestion** | 75 (96) | 75 (96) | Z=6.1; p<0.001 | 72 (96) | 70 (97) | Z=5.8; p<0.001 |
| **13 Nasal discharge** | 78 (100) | 73 (94) | Z=9.1; p<0.001 | 75 (100) | 68 (94) | Z=9.0; p<0.001 |
| **14 Sneezing** | 77 (99) | 78 (100) | Z=13.7; p<0.001 | 74 (99) | 72 (100) | Z=13.1; p<0.001 |
| **15 Sore throat** | 78 (100) | 77 (99) | Z=15.7; p<0.001 | 75 (100) | 71 (99) | Z=14.5; p<0.001 |
| **16 Cough** | 66 (85) | 65 (83) | Z=3.4; p<0.001 | 63 (84) | 60 (83) | Z=3.2; p<0.001 |
| **All catarrhal symptoms** | **65 (83)** | **60 (77)** | **Z=3.9; p<0.001** | **62 (83)** | **55 (76)** | **Z=3.7; p<0.001** |
| **All 16 study influenza symptoms** | **35 (45)** | **39 (50)** | **Z=1.7; p=0.044** | **35 (47)** | **35 (49)** | **Z=2.0; p=0.021** |

*Note.* The results are presented as n (%). "Statistics" column contains the data of frequency analysis (Wald method)

***ITT-analysis*** of presence/absence of individual symptoms demonstrated that by the end of the follow-up 60% subjects from the Brillia Health Cold-Flu Recovery group had intoxication signs completely eliminated, 83% - catarrhal signs (vs. 64% and 77% in reference group), while the absence of all influenza symptoms (i.e. complete clinical convalescence) was noted in 45% and 50% subjects, respectively (Table 14.1.2). The lower percentage of subjects with complete absence of all influenza manifestations is explained by a discrepancy of negative results in terms of various symptoms (i.e. some subjects with no intoxication signs could have respiratory catarrhal signs and vice versa).

Analysis of data of ***PP-subjects*** did not reveal significant differences in proportions of subjects in the Brillia Health Cold-Flu Recovery and Oseltamivir groups with no fever (75% and 72%), intoxication (61% and 64%) catarrhal (83% and 76%) syndromes (Table 14.2.1; fig. 14.2.1). Proportion of "full convalescents", i.e. the subjects with no influenza symptoms comprised 47% subjects in Brillia Health Cold-Flu Recovery group and 49% in Oseltamivir group.

**Figure 14.2.1. Proportions of subjects with clinical manifestations of influenza eliminated on day 7 of the follow-up (mean values for PP-analysis).**

Frequency analysis (Wald method) in ITT and PP populations of the two groups for each of the 16 clinical symptoms and their cumulated data (intoxication signs, catarrhal symptoms and summarized clinical manifestations of influenza including fever) demonstrated significant results evidencing comparability of Brillia Health Cold-Flu Recovery and Oseltamivir values (Table 14.1.2).

**14.3 Terms of influenza elimination in the groups**

Analysis of the terms of elimination of clinical manifestations of influenza also evidenced comparable therapeutic efficacy of the two drugs. As shown in Table 14.3.1, the number of days required for elimination of most clinical symptoms of the disease was 3 days on average and was not significantly different between the Brillia Health Cold-Flu Recovery and Oseltamivir groups in ITT and PP populations.

**ITT-analysis**

Average duration of fever in subjects from the Brillia Health Cold-Flu Recovery group was 2.1±1.5 days and in the Oseltamivir group, 2.3±1.6 days. Intoxication signs were eliminated within 2.7±2.2 days against Brillia Health Cold-Flu Recovery therapy and 2.4±2.1 days − Oseltamivir, catarrhal manifestations - 2.8±2.5 and 2.6±2.6 days, respectively. Average duration of all symptoms of influenza was 2.7±2.3 and 2.5±2.2 days in the Brillia Health Cold-Flu Recovery and Oseltamivir groups, respectively.

**Table 14.1.3: Terms of elimination of influenza symptoms against the treatment in both groups**

| **Symptom** | **Duration of symptoms**, days | | | | | |
|---|---|---|---|---|---|---|
| | ***ITT-analysis*** | | | ***PP-analysis*** | | |
| | **Brillia Health Cold-Flu** | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health Cold-Flu** | **Oseltamivir** (n=72) | **Statistics** |
| **Body temperature** | 2.1±1.5 | 2.3±1.6 | t=-2.4; p=0.01 | 2.1 ±1.4 | 2.3±1.6 | t=-2.8; p=0.002 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Intoxication signs** | 2.7±2.2 | 2.4±2.1 | t=−1.7; p=0.04 | 2.6±2.2 | 2.4±2.1 | t=−1.96; p=0.025 |
| **Catarrhal symptoms** | 2.8±2.5 | 2.6±2.6 | t=-2.1; p=0.02 | 2.7±2.5 | 2.6±2.6 | t=-2.3; p=0.01 |
| **All influenza symptoms** | 2.7±2.3 | 2.5±2.2 | t=-3.0; p=0.001 | 2.6±2.3 | 2.5±2.2 | t=-3.4; p=0.0003 |

*Note*. The results are presented as Mean ± SD. "Statistics" column contains data of of Student's test modified for calculations of comparability (non-inferiority) calculated for the difference of mean values to determine significance and its difference from pre-established delta (margin), "p"-value − error of the first kind.

**PP-analysis**

The results of PP-population due to insignificant differences in the number of the subjects almost coincided with the results of ITT-analysis. Average duration of the febrile period against Brillia Health Cold-Flu Recovery therapy was 2.1±1.4 days, Oseltamivir – 2.3±1.6 days; intoxication signs persisted for 2.6±2.2 and 2.4±2.1 days in the two groups, respiratory − 2.7±2.5 and 2.6±2.6 days, respectively. Average duration of all clinical symptoms of influenza was equal to 2.6±2.3 and 2.5±2.2 days in the two groups, respectively.

Statistical analysis of ITT and PP-sets using Student's test modified for calculations of comparability performed for parameters of body temperature averaged by five intoxication and ten catarrhal symptoms demonstrating significant results evidencing comparability of the results in the Brillia Health Cold-Flu Recovery and Oseltamivir groups (Table 14.1.3).

It should be noted that efficacy of Oseltamivir in terms of its effect on fever in subjects with influenza observed in this study is not different from the results of the previous and published clinical studies of the drug [28-30].

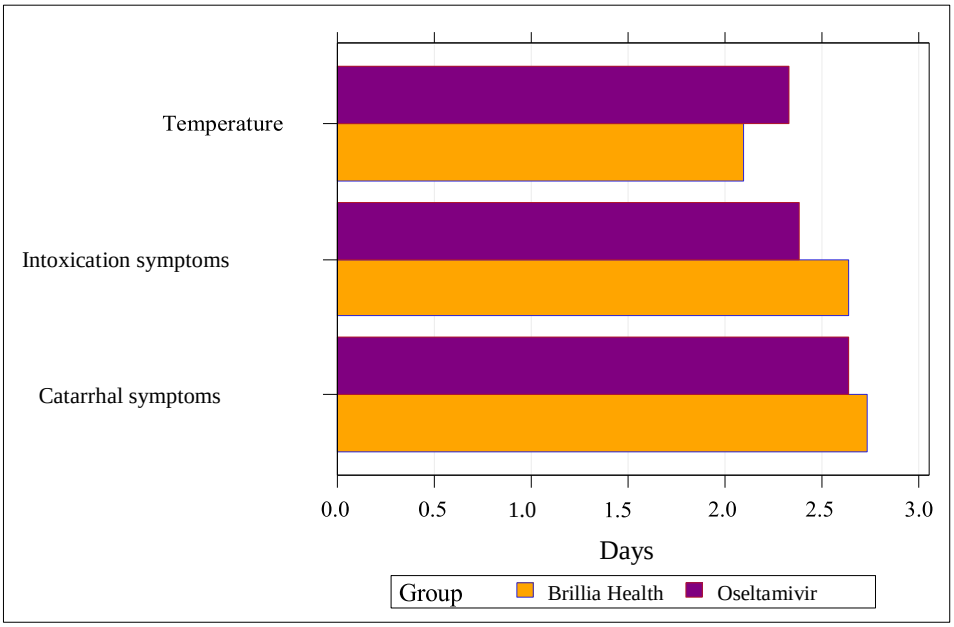


**Figure 14.3.1. Terms of elimination of influenza symptoms in subjects of the two groups (PP-analysis)**

Therefore, duration of fever (the main clinical symptom of influenza) and other manifestations of intoxication and respiratory catarrhal against Brillia Health Cold-Flu Recovery therapy was less than 3 days,

Elimination of symptoms and convalescence of subjects receiving Brillia Health Cold-Flu Recovery and Oseltamivir took place within the same term.

**14.4 Intensity of clinical manifestations of influenza (body temperature, intoxication signs, catarrhal symptoms ins cores) on days 1, 3 and 7 of the follow-up**

Prior to therapy, severity of fever syndrome, intoxication and catarrhal symptoms in the subjects of both groups was comparable (see Table 14.1.4).

ITT [PP] analysis of mean values of morning and evening thermometry demonstrated that body temperature reduced from baseline 38.2±0.4 [38.3±0.4] °C in group 1 and 38.3±0.4 [38.3±0.4] °C in group 2 to 37.0±0.5°C in both groups being consistently below 37.0°C on subsequent days of the follow-up (Table 14.4.1; fig. 14.4.1).

Statistical analysis (Student's test modified for calculations of comparability) evidenced that on day 3 of therapy severity of fever in subjects from the Brillia Health Cold-Flu Recovery group did not fall outside of acceptable limits of δ as compared to Oseltamivir therapy (ITT-analysis: $\Delta^0$=0.01; 95% CI < 0.14; t=−2.5; p=0.007; PP-analysis: $\Delta^0$=0.005; 95% CI < 0.14; t=−2.4; p=0.008) confirming comparability of the effects of test drug and reference drug (Table 14.4.1).

