Effect of Venetron™ on Symptoms of Depression in Individuals with Mild Depression

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LIST OF ABBREVIATIONS

5-HT – Serotonin
Alk. Phosphatase – Alkaline Phosphatase
AV – *Apocynum Venetum*
BUN – Blood Urea Nitrogen
CGI – Clinical Global Impression
DA – Dopamine
HAM-D – Hamilton Depression Rating Scale
INR – International Normalized Ratio (PTT)
MCH – Mean Corpuscular Hemoglobin
MCHC – Mean Corpuscular Hemoglobin Concentration
MCV – Mean Corpuscular Volume
MHPG – 3-Methoxy-4-hydoxy-phenylglycol
NE – Norepinephrine
RBC – Red Blood Count
RDW – Red Cell Distribution Width
SGOT (AST) – Serum Glutamic Oxaloacetic Transaminase
SGPT (ALT) – Serum Glutamic Pyruvic Transaminase
WBC – White Blood Cells

OBJECTIVES

To evaluate the efficacy and safety of Venetron™ (extract obtained from *Apocynum venetum* leaves) in individuals with mild depression. The endpoints to be determined were Hamilton Depression Rating Scale scores (HAM-D), Clinical Global Impression scores (physician rated; CGI) and blood neurotransmitters, after use of:

Group A – Venetron™

Group B – Placebo

for a period of 8 weeks.

Hypothesis

In individuals with depression, recommended use of Venetron™ tablets produces statistically significant improvement in:

- HAM-D scores
- CGI scores
- blood neurotransmitters

compared to a matching group of patients using placebo.

ABSTRACT

The objective of the study was to determine the efficacy and safety of 8 weeks use of Venetron™ (***APOCYNUM VENETUM)*** in individuals with mild depression. The endpoints to be determined were weekly adverse effects, HAM-D and CGI scores and blood neurotransmitters (platelet serotonin and plasma 3-methoxy-4-hydroxy-phenylglycol; MHPG).

Venetron™ had no negative effect on blood pressure. Side effects were noted in both groups (Venetron™ and placebo). There was no difference in the number of adverse events rated to be 'probably' or 'definitely' related to study product between the Venetron™ and placebo groups. The total of 'possibly' related adverse events was higher in the Venetron™ group. Also, the number of adverse events rated as moderate or severe were the same in the Venetron™ group as the placebo group. The number of adverse events rated as mild was higher in the Venetron™ group.

There was no effect of Venetron™ on total HAM-D and CGI scores as compared with placebo ($P>0.05$). Total HAM-D and CGI scores decreased significantly in both groups versus baseline. Improvements were noted in the Venetron™ group in individual questions (depressed mood, insomnia middle, insomnia late, work and activities, anxiety somatic) between baseline and week 8. Only scores for work and activities significantly improved in the placebo group.

In the Venetron™ group, there was a significant difference in HAM-D scores between 4 weeks and 8 weeks of use. This difference was not apparent in the placebo group. This possibly reflects a lack of change after 4 weeks in the placebo group and a continual improvement in the Venetron™ group over time.

There was no effect of Venetron™ on platelet serotonin or plasma 5-MHPG as compared with placebo, or vs. baseline ($P>0.05$). 50% of subjects in the Venetron™ group responded to Venetron™ in terms of increased serotonin (increase of 67%). Decreased MHPG was noted in 65% of subjects in the Venetron™ group (decrease of 41%).

The results of this study suggest that use of Venetron™ by individuals with depression is generally safe, with few side effects. Although the preliminary evidence does not suggest a statistically significant benefit of Venetron™ over placebo, positive trends have been observed in the Venetron™ group for depression rating scales and blood neurotransmitters. However, this was a small pilot trial and may not have been adequately powered to detect significant changes over placebo. As has been indicated in other large multicentered studies, it is very difficult to show a difference between antidepressants and placebo. Future work should focus on a larger study group and/or increased time frame of study and a comparison directly to antidepressant drug to demonstrate the significant benefits of Venetron™ use.

INTRODUCTION

Depression afflicts approximately 19 million Americans, and nearly 3 million Canadians, from children to the elderly. Current treatments include drugs such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. Unfortunately, conventional drugs often have limited tolerability and show significant side effects (1). Thus, many individuals suffering from depression seek alternative therapies including herbal remedies. A number of herbal products, such as ginko, ginseng, kava kava or yohimbine, are marketed with anecdotal claims of efficacy as antidepressants but so far, medical research provide limited support for their effectiveness. The most common and the most extensively studied herbal product, St. John's wort, showed evidence for superiority over placebo in several clinical trials, and is now considered to be effective in mildly to moderately depressed individuals (2-3). However, St. John's wort has also been reported to reduce plasma levels and efficacy of several pharmaceutical drugs, including cyclosporin, indinavir, digitonin, statins and many others (4). Thus there is a need to seek other natural products that show effectiveness against depression without interacting with absorption and metabolism of conventional drugs.

Apocynum venetum (AV) is a wild shrub growing in China and its leaves are used as tea in traditional Chinese medicine. AV tea has also become a popular healthy drink in Japan and has recently come onto the market as health food in the US. Extracts from AV leaves have been reported to produce various pharmacological responses including diuretic, antihypertensive, antihyperlipidemic and sedative effects (5-9). In addition, recent preclinical studies demonstrated that AV extract has antidepressant potential comparable to that of the synthetic tricyclic antidepressant, imipramine. In the acute experiment, 30 and 125 mg/kg doses of AV, and 20 mg/kg dose of imipramine similarly shortened the immobility of rats in the forced swimming test (10). Consistently, in the subsequent long term study, 15 mg/kg and 60 mg/kg doses of AV extract administered daily for 2 weeks or 8 weeks significantly reduced or tended to reduce concentrations of depression-related neurotransmitters norepinephrine (NE) and dopamine (DA) without affecting another neurotransmitter, serotonin (5-HT), in the rat brain tissues. In contrast, imipramine administered at the dose of 15 mg/kg for the same period of time reduced NE and DA and increased 5-HT concentrations in the brain (11). The antidepressant effects of AV have been postulated to be due to its high content of flavonoids, especially hyperoside and isoquercitrin, which are also known to be major phytochemicals in St. John's wort (10). In spite of this similarity, there is no evidence so far that AV, like St. John's wort, might affect drug disposal. In rats, a 2 week treatment with AV extract at the recommended human dose (3.3 mg/kg) had no effect on absorption of nifedipine, a drug metabolized by the most common hepatic cytochrom 450 enzyme, CYP3A whereas treatment with St. John's wort at the recommended human dose (15 mg/kg) significantly reduced plasma concentration of the drug. In the same animal model, St. John's wort, but not AV, also reduced intestinal absorption of methylprednisolone, a drug metabolized via intestinal P-glycoprotein (12).

So far, the AV extract marketed under the trademark Venetron™ has not been tested in any placebo-controlled clinical trials but several case reports (Table 1) indicate that doses of 50 mg/day could help to reduce symptoms of mild to moderate depression. Future clinical studies should establish if Venetron™ is more active than placebo in combating mild

depression and if its effect is associated with modulation of neurotransmitters. Previous reports suggest that blood levels of neurotransmitters can be altered by antidepressant use and changes in blood neurotransmitters concentrations may also correlate with severity of depression (13-19).

Previous toxicity studies in animals (rats) did not reveal any evidence of AV acute toxicity. In rats, single administration of AV at the dose 2 g/kg body weight did not adversely affect body weights after a period of 2 weeks. Also, a longer term, 8-week administration of AV at the doses ranging from 15 to 250 mg/kg did not reduce body weights and organ weights of male and female rats (unpublished).

The specific objective of the trial was to determine the efficacy of Venetron™ (extract obtained from *Apocynum venetum* leaves) in individuals with mild depression. The endpoints to be determined were HAM-D and CGI scores and blood neurotransmitters. The potential for side effects of Venetron™ was also evaluated.

The HAM-D rating scale is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. It was one of the first rating scales developed to quantify depression and has been used since 1960. It has since become the most widely used and accepted measure for evaluating depression. The 17 items are rated on either a 5-point (0-4) or a 3-point scale (0-2), with the highest rating for more extreme symptoms. More recently, subscales of the HAM-D, as well as individual questions, have been examined for changes in clinical trials (20).

The clinical global impression score is a commonly used score, to indicate the physician's impression of severity of illness. It is based on a 7-point scale (1-7; 7-extremelely ill and 1-not ill).

Blood neurotransmitters determined in this study included platelet serotonin and plasma 3-methoxy-4-hydroxyphenylglycol. Low levels of central serotonin are related to depression, resulting in the development of selective serotonin reuptake inhibitors (SSRIs). Platelet serotonin have been suggested to reflect neuronal serotonin changes (21).

Plasma 3-MHPG has been suggested to provide information regarding central noradrenergic activity(22). Furthermore, baseline levels may indicate response to certain anti-depressant medications. Not all clinical trials show a change in 3-MHPG levels with anti-depressant use.

Table 1. Venetron™ case reports.

Gender	Age	Daily dose	Treatment time	Comments
Male	62	50 mg caps	3.5 years	Decrease in cigarettes, became stronger to stress
Male	36	50 mg pill	6 months	Improvement in concentration, more optimistic
Female	55	50 mg caps	1 month	Decrease in fatigue and grief
Female	29	50 mg caps	3 months	Decrease in hypersensitiveness large enteritis, PMS
Male	66	50 mg pill	2 weeks	Decrease in frequency of awaking at night, deep re-sleeps
Male	75	50 mg pill	2 weeks	Decrease in frequency of awaking at night, deep re-sleeps

METHODS

Participants

Inclusion Criteria:

- Men and women, 18-65 years
- BMI 18-35 kg/m^2
- Healthy as determined by blood chemistry, hematology and physical examination by physician
- Signed informed consent
- Mild depression as confirmed by HAM-D scores in the range 14-20.

Exclusion Criteria:

- Non-compliance
- Anticipated problems with product consumption
- Moderately severe co-morbid disease including cardiac, pulmonary, renal, hepatic, active cancer, diabetes, hypertension, immunological, neurological
- Consumption of nutritional, herbal or prescription product containing St. John's wort, hypericin, hyperforin, hyperoside or isoquercetrin acid within past 30 days
- High alcohol intake (more than two drinks per day)
- Pregnant or breastfeeding
- Use of antidepressant prescription medication
- Use of or herbal products within 1 week before the study

Study Outline

The study was a double-blinded, randomised parallel group pilot trial. The study protocol is attached as Appendix 1 (original) and 2 (revision). Individuals with mild depression were recruited for the study by advertisement. Each participant was to have avoided consumption of herbal products for one week prior to study which may effect depression (based on information available at http://www.nlm.nih.gov/medlineplus/medlineplus.html, as well as antidepressant prescription medication and nutritional, herbal or prescription products containing St. John's wort, hypericin, hyperforin, hyperoside or isoquercetrin acid within 30 days of the study start. At the screening visit, the informed consent form was signed and the potential subject completed the HAM-D questionnaire (Appendix 3). Those who fulfilled the inclusion criteria for mild to moderate depression (total score 14 to 20 on the Hamilton Depression rating scale (HAM-D 17 item version), but with a maximum score of 1 on HAM-D question 3, regarding suicidality) were asked to undergo a physical examination by the study physician. At the first study site (CA) CGI (Appendix 4) score was determined at this point. The physical examination was to include blood pressure and anthropometric measurements as well as health tests (glucose, urea, creatinine, sodium, potassium, chloride, TSH, bilirubin, Alk Phos, AST, SGOT, SGPT, total protein, CBC, hemoglobin, RBC, WBC, platelets). Upon confirmation that the individual was mildly depressed but healthy and eligible according to blood tests, an appointment was arranged for the study to commence. Source documents for visit 1 (screening) are attached as appendices 5 (CA) and 6 (MN).

At baseline (Day 0), eligible subjects were randomly divided, using randomization tables, into two groups, and blindly assigned to receive an 8 week supply of either Venetron™ or placebo. Instructions were given to take two tablets per day. Subjects were given forms to report weekly adverse effects (journals weeks 0-4 and 5-8; appendices 7 and 8). HAM-D and CGI (at the second study site; MN) were completed. Blood pressure was taken. Blood samples were taken for the determination of blood neurotransmitters. To protect identity, participants were assigned code numbers, which appeared on all study questionnaires and records. Baseline information forms are attached as Appendices 9 (CA) and 10 (MN) (visit 2).

At 4 weeks, HAM-D scores and blood pressure was determined. The visit 3 information form is attached as Appendices 11 (CA) and 12 (MN).

At the end of the 8-week study period, completed symptom/side effect forms and unused study product was collected. Subjects were asked to provide a second blood sample for determination of blood neurotransmitters. HAM-D and CGI scores, as well as blood pressure, were determined. The visit 4 (8 week visit) information form is attached as Appendices 13 (CA) and 14 (MN). Although, in the original protocol it stated that during the 8 week visit, subjects were to be given an option to continue on the same medication for an additional 8 weeks, this did not occur. This decision was made by the sponsor prior to the study start.

Outcomes

Primary outcome measure:

Changes in HAM-D score.

