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*APPLICATION NUMBER:*

**22-102**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Reviewer Name Hylton V. Joffe, M.D., M.M.Sc.  
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Established Name Cyanocobalamin, USP  
(Proposed) Trade Name (b) (4) Nasal Spray  
Therapeutic Class Synthetic vitamin B<sub>12</sub>  
Applicant Fleming & Co. Pharmaceuticals

Priority Designation S

Formulation Nasal spray  
Dosing Regimen One puff in each nostril daily  
Indication Maintenance/supplemental therapy  
Intended Population Persons with vitamin B<sub>12</sub> deficiency

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

I recommend APPROVAL of this 505(b)(2) new drug application based on my clinical review of the efficacy and safety data.

Fleming & Co. Pharmaceuticals has submitted this application for (b) (4) Nasal Spray, a non-sterile solution of cyanocobalamin, USP (synthetic vitamin B<sub>12</sub>) administered via a metered nasal spray for the treatment of vitamin B<sub>12</sub> deficiency. The Sponsor proposes using Nascobal (cyanocobalamin, USP) nasal spray (QOL Medical, LLC) NDA 21-642 as the Reference Listed Drug. (b) (4) contains the same active ingredient (cyanocobalamin, USP) as Nascobal, but the proposed dose for (b) (4) is 50 mcg daily vs. 500 mcg once-weekly for Nascobal. The Sponsor is proposing that (b) (4)

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b(4)

This application is based on a single, pivotal, clinical bioequivalence study that has assessed whether (b) (4) maintains adequate vitamin B<sub>12</sub> levels compared to intramuscular vitamin B<sub>12</sub> injections in 25 patients with vitamin B<sub>12</sub> deficiency. Of note, there is no bridging study comparing (b) (4) to the Reference Listed Drug. Nonetheless, I accept the Sponsor's approach for supporting approvability via the 505(b)(2) route because

- Cyanocobalamin, the active ingredient in (b) (4) has been used in different vitamin B<sub>12</sub> formulations for decades and has a well established safety record.
- The excipients in (b) (4) have been used in previously approved nasal products in concentrations that exceed those in (b) (4). In addition, (b) (4) and the currently available over-the-counter OCEAN nasal spray (which has been marketed for decades) have identical amounts (wt %) of all excipients, except for minor, clinically insignificant differences in the amount of purified water

### 1.2 Recommendation on Postmarketing Actions

#### 1.2.1 Risk Management Activity

None.

### 1.2.2 Required Phase 4 Commitments

None. The Sponsor requests a full waiver of pediatric studies, claiming that (b) (4) does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and that (b) (4) is not likely to be used in a substantial number of pediatric patients. Based on these considerations, a full waiver of pediatric studies is acceptable.

### 1.2.3 Other Phase 4 Requests

None.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

The Sponsor conducted a single, pivotal, open-label, clinical bioequivalence study in patients with vitamin B<sub>12</sub> deficiency. This study assessed whether intranasal (b) (4) 50 mcg daily adequately maintains normal serum vitamin B<sub>12</sub> concentrations over an eight-week period in 25 patients previously requiring intramuscular vitamin B<sub>12</sub> injections.

Visit 1 occurred 2-4 weeks after the patient received the last vitamin B<sub>12</sub> injection (i.e. midpoint of the 4-8 week interval between maintenance intramuscular injections). Patients started (b) (4) at Visit 2, which coincided with the timepoint when the patient would otherwise be scheduled to receive the next injection of vitamin B<sub>12</sub>. Thereafter, patients returned to the site at two-week intervals over eight weeks. The Sponsor measured vitamin B<sub>12</sub> and homocysteine concentrations at all visits. Methylmalonic acid concentrations were measured at Visit 2 and study end (methylmalonic acid and homocysteine are more sensitive markers of vitamin B<sub>12</sub> status when serum vitamin B<sub>12</sub> concentrations are in the low-normal range).

The protocol permitted the investigators to increase the frequency of (b) (4) dosing from once daily to twice daily if vitamin B<sub>12</sub> levels were not maintained with the 50 mcg dose (one patient required an increase in (b) (4) dose).

### 1.3.2 Efficacy

The pivotal study's primary efficacy endpoint was the mean vitamin B<sub>12</sub> concentration from Weeks 2, 4, 6, and 8 on (b) (4) treatment relative to the baseline vitamin B<sub>12</sub> concentration at Visit 1. This endpoint was evaluated with a repeated measures model. The Sponsor calculated a 90% two-sided confidence interval for this ratio and pre-defined the criteria for "success" as a lower bound for this confidence interval >0.8.

Based on review of the submitted trial, I conclude that the Sponsor provides adequate evidence of efficacy to support the proposed indications:

- The Sponsor and Division reached agreement regarding the study duration, sample size, and dose of study medication prior to study initiation.
- Mean vitamin B<sub>12</sub> levels during (b) (4) treatment were higher than the mean vitamin B<sub>12</sub> level at Visit 1 (the mid-point between maintenance vitamin B<sub>12</sub> injections). The primary efficacy endpoint, defined as the mean ratio of vitamin B<sub>12</sub> levels on (b) (4) to vitamin B<sub>12</sub> levels at Visit 1 was 1.15 (90% confidence interval 1.06, 1.24), which is statistically significant (p=0.0096).
- No (b) (4) treated patients developed abnormally low vitamin B<sub>12</sub> levels (<200 pg/mL).
- Three (b) (4) treated patients had a single borderline-low vitamin B<sub>12</sub> value (>200 but <300 pg/mL) and one patient had two non-consecutive borderline-low vitamin B<sub>12</sub> values. However, these isolated events were all associated with normal homocysteine concentrations, and these patients had normal methylmalonic acid levels at study end.
- Patients <65 years old had lower mean vitamin B<sub>12</sub> levels compared to patients ≥65 years old, but both groups had mean vitamin B<sub>12</sub> levels >300 pg/mL at all visits.

The major limitations of the pivotal study include:

- The small sample size, which prevents a robust assessment of efficacy across age, gender, and racial demographic subgroups
- No efficacy data in patients with newly diagnosed vitamin B<sub>12</sub> deficiency (by design)
- No data assessing efficacy in the presence of nasal disease (e.g., upper respiratory tract infection, allergic rhinitis) and nasal medications (e.g., intranasal glucocorticoids)
- Lack of a control group (which would have definitively shown the time course and extent of decline in vitamin B<sub>12</sub> levels when vitamin B<sub>12</sub> supplementation is withheld). Nonetheless, mean vitamin B<sub>12</sub> levels were higher with (b) (4) compared to the mid-point between maintenance vitamin B<sub>12</sub> injections
- No written, confirmatory documentation of the timing and frequency of prior vitamin B<sub>12</sub> injections in one-half of the (b) (4) treated patients (the Sponsor relied on verbal reports from these patients). Nonetheless, mean vitamin B<sub>12</sub> levels were higher on (b) (4) compared to the mid-point between maintenance vitamin B<sub>12</sub> injections and continued to trend upwards by Week 8 regardless of whether there was confirmatory documentation of the timing/frequency of vitamin B<sub>12</sub> injections
- No measurement of methylmalonic acid at Weeks 2-8 for patients with borderline-low vitamin B<sub>12</sub> measurements. However, none of the four patients with borderline-low vitamin B<sub>12</sub> levels had elevated homocysteine values. Methylmalonic acid is more specific than homocysteine for vitamin B<sub>12</sub> deficiency, and would have been required to definitively rule out vitamin B<sub>12</sub> deficiency in these patients if the homocysteine values had been elevated

### 1.3.3 Safety

Safety data are derived from the single pivotal clinical trial and by way of reference from the Nascobal new drug application. The safety results from the (b) (4) pivotal study are limited by the small sample size (n=25) and the lack of a control group (inability to assess the background rates of adverse events). In addition, safety data are only derived from patients previously treated with stable doses of intramuscular vitamin B<sub>12</sub> injections; therefore, results

cannot be extrapolated to patients with newly diagnosed, previously untreated vitamin B<sub>12</sub> deficiency. The major findings are summarized below:

- The pivotal study did not have deaths, relevant serious adverse events, or treatment-associated dropouts.
- The most common adverse events were nasopharyngitis, rhinorrhea, arthralgia, dizziness, and headache – each were reported by three (12%) of the 25 patients dosed with (b) (4). One patient with a history of allergic rhinitis treated with Flonase had epistaxis approximately two weeks after initiating (b) (4) and was found to have right septal irritation/lesion with scant bleeding on physical exam at study end. This patient had doubled her daily dose of (b) (4) one week prior to the last physical exam because of declining vitamin B<sub>12</sub> levels. This patient completed the study and noted on the post-treatment product assessment form that the method of dosing was “very acceptable” and reported only “slight” nasal irritation or stinging.
- Patients reporting adverse events in the nasal region (e.g., rhinorrhea) had resolution of these events (except for the right septal irritation/lesion described above, which was noted on the last study visit) and successfully completed the study despite ongoing treatment with (b) (4). I anticipate that patients who use (b) (4) (if approved) will switch back to injections if bothersome nasal and head symptoms occur.
- In a post-study questionnaire, all patients reported that the method of dosing was “acceptable” or “very acceptable”. Three patients reported nasal irritation or stinging. Limitations of these data include a lack of validation and potential recollection bias.
- There are no concerning changes in hematologic data attributable to vitamin B<sub>12</sub> status. Chemistry data and electrocardiograms were not collected, but I do not expect alterations in these parameters in patients receiving maintenance vitamin B<sub>12</sub> administration.
- Using AERS DataMart, I have identified several postmarketing reports of angioedema and angioedema-like events with cyanocobalamin listed as the suspect drug (or role unknown). None of these reports appear to have occurred with the intranasal form of cyanocobalamin (two postmarketing reports did not specify the route of administration). I recommend adding angioedema and angioedema-like events to the (b) (4) label and sending a Supplement Request Letter to the Sponsors of the other vitamin B<sub>12</sub> agents.

#### 1.3.4 Dosing Regimen and Administration

The Sponsor studied a 50 mcg daily dose of (b) (4) (i.e. total monthly dose of 1,500 mcg). This decision was based on currently used doses of Nascobal vitamin B<sub>12</sub> nasal spray (500 mcg once weekly, corresponding to 2,000 mcg monthly) and intramuscular vitamin B<sub>12</sub> (100-1,000 mcg monthly). The 50 mcg daily dose appears efficacious for most patients, although some patients may require higher doses (more frequent dosing) to maintain adequate vitamin B<sub>12</sub> levels. There are no adequate data assessing (b) (4) efficacy in the presence of nasal disease and nasal medications (in the clinical trial, one patient on Flonase for allergic rhinitis required a doubling of the (b) (4) dose). Also, the prescribing information for currently approved vitamin B<sub>12</sub> products reports that patients with renal or hepatic disease may require increased doses or more frequent administration of cyanocobalamin. Because of these considerations, all (b) (4) treated patients should have regular assessments of vitamin B<sub>12</sub>

levels to assure long-term efficacy. Patients with nasal pathology that may result in erratic vitamin B<sub>12</sub> absorption should not be prescribed (b) (4) and patients should not use (b) (4) within several hours of administering other intranasal drugs.

### 1.3.5 Drug-Drug Interactions

The Sponsor did not perform any drug-drug interaction studies. Prescribing information for currently available vitamin B<sub>12</sub> products lists the following drug interactions:

- Most antibiotics, methotrexate, and pyrimethamine invalidate folic acid and vitamin B<sub>12</sub> diagnostic assays
- Colchicine, para-aminosalicylic acid, and heavy alcohol intake may cause malabsorption of vitamin B<sub>12</sub>
- Long-term aminosalicylic acid therapy may reduce absorption of cyanocobalamin from the gastrointestinal tract, possibly increasing the requirement for oral cyanocobalamin
- Ascorbic acid may destroy a substantial proportion of cyanocobalamin in a vitamin-B<sub>12</sub> containing meal
- Chloramphenicol may result in a suboptimal clinical response to cyanocobalamin in vitamin B<sub>12</sub>-deficient patients
- Omeprazole therapy for two weeks in healthy volunteers substantially reduced protein-bound cyanocobalamin absorption

However, most of these drug interactions are irrelevant for (b) (4) which is absorbed across the nasal mucosa and not in the gastrointestinal tract. Therefore, for the (b) (4) label, I favor only including the first bullet point pertaining to drugs that invalidate the folic acid and vitamin B<sub>12</sub> diagnostic assays.

It is possible that nasal pathology (e.g., allergic rhinitis, viral infection) or co-administered intranasal drugs (e.g., nasal steroids) may affect (b) (4) absorption. One of the 25 treated patients in the clinical study who was using Flonase for allergic rhinitis required an increase in (b) (4) dose. Therefore, I recommend that patients do not use (b) (4) within several hours of administering other intranasal drugs, and that healthcare providers closely monitor vitamin B<sub>12</sub> levels in (b) (4) treated patients with nasal pathology and those using other nasally administered drugs. Patients with nasal pathology that may result in erratic vitamin B<sub>12</sub> absorption should not be prescribed (b) (4).

### 1.3.6 Special Populations

The Sponsor reports that gender, age, and race have no meaningful effects on the response to (b) (4). However, this conclusion is based on small sample sizes, and is, therefore, not robust. Although patients <65 years old had lower mean vitamin B<sub>12</sub> levels at all clinic visits compared to those ≥65 years old, no patients on (b) (4) developed frankly low vitamin B<sub>12</sub> levels (<200 pg/mL) or persistently borderline-low vitamin B<sub>12</sub> levels (200-300 pg/mL). If approved, all (b) (4) treated patients should have regular assessments of vitamin B<sub>12</sub> levels to assure long-term treatment compliance and efficacy – I do not see a need for altering this

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(b) (4) (cyanocobalamin) Nasal Spray

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recommendation based on demographic subgroup analyses from the small study reviewed in this 505(b)(2) application.

The Sponsor did not conduct studies of (b) (4) in patients with hepatic or renal insufficiency. The prescribing information for currently approved vitamin B<sub>12</sub> products reports that patients with renal or hepatic disease may require increased doses or more frequent administration of cyanocobalamin. This information is reported for intramuscular cyanocobalamin but would presumably also apply to (b) (4)

Cyanocobalamin is a Pregnancy Category C drug that is excreted in the milk of nursing mothers. Prescribing information for currently approved vitamin B<sub>12</sub> products state that vitamin B<sub>12</sub> is an essential vitamin and that amounts recommended by the Food and Nutrition Board of the National Academy of Science/National Research Council be consumed during pregnancy and lactation. Similar wording will be used in the (b) (4) package insert.

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## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Fleming & Co. Pharmaceuticals is submitting this 505(b)(2) new drug application (NDA) for (b) (4) Nasal Spray, a non-sterile solution of cyanocobalamin, USP (synthetic vitamin B<sub>12</sub>) administered via a metered nasal spray for the treatment of vitamin B<sub>12</sub> deficiency. The Sponsor proposes using Nascobal (cyanocobalamin, USP) nasal spray (QOL Medical, LLC) NDA 21-642 as the Reference Listed Drug (RLD). (b) (4) contains the same active ingredient (cyanocobalamin, USP) as Nascobal, but the proposed dose for (b) (4) is 50 mcg daily (one spray of 25 mcg in each nostril) vs. 500 mcg once-weekly for Nascobal. The Sponsor is proposing that (b) (4)

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b(4)

Reviewer's comments: The proposed indications for (b) (4)

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b(4)

### 2.2 Currently Available Treatment for Indications

The Food and Drug Administration (FDA) has approved injection and nasal formulations of cyanocobalamin (vitamin B<sub>12</sub>) for the treatment of vitamin B<sub>12</sub> deficiency. Newly diagnosed vitamin B<sub>12</sub> deficiency is typically treated with intramuscular injections of cyanocobalamin (available as Rubramin PC, Vibisone, and as several generic formulations) 1 mg daily for one week then 1 mg weekly for four weeks then (for patients requiring indefinite treatment) 100 mcg

to 1 mg monthly. Cyanocobalamin is also available as a once-weekly 500 mcg dose in a metered nasal spray (Nascobal). A once-weekly intranasal gel formulation (Nascobal gel) is no longer available.