**Table 14.4.1: Body temperature of the subjects on days 1, 3 and 7 of the follow-up**

| Day | *ITT-analysis* | | | *PP-analysis* | | |
|---|---|---|---|---|---|---|
| | **Brillia Health Cold-Flu Recovery** (n=78) | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health Cold-Flu Recovery** (n=75) | **Oseltamivir** (n=72) | **Statistics** |
| **1** | 38.2±0.4 | 38.2±0.4 | Δ°=0.0; 95% CI < 0.08; t=−3.6; p=0.0002 | 38.3±0.4 | 38.3±0.4 | Δ°=0.0; 95% CI < 0.08; t=−3.5; p=0.0003 |
| **3** | 37.0±0.5 | 37.0±0.5 | Δ°=0.01; 95% CI < 0.14; t=−2.5; p=0.007 | 37.0±0.5 | 37.0±0.5 | Δ°=0.005; 95% CI < 0.14; t=−2.4; p=0.008 |
| **7** | 36.5±0.2 | 36.6±0.3 | - | 36.5±0.2 | 36.6±0.3 | - |

*Note.* The data are presented in $^0$C as Mean ± SD; Δ°− difference in body temperature between the two groups; CI – confidence interval; t – Student's test, p − error of the first kind. The data on day 7 of the follow-up were not compared since body temperature was normal in both groups.

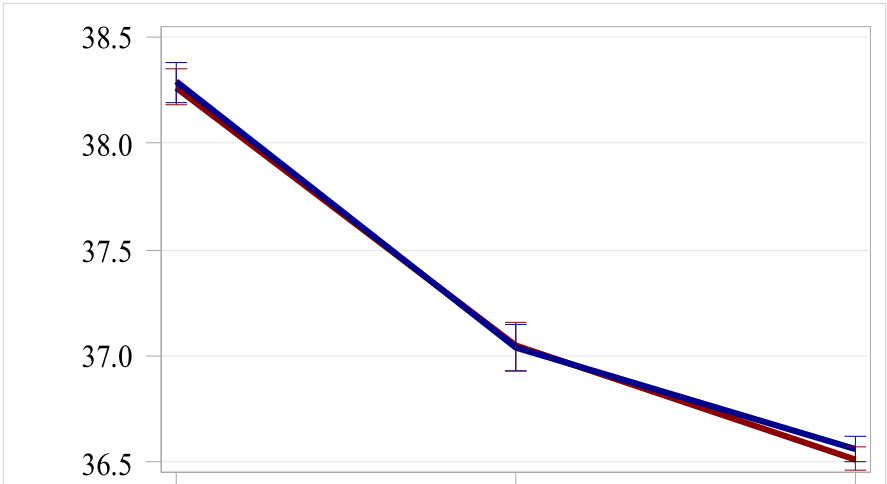

**Figure 14.4.1. Body temperature changes in subjects on days 1, 3 and 7 of the follow-up (PP-analysis)**

Therefore, both duration and severity of fever, i.e. the main clinical marker of viremia and activity of infectious and inflammatory process in influenza, was similar in both groups evidencing that the antiviral efficacy of Brillia Health Cold-Flu Recovery was non-inferior to that of Oseltamivir. The effect of Brillia Health Cold-Flu Recovery unfolded rapidly as soon as three days of therapy most subjects had body temperatures below $37.0^0$C.

Simultaneously with fever, relatively rapid and expressed therapeutic activity of Brillia Health Cold-Flu Recovery regarding the most relevant intoxication symptoms in clinical presentation of influenza - headache and other types of pain (muscle, joint, etc.), asthenic neurovegetative disorders (weakness, malaise, insomnia) etc. was observed.

Based on the results of ***ITT-analysis***, severity of intoxication syndrome as compared to baseline 18.8±6.6 scores (vs. 18.6±6.2 scores in the Oseltamivir group) reduced more than two-fold on day 3 of therapy making 9.2±5.0 scores (vs. 7.7±4.4 scores, respectively) (Table 14.4.2). By the end of the 5-day therapy (on day 7 of the follow-up) intensity of intoxication symptoms was 2.4±2.9 scores (vs. 2.0±2.5 scores in the Oseltamivir group).

**Table 14.4.2: Total score of intoxication symptom severity on days 1, 3 and 7 of the follow-up**

| Day | *ITT-analysis* | | | *PP-analysis* | | |
|---|---|---|---|---|---|---|
| | **Brillia Health Cold-Flu Recovery** (n=78) | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health Cold-Flu Recovery** (n=75) | **Oseltamivir** (n=72) | **Statistics** |
| **1** | 18.8±6.6 | 18.6±6.2 | Δ=0.2; 95% CI < 1.9; t=−2.7; p=0.003 | 19.0±6.7 | 18.6±6.3 | Δ=0.4; 95% CI < 2.1; t=−2.5; p=0.007 |
| **3** | 9.2±5.0 | 7.7±4.4 | Δ=1.5; 95% CI < 2.8; t=−2.0; p=0.025 | 9.2±5.1 | 7.8±4.3 | Δ=0.45; 95% CI < 2.8; t=−2.0; p=0.02 |
| **7** | 2.4±2.9 | 2.0±2.5 | Δ=0.4; 95% CI < 1.1; t=−5.9; p<0.0001 | 2.3±2.7 | 1.9±2.3 | Δ=0.39; 95% CI < 1.1; t=−6.3; p<0.0001 |

*Note.* The data are presented as Mean ± SD; Δ – difference in mean values between Brillia Health Cold-Flu Recovery and Oseltamivir groups; CI – confidence interval; t – Student's test, p − error of the first kind.

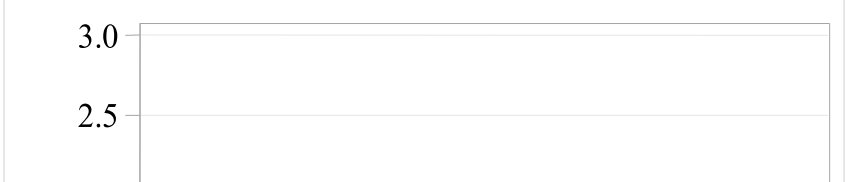

**Figure 14.4.2. Intoxication symptom changes in subjects on days 1, 3 and 7 of the follow-up (PP-analysis)**

The results of PP-analysis demonstrated almost the same values (Table 14.4.2; fig. 14.4.2). Statistical analysis evidenced that the effect of Brillia Health Cold-Flu Recovery on the severity of the intoxication symptoms during the treatment was significantly comparable with the results of Oseltamivir application (Table 14.4.2).

**Table 14.4.3: Total score of catarrhal symptom severity on days 1, 3 and 7 of the follow-up**

| Visit | *ITT-analysis* | | | *PP-analysis* | | |
|---|---|---|---|---|---|---|
| | **Brillia Health Cold-Flu Recovery** (n=78) | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health Cold-Flu Recovery** (n=75) | **Oseltamivir** (n=72) | **Statistics** |
| **1** | 6.1±3.7 | 5.9±3.7 | Δ=0.2; 95% CI < 1.2; t=2.1; p=0.02 | 6.1±3.7 | 5.9±3.6 | Δ=0.2; 95% CI < 1.2; t=−2.1; p=0.02 |
| **2** | 4.3±2.4 | 3.9±2.7 | Δ=0.4; 95% CI < 1.1; t=−2.7; p=0.004 | 4.3±2.4 | 4.0±2.7 | Δ=0.3; 95% CI < 1.0; t=−2.8; p=0.003 |
| **3** | 1.3±1.5 | 1.4±1.9 | Δ=−0.1; 95% CI < 0.4; t=−5.8; p<0.0001 | 1.3±1.5 | 1.4±1.8 | Δ=−0.1; 95% CI < 0.4; t=−5.9; p<0.0001 |

*Note.* Data are presented as Mean ± SD; Δ – difference in mean values between the groups Brillia Health Cold-Flu Recovery and Oseltamivir, CI - confidence interval, t - Student's test, p - error of the first kind

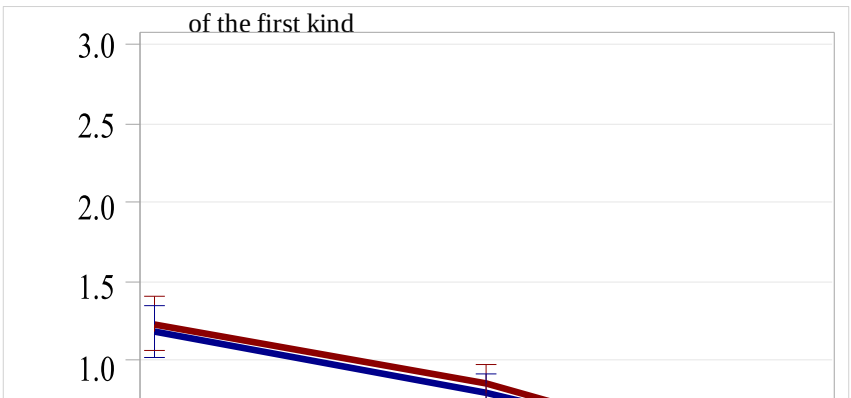

**Figure 14.4.3. Changes in severity of catarrhal symptoms of subjects ins cores on days 1, 3 and 7 of the follow-up**

Catarrhal symptoms, despite their mild baseline nature (about 6.0 scores in both groups of ITT and PP-sets) also reduced significantly as soon as day 3 of therapy, and such decrease, according to statistical analysis, was also significantly comparable between Brillia Health Cold-Flu Recovery and Oseltamivir groups (ITT and PP-analysis). By the end of therapy individual subjects had "residual" respiratory catarrhal symptoms evidenced in the mean values of the total score slightly > 1.0 (Table 14.4.3; fig. 14.4.3).

**14.5 Changes in dosing frequency of antipyretics on days 2, 3, 4 and 5 of therapy**

According to the inclusion criteria, the first day of participation in the study was the first 24 hours from manifestation of influenza. Most subjects (also in accordance with inclusion criteria) in this period of the disease had pyretic fever (mean value in both groups > $38^0$C) treated by a lot of subjects with allowed antipyretic drugs. The number of doses of antipyretics on day 1 of therapy per one subject was 0.65±0.48 in Brillia Health Cold-Flu Recovery group (ITT and PP-sets) and 0.69±0.46 [0.72±0.45] in the Oseltamivir group (ITT [PP] sets, respectively) (Table 14.1.5).

On day 2 of therapy, average antipyretic dosing frequency reduced to 0.40±0.49 and 0.49±0.50 in the Brillia Health Cold-Flu Recovery and Oseltamivir groups (similar values in ITT and PP sets); on day 3 – to 0.19±0.40 and 0.15±0.36, respectively. On the following days 4 and 5 only individual subjects received antipyretics (Table 14.1.5).

