11.4 Efficacy Results and Tabulations of Individual Subject Data

Table 11-1 Effect of COLD-fX / Placebo treatment on the duration of primary symptoms related to a respiratory infection‡

	Runny nose	Stuffy nose	Cough	Sore throat
	days, mean ± SD			
COLD-fX (n = 128)	5.7 ± 4.6	6.5 ± 4.8	5.4 ± 5.4	4.9 ± 4.2
Placebo (n = 119)	5.7 ± 4.8	6.1 ± 4.9	4.5 ± 4.9	4.5 ± 3.8
p value†	0.9	0.5	0.2	0.4

‡ data from daily self-assessment logs
†Unpaired t-test

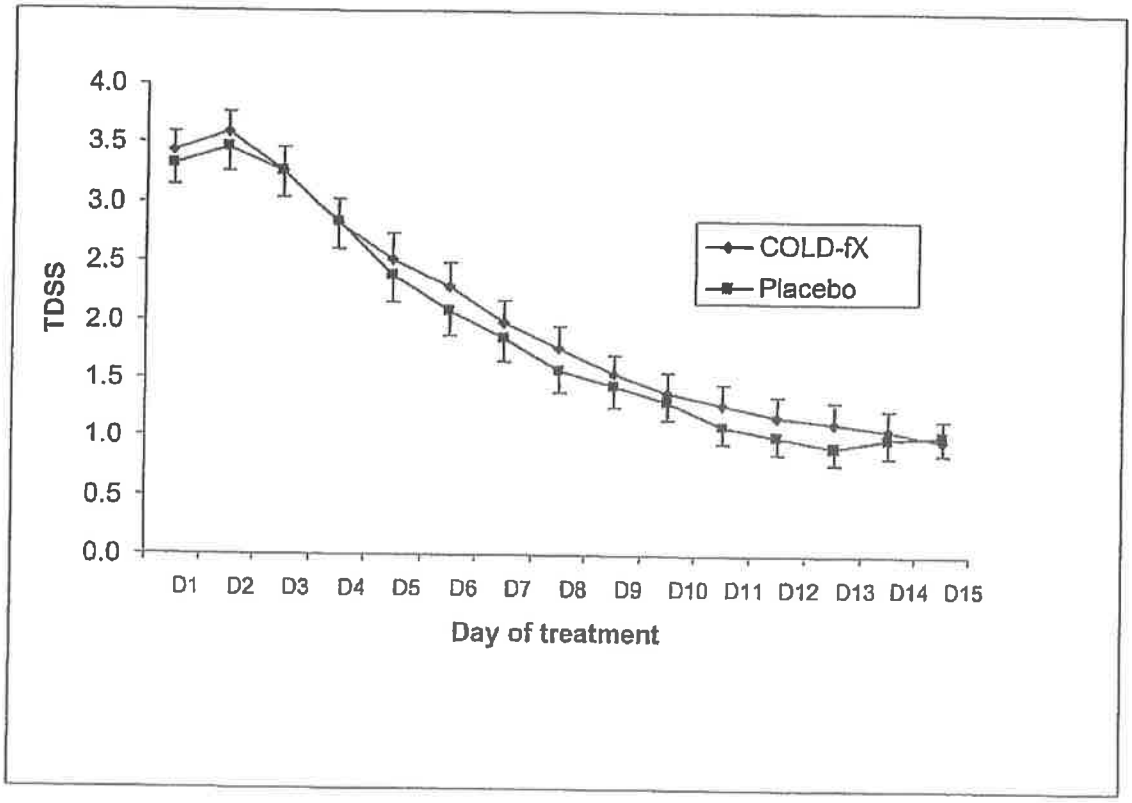

Figure 11-1 Effect of COLD-fX/placebo treatment on the total daily symptom score (TDSS)