Oral cyanocobalamin is typically dosed at 1-2 mg/day (>200x the minimum daily requirement for normal individuals), and is effective even in patients with pernicious anemia who lack intrinsic factor (a protein needed for intestinal absorption of vitamin B<sub>12</sub>) because these high amounts are absorbed via a low efficiency transport system that does not require intrinsic factor or a functioning ileum.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Cyanocobalamin is widely available in the United States (see Section 2.2). Because of frequent dosing, the oral and nasal formulations of vitamin B<sub>12</sub> require high levels of patient compliance, which can be confirmed with frequent monitoring of vitamin B<sub>12</sub> concentrations. Experts typically recommend using intramuscular formulations of vitamin B<sub>12</sub> for the treatment of newly diagnosed vitamin B<sub>12</sub> deficiency and in patients with neurological involvement. The oral and nasal formulations are considered more appropriate for maintenance therapy.

### **2.4 Important Issues With Pharmacologically Related Products**

During initial treatment of vitamin B<sub>12</sub> deficiency, patients (particularly those with severe anemia) can develop significant hypokalemia and sudden death due to potassium utilization during production of new hematopoietic cells. These patients should be monitored closely and treated with potassium supplementation, if needed. Other known risks/clinical considerations of vitamin B<sub>12</sub> therapy include:

- Vitamin B<sub>12</sub> causes severe and rapid optic atrophy in patients with early Leber's disease (hereditary optic nerve atrophy)
- Although folic acid may improve vitamin B<sub>12</sub>-deficient anemia, exclusive use of folic acid without vitamin B<sub>12</sub> in this setting may result in progressive and irreversible neurologic damage
- Anaphylactic shock and death have been reported after parenteral vitamin B<sub>12</sub> administration

### **2.5 Presubmission Regulatory Activity**

#### **Pre-IND Meeting (February 3, 1999)**

- The Division confirmed that (b) (4) will be treated as a drug and not as a dietary supplement
- The Division required demonstration that (b) (4) maintains adequate vitamin B<sub>12</sub> concentrations for two months after a switch from a stable intramuscular vitamin B<sub>12</sub> regimen in 20 patients with a documented history of vitamin B<sub>12</sub> deficiency

- The Division asked the Sponsor to validate (b) (4) delivery system (e.g. amount of drug delivered)
- The Division did not require new animal studies to assess nasal mucosa irritation (we agreed with referencing the animal studies from Nascobal, hydroxocobalamin, and the published literature)
- The Division agreed that no phase 1 study was needed

#### **FDA Response to IND Amendment Serial 004 Request for Guidance (March 26, 2004)**

The Division stated that the approved indication for (b) (4) will take into account the fact that patients in the clinical trial had stabilized hematologic indices prior to initiation of the nasal spray formulation.

#### **FDA Response to Pre-NDA Package Questions (May 11, 2006)**

Please see Dr. Yvonne Yang's review for details regarding several chemistry-related issues discussed in the pre-NDA correspondence.

The Sponsor noted two differences in the nasal spray pump assembly used for clinical testing and the proposed product developed for commercialization. First, the commercialization form has a shorter diptube due to a smaller bottle size. Second, these two forms have a ~1% difference in \_\_\_\_\_ ratios due to different suppliers of the \_\_\_\_\_

The Sponsor proposed to include in the NDA a side-by-side comparison of all attributes for these two products, including data demonstrating equivalency of the gaskets, drug product release, and stability. This proposal was acceptable to the Division.

**Reviewer's comments: The Sponsor has confirmed that the drug product formulation used during clinical testing is identical to that developed for commercialization.**

The Sponsor requested a full waiver of pediatric requirements. The Division stated that the Sponsor should submit a formal request, including justification for why a pediatric study would not be feasible.

## **2.6 Other Relevant Background Information**

### **Vitamin B<sub>12</sub> Deficiency**

Normal absorption of vitamin B<sub>12</sub> requires adequate dietary intake (animal products are the only dietary source of vitamin B<sub>12</sub>), gastric acid, intrinsic factor (a glycoprotein produced by the gastric parietal cells), pancreatic proteases, and a functioning terminal ileum. The gastric acid frees dietary vitamin B<sub>12</sub> from protein food sources. Vitamin B<sub>12</sub> binds to intrinsic factor in the alkaline pancreatic enzyme milieu of the duodenum. The vitamin B<sub>12</sub>-intrinsic factor complex is absorbed via a specific receptor in the terminal ileum (vitamin B<sub>12</sub> unbound to intrinsic factor cannot be efficiently absorbed in the ileum).

Therefore, problems with any of the above processes will impair vitamin B<sub>12</sub> absorption and may lead to deficiency. Examples include insufficient intake (particularly vegans), inadequate gastric acid production (achlorhydria), non-alkaline duodenum (pancreatic insufficiency), pernicious anemia (auto-immune destruction of the intrinsic factor-producing cells of the stomach), gastric or ileal resection, and disorders of the small intestine (e.g. celiac disease, Crohn's disease, and ileitis). Any of these abnormalities will typically take years to cause vitamin B<sub>12</sub> deficiency because there are large body stores of vitamin B<sub>12</sub> and significant enterohepatic circulation.

Vitamin B<sub>12</sub> deficiency causes megaloblastic anemia with ineffective erythropoiesis (vitamin B<sub>12</sub> is required for nucleic acid synthesis) and a specific neurological condition known as subacute combined degeneration of the posterolateral spinal columns (due to a defect in myelin formation). The symmetrical neuropathy, which affects the legs more than the arms, ranges from loss of vibration and position sense to severe weakness and paraplegia. The neurological symptoms can occur in vitamin B<sub>12</sub> deficient patients who have normal hematological indices.

Abnormally low serum vitamin B<sub>12</sub> levels (i.e. <200 pg/mL) are consistent with vitamin B<sub>12</sub> deficiency (falsely low vitamin B<sub>12</sub> levels can occur with folate deficiency, which should be excluded). However, patients with serum vitamin B<sub>12</sub> levels in the low-normal range (200-300 pg/mL) may also have vitamin B<sub>12</sub> deficiency. Patients in this indeterminate range should undergo measurement of methylmalonic acid and homocysteine. These two metabolites accumulate in the setting of vitamin B<sub>12</sub> deficiency and are considered more sensitive markers of vitamin B<sub>12</sub> status than serum vitamin B<sub>12</sub> concentrations. Therefore, in the setting of low-normal vitamin B<sub>12</sub> concentrations, vitamin B<sub>12</sub> deficiency is confirmed if both metabolites are increased (methylmalonic acid >270 nmol/L; homocysteine >14 mcumol/L) and excluded if both metabolites are normal. Importantly, homocysteine is also elevated in patients with folate deficiency. Therefore, patients with elevations of both metabolites may also have concurrent folate deficiency. This approach to testing for vitamin B<sub>12</sub> deficiency is adapted from Antony AC. Megaloblastic anemias. In: Hematology: Basic principles and practice, 4<sup>th</sup> ed, Hoffman R, Benz EJ, Shattil SJ et al. (Eds), Churchill Livingstone, New York 2005. p. 519.

Treatment of vitamin B<sub>12</sub> deficiency is discussed in Sections 2.2-2.4.

### **Other Regulatory Background Information**

The Division requested consultations on 13-December-2006 with

- The Division of Medication Errors and Technical Support (DMETS) for review of the package insert, carton and container labeling, and trade name (the Sponsor has proposed CaloMist Nasal Spray and \_\_\_\_\_ as preferred alternatives to (b) (4). The DMETS' review is still pending as of June 22, 2007.
- The Division of Surveillance, Research and Communication Support (DSRCS) for review of the patient instruction sheet. Please see Ms. Jeanine Best's review, which includes wording and formatting changes to the Patient Instruction Sheet, and recommends that the Sponsor submit a Patient Package Insert.

b(4)

As mentioned above, the Sponsor has filed a 505(b)(2) application for (b) (4) using Nascobal as the RLD (Table 2.1). The Sponsor has submitted Letters of Authorization permitting the use of data by way of reference for cyanocobalamin, the bottle, pump, pump components, \_\_\_\_\_, and white colorant. The Sponsor reports that there is no unexpired marketing exclusivity for the RLD.

b(4)

The Sponsor's pivotal trial is a clinical bioequivalence study that has assessed whether (b) (4) maintains adequate vitamin B<sub>12</sub> levels compared to intramuscular vitamin B<sub>12</sub> injections. Of note, there is no bridging study comparing (b) (4) to the RLD. Nonetheless, I accept the Sponsor's approach for supporting approvability via the 505(b)(2) route (if there is adequate evidence of efficacy and safety) because

- The tested drug product and the product proposed for marketing have identical formulations; therefore, the observed vitamin B<sub>12</sub> levels with the tested product are expected to be representative of levels seen with the marketed formulation
- The excipients in (b) (4) have been used in previously approved nasal products in concentrations that exceed those in (b) (4). In addition, (b) (4) and the currently available OCEAN nasal spray (which has been marketed for decades) have identical amounts (wt %) of all excipients, except for minor, clinically insignificant differences in the amount of purified water (please see Dr. Karen Davis-Bruno's review for details)
- Cyanocobalamin, the active ingredient in (b) (4) has been used in different vitamin B<sub>12</sub> formulations for decades and has a well established safety record in humans and animal studies. (please see Dr. Karen Davis-Bruno's review for details)

Table 2.1. Comparison of (b) (4) and Nascobal		
Item	RLD (NDA 21-642)	Proposed drug product
Active Ingredient	Cyanocobalamin, USP	Cyanocobalamin, USP
Inactive Ingredients	Sodium citrate	Sodium chloride
	Citric acid	Sodium phosphate monobasic
	Glycerin	Benzyl alcohol
	Benzalkonium chloride	Sodium hydroxide
	Purified water	Benzalkonium chloride
Route of Administration	Intranasal	Intranasal
Dosage Form	Solution	Solution
Strength	500 mcg (One 500 mcg/0.1 mL actuation)	50 mcg (Two 25 mcg/0.1 mL actuations)
Dosing Scheme	Once weekly (One spray in one nostril)	Once daily (One spray in each nostril)

### 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

#### 3.1 CMC (and Product Microbiology, if Applicable)

The Sponsor reports that the formulation and manufacturing process for the clinical product and the proposed commercial product are identical except for changes to the container closure system dimensions and pump gasket composition. The manufacturing process is based on OCEAN Premium Saline Nasal Spray (Table 3.1), which has been marketed in the United States by Fleming since the 1960s as an over-the-counter, isotonic, non-sterile, aqueous moisturizing nasal spray. Please see the reviews of Dr. Yvonne Yang (CMC) and Dr. Vinayak B. Pawar (Microbiology) for details.

**Table 3.1. Comparison of OCEAN Premium Saline Nasal Spray and (b) (4) Nasal Spray**

Ingredient	Amount (wt %)	
	OCEAN® Premium Saline Nasal Spray	(b) (4)™ Nasal Spray
<b>Drug Substance</b> Cyanocobalamin, USP	-	0.025
<b>Excipients</b> Sodium Chloride, USP Monobasic Sodium Phosphate, — USP Benzyl Alcohol, NF Sodium Hydroxide, NF Benzalkonium Chloride, — NF Purified Water, USP	100.000	100.000
<b>Total</b>	100.000	100.000

b(4)

#### 3.2 Animal Pharmacology/Toxicology

At the Pre-IND meeting, the Division agreed that non-clinical studies of (b) (4) were not needed (we agreed with referencing the animal studies from Nascobal, hydroxocobalamin, and the published literature). The Sponsor claims that the (b) (4) excipients are commonly used in other approved nasal products, sometimes at concentrations exceeding those in (b) (4). These excipients are used in the over-the-counter OCEAN Premium Saline Nasal Spray.

### 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

#### 4.1 Sources of Clinical Data

Clinical data for this 505(b)(2) application are derived solely from the Sponsor's pivotal, open-label, clinical bioequivalence study (PR99-063), which is summarized in Table 4.1. This study

was conducted in accordance with agreements previously reached with the Division. There are no ongoing or planned additional studies.

#### 4.2 Tables of Clinical Studies

Table 4.1. Tabular listing of the pivotal clinical trial (PR99-063) included in this application			
Objective(s) of the Study	Study Design and Type of Control	Dosage Regimen Route of Administration Duration Test Product(s)	Patient Population Number of Subjects
To determine if daily intranasal vitamin B <sub>12</sub> in physiological saline is sufficient to maintain normal serum vitamin B <sub>12</sub> levels over an 8-week period in patients who have previously required intramuscular injections to maintain normal serum B <sub>12</sub> levels	Open-label Single-arm	<u>Dosage regimen:</u> 1 puff of (b) (4) self-administered daily in each nostril  <u>Route of administration:</u> Intranasal  <u>Duration of treatment:</u> 8 wks  <u>Test product:</u> Each puff of nasal spray contained ~100 mcL of saline solution and ~25 mcg cyanocobalamin	Patients with documented vitamin B <sub>12</sub> deficiency on maintenance intramuscular vitamin B <sub>12</sub> injections  All patients had normal vitamin B <sub>12</sub> levels at study entry  30 patients enrolled 25 patients treated 25 patients analyzed

#### 4.3 Review Strategy

The clinical efficacy and safety assessment is based solely on review of the above-mentioned pivotal clinical bioequivalence study PR99-063.

#### 4.4 Data Quality and Integrity

The study was conducted at a single clinical site \_\_\_\_\_  
\_\_\_\_\_ The Sponsor visited the study site periodically and performed a reasonable review of relevant study documentation. All clinical data entered into the database were confirmed by a second member of the study personnel to ensure 100% quality control.

b(4)

#### 4.5 Compliance with Good Clinical Practices

The pivotal study was conducted in compliance with Good Clinical Practices. The following irregularities were noted during the study (all were reported to the Institutional Review Board):

Six of the 30 consent forms were signed by the study coordinator and then co-signed by the investigator/sub-investigators at a later date (the site responsibility log did not indicate that the

study coordinator was able to administer informed consent). There was no witness noted for three of the consented patients.

#### 4.6 Financial Disclosures

I have reviewed the financial certification and disclosure documents submitted by the clinical investigator \_\_\_\_\_ who conducted pivotal study \_\_\_\_\_. There is no apparent financial conflict of interest (e.g. the investigator was not compensated based on the outcome of the study, and the investigator did not have a proprietary interest in the tested product or significant equity interest in the Sponsor). b(4)

Six sub-investigators (physicians in the \_\_\_\_\_) were involved in the conduct of the study. Erroneously, none of these sub-investigators completed financial disclosure forms (Note to File 23-August-2005). The Sponsor is unable to remedy this oversight, because only one sub-investigator was still at the study site when this error was noted. b(4)

### 5 CLINICAL PHARMACOLOGY

I have reviewed pivotal study PR99-063 in Sections 6 (efficacy) and 7 (safety). Please see Dr. Sang Chung's pharmacology review for additional details.

The Sponsor chose to study only the 50 mcg daily dose of (b) (4) (i.e. total monthly dose of 1,500 mcg). This decision was based on currently used doses of intranasal vitamin B<sub>12</sub> (500 mcg once weekly; corresponding to 2,000 mcg monthly) and intramuscular vitamin B<sub>12</sub> (100-1,000 mcg monthly). Prior to study start, the tested dose was increased from 40 mcg daily to 50 mcg daily based on recommendations from the Division.

**Reviewer's comments:** The 50 mcg daily dose is reasonable, assuming the bioavailability of (b) (4) is not substantially lower than the bioavailability of Nascobal and intramuscular vitamin B<sub>12</sub>.

### 6 INTEGRATED REVIEW OF EFFICACY

#### 6.1 Indication

The proposed indications for (b) (4) are:

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b(4)

b(4)

### 6.1.1 Methods

The single, pivotal, clinical bioequivalence study PR99-063 was used to establish the efficacy of (b) (4)

### 6.1.2 General Discussion of Endpoints

The primary efficacy endpoint in the pivotal trial is based on vitamin B<sub>12</sub> levels. Supportive analyses use methylmalonic acid and homocysteine levels.