**Table 14.1.5: Number of doses of antipyretics in both groups**

| **Day of therapy** | ***ITT-analysis*** | | | ***PP-analysis*** | | |
|---|---|---|---|---|---|---|
| | **Brillia Health Cold-Flu Recovery** (n=78) | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health Cold-Flu Recovery** (n=75) | **Oseltamivir** (n=72) | **Statistics** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **1** | 0.65±0.48 | 0.69±0.46 | Δ=−0.04; 95% CI < 0.09; t=−3.16; p=0.001 | 0.65±0.48 | 0.72±0.45 | Δ=−0.07; 95% CI < 0.06; t=−3.5; p=0.0003 |
| **2** | 0.40±0.49 | 0.49±0.50 | Δ=−0.09; 95% CI < 0.04; t=−3.63; p=0.0002 | 0.40±0.49 | 0.49±0.50 | Δ=−0.09; 95% CI < 0.05; t=−3.48; p=0.0003 |
| **3** | 0.19±0.40 | 0.15±0.36 | Δ=0.04; 95% CI < 0.14; t=−2.65; p=0.0044 | 0.19±0.39 | 0.15±0.36 | Δ=0.03; 95% CI < 0.14; t=−2.66; p=0.0043 |
| **4** | 0.01±0.11 | 0.04±0.19 | Δ=−0.03; 95% CI < 0.02; t=−8.89; p<0.0001 | 0.01±0.12 | 0.04±0.20 | Δ=−0.03; 95% CI < 0.02; t=−8.48; p<0.0001 |
| **5** | 0.01±0.11 | 0.03±0.16 | Δ=−0.01; 95% CI < 0.02; t=−9.63; p<0.0001 | 0.01±0.12 | 0.03±0.17 | Δ=−0.01; 95% CI < 0.02; t=−9.14; p<0.0001 |
| **6** | 0.00±0.00 | 0.01±0.11 | Δ=−0.01; 95% CI < 0.01; t=−16.6; p<0.0001 | 0.00±0.00 | 0.01±0.12 | Δ=−0.01; 95% CI < 0.01; t=−15.7; p<0.0001 |

*Note.* The data are presented as Mean ± SD; Δ – difference in average values between Brillia Health Cold-Flu Recovery and Oseltamivir groups; CI – confidence interval; t – Student's test, p − error of the first kind.

Statistical analysis evidenced significant comparability of the study parameters in the two groups (Table 14.5.1; fig. 14.5.1) and verified that Brillia Health Cold-Flu Recovery was similarly effective as Oseltamivir in inhibiting influenza infection and its main manifestation, pyretic fever, thus reducing the need of antipyretics rapidly.

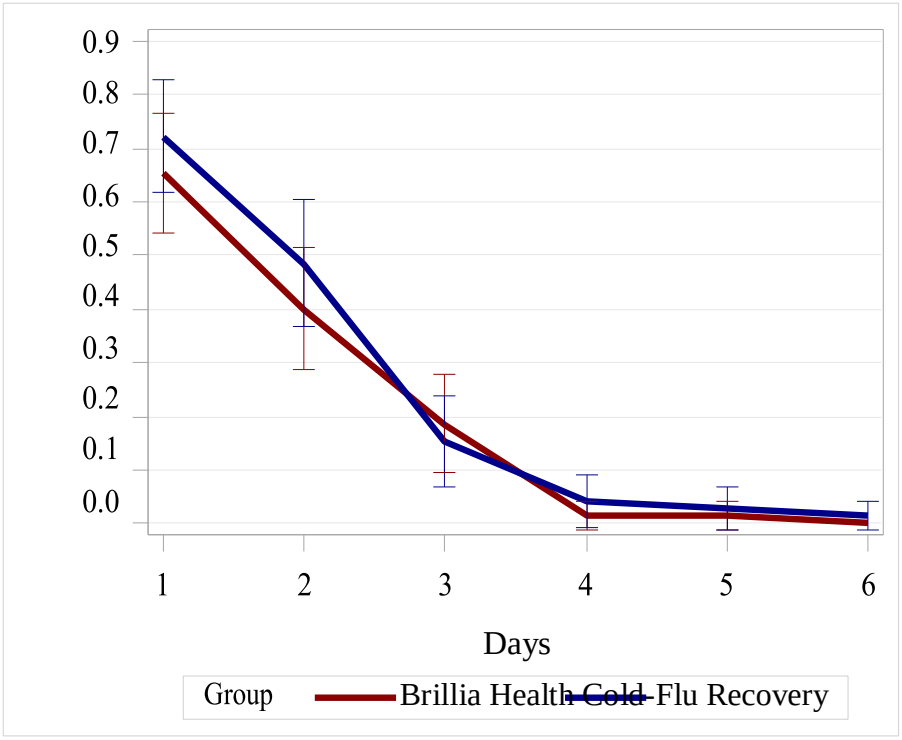

**Figure 14.5.1. Changes in the number of antipyretics (per one subject per day)**

Therefore, concluding the analysis by the principal endpoints associated with therapeutic effect on the clinical manifestations of influenza it should be stressed that the study results demonstrate efficacy of Brillia Health Cold-Flu Recovery in the treatment of influenza. The drug exerted a rapid effect on fever with its duration not exceeding three days. Most subjects had body temperature below $37.0^0$C on day 3 of therapy. Furthermore, Brillia Health Cold-Flu Recovery manifested therapeutic activity regarding the most relevant intoxication symptoms, severity of which was reduced significantly within the first three days of therapy. Efficacy of Brillia Health Cold-Flu Recovery in influenza was comparable to the effects of Oseltamivir (Tamiflu®).

**14.6 Changes in total score of quality of life questionnaire by the end of therapy vs. baseline (Day 7 vs. Day 1)**

Evaluation of quality of life of the subjects with influenza at baseline and by the end of therapy was performed using European Quality of Life Questionnaire (EQ5D) allowing to evaluate health status of the subject by five components: mobility, self-care, usual activities, pain/discomfort, anxiety/depression (each component was evaluated in scores from 1 to 3, minimum value corresponding to the best condition).

According to ***ITT-analysis*** , average total EQ5D score in subjects from Brillia Health Cold-Flu Recovery group on day 7 of the follow-up was 5.4±0.8 (vs. 9.4±1.9 at baseline) scores evidencing significant health improvement ($\Delta_{1-7}$=−4.0). In the reference group these values were 9.2±2.3 and 5.5±0.9 scores, respectively ($\Delta_{1-7}$=−3.7) (Table 14.1.6).

**Table 14.1.6: Total score of quality of life questionnaire EQ5D and health status scale in both groups**

| Day | *ITT-analysis* | | | *PP-analysis* | | |
|---|---|---|---|---|---|---|
| | **Brillia Health** | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health** | **Oseltamivir** (n=72) | **Statistics** |
| ***EQ5D questionnaire,*** *scores* | | | | | | |
| **1** | 9.4±1.9 | 9.2±2.3 | $\Delta_{E-O}$=−0.4; 95% CI < 0.2; t=-3.4; p=0.0005 | 9.6±1.9 | 9.4±2.2 | $\Delta_{Э-O}$=-0.3; 95% CI < 0.3; t=-3.2; p=0.0009 |
| **7** | 5.4±0.8 | 5.5±0.9 | | 5.3±0.9 | 5.4±0.8 | |
| | $\Delta_{1-7}$=−4.0 | $\Delta_{1-7}$=-3.7 | | $\Delta_{1-7}$=-4.3 | $\Delta_{1-7}$=-4.0 | |
| ***Health Status scale,*** *scores* | | | | | | |
| **1** | 42.1±18.4 | 46.7±15.1 | $\Delta_{E-O}$ =4.5; 95% CI > −0.5; t=4.3; | 41.6±18.2 | 46.2±15.4 | $\Delta_{E-O}$=4.3; 95% CI > − 0.7; t=4.3; |
| **7** | 87.7±10.6 | 87.8±11.4 | | 87.7±10.7 | 88.0±10.6 | |
| | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | $\Delta_{1-7}$=45.6 | $\Delta_{1-7}$=41.1 | p<0.0001 | $\Delta_{1-7}$=46.1 | $\Delta_{1-7}$=41.8 | p<0.0001 |

*Note.* The data are presented as Mean ± SD; CI – confidence interval; t –Student's test, p – error of the first kind; $\Delta_{1-7}$ – difference between the parameters within one group on days 1 and 7 of the follow-up; $\Delta_{Э-О}$ – difference between Brillia Health Cold-Flu Recovery and Oseltamivir groups in Δ values$_{1-7}$.