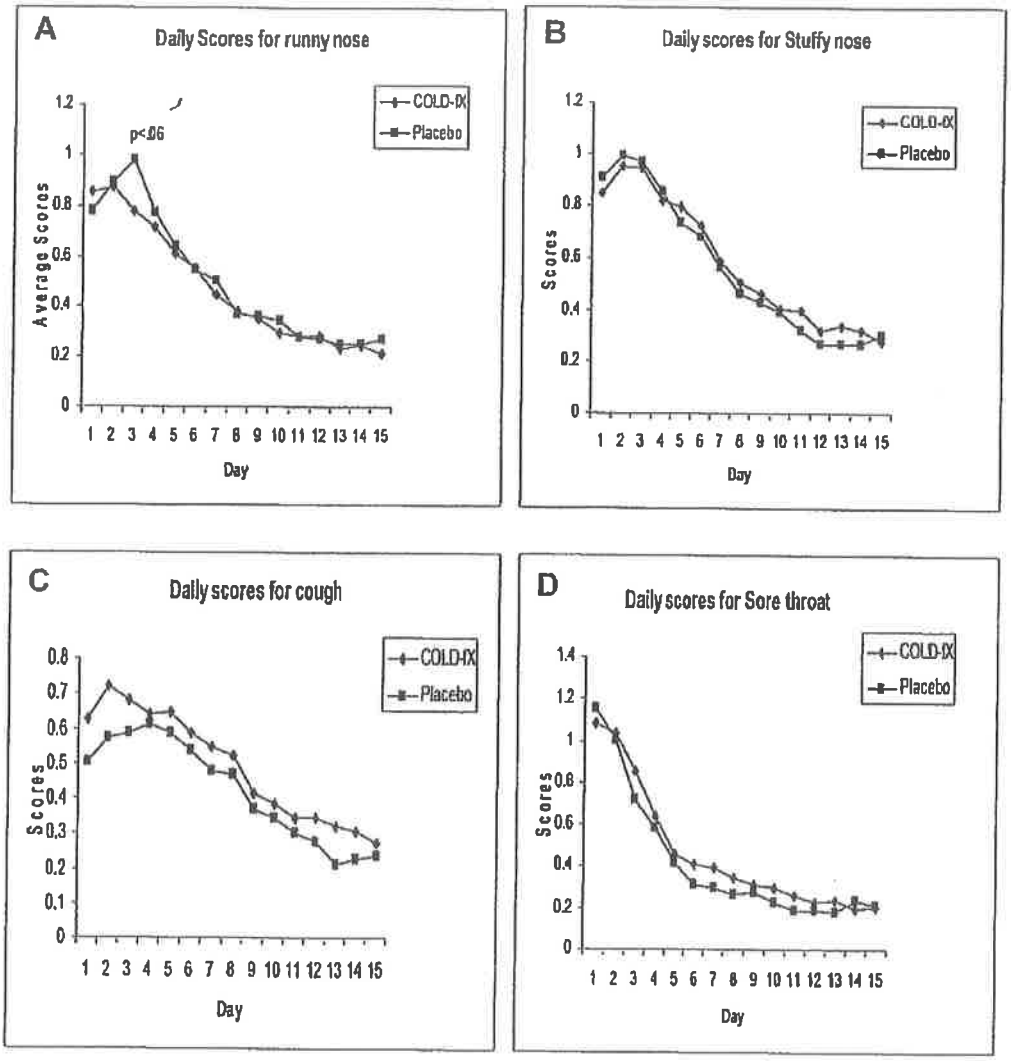

Figure 11-2 The Effects of COLD-fX or Placebo Treatment on the Daily Scores of Primary Symptoms Related to a Respiratory Infection in Healthy Adults

Secondary efficacy parameter: There was no difference in the number of physician visits with 6 visits each in the COLD-fX and placebo groups.

12 SAFETY EVALUATION

12.1 Extent of Exposure

Only the subjects experiencing the cold related symptoms (runny nose, stuffy nose, cough, sore throat) during the study consumed the study medication. This included 140 subjects in the COLD-fX group and 132 subjects in the placebo group. The treatment was taken for three days commencing at first sign of any of the above listed symptoms.

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

Table-4 lists the adverse events experienced during the study, along with their incidence rate in either group. A few adverse events including headache, nausea, rash, severe cold, severe sore throat, severe cough, sinus infection sore knee, seizure, stomach upset and ITP were reported during the trial. However, the incidence of these events was found to be similar between the two treatment groups.