Vitamin B<sub>12</sub> deficiency is virtually excluded with vitamin B<sub>12</sub> levels >300 pg/mL and confirmed with levels <200 pg/mL (falsely low vitamin B<sub>12</sub> levels can occur with folate deficiency, which was not assessed in the current study). Current clinical practice is to measure methylmalonic acid and homocysteine levels in patients with serum vitamin B<sub>12</sub> levels in the low-normal range (200-300 pg/mL). These two metabolites accumulate in the setting of vitamin B<sub>12</sub> deficiency and are considered more sensitive markers of vitamin B<sub>12</sub> status than serum vitamin B<sub>12</sub> concentrations (Table 6.1). Therefore, in the setting of low-normal vitamin B<sub>12</sub> concentrations, vitamin B<sub>12</sub> deficiency is confirmed if both metabolites are increased (methylmalonic acid >270 nmol/L; homocysteine >14 mcmmol/L) and excluded if both metabolites are normal. Because folate deficiency raises homocysteine levels, elevations of both metabolites do not rule out concurrent folate deficiency (ideally, folate status should be assessed prior to measurement of these metabolites).

<b>Parameter</b>	<b>Prevalence in patients with vitamin B<sub>12</sub> deficiency</b>
Serum vitamin B <sub>12</sub> >200 pg/mL	12/419 = 3.9%
Elevated serum methylmalonic acid	427/434 = 98.4%
Elevated serum homocysteine	416/434 = 95.9%
Elevated methylmalonic acid AND normal homocysteine	17/434 = 3.9%
Elevated homocysteine AND normal methylmalonic acid	6/434 = 1.4%
Elevated methylmalonic acid AND elevated homocysteine	410/434 = 94.5%
Normal methylmalonic acid AND normal homocysteine	1/434 = 0.2%
Elevated = more than 3 SD above the mean in normal control subjects From Lindenbaum et al. 1990 and Savage et al. 1994	

### 6.1.3 Study Design: PR99-063

**Objective:** To assess whether daily intranasal administration of cyanocobalamin in physiological saline is sufficient to maintain normal serum vitamin B<sub>12</sub> concentrations over an eight-week period in patients who have previously required intramuscular injections to maintain normal serum vitamin B<sub>12</sub> levels.

**Study Design:** Open-label study without a placebo arm (the Sponsor considered placebo to be unethical) that used patients as their own (historical) control.

**Reviewer's comments:** I am not convinced that there are ethical concerns related to withholding vitamin B<sub>12</sub> supplementation for only eight weeks, particularly in patients without pre-existing neurological complications of vitamin B<sub>12</sub> deficiency.

At Visit 1 (screening; Week -2 or -4), patients entered the study 2-4 weeks after receiving their usual maintenance vitamin B<sub>12</sub> injection – i.e. midpoint of the 4-8 week interval between maintenance intramuscular injections.

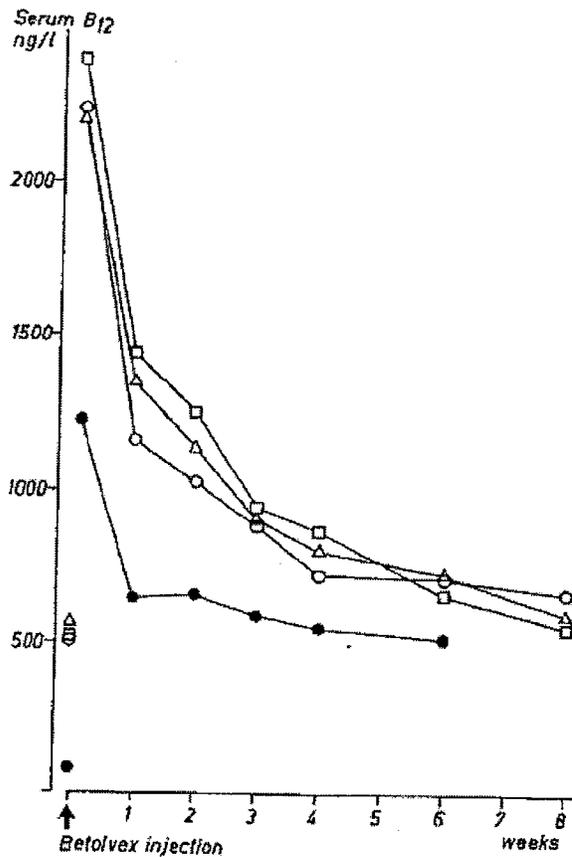
Patients started (b) (4) at Visit 2 (Day 0; i.e. the time the patient would otherwise be scheduled to receive the next injection of vitamin B<sub>12</sub>). Patients returned to the site at two-week intervals for eight weeks (Visits 3-6).

**Reviewer's comments:** The duration of this study is adequate. I would expect a continued decline in vitamin B<sub>12</sub> levels over the eight weeks if vitamin B<sub>12</sub> is not administered during this time period (Figure 6.1).

Patients were instructed to spray one puff of (b) (4) directly into each nostril every morning during the eight-week treatment period. Each puff contained 25 mcg cyanocobalamin in 100 mcL saline solution; therefore, the total daily dose of (b) (4) was 50 mcg. The protocol permitted the investigator to increase the vitamin B<sub>12</sub> dose to one puff in each nostril twice daily if vitamin B<sub>12</sub> levels were not maintained with the 50 mcg dose. The study protocol prohibited concomitant use of oral forms of vitamin B<sub>12</sub>. Patients were asked to complete a daily diary card, which was used to assess treatment compliance.

**Reviewer's comments:** Visits 1 and 2 were scheduled after patients provided information about the timing and frequency of their vitamin B<sub>12</sub> injections to study staff. The Sponsor accepted confirmatory documentation of this information, when available (12 of the 25 treated patients did not have confirmatory documentation). I will perform sensitivity analyses to explore whether the patients with confirmatory documentation and those without confirmatory documentation had different responses to (b) (4).

**Figure 6.1. Serum vitamin B12 levels after injection of 1 mg sustained-release cyanocobalamin (Betolvex). From Berlin et al. 1978.**



Squares (n=10): Pernicious anemia patients treated for several years with 1 mg intramuscular hydroxocobalamin every third month (last injection ~3 months prior to study start)

Triangles (n=11): Pernicious anemia patients treated for several years with cyanocobalamin tablets 1 mg daily (last dose two weeks before study start)

Open circles (n=7): Healthy subjects

Filled circles (n=9): Untreated pernicious anemia patients.

Inclusion criteria included:

1. Men and women 18-85 years old in otherwise good health
2. On stable doses of maintenance intramuscular injections of vitamin B<sub>12</sub> for the treatment of vitamin B<sub>12</sub> deficiency due to a chronic condition
3. Serum vitamin B<sub>12</sub> levels within normal limits at screening

Exclusion criteria included:

1. Low serum vitamin B<sub>12</sub> level or anemia at study entry
2. Significant nasal disease or requirement for other transnasal medications that may alter delivery/absorption of the full dose of administered (b) (4)
3. Woman of childbearing potential not using contraception
4. Pregnancy

Efficacy assessments:

1. Vitamin B<sub>12</sub> and homocysteine at all visits (Screening, Day 0, and Weeks 2, 4, 6, and 8)
2. Methylmalonic acid on Day 0 and Week 8
3. Post-study "Product Assessment Form" (non-validated questionnaire) at Week 8

**Reviewer's comments: Methylmalonic acid is more specific than homocysteine for vitamin B<sub>12</sub> deficiency (homocysteine levels are increased in patients with folate deficiency and are affected by smoking and some medications). I would have preferred the Sponsor to measure methylmalonic acid levels at all visits particularly when patients had vitamin B<sub>12</sub> concentrations <300 pg/mL.**

Methylmalonic acid (reference range 90-279 nmol/L) was measured with GC/MS using isotope spiked controls. The Sponsor reports that this method is validated from 100-2,000 nmol/L with a coefficient of variation (CV) ≤5.7%.

Homocysteine (reference range 4.9-14.6 mcmmol/L) was measured using fluorescence polarization immunoassay. The Sponsor reports that this method is validated from the quantitation limit (QL) to 50 mcmmol/L with the CV ranging from 4% near 50 mcmmol/L to 16% near the QL.

Vitamin B<sub>12</sub> (reference range ≥200 pg/mL) was measured using a radioassay with spiked radiolabeling. The Sponsor reports that this method is validated from 100-2,000 pg/mL with a CV of 6-8%.

**Reviewer's comments: Dr. Sang Chung has confirmed that these assays have been adequately validated. Please see his review for details.**

Statistical populations: The Sponsor pre-specified three statistical populations:

- **Safety population (n=25):** All patients who received ≥1 dose of (b) (4)
- **Efficacy population (n=25):** All patients with a baseline vitamin B<sub>12</sub> measurement and at least one post-treatment vitamin B<sub>12</sub> measurement
- **Preferred efficacy population (n=24):** Efficacy population excluding patients with a screening vitamin B<sub>12</sub> level <200 pg/mL, patients with non-compliance (missed >20% of doses), and patients lacking documentation of vitamin B<sub>12</sub> deficiency. Only one treated patient (528) was excluded from this population (the patient had undocumented vitamin B<sub>12</sub> deficiency).

**Statistical Plan:** The primary efficacy endpoint was the mean vitamin B<sub>12</sub> level from Visits 3, 4, 5, and 6 relative to the baseline vitamin B<sub>12</sub> level at Visit 1. This endpoint was evaluated with a repeated measures model using the ratio of post-treatment vitamin B<sub>12</sub> levels to Visit 1 levels as a function of visit and the subject as a random effect. The Sponsor calculated 90% two-sided confidence intervals for the average ratio observed from Visits 3-6 relative to Visit 1. The Sponsor pre-defined the criteria for “success” as a lower bound for this confidence interval >0.8.

**Reviewer's comments:** This is the typical statistical approach used for bioequivalence studies.

**Changes to the planned analyses:** The Sponsor added p-values to the presentation of the 90% confidence intervals that were calculated using the least squares mean estimates obtained from the repeated measures model. The Sponsor also used a linear regression model to assess Week 8 vitamin B<sub>12</sub> levels as a function of screening vitamin B<sub>12</sub> levels.

The Sponsor chose a sample size of 20-35 patients to ensure inclusion of 20 evaluable patients based on an agreement reached with the Division at the Pre-IND meeting.

**Substantive amendments to the protocol include:**

1. **21-April-1999** (based on FDA comments):
  - Increased the sample size to ensure the inclusion of at least 20 evaluable patients
  - Added one additional visit 2-4 weeks after vitamin B<sub>12</sub> injection during the screening/baseline period to collect more baseline data on serum B<sub>12</sub> levels resulting from B<sub>12</sub> injections
  - Increased the daily dose of (b) (4) from 40 mcg to 50 mcg
2. **20-April-2000:** Increased the upper age limit for study inclusion from 80-85 years to enhance enrollment and include more geriatric patients so that the study population would be more representative of the patients that would likely take the drug, if approved

When the protocol was written, the threshold for a normal vitamin B<sub>12</sub> level was 240 pg/mL as defined by the laboratory projected to do the assays. During the conduct of the study, vitamin B<sub>12</sub> samples were sent to \_\_\_\_\_ which defined 200 pg/mL as the threshold for a normal vitamin B<sub>12</sub> level. Therefore, the 200 pg/mL cutpoint was used for all post-study analyses.

b(4)

**Reviewer's comments:** This is acceptable. However, as explained above, patients with vitamin B<sub>12</sub> levels in the 200-300 pg/mL range may still have vitamin B<sub>12</sub> deficiency. Therefore, in addition to vitamin B<sub>12</sub> levels, I will use supportive data from methylmalonic acid and homocysteine levels to assess the presence of vitamin B<sub>12</sub> deficiency.

#### 6.1.4 Efficacy Findings

The Sponsor assessed treatment compliance using dosing information recorded in the patient diaries. All but two of the treated patients took between 95-100% of the scheduled doses (Patient 516 took 93% of the scheduled doses, and Patient 502 took 102% of the scheduled doses).

The study protocol permitted an increase in the daily dose of (b) (4) from 50 mcg to 100 mcg for patients with declining vitamin B<sub>12</sub> levels during the study. Only one patient (526) was instructed to increase the dose to 100 mcg/day – the increase occurred during the last week of the study and was prompted by a decline in vitamin B<sub>12</sub> levels from 491 pg/mL at Visit 4 to 424 pg/mL Visit 5 – this patient’s vitamin B<sub>12</sub> levels at other visits were 400 pg/mL (Visit 1), 259 pg/mL (Visit 2), 593 pg/mL (Visit 3), and 455 pg/mL (Visit 6).

Protocol violations included:

1. Patient 511 had a low screening vitamin B<sub>12</sub> level (176 pg/mL; lower limit of normal = 200 pg/mL).

**Reviewer's comments: This patient became eligible for enrollment six weeks later after increasing the frequency of vitamin B<sub>12</sub> injections from once monthly to twice monthly (repeat vitamin B<sub>12</sub> concentration = 267 pg/mL)**

2. Patient 528 did not have a documented history of vitamin B<sub>12</sub> deficiency (this patient was reported to have “neurologic abnormalities”, but the Schilling’s test was normal and the Sponsor does not have confirmation of low vitamin B<sub>12</sub> measurements prior to initiation of treatment). The data from this patient were included in the “safety” and “efficacy population” analyses but were excluded from the “preferred efficacy population” analyses
3. Twelve of the 25 treated patients did not have documentation of the date of the last vitamin B<sub>12</sub> injection, of the next scheduled vitamin B<sub>12</sub> injection, or of the frequency of the vitamin B<sub>12</sub> injections

**Reviewer's comments: Visits 1 and 2 were scheduled only after the patient provided the above information verbally to study staff (confirmatory documentation was accepted, if available, but was not required by the study personnel).**

4. Three of the 25 treated patients each had one instance of taking study drug twice in one day without being instructed to do so (Patient 502 took two doses on one day during Week 5; Patient 520 took two doses on one day in Week 5 but missed one dose in Week 6; Patient 525 took two doses on one day in Week 9 but had missed one dose in Week 5).
5. Eight of the 25 treated patients missed one or more doses (Patients 520 and 525 described above; Patient 504 missed one dose in Week 8; Patient 507 missed one dose in Week 4 and one dose in Week 5; Patient 510 missed one dose in Week 5; Patient 516 missed one dose in Week 3, one dose in Week 4 and two doses in Week 5; Patient 526 missed two doses in Week 3).
6. Nineteen of the 25 treated patients took at least one dose in the afternoon rather than in the morning as indicated in the protocol.

**Reviewer's comments: The minor dosing irregularities in bullets 4-6 above are not expected to meaningfully affect the interpretation of the study results.**

**Primary Efficacy Endpoint**

The primary efficacy endpoint was defined as the mean ratio of vitamin B<sub>12</sub> concentrations from Visits 3-6 (Weeks 2, 4, 6, 8 on (b) (4) to levels at Visit 1 (Week -2 or -4; i.e. the midpoint of the 4-8 week interval between maintenance intramuscular injections). This ratio was 1.15 (90% confidence interval 1.06, 1.24), which is statistically significant (p=0.0096).

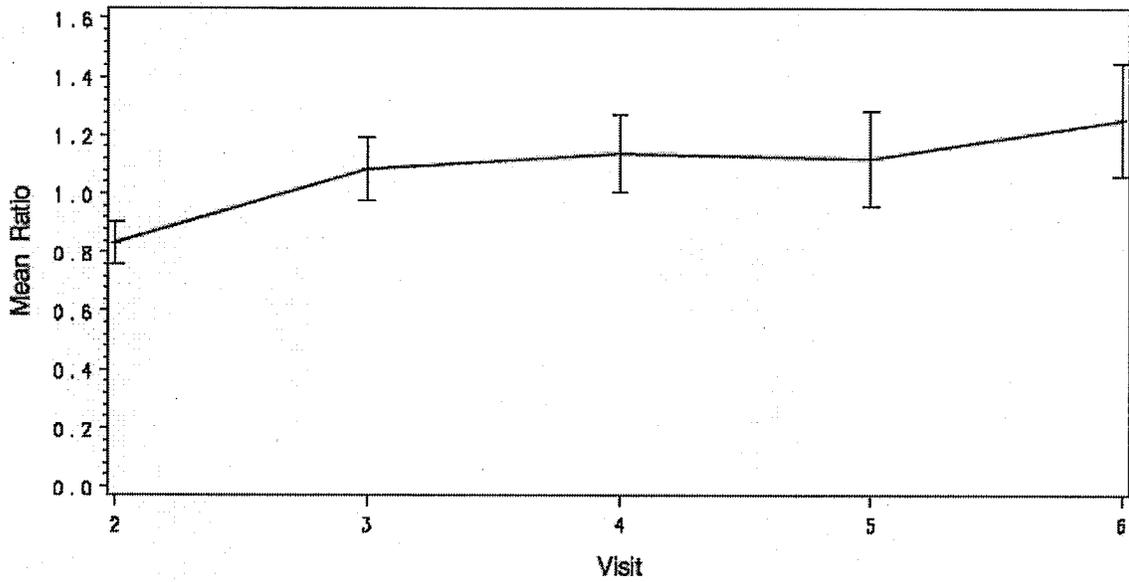
**Other Efficacy Analyses**

Similar ratios were calculated separately for vitamin B<sub>12</sub> levels on Visits 3, 4, 5, and 6 relative to vitamin B<sub>12</sub> levels on Visit 1. With the exception of Visit 3, the lower bound of the two-sided 90% confidence interval for these ratios was >1.0 (Table 6.2; Figure 6.2). Mean vitamin B<sub>12</sub> levels at Visits 3-6 were higher than the mean vitamin B<sub>12</sub> level at Visit 1 (Table 6.2).