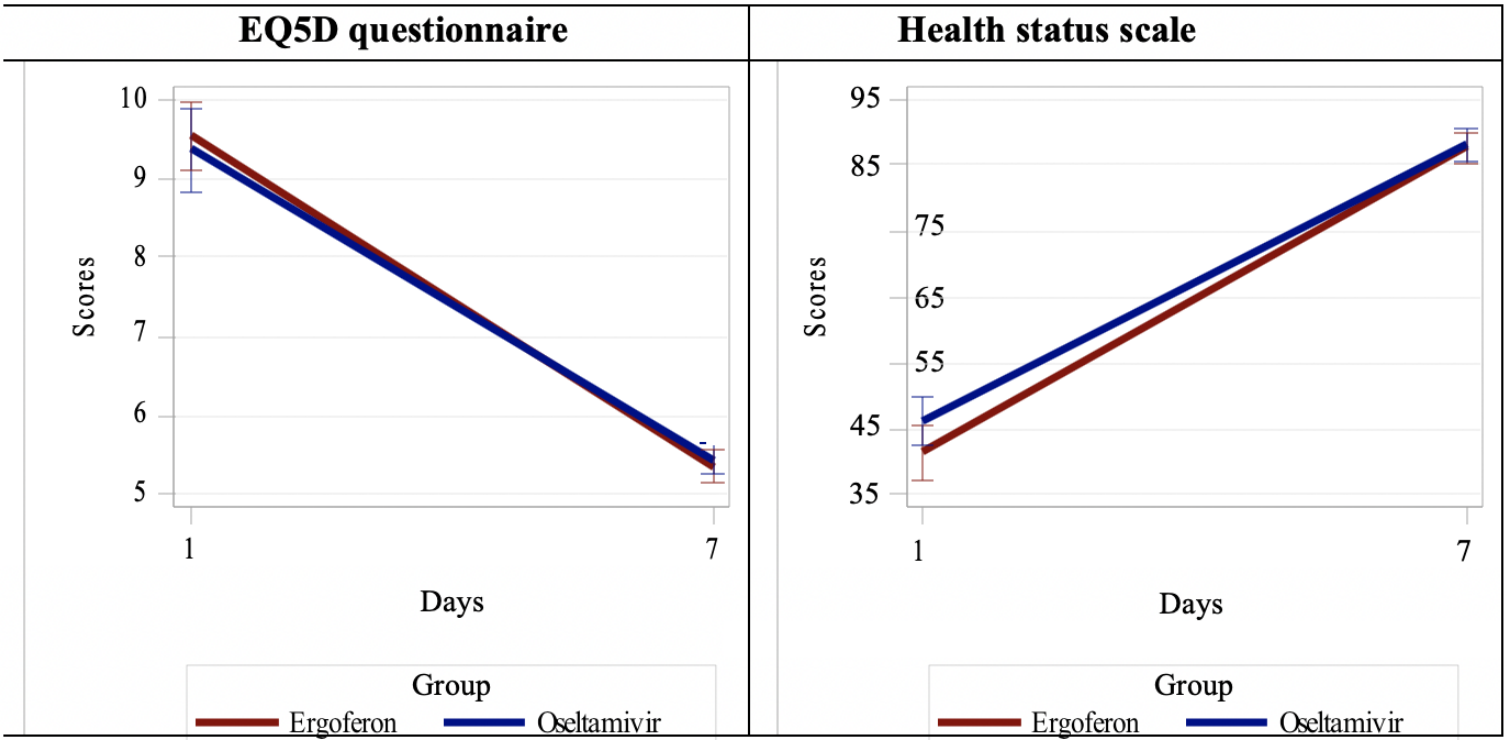


**Figure 14.6.1. Changes in total score of EQ5D quality of life questionnaire and health status scale (PP-analysis)**

Subjective evaluation of health status using visual analogue scale (VAS) demonstrated that Brillia Health Cold-Flu Recovery therapy ensured more than 2-fold increase in average total score - from baseline 42.1±18.4 to 87.7±10.6($\Delta_{1-7}$=45.6). Subjects receiving Oseltamivir had total score increased from 46.7±15.1 to 87.8±11.4 ($\Delta_{1-7}$=41.1) (Table 14.1.6). Similar results were obtained in PP-analysis of data (Table 14.6.1; fig. 14.1.6).

Statistical analysis of changes in total EQ5D and health status scale scores verified significant comparability of the results in both groups (Table 14.1.6).

## 14.7 Proportions of subjects with aggravated disease (complications requiring antibiotics or hospitalization)

The Brillia Health Cold-Flu Recovery group did not show any cases of aggravated disease, without complications requiring antibiotics or hospitalization. All subjects receiving Brillia Health Cold-Flu Recovery and completing the study were at the convalescence period either without clinical manifestations of the disease or with "residual" symptoms.

In the Oseltamivir group, 2 subjects had influenza complications such as secondary bacterial infections including community-acquired pneumonia of the inferior lobe of left lung (n=1) and acute maxillary sinusitis (highmoritis, n=1) requiring antibiotics. Frequency analysis of proportions of the subjects with aggravated

disease, despite "zero" result in the Brillia Health Cold-Flu Recovery group did not reveal significant difference between the groups (Table 14.1.7).

**Table 14.1.7: Proportion of subjects with aggravated disease**

| *ITT-analysis* | | | *PP-analysis* | | |
|---|---|---|---|---|---|
| **Brillia Health** | **Oseltamivir** (n=78) | **Statistics** | **Brillia Health** | **Oseltamivir** (n=72) | **Statistics** |
| 0 | 2 (2.6%) | Δ=−2.6%; $\chi_2$=2.0; p=0.15 | 0 | 1 (1.4%) | Δ=−1.4%; $\chi_2$=1.0; p=0.31 |

*Note.* "Statistics" column contains the data of frequency analysis (Wald method).

Nevertheless, it should be noted that Brillia Health Cold-Flu Recovery prevented additional secondary bacterial complications typical of influenza which is known to have potential to result in immunosuppression with secondary invasive/generalized infections. Therapeutic and preventive activity of Brillia Health Cold-Flu Recovery towards bacterial complications is explained by the fact that the drug ensures adequate antiviral response and prevention of cytopenic syndrome characteristic of the subjects after influenza.

**14.8 Therapeutic efficacy index by CGI-EI scale (additional criterion)**

By the end of the treatment the investigators evaluated therapeutic efficacy of the drug and adverse effects, thus calculating an efficacy index (using Clinical Global Impression scale, CI-EI). Data of ***ITT*** and ***PP-analyses*** of final evaluations were almost similar in both groups (Table 14.8.1; fig. 14.8.1). Average total score of "therapeutic efficacy" domain in the Brillia Health Cold-Flu Recovery group was 3.5±0.5 evidencing that the investigators in most cases evaluated clinical effect as expressed since the drug ensured significant improvement of the subjects' condition. Efficacy of Oseltamivir, according to the investigators, was generally the same (3.7±0.5 scores).

Adverse effects of therapy, according to the investigators, were single and did not exert significant effects on the functional potential of the subject. Average total scores of adverse effects in the Brillia Health Cold-Flu Recovery and Oseltamivir groups were 1.1±0.3 and 1.1±0.4 (ITT-analysis) and 1.1±0.3 and 1.1±0.3 (PP-analysis) and were comparable (Table 14.1.8).

**Table 14.8.1: Evaluation of therapeutic efficacy by CGI scale**

| Day | *ITT-analysis* | | | *PP-analysis* | | |
|---|---|---|---|---|---|---|
| | **Ergoferon** (n=78) | **Oseltamivir** (n=78) | **Statistics** | **Ergoferon** (n=75) | **Oseltamivir** (n=72) | **Statistics** |
| **Therapeutic effect** | 3.5±0.5 | 3.7±0.5 | Δ=−0.2; 95% CI > −0.4; t=6.5; | 3.5±0.5 | 3.7±0.5 | Δ=−0.2; 95% CI > −0.4; t=6.3; |
| **Adverse events** | 1.1±0.3 | 1.1±0.4 | Δ=−0.03; 95% CI < 0.2; t=−4.8; | 1.1±0.3 | 1.1±0.3 | Δ=−0.02; 95% CI < 0.1; t=−4.7; |
| **Efficacy index** | 3.3±0.7 | 3.5±0.8 | Δ=−0.2; 95% CI > −0.4; t=−4.8; | 3.4±0.7 | 3.6±0.7 | Δ=−0.19; 95% CI > −0.4; t=4.5; |

*Note*. The results are presented as Mean ± SD. "Statistics" column contains the data of Student's test modified for calculation of comparability (non-inferiority) calculated for the difference of average values to determine significance of its difference vs. pre-established delta (margin) and p-value (error of the first kind).

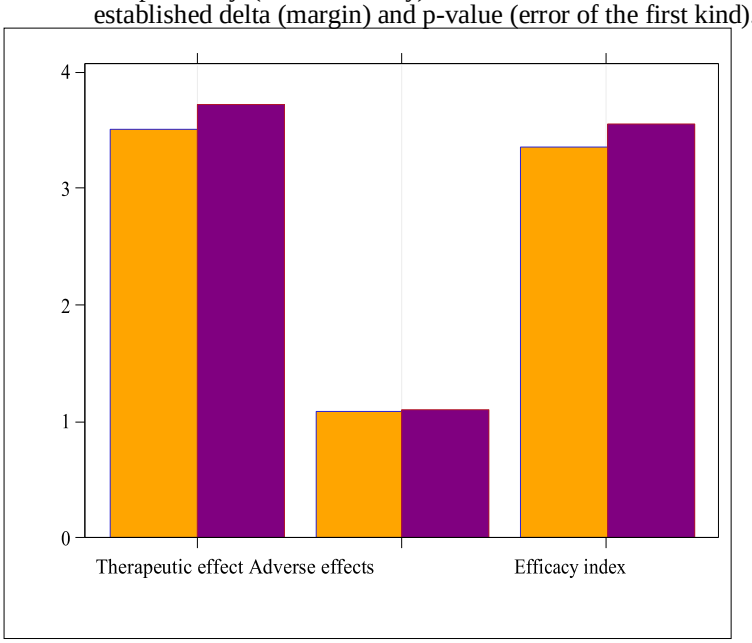


**Figure 14.8.1. Average parameters of Clinical Global Impression scale CGI (PP-analysis)**

Efficacy index, i.e. the ratio of therapeutic and adverse effects, in subjects of both groups was high being 3.3±0.7 and 3.4±0.7 scores, respectively, evidencing comparability of Brillia Health Cold-Flu Recovery and Oseltamivir (Table 14.8.1; fig. 14.8.1).

In conclusion of the analysis of the study results on all primary and secondary endpoints, it should be stressed once again that Brillia Health Cold-Flu Recovery demonstrated therapeutic efficacy in the treatment of influenza exerting effect on the main clinical symptoms of the disease - severity and duration of fever, intoxication signs and respiratory catarrhal symptoms. Based on the results of the analysis of clinical data and final evaluations of the investigations, efficacy of Brillia Health Cold-Flu Recovery was comparable to that of Oseltamivir (Tamiflu®), an anti-influenza drug with verified efficacy. In addition to a positive effect on the course of influenza, Brillia Health Cold-Flu Recovery prevented secondary bacterial complications ensuring convalescence of 100% of the subjects.

**15. Safety evaluation**

Safety and tolerability evaluations were based on the data from all randomized subjects receiving at least one dose of the study drug (n=161; *Safety population*). Vital signs of the study subjects, changes in laboratory data (complete blood analysis, urinalysis, biochemistry) were evaluated and adverse effects (AE) were recorded during the treatment. In case of AE, causal relationship with the study drug was specified (such evaluation was based on the investigator's opinion) as well as severity and outcome of AE [37, 40, 41].

**Presentation of safety parameters**

Vital signs (according to the investigator's examination on days 1, 3 and 7 of the follow-up) and laboratory data (biochemistry, complete blood analysis and urinalysis) are presented in tables as average values in the groups; cases of deviations of laboratory values outside normal range (shift tables) are also demonstrated. Adverse effects revealed during the study are grouped in frequency tables specifying severity, seriousness and causal relationship with the study therapy.

**15.1 Changes in vital signs**

Brillia Health Cold-Flu Recovery did not exert negative effects on vital signs of the study subjects, including respiratory rate (RR) and heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure.

Baseline tachycardia (mean HR value > 90 bpm) typical of the pyretic period of an infectious disease was normalized during therapy, while HR at convalescence stage (Day 7, Visit 3) in all study subjects was within normal range (ITT and PP-analysis). Average and individual HR, SBP and DBP values throughout the study were consistent with normal values (Table 15.1.1). One-way Repeated Measures ANCOVA did not reveal differences between the two groups in terms of HR, RR, SBP and DBP at visits 1 (Day 1), 2 (Day 3) and 3 (Day 7).