Secondary outcome measures:

Changes in CGI score, blood neurotransmitter levels, blood pressure and adverse events.

Sample Size

No formal calculation was done to determine appropriate sample size for this study. This is a pilot study.

Blinding

The participants, clinical assistants and those assessing outcome were blinded to group assignment.

STATISTICAL METHODS

ANOVA was used to assess differences in markers of depression (scores and neurotransmitter concentrations). Baseline comparisons between groups, and comparisons of responders for neurotransmitters, were done using t-test.

RESULTS

Participant Flow

Sixty-six subjects were assessed for eligibility; 47 were enrolled in the study. Out of this group, 27 were randomized to Venetron™ and 20 to placebo. Of those enrolled in the study, there were five dropouts from the Venetron™ group and one from the placebo group. Two individuals in the Venetron™ group were inappropriately enrolled (use of SAMe supplement and inadequate disclosure of medical history). The data from these subjects was not included. The subject who used SAMe supplement did not disclose any adverse events. The subject who did not fully disclose medical history was later voluntarily hospitalized and this was not included in adverse events as it was due to prior medical history. The diagram of trial progress is presented in Figure 1. Reasons for removing consent to participate in the study, by the five participants, included: loss to follow-up and personal decision (reason not indicated). No subject indicated they were removing consent based on adverse events.

The primary outcome measure (HAM-D score) was analyzed in all subjects who completed the study.

One subject in the Venetron™ group was not given a physical exam prior to study start. One subject in the Venetron™ group had 66% compliance due to an adverse event (moderate chest pain which was considered to be possibly due to test product use).
One subject in the Venetron™ group had abnormally low glucose levels at screening.

Recruitment

Subjects were recruited during the period of August, 2005-March 2006. The follow up of the last patient ended in May 2006.

Baseline Data

Individual medical and medication histories, as well as physical exam results are given in Appendices 15 (CA site) and 16 (MN site). There were no serious illnesses among participants.

Baseline characteristics of all study subjects are summarized in Table 1. There are no significant differences between baseline characteristics in the two groups.

Screening medical history results are summarized in Table 2.

Baseline blood chemistry parameters of the participants were generally within the normal range. One subject had low blood glucose. There are no significant differences between baseline blood chemistry parameters in the two groups.

Baseline/screening HAM-D values were not significantly different between groups. The HAM-D range, at screening/baseline was 14-20.

Age, gender, height, weight, BMI and blood pressure were all similar between the two groups at screening.

Numbers Analyzed

Primary outcome measure (HAM-D score): Analyzed in 20 out of 27 subjects in the Venetron™ group and in 19 out of 20 patients in the placebo group.

Secondary outcome measures: Blood pressure data was obtained for all subjects between baseline and week 8. Adverse events were also collected.

Effect of Venetron™ on Adverse Events: Individual information on adverse events is summarized in Appendix 17. Adverse event data is summarized in Table 4. A total of 30 adverse events were noted in the Venetron™ group; 22 in the placebo group. The actual number of patients reporting adverse events was similar between the two groups (9 subjects in each group). The number of adverse events rated to be definitely, probably or possibly related to study product was 23 in the Venetron™ group (77% of all events) and 12 in the placebo group (55% of all events). Most adverse events were rated as mild, with some rated as moderate. In the Venetron™ group, 47% of adverse events were gastrointestinal; other common ones were headache and dizziness. In the placebo group, the most common adverse events were gastrointestinal and dermatological. Moderate chest pain, which resulted in the interruption of supplementation with the test article, resulted in the Venetron™ group. Mild palpitations and hot flashes, which did not require study interruption or action, resulted in the placebo group. Adverse events deemed to be possibly related to study supplement (Venetron™) included insomnia, decreased appetite, abnormal dreams, indigestion, chest pain, dizziness, increased appetite, diarrhea, nausea, shakiness, dry mouth, headache, acne, flatulence, burping, bloating, tinnitus, drowsiness, and decreased libido. Adverse events deemed to be probably related to study supplement (placebo) included palpitations, dry mouth, dry skin, acne, headache, metorrhagia, flatulence, hot flashes, and constipation. Adverse events deemed to be probably related to both Venetron™ and placebo included taste disturbance.

There was no difference in the number of adverse events rated to be ‘probably’ or 'definitely' related to study product between the Venetron™ and placebo groups. The total of 'possibly' related adverse events was higher in the Venetron™ group. Also, the number of adverse events rated as moderate or severe were the same in the Venetron™ group as the placebo group. The number of adverse events rated as mild was higher in the Venetron™ group. No subject dropped out of the study due to side effects.

Effect of Venetron™ on Blood Pressure: Analysis of blood pressure at baseline, 4 weeks and at the end of the study showed no significant changes. Blood pressure data is summarized in Table 5. These results demonstrate the lack of effect of Venetron™ on blood pressure, and support its safe use.

Effect of Venetron™ on HAM-D and CGI scores: The data presented in Table 6 show the HAM-D scores at baseline, 4 weeks and at the end of the study in both the treatment and placebo groups. When the study began, the total HAM-D score was 16±2 in the Venetron™ group and 16±2 in the placebo group; at study end, respective decreases in the score of 44%

(9±4) and 44% (9±4) were recorded. The decrease was highly significant in both groups but not significantly different between groups. There was no mean score difference between Venetron™ and placebo after 8 weeks of use.

In the Venetron™ group, there was a significant difference in HAM-D scores between 4 weeks and 8 weeks of use. This difference was not apparent in the placebo group.

Improvements were noted in the Venetron™ group in certain individual questions; the most notable being an improvement in the rating for item 1 (depressed mood). Other individual questions which resulted in significant improvements within the Venetron™ group included insomnia middle, insomnia late, work and activities, anxiety (somatic) between baseline and week 8. Only the individual score for work and activities significantly improved within the placebo group. The overall reduction in HAM-D score was 47.3% in the Venetron™ group and 43.9% in the placebo group.

After 8 weeks of treatment, 40% of the subjects in the Venetron™ group showed greater than a 10 point decrease in total HAM-D score as compared to 31.6% of the placebo group. Furthermore, 50% of Venetron™ group showed a decrease in HAM-D score of 50% or greater compared to only 36.8% of the placebo group. Also, 60% of the Venetron™ group had a HAM-D score of 8 or less by week 8, compared to 52.6% of the placebo group.

The data presented in Table 6 show the CGI scores at baseline, and at the end of the study in both the treatment and placebo groups. When the study began, the CGI score was 3±1 in the Venetron™ group and 3±0 in the placebo group; at study end, respective decreases in the score of 34% (2±1) and 34% (2±1) were recorded. The decrease was significant in both groups but not significantly different between groups. There was no mean score difference between Venetron™ and placebo.

Effect of Venetron™ on Blood Neurotransmitters:

The data presented in Table 7 show the levels of platelet serotonin and plasma 3-MHPG at baseline and at the end of the study in both the treatment and placebo groups. When the study began, the total platelet serotonin was 15.4±9.1 ng/ml in the Venetron™ group and 18.6±8.4 ng/ml in the placebo group; at study end, respective decreases in the levels of 2% (15.0±6.0 ng/ml) and 15% (15.9±10.5 ng/ml) were recorded. The change was not significant in either group and was not significantly different between groups.

The data presented in Table 7 show the levels of plasma 3-MHPG at baseline and at the end of the study in both the treatment and placebo groups. When the study began, the total 3-MHPG was 2.5±2.6 ng/ml in the Venetron™ group and 1.7±1.0 ng/ml in the placebo group; at study end, there were no decreases in the levels in either group. There was no mean difference between Venetron™ and placebo and no statistically significant differences between the groups.

Further analysis revealed that 50% of subjects in the Venetron™ group responded to Venetron™ in terms of increased serotonin (increase of 67%; 10.6±6.3 ng/ml to 17.7±7.2 ng/ml), as compared with 31.6% of subjects in the placebo group. Of the 20 subjects in the Venetron™ group, 35% showed an increase of at least 20%. Of the 19 subjects in the Placebo group, 21.1% demonstrated an increase of at least 20%.

MHPG decreased in 65% of subjects in the Venetron™ group (decrease of 41%; 3.3±2.9 ng/ml to 1.9±1.8 ng/ml). These changes were significant ($p<0.05$) within the responders of the Venetron™ group.

DISCUSSION

The objective of the study was to determine the efficacy and safety of 8 weeks use of Venetron™ in individuals with mild depression. The endpoints to be determined were adverse effects, HAM-D and CGI scores and blood neurotransmitters (platelet serotonin and plasma 3-methoxy-4-hydroxy-phenylglycol; MHPG). As discussed in the objectives section, the HAM-D scale is a widely used and respected clinical scale for depression. The CGI score (clinical global impression) is a standard rating of severity of mental illness. Blood neurotransmitters, such as platelet serotonin and plasma MHPG, may be markers associated with depression. Although increased platelet serotonin has been suggested to be indicative of increased neuronal serotonin, and medical treatment may positively affect these levels, it is not clear whether MHPG concentrations are modified by all conventional medical treatments.

There was no statistically significant effect of Venetron™ on total HAM-D and CGI scores as compared with placebo. Total HAM-D and CGI scores decreased significantly in both groups versus baseline. Improvements were noted in the Venetron™ group in individual questions (depressed mood, insomnia middle, insomnia late, work and activities, anxiety somatic) between baseline and week 8. Only scores for work and activities significantly improved in the placebo group. This suggests that Venetron™ may offer benefit to certain individuals. Furthermore, due to the nature of a pilot trial, it is possible that statistical significance was missed given the small number of subjects and the short trial period. The lack of significant change between 4 and 8 weeks in the placebo group, suggests the potential for an early placebo effect, which may be eliminated in a longer term study. Furthermore, the significant improvement within the Venetron™ group for question #1 (depressed mood), which was not found to be statistically significant within the placebo group, suggests a potential for benefit of Venetron™ in a population of individuals with mild depression. As indicated above, more subjects in the Venetron™ group showed a decrease in the HAM-D score of at least 50%, as well as a final score of less than 8. These analyses demonstrate overall improvement from baseline in the Venetron™ group.

There was no statistically significant effect of Venetron™on platelet serotonin or plasma 5-MHPG as compared with placebo, or vs. baseline. However, 50% of subjects in the Venetron™ group responded to Venetron™ in terms of increased platelet serotonin, 35% of whom showed an increase of at least 20%, and MHPG decreased in 65% of subjects in the Venetron™ group. As discussed above, changes in platelet serotonin may indicate neuronal changes. Thus, an increase in serotonin of 67%, suggests a possibility of increased neuronal serotonin and thus the potential to offer clinical benefits. It is unclear, what effect if any, a decrease in plasma MHPG has on clinical benefits.

It has been increasingly reported in the scientific literature, that treating patients with mild or moderate depression is difficult. These patients may not be suitable candidates for medications such as SSRIs and tricyclic antidepressants, partially due to the side effects associated with them. A product which has antidepressant effects, with a lower risk of serious side effects, would be preferable to most individuals. This theory has been the basis for many recent clinical trials on natural products, including St. Johns' wort. Frustratingly, more than

one large multicentered study has failed to show any statistically significant differences between antidepressants and placebo (23, 24). Various reasons may account for this, including treatment adherence and defined entry criteria, however; this is unlikely to account for this surprising lack of effect. When dealing with an endpoint such as depression, the placebo effect may be so large that any effect of the drug is partially masked. In the present pilot trial, the subject number was likely not large enough to allow for any potential benefit of Venetron™ to be statistically significant. However, the fact that Venetron™ group showed positive trends given the small sample size is indicative of the potential benefits for mild depression.

In conclusion, although Venetron™ did not have statistically significant effects on CGI or HAM-D scores, it showed good positive trends in this population. This was a small pilot trial and may not have been adequately powered to detect significant changes. Given the promising effects in some of the study participants, Venetron™ may be considered as an alternative for patients with mild depression. Future work may focus on a larger study group and/or increased time frame of study as well as a direct comparison to some antidepressant drugs to demonstrate significant benefits of Venetron™ use.

ADVERSE EVENTS

Individual information on adverse events is summarized in Appendix 17. Adverse event data is summarized in Table 4.

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Table 1: Screening Characteristics of Study Subjects (Mean ± SD).