<b>Dependent Variable</b>	<b>Visit</b>	<b>LS Means</b>	<b>90% confidence interval</b>	<b>P-value</b>
Ratio of B <sub>12</sub> at each visit to B <sub>12</sub> at Visit 1	2 (Day 0)	0.83	(0.72, 0.95)	<b>0.0096<sup>2</sup></b>
	3 (Week 2)	1.08	(0.97, 1.20)	
	4 (Week 4)	1.14	(1.02, 1.25)	
	5 (Week 6)	1.12	(1.01, 1.23)	
	6 (Week 8)	1.25	(1.14, 1.36)	
	<b>Average (V3 – V6)<sup>1</sup></b>	<b>1.15<sup>1</sup></b>	<b>(1.06, 1.24)<sup>1</sup></b>	
Vitamin B <sub>12</sub> levels (pg/mL)	1 (Week -2 to -4)	484	(432, 536)	<b>0.0627<sup>3</sup></b>
	2 (Day 0)	403	(351, 455)	
	3 (Week 2)	506	(454, 558)	
	4 (Week 4)	520	(468, 572)	
	5 (Week 6)	511	(459, 563)	
	6 (Week 8)	568	(516, 620)	
	<b>Average (V3 – V6)</b>	<b>526</b>	<b>(483, 570)</b>	
<b>Average minus baseline</b>	<b>42</b>	<b>(5, 79)</b>		
<p>1 Primary efficacy endpoint  2 p-value for test of null hypothesis that ratio equals 1  3 p-value for test of null hypothesis that change from baseline equals 0</p>				

Table 6.3 summarizes the median change in vitamin B<sub>12</sub> levels for Visits 2-6 relative to Visit 1. Nineteen (19/25 or 76%) patients had lower vitamin B<sub>12</sub> levels at Visit 2 (Day 0, i.e. the time the patient would otherwise be scheduled to receive the next injection of vitamin B<sub>12</sub>) compared to Visit 1. At each visit thereafter, more patients had higher rather than lower vitamin B<sub>12</sub> levels relative to Visit 1 (13 vs. 12 for Visit 3; 16 vs. 9 for Visit 4; 14 vs. 11 for Visit 5; 15 vs. 10 for Visit 6).

**Figure 6.2. Mean ratio of post-Visit 1 vitamin B<sub>12</sub> levels to Visit 1 vitamin B<sub>12</sub> levels with 95% confidence intervals.**



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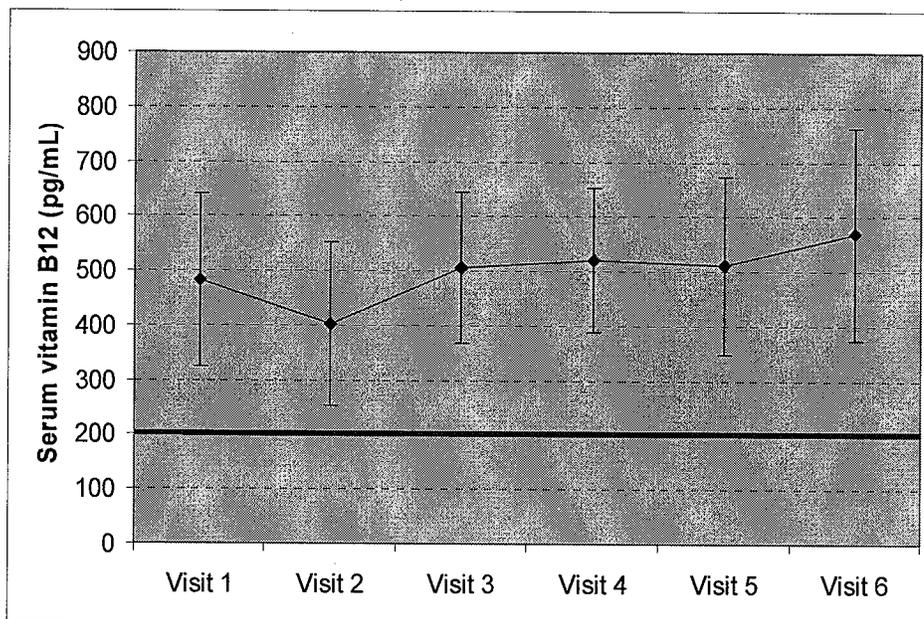
Parameter	Visit	N	Mean	SD	Median	Min, Max
Vitamin B <sub>12</sub> Levels (pg/mL)	1 (Week -2 to -4)	25	484	158	484	226, 993
	2 (Day 0)	25	403	150	361	166, 741
	3 (Week 2)	25	506	137	474	254, 779
	4 (Week 4)	25	520	133	516	211, 830
	5 (Week 6)	25	511	162	482	269, 836
	6 (Week 8)	25	568	194	524	247, 1107
	Average (V3-V6)	25	526	143	501	312, 846
Vitamin B <sub>12</sub> Levels (ratio to Visit 1)	2 (Day 0)	25	0.83	0.17	0.80	0.47, 1.21
	3 (Week 2)	25	1.08	0.26	1.00	0.70, 1.77
	4 (Week 4)	25	1.14	0.32	1.14	0.42, 1.70
	5 (Week 6)	25	1.12	0.39	1.06	0.49, 2.10
	6 (Week 8)	25	1.25	0.47	1.13	0.50, 2.56
	Average (V3-V6)	25	1.15	0.33	1.14	0.60, 1.83
Change from Visit 1 in vitamin B <sub>12</sub> Levels	2 (Day 0)	25	-81	89	-82	-253, 92
	3 (Week 2)	25	22	125	1	-295, 229
	4 (Week 4)	25	36	153	78	-411, 238
	5 (Week 6)	25	26	187	24	-429, 406
	6 (Week 8)	25	84	222	55	-439, 674
	Average (V3-V6)	25	42	161	67	-394, 361

Table 6.4 and Figure 6.3 summarize the mean vitamin B<sub>12</sub> concentrations at each of the clinic visits relative to the lower limit of the vitamin B<sub>12</sub> reference range (200 pg/mL).

Parameter	Visit	LS mean with 90% CI	Median	Min, Max
Vitamin B <sub>12</sub> levels (ratio to 200 pg/mL)	1 (Week -2 to -4)	2.4 (2.2, 2.7)	2.4	1.1, 5.0
	2 (Day 0)	2.0 (1.8, 2.3)	1.8	0.8, 3.7
	3 (Week 2)	2.5 (2.3, 2.8)	2.4	1.3, 3.9
	4 (Week 4)	2.6 (2.3, 2.9)	2.6	1.1, 4.2
	5 (Week 6)	2.6 (2.3, 2.8)	2.4	1.4, 4.2
	6 (Week 8)	2.8 (2.6, 3.1)	2.6	1.2, 5.5
	Average (V3-V6)	2.6 (2.4, 2.9)*	2.5	1.6, 4.2

\*p-value <0.0001 for test of null hypothesis that ratio equals 1  
n=25 for all visits.

**Figure 6.3. Vitamin B<sub>12</sub> concentrations by study visit (mean with standard deviation). The red line shows the lower limit of the reference range.**



**Patients with Low Vitamin B<sub>12</sub> Concentrations**

Two of the 25 (b) (4) treated patients had a vitamin B<sub>12</sub> measurement below the lower limit of the reference range (<200 pg/mL). Table 6.5 summarizes the vitamin B<sub>12</sub> related labs by clinic visit for these patients. The low vitamin B<sub>12</sub> levels were reported on Visits 1 or 2 (i.e. before patients started (b) (4)). Both patients had normal vitamin B<sub>12</sub> levels on Visits 3-6 (in fact, their vitamin B<sub>12</sub> levels trended upwards over the course of these visits). Patient 511 had a screening vitamin B<sub>12</sub> level of 176 pg/mL but is not included in this section because this patient was only enrolled after the vitamin B<sub>12</sub> level had been normalized.

**Table 6.5. Enrolled patients with at least one abnormally low vitamin B<sub>12</sub> measurement**

ID	Parameter (reference range)	Visit 1 (Wk -2/-4)	Visit 2 (Day 0)	Visit 3 (Wk 2)	Visit 4 (Wk 4)	Visit 5 (Wk 6)	Visit 6 (Wk 8)
507	Vitamin B <sub>12</sub> (≥200 pg/mL)	226	180	254	346	359	355
	Homocysteine (4.9-14.6 mc mol/L)	9.6	11.2	8.9	9.3	13.9	9.8
	Methylmalonic acid (90-279 nmol/L)	-	378	-	-	-	215
522	Vitamin B <sub>12</sub> (≥200 pg/mL)	353	166	479	431	563	529
	Homocysteine (4.9-14.6 mc mol/L)	9.5	14.1	12.4	12.9	12.5	13.4
	Methylmalonic acid (90-279 nmol/L)	-	181	-	-	-	143

**Patients with Borderline Vitamin B<sub>12</sub> Concentrations**

There were four (b) (4) treated patients with “borderline” vitamin B<sub>12</sub> values (>200 but <300 pg/mL) (Table 6.6). None of these borderline-low values were associated with missed doses of (b) (4) or nasal adverse events. For patients 504, 507, and 511, these low-normal values appear to be isolated events, with other values comparable to or higher than baseline values on intramuscular injections. The two low-normal values for Patient 508 occurred on Visits 4 and 6. This patient reported 100% compliance with study medication, and had higher values on Visits 3 and 5 – the reason for the variability in this patient is unclear. Of note, these borderline values were all associated with homocysteine concentrations within the normal range. In addition, these patients had methylmalonic acid levels within the normal range at study end.

All other vitamin B<sub>12</sub> values were ≥300 pg/mL.

**Reviewer's comments:** Patient 525 was dosed with (b) (4) for almost 11 weeks because of scheduling issues related to transportation problems and cataract surgery. This patient’s vitamin B<sub>12</sub> levels at Visits 4-6 were ≥300 pg/mL.

**Table 6.6. Patients with low-normal serum vitamin B<sub>12</sub> concentrations (>200 but <300 pg/mL)**

ID	Parameter (reference range)	Visit 1 (Wk -2/-4)	Visit 2 (Day 0)	Visit 3 (Wk 2)	Visit 4 (Wk 4)	Visit 5 (Wk 6)	Visit 6 (Wk 8)
504 71 y/o	Vitamin B <sub>12</sub> (≥200 pg/mL)	548	448	438	482	269	524
	Homocysteine (4.9-14.6 mcmol/L)	7.8	7.3	8.3	6.5	8.3	7.1
	Methylmalonic acid (90-279 nmol/L)	-	220	-	-	-	182
507 63 y/o	Vitamin B <sub>12</sub> (≥200 pg/mL)	226	180	254	346	359	355
	Homocysteine (4.9-14.6 mcmol/L)	9.6	11.2	8.9	9.3	13.9	9.8
	Methylmalonic acid (90-279 nmol/L)	-	378	-	-	-	215
508 27 y/o	Vitamin B <sub>12</sub> (≥200 pg/mL)	497	360	460	211	330	247
	Homocysteine (4.9-14.6 mcmol/L)	10.0	8.5	8.4	8.3	6.7	9.0
	Methylmalonic acid (90-279 nmol/L)	-	135	-	-	-	159
511 60 y/o	Vitamin B <sub>12</sub> (≥200 pg/mL)	267	277	262	460	367	395
	Homocysteine (4.9-14.6 mcmol/L)	5.9	8.2	8.1	8.3	8.0	9.6
	Methylmalonic acid (90-279 nmol/L)	-	161	-	-	-	162

Three patients (see individual plots for Patient 501, 502, and 514 in Appendix 10.1) had comparable vitamin B<sub>12</sub> levels at Visit 1 (i.e. midpoint between maintenance intramuscular injections) and Visit 2 (the time the patient would otherwise be scheduled to receive the next injection of vitamin B<sub>12</sub>), and stable (501 and 502) or slightly declining (514) vitamin B<sub>12</sub> levels during Visits 3-6. I cannot rule out the possibility that (b) (4) had no or minimal efficacy in these three patients because vitamin B<sub>12</sub> levels were stable prior to (b) (4) initiation and levels did not increase during (b) (4) treatment.

There were no significant differences between the efficacy population and preferred efficacy population with regard to the vitamin B<sub>12</sub> related analyses.

### **Methylmalonic Acid and Homocysteine**

Table 6.7 summarizes methylmalonic acid and homocysteine levels. Mean methylmalonic acid levels decreased from 237 nmol/L at Visit 2 (Day 0) [not measured at Visit 1] to 204 nmol/L at Visit 6. This change was accompanied by a mean increase in vitamin B<sub>12</sub> concentrations at the same timepoints (403 pg/mL at Visit 2 to 568 pg/mL at Visit 6).

Eight patients had high methylmalonic acid values (>279 nmol/L) at Visit 2 (range 295-460 nmol/L). Three of these patients (520, 523, 525) had persistently high methylmalonic acid values at Visit 6 (one had an increase, another was unchanged, and the third had a decrease in methylmalonic acid values). None of these three patients had low or borderline vitamin B<sub>12</sub> measurements (the patient with an increase in methylmalonic acid from Visit 2 to Visit 6 had vitamin B<sub>12</sub> levels of 741 pg/mL at Visit 2 and 554 pg/mL at Visit 6). All three had normal homocysteine concentrations from Visits 2-6, except for a one-time elevation in Patient 523 to 14.9 mcmmol/L (upper limit of normal = 14.6 mcmmol/L) at Visit 3.

The remaining five patients with high methylmalonic acid values at Visit 2 had normalization of methylmalonic acid at Visit 6. One of these five patients (507) had low vitamin B<sub>12</sub> concentrations at Visit 2 (180 pg/mL) but normal vitamin B<sub>12</sub> concentrations thereafter (355 pg/mL on Visit 6). The remaining four patients had normal (all >300 pg/mL) vitamin B<sub>12</sub> levels at all study visits (three of these four patients had stable values or increases in vitamin B<sub>12</sub> from Visits 2 to 6; the fourth patient [501] had declining vitamin B<sub>12</sub> levels at Visits 3-5, but levels at Visit 6 were comparable to levels at Visit 1). Three of these five patients had normal homocysteine values at all visits. Patient 501 had persistent, but stable elevations in homocysteine at Visits 1-6 (15.2-21.3 mcmmol/L). Patient 516 had elevated homocysteine values at Visits 1-5 (16.6-21.3 mcmmol/L) but normal homocysteine at Visit 6 (12.3 mcmmol/L).

One patient (518) had a shift in methylmalonic acid from normal at Visit 2 (253 nmol/L) to high at Visit 6 (303 nmol/L). However, this patient's vitamin B<sub>12</sub> levels increased from 354 pg/mL at Visit 2 to 518 pg/mL at Visit 6, and this patient's homocysteine concentrations were well within the normal range at all visits (range 5.8-9.9 mcmmol/L).