12.2.2 Display of Adverse Events

Incidence of adverse events reported during the trial†

Adverse event	COLD-fX (n = 140)	Placebo (n = 132)
	n, (%)	
Headache	10 (7.1)	8 (6.1)
Nausea	2 (1.4)	1 (0.7)
Rash	1 (0.7)	1 (0.7)
Severe cold	1 (0.7)	1 (0.7)
Sinus Headache	2 (1.4)	1 (0.7)
Sinus infection	1 (0.7)	1 (0.7)
Severe sore throat	2 (1.4)	1 (0.7)
Severe cough	1 (0.7)	1 (0.7)
Seizure	0 (0)	1 (0.7)
Sore knee	0 (0)	1 (0.7)
Stomach upset	0 (0)	1 (0.7)
ITP	1 (0.7)	0 (0)

†Chi square comparisons between the groups were found to be non-significant for all the events.

12.2.3 Analysis of Adverse Events

Pearson chi-square tests were used to compare the proportions of subjects reporting adverse events and no significant differences were observed between the two groups. None of the reported adverse events could be associated with the use of COLD-fX.

12.2.4 Listing of Adverse Events by Subject

Adverse event	Treatment group (ID)	
	COLD-fX	Placebo
Headache	20,86,97,212,496,547,590,630,455,490	4,6,11,281,294,306,316,409
Nausea	12,535	58
Rash	267	602
Severe cold	482	233
Sinus Headache	164,562	333
Sinus infection	438	175
Severe sore throat	209, 282	347
Severe cough	535	335
Seizure	-	180
Sore knee	-	326
Stomach upset	-	354
ITP	411	

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

Not applicable as no deaths occurred during this study.

12.3.1.2 Other Serious Adverse Events

Not applicable as no other serious adverse events occurred during this study.

12.3.1.3 Other Significant Adverse Events

Not applicable as no other significant adverse events occurred during this study.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not applicable as no deaths, other serious adverse events or other significant adverse events occurred during this study.

12.3.3 *Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse* Events

Not applicable as no deaths, other serious adverse events or other significant adverse events occurred during this study.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Not applicable as no laboratory measurements were made in the study.

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Not applicable as no laboratory measurements were made in the study.

12.4.2.2 Individual Subject Changes

Not applicable as no laboratory measurements were made in the study.

12.4.2.3 Individual Clinically Significant Abnormalities

Not applicable as no laboratory measurements were made in the study.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

No vital sign measurements were made.

12.6 Safety Conclusions

The products taken were well tolerated by the subjects. In a few instances, certain adverse events were reported. However, the frequency of events was not significantly different between the two groups. Furthermore, none of the subjects withdrew because of adverse events.

13 DISCUSSION AND OVERALL CONCLUSIONS

The results indicate that an early treatment with COLD-fX is associated with efficacy in reducing the severity of runny nose during the early part of a respiratory infection. This is an intriguing observation considering the fact that runny nose has been reported as one of the most bothersome symptoms during an earlier part of a respiratory infection. This observation is in agreement with our earlier study in which daily dosing of COLD-fX treatment was found efficacious in reducing the severity and duration of a respiratory infection in healthy adults (Predy *et al.*, 2005). Similarly, in another study on institutionalized seniors (McElhaney *et al.*, 2004), daily dosing of COLD-fX was found to be effective in reducing the relative risk of contracting an acute respiratory infection related to influenza or respiratory syncytial virus by 89%. The dosing regime employed in the present study was found to be safe and was well tolerated by the study subjects.

In the present study, COLD-fX treatment was found to have limited efficacy in the treatment of other symptoms. It should, however, be pointed out that the treatment was administered only for 3 days, and the symptoms particularly cough and stuffy nose usually develop during the later part of a respiratory infection (Eccles, 2005). It is possible; therefore, that additional dosing for a longer duration was potentially required for the efficacious treatment of the other symptoms.

The present study had certain limitations which possibly affected the outcome of the trial. These limitations include complete reliance on the subjects' judgment for initiation of treatment, absence of a physical examination or laboratory measurements (blood analysis) during the infection, lack of assessment of constitutional symptoms of a respiratory infection, and, the first season of study being early spring when allergies causing respiratory illness-like symptoms are common.

In conclusion, the results of the present study indicate the potential use of COLD-fX for the immediate relief of runny nose during a respiratory infection.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Not applicable

14.2 Efficacy Data

Not applicable

14.3 Safety Data

14.3.1 Displays of Adverse Events

Not applicable

14.3.2 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not applicable

14.3.3 Narratives of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not applicable

14.3.4 Abnormal Laboratory Value Listing

Not applicable

15 REFERENCE LIST

Coon JT and Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. Drug Safety 2002, 25(5): 323-344.