	Venetron™	Placebo
Age	48 ± 9	50 ± 8
Gender (M/F)	8/12	5/14
Height (cm)	171.2 ± 10.1	168.7 ± 7.0
Weight (kg)	80.0 ± 17.9	79.4 ± 12.0
BMI (kg/m^2)	27.2 ± 5.0	27.5 ± 4.3
Systolic Blood Pressure (mmHg)	132 ± 16	128 ± 15
Diastolic Blood Pressure (mmHg)	79 ± 11	79 ± 9
HAM-D (Total)	16 ± 2	16 ± 2

Table 2. Medical History of Study Subjects

	Venetron™	Placebo
Head, eyes, ears, nose throat	1	3
Pulmonary/respiratory		1
Gastrointestinal/hepatobiliary	1	
Metabolic/endocrine	4	4
Renal/urinary tract		
Musculoskeletal/dermatological	11	3
Neurological		
Cardiovascular	3	2
Others	5	4

Table 3. Screening Results of Blood Chemistry before Treatment with Venetron or Placebo (Means ± SD)

	Venetron™	Placebo
Total Protein (g/dL)	7.1 ± 0.4	7.1 ± 0.3
Albumin (g/dL)	4.4 ± 0.2	4.4 ± 0.2
Globulin (Calc.) (g/dL)	2.8 ± 0.4	2.7 ± 0.2
Albumin/Globulin Ratio (Calc.)	1.6 ± 0.2	1.7 ± 0.2
SGOT (AST) (IU/L)	19 ± 4	19 ± 4
SGPT (ALT) (IU/L)	18 ± 7	20 ± 10
Alk. Phosphatase (IU/L)	65 ± 15	67 ± 20
Total Bilirubin (mg/dL)	0.7 ± 0.5	0.5 ± 0.2
Glucose (mg/dL)	91 ± 22	98 ± 29
Calcium (mg/dL)	9.5 ± 0.5	9.5 ± 0.3
Chloride (mEq/L)	104 ± 2	104 ± 2
CO_2 (mEq/L)	26 ± 3	25 ± 2
Sodium (mEq/L)	140 ± 1	140 ± 2
Potassium (mEq/L)	4.3 ±0.2	4.4 ±0.3
BUN (mg/dL)	15 ± 4	14 ± 4
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.1
BUN/Creatinine (calc)	16 ± 4	17 ± 5
RBC (10^6/uL)	4.6 ± 0.5	4.5 ± 0.4
Hemogloblin (g/dL)	14.4 ± 1.5	14.1 ± 1.0
Hematocrit (%)	41.8 ± 4.3	41.1 ± 2.6
MCV (fL)	90.4 ± 3.8	91.5 ± 4.5
MCH (pg)	31.1 ± 1.5	31.4 ± 1.7
MCHC (g/dL)	34.3 ± 0.6	34.3 ± 0.7
RDW (%)	13.5 ± 0.8	13.3 ± 0.8
Platelets (10^3/ul)	278 ± 49	282 ± 48
WBC (10^3/uL)	6.8 ± 2.5	6.9 ± 1.6
Lymphocytes (%)	26.5 ± 6.7	29.8 ± 5.9
Monocytes % (%)	7.3 ± 2.2	7.2 ± 2.1
Eosinophils (%)	1.9 ± 1.2	1.9 ± 1.1
Basophils (%)	0.5 ± 0.4	0.4 ± 0.2
TSH (mIU/mL)	1.7 ± 0.7	1.6 ± 0.7

Table 4: Frequencies of Adverse Events

	Venetron™	Placebo
No. of adverse events	30	22
No. of patients reporting adverse events	9	9
Events rated as mild	28	20
Events rated as moderate	2	2
Events rated as severe	0	0
No. of adverse events explained as not related to study product	7	10
No. of adverse events rated to be 'possibly' related to study product	22	11
No. of adverse events rated to be 'probably' related to study product	1	1
No. of adverse events rated to be 'definitely' related to study product	0	0
Head, eyes, ears, nose, throat	1	1
Pulmonary/respiratory	0	3
Gastrointestinal	14	5
Metabolic/endocrine	0	1
Renal/genitourinary tract	1	1
Musculoskeletal	2	3
Dermatological	1	3
Neurological	9	4
Cardiovascular	2	1
Psychiatric	0	0
Others	0	0

Table 5: Effect of Venetron™ on Blood Pressure (Means ± SD).

	Venetron™			Placebo		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
Systolic Blood Pressure (mmHg)	128±18	131±14	127±11	127±13	134±14	128±13
Diastolic Blood Pressure (mmHg)	77±10	79±10	78±10	80±7	78±12	79±10

Table 6: Effect of Venetron™ on Total HAM-D and CGI Scores and HAM-D Item 1 Score (Means ± SD).

	Venetron™			Placebo		
	Baseline	4 weeks	8 weeks	Baseline	4 weeks	8 weeks
HAM-D (Total Score)	16±2	12±4*	9±4*,a	16±1	11±4*	9±4*
CGI	3±1	NA	2±1*	3±0	NA	2±1*
HAM-D (Item 1; Depressed Mood)	2±1	1±1*	1±1*,a	2±1	2±1	1±1

***P<0.05 vs. baseline data**
[a]P<0.05 vs. week 4 data
Not significantly different vs. placebo

Table 7: Clinical Response Rates.

	Venetron™	Placebo
HAM-D Responders at Week 8 (≥50% decrease) n (%)	10 (50.0)	7 (36.8)
HAM-D Responders at Week 8 (≥20% decrease) n (%)	16 (80.0)	15 (78.9)
HAM-D Responders at Week 8 (≥10 point decrease) n (%)	8 (40.0)	6 (31.6)
Ham-D score of 8 or less at week 8, n (%)	12 (60.0)	10 (52.6)
Ham-D score of 6 or less at week 8, n (%)	7 (35.0)	6 (31.5)

Not significantly different vs. placebo.

Table 8: Effect of Venetron™ on Blood Neurotransmitters (Means ± SD).

	Venetron™		Placebo	
	Baseline	8 weeks	Baseline	8 weeks
Platelet serotonin (ng/ml)	15.4±9.1	15.0±6.0	18.6±8.4	15.9±10.5
Plasma 3-MHPG (ng/ml)	2.5±2.6	2.6±4.2	1.7±1.0	1.7±1.0

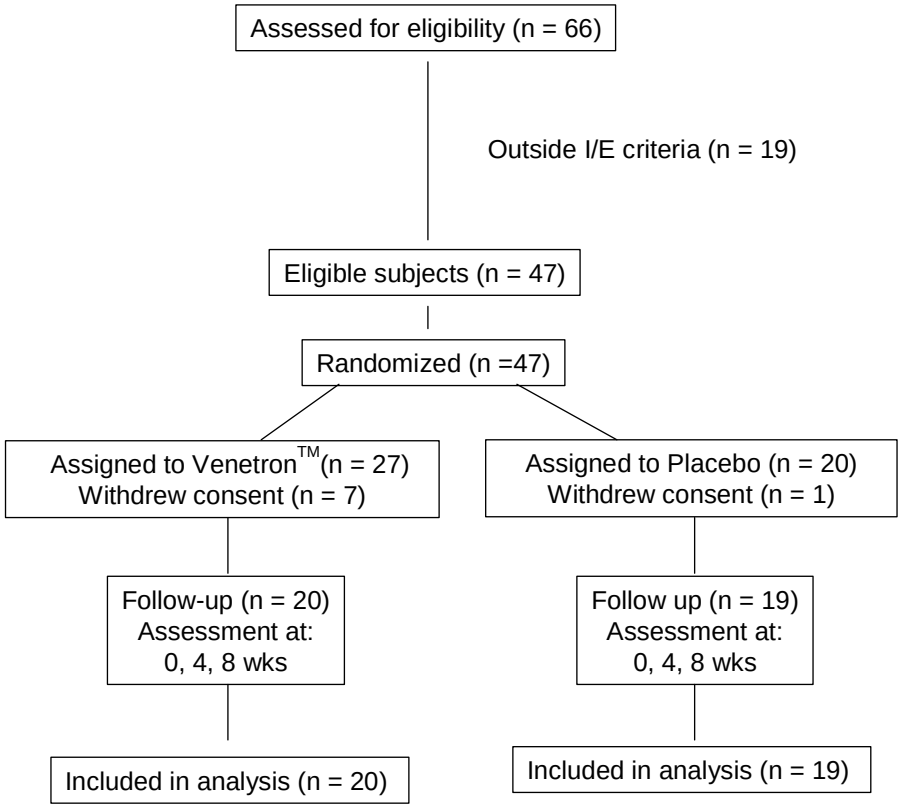
Not significantly different vs. placebo.

Table 9: Effect of Venetron™ on Response Rate to Serotonin.

	Venetron™		Placebo	
	n	%	n	%
Subjects with Increase in Serotonin	10	50.0%	6	31.6%
Subjects with > 20% Increase in Serotonin	7	35.0%	4	21.1%

Not significantly different vs. placebo.

Figure 1. Profile of Trial Progress



SIGNATURES

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APPENDICES

APPENDIX 1

Study Protocol (original; CA)

CLINICAL PROTOCOL

Effect of Venetron™ on Symptoms of Depression in Individuals with Mild Depression

Protocol Number: 05-VDHS Activation Date: June, 2005
IRB Approval Date:

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1. INTRODUCTION

1.1 1.1. NATURAL PRODUCTS AS MOOD IMPROVING AND ANTIDEPRESSANT AGENTS

Depression afflicts approximately 19 million Americans, and nearly 3 million Canadians, from children to the elderly. Current treatments include drugs such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. Unfortunately, conventional drugs often have limited tolerability and show significant side effects (1). Thus, many individuals suffering from depression seek alternative therapies including herbal remedies. A number of herbal products, such as ginko, ginseng, kava kava or yohimbine, are marketed with anecdotal claims of efficacy as antidepressants but so far, medical research provided limited support for their effectiveness. The most common and the most extensively studied herbal product, St. John's wort, showed evidence for superiority over placebo in several clinical trials, and is now considered to be effective in mildly to moderately depressed individuals (2-3). However, St. John's wort has also been reported to reduce plasma levels and efficacy of several pharmaceutical drugs, including cyclosporin, indinavir, digitonin, statins and many others (4). Thus there is a need to seek other natural products that show effectiveness against depression without interacting with absorption and metabolism of conventional drugs.

1.2 1.2. APOCYNUM VENETUM *EXTRACT – A NOVEL NATURAL PRODUCT WITH ANTIDEPRESSANT ACTIVITY*

Apocynum venetum (AV) is a wild shrub growing in China and its leaves are used as tea in traditional Chinese medicine. AV tea has also become a popular healthy drink in Japan and has recently come onto the market as health food in US. Extracts from AV leaves have been reported to produce various pharmacological responses including diuretic, antihypertensive, antihyperlipidemic and sedative effects (5-9). In addition, recent preclinical studies demonstrated that AV extract has antidepressant potential comparable to that of the synthetic tricyclic antidepressant, imipramine. In the acute experiment, 30 and 125 mg/kg doses of AV, and 20 mg/kg dose of imipramine similarly shortened the immobility of rats in the forced swimming test (10). Consistently, in the subsequent long term study, 15 mg/kg and 60 mg/kg doses of AV extract administered daily for 2 weeks or 8 weeks significantly reduced or tended to reduce concentrations of depression-related neurotransmitters norepinephrine (NE) and dopamine (DA) without affecting another neurotransmitter, serotonin (5-HT), in the rat brain tissues. In contrast, imipramine administered at the dose 15 mg/kg for the same period of time reduced NE and DA and increased 5-HT concentrations in the brain (11). The antidepressant effects of AV have been postulated to be due to its high content of flavonoids, especially hyperoside and isoquercitrin, which are also known to be major phytochemicals in St. John's wort (10). In spite of this similarity, there is no evidence so far that AV, like St. John's wort, might affect drug disposal. In rats, a 2 wk treatment with AV extract at the recommended human dose (3.3 mg/kg) had no effect on absorption of nifedipine, a drug metabolized by the most common hepatic cytochrom 450 enzyme, CYP3A whereas a treatment with St. John's wort at the recommended human dose (15 mg/kg) significantly reduced plasma concentration of the drug. In the same animal model, St. John's wort, but not AV, also reduced intestinal absorption of methylprednisolone, a drug metabolized via intestinal P-glycoprotein (12).

So far, the AV extract marketed under the trademark Venetron™ has not been tested in any placebo-controlled clinical trials but several case reports (Table 1) indicate that doses 50 mg/day could help to reduce symptoms of mild to moderate depression. Future clinical studies should establish if Venetron™ is more active than placebo in combating mild depression and if its effect is associated with modulation of

neurotransmitters. Previous reports suggest that blood levels of neurotransmitters can be altered by antidepressant use and that changes in blood neurotransmitters concentrations might also correlate with severity of depression (13-19). Thus, in the proposed clinical trial with Venetron™, plasma concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of NE, and platelet concentration of 5-HT will be monitored.

Previous toxicity studies in animals (rats) did not reveal any evidence of AV acute toxicity. In rats, single administration of AV at the dose 2 g/kg body weight did not adversely affect body weights after a period of 2 weeks. Also, a longer term, 8-week administration of AV at the doses ranging from 15 to 250 mg/kg did not reduce body weights and organ weights of male and female rats (unpublished).

Table 1. Venetron™ case reports.

Gender	Age	Daily dose	Treatment time	Comments
Male	62	50 mg caps	3.5 years	Decrease in cigarettes, became stronger to stress
Male	36	50 mg pill	6 months	Improvement in concentration, more optimistic
Female	55	50 mg caps	1 month	Decrease in fatigue and grief
Female	29	50 mg caps	3 months	Decrease in hypersensitiveness large enteritis, PMS
Male	66	50 mg pill	2 weeks	Decrease in frequency of awaking at night, deep re-sleeps
Male	75	50 mg pill	2 weeks	Decrease in frequency of awaking at night, deep re-sleeps

1.3 1.3 PROPOSED INTERVENTION

1.3.1 1.3.1 Supplement information

The commercial AV extract (Venetron™) is prepared from dried AV leaves by extraction in 70% ethanol. The final product is made into a dry powder tablets.Venetron™ is standardized to contain not less than 4% total amount of hyperoside and isoquercitrin but also contains significant amounts of chlorogenic acid, quercitin and miquelianin. Other minor components identified in the extract include catechins and kaempferol and possibly also apocynins and apocynosides. The last two classes of phytochemicals have been isolated from roasted AV leaves but have not been found in ethanol extract of dried AV leaves.