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Parameter	Visit	Mean (SD or 90% CI)*	Median (Min, Max)
Homocysteine	1 (Week -2 to -4)	9.5 (8.2, 10.8)	8.7 (5.1, 20.3)
	2 (Day 0)	9.7 (8.4, 11.0)	8.1 (5.1, 21.3)
	3 (Week 2)	9.4 (8.1, 10.7)	8.2 (5.0, 20.1)
	4 (Week 4)	9.3 (8.0, 10.6)	8.3 (5.7, 21.6)
	5 (Week 6)	9.7 (8.4, 11.0)	8.0 (5.3, 20.8)
	6 (Week 8)	9.1 (7.8, 10.4)	8.3 (5.1, 20.2)
	Average (V3-V6)	9.4 (8.2, 10.6)	8.5 (5.8, 20.0)
Homocysteine ratio (relative to Visit 1)	2 (Day 0)	1.05 (0.97, 1.13)	1.04 (0.39, 1.48)
	3 (Week 2)	1.02 (0.94, 1.10)	1.00 (0.39, 1.57)
	4 (Week 4)	0.99 (0.91, 1.07)	0.97 (0.44, 1.42)
	5 (Week 6)	1.04 (0.96, 1.12)	1.06 (0.37, 1.45)
	6 (Week 8)	0.99 (0.91, 1.07)	0.97 (0.46, 1.63)
	Average (V3-V6)	1.01 (0.94, 1.08) [p=0.76]	1.00 (0.42, 1.44)
Homocysteine change from baseline	2 (Day 0)	0.2 (3.3)	0.3 (-12.3, 6.1)
	3 (Week 2)	-0.1 (3.3)	0.0 (-12.3, 4.9)
	4 (Week 4)	-0.2 (3.0)	-0.3 (-11.4, 6.4)
	5 (Week 6)	0.2 (3.2)	0.5 (-12.7, 4.3)
	6 (Week 8)	-0.4 (3.3)	-0.2 (-11.0, 5.0)
	Average (V3-V6)	-0.2 (-0.8, 0.5) [p=0.69]	0.0 (-11.9, 4.8)
Methylmalonic acid (nmol/L)	2 (Day 0) (n=23)	237 (113)	181 (111, 460)
	6 (Week 8)	204 (100)	162 (106, 457)

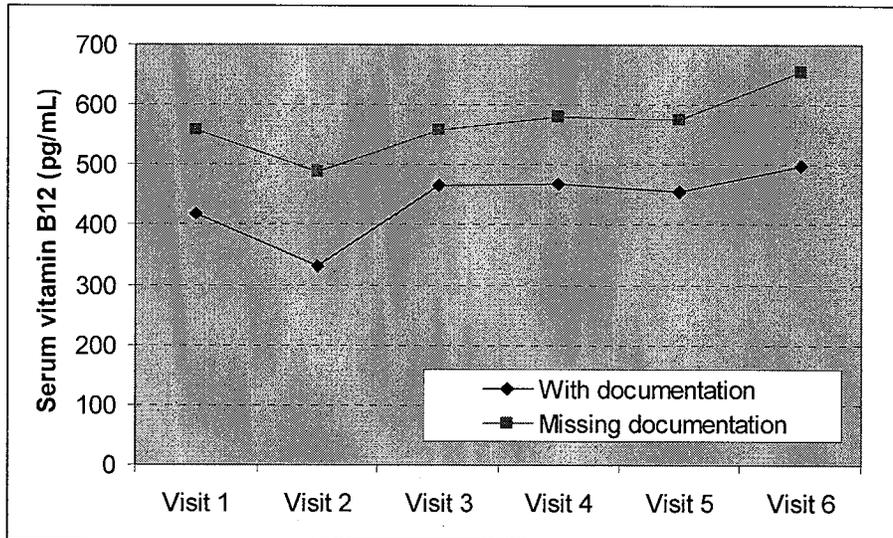
n=25 for all analyses, unless specified otherwise  
\*90% CI if two values are presented in parentheses; SD if only one value is presented in parentheses

### Sensitivity Analyses

Visits 1 and 2 were scheduled after patients provided verbal information about the timing and frequency of their vitamin B<sub>12</sub> injections. The Sponsor accepted confirmatory documentation of this information, when available (12 of the 25 treated patients did not have confirmatory documentation). Mean vitamin B<sub>12</sub> levels at all visits were higher among patients without confirmatory documentation compared to patients with confirmatory documentation (Figure 6.4). Nonetheless, the shape of the two curves were similar; therefore, the upward shift of the curve for the patients with missing confirmatory documentation is most likely driven by the group's higher baseline (Visit 1 and Visit 2) vitamin B<sub>12</sub> concentrations. This discrepancy raises the possibility that (b) (4) may have been initiated too early (i.e. too soon after the last vitamin B<sub>12</sub> injection) in the group with missing confirmatory documentation. Four patients with confirmatory documentation had a borderline-low vitamin B<sub>12</sub> value (200-300 pg/mL) on (b) (4) compared to no cases among patients lacking this documentation (see above).

Six of the 24 patients in the preferred efficacy population had higher vitamin B<sub>12</sub> values at Visit 2 (immediately prior to the start of (b) (4) i.e. at the time of the next scheduled vitamin B<sub>12</sub> injection) compared to Visit 1 (i.e. at the midpoint between injections) (Table 6.8).

**Figure 6.4. Mean vitamin B<sub>12</sub> concentrations in the preferred efficacy population for patients with and without confirmatory documentation of the timing, frequency, and last dose of intramuscular vitamin B<sub>12</sub> administration.**



Patient	Vitamin B <sub>12</sub> concentrations					
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
<b>With confirmatory documentation of timing/frequency of vitamin B<sub>12</sub> injections</b>						
501	416	428	409	385	342	409
511	267	277	262	460	367	395
524	414	443	497	550	482	571
<b>Missing confirmatory documentation of timing/frequency of vitamin B<sub>12</sub> injections</b>						
514	677	722	678	600	594	567
519	572	590	779	676	761	885
521	433	525	662	636	772	1,107

**Reviewer's comments:** It is reassuring that mean vitamin B<sub>12</sub> values declined from Visit 1 to Visit 2 then increased by Visit 3 (i.e., within two weeks after starting (b) (4) I cannot rule out residual, contributory effects of the prior injections on vitamin B<sub>12</sub> levels during (b) (4) administration. Nonetheless, mean vitamin B<sub>12</sub> levels were higher on (b) (4) than on injections and continue to trend upwards by Visit 6 (regardless of

whether there is confirmatory documentation of the timing/frequency of vitamin B<sub>12</sub> injections). In my view, these data provide adequate evidence of efficacy for (b) (4)

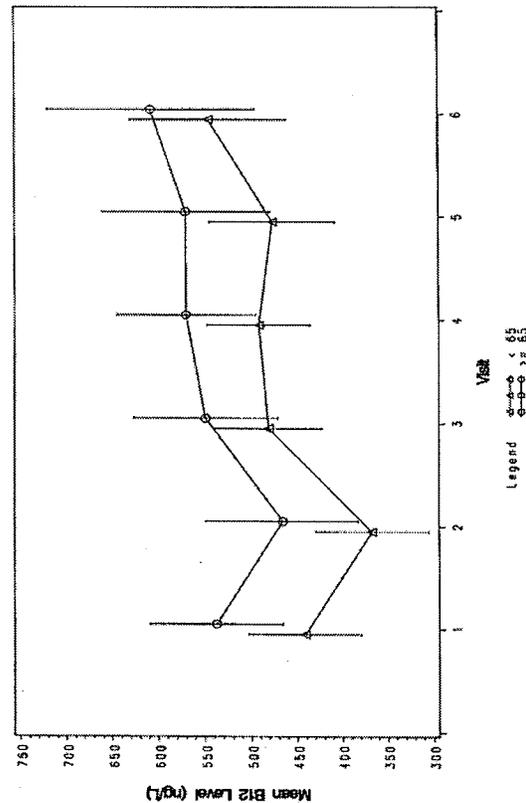
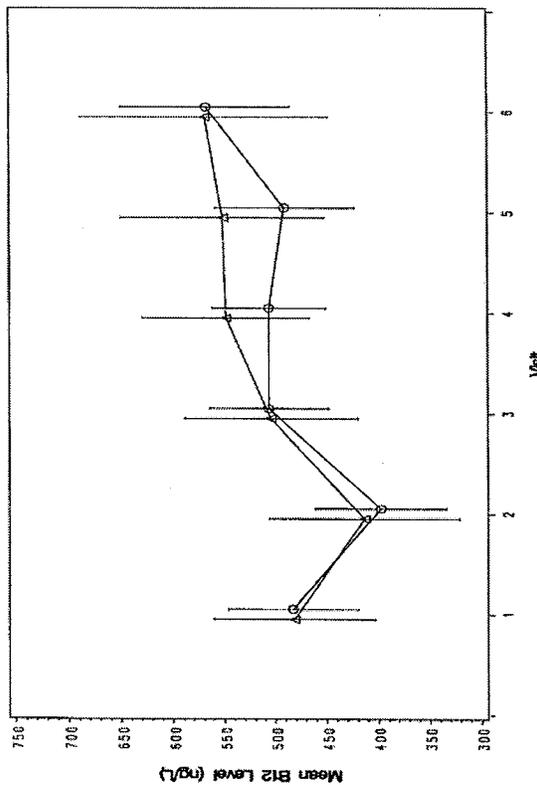
**Subgroup efficacy analyses**

The Sponsor modeled the average ratio of each patient’s vitamin B<sub>12</sub> values from Visits 3-6 relative to Visit 1 as a function of gender, age, race, and baseline vitamin B<sub>12</sub> concentrations (each covariate was used in a separate model). The Sponsor reports no meaningful effects of gender (p=0.90), age (p=0.65 comparing age<65 vs. ≥65 years), or race (p=0.64) on patient response. The race conclusion is limited by the small sample size of non-Caucasians (n=4).

Figure 6.5 summarizes mean vitamin B<sub>12</sub> levels by gender. Compared to the men, the women had slightly lower mean vitamin B<sub>12</sub> values for Visits 4-5 but comparable mean values at Visit 6. Figure 6.6 summarizes mean vitamin B<sub>12</sub> levels by age (<65 vs. ≥65 years). The younger age group had lower mean vitamin B<sub>12</sub> levels at all clinic visits. The variability in measurements (overlapping large standard deviations) results in non-statistically significant differences between these subgroups.

**Figure 6.5. Mean B<sub>12</sub> levels by gender**

**Figure 6.6. Mean B<sub>12</sub> by age (<65 vs. ≥65 yrs)**



### 6.1.5 Clinical Microbiology

Not applicable. (b) (4) is not an antimicrobial agent.

### 6.1.6 Efficacy Conclusions

The Sponsor provides adequate evidence of efficacy to support the proposed indications:

- Mean vitamin B<sub>12</sub> levels during (b) (4) treatment were higher than the mean vitamin B<sub>12</sub> level at Visit 1 (the mid-point between maintenance vitamin B<sub>12</sub> injections). The primary efficacy endpoint, defined as the mean ratio of vitamin B<sub>12</sub> levels on (b) (4) to vitamin B<sub>12</sub> levels at Visit 1 was 1.15 (90% confidence interval 1.06, 1.24), which is statistically significant (p=0.0096).
- No (b) (4) treated patients developed abnormally low vitamin B<sub>12</sub> levels (<200 pg/mL).
- Three (b) (4) treated patients had a single borderline-low vitamin B<sub>12</sub> value (>200 but <300 pg/mL) and one patient had two non-consecutive borderline-low vitamin B<sub>12</sub> values. However, these isolated events were all associated with normal homocysteine concentrations, and these patients had normal methylmalonic acid levels at study end.
- Patients <65 years old had lower mean vitamin B<sub>12</sub> levels compared to patients ≥65 years old, but both groups had mean vitamin B<sub>12</sub> levels >300 pg/mL at all visits.

The major limitations of the pivotal study include:

- The small sample size, which prevents a meaningful assessment of efficacy across age, gender, and racial demographic subgroups
- No efficacy data in patients with newly diagnosed vitamin B<sub>12</sub> deficiency
- No data assessing efficacy in the presence of nasal disease (e.g., upper respiratory tract infection, allergic rhinitis) and nasal medications (e.g., intranasal glucocorticoids)
- Lack of a control group (which would have definitively shown the time course and extent of decline in vitamin B<sub>12</sub> levels when vitamin B<sub>12</sub> supplementation is withheld). Nonetheless, mean vitamin B<sub>12</sub> levels were higher with (b) (4) compared to the mid-point between maintenance vitamin B<sub>12</sub> injections
- No confirmatory documentation of the timing and frequency of prior vitamin B<sub>12</sub> injections in one-half of the (b) (4) treated patients (the Sponsor relied on verbal reports from these patients). Nonetheless, mean vitamin B<sub>12</sub> levels were higher on (b) (4) compared to the mid-point between maintenance vitamin B<sub>12</sub> injections and continued to trend upwards by

Week 8 regardless of whether there was confirmatory documentation of the timing/frequency of vitamin B<sub>12</sub> injections

- No measurement of methylmalonic acid at Weeks 2-8 for patients with borderline-low vitamin B<sub>12</sub> measurements. However, none of the four patients with borderline-low vitamin B<sub>12</sub> levels had elevated homocysteine values. Methylmalonic acid is more specific than homocysteine for vitamin B<sub>12</sub> deficiency, and would have been required to definitively rule out vitamin B<sub>12</sub> deficiency in these patients if the homocysteine values had been elevated

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

Safety data for (b) (4) are derived from the same single pivotal study described above. The Sponsor collected treatment-emergent adverse event data from Day 0 to Week 8 (including review of patient diaries for adverse events), and coded these to preferred terms using MedDRA version 8.1.

#### 7.1.1 Deaths

There were no deaths reported during this study.

#### 7.1.2 Other Serious Adverse Events

There was only one treatment-emergent serious adverse event reported during this study. A 51 year-old woman (Patient 521) was diagnosed with intervertebral L4/L5 disc protrusion on Day 52 (she reported back pain and left leg pain at screening). She was treated with surgery and pain medications, and subsequently completed the study.

Patient 520 reported a serious adverse event of chest pain, but this occurred prior to starting (b) (4)

#### 7.1.3 Dropouts and Other Significant Adverse Events

##### 7.1.3.1 Overall profile of dropouts

Thirty patients were enrolled in the study. Five of these 30 patients discontinued prior to dosing (two had low vitamin B<sub>12</sub> levels at screening, one had a low absolute neutrophil count at screening, and two decided not to participate). The remaining 25 patients completed the study (Table 7.1).

<b>Table 7.1. Patient Accountability</b>		
<b>Disposition</b>	<b>(b) (4)</b>	
	<b>n</b>	<b>%</b>
Patients enrolled	30	100%
Patients who received study drug	25	83%
Patients who completed study	25	83%
Patients who discontinued early	5*	17%
Failed to qualify for study	3*	60%
Patient decision	2*	40%
* All discontinuations occurred prior to the initial dose of (b) (4)		

#### 7.1.3.2 Adverse events associated with dropouts

No patients discontinued the study due to an adverse event.

#### 7.1.4 Other Search Strategies

None.

#### 7.1.5 Common Adverse Events

##### 7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited from two sources. Patient were asked to complete diaries on a daily basis, which were reviewed at the clinic visits. In addition patients were asked open-ended questions at each visit about whether there had been any problems since the prior visit.

##### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

I have reviewed all verbatim terms and the corresponding preferred terms for the reported adverse events. All events were categorized appropriately.

##### 7.1.5.3 Incidence of common adverse events

Seventeen (68%) of the 25 patients reported at least one treatment-emergent adverse event. The most common adverse events occurred in the following categories (Table 7.2): Musculoskeletal and Connective Tissue Disorders (n=7 or 28%), Nervous System Disorders (n=6 or 24%), and Respiratory Disorders (n=6 or 24%). The most common adverse events were nasopharyngitis, arthralgia, dizziness, headache, and rhinorrhea – each were reported by three (12%) patients. Adverse events experienced by two (8.0%) patients included pain, bronchitis, pain in extremity, nasal discomfort, and rash.

Adverse events that are perhaps more likely to be related to study drug (e.g. nose and upper airway events) are reviewed in Section 7.1.1.5.

Only two of the 50 (71%) adverse events with intensity data were categorized as severe (sinus headache and arthralgia). Both of these events resolved within two days with no change in (b) (4) administration.

**Reviewer's comments:** Six patients experienced a total of eight adverse events during the pre-treatment period (i.e. after screening up until initiation of (b) (4)). During this 2-4 week period, there were three reports of urinary tract infection and one report each of sinusitis, cardiac discomfort, pyrexia, pain in extremity, and nephrolithiasis. The higher incidence of treatment-emergent adverse events (i.e. adverse events occurring after initiation of (b) (4)) is expected because the treatment-emergent adverse events were assessed over a longer time period (eight weeks vs. 2-4 weeks).