**Table 15.1.1: Changes in vital signs**

| **Parameter /** | **Visit** | **Group** | |
|---|---|---|---|
| | | **Brillia Health Cold-Flu Recovery (n=81)** | **Oseltamivir (n=80)** |
| **HR** | | | |
| | Visit 1 | **93.0±8.3** | **93.4±9.6** |
| | Visit 2 | **80.4±7.5** | **79.1±6.5** |
| | Visit 3 | **73.4±4.8** | **74.0±5.6** |
| **RR** | | | |
| | Visit 1 | 17.7±2.1 | 17.8±2.4 |
| | Visit 2 | 16.4±1.5 | 16.5±1.2 |
| | Visit 3 | 16.1±1.3 | 16.1±1.3 |
| **SBP** | | | |
| | Visit 1 | 120.1±8.9 | 122.0±11.8 |
| | Visit 2 | 118.4±7.0 | 119.6±8.6 |
| | Visit 3 | 118.4±6.5 | 119.4±6.9 |

| | | | |
|---|---|---|---|
| **DBP** | | | |
| | Visit 1 | 75.0±8.1 | 76.6±8.3 |
| | Visit 2 | 73.2±7.5 | 76.2±7.6 |
| | Visit 3 | 73.4±6.8 | 74.8±6.6 |

## 15.2 Changes in laboratory parameters

Laboratory parameters (biochemistry, complete blood analysis and urinalysis) were evaluated at baseline (Visit 1) and on day 7 of the follow-up (Visit 3). Average laboratory values presented in Table 15.2.1 were within normal range both at baseline and by the end of the treatment course.

**Table 15.1.2: Changes in blood and urine values**

| Parameter | Units | Brillia Health Cold-Flu Recovery (n=81) | | Oseltamivir (n=80) | |
|---|---|---|---|---|---|
| | | Visit 1 | Visit 3 | Visit 1 | Visit 3 |
| **Biochemistry** | | | | | |
| **Total bilirubin** | μmol/L | 11.4±4.0 | 12.1±6.5 | 11.5±4.0 | 11.4±3.3 |
| **ALT** | U/L | 24.1±10.1 | 25.5±13.1 | 23.6±10.5 | 23.1±9.1 |
| **AST** | U/L | 23.4±7.6 | 23.3±7.8 | 23.4±8.9 | 23.0±8.9 |
| **Creatinine** | μmol/L | 78.9±17.3 | 78.0±16.0 | 81.3±18.4 | 81.4±16.0 |
| **Complete blood analysis** | | | | | |
| **Erythrocytes** | $\times 10^{12}$/L | 4.6±0.4 | 4.6±0.4 | 4.6±0.4 | 4.6±0.4 |
| **Hemoglobin** | g/L | 138.8±13.9 | 138.7±12.4 | 137.9±11.5 | 138.7±11.1 |
| **Packed cell volume** | % | 41.7±4.2 | 41.8±4.0 | 41.3±3.8 | 41.6±3.2 |
| **Leukocytes** | $\times 10^{9}$/L | 6.6±2.0 | 6.0±1.3 | 6.5±1.7 | 6.0±1.2 |
| **Stab** | % | 2.5±2.7 | 2.0±1.5 | 2.0±1.4 | 2.5±1.8 |
| **Segmented** | % | 56.5±8.7 | 55.0±7.8 | 58.6±8.4 | 55.5±8.7 |
| **Eosinophils** | % | 2.2±1.3 | 2.2±1.3 | 2.2±1.3 | 2.5±1.9 |
| **Basophiles** | % | 0.5±0.6 | 0.3±0.5 | 0.5±0.6 | 0.4±0.5 |
| **Lymphocytes** | % | 31.7±7.5 | 34.1±7.7 | 31.1±6.7 | 33.3±7.6 |
| **Monocytes** | % | 7.0±3.0 | 6.5±2.7 | 6.4±3.3 | 6.3±2.4 |
| **Platelets** | $\times 10^{9}$/L | 240.6±50.0 | 261.4±58.2 | 245.1±50.2 | 251.4±50.6 |
| **BSR** | mm/hr | 8.4±4.3 | 8.4±7.3 | 8.8±4.2 | 9.3±7.8 |
| **Urinalysis** | | | | | |
| **Density** | | 1017.0±4.9 | 1017.2±5.2 | 1016.8±5.5 | 1016.9±5.1 |

**Table 15.2.2: Presence/absence of deviations of laboratory paramters**

| Parameter | Brillia Health Cold-Flu Recovery (n=81) | | | | Oseltamivir (n=80) | | | | Statistics |
|---|---|---|---|---|---|---|---|---|---|
| | Visit 1 | | Visit 3 | | Visit 1 | | Visit 3 | | |
| | n (%) | Subject code | n (%) | Subject code | n (%) | Subject code | n (%) | Subject code | |
| ***Biochemistry*** | | | | | | | | | |
| **Total bilirubin** | 1 (1.2%) | 07-050-218 | 2 (2.5%) | 07-050-218<br>08-008-028 | 0 | - | 0 | - | $\chi 2=2.0$; p=0.2 |
| **ALT** | 0 | - | 1 (1.2%) | 04-007-609 | 0 | - | 1 (1.3%) | 06-010-650 | $\chi 2=0.0$; p=1.0 |
| **AST** | 0 | - | 1 (1.2%) | 04-007-609 | 0 | - | 1 (1.3%) | 06-010-650 | $\chi 2=0.0$; p=1.0 |
| **Creatinine** | 0 | - | 0 | - | 1 (1.3%) | 08-005-024 | 0 | | NA |
| Complete blood analysis | | | | | | | | | |
| **Erythrocytes** | 0 | –– | 0 | | 0 | | 0 | | NA |
| **Hemoglobin** | 0 | – | 0 | | 0 | | 0 | | NA. |
| **Packed cell volume** | 0 | – | 0 | | 0 | | 0 | | NA |
| **Leukocytes** | 1 (1.2%) | 07-054-222 | 1 (1.2%) | 07-044-193 | 1 (1.3%) | 07-057-225 | 0 | | $\chi^2=1.0$; p=0.3 |
| **Stab neutrophils** | 0 | – | 0 | | 0 | | 0 | | NA |
| **Segmented neutrophils** | 0 | – | 1 (1.2%) | 07-043-192 | 0 | | 1 (1.3%) | 07-049-217 | $\chi 2=0.0$; p=1.0 |
| **Eosinophils** | 0 | – | 0 | | 0 | | 1 (1.3%) | 04-025-118 | $\chi^2=1.0$; p=0.3 |
| **Basophiles** | 0 | – | 0 | | 0 | | 0 | | NA |
| **Lymphocytes** | 0 | – | 0 | | 0 | | 1 (1.3%) | 07-049-217 | $\chi^2=1.0$; p=0.3 |
| **Monocytes** | 0 | – | 2 (2.5%) | 07-029-018<br>07-036-191 | 0 | | 1 (1.3%) | 07-012-016 | $\chi 2=0.3$; p=0.6 |
| **Platelets** | 0 | | 1 (1.2%) | 07-043-192 | 1 (1.3%) | 08-001-021 | 1 (1.3%) | 08-001-021 | $\chi 2=0.0$; p=1.0 |
| **BSR** | 0 | | 0 | | 1 (1.3%) | 02-001-076 | 1 (1.3%) | 07-045-194 | $\chi 2=1.0$; p=0.3 |
| ***Urinalysis*** | | | | | | | | | |
| **Specific gravity** | 0 | | 0 | | 0 | | 1 (1.3%) | 07-051-219 | 07-051-219 $\chi 2=1.0$; p=0.3 |
| **Colour** | 0 | | 0 | | 0 | | 0 | | NA |
| **Protein** | 0 | | 4 (4.9%) | 04-007-609<br>04-024-117<br>07-036-191<br>07-043-192 | 0 | | 3 (3.8%) | 07-003-012<br>07-045-194<br>07-046-195 | $\chi 2=0.1$; p=0.7 |
| **Glucose** | 0 | | 1 (1.2%) | 08-012-631 | 0 | | 0 | | $\chi^2=1.0$; p=0.3 |
| **Ketone bodies** | 0 | 0 | | 0 | 0 | NA | | | |
| **Leukocytes** | 1 (1.2%) | 07-050-218 | 2 (2.5%) | 04-007-609<br>07-036-191 | 1 (1.3%) | 07-051-219 | 1 (1.3%) | 07-052-220 | $\chi 2=0.3$; p=0.6 |
| **Erythrocytes** | 1 (1.2%) | 07-050-21 | 2 (2.5%) | 07-036-191 | | | 2 (2.5%) | 07-046-195 | $\chi 2=0.0$; p=1.0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 07-043-192 | | | | 07-052-220 | |
| **Squamous epithelium** | 1 (1.2%) | 07-050-218 | 0 | | 1 (1.3%) | 07-051-219 | 1 (1.3%) | 07-051-219 | $\chi 2=1.0$; p=0.3 |
| **Casts** | 0 | | 0 | | 0 | | 0 | | NA |
| **Salts** | 0 | | 1 (1.2%) | 07-036-191 | 0 | | 0 | | $\chi^2=1.0$; p=0.3 |
| **Bacteria** | 0 | | 2 (2.5%) | 07-036-191<br>07-043-192 | 1 (1.3%) | 07-051-219 | 1 (1.3%) | 07-045-194 | $\chi 2=0.3$; p=0.6 |
| **Mucus** | 0 | | 3(3.7%) | 04-007-609<br>07-036-191<br>07-011-188 | 1 (1.3%) | 07-051-219 | 1 (1.3%) | 07-045-194 | $\chi 2=1.0$; p=0.3 |

*Note.* "Statistics" column presents findings of frequency analysis - comparison of the results in two groups at visit 3. NA – Not Applicable due to two zero values.

Biochemistry revealed baseline bilirubinemia at 24 μmol/L in one subject from the Brillia Health Cold-Flu Recovery group (No. 07-050-218) which increased to 31 μmol/L by the end of the study. Such change is described as a mild AE in section 15.3.

Baseline creatininemia in one subject from the Oseltamivir group (No. 08-005-024) was interpreted as a concomitant condition.

Changes in transaminase levels revealed in 2 subjects (one in each group) at Visit 3 are described in section 15.3 as AE.

Complete blood analysis revealed baseline changes in the form of leuko- and thrombocytosis, increased BSR in one subject of the Brillia Health Cold-Flu Recovery group and 3 subjects from the Oseltamivir group. Such shifts typical of acute infectious process were interpreted as concomitant conditions. In repeated blood tests by the end of the treatment these values were within reference values.

Changes in control blood tests in 3 subjects from the Brillia Health Cold-Flu Recovery group (including leukopenia, n=1; monocytosis, n=1; granulocytopenia+thrombocytosis, n=1) typical of influenza convalescence period, are described as AEs in section 15.3.