Venetron™ supplement will be administered at the dose 50 mg/day. The matching placebo will consist of cellulose tablets instead of phytochemical supplement.

1.3.2 1.3.2 Efficacy and safety of Venetron™ supplement

The first evidence for efficacy and safety of AV is its confirmed traditional use in China. The second evidence are six case reports of subjects with depression who took Venetron™ tablets at the dose 50 mg/day for periods ranging from 2 weeks to 3.5 years. All subjects experienced beneficial effects without reporting adverse reactions (Table 1). The antidepressant potential and safety of AV extract and commercial Venetron™ product have also been evaluated in animal models (see Introduction). The whole extract as well as isolates containing hyperoside, isoquercitrin, miquelianin and quercitin were active in FST (10 and unpublished). Venetron™ toxicity tests showed no acute adverse reaction after single

administration of 2 g/kg body weight and no reduction in body weights and organ weights in rats exposed to oral doses 15-250 mg/kg body weight for 8 weeks. In contrast, imipramine administered at the dose 15 mg/kg for the same period of time significantly reduced rats' final body weights as well as liver, prostate, heart and spleen weights (unpublished).

1.4 1.4. DOSING JUSTIFICATION AND RATIONALE

The combined results from experimental studies in animals and very preliminary clinical data from uncontrolled case reports imply that supplemental dosages of Venetron™ may have the ability to reduce symptoms of mild to moderate depression in humans. Thus, in the proposed study we plan to examine the effects of Venetron™ dose 50 mg/day on symptoms of mild depression as determined by study questionnaires and blood concentrations of neurotransmitters previously implied to be altered by depression. The study will be conducted in individuals with mild depression, as assessed by the score from the depression rating questionnaire.

2. STUDY OBJECTIVES

- To observe the efficacy of an extract obtained from *Apocynum venetum* leaves (Venetron™), against symptoms of mild depression and against blood markers of depression, platelet serotonin and plasma MHPG.

- To observe the safety of Venetron™ in individuals with mild depression.

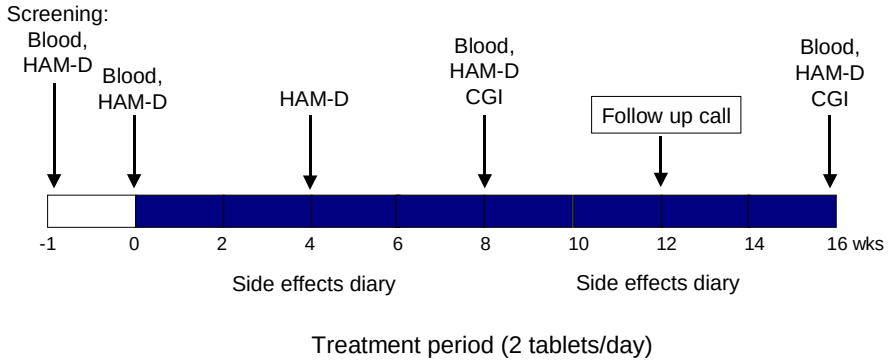
3. OVERALL STUDY DESIGN AND PLAN

The study will be a two-centre, double blind, vehicle controlled, and randomized, two-arm parallel groups study conducted in London, ON, Canada and in Northridge, CA, U.S. Subjects will be treated with tablets of the supplement versus placebo as below:

1.4.1.1 Table 2. Treatment groups

Treatment group	**# subjects**
Study arm 1: tablets of supplement	**20**
Study arm 2: tablets of placebo	**20**
Total	**40**

Study design is depicted in the diagram below:



1.5 3.1. SCREENING (VISIT 1)

Individuals will be recruited from the patient database of the Principal Investigator or by advertisement (texts enclosed). Members of the clinical research team of KGK Synergize Inc. will contact those interested. From the initial phone conversation an initial eligibility assessment will be made. Detailed information on the study will be given to the individual.

If the individual is deemed likely eligible to take part in the study and appears interested, a meeting with the study physician will be arranged. At this meeting, the clinical coordinator will discuss the information and consent form. If agreeable, the individual and the clinical coordinator will sign the consent form. The individuals will be subsequently asked to complete the Hamilton scale questionnaire (administered by a trained clinical coordinator or by study physician). Those who fulfill the inclusion criteria for mild depression (total score 7 to 17 on the Hamilton Depression rating scale (HAM-D 17 item version), but with a maximum score of 1 on HAM-D question 3, regarding suicidality) will be asked to undergo physical examination by study physician. The physical examination will include blood pressure and anthropometric measurements as well as routine blood tests (see Appendix 1). Upon confirmation that the individual is mildly depressed but healthy and eligible according to blood tests, an appointment will be arranged for the study to commence. Any abnormalities on these examinations will be reported to the patient confidentially and, if necessary, referral to a health care professional will be made.

1.6 3.2. TREATMENT PHASE (DURATION 8 TO 16 WEEKS, VISITS 2-3 OR 2-4)

Eligible participants will be advised to avoid taking St. John's wort or products containing its active ingredients (hypericin, hyperforin, hyperoside, isoquercitrin) for four weeks prior to the study and during the study. They will also be asked to discontinue other herbal medications. for 7 days prior to study start and during the study. Subjects will be randomly divided into two groups, and blindly assigned to active study medication or to placebo, 2 tablets/day, for a period of 8 weeks.

Following the screening visit, participants will be asked to return to the clinic 3 times over a period of 8 weeks, or 4 times if they agree to continue the treatment for another 8 weeks period. During the baseline visit, subjects will obtain a supply of study medication for the first 8 weeks and side effects diaries. During all visits, they will complete the Hamilton depression rating scale (administered by clinical coordinator) and they will have blood pressure measured. During all visits except week 4 they will also be asked to provide blood samples for determination of neurotransmitters. During the 8-week visit, subjects might be given an option to continue on the same medication for another 8 weeks and if agreeable (the second consent form signed), they will be given another 8-week supply of tablets and a set of side effect forms to complete. Unused tablets and completed side-effect forms will be collected during week-8 and if applicable during week-16 visits. During both wk 8 and wk 16 visits, subjects scores will additionally be rated (by study coordinator) on a Clinical Global Impression (CGI) scale. If applicable, follow up phone calls will be made at 12 weeks to ensure subject's compliance.

Table 3. Schedule of observations and procedures

Visit	**Visit 1 (screen)**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
	Week –1	**Week 0**	**Week 4**	**Week 8**	**Week 16**
Informed consent	**X**				
HAM-D	**X**	**X**	**X**	**X**	**X**
Physical exam	**X**				
Concomitant therapies	**X**	**X**	**X**	**X**	**X**
Review incl./excl. criteria	**X**	**X**	**X**	**X**	**X**
Laboratory assessments	**X**				
Randomization		**X**			
Distribution of supplements		**X**		**X**	
Anthropometric measurements	**X**				
Blood pressure	**X**	**X**	**X**	**X**	**X**
Blood neurotransmitters		**X**		**X**	**X**
CGI	**X**			**X**	**X**
Distribution of side effect diaries		**X**		**X**	
Collection of side effect diaries				**X**	**X**
Collection of leftover study products				**X**	**X**

1.7 3.3. ASSIGNMENT OF STUDY TREATMENT, RANDOMIZATION

The study will be a double-blind, vehicle controlled, randomized, two-arm parallel design. Randomization will be performed using computer-generated random number tables.

4. SELECTION OF STUDY POPULATION

4.1. INCLUSION CRITERIA

- Males and females 18-65 years old
- BMI- 18-35 kg/m^2
- Healthy as determined by blood chemistry, hematology and physical examination
- Signed informed consent
- Mild depression as confirmed by HAM-D scores in the range 14-20.

1.8 4.2. EXCLUSION CRITERIA

- Non-compliance
- Anticipated problems with product consumption
- Moderately severe co-morbid disease including cardiac, pulmonary, renal, hepatic, active cancer, diabetes, hypertension, immunological, neurological
- Consumption of nutritional, herbal or prescription product containing St. John's wort, hypericin, hyperforin, hyperoside or isoquercetrin acid within past 30 days
- High alcohol intake (more than two drinks per day)
- Pregnant or breastfeeding
- Use of antidepressant prescription medication
- Use of or herbal products within 1 week before the study

1.9 4.3. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

Criteria for removal of patients from the study will include:

- Adverse events
- Personal reasons
- Clinical judgment of physician
- Protocol violation

5. INVESTIGATIONAL PRODUCTS

1.10 5.1. PHARMACEUTICAL INFORMATION

5.1.1 Study formulation

Powdered Venetron™ extract will be prepared from dried leaves of *Apocynum venetum* by 70% ethanol extraction, filtration, purification and drying. The extract will be standardized to contain not less than 4% total amount of hyperoside and isoquercitrin. For quality control, product will be analyzed by HPLC by manufacturer.

Venetron™ extract will be administered in tablets. Each 200 mg tablet will contain:

Venetron™	25.0 mg
α-starch	84.0 mg
Lactose	25.2 mg
Crystalline cellulose	59.5 mg
Rapeseed oil	6.3 mg

Certificate of Analysis and Material Safety Data Sheet enclosed.

Venetron™ manufacturer:/co sposor Tokiwa Phytochemical Co., Ltd.
158 Kinoko
Sakure-shi, Chiba
285-0801 Japan.

Tablet Distributor/study sponsor:
Soft Gel Technologies Inc.
6982 Bandini Blvd. Los Angeles, CA 90040
Tel. 323-726-0700

5.1.2 Placebo

Placebo (cellulose) will be administered in tablets with the same color and appearance as active product. Each 200 mg tablet will contain:

Crystalline cellulose	144.0 mg
Safflower natural yellow color[1]	36.0 mg
Annatto color[2]	14.0 mg
Sucrose fatty acid ester	4.0 mg
Silicol dioxide fine powder	2.0 mg

[1]Containing 80% and 20% dextrin.
[2]Containing 10% Annatto color and 90% lactose.

Manufacturer:/co sponsor Tokiwa Phytochemical Co., Ltd.
158 Kinoko
Sakure-shi, Chiba
285-0801 Japan.

Placebo Distributor/study sponsor:

Soft Gel Technologies Inc.
6982 Bandini Blvd. Los Angeles, CA 90040
Tel. 323-726-0700

1.11 5.2. PACKAGING AND LABELLING

Study supplements will be provided in bottles containing 8-week supply of tablets. The same color of tablets will be used for active product and for matching placebo.

1.12 5.3. DOSING SCHEDULE, STORAGE AND DISPENSING

Participants will be asked to take 2 tablets/day, 1 tablet after breakfast and 1 tablet after dinner.

Subjects will be instructed to store each of the 8-week supply of tablets at room temperature, protected from heat, moisture, and direct light. Any unused products will be returned to the clinic during visits 3 and 4.

1.13 5.4. DURATION OF TREATMENT

The treatment period will commence for 8 weeks, with possibility of extension for another 8 weeks.

6. STUDY ASSESSMENTS

1.14 6.1. MEASUREMENT OF PRIMARY OBJECTIVE

To determine whether supplementation withVenetron™ tablets reduces symptoms of mild depression, changes in HAM-D score will be compared between the treatment and placebo group. Additionally, CGI scores, plasma concentrations of MHPG and platelet concentration of serotonin will be compared between the active product and placebo.

1.15 6.2. TOLERABILITY AND SAFETY ASSESSMENT

1.15.1 6.2.1 Tolerability

The Venetron™ formulation was well tolerated in humans as demonstrated by available case reports. Venetron's major components, hyperoside and isoquercitrin, are also present in St. John's wort extracts available on the market, and there is no evidence for poor tolerability of these products.

1.15.2 6.2.2 Clinical laboratory tests

Samples of blood will be collected throughout the trial. These samples will be obtained directly from the subjects for the sole purpose of accomplishing this proposed research. These samples will be alphanumerically coded. The persons performing the laboratory analysis will be unaware of the identity of the codes. All clinical measurements are listed in Appendix 1.

All blood samples will be taken by venipuncture. EDTA plasma will be separated immediately and aliquots will be stored at –80oC for determination of norepinephrine metabolite, MHPG, by HPLC (20). Separate blood sample will be drawn into a plastic tube with citrate anticoagulant. Platelets will be isolated for determination of serotonin following protocol from platelet serotonin Elisa kit (Rocky Mountains Diagnostics, Colorado Springs, CO).

1.15.3 6.2.3 Adverse events

Subjects will be completing adverse effect questionnaires during treatment period. Any adverse events will be documented and recorded in the study record. Notification of any adverse events or symptoms will be made to the CRO and the IRB within 15 days of the event. Any unusual, unsuspected, or severe toxicity will be reported.