To help place the treatment-emergent adverse events into perspective, I have reviewed the Nascobal package insert, which reports adverse events for 24 Nascobal gel treated patients and 25 patients administered intramuscular vitamin B<sub>12</sub> (treatment duration is not specified). Adverse events in the Nascobal group included three reports of infection (sore throat/common cold) and one report of headache and rhinitis. Adverse events in the intramuscular vitamin B<sub>12</sub> group included five reports of headache, three reports of dizziness, three reports of infection (sore throat/common cold), two reports of rhinitis, and two reports of arthritis. These types of adverse events are similar to those reported with (b) (4).

#### 7.1.5.4 Common adverse event tables

Table 7.2 summarizes all treatment-emergent adverse events.

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<b>Table 7.2. Treatment-emergent adverse events by system-organ-class and preferred term</b>		
<b>System Organ Class</b>	<b>Preferred Term (verbatim term)</b>	<b>No. Patients (Occurrences)</b>
Ear and Labyrinth Disorders	Ear Discomfort (ear clogged)	1 (1)
	Ear Pain	1 (1)
Eye Disorders	Visual Acuity Reduced	1 (2)
Gastrointestinal Disorders	Constipation	1 (1)
	Gingival Pain	1 (2)
	Stomach Discomfort	1 (1)
General Disorders and Administration Site Conditions	Influenza Like Illness	1 (1)
	Malaise	1 (1)
	Pain	2 (3)
	Pyrexia	1 (1)
Infections and Infestations	Bronchitis	2 (2)
	Nasopharyngitis	3 (3)
	Oral Candidiasis (inhaled steroids for asthma)	1 (1)
	Sinusitis	1 (1)
	Tooth Abscess	1 (1)
Injury, Poisoning, and Procedural Complications	Injury	1 (1)
	Joint Sprain	1 (1)
	Procedural Pain	1 (1)
Metabolism/Nutrition Disorders	Hypoglycemia (on insulin)	1 (1)
Musculoskeletal and Connective Tissue Disorders	Arthralgia	3 (4)
	Back Pain	1 (1)
	Intervertebral Disc Protrusion	1 (1)
	Musculoskeletal Stiffness	1 (1)
	Neck Pain	1 (1)
	Pain in Extremity	2 (2)
	Shoulder Pain	1 (1)
Nervous System Disorders	Dizziness	3 (4)
	Headache	3 (6)
	Hypersomnia	1 (2)
	Sinus Headache	1 (3)
Psychiatric Disorders	Confusional State	1 (1)
Respiratory, Thoracic, and Mediastinal Disorders	Asthma	1 (1)
	Cough	1 (1)
	Epistaxis	1 (1)
	Nasal Discomfort	2 (2)
	Pharyngolaryngeal Pain	1 (1)
	Postnasal Drip	1 (4)
	Rhinorrhea	3 (3)
Skin and Subcutaneous tissue Disorders	Ingrowing Nail	1 (1)
	Rash	2 (2)
	Scab	1 (1)

#### 7.1.5.5 Identifying common and drug-related adverse events

The background rate of incident adverse events cannot be assessed from this study, because there are no adequate control data. However, some adverse events are more likely to be related to study drug (e.g. nasal and upper airway symptoms). These potential drug-related events are reviewed in Section 7.1.5.6 below.

#### 7.1.5.6 Additional analyses and explorations

Table 7.3 summarizes adverse events involving the head and neck region that could be related to study drug because of the proximity to the site of (b) (4) administration. Patient 526 had epistaxis on Day 12 that resolved after two minutes (the patient reported epistaxis as being “very unusual”), and was found to have right septal irritation/lesion with scant bleeding on physical exam at Visit 6. This patient had increased her daily dose of (b) (4) to two puffs in each nostril one week prior to Visit 6 because of declining vitamin B<sub>12</sub> concentrations from Visit 4 to Visit 5. She had a history of allergic rhinitis (exam at Visit 1 showed mild edema of the turbinates) and started Flonase 10 days prior to study start. It is unclear whether the epistaxis on Day 12 is related to the exam findings on Week 8. Nonetheless, the patient completed the study, and noted on the post-treatment product assessment form that the method of dosing was “very acceptable” and reported only “slight” nasal irritation or stinging.

All patients listed in Table 7.3 had resolution of their adverse events within <1 day to 18 days (except for the right septal irritation/lesion described above, which was noted on the last study visit) and successfully completed the study. There was no clear pattern for time to onset of the adverse events. There was a wide range of ages, but only one of the patients listed in this Table was a man.

**Reviewer's comments: Without background rates in a control group, it is difficult to place these adverse events into perspective. However, it is reassuring that the above adverse events were minor and that the patients successfully completed the study despite ongoing treatment with (b) (4). I cannot rule out the possibility that (b) (4) may have irritated the nasal mucosa of the woman who developed epistaxis and septal irritation. Nonetheless, I anticipate that patients who use (b) (4) (if approved) will switch back to injections if bothersome nasal and head symptoms occur with the nasal formulation.**

Table 7.4 summarizes the tolerability profile for (b) (4). All patients reported that the method of dosing was “acceptable” or “very acceptable”. Three patients reported nasal irritation or stinging (two had “slight” symptoms [Patients 521 and 526 in Table 7.4] and one had “moderate” symptoms [this patient did not report a nasal or upper respiratory adverse event]). All but one of the patients rated compliance with dosing as “easy” or “fairly easy”. Eighty percent of patients were “definitely yes” or “probably” willing to use (b) (4) instead of intramuscular injections.

**Reviewer's comments: Limitations of these patient-reported outcome data include a lack of validation and potential recollection bias (these data were collected at the end of the study).**

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 NDA 22-102  
 (b) (4) (cyanocobalamin) Nasal Spray

**Table 7.3. Adverse events in the head and upper respiratory system**

ID	Age and gender	Adverse event (Verbatim term)	Day of onset	Duration	Outcome/comments
<b>Ear events</b>					
504	71; female	Earache	12	4 days	Resolved with acetaminophen
<b>Infections</b>					
510	60; female	Nasopharyngitis (cough/runny nose/chills/dyspnea) Bronchitis	8 18	18 days 8 days	History of diabetes and asthma
511	56; female	Sinusitis Nasopharyngitis (sneezing/coughing/stuffy nose)	27 40	11 days 5 days	History of allergic rhinitis
519	50; female	Nasopharyngitis (head cold)	1	4 days	None
<b>Nervous system disorders</b>					
508	28; female	Headache	18, 27, 44	5 hr-1 day	Headache not reported as a past medical condition Treated with acetaminophen
517	49; female	Headache	33, 57	1 day	Headache not reported as a past medical condition
<b>Respiratory</b>					
500	57; female	Asthma and bronchitis	47	11 days	Resolved without treatment History of asthma and mastocytosis
520	82; male	Cough and rhinorrhea	20	≤11 days	Resolved without treatment
521	51; female	Nasal discomfort (sinuses burning) Rhinorrhea (runny nose)	11 8	2 days 1 day	This patient reported sinus headaches on Days 5-7, 9-11, and 13-15
526	32; female	Epistaxis Nasal discomfort (right septal irritation/lesion with scant bleeding at Visit 6)*	12 65	2 minutes Continuing	History of allergic rhinitis Started Flonase 10 days prior to study start Visit 1 exam showed mild edema of the turbinates
529	39; female	Pharyngolaryngeal pain (sore throat) Postnasal drip	42 45, 47, 50, 54	3 days 1 day	History of seasonal allergies
516	66; female	Rhinorrhea (runny nose)	2	1 day	CREST syndrome
*Daily dose increased to 100 mcg for the last week of the study because of a decline in vitamin B <sub>12</sub> levels from 491 pg/mL (Visit 4) to 424 pg/mL (Visit 5)					

<b>Table 7.4. Patient Product Assessment: Efficacy Population (n=25)</b>	
<b>Parameter</b>	<b>(b) (4)</b>
<b>Does product have taste?</b>	
No	24 (96%)
Yes	1 (4%)
<b>Method of dosing was</b>	
Very Acceptable	19 (76%)
Acceptable	6 (24%)
Somewhat unacceptable	0
Very unacceptable	0
<b>Any experience of nasal irritation or stinging?</b>	
Not at all	22 (88%)
Slight	2 (8%)
Moderate	1 (4%)
Significant	0
<b>Notice of unpleasant odor?</b>	
None	25 (100%)
Slight, moderate, or severe	0
<b>Notice of unpleasant aftertaste?</b>	
None	25 (100%)
Slight, moderate, or severe	0
<b>Compliance with dosing was</b>	
Easy	20 (80%)
Fairly easy	4 (16%)
Somewhat difficult	1 (4%)
Difficult	0
<b>Willing to take this in place of intramuscular injections?</b>	
Definitely yes	17 (68%)
Probably	3 (12%)
Possibly	3 (12%)
Definitely no	2 (8%)

Source: Section 10, Statistical Table 11

## 7.1.6 Laboratory Findings

### 7.1.6.1 Overview of laboratory testing in the development program

The Sponsor collected standard hematology data and urine pregnancy testing at Visit 1 (screening) and Visit 6 (Week 8) in pivotal study PR99-063. Clinical biochemistry data and urinalysis were not obtained.

#### 7.1.6.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This application only contains clinical laboratory data for the pivotal study PR99-063.

#### 7.1.6.3 Standard analyses and explorations of laboratory data

##### 7.1.6.3.1 *Analyses focused on measures of central tendency*

Based on central tendency analyses, there were no clinically relevant differences in any of the hematology variables between Visits 1 and 6 (Table 7.5).

##### 7.1.6.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

Table 7.6 summarizes the proportion of patients with shifts from normal to abnormal or abnormal to normal for each of the standard hematology parameters. As shown in Tables 7.7 and 7.8, most of these shifts are not clinically significant. All patients with abnormally low hematology values at baseline had stable results or improved results at study end. There were five patients with a shift in hemoglobin and/or hematocrit from normal at baseline to low at study end. The reductions in these parameters were minor (e.g. hemoglobin reduction of 1.3-1.6 g/dL), except for Patient 521 (this patient had a 3.1 g/dL decline in hemoglobin that is most likely related to her spine surgery on Day 52 – see the Serious Adverse Event section for additional details – her vitamin B<sub>12</sub> concentrations during Visits 3-6 ranged from 662-1,107 pg/mL, well above the 200 pg/mL lower limit of normal for the vitamin B<sub>12</sub> assay). The hemoglobin/hematocrit data for these five patients are summarized together with the corresponding vitamin B<sub>12</sub>, homocysteine, and methylmalonic acid values in Table 7.9. In general, Visit 3-6 vitamin B<sub>12</sub> levels were similar to or higher than the corresponding levels on Visit 1. Vitamin B<sub>12</sub> measurements on Visits 4 and 5 for Patient 501 were lower than the Visit 1 value (342-385 vs. 416 pg/mL). However, this patient's Visit 6 measurement was similar to the Visit 1 value.

**Reviewer's comments: Of note, the Sponsor did not submit data on mean corpuscular volume (MCV) or red blood cell distribution width (RDW). Nonetheless, there are no changes in the submitted hematology data that are likely to be related to vitamin B<sub>12</sub> status. For unclear reasons, hematology data were not obtained at study end for Patient 527. However, this patient did not have frankly low (<200 pg/mL) or low-normal (200-300 pg/mL) vitamin B<sub>12</sub> levels at any point during the study.**

**Table 7.5. Hematology results**

Parameter	Visit	N	Mean	SD	Median	Min, Max	Low	Normal	High
Basophils (%)	1	25	0.3	0.2	0.3	0.0, 0.9	0	25 (100%)	0
	6	24	0.3	0.2	0.3	0.0, 0.9	0	24 (100%)	0
Eosinophils (%)	1	25	2.7	2.0	2.6	0.1, 8.8	0	24 (96%)	1 (4%)
	6	24	2.9	2.0	2.5	0.1, 9.0	0	23 (96%)	1 (4%)
Hemoglobin (g/dL)	1	25	13.1	1.2	13.0	9.3, 15.5	3 (12%)	22 (88%)	0
	6	24	12.6	1.2	12.5	10.1, 15.2	6 (25%)	18 (75%)	0
Hematocrit (%)	1	25	39.7	3.3	39.7	30.8, 46.7	3 (12%)	22 (88%)	0
	6	24	38.3	3.7	37.9	30.4, 45.8	5 (21%)	19 (79%)	0
Lymphocytes (%)	1	25	26.3	8.7	26.0	11.0, 42.3	4 (16%)	21 (84%)	0
	6	24	29.4	8.5	29.6	10.9, 48.9	1 (4%)	22 (92%)	1 (4%)
Monocytes (%)	1	25	4.5	2.1	4.4	0.0, 8.3	0	25 (100%)	0
	6	24	4.8	2.4	4.7	0.0, 9.8	0	24 (100%)	0
Neutrophils (%)	1	25	66.3	9.2	65.0	46.3, 85.0	0	21 (84%)	4 (16%)
	6	24	62.6	8.9	63.2	38.8, 77.5	1 (4%)	20 (83%)	3 (13%)
Platelets (x10 <sup>3</sup> /mm <sup>3</sup> )	1	25	270	70	275	138, 413	0	23 (92%)	2 (8%)
	6	24	273	76	269	130, 463	0	23 (96%)	1 (4%)
RBC (x10 <sup>6</sup> /MCL)	1	25	4.3	0.4	4.4	3.5, 5.2	3 (12%)	22 (88%)	0
	6	24	4.1	0.4	4.2	3.4, 5.2	5 (21%)	19 (79%)	0
WBC (x10 <sup>3</sup> /MCL)	1	25	6.6	1.9	6.2	3.3, 12.7	1 (4%)	23 (92%)	1 (4%)
	6	24	6.0	2.3	5.4	3.4, 14.9	3 (13%)	20 (83%)	1 (4%)

<b>Table 7.6. Hematology shift analyses from Visit 1 to Visit 6 for the 25 patients</b>		
<b>Parameter</b>	<b>Shift</b>	<b>Total patients</b>
Abs. eosinophils	No change	23
	Normal to high	1 (4%)
Hematocrit	No change	20
	Normal to low	3 (12%)
	Low to normal	1 (4%)
Hemoglobin	No change	19
	Normal to low	4 (16%)
	Low to normal	1 (4%)
Abs. lymphocytes	No change	23
	Low to normal	1 (4%)
Abs. monocytes	No change	19
	Normal to low	4 (16%)
	Low to normal	1 (4%)
Abs. neutrophils	No change	23
	Normal to low	1 (4%)
Platelets	No change	21
	High to normal	2 (8%)
	Normal to high	1 (4%)
Red blood cell count	No change	18
	Normal to low	4 (16%)
	Low to normal	2 (8%)
White blood cell count	No change	22
	Normal to low	1 (4%)