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Predy GN, Goel V, Lovlin R, Donner A, Stitt L, Basu TK. Efficacy of COLD-fX in the prevention of recurrent respiratory tract infections in a susceptible population: a randomized, double-blind, placebo-controlled trial. Canadian Medical Association Journal. *In press*

Wang M, Guilbert LJ, Li J, Wu Y, Pang P, Basu TK, Shan JJ. A proprietary extract from North American ginseng (Panax quinquefolium) enhances IL-2 and IFN-g productions in murine spleen cells induced by Con-A. Int. Immunopharmacol.2004, 4(2):311-5.

Wang M, Guilbert LJ, Ling L, Li J, Wu Y, Xu S, Pang P, Shan JJ. Immunomodulating activity of CVT-E002, a proprietary extract from North American ginseng (*Panax quinquefolium*). J Pharm Pharmacol. 2001;53:1515-1523.

16 APPENDICES

16.1 Study Information

16.1.1 Protocol and protocol amendments

16.1.1.1 Protocol

Efficacy of COLD-fX® in the treatment of upper respiratory tract infections in healthy adults.

Background / Rationale

Panax ginseng C.A. Meyer, commonly called Asian ginseng has been traditionally used to prevent and treat many diseases such as stress, diabetes, cardiovascular disease and respiratory infections. Mechanistically, it is believed to perform by stimulating both innate and acquired immune systems. However, because of wide variation in chemical composition of ginseng due to variation in source, the effects can not be generalized to all varieties. Recent evidence indicates that the American ginseng (*Panax quinquefolium*) also has immune stimulating properties. In experimental animals, the herb increased B lymphocyte proliferation in the spleen, increased macrophage production of IL-1, TNF-α and IL-6, and also increased the production of IL-2 and IFN-γ by spleen lymphocytes. Moreover, it was also found to increase the proportion of NK cells, $CD4^+$ and $CD8^+$ lymphocytes in human peripheral blood in the presence of active influenza virus. COLD-fX® is a proprietary, commercially available powdered extract of American ginseng. The extract has been subjected to rigorous quality control procedures and therefore, assures consistency in physiochemical properties among different batch preparations.

Initial studies with COLD-fX®, on institutionalized older adults, revealed that its regular dosing for 8-12 weeks reduced the relative risk of developing a respiratory syncytial virus infection by 89%. The rate of adverse events was comparable in the placebo and treatment groups.

Trial Objectives

Primary:

1. To compare the duration of upper respiratory infection (URI) symptoms in days between the treatment and the placebo groups and
2. To compare the severity of sore throat, runny/stuffy nose and cough in the treatment and placebo groups.

Secondary:

1. To compare the rate of adverse events reported in the treatment and placebo groups and
2. To compare the rate of physician visits between treatment and placebo groups.

Study Design

The purpose of the study is to determine the effects of COLD-fX® acute treatment for upper respiratory tract infections in healthy adults. Therefore, a randomized, double blind and placebo-controlled study, involving healthy adults recruited from the general population of the Capital Health region, will be conducted.

Study Duration

Approximately 3.5 months (1 month for recruitment, 2.5 months (10 weeks) active study).

Number of Centres/Canadian

One.

List of Investigators

Dr. Gerry Predy, MD, Medical Officer of Health, Capital Health Region, Public Health Division, #300, 10216 - 124 Street Edmonton, AB T5N 4A3.

Sample Size

Approximately 600 volunteers.

Patient Population

Approximately 600 volunteers will be recruited from a population of generally healthy, non-institutionalized adults between the ages of 18 and 65 years who will be randomized into experimental and control groups. Randomization will be done using an Excel data analysis program with random number generation through Bernoulli distribution.

The sample size was calculated to have a power of 80% to detect differences of 30% or more ($p \leq 5\%$) in the duration of symptoms between treatment and placebo groups.

Inclusion Criteria

- Generally healthy, non-institutionalized adults between the ages of 18 and 65 years.
- Able to provide written informed consent.