1.16 6.3. COMPLIANCE ASSESSMENT

Compliance will be assessed by counting leftover tablets at visits 3 and if applicable at visit 4.

7. STATISTICAL EVALUATION

1.17 7.1. DETERMINATION OF SAMPLE SIZE

Primary outcome measure: HAM-D score.
This is a pilot study. Normally the sample size in this type of trials is more than 300.

1.18 7.2. STATISTICAL ANALYSIS

ANCOVA will be used to assess differences in markers of depression (scores and neurotransmitter concentrations) between baseline and end of each 8-wk treatment.
Repeated measures 1-way ANOVA followed by Newman-Keuls test will be used to assess differences between the groups from baseline to 16 weeks.

1.19 7.3. HANDLING OF MISSING AND INCOMPLETE DATA

Data will be evaluated only for subjects who completed at least 8 weeks of treatment.

8. RESEARCH MATERIAL AND DATA COLLECTION AND STORAGE

1.20 8.1. RESEARCH MATERIALS

All research samples taken from subjects will be alphanumerically coded. The persons performing the laboratory analysis will be unaware of the identity of the codes.

1.21 8.2. DATA COLLECTION PROCEDURES/RECORDS TO BE KEPT

All data collection and record storage will be done in compliance with GCP and ICH guidelines. Records will be retained at the site and by the CRO.

9. ECONOMIC CONSIDERATIONS

For participation in this study, patients will receive $20.00 per each study visit (London site) or $50.00 plus mileage ($0.32 per mile) per each study visit, except for the screening visit (U.S. site). Expenses such as parking will be compensated.

10. POTENTIAL RISKS AND PROCEDURES TO MINIMIZE RISKS

Potential Risks: All potential risks are disclosed to study participants prior to their participation. The potential risks include HAM-D scores worsening after the first 4 weeks of treatment. In the event of total score ≥ 25 or any score over 1 on question #3 (suicide), participants will be withdrawn from the study and referred to a mental health professional. The potential risks associated with this study also include venipuncture and oral ingestion of investigational product. All components of the proposed formulations have been tested in animals and in clinical trials either alone or in combinations. Administration of these products was not associated with any adverse effects. Risks associated with venipuncture include bruising at the site.

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APPENDIX 1-Schedule of blood tests performed throughout the protocol

Visit	**Visit 1 (screen)**	**Visit 2**	**Visit 3**	**Visit 4**
	Week -1	**Week 0**	**Week 8**	**Week 16**
Glucose	**X**			
Urea	**X**			
Creatinine	**X**			
Total protein	**X**			
Bilirubin	**X**			
Urate	**X**			
Sodium	**X**			
Potassium	**X**			
Chloride	**X**			
ALT	**X**			
AST	**X**			
Hemoglobin	**X**			
RBC	**X**			
Platelets	**X**			
WBC count	**X**			
TSH	**X**			
Urine dip	**X**			
Platelet serotonin		**X**	**X**	**X**
Plasma MHPG		**X**	**X**	**X**

APPENDIX 2

Study Protocol (Revised for second study site; MN)

CLINICAL PROTOCOL

Effect of Venetron™ on Symptoms of Depression in Individuals with Mild Depression

Protocol Number: 05-VDHS Activation Date: June, 2005
IRB Approval Date:

Principal Investigator: Dr. John Zenk
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1. INTRODUCTION

1.22 1.1. NATURAL PRODUCTS AS MOOD IMPROVING AND ANTIDEPRESSANT AGENTS

Depression afflicts approximately 19 million Americans, and nearly 3 million Canadians, from children to the elderly. Current treatments include drugs such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. Unfortunately, conventional drugs often have limited tolerability and show significant side effects (1). Thus, many individuals suffering from depression seek alternative therapies including herbal remedies. A number of herbal products, such as ginko, ginseng, kava kava or yohimbine, are marketed with anecdotal claims of efficacy as antidepressants but so far, medical research provided limited support for their effectiveness. The most common and the most extensively studied herbal product, St. John's wort, showed evidence for superiority over placebo in several clinical trials, and is now considered to be effective in mildly to moderately depressed individuals (2-3). However, St. John's wort has also been reported to reduce plasma levels and efficacy of several pharmaceutical drugs, including cyclosporin, indinavir, digitonin, statins and many others (4). Thus there is a need to seek other natural products that show effectiveness against depression without interacting with absorption and metabolism of conventional drugs.

1.23 1.2. APOCYNUM VENETUM *EXTRACT – A NOVEL NATURAL PRODUCT WITH ANTIDEPRESSANT ACTIVITY*

Apocynum venetum (AV) is a wild shrub growing in China and its leaves are used as tea in traditional Chinese medicine. AV tea has also become a popular healthy drink in Japan and has recently come onto the market as health food in US. Extracts from AV leaves have been reported to produce various pharmacological responses including diuretic, antihypertensive, antihyperlipidemic and sedative effects (5-9). In addition, recent preclinical studies demonstrated that AV extract has antidepressant potential comparable to that of the synthetic tricyclic antidepressant, imipramine. In the acute experiment, 30 and 125 mg/kg doses of AV, and 20 mg/kg dose of imipramine similarly shortened the immobility of rats in the forced swimming test (10). Consistently, in the subsequent long term study, 15 mg/kg and 60 mg/kg doses of AV extract administered daily for 2 weeks or 8 weeks significantly reduced or tended to reduce concentrations of depression-related neurotransmitters norepinephrine (NE) and dopamine (DA) without affecting another neurotransmitter, serotonin (5-HT), in the rat brain tissues. In contrast, imipramine administered at the dose 15 mg/kg for the same period of time reduced NE and DA and increased 5-HT concentrations in the brain (11). The antidepressant effects of AV have been postulated to be due to its high content of flavonoids, especially hyperoside and isoquercitrin, which are also known to be major phytochemicals in St. John’s wort (10). In spite of this similarity, there is no evidence so far that AV, like St. John’s wort, might affect drug disposal. In rats, a 2 wk treatment with AV extract at the recommended human dose (3.3 mg/kg) had no effect on absorption of nifedipine, a drug metabolized by the most common hepatic cytochrom 450 enzyme, CYP3A whereas a treatment with St. John’s wort at the recommended human dose (15 mg/kg) significantly reduced plasma concentration of the drug. In the same animal model, St. John’s wort, but not AV, also reduced intestinal absorption of methylprednisolone, a drug metabolized via intestinal P-glycoprotein (12).

So far, the AV extract marketed under the trademark Venetron™ has not been tested in any placebo-controlled clinical trials but several case reports (Table 1) indicate that doses 50 mg/day could help to reduce symptoms of mild to moderate depression. Future clinical studies should establish if Venetron™ is more active than placebo in combating mild depression and if its effect is associated with modulation of

neurotransmitters. Previous reports suggest that blood levels of neurotranmitters can be altered by antidepressant use and that changes in blood neurotransmitters concentrations might also correlate with severity of depression (13-19). Thus, in the proposed clinical trial with Venetron™, plasma concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of NE, and platelet concentration of 5-HT will be monitored.

Previous toxicity studies in animals (rats) did not reveal any evidence of AV acute toxicity. In rats, single administration of AV at the dose 2 g/kg body weight did not adversely affect body weights after a period of 2 weeks. Also, a longer term, 8-week administration of AV at the doses ranging from 15 to 250 mg/kg did not reduce body weights and organ weights of male and female rats (unpublished).

Table 1. Venetron™ case reports.

Gender	Age	Daily dose	Treatment time	Comments
Male	62	50 mg caps	3.5 years	Decrease in cigarettes, became stronger to stress
Male	36	50 mg pill	6 months	Improvement in concentration, more optimistic
Female	55	50 mg caps	1 month	Decrease in fatigue and grief
Female	29	50 mg caps	3 months	Decrease in hypersensitiveness large enteritis, PMS
Male	66	50 mg pill	2 weeks	Decrease in frequency of awaking at night, deep re-sleeps
Male	75	50 mg pill	2 weeks	Decrease in frequency of awaking at night, deep re-sleeps

1.24 1.3 PROPOSED INTERVENTION

1.24.1 1.3.1 Supplement information

The commercial AV extract (Venetron™) is prepared from dried AV leaves by extraction in 70% ethanol. The final product is made into a dry powder tablets. Venetron™ is standardized to contain not less than 4% total amount of hyperoside and isoquercitrin but also contains significant amounts of chlorogenic acid, quercitin and miquelianin. Other minor components identified in the extract include catechins and kaempferol and possibly also apocynins and apocynosides. The last two classes of phytochemicals have been isolated from roasted AV leaves but have not been found in ethanol extract of dried AV leaves.

Venetron™ supplement will be administered at the dose 50 mg/day. The matching placebo will consist of cellulose tablets instead of phytochemical supplement.

1.24.2 1.3.2 Efficacy and safety of Venetron™ supplement

The first evidence for efficacy and safety of AV is its confirmed traditional use in China. The second evidence are six case reports of subjects with depression who took Venetron™ tablets at the dose 50 mg/day for periods ranging from 2 weeks to 3.5 years. All subjects experienced beneficial effects without reporting adverse reactions (Table 1). The antidepressant potential and safety of AV extract and commercial Venetron™ product have also been evaluated in animal models (see Introduction). The whole extract as well as isolates containing hyperoside, isoquercitrin, miquelianin and quercitin were active in FST (10 and unpublished). Venetron™ toxicity tests showed no acute adverse reaction after single

administration of 2 g/kg body weight and no reduction in body weights and organ weights in rats exposed to oral doses 15-250 mg/kg body weight for 8 weeks. In contrast, imipramine administered at the dose 15 mg/kg for the same period of time significantly reduced rats' final body weights as well as liver, prostate, heart and spleen weights (unpublished).

1.25 1.4. DOSING JUSTIFICATION AND RATIONALE

The combined results from experimental studies in animals and very preliminary clinical data from uncontrolled case reports imply that supplemental dosages of Venetron™ may have the ability to reduce symptoms of mild to moderate depression in humans. Thus, in the proposed study we plan to examine the effects of Venetron™ dose 50 mg/day on symptoms of mild depression as determined by study questionnaires and blood concentrations of neurotransmitters previously implied to be altered by depression. The study will be conducted in individuals with mild depression, as assessed by the score from the depression rating questionnaire.

2. STUDY OBJECTIVES

- To observe the efficacy of an extract obtained from *Apocynum venetum* leaves (Venetron™), against symptoms of mild depression and against blood markers of depression, platelet serotonin and plasma MHPG.

- To observe the safety of Venetron™ in individuals with mild depression.

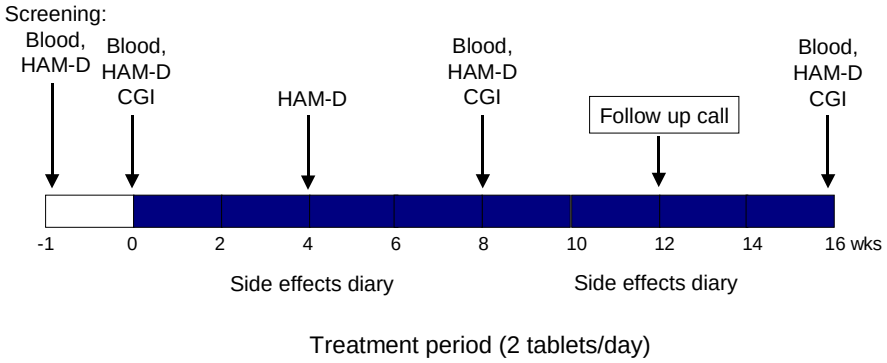
3. OVERALL STUDY DESIGN AND PLAN

The study will be a three-centre, double blind, placebo controlled, and randomized, two-arm parallel groups study conducted in London, ON, Canada, Northridge, CA, U.S, and Edina, Minnesota, U.S. Subjects will be treated with tablets of the supplement versus placebo as below:

1.25.1.1 Table 2. Treatment groups

Treatment group	**# subjects**
Study arm 1: tablets of supplement	**20**
Study arm 2: tablets of placebo	**20**
Total	**40**

Study design is depicted in the diagram below:



1.26 3.1. SCREENING (VISIT 1)

Individuals will be recruited from the patient database of the Principal Investigator or by advertisement (texts enclosed). Members of the clinical research team will contact those interested. From the initial phone conversation an initial eligibility assessment will be made. Detailed information on the study will be given to the individual.

If the individual is deemed likely eligible to take part in the study and appears interested, a meeting with the study physician will be arranged. At this meeting, the clinical coordinator will discuss the information and consent form. If agreeable, the individual and the clinical coordinator will sign the consent form. The individuals will be subsequently asked to complete the Hamilton scale questionnaire (administered by a trained clinical coordinator or by study physician). Those who fulfill the inclusion criteria for mild depression (total score 7 to 17 on the Hamilton Depression rating scale (HAM-D 17 item version), but with a maximum score of 1 on HAM-D question 3, regarding suicidality) will be asked to undergo physical examination by study physician. The physical examination will include blood pressure and anthropometric measurements as well as routine blood tests (see Appendix 1). Upon confirmation that the individual is mildly depressed but healthy and eligible according to blood tests, an appointment will be arranged for the study to commence. Any abnormalities on these examinations will be reported to the patient confidentially and, if necessary, referral to a health care professional will be made.