Control blood test changes revealed in 4 subjects from the Oseltamivir group including eosinophilia (n=1), granulocytopenia+lymphocytosis (n=1) and monocytosis (n=1) are also described as AEs (section 15.3). Changes in the primary urinalysis including leukocyturia+erythrocyturia (one subject from the Brillia Health Cold-Flu Recovery group), leukocyturia + bacteriuria + mucus (one subject from the Oseltamivir group) were interpreted as concomitant conditions.

Isolated or combined changes in urinary sediment recorded at repeated examination in 6 subjects from the Brillia Health Cold-Flu Recovery group and in 5 subjects from the Oseltamivir group are described in section 15.3 as AEs.

Frequency analysis (Wald method) did not demonstrate significant differences between the groups in terms of the frequency of deviations in laboratory values.

**15.3 Adverse events**

Collection of information on AEs started from enrollment and signing an informed consent form and terminated after all study procedures were over. The data obtained from the subject and medical personnel involved in the clinical study were taken into account. At each visit the subjects were asked questions concerning their health condition, any unfavorable events which could have occurred since the latest visit. Coding and terminology to describe AEs are presented in accordance with MedDRA.

AE reports were recorded during the follow-up by the investigators and medical personnel of the clinical sites; individual reports from the subjects have not been obtained.

In total, both the treatment and follow-up periods in the Brillia Health Cold-Flu Recovery group were associated with 15 cases of AEs in 11 subjects, in the Oseltamivir group − 16 AEs in 15 study subjects (Table 15.3.1; 15.3.2).

Percentage of the subjects with AEs in the Brillia Health Cold-Flu Recovery group was 13.6%, Oseltamivir - 18.8%. Average incidence of AEs per one subject was 0.185 and 0.20, respectively.

Percentage of the subjects with AEs and incidence of AEs did not show significant differences between the groups.

**Table 15.1.3: Distribution of subjects with adverse effects by groups**

| Parameter | Group | | Statistics |
|---|---|---|---|
| | Brillia Health Cold-Flu Recovery (n=81) | Oseltamivir (n=80) | |
| **Number of subjects with AEs, n (%)** | 11 (13.6%) | 15 (18.8%) | Δ=−5.2%; $\chi_2$=0.8; p=0.36* |
| **Incidence of AEs per 1 subject** | 0.185 | 0.2 | Δ=−0.015; t=−0.7; p=0.46** |

*Note.* AE – adverse effect

* data of frequency analysis (Wal method); ** Student's test data.

All AEs in the Brillia Health Cold-Flu Recovery group (n=15) were mild, did not have distinct (verified) relationship with the study therapy and in most cases (n=13) were laboratory changes revealed following repeated examination of the subjects (Table 15.3.2). In the Oseltamivir group, 6 AEs out of 16 were moderate (including pneumonia and highmoritis) and 10 AEs were mild.

**Table 15.2.3: List of adverse effects**

| Subject No. | AE description | AE severity | Relationship with the study therapy | LLT Code | SOC Code |
|---|---|---|---|---|---|
| **Brillia Health Cold-Flu Recovery** | | | | | |
| 07-050-218 | Changes in biochemistry (increased bilirubin level (up tp 31 μmol/L) | Mild | Unlikely/ doubtful | 10004690 | 10022891 |
| 08-008-028 | Changes in biochemistry (increased bilirubin level (up tp 53.8 μmol/L) | Mild | No relationship | 10004690 | 10022891 |
| 04-007-609 | Changes in biochemistry (increased AST to 61 U/L, ALT to 83 U/L) | Mild | Unlikely/ doubtful | 10054889 | 10022891 |
| 04-007-609 | Changes in urinalysis (proteinuria, leukocyturia, mucus) | Mild | No relationship | 10001580<br>10047943<br>10050805 | 10038359<br>10022891 |
| 04-010-610 | Other changes (R19.5) | Mild | Possible | 10000134 | 10017947 |
| 07-029-018 | Changes in complete blood analysis (monocytosis 9.1%) | mild | Probable | 10027906 | 10005329 |

| | | | | | |
|---|---|---|---|---|---|
| 07-043-192 | Changes in complete blood analysis (thrombocytosis 381×109/L, granulocytopenia 35.7%) | Mild | Unlikely/ doubtful | 10043563 10018687 | 10005329 |
| 07-043-192 | Changes in urinalysis (proteinuria, erythrocyturia, bacteriuria) | Mild | Unlikely/ doubtful | 10046669 10060857 10037032 | 10038359 10022891 |
| 07-044-193 | Changes in complete blood analysis (leukopenia $3.9\times10^9$/L) | Mild | Unlikely/ doubtful | 10024384 | 10005329 |
| 07-036-191 | Changes in complete blood analysis (monocytosis 9.5%) | Mild | Unlikely/ doubtful | 10005670 | 10022891 |
| 07-036-191 | Changes in urinalysis (proteinuria, erythrpcyturia, bacteriuria, salts++ bacteria, mucus) | Mild | Unlikely/ doubtful | 10001580 10047943 10058391 10053114 10060857 10050805 | 10038359 10022891 |
| 04-024-117 | Changes in urinalysis (proteinuria) | Mild | No relationship | 10037032 | 10038359 |
| 08-012-631 | Changes in urinalysis (glucosuria) | Mild | No relationship | 10018473 | 10038359 |
| 07-011-188 | Changes in urinalysis (mucus in urine) | Mild | No relationship | 10050805 | 10038359 |
| 07-011-188 | Burning in mouth | Mild | Possible | 10043514 | 10038738 10017947 |
| **Oseltamivir** | | | | | |
| 04-021-116 | Community-acquired pneumonia of the inferior lobe | Moderate | No relationship | 10066724 | 10021881 |
| 09-026-649 | Acute maxillary sinusitis (highmoritis; J01.0) | Moderate | No relationship | 10001076 | 10021881 |
| 04-001-178 | Seeking emergency care due to impaired breathing against cough episodes | Moderate | No relationship | 10012791 | 10038738 10007541 |
| 06-010-650 | Situation-based depression | Moderate | Unlikely/ doubtful | 10012378 | 10037175 |

| | | | | | |
|---|---|---|---|---|---|
| 06-010-650 | Changes in biochemistry (AST up to 58.9 U/L, ALT up to 59.2 U/L) | Mild | Unlikely/ doubtful | 10054889 | 10022891 |
| 15-021-682 | Nausea | Mild | Possible | 10028813 | 10017947 |
| 07-010-187 | Nausea | Mild | Possible | 10028813 | 10017947 |
| 04-025-118 | Changes in complete blood analysis (eosinophilia 13%) | Mild | No relationship | 10014950 | 10005329 |
| 07-012-016 | Changes in complete blood analysis (monocytosis 9.7%) | Mild | Unlikely/ doubtful | 10027906 | 10005329 |
| 07-049-217 | Changes in complete blood analysis (lymphocytosis 57.1% and granulocytopenia 35.9%) | Mild | Unlikely/ doubtful | 10025280<br>10018687 | 10005329 |
| 07-045-194 | Changes in complete blood analysis (BSR increase to 50 mm/hr) | Moderate | Unlikely | 10015480 | 10022891 |
| 07-045-194 | Changes in urinalysis (protein – 0.0337 g/L, mucus +, bacteria ++) | Mild | Unlikely/ doubtful | 10001580<br>10050805<br>10060857 | 10038359<br>10022891 |
| 07-046-195 | Changes in urinalysis (proteinuria, erythrocyturia) | Mild | Unlikely/ doubtful | 10037032<br>10046669 | 10038359<br>10022891 |
| 07-003-012 | Changes in urinalysis (proteinuria) | Mild | No relationship | 10037032 | 10038359 |
| 07-051-219 | Changes in urinalysis (increased density, squamous epithelium) | Mild | Unlikely/ doubtful | 10050773 | 10022891 |
| 07-052-220 | Changes in urinalysis (proteinuria, leukocyturia, erythrocyturia) | Moderate | Unlikely/ doubtful | 10047943<br>10046669<br>10001580 | 10038359<br>10022891 |

Subject No. 07-011-188 in the Brillia Health Cold-Flu Recovery group had an AE in the form of a burning cavity in the mouth, potentially associated with the study therapy; no actions regarding the study drug have been taken. Subject No. 04-010-610 revealed transient changes in frequency and consistence of feces (R 19.5 - Other

fecal changes), in this case relationship with the study therapy was also considered as possible, the subject was prescribed with concomitant therapy, no actions regarding the study drug were taken.

Brillia Health Cold-Flu Recovery had 13 cases of AEs (in 11 subjects) in the form of laboratory changes (Table 15.3.1) including:

**1)** *Biochemistry* − increased total bilirubin level (in subject No. 07-050-218 from 24 µmol/L [at baseline] to 31 µmol/L; in subject No. 08-008-028 – to 53.8 µmol/L), increased AST to 61 U/L and ALT to 83 U/L (in subject No. 04-007-609 with hepatic steatosis and biliary dyskinesia). All three changes were mild and were not related to or unlikely related to Brillia Health Cold-Flu Recovery. In 2 cases (No. 07-050-218 and No.04-007-609) such biochemical deviations were revealed in subjects previously as well.

**2)** *Complete blood analysis* − monocytosis (subject No. 07-036-191 and No. 07-029- 018), thrombocytosis and granulocytopenia (subject No. 07-043-192), leukopenia (subject No. 07-044-193). These changes are possible during convalescence from viral infection.

**3)** *Urinalysis* – increased levels of protein, glucose, leukocytes, erythrocytes, mucus, bacteria − as isolated or combined deviations were revealed in 6 subjects. These deviations are also possible after infection.

Significance of the causal relationship between laboratory changes and Brillia Health Cold-Flu Recovery was considered as probable/possible/doubtful or was absent (no relationship); in all cases no actions regarding the study drug were made.

In the Oseltamivir group subject No. 04-021-116 was diagnosed with community-acquired pneumonia of the inferior lobe of left lung (Table 15.3.1) not related to the study therapy, severity of AE was moderate, and the drug was discontinued. Since antibacterial therapy was indicated as forbidden within the protocol, the subject was excluded from the study.

Aggravation of the condition in the form of influenza complications - acute maxillary sinusitis (highmoritis) was revealed in subject No. 09-026-649 from the Oseltamivir group; AE was considered to be unrelated to the therapy, was moderate and concomitant therapy was prescribed.

Situation-based depression (No. 06-010-650) and impaired breathing against cough episodes (No. 04-001-178) in subjects from the Oseltamivir group were moderate; therapy was continued and the subject with depression was prescribed with neurologist's consultation. Two subjects (No. 07-010-187 and 15-021-682) had nausea against Oseltamivir therapy, possibly related to the treatment, in both cases no actions regarding the study drug were taken.