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<b>Table 7.7. Shifts from Normal to Abnormal: Hematology</b>			
<b>ID</b>	<b>Parameter (reference range)</b>	<b>Visit 1 → Visit 6</b>	<b>Comments</b>
<b>Shift from Normal at Visit 1 to High at Visit 6</b>			
500	Platelet count (130-400 x 10 <sup>3</sup> /mL)	342 → 463	NCS
514	Abs. eosinophils (0.05-0.55 x 10 <sup>3</sup> /mL)	0.50 → 0.57	NCS
<b>Shift from Normal at Visit 1 to Low at Visit 6</b>			
501	Hemoglobin (12-15.6 g/dL)	12.8 → 11.4	See Table 7.9 and text
	WBC (3.8-10.8 x 10 <sup>3</sup> /mL)	5.1 → 3.4	
	Abs neutrophils (1.8-8 x 10 <sup>3</sup> /mL)	2.6 → 1.3	
502	Hemoglobin (12-15.6 g/dL)	13.5 → 11.9	See Table 7.9 and text
507	Abs. monocytes (0.2-1.1 x 10 <sup>3</sup> /mL)	0.20 → 0.16	NCS
508	Abs. monocytes (0.2-1.1 x 10 <sup>3</sup> /mL)	0.46 → 0.14	NCS
511	WBC (3.8-10.8 x 10 <sup>3</sup> /mL)	8.3 → 3.5	NCS*
517	Abs. monocytes (0.2-1.1 x 10 <sup>3</sup> /mL)	0.21 → 0.19	NCS
	RBC count (3.9-5.2 x 10 <sup>6</sup> /mL)	3.9 → 3.8	
519	Abs. monocytes (0.2-1.1 x 10 <sup>3</sup> /mL)	0.2 → 0.0	NCS
520	Hematocrit (36-49%)	38.1 → 35.7	See Table 7.9 and text
521	Hemoglobin (12-15.6 g/dL)	13.2 → 10.1	Spine surgery on Day 52 See Table 7.9 and text
	Hematocrit (35-46%)	40.5 → 30.4	
	RBC count (3.9-5.2 x 10 <sup>6</sup> /mL)	4.5 → 3.4	
522	Hemoglobin (12-15.6 g/dL)	12.7 → 11.4	See Table 7.9 and text
	Hematocrit (36-49%)	38.2 → 35.0	
	RBC count (3.9-5.2 x 10 <sup>6</sup> /mL)	4.0 → 3.6	
517	RBC count (3.9-5.2 x 10 <sup>6</sup> /mL)	3.9 → 3.8	NCS
NCS = not clinically significant change (based on reviewer's assessment)			
*Patient 511 had a WBC of 3.3 x 10 <sup>3</sup> /mL six weeks prior to the 8.3 x 10 <sup>3</sup> /mL recording			

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(b) (4) (cyanocobalamin) Nasal Spray

<b>Table 7.8. Shifts from Abnormal to Normal or Persistently Abnormal Labs: Hematology</b>				
<b>ID</b>	<b>Parameter (reference range)</b>	<b>Visit 1 → Visit 6</b>	<b>Comments</b>	
<b>High at Visit 1 and High at Visit 6</b>				
500	WBC (3.8-10.8 x 10 <sup>3</sup> /mL) Abs. neutrophils (1.8-8 x 10 <sup>3</sup> /mL)	12.7 → 14.9 9.2 → 11.6	NCS	
<b>Shift from High at Visit 1 to Normal at Visit 6</b>				
516	Platelet count (130-400 x 10 <sup>3</sup> /mL)	406 → 344	Normalized	
518	Platelet count (130-400 x 10 <sup>3</sup> /mL)	413 → 382	Normalized	
<b>Low at Visit 1 and Low at Visit 6</b>				
509	Hemoglobin (12-15.6 g/dL) Hematocrit (35-46%) WBC (3.8-10.8 x 10 <sup>3</sup> /mL) Abs. eosinophils (0.05-0.55 x 10 <sup>3</sup> /mL)	9.3 → 10.9 30.8 → 34.1 3.3 → 3.7 0.00 → 0.03	Values were essentially stable or increased from Visit 1 to Visit 6	
510	Abs. eosinophils (0.05-0.55 x 10 <sup>3</sup> /mL)	0.02 → 0.04		
511	WBC (3.8-10.8 x 10 <sup>3</sup> /mL)	3.3 → 3.5		
515	RBC count (3.9-5.2 x 10 <sup>6</sup> /mL)	3.6 → 3.5		
521	Abs. monocytes (0.2-1.1 x 10 <sup>3</sup> /mL)	0.11 → 0.18		
522	Abs. monocytes (0.2-1.1 x 10 <sup>3</sup> /mL)	0.16 → 0.12		
523	RBC count (3.9-5.2 x 10 <sup>6</sup> /mL) Abs. lymphocytes (0.85-4.1 x 10 <sup>3</sup> /mL)	3.5 → 3.7 0.7 → 0.77		
525	Abs. eosinophils (0.05-0.55 x 10 <sup>3</sup> /mL)	0.01 → 0.01		
<b>Shift from Low at Visit 1 to Normal at Visit 6</b>				
509	Abs. lymphocytes (0.85-4.1 x 10 <sup>3</sup> /mL)	0.74 → 1.07		Normalized
512	Hematocrit (36-49%)	34.9 → 37.9	Normalized	
519	RBC count (3.9-5.2 x 10 <sup>6</sup> /mL)	3.7 → 4.0	Normalized	
523	Hemoglobin (12-15.6 g/dL) Hematocrit (36-49%) RBC count (3.7-5.5 x 10 <sup>6</sup> /mL)	11.4 → 12.3 34.2 → 36.3 3.5 → 3.7	Normalized	
525	Abs. monocytes (0.2-1.1 x 10 <sup>3</sup> /mL)	0.00 → 0.23	Normalized	
NCS = not clinically significant change (based on reviewer's assessment)				

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**Table 7.9. Vitamin B<sub>12</sub> parameters for patients with shifts in hemoglobin/hematocrit from Normal at Visit 1 to Low at Visit 6**

ID	Parameter (reference range)	Visit 1 (Wk -2/-4)	Visit 2 (Day 0)	Visit 3 (Wk 2)	Visit 4 (Wk 4)	Visit 5 (Wk 6)	Visit 6 (Wk 8)
501	Hemoglobin (12-15.6 g/dL)	12.8	-	-	-	-	11.4
	Vitamin B <sub>12</sub> (≥200 pg/mL)	416	428	409	385	342	409
	Homocysteine (4.9-14.6 mcmol/L)	15.2	21.3	20.1	21.6	18.1	20.2
	Methylmalonic acid (90-279 nmol/L)	-	304	-	-	-	255
502	Hemoglobin (12-15.6 g/dL)	13.5	-	-	-	-	11.9
	Vitamin B <sub>12</sub> (≥200 pg/mL)	378	347	345	380	391	400
	Homocysteine (4.9-14.6 mcmol/L)	6.7	6.8	6.6	6.7	7.0	6.5
	Methylmalonic acid (90-279 nmol/L)	-	306	-	-	-	275
520	Hematocrit (36-49%)	38.1	-	-	-	-	35.7
	Vitamin B <sub>12</sub> (≥200 pg/mL)	646	498	563	709	627	570
	Homocysteine (4.9-14.6 mcmol/L)	11.8	12.8	11.0	10.2	12.2	7.4
	Methylmalonic acid (90-279 nmol/L)	-	442	-	-	-	383
521	Hemoglobin (12-15.6 g/dL)	13.2	-	-	-	-	10.1
	Hematocrit (35-46%)	40.5	-	-	-	-	30.4
	Vitamin B <sub>12</sub> (≥200 pg/mL)	433	525	662	636	772	1,107
	Homocysteine (4.9-14.6 mcmol/L)	7.2	7.5	5.0	5.7	7.0	6.2
	Methylmalonic acid (90-279 nmol/L)	-	111	-	-	-	188
522	Hemoglobin (12-15.6 g/dL)	12.7	-	-	-	-	11.4
	Hematocrit (36-49%)	38.2	-	-	-	-	35.0
	Vitamin B <sub>12</sub> (≥200 pg/mL)	353	166	479	431	563	529
	Homocysteine (4.9-14.6 mcmol/L)	9.5	14.1	12.4	12.9	12.5	13.4
	Methylmalonic acid (90-279 nmol/L)	-	181	-	-	-	143

7.1.6.4 Additional analyses and explorations

None.

7.1.6.5 Special assessments

None.

## 7.1.7 Vital Signs

### 7.1.7.1 Overview of vital signs testing in the development program

In pivotal Study PR99-063, the Sponsor conducted physical exams at screening and Week 8 that included measurement of blood pressure, heart rate, respiratory rate, temperature, height, and weight. At Week 8, Patient 526 is missing a complete set of vital signs, Patient 509 is missing a heart rate assessment, and Patient 525 is missing a blood pressure and temperature assessment.

### 7.1.7.2 Selection of studies and analyses for overall drug-control comparisons

This application only includes clinical data from pivotal study PR99-063.

### 7.1.7.3 Standard analyses and explorations of vital signs data

Based on central tendency analyses, there were no clinically relevant changes in any of the vital signs between Visits 1 and 6 (Table 7.10). Cyanocobalamin and the excipients in (b) (4) are not known to cause hemodynamic effects (except for rare reports of anaphylaxis with parenteral cyanocobalamin).

Parameter	Observed Information			Change from Baseline		
	Visit	N	Mean (SD)	N	Mean (SD)	P-Value
Heart rate (bpm)	1	25	73 (11)	23	-1 (13)	0.78
	6	23	73 (10)			
Systolic blood pressure (mmHg)	1	25	124 (17)	23	1 (14)	0.86
	6	23	125 (16)			
Diastolic blood pressure (mmHg)	1	25	75 (9)	23	3 (8)	0.085
	6	23	78 (8)			
Respiratory rate (min)	1	25	17 (3)	24	-1 (6)	0.48
	6	24	17 (5)			
Temperature (F)	1	25	98.1 (0.7)	23	0.2 (0.8)	0.34
	6	23	98.3 (0.7)			
Height (inches)	1	25	66.1 (3.9)	24	0.1 (0.5)	0.59
	6	24	66.4 (3.8)			
Weight (lbs)	1	25	178 (41)	24	-0.2 (4.9)	0.87
	6	24	179 (41)			

#### 7.1.7.4 Additional analyses and explorations

Physical exams (including examination of the nasal mucosa) were conducted at Visits 1 and 6. Two patients had new abnormal findings. Patient 525 reported mild conjunctivitis on Visit 6 after cataract surgery (this patient reported two occurrences of poor visual acuity during the study, which are consistent with the reported cataract surgery). Patient 526 had right septal irritation and lesion with scant bleeding on Visit 6 physical exam (reported as “nasal discomfort” adverse event – see Section 7.1.5.6 for further details).

#### 7.1.8 Electrocardiograms (ECGs)

The Sponsor did not collect electrocardiograms in pivotal study PR99-063. Cyanocobalamin and the excipients in (b) (4) are not known to cause electrocardiographic effects.

#### 7.1.9 Immunogenicity

(b) (4) a non-peptide, is not expected to elicit an immune response in humans. This application does not contain immunogenicity data.

#### 7.1.10 Human Carcinogenicity

There is no evidence that vitamin B<sub>12</sub> is carcinogenic based on long-term use in patients with pernicious anemia. Pernicious anemia is associated with an increased incidence of gastric adenocarcinoma, but this finding has been attributed to the underlying pathology of the disorder and not to treatment with vitamin B<sub>12</sub>.

#### 7.1.11 Special Safety Studies

None.

#### 7.1.12 Withdrawal Phenomena and/or Abuse Potential

Vitamin B<sub>12</sub> has no known potential for drug abuse. The administration of intranasal vitamin B<sub>12</sub> has no effect on mental function or on the ability to drive or operate machinery.

#### 7.1.13 Human Reproduction and Pregnancy Data

No pregnancies were reported in pivotal study PR99-063.

Vitamin B<sub>12</sub> has not been tested in animal reproductive studies or in adequate and well-controlled studies in pregnant women. However, vitamin B<sub>12</sub> is an essential vitamin, and requirements are increased during pregnancy. Vitamin B<sub>12</sub> appears in the milk of nursing mothers in concentrations that approximate the mother’s vitamin B<sub>12</sub> blood level.

#### 7.1.14 Assessment of Effect on Growth

Vitamin B<sub>12</sub> deficiency or supplementation is not known to affect growth in pediatric patients.

#### 7.1.15 Overdose Experience

There were no cases of (b) (4) overdose in Study PR99-063. There are no overdose concerns with intramuscular cyanocobalamin (the active ingredient in (b) (4) which is typically initially dosed at 1,000 mcg daily for one week then 1,000 mcg weekly for one month in patients with newly diagnosed vitamin B<sub>12</sub> deficiency (total dose of 11,000 mcg or 11 mg over five weeks). Each nasal spray of (b) (4) contains 25 mcg of cyanocobalamin. Therefore, patients would need to administer 440 puffs in five weeks (>12 puffs per day) to receive a similar exposure to five weeks of intramuscular cyanocobalamin (assuming similar bioavailability to the intramuscular form).

#### 7.1.16 Postmarketing Experience

Using AERS DataMart, I identified all postmarketing reports listing cyanocobalamin (the active ingredient in (b) (4) as the suspect drug (or role unknown) submitted to the FDA through June 2007.

Using the above search criteria, I have identified several postmarketing reports of angioedema and angioedema-like events (Table 7.11), although none of these reports appear to have occurred with the intranasal form of cyanocobalamin (two postmarketing reports did not specify the route of administration). The currently-approved labeling for Nascobal nasal spray (the Reference Listed Drug) and the proposed labeling for (b) (4) state that anaphylactic shock and death have been reported with parenteral vitamin B<sub>12</sub>. However, these labels do not include angioedema and angioedema-like events.

**Reviewer's comments:** I recommend adding angioedema and angioedema-like events to the (b) (4) label and sending a Supplement Request Letter to the Sponsors of the other vitamin B<sub>12</sub> agents.

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<b>Table 7.11. Postmarketing reports for cyanocobalamin of potential interest</b>				
<b>ISR</b>	<b>Patient demographics</b>	<b>Cyanocobalamin dose and route</b>	<b>Concomitant medications</b>	<b>Details</b>
<b>Angioedema</b>				
652794	47 year-old woman	Not specified	Folic acid Vitamin K Ranitidine	None provided
685062	Not specified	Intramuscular	None reported	None provided
<b>Tongue edema</b>				
1460276	40 year-old woman	Not specified	None reported	None provided
<b>Face edema</b>				
1676695	36 year-old woman	Intramuscular	None reported	None provided
3618642	75 year-old woman	Intravenous	“Many” unspecified	Also reported petechiae, mouth ulceration, and dermatitis bullous
3467421	Woman ?age	Intramuscular	None reported	Also reported pruritis
1927396	32 year-old woman	Intramuscular	None reported	Also reported hypersensitivity
1988910	97 year-old man	Intramuscular 200 mcg	Amlodipine Colchicine Terazosin	None provided

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

#### 7.2.1.1 Study type and design/patient enumeration

Please see Section 6 for the design of pivotal study PR99-063.

#### 7.2.1.2 Demographics

Table 7.12 summarizes the baseline demographic data for the 25 treated patients. The mean age was 59 years (range 27-82 years). Two-thirds were women and most of the participants were Caucasian. Visit 1 vitamin B<sub>12</sub> levels ranged from 226-993 pg/mL. Three patients had borderline-low vitamin B<sub>12</sub> levels (>200 but <300 pg/mL) on Visit 1 – 226 pg/mL (Patient 507), 267 pg/mL (Patient 511), and 291 pg/mL (Patient 510). All three of these patients had normal Visit 1 homocysteine concentrations (methylmalonic acid was not measured at this visit).

Most patients had pernicious anemia (n=12 or 48%), although one-third of the participants had an unknown cause of vitamin B<sub>12</sub> deficiency. The mean duration of vitamin B<sub>12</sub> deficiency from diagnosis to study entry was almost six years (range 1-29 years).

<b>Table 7.12. Summary of Demographics and Baseline Characteristics</b>	
<b>Characteristic</b>	<b>(b) (4) (N=25)</b>
<b>Age (years)</b>	
Mean (SD)	59 (16)
Min, Max	27, 82
<b>Gender, n (%)</b>	
Female	17 (68%)
Male	8 (32%)
<b>Race, n (%)</b>	
Caucasian	21 (84%)
African American	4 (16%)
<b>Visit 1 vitamin B<sub>12</sub> (pg/mL)</b>	
Mean (SD)	485 (158)
Min, Max	226, 993
<b>Cause of vitamin B<sub>12</sub> deficiency, n (%)</b>	
Pernicious anemia	12 (48%)
Gastrointestinal surgery	4 (16%)
Unknown	9 (36%)
<b>Duration of vitamin B<sub>12</sub> deficiency (years)</b>	
Mean (SD)	5.8 (8.0)
Min, Max	1, 29

### 7.2.1.3 Extent of exposure (dose/duration)

Table 7.13 summarizes the exposure data for the 25 treated patients in pivotal Study PR99-063. Study personnel asked only one participant (Patient 526) to increase the (b) (4) dose from 50 mcg daily to 100 mcg daily.

<b>Characteristic</b>	<b>(b) (4)</b>
<b>Number of subjects</b>	
1 dose/day	24 (96%)
2 doses/day (Patient 526 took 2 doses/day in Week 8)	1 (4%)
<b>Number of days dosed</b>	
Mean (SD)	60 (5)
Median (min, max)	58 (55, 73)
<b>Percentage of doses (50 mcg/day) taken by patient</b>	
>120%	0
101-120%	1 (4%)
80-100%	24 (96%)
<80%	0

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

### 7.2.2.1 Other studies

None.