1.27 3.2. TREATMENT PHASE (DURATION 8 TO 16 WEEKS, VISITS 2-3 OR 2-4)

Eligible participants will be advised to avoid taking St. John's Wort or products containing its active ingredients (hypericin, hyperforin, hyperoside, isoquercitrin) for four weeks prior to the study and during the study. They will also be asked to discontinue other herbal medications. for 7 days prior to study start and during the study. Subjects will be randomly divided into two groups, and blindly assigned to active study medication or to placebo, 2 tablets/day, for a period of 8 weeks.

Following the screening visit, participants will be asked to return to the clinic 3 times over a period of 8 weeks. During the baseline visit, subjects will obtain a supply of study medication for the first 8 weeks and side effects diaries. During all visits, they will complete the Hamilton depression rating scale (administered by clinical coordinator) and they will have blood pressure measured. During all visits except week 4 they will also be asked to provide blood samples for determination of neurotransmitters. Unused tablets and completed side-effect forms will be collected during week-8 and if applicable during week-16 visits. During baseline, wk 8 and wk 16 visits, subjects scores will additionally be rated (by study coordinator) on a Clinical Global Impression (CGI) scale. If applicable, follow up phone calls will be made at 12 weeks to ensure subject's compliance.

Table 3. Schedule of observations and procedures

Visit	**Visit 1 (screen)**	**Visit 2**	**Visit 3**	**Visit 4**
	Week –1	**Week 0**	**Week 4**	**Week 8**
Informed consent	**X**			
HAM-D	**X**	**X**	**X**	**X**
Physical exam	**X**			
Concomitant therapies	**X**	**X**	**X**	**X**
Review incl./excl. criteria	**X**	**X**	**X**	**X**
Laboratory assessments	**X**			
Randomization		**X**		
Distribution of supplements		**X**		**X**
Anthropometric measurements	**X**			
Blood pressure	**X**	**X**	**X**	**X**
Blood neurotransmitters		**X**		**X**
CGI		**X**		**X**
Distribution of side effect diaries		**X**		
Collection of side effect diaries				**X**
Collection of leftover study products				**X**

1.28 3.3. ASSIGNMENT OF STUDY TREATMENT, RANDOMIZATION

The study will be a double-blind, vehicle controlled, randomized, two-arm parallel design. Randomization will be performed using computer-generated random number tables.

4. SELECTION OF STUDY POPULATION

A. INCLUSION CRITERIA

- Males and females 18-65 years old
- BMI- 18-35 kg/m^2
- Healthy as determined by blood chemistry, hematology and physical examination
- Signed informed consent
- Mild depression as confirmed by HAM-D scores in the range 14-20.

1.29 4.2. EXCLUSION CRITERIA

- Non-compliance
- Anticipated problems with product consumption
- Moderately severe co-morbid disease including cardiac, pulmonary, renal, hepatic, active cancer, diabetes, hypertension, immunological, neurological
- Consumption of nutritional, herbal or prescription product containing St. John's wort, hypericin, hyperforin, hyperoside or isoquercetrin acid within past 30 days
- High alcohol intake (more than two drinks per day)
- Pregnant or breastfeeding
- Use of antidepressant prescription medication
- Use of or herbal products within 1 week before the study

1.30 4.3. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

Criteria for removal of patients from the study will include:

- Adverse events
- Personal reasons
- Clinical judgment of physician
- Protocol violation

5. INVESTIGATIONAL PRODUCTS

1.31 5.1. PHARMACEUTICAL INFORMATION

5.1.2 Study formulation

Powdered Venetron™ extract will be prepared from dried leaves of *Apocynum venetum* by 70% ethanol extraction, filtration, purification and drying. The extract will be standardized to contain not less than 4% total amount of hyperoside and isoquercitrin. For quality control, product will be analyzed by HPLC by manufacturer.

Venetron™ extract will be administered in tablets. Each 200 mg tablet will contain:

Venetron™	25.0 mg
α-starch	84.0 mg
Lactose	25.2 mg
Crystalline cellulose	59.5 mg
Rapeseed oil	6.3 mg

Certificate of Analysis and Material Safety Data Sheet enclosed.

Venetron™ manufacturer /co sponsor: Tokiwa Phytochemical Co., Ltd.
158 Kinoko
Sakure-shi, Chiba
285-0801 Japan.

Tablet Distributor/study sponsor:
Soft Gel Technologies Inc.
6982 Bandini Blvd. Los Angeles, CA 90040
Tel. 323-726-0700

5.1.2 Placebo

Placebo (cellulose) will be administered in tablets with the same color and appearance as active product. Each 200 mg tablet will contain:

Crystalline cellulose	144.0 mg
Safflower natural yellow color[1]	36.0 mg
Annatto color[2]	14.0 mg
Sucrose fatty acid ester	4.0 mg
Silicol dioxide fine powder	2.0 mg

[1]Containing 80% and 20% dextrin.
[2]Containing 10% Annatto color and 90% lactose.

Manufacturer/co sponsor: Tokiwa Phytochemical Co., Ltd.
158 Kinoko
Sakure-shi, Chiba
285-0801 Japan.

Placebo Distributor/study sponsor:

Soft Gel Technologies Inc.
6982 Bandini Blvd. Los Angeles, CA 90040
Tel. 323-726-0700

1.32 5.2. PACKAGING AND LABELLING

Study supplements will be provided in bottles containing 8-week supply of tablets. The same color of tablets will be used for active product and for matching placebo.

1.33 5.3. DOSING SCHEDULE, STORAGE AND DISPENSING

Participants will be asked to take 2 tablets/day, 1 tablet after breakfast and 1 tablet after dinner.

Subjects will be instructed to store each of the 8-week supply of tablets at room temperature, protected from heat, moisture, and direct light. Any unused products will be returned to the clinic during visits 4 and 5.

1.34 5.4. DURATION OF TREATMENT

The treatment period will commence for 8 weeks, with possibility of extension for another 8 weeks.

6. STUDY ASSESSMENTS

1.35 6.1. MEASUREMENT OF PRIMARY OBJECTIVE

To determine whether supplementation with Venetron™ tablets reduces symptoms of mild depression, changes in HAM-D score will be compared between the treatment and placebo group. Additionally, CGI scores, plasma concentrations of MHPG and platelet concentration of serotonin will be compared between the active product and placebo.

1.36 6.2. TOLERABILITY AND SAFETY ASSESSMENT

1.36.1 6.2.1 Tolerability

The Venetron™ formulation was well tolerated in humans as demonstrated by available case reports. Venetron's major components, hyperoside and isoquercitrin, are also present in St. John's wort extracts available on the market, and there is no evidence for poor tolerability of these products.

1.36.2 6.2.2 Clinical laboratory tests

Samples of blood will be collected throughout the trial. These samples will be obtained directly from the subjects for the sole purpose of accomplishing this proposed research. These samples will be alphanumerically coded. The persons performing the laboratory analysis will be unaware of the identity of the codes. All clinical measurements are listed in Appendix 1.

All blood samples will be taken by venipuncture. EDTA plasma will be separated immediately and aliquots will be stored at –30oC for determination of norepinephrine metabolite, MHPG, by HPLC (20). Separate blood sample will be drawn into a plastic tube with citrate anticoagulant. Platelets will be isolated for determination of serotonin following protocol from platelet serotonin Elisa kit (Rocky Mountains Diagnostics, Colorado Springs, CO).

1.36.3 6.2.3 Adverse events

Subjects will be completing adverse effect questionnaires during treatment period. Any adverse events will be documented and recorded in the study record. Notification of any adverse events or symptoms will be made to the CRO and the IRB within 15 days of the event. Any unusual, unsuspected, or severe toxicity will be reported.

1.37 6.3. COMPLIANCE ASSESSMENT

Compliance will be assessed by counting leftover tablets at visits 4 and if applicable at visit 5.

7. STATISTICAL EVALUATION

1.38 7.1. DETERMINATION OF SAMPLE SIZE

Primary outcome measure: HAM-D score.
This is a pilot study. Normally the sample size in this type of trial is more than 300.

1.39 7.2. STATISTICAL ANALYSIS

ANOVA will be used to assess differences in markers of depression (scores and neurotransmitter concentrations) between baseline and end of each 8-wk treatment.
Repeated measures 1-way ANOVA followed by Newman-Keuls test will be used to assess differences between the groups from baseline to 16 weeks.

1.40 7.3. HANDLING OF MISSING AND INCOMPLETE DATA

Data will be evaluated only for subjects who completed at least 8 weeks of treatment.

8. RESEARCH MATERIAL AND DATA COLLECTION AND STORAGE

1.41 8.1. RESEARCH MATERIALS

All research samples taken from subjects will be alphanumerically coded. The persons performing the laboratory analysis will be unaware of the identity of the codes.

1.42 8.2. DATA COLLECTION PROCEDURES/RECORDS TO BE KEPT

All data collection and record storage will be done in compliance with GCP and ICH guidelines. Records will be retained at the site and by the CRO.

9. ECONOMIC CONSIDERATIONS

For participation in this study, patients will receive $20.00 per each study visit (London site) or $35.00) per each study visit, except for the screening visit (Minnesota, U.S. site). Expenses such as parking will be compensated (London, Canada site).

10. POTENTIAL RISKS AND PROCEDURES TO MINIMIZE RISKS

Potential Risks: All potential risks are disclosed to study participants prior to their participation. The potential risks include HAM-D scores worsening after the first 4 weeks of treatment. In the event of total score ≥ 25 or any score over 1 on question #3 (suicide), participants will be withdrawn from the study and referred to a mental health professional. The potential risks associated with this study also include venipuncture and oral ingestion of investigational product. All components of the proposed formulations have been tested in animals and in clinical trials either alone or in combinations. Administration of these products was not associated with any adverse effects. Risks associated with venipuncture include bruising at the site.

11. REFERENCE LIST

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APPENDIX 1-Schedule of blood tests performed throughout the protocol

Visit	Visit 1 (screen)	Visit 2	Visit 3
	Week -1	Week 0	Week 8
Glucose	**X**		
Urea	**X**		
Creatinine	**X**		
Total protein	**X**		
Bilirubin	**X**		
Urate	**X**		
Sodium	**X**		
Potassium	**X**		
Chloride	**X**		
ALT	**X**		
AST	**X**		
Hemoglobin	**X**		
RBC	**X**		
Platelets	**X**		
WBC count	**X**		
TSH	**X**		
Urine dip	**X**		
Platelet serotonin		**X**	**X**
Plasma MHPG		**X**	**X**

APPENDIX 3 (The Hamilton Rating Scale for Depression; HAM-D)

Name:_____ Date:_____

Effect of Venetron™ on Symptoms of Depression in Individuals with Mild Depression

The Hamilton Rating Scale for Depression

For each item, write the correct number on the line next to the item. (Only one response per item)

1. DEPRESSED MOOD (Sadness, hopeless, helpless, worthless)

_____ **0=** Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported verbally
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. FEELINGS OF GUILT

_____ **0=** Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUIDICE

_____ **0=** Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)

4. INSOMNIA EARLY

_____ **0=** No difficulty falling asleep
1= Complains of occasional difficulty falling asleep—i.e., more that ½ hour
2= Complains of nightly difficulty sleeping

5. INSOMNIA MIDDLE

_____ **0=** No difficulty
1= Patient complains of being restless and disturbed during the night
2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA LATE

_____ **0=** No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

7. WORK AND ACTIVITIES

_____ **0=** No difficulty
1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2= Loss of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent on activities or decrease in productivity
4= Stopped working because of present illness

8. RETARDATION: PSYCOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____ **0=** Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9. AGITATION

_____ **0=** None
1= Fidgetiness
2= Playing with hands, hair, ect.
3= Moving about, cant sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY (PSYCOLOGICAL)

_____ **0=** No difficulty
1= Subjective tension and irritability
2= Worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, 'butterflies,' indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____ **0=** Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____ **0=** None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. SOMATIC SYMPTOMS GENERAL

_____ **0=** None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____ **0=** Absent
1= Mild
2= Severe

15. HYPOCHONDRIASIS

_____ **0=** Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, ect.
4= Hypchondriacal delusions

16. LOSS OF WEIGHT

_____ **A.** When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17. INSIGHT

_____ **0=** Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, ect.
2= Denies being ill at all

APPENDIX 4 (**Clinical Global Impression; CGI)**

Subject Initials: _____ Subject Number: _____

Date: _____ Visit: _____

Effect of Venetron™ on Symptoms of Depression in Individuals with Mild Depression

Clinical Global Impression (CGI)

Considering your total clinical experience with this particular population, how severe is the subject's mental illness at this time?