Exclusion Criteria

- Use of any investigational or non-registered drug or vaccine within 30 days preceding the study period or for the duration of the study period.
- Chronic administration of immunosuppressants (topical steroids are allowed)
- Use of antibiotics within 7 days of beginning treatment
- Medical conditions: HIV infection, malignancy, cardiovascular disease, hypertension, diabetes, pulmonary or hepatic abnormalities; neurologic or psychiatric disease, tuberculosis, multiple sclerosis, acute respiratory infection within the last two weeks.
- Medications: warfarin, immunosuppressive therapy, corticosteroids, phenalzine, pentobarbital, haloperidol
- History of alcohol/drug abuse
- Pregnancy and lactation
- Inability to be reached by telephone

Drug Formulation

Oral capsule containing either 200 mg of an aqueous extract of *Panax quinquefolium* (North American Ginseng) or 200 mg of microcrystalline cellulose (placebo). Contains no filler or other additives.

Dosage Regimen

Subjects will be given a three day supply of the investigational medication (COLD-fX® or placebo) and instructed to take it only if they begin to have symptoms of an upper respiratory infection. Once they begin taking the medication, the dosage regimen is:

3 capsules three times on day 1
2 capsules three times on day 2
1 capsule three times on day 3.

Pre-study Screening and Baseline Evaluation

Interested volunteers will be initially screened over the phone by staff in Capital Health, Public Health Division regarding inclusion/exclusion criteria using a screening questionnaire.

Current Problems/Concerns

Although *Panax ginseng*, in isolated cases, has been found to cause some adverse effects such as insomnia, diarrhea, vaginal bleeding, headaches and schizophrenia, clinical and experimental studies on the safety profile of COLD-fX® (*Panax quinquefolius)* have found it safe, both for chronic and acute use. Subjects, however, experiencing any adverse effects will be free to withdraw immediately and/or seek the advice of their own physician.

Protocol Amendments

CLINICAL TRIAL AMENDMENT -
Module 1: Administrative / Clinical Information

Information on Prior-related Applications
The clinical trial with the Therapeutic Products Directorate (TPD) under Control # 088450, File # 9427-C2199-22C was closed on April 27, 2004 and the clinical trial report was filed to TPD on August 31, 2004. This clinical trial report was also filed with NHPD on August 31, 2004 as an amendment to the currently pending PLA for Cold-fX® (Submission # 100774, File # 100774) to support the non-traditional claims for that application.

Cold-fX® also currently carries the herbal DIN 02242024.

Investigator Brochure
No updates to be provided for the Investigator Brochure for this amendment.

Submission Rationale / Brief Summary of the Drug
No updates to be provided on this information for this amendment.

Study Protocol
The study protocol will be identical to that submitted with the original CTA application. At the end of the cold and flu season, only 391 subjects had been recruited for the clinical trial out of a total of 600 subjects required. It was subsequently determined that insufficient numbers of subjects had been recruited into the study to effectively determine any differences between Cold-fX® and the placebo (data remains blinded and will do so until this latest recruitment phase is complete). It is therefore requested that this clinical trial application be re-opened under the same protocol to continue recruiting subjects to achieve the 600 total subjects required to properly assess the data collected. The recruitment will take place during the 2004 – 2005 cold and flu season until 600 subjects have been recruited in total.

To date, only one serious adverse event has been reported which was judged not to be related to administration of the study product. The subject was unblinded and found to be taking placebo.

Informed Consent Document
There are no changes to be made to the informed consent document.

Clinical Trial Site Information
The amended protocol will be conducted at the same clinical trial site as specified in the original submission and the subsequently filed Clinical Trial Site Information Form (details of which are provided below). The clinical trial will not proceed until approval of this amendment has been provided by NHPD.

Information submitted with initial application is summarised below for the reviewers' convenience:

This trial shall be conducted at only one site –.

Northern Alberta Vaccine Trials and Evaluation Centre, 18th Floor, 8215 – 112 St., Edmonton, Alberta, T6G 2C8

The proposed date of commencement for this amendment is:
November 1, 2004

The qualified investigator is:
Dr. Gerry Predy, Medical Officer of Health, Public Health Division, Capital Health, #300, 10216 – 124 St., Edmonton, Alberta T5N 4A3

The REB approving the trial is:
Capital Health Research Ethics Board, 2J2 27 Walter Mackenzie Centre, Edmonton, Alberta, T6G 2B7.

16.1.2 REB Name and Address

Health Research Ethics Board
Capital Health Region
Edmonton, AB