### 7.2.2.2 Postmarketing experience

Please see Section 7.1.16 above.

### 7.2.2.3 Literature

The Sponsor provides references for three clinical articles discussing intranasal absorption of vitamin B<sub>12</sub> (Slot, 1997; Van Asselt 1998; Monto 1955) as well as the package insert for Nascobal nasal spray (QOL Medical Company, 2005). The three references used different formulations and dosing regimens of vitamin B<sub>12</sub> and different patient populations (Table 7.14). Therefore, results were not integrated into the efficacy and safety analyses of (b) (4) but were instead used to show the feasibility of an intranasal formulation of vitamin B<sub>12</sub> for the treatment of vitamin B<sub>12</sub> deficiency.

Using PubMed search terms of “nasal” and “cobalamin”, I identified one additional published article of potential relevance. Van den Berg 2003 showed no additional uptake of hydroxocobalamin in the cerebrospinal fluid of rats and humans after nasal delivery compared to intravenous administration.

**Table 7.14. Published studies of intranasal vitamin B12 submitted by the Sponsor**

Study	Population	Sample size	Design	Efficacy	Adverse events
Slot, et al.	Vitamin B <sub>12</sub> <200 pg/mL due to Crohn's or radiation enteritis	n=6	Hydroxocobalamin 1,500 mcg intranasally on Days 0, 14, and 21	Mean 1-hr post-treatment vitamin B <sub>12</sub> was 8x higher than baseline values  Vitamin B <sub>12</sub> levels on Days 7, 28, and 35 were all higher than baseline values	None
Van Asselt, et al.	Healthy elderly adults	n=10	Single-dose crossover study testing hydroxocobalamin 750 mcg and 1,500 mcg  Crystalline vitamin B <sub>12</sub> placed directly on the mucosa of the inferior nasal turbinate bone	Pharmacokinetic data showing rapid absorption	None
Monto, et al.	Pernicious anemia	Case series of three patients  A few sentences reporting successful treatment of 87 pernicious anemia patients	B <sub>12</sub> -lactose powder (~100 mcg B <sub>12</sub> ) delivered with a rubber bulb to the nasal mucosa	Improvement or normalization in clinical signs and symptoms (e.g. hematologic indices, glossitis)	None reported

### 7.2.3 Adequacy of Overall Clinical Experience

The Sponsor and Division reached agreement regarding the study duration, sample size, and dose of study medication prior to study initiation. The main objective of the small pivotal study was to show efficacy of the 50 mcg (b) (4) dose. The major basis for (b) (4) safety is derived by way of reference from the Reference Listed Drug and from the extensive prior experience with the ingredients in (b) (4)

Limitations of the pivotal trial include:

- The small sample size, which prevents a robust assessment of efficacy and safety across age, gender, and racial demographic subgroups
- No efficacy or safety data in patients with newly diagnosed vitamin B<sub>12</sub> deficiency
- No data assessing efficacy or safety in the presence of nasal disease (e.g., upper respiratory tract infection, allergic rhinitis) and nasal medications (e.g., intranasal glucocorticoids)
- Lack of a control group (which would have definitively shown the time course and extent of decline in vitamin B<sub>12</sub> levels when vitamin B<sub>12</sub> supplementation is withheld). Nonetheless, mean vitamin B<sub>12</sub> levels were higher with (b) (4) compared to the mid-point between maintenance vitamin B<sub>12</sub> injections

Because of these limitations, (b) (4) should not be used in patients with newly diagnosed, untreated vitamin B<sub>12</sub> deficiency or in patients with significant nasal pathology that is likely to result in erratic vitamin B<sub>12</sub> absorption. Healthcare providers should monitor vitamin B<sub>12</sub> levels regularly in all patients on (b) (4) to ensure long-term compliance and continued effectiveness. Patients should not use (b) (4) within several hours of administering other intranasal drugs.

### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

According to Dr. Davis-Bruno (pharmacology-toxicology reviewer), the non-clinical data used by way of reference adequately cover the use of (b) (4). There are no new safety signals in the clinical database requiring further evaluation in non-clinical testing.

### 7.2.5 Adequacy of Routine Clinical Testing

The Sponsor appropriately elicited adverse events (open questioning and daily diaries) during the pivotal trial and adequately obtained measurements of vitamin B<sub>12</sub>, homocysteine, and the complete blood count at reasonable intervals during (b) (4) treatment. The Sponsor only measured methylmalonic acid concentrations at Visit 2 (immediately prior to initiation of (b) (4) and at study end (Week 8). For completeness, the Sponsor should probably have measured methylmalonic acid at all visits (as was done for homocysteine), because methylmalonic acid is more specific than homocysteine for vitamin B<sub>12</sub> deficiency. Fortunately, the (b) (4) results are interpretable without the additional methylmalonic acid

measurements. Clinical practice guidelines recommend measurement of methylmalonic acid and homocysteine when vitamin B<sub>12</sub> levels are borderline-low (200-300 pg/mL). In the pivotal trial, there were four patients who experienced an isolated borderline-low vitamin B<sub>12</sub> value (200-300 pg/mL) on (b) (4) but all had normal homocysteine values at the time of the measurement and all had vitamin B<sub>12</sub> values >300 pg/mL on subsequent assessment or normal methylmalonic acid measurements at study end.

Some patients had elevated homocysteine concentrations despite apparently adequate vitamin B<sub>12</sub> supplementation. Because the Sponsor did not measure folic acid concentrations during the pivotal trial, I cannot rule out concurrent folate deficiency as an explanation for these findings.

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The Sponsor is relying on metabolic, clearance, and interaction data for cyanocobalamin by way of reference and did not conduct new studies in these areas. This approach provides adequate information given our extensive experience with previously approved vitamin B<sub>12</sub> products.

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The safety profile for vitamin B<sub>12</sub> products is well established. Therefore, the main purpose of the current application is to show that (b) (4) adequately maintains vitamin B<sub>12</sub> levels in patients with vitamin B<sub>12</sub> deficiency. There are some safety data available from the small pivotal study, but most of the safety database is derived by way of reference from the RLD and the extensive knowledge known about other vitamin B<sub>12</sub>-containing products.

#### 7.2.8 Assessment of Quality and Completeness of Data

The Sponsor provided data of sufficient quality to support the safety review. The pivotal study was intentionally designed to exclude patients with newly diagnosed, previously untreated vitamin B<sub>12</sub> deficiency. Other limitations of the safety data include the lack of a control group to assess background rates of adverse events and the small sample size. Also, the Sponsor did not collect clinical biochemistry, urinalysis, or electrocardiographic data. These limitations do not affect the approvability of (b) (4) for maintenance treatment of vitamin B<sub>12</sub> deficiency because there are well established safety data for cyanocobalamin and the excipients in (b) (4) (the main purpose of the current application is to show that vitamin B<sub>12</sub> levels are adequately maintained with (b) (4)).

#### 7.2.9 Additional Submissions, Including Safety Update

The Sponsor did not submit a 120-Day Safety Update – this is acceptable because there are no new data (the Sponsor does not have any ongoing or planned additional studies with (b) (4)).

### 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Safety results of the pivotal study are limited by the small sample size (n=25) and the lack of a control group (inability to assess the background rates of adverse events). In addition, safety data are only derived from patients previously treated with stable doses of intramuscular vitamin B<sub>12</sub> injections; therefore, results cannot be extrapolated to patients with newly diagnosed, previously untreated vitamin B<sub>12</sub> deficiency. The major findings are summarized below:

- The pivotal study did not have deaths, relevant serious adverse events, or treatment-associated dropouts.
- The most common adverse events were nasopharyngitis, rhinorrhea, arthralgia, dizziness, and headache – each were reported by three (12%) of the 25 patients dosed with (b) (4). One patient with a history of allergic rhinitis treated with Flonase had epistaxis approximately two weeks after initiating (b) (4) and was found to have right septal irritation/lesion with scant bleeding on physical exam at study end. This patient had increased her daily dose of (b) (4) to two puffs in each nostril one week prior to the last physical exam because of declining vitamin B<sub>12</sub> levels. This patient completed the study and noted on the post-treatment product assessment form that the method of dosing was “very acceptable” and reported only “slight” nasal irritation or stinging.
- Patients reporting adverse events in the nasal region (e.g., rhinorrhea) had resolution of these events (except for the right septal irritation/lesion described above, which was noted on the last study visit) and successfully completed the study despite ongoing treatment with (b) (4). I anticipate that patients who use (b) (4) (if approved) will switch back to injections if bothersome nasal and head symptoms occur with the nasal formulation.
- In a post-study questionnaire, all patients reported that the method of dosing was “acceptable” or “very acceptable”. Three patients reported nasal irritation or stinging. Limitations of these data include a lack of validation and potential recollection bias (these data were collected at the end of the study).
- There are no concerning changes in hematologic data attributable to vitamin B<sub>12</sub> status. Clinical chemistry data and electrocardiograms were not collected, but I do not expect alterations in these parameters in patients receiving maintenance vitamin B<sub>12</sub> administration.
- Using AERS DataMart, I have identified several postmarketing reports of angioedema and angioedema-like events with cyanocobalamin listed as the suspect drug (or role unknown). None of these reports appear to have occurred with the intranasal form of cyanocobalamin (two postmarketing reports did not specify the route of administration). Therefore, I recommend adding angioedema and angioedema-like events to the (b) (4) label and sending a Supplement Request Letter to the Sponsors of the other vitamin B<sub>12</sub> agents.

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

No pooling was performed because only a single clinical study was submitted with this application.

### 7.4.2 Explorations for Predictive Factors

The small sample size (25 treated patients) and lack of a control group significantly limit my ability to explore predictive factors for adverse events. There were no clear patterns with regard to time of onset or predisposing factors for adverse events originating in the nasal and upper airway region. In addition, all these adverse events were minor and resolved despite continued treatment with (b) (4). The one patient with epistaxis on Day 12 and right septal irritation at study end had an increase in the (b) (4) dose from 50 mcg to 100 mcg daily during the last week of the study and was also receiving Flonase for the treatment of allergic rhinitis.

### 7.4.3 Causality Determination

See Section 7.3 for details.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The Sponsor studied a 50 mcg daily dose of (b) (4) (i.e. total monthly dose of 1,500 mcg). This decision was based on currently used doses of Nascobal vitamin B<sub>12</sub> nasal spray (500 mcg once weekly, corresponding to 2,000 mcg monthly) and intramuscular vitamin B<sub>12</sub> (100-1,000 mcg monthly). The 50 mcg daily dose appears efficacious for most patients, although some patients may require higher doses (more frequent dosing) to maintain adequate vitamin B<sub>12</sub> levels. There are no adequate data assessing (b) (4) efficacy in the presence of nasal disease and nasal medications (in the clinical trial, one patient on Flonase for allergic rhinitis required a doubling of the (b) (4) dose). Also, the prescribing information for currently approved vitamin B<sub>12</sub> products reports that patients with renal or hepatic disease may require increased doses or more frequent administration of cyanocobalamin. Because of these considerations, all (b) (4) treated patients should have regular assessments of vitamin B<sub>12</sub> levels to assure long-term efficacy. Patients with nasal pathology that may result in erratic vitamin B<sub>12</sub> absorption should not be prescribed (b) (4) and patients should not use (b) (4) within several hours of administering other intranasal drugs.

### 8.2 Drug-Drug Interactions

The Sponsor did not perform any drug-drug interaction studies.

The Nascobal package insert (November 2005) states that

- Most antibiotics, methotrexate, and pyrimethamine invalidate folic acid and vitamin B<sub>12</sub> diagnostic assays
- Colchicine, para-aminosalicylic acid, and heavy alcohol intake for longer than two weeks may produce malabsorption of vitamin B<sub>12</sub>

Micromedex describes the following drug-drug interactions for cyanocobalamin (route of administration unspecified):

- Aminosalicic acid – long-term therapy may reduce absorption of cyanocobalamin from the gastrointestinal tract, possibly increasing the requirement for oral cyanocobalamin
- Ascorbic acid – may destroy a substantial proportion of cyanocobalamin in a vitamin-B<sub>12</sub> containing meal, and should, therefore, be taken two or more hours after a meal or vitamin B<sub>12</sub> supplements
- Chloramphenicol (an antibiotic) – may result in a suboptimal clinical response to cyanocobalamin in vitamin B<sub>12</sub>-deficient patients
- Omeprazole therapy for two weeks in healthy volunteers substantially reduced protein-bound cyanocobalamin absorption

**Reviewer's comments:** The relevance of most of these drug-drug interactions is unclear, because (b) (4) is absorbed across the nasal mucosa and not in the gastrointestinal tract. Therefore, for the (b) (4) label, I favor only including the first bullet point pertaining to drugs that invalidate the folic acid and vitamin B<sub>12</sub> diagnostic assays.

It is possible that nasal pathology (e.g., allergic rhinitis) or co-administered intranasal drugs (e.g., nasal steroids) may affect (b) (4) absorption. One of the 25 treated patients in the clinical study required an increase in (b) (4) dose (this patient was using Flonase for allergic rhinitis). Therefore, I recommend that patients do not use (b) (4) within several hours of administering other intranasal drugs, and that healthcare providers closely monitor vitamin B<sub>12</sub> levels in these patients.

### 8.3 Special Populations

The Sponsor reports that gender, age, and race have no meaningful effects on the response to (b) (4). However, the analysis for race is limited by the small sample size of non-Caucasians (n=4). In addition, patients <65 years old had lower mean vitamin B<sub>12</sub> levels at all clinic visits compared to those ≥65 years old (the variability in measurements and small sample sizes resulted in non-statistically significant differences between these subgroups). Nonetheless, no patients on (b) (4) developed frankly low vitamin B<sub>12</sub> levels (<200 pg/mL) or persistently borderline-low vitamin B<sub>12</sub> levels (200-300 pg/mL). If approved, all (b) (4) treated patients should have regular assessments of vitamin B<sub>12</sub> levels to assure long-term treatment compliance - I do not see a need for altering this recommendation based on demographic subgroups.

The Sponsor did not conduct studies of (b) (4) in patients with hepatic or renal insufficiency. Micromedex states that patients with renal or hepatic disease may require increased doses/more frequent administration of cyanocobalamin. This information is reported for intramuscular cyanocobalamin but would presumably also apply to (b) (4).

Micromedex and the Nascobal package insert state that cyanocobalamin is a Pregnancy Category C drug that is excreted in the milk of nursing mothers. Both documents state that vitamin B<sub>12</sub> is an essential vitamin and that amounts recommended by the Food and Nutrition Board of the National Academy of Science/National Research Council be consumed during pregnancy and lactation.

#### 8.4 Pediatrics

The Sponsor requests a full waiver of pediatric studies. The Sponsor claims that (b) (4) does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. In addition, the Sponsor states that (b) (4) is based on the Nascobal prescribing information, which includes the following pediatric use indication: "Intake in pediatric patients should be in the amount recommended by the Food and Nutrition Board, National Academy of Science-National Research Council".

**Reviewer's comments:** Based on these considerations, a full waiver of pediatric studies is acceptable.

#### 8.5 Advisory Committee Meeting

Not applicable – this 505(b)(2) application did not go to Advisory Committee.

#### 8.6 Literature Review

Please see Section 7.2.2.3. All citations are listed at the end of this review.

#### 8.7 Postmarketing Risk Management Plan

Not applicable – the Sponsor has not submitted a postmarketing risk management plan.

#### 8.8 Other Relevant Materials

None.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

See Sections 6.1.6 (efficacy conclusions), 7.3 (safety conclusions), and 8.1-8.3 (dosing considerations) for details.

The ingredients in (b) (4) have a well-established safety record. Patients who develop bothersome nasal symptoms (e.g., rhinorrhea, nasal irritation) with (b) (4) will likely ask to be switched to Nascobal (once-weekly vitamin B<sub>12</sub> formulation) or once-monthly intramuscular injections.

The 50 mcg daily dose appears efficacious for most patients, although some patients may require higher doses (more frequent dosing) to maintain adequate vitamin B<sub>12</sub> levels. There are no adequate data assessing (b) (4) efficacy in the