11 subjects from the Oseltamivir group had 11 cases of laboratory deviations.

**1)** *Biochemistry* – increased transaminases (subject No. 06-010- 650) considered to be a mild AE having unlikely/doubtful relationship with the treatment, no changes regarding Oseltamivir were made, the drug was not discontinued);

**2)** *Complete blood analysis*– accelerated BSR (in subject No. 07-045-194), eosinophilia (subject No. 04-

025-118), monocytosis (No. 07-012-016), lymphocytosis combined with granulocytopenia (No. 07-049-217);

**3)** *urinalysis* – isolated combined changes such as proteinuria, erythrocyturia, leukocyturia and bacteriuria, increased urine density, amount of salts and mucus.

Causal relationship between laboratory shifts and Oseltamivir was considered to be unlikely/doubtful or was absent (no relationship); no cases regarding the study drug was made in any of cases.

During the present clinical study no data on Brillia Health Cold-Flu Recovery interactions with drugs of various classes used as concomitant therapy were obtained including antipyretics and non-steroidal anti-inflammatory drugs, expectorants, broncholytics, antihypertensive drugs (ACE inhibitors, angiotensin receptor antagonists, beta-adrenoblockers, calcium channel blockers), diuretics, statins, drugs for the treatment of thyroid diseases. Co-administration of these drugs with Brillia Health Cold-Flu Recovery did not result in pharmacological incompatibility reactions, antagonistic or synergistic effects.

Therefore, results of safety analysis demonstrated that Brillia Health Cold-Flu Recovery was safe for the treatment of influenza in adult subjects. Brillia Health Cold-Flu Recovery did not impair vital signs or result in serious AEs or AEs which could be interpreted as definitely related to the drug. All cases of AEs were mild. Laboratory changes revealed on day 7 of the study (this day was simultaneously the last day of the disease since all subjects were enrolled within 24 hours from manifestations of the first symptoms) were typical for the convalescence period. No subjects from the Brillia Health Cold-Flu Recovery group, unlike the Oseltamivir group, had secondary bacterial complications requiring antibacterial therapy. All subjects showed 100% compliance, tolerated Brillia Health Cold-Flu Recovery well and completed the study with convalescence or significant improvement.

## 16. Conclusion

This study was designed to perform comparative evaluation of the efficacy and safety of Brillia Health Cold-Flu Recovery in the treatment of influenza; an antiviral drug with verified antiviral efficacy – Oseltamivir (Tamiflu®) was chosen as a reference drug.

The study enrolled and randomized 161 subjects aged 18-60 years old (average age 34.7±12.1 years old) seeking medical advice within 24 hours from the first influenza symptoms - fever (axillary body temperature > $37.8^0$C) and at least one systemic and catarrhal symptom. The diagnosis was verified by an immunological rapid test detecting influenza virus antigens in the nasal epithelium. Subjects of group 1 (n=81) received Brillia Health Cold-Flu Recovery using a therapeutic scheme, group 2 (n=80) – Oseltamivir 75 mg twice daily. Treatment periods in both groups were 5 days, with a follow-up at 7 days. During the study the subjects were examined three times by the investigator who recorded severity of influenza symptoms in scores, monitored therapeutic safety and compliance of the subjects.

Evaluation of therapeutic efficacy was based on ITT and PP data analysis in ITT (n=156) and PP (n=17) sets, respectively, the results were comparable due to small differences in the number of sets (results of PP-

analysis are presented in square brackets). Safety and tolerability of therapy was evaluated based on the data of subjects from ITT-set.

The subjects from the Brillia Health Cold-Flu Recovery and Oseltamivir groups were not different in terms of the main clinical and demographic characteristics. Acute onset, pyretic fever and expressed intoxication signs typical of influenza were noted in all subjects. Average body temperature on day 1 was 38.2±0.4$^0$C [38.3±0.4$^0$C] in the Brillia Health Cold-Flu Recovery group and 38.3±0.4$^0$C [38.3±0.4$^0$C] in the Oseltamivir group (the data are specified in ITT [PP] sets, respectively). Severity of intoxication signs was 18.8±6.2 [19.0±6.7] in Brillia Health Cold-Flu Recovery group and 18.6±6.2 [18.6±6.3] in the Oseltamivir group. Severity of respiratory symptoms was also generally identical between the groups making about 6 scores on average.

More than 30% subjects had various comorbidities, at that most of them had 2 or more diagnoses. Most commonly gastrointestinal diseases (>20%) and circulatory disorders (15%).

About 90% of subjects received antipyretics on day 1, a lot of them used vasoconstrictor nasal drops and sprays, some – secretolytics and expectorants, vitamins and phytodrugs. For the treatment of background pathologies antihypertensive drugs (ACE inhibitors, angiotensin receptor antagonists, beta-adrenoblockers, calcium channel blockers), diuretics, bronchodilators, statins, drugs for the treatment of thyroid disease were used.

Proportion of subjects with axillary temperature decreased to 37.00C and below (without subsequent increase) during the follow-up was used as the primary efficacy criterion.

Percentage of subjects with normal morning body temperature increased in the Brillia Health Cold-Flu Recovery group from 19 [19]% on day 2 (vs. 10 [10]% in the Oseltamivir group) to 100 [100]% by the end of the treatment course (vs. 92 [92]% in the Oseltamivir group). Evening thermometry indicated that by the end of day 4 more than two thirds of subjects (68 [68]%) had temperatures $\leq$37.0$^0$C, by the end of day 5 normalization of body temperature was noted in most subjects (85 [84]%) from the Brillia Health Cold-Flu Recovery group. Values in the Oseltamivir group were generally identical (from 69 [72]% to 86 [88]%, respectively). Frequency analysis (Wald method) in ITT and PP-sets demonstrated that Brillia Health Cold-Flu Recovery exerted positive therapeutic effects on fever reactions which is known to be the marker of activity of the infectious process of influenza, and such effect was similar to that of Oseltamivir.

Secondary efficacy criteria were several; one of them - percentage of the subjects having no clinical manifestations of influenza on day 7 of the study including fever, intoxication and respiratory symptoms evaluated by the investigator using 4-point scale in scores (from 0 to 3). Headache as well as other types of pain (muscle, joint, eye) was absent in 99 [100]% subjects from Brillia Health Cold-Flu Recovery group and 100 [100]% from the Oseltamivir group; asthenic manifestations (weakness, sweatiness, malaise, somnolence) − in 82 [83]%, 87 [88]%, 90 [91]%, 96 [96]% and 74 [75]%, 86 [86]%, 91 [92]% and 97 [99]% subjects, respectively.

All intoxication signs were eliminated by day 7 in 60 [61]% and 64 [64%] subjects, respectively (significant comparability based on Wald method: Z=1.9 [2.0]; p=0.028 [0.22]). Catarrhal symptoms persisting for more than one week in a small number of subjects were absent on day 7 in 83 [83]% subjects from the Brillia

Health Cold-Flu Recovery group and 77 [76]% from the Oseltamivir group (significant comparability based on Wald method: Z=3.9 [2.0]; p<0.001 [0.021]). Proportion of "full convalescents", i.e. the subjects without influenza symptoms was 45 [47%] in Brillia Health Cold-Flu Recovery group and 50 [49]% in the Oseltamivir group (significant comparability based on Wald method: Z=1.7 [2.0]; p=0.044 [0.021]). The results of ITT and PP analysis evidenced that 5-day course of Brillia Health Cold-Flu Recovery was significantly comparable with Oseltamivir effects: day 7 of the follow-up was characterized by both normal body temperature in all subjects and absence of intoxication and respiratory catarrhal signs in most subjects of both groups.

Average duration of fever in subjects from the Brillia Health Cold-Flu Recovery group was 2.1±1.5 [2.1±1.4] days, Oseltamivir – 2.3±1.6 [2.3±1.6] days, intoxication symptoms − 2.7±2.2 [2.6±2.2] and 2.4±2.1 [2.4±2.1] days, catarrhal manifestations –2.8±2.5 [2.7±2.5] and 2.6±2.6 [2.6±2.6] days, average duration of all influenza symptoms − 2.7±2.3 [2.6±2.3] and 2.5±2.2 [2.5±2.2] days, respectively. It should be noted that Oseltamivir efficacy demonstrated in this study is not different from the results of previous and published clinical studies of the drug [28-30]. Analysis of elimination terms of influenza manifestations evidenced comparable therapeutic efficacy of the two drugs. Most clinical signs of the disease were 3 days on average and did not vary significantly between Brillia Health Cold-Flu Recovery and Oseltamivir ITT and PP-sets.

The effects of Brillia Health Cold-Flu Recovery unfolded rapidly and as soon as day 3 of its application average body temperature was 37.0±0.5$^0$C (ITT and PP-sets), remaining below 37.0$^0$C on the following days of the follow-up. Severity of fever or its reduction on day 3 were comparable in both groups (ITT-analysis: $\Delta^0$=0.01; 95% CI < 0.14; t=−2.5; p=0.007; PP-analysis: $\Delta^0$=0.005; 95% CI < 0.14; t=−2.4; p=0.008).

Along with fever, severity of intoxication and respiratory syndromes decreased as well. Total score of intoxication symptoms on day 3 of therapy reduced two-fold - from baseline 18.8±6.6 [19.0±6.7] (vs. 18.6±6.2 [18.6±6.3] in the Oseltamivir group) to 9.2±5.0 [9.2±5.1] (vs. 7.7±4.4 [7.8±4.3] respectively), by the end of therapy − to 2.4±2.9 [2.3±2.7] (v.s 2.0±2.5 [1.9±2.3] in the Oseltamivir group). Mild respiratory catarrhal (6.1±3.7 [6.1±3.7] and 5.9±3.7 [5.9±3.6] scores at the disease debut) typical of influenza was almost absent at the end of the treatment and follow-up (1.3±1.5 [1.3±1.5] and 1.4±1.9 [1.4±1.8] scores in groups, respectively). Statistical analysis of the severity of influenza symptoms on days 3 and 7 of the follow-up also evidenced comparability of the results of therapy with two drugs.

Significant and positive changes against Brillia Health Cold-Flu Recovery and Oseltamivir therapy exerted similar effects on the necessity of symptomatic therapy (antipyretics). While on day 1 of the study (also the first day of influenza) numerous subjects used antipyretics allowed (with frequency of 0.65±0.48 [0.65±0.48] on average per one subject in the Brillia Health Cold-Flu Recovery group and 0.69±0.46 [0.72±0.45] − in the Oseltamivir group), on the following 2 days their application reduced drastically (to 0.19±0.40 [0.19±0.39] and 0.15±0.36 [0.15±0.36] on day 3, respectively). On days 4 and 5 only individual subjects of both groups required antipyretics. Statistical analysis verified that Brillia Health Cold-Flu Recovery was as effective as Oseltamivir in

reducing necessity in antipyretics for pyretic fever, i.e. the main manifestation of influenza infection.