1. Not ill
2. Very mild
3. Mild
4. Moderately ill
5. Marked
6. Severe
7. Extremely severe

Score (1 – 7): _____

NOTES:

APPENDIX 5 (Visit 1 source documents; CA)

See attached

APPENDIX 6 (Visit 1 source documents; MN)

See attached

APPENDIX 7 (Journal week 0-4)

See attached

APPENDIX 8 (Journal week 4-8)

See attached

APPENDIX 9 (Visit 2 source documents; CA)

See attached

APPENDIX 10 (Visit 2 source documents; MN)

See attached

APPENDIX 11 (Visit 3 source documents; CA)

See attached

APPENDIX 12 (Visit 3 source documents; MN)

See attached

APPENDIX 13 (Visit 4 source documents; CA)

See attached

APPENDIX 14 (Visit 4 source documents; MN)

See attached

Appendix 15

Medication and Medical History California Site

Medical History

Subject A-B 02:
Hypothyroidism
Hypercholesterolemia
Gastroesophageal reflux disease
Herniated discs
Upcoming ankle replacement surgery
Chronic pain
Allergies: sulfa, latex, codeine
Alcohol use: very rare

Subject FLA 07:
Chronic pain
Eczema
Allergies: vioxx, vicodin, codeine

Subject M-F 13:
Hypertension
Alcohol use: red wine

Subject TLM 14:
Headaches
Alcohol use: occasional social

Subject SMF 15:
Hypertension
Hyperlipidemia
Asthma
Tobacco use: 1-2 cigarettes a day
Alcohol use: social
Recreational drug use: rare and occasional marijuana use

Concomitant Medications

Subject Initials/ Number	Drug Name	Total Daily Dose (mg)	Indication	Start Date	End Date
A-B/02	Synthroid	0.88 mg	Hypothyroidism	2005	Continues
	Motrin	250 mg	BID Pain	2000	Continues
	Soma	350 mg	Back pain	2003	Continues

	Zocor	40 mg	Hypercholesterolemia	2000	Continues
	Nexium	40 mg	Gastroesophageal reflux disease	2000	Continues
FLA/07	None	N/A	N/A	N/A	N/A
M-F/13	None	N/A	N/A	N/A	N/A
TLM/14	Zovia	1 tablet	Oral contraception	Unknown	Continues
	Advil	200 mg	PRN Headeaches	Unknown	Continues
	Tylenol PM	2 capsules	PRN at bedtime Headaches and sleeplessness	Unknown	Continues
SMF/15	Lotensin	20 mg	Hypertension	2005	Continues
	Azmacort	Unknown	Inhaler for Asthma	Unknown	Continues
	Niacin	1 mg	Hyperlipidemia	2005	Continues
	Folic Acid	Unknown	Supplement	Unknown	Continues

Physical Exam Results

Subject A-B 02:
Blood pressure = 116/87 mmHg
Pulse = 81 beats per minute
Temperature = Not done ° F
Height = 165.1 cm
Weight = 84.5 kg
BMI = 31 kg/m^2
Physical exam = Not done

Subject FLA 07:
Blood pressure = 121/66 mmHg
Pulse = 61 beats per minute
Temperature = 98.1 ° F
Height = 170.1 cm
Weight = 74.5 kg
BMI = 25 kg/m^2
Physical exam =
Finding noted for Skin - eczema

Subject M-F 13:
Blood pressure = 138/90 mmHg
Pulse = 64 beats per minute
Temperature = 97.6 ° F
Height = 175.3 cm
Weight = 98.6 kg
BMI = 32 kg/m^2
Physical exam = Normal

Subject TLM 14:
Blood pressure = 118/78 mmHg
Pulse = 68 beats per minute

Temperature = 96.9 ° F
Height = 173 cm
Weight = 78 kg
BMI = 26.1 kg/m^2
Physical exam = Normal

Subject SMF 15: Blood pressure = 138/70 mmHg
Pulse = 62 beats per minute
Temperature = 98.2 ° F
Height = 157.5 cm
Weight = 80.6 kg
BMI = 32.5 kg/m^2
Physical exam = Normal

Appendix 16

Medication and Medical History Minnesota Site

Medical History

Subject LKC 012:	Nothing noted
Subject TLC 013:	Acne Bulging disc (L3) since 1994 Allergies to: Sulfa drugs, penicillin, morphine
Subject ALP 015:	Torn meniscus (left knee) Hypertension Breast cancer in remission
Subject NNL 017:	Nothing noted
Subject CSH 018:	Nothing noted
Subject LAD 019:	Hearing loss since childhood Allergic to an antibiotic - unsure which one
Subject CLS 020:	Diabetes Type II - diet controlled Carpel Tunnel Syndrome
Subject WKN 021:	Nothing noted
Subject MRC 022:	Hypertension Hypercholesterolemia
Subject JDN 023:	Nothing noted
Subject PGM 024:	Nothing noted
Subject MLE 025:	Nothing noted
Subject DJE 026:	Nothing noted
Subject MKW 030:	Headaches Muscle aches
Subject SJL 031:	Hypertension Allergies - unspecified
Subject AMW 032:	Nothing noted

Subject LMF 033:	Nothing noted
Subject RYN 034:	Wears glasses
Subject DGS 035:	Nothing noted
Subject GWS 036:	Allergies - unspecified
Subject WLM 037:	Nothing noted
Subject JBR 038:	Psoriasis Knee pain Allergic to prednisone
Subject DMA 039:	Diabetes mellitus Type II Hyperlipidemia
Subject DRK 041:	Nothing noted
Subject LGC 042:	Nothing noted
Subject BJR 043:	Hysterectomy
Subject MAJ 047:	Nothing noted
Subject RDH 048:	Nothing noted
Subject DSM 051:	Nothing noted
Subject CLT 052:	Tubal ligation
Subject SND 054:	Hyperlipidemia in past Surgery on left ankle - reduction and surgical plate for fracture
Subject CHW 055:	Arthritis Hypertension Allergy to penicillin
Subject JMD 056:	Nothing noted
Subject KHW 057:	Chronic back pain

Concomitant Medications

Subject Initials/ Number	Drug Name	Dose	Indication	Start Date	End Date
LKC/012	Polytrim Ophthalmic Solution	1 drop 6 x day	Conjunctivitis	Jan 21, 2006	Jan 31, 2006
TLC/013	Flexeril	10 mg QD	Bulging disc (L3)	1994	Continues
ALP/015	Toprol	100 mg QD	Hypertension	Unknown	Continues
	Lisinopril	10 mg QD	Hypertension	Unknown	Continues
	Hydrochlorothiazide	25 mg QD	Hypertension	Unknown	Continues
	Fosamax	70 mg / week	Prophylaxis osteoporosis	Unknown	Continues
	Vitamin B complex	1 Tablet QD	Supplement	Unknown	Continues
	Calcium with vitamin D	1 Tablet QD	Supplement	Unknown	Continues
	Femara	2.5 mg QD	Breast cancer (remission)	Unknown	Continues
NNL/017	None	N/A	N/A	N/A	N/A
CSH/018	Amoxicillin	500 mg BID	Sinusitis	Jan 28, 2006	Feb 12, 2006
LAD/019	Benadryl	50 mg QD	Sleeping aid	2003	Continues
	Aspirin	325 mg PRN	Cold symptoms	Jan 20, 2006	Feb 28, 2006
CLS/020	MVI	1 QD	Supplement	Unknown	Continues
	TMG	500 mg QD	Supplement	Unknown	Continues
	Fish oil	2000 mg QD	Supplement	Unknown	Continues
	DHEA	100 mg QD	Supplement	Unknown	Continues
	Lipoic Acid	150mg QD	Supplement	Unknown	Continues
	Ester C	1000 mg QD	Supplement	Unknown	Continues
	Ibuprofen	200 mg PRN	Pain	Feb 6, 2006	Mar 3, 2006
	Tylenol PM	250 mg PRN	Pain/sleep aid	Feb 20, 2006	Mar 14, 2006
WKN/021	None	N/A	N/A	N/A	N/A
MRC/022	Diovan	80 mg QD	Hypertension	2003	Continues
	Lipitor	10 mg QD	Hypercholesterolemia	Apr 2004	Continues
JDN/023	None	N/A	N/A	N/A	N/A
PGM/024	None	N/A	N/A	N/A	N/A
MLE/025	None	N/A	N/A	N/A	N/A
DJE/026	Benadryl	25 mg PRN	Post Nasal Drip	Feb 2, 2006	Continues
MKW/030	Advil	200 mg PRN	Headaches and muscle aches	1990	Continues

SJL/031	Lisinopril	10 mg QD	Hypertension	Aug 2005	Continues
	Caritin	10 mg	Allergies	2003	Continues
AMW/032	None	N/A	N/A	N/A	N/A
LMF/033	None	N/A	N/A	N/A	N/A
RYN/034	None	N/A	N/A	N/A	N/A
DGS/035	None	N/A	N/A	N/A	N/A
GSW/036	Nasonex	55 mg	Allergies	2004	Continues
	ASA	81 mg	Prophylaxis	2001	Continues
	Multivitamin	1 tablet	Supplement	Unknown	Continues
WLM/037	Vision Formula	6 mg	Eye protection	Dec 2005	Continues
	Calcium Plus	600 mg	Supplement	2000	Continues
	Multivitamin	1 tablet	Supplement	2000	Continues
	Glucosamine and Chondroitin	500 mg /400 mg	Supplement	2000	Continues
JBR/038	Tylenol PM	2 tablets QD	Sleep aid and knee pain	1990	Continues
	Glucosamine	1 tablet QD	Supplement	2005	Continues
	Aleve	225 mg PRN	Knee pain	Jan 2006	Continues
DMA/039	Glipizide	10 mg BID	Diabetes mellitus type II	2003	Continues
	Metformin	500 mg BID	Diabetes mellitus type II	2003	Continues
	Tricor	80 mg QD	Hyperlipidemia	2005	Continues
DRK/041	None	N/A	N/A	N/A	N/A
LGC/042	None	N/A	N/A	N/A	N/A
BJR/043	Climara	0.75 mg QWK	Hormone replacement therapy	Jan 2004	
MAJ/047	None	N/A	N/A	N/A	N/A
RDH/048	TUMS	1 tablet PRN	Upset stomach	May 8, 2006	May 8, 2006
DSM/051	None	N/A	N/A	N/A	N/A
CLT/052	None	N/A	N/A	N/A	N/A
SND/054	None	N/A	N/A	N/A	N/A
CHW/055	Glucosamine and Chondroitin	750 mg	Arthritis	Sep 2005	
	Magnesium	250 mg	Supplement	2002	
	Vitamin B Complex	1 tablet	Supplement	2002	
	Calcium with Vitamin D	1 tablet	Supplement	2002	
	Vitamin C	1 tablet	Supplement	2002	
	Melatonin	1 tablet	Sleep aid supplement	Feb 2006	
	Hydrochlorothiazide	25 mg QD	Hypertension	2001	
JMD/056	None	N/A	N/A	N/A	N/A
KHW/057	Vicodin	1 tablet PRN	Back pain	2004	

Physical Exam Results

Subject LKC 012: Blood pressure = 107/72 mmHg

Pulse = 72 beats per minute
Temperature = 98.1 ° F
Respiratory rate = 16 breaths per minute
Height = 66 inches
Weight = 120 lbs
BMI = 19.5 kg/m^2
Physical exam = Normal

Subject TLC 013: Blood pressure = 121/70 mmHg
Pulse = 67 beats per minute
Temperature = 97.3 ° F
Respiratory rate = 14 breaths per minute
Height = 62.25 inches
Weight = 146.2 lbs
BMI = 27 kg/m^2
Physical exam = Normal

Subject ALP 015: Blood pressure = 145/90 mmHg
Pulse = 76 beats per minute
Temperature = 97.3 ° F
Respiratory rate = 13 breaths per minute
Height = 68.25 inches
Weight = 209.4 lbs
BMI = 32 kg/m^2
Physical exam = Finding noted
Musculoskeletal: Torn meniscus left knee

Subject NNL 017: Blood pressure = 108/64 mmHg
Pulse = 58 beats per minute
Temperature = 97.5 ° F
Respiratory rate = 15 breaths per minute
Height = 68.75 inches
Weight = 147.2 lbs
BMI = 22 kg/m^2
Physical exam = Normal

Subject CSH 018: Blood pressure = 128/84 mmHg
Pulse = 65 beats per minute
Temperature = 98.4 ° F
Respiratory rate = 17 breaths per minute
Height = 62.25 inches
Weight = 146.8 lbs
BMI = 27 kg/m^2
Physical exam = Normal

Subject LAD 019: Blood pressure = 130/89 mmHg

Pulse = 69 beats per minute
Temperature = 97.8 ° F
Respiratory rate = 16 breaths per minute
Height = 69.25 inches
Weight = 188 lbs
BMI = 28 kg/m^2
Physical exam = Finding noted
Ears: hearing aids
Eyes: glasses

Subject CLS 020: Blood pressure = 108/65 mmHg
Pulse = 81 beats per minute
Temperature = 98.1 ° F
Respiratory rate = 14 breaths per minute
Height = 63.25 inches
Weight = 189.2 lbs
BMI = 34 kg/m^2
Physical exam = Normal

Subject WKN 021: Blood pressure = 126/80 mmHg
Pulse = 83 beats per minute
Temperature = 97.3 ° F
Respiratory rate = 16 breaths per minute
Height = 65.5 inches
Weight = 192.6 lbs
BMI = 32 kg/m^2
Physical exam = Normal