Average total score of European Quality of Life Questionnaire (EQ5D) in subjects from Brillia Health Cold-Flu Recovery group within 7 days modified almost 2-fold making 5.4±0.8 [5.3±0.9] vs. baseline 9.4±1.9 [9.6±1.9] scores ($\Delta_{1-7}$=−4.0 [−4.3]) reflecting positive changes in the quality of life of the study subjects. In the reference group similar values were 5.5±0.9 [5.4±0.8] and 9.2±2.3 [9.4±2.2] scores, respectively ($\Delta_{1-7}$=−3.7 [−4.0]).

The results of the visual analog scale demonstrated more than two-fold improvement in subjective evaluation of health status (in scores) in subjects in both groups (changes from baseline 42.1±18.4 [41.6±18.2] to 87.7±10.6 [87.7±10.6] by the end of therapy; $\Delta_{1-7}$=+45.6 [+46.1] and from 46.7±15.1 [46.2±15.4] to 87.8±11.4 [88.0±10.6]; $\Delta_{1-7}$=+41.1 [+41.8], respectively. According to statistical analysis, positive changes in total EQ5D score and health status score were significantly identical in the two groups.

Ensuring adequate antiviral response, Brillia Health Cold-Flu Recovery therapy prevented bacterial complications typical of influenza which is known to result in immunosuppression and addition of secondary infections. The Brillia Health Cold-Flu Recovery group did not have cases of aggravation of the disease including complications requiring antibiotics or hospitalization; all subjects completing the study were at convalescence period or had evident (significant) improvement. In the Oseltamivir group 2 subjects had secondary bacterial complications including community-acquired pneumonia in one subject and acute sinusitis in the other subject requiring antibiotics.

Average total score of "therapeutic efficacy" domain of CGI-EI scale in the Brillia Health Cold-Flu Recovery group was 3.5±0.5 [3.5±0.5], i.e. the investigators evaluated clinical effect in most cases as expressed, since the drug application resulted in recovery/significant improvement of the subjects' condition. Efficacy of Oseltamivir, according to the investigators, was similar (3.7±0.5 [3.7±0.5] scores). Average total scores of adverse effects of Brillia Health Cold-Flu Recovery and Oseltamivir were low (1.1±0.3 [1.1±0.3] and 1.1±0.4 [1.1±0.3] respectively), efficacy index – ratio of therapeutic and adverse effects – high (3.3±0.7 [3.4±0.7] and 3.5±0.8 [3.6±0.7] scores) and comparable in two groups.

Brillia Health Cold-Flu Recovery did not exert negative effect on vital signs of the subjects. Baseline tachycardia (mean HR > 90 bpm) typical of acute period of an infectious disease was levelled during therapy in HR at convalescence period (on day 7 of the follow-up) in all study subjects was within normal range (ITT and PP-analysis data). Average and individual values of HR, SBP and DBP throughout the study were within normal range. Laboratory deviations revealed by the end of the study were typical for convalescence period, were mild and considered as clinically irrelevant. Absence of serious AEs or AEs with significant causal relationship with Brillia Health Cold-Flu Recovery verified high safety of the drug.

Therefore, the study results demonstrated that Brillia Health Cold-Flu Recovery is an effective and safe drug for the treatment of influenza. Rapid effect of the drug on infectious and inflammatory process caused by

influenza virus manifested and were effective against fever which reduced from febrile values to normal body temperature within 3 days on average. Severity of intoxication syndrome typical of influenza reduced significantly within the first three days of Brillia Health Cold-Flu Recovery therapy as well. Efficacy of the drug based on the results of analysis of primary and secondary study endpoints was significantly comparable with the effects of anti-influenza drug Oseltamivir. The study demonstrated good tolerability of Brillia Health Cold-Flu Recovery and its potential combined use with the drugs of various classes.

**Conclusions**:

1. Brillia Health Cold-Flu Recovery is an effective and safe drug for the treatment of influenza, its therapeutic efficacy is comparable to that of Oseltamivir (Tamiflu®).
2. Intensity and duration of fever, i.e. the main clinical marker of viremia and activity of infectious and inflammatory processes against Brillia Health Cold-Flu Recovery therapy were not different from those in Oseltamivir group thus indirectly confirming similar antiviral efficacy of both drugs.
3. Brillia Health Cold-Flu Recovery's effect initiated rapidly and after 3-day therapy most subjects had body temperature below 37.00°C. Average duration of fever period in subjects with influenza was about two days.
4. Along with fever, rapid and expressed therapeutic effect of Brillia Health Cold-Flu Recovery on the most marked influenza intoxication signs was observed, i.e. Headache and other types of pain (muscle, joint), asthenic and neurovegetative disorders (weakness, malaise, insomnia). Severity of intoxication syndrome on day 3 of therapy reduced two-fold.
5. Five-day course of Brillia Health Cold-Flu Recovery therapy demonstrated efficacy comparable to that of Oseltamivir, both in terms of individual symptoms and total clinical manifestations of influenza, while the terms of their elimination was less than 3 days. Percentage of "full convalescents" by the end of therapeutic course was significantly comparable between the groups.
6. The effects of Brillia Health Cold-Flu Recovery on influenza infection and its main manifestation, i.e. pyretic fever, resulted in a rapid reduction of dosing frequency of antipyretic drugs required predominantly within only the first day of therapy.
7. Brillia Health Cold-Flu Recovery administration ensured adequate antiviral response preventing secondary bacterial complications typical of influenza.
8. Improved quality of life against Brillia Health Cold-Flu Recovery therapy was confirmed by significant positive changes in total score of EQ5D and the objective health status scale.
9. Brillia Health Cold-Flu Recovery did not affect vital functions of the subjects and did not cause serious adverse effects. All adverse events recorded during the study were mild and were not definitely (significantly) associated with Brillia Health Cold-Flu Recovery.
10. No data on Brillia Health Cold-Flu Recovery interactions with medicinal products used as concomitant

therapy have been obtained including antipyretics and non-steroidal anti-inflammatory drugs, expectorants, broncholytics, antihypertensive drugs (ACE inhibitors, angiotensin receptor antagonists, beta-adrenolytics, calcium channel antagonists), diuretics, statins, drugs for the treatment of thyroid diseases.

11. High total average score of therapeutic activity against low adverse event frequency yielded efficacy indexes close to the maximum, comparable between the Brillia Health Cold-Flu Recovery and Oseltamivir groups.
12. All subjects were 100% compliant and completed the study with convalescence or significant improvement of influenza.

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**Appendix 1**

**Intensity of influenza symptoms**

| | **Symptom** | **Absent (0 scores)** | **Mild (1 score)** | **Moderate (2 scores)** | **Severe (3 scores)** |
|---|---|---|---|---|---|
| **1** | **Body temperature:** \| \| \|, \| \|°**C** | | | | |
| **2** | **Intoxication signs** | | | | |
| | Headache | | | | |
| | Chill | | | | |
| | Sweatiness | | | | |
| | Weakness | | | | |
| | Malaise | | | | |
| | Muscle pain | | | | |
| | Joint pain | | | | |
| | Eye pain | | | | |
| | Photophobia | | | | |
| | Somnolence | | | | |
| **3** | **Catarrhal symptoms** | | | | |
| | Nasal congestion | | | | |
| | Nasal discharge | | | | |
| | Sneezing | | | | |
| | Sore throat | | | | |
| | Cough | | | | |

## Appendix 2

**EQ5D (EUROQUAL) Quality of Life Questionnaire**

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**1. Mobility**

I have no problems in walking about……. ☐

I have some problems in walking about..... 2 ☐

I am confined to bed …… 3 ☐

**2. Self-care**

I have no problems with self-care 1☐

I have some problems washing or dressing myself 2☐

I am unable to wash or dress myself 3☐

**3. Usual Activities (e.g.** *work, study, housework, leisure activities)*

I have no problems with performing my usual activities 1☐

I have some problems with performing my usual activities 2☐

I am unable to perform my usual activities 3☐

**4. Pain/Discomfort**

I have no pain or discomfort 1☐

I have moderate pain or discomfort 2☐

I have extreme pain or discomfort 3☐

**5. Anxiety/Depression**

I am not anxious or depressed 1☐

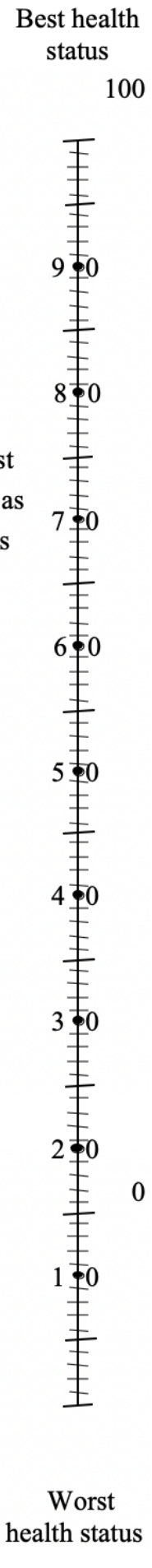
I am moderately anxious or depressed 2☐

I am extremely anxious or depressed 3☐

**6. Assessment using visual scale** / / / /

To facilitate evaluation of how bad or well they are feeling we are suggesting a scale (similar to thermometer) at which the best health status is marked as 100 and the worst as 0. We would like you to mark on the scale how good or bad you are feeling today as it seems to you. Please draw a line from the square below to the mark which indicates best your health state today.

**Your health status today**



## Appendix 3

## Clinical Global Impression (CGI)

| EFFICACY INDEX | | | | | |
|---|---|---|---|---|---|
| | **Adverse effects** | No | Do not affect functional potential of the subject significantly | Affect functional potential of the subject significantly | Exceed therapeutic effect |
| Therapeutic effect | **4.** Expressed Significant improvement Complete/almost complete remission of all symptoms | 4.00 | 2.00 | 1.33 | 1.00 |
| | **3.** Moderate Evident improvement. Partial remission of the symptoms. | 3.00 | 1.50 | 1.00 | 0.75 |
| | **2.** Minimum Slight improvement not modifying the need in therapy | 2.00 | 1.00 | 0.67 | 0.50 |
| | **1.** No changes or aggravation | 1.00 | 0.50 | 0.33 | 0.25 |