Subject MRC 022: Blood pressure = 141/81 mmHg
Pulse = 76 beats per minute
Temperature = 98.4 ° F
Respiratory rate = 16 breaths per minute
Height = 66.25 inches
Weight = 147.2 lbs
BMI = 24 kg/m^2
Physical exam = Normal

Subject JDN 023: Blood pressure = 123/69 mmHg
Pulse = 66 beats per minute
Temperature = 98.1 ° F
Respiratory rate = 16 breaths per minute
Height = 70 inches
Weight = 170.0 lbs
BMI = 24.4 kg/m^2
Physical exam = Normal

Subject PGM 024: Blood pressure = 135/83 mmHg
Pulse = 50 beats per minute
Temperature = 98 ° F
Respiratory rate = 16 breaths per minute
Height = 72.5 inches
Weight = 201 lbs
BMI = 27 kg/m^2
Physical exam = Normal

Subject MLE 025: Blood pressure = 133/98 mmHg
Pulse = 74 beats per minute
Temperature = 98.1 ° F
Respiratory rate = 16 breaths per minute
Height = 66 inches
Weight = 186.4 lbs
BMI = 30 kg/m^2
Physical exam = Normal

Subject DJE 026: Blood pressure = 132/65 mmHg
Pulse = 60 beats per minute
Temperature = 97.1 ° F
Respiratory rate = 14 breaths per minute
Height = 65 inches
Weight = 151 lbs
BMI = 25.1 kg/m^2
Physical exam = Normal

Subject MKW 030: Blood pressure = 138/89 mmHg
Pulse = 62 beats per minute
Temperature = 97.2 ° F
Respiratory rate = 16 breaths per minute
Height = 63 inches
Weight = 117 lbs
BMI = 21 kg/m^2
Physical exam = Normal

Subject SJL 031: Blood pressure = 174/110 mmHg
Pulse = 62 beats per minute
Temperature = 97.2 ° F
Respiratory rate = 14 breaths per minute
Height = 72 inches
Weight = 185 lbs
BMI = 26 kg/m^2
Physical exam = Finding noted
Ears: Cerumen - Left ear canal

Subject AMW 032: Blood pressure = 124/74 mmHg
Pulse = 74 beats per minute
Temperature = 98.4 ° F
Respiratory rate = 14 breaths per minute
Height = 66 inches
Weight = 168 lbs
BMI = 27 kg/m^2
Physical exam = Normal

Subject LMF 033: Blood pressure = 143/89mmHg
Pulse = 63 beats per minute
Temperature = 97.8 ° F
Respiratory rate = 14 breaths per minute
Height = 66.25 inches
Weight = 141 lbs
BMI = 23 kg/m^2
Physical exam = Normal

Subject RYN 034: Blood pressure = 91/73 mmHg
Pulse = 75 beats per minute
Temperature = 98.1 ° F
Respiratory rate = 20 breaths per minute
Height = 67 inches
Weight = 174.8 lbs
BMI = 27 kg/m^2
Physical exam = Finding noted
Throat: Post nasal drip, erythematous

Subject DGS 035: Blood pressure = 129/79 mmHg
Pulse = 78 beats per minute
Temperature = ° F
Respiratory rate = 12 breaths per minute
Height = 71 inches
Weight = 155 lbs
BMI = 21 kg/m^2
Physical exam = Normal

Subject GWS 036: Blood pressure = 133/79 mmHg
Pulse = 64 beats per minute
Temperature = 97.9 ° F
Respiratory rate = 14 breaths per minute
Height = 71 inches
Weight = 182 lbs
BMI = 26 kg/m^2
Physical exam = Finding noted
Ears: Cerumen both canals

Subject WLM 037: Blood pressure = 144/82 mmHg
Pulse = 73 beats per minute
Temperature = 98.2 ° F
Respiratory rate = 12 breaths per minute
Height = 65 inches
Weight = 149 lbs
BMI = 25 kg/m^2
Physical exam = Normal

Subject JBR 038: Blood pressure = 136/82 mmHg
Pulse = 81 beats per minute
Temperature = 97.9 ° F
Respiratory rate = 14 breaths per minute
Height = 67 inches
Weight = 218 lbs
BMI = 34 kg/m^2
Physical exam = Normal

Subject DMA 039: Blood pressure = 130/83 mmHg
Pulse = 75 beats per minute
Temperature = 97.9 ° F
Respiratory rate = 14 breaths per minute
Height = 68 inches
Weight = 210 lbs
BMI = 32 kg/m^2
Physical exam = Normal

Subject DRK 041: Blood pressure = 96/63 mmHg
Pulse = 69 beats per minute
Temperature = 97.6 ° F
Respiratory rate = 12 breaths per minute
Height = 62 inches
Weight = 138 lbs
BMI = 25 kg/m^2
Physical exam = Normal

Subject LGC 042: Blood pressure = 124/78 mmHg
Pulse = 74 beats per minute
Temperature = 97.6 ° F
Respiratory rate = 14 breaths per minute
Height = 66 inches
Weight = 232 lbs
BMI = 37 kg/m^2
Physical exam = Normal

Subject BJR 043: Blood pressure = 149/80 mmHg
Pulse = 96 beats per minute
Temperature = 97.8 ° F
Respiratory rate = 12 breaths per minute
Height = 67 inches
Weight = 203 lbs
BMI = 33 kg/m^2
Physical exam = Finding noted
Throat: Post nasal drip

Subject MAJ 047: Blood pressure = 143/81 mmHg
Pulse = 64 beats per minute
Temperature = 98.4 ° F
Respiratory rate = 12 breaths per minute
Height = 75 inches
Weight = 256.4 lbs
BMI = 33 kg/m^2
Physical exam = Normal

Subject RDH 048: Blood pressure = 125/68 mmHg
Pulse = 80 beats per minute
Temperature = 98.8 ° F
Respiratory rate = 16 breaths per minute
Height = 66 inches
Weight = 129 lbs
BMI = 21 kg/m^2
Physical exam = Normal

Subject DSM 051: Blood pressure = 142/74 mmHg
Pulse = 84 beats per minute
Temperature = 97.6 ° F
Respiratory rate = 14 breaths per minute
Height = 70 inches
Weight = 164 lbs
BMI = 23 kg/m^2
Physical exam = Normal

Subject CLT 052: Blood pressure = 130/78 mmHg
Pulse = 64 beats per minute
Temperature = 96.8 ° F
Respiratory rate = 12 breaths per minute
Height = 66 inches
Weight = 144.8 lbs
BMI = 23 kg/m^2
Physical exam = Normal

Subject SND 054: Blood pressure = 121/79 mmHg
Pulse = 68 beats per minute
Temperature = 98.1 ° F
Respiratory rate = 18 breaths per minute
Height = 66.5 inches
Weight = 162 lbs
BMI = 25.4 kg/m^2
Physical exam = Finding noted
Musculoskeletal: Left ankle - lateral surgical scar

Subject CHW 055: Blood pressure = 126/86 mmHg
Pulse = 75 beats per minute
Temperature = 98.0 ° F
Respiratory rate = 16 breaths per minute
Height = 64.5 inches
Weight = 117.4 lbs
BMI = 20 kg/m^2
Physical exam = Normal

Subject JMD 056: Blood pressure = 145/80 mmHg
Pulse = 76 beats per minute
Temperature = 98.2 ° F
Respiratory rate = 12 breaths per minute
Height = 63 inches
Weight = 194.6 lbs
BMI = 34 kg/m^2
Physical exam = Normal

Subject KHW 057: Blood pressure = 135/82 mmHg
Pulse = 64 beats per minute
Temperature = 99.1 ° F
Respiratory rate = 12 breaths per minute
Height = 75 inches
Weight = 246 lbs
BMI = 30.7 kg/m^2
Physical exam = Finding noted
Musculoskeletal: Antalgic gait - decreased strength both lower extremites

Appendix 17

Adverse Events

Subject Initials/ Number	Description	Date of onset	Date resolved	Severity	Action taken	Relatedness to Test Article
LCK/012	Palpitation	Jan 19, 2006	Jan 19, 2006	Mild	None	Possible
	Upper respiratory tract infection	Jan 10, 2006	Jan 31, 2006	Mild	None	Not related
	Conjunctivitis	Jan 10, 2006	Jan 31, 2006	Mild	Antibiotics used	Not related
	Headaches	Mar 8, 2006	Mar 13, 2006	Mild	None	Not related
	Nausea	Mar 11, 2006	Mar 11, 2006	Mild	None	Not related
TLC/013	Dry mouth	Jan 24, 2006	Continuing on Mar 14, 2006	Mild	None	Possible
	Dry skin on face	Feb 9, 2006	Continuing on Mar 14, 2006	Mild	None	Possible
	Increased Acne	Feb 9, 2006	Feb 28, 2006	Mild	None	Possible
	Metrorrhagia	Jan 17, 2006	Jan 19, 2006	Mild	None	Possible
ALP/015	Increased flatulence	Jan 17, 2006	Jan 20, 2006	Mild	None	Possible
	Shoulder pain (right)	Jan 25, 2006	Jan 30, 2006	Moderate	None	Not related
CSH/018	Taste disturbance	Jan 17, 2006	Jan 19, 2006	Mild	None	Probably
	Sinusitis	Jan 28, 2006	Feb 12, 2006	Moderate	Antibiotics taken	Not related
	Cold sore	Feb 13, 2006	Feb 18, 2006	Mild	None	Not related
LAD/019	Cold symptoms	Jan 19, 2006	Feb 28, 2006	Moderate	Aspirin taken	Not related
CLS/020	Nausea	Jan 23, 2006	Jan 23, 2006	Mild	None	Not related
	Nausea	Feb 16, 2006	Feb 16, 2006	Mild	None	Not related

	Occasional leg cramps	Feb 19, 2006	Mar 3, 2006	Moderate	Pain reliever taken	Not related
PGM/024	Headaches	Feb 13, 2006	Feb 16, 2006	Mild	None	Possible
	Increased acne	Feb 12, 2006	Feb 17, 2006	Mild	None	Possible
MLE/025	Headaches	Jan 20, 2006	Continuing on Mar 17, 2006	Mild	None	Possible
	Hot flashes	Jan 20, 2006	Jan 20, 2006	Mild	None	Possible
DJE/026	Increased flatulence, burping and bloating	Feb 23, 2006	Continuing on Mar 31, 2006	Mild	None	Possible
	Tinnitus	Mar 4, 2006	Continuing on Mar 31, 2006	Mild	None	Possible
SJL/031	Increased drowsiness	Mar 22, 2006	Apr 10, 2006	Mild	None	Possible
	Low libido	Mar 22, 2006	Apr 4, 2006	Mild	None	Possible
	Headaches	Mar 28, 2006	Mar 31, 2006	Mild	None	Possible
	Dizziness	Mar 29, 2006	Mar 29, 2006	Mild	None	Possible
	Dry mouth	Apr 4, 2006	Apr 4, 2006	Mild	None	Possible
RYN/034	Intermittent Constipation	Mar 7, 2006	Apr 4, 2006	Mild	None	Possible
	Increased flatulence	Mar 21, 2006	Mar 30, 2006	Mild	None	Possible
WLM/037	Backache	Mar 25, 2006	Apr 16, 2006	Mild	None	Not related
	Neck tension	Mar 30, 2006	Apr 4, 2006	Mild	None	Not related
DRK 041	Dry mouth	Feb 23, 2006	Feb 28, 2006	Mild	None	Possible
	Shakiness	Feb 24, 2006	24 Feb, 2006	Mild	None	Possible
	Nausea	Feb 24, 2006	Feb 24, 2006	Mild	None	Possible
	Diarrhea	Feb 25, 2006	Feb 25, 2006	Mild	None	Possible

	Increased appetite	Mar 2, 2006	Mar 3, 2006	Mild	None	Possible
BJR/043	Headaches	Apr 12, 2006	Apr 28, 2006	Mild	None	Possible
NJM/046	Nocturia	Mar 10, 2006		Mild	None	Possible
	Abnormal dreams	Mar 13, 2006		Mild	None	Possible
RDH/048	Migraine headache	Apr 9, 2006	Apr 10, 2006	Mild	None	Not related
	Taste disturbance	Mar 22, 2006	Apr 14, 2006	Mild	None	Probably
	Upset Stomach	May 8, 2006	May 8, 2006	Mild	Antacid taken	Not related
SND/054	Dizziness	Mar 30, 2006	Mar 30, 2006	Mild	None	Possible
	Chest pain	Mar 31, 2006	Continuing on May 16, 2006	Moderate	Test article interrupted	Possible
CHW/055	Indigestion	Mar 27, 2006	Apr 5, 2006	Mild	None	Possible
	Decrease in appetite	Apr 4, 2006	Apr 4, 2006	Mild	None	Possible
	Difficulty sleeping	Apr 5, 2006	Apr 19, 2006	Mild	None	Possible
	Stomach cramps	May 10, 2006	May 10, 2006	Mild	None	Not related
KHW/057	Abnormal dreams	Mar 31, 2006	May 5, 2006	Mild	None	Possible
	Bradycardia	May 5, 2006	Continuing on May 19, 2006	Mild	None	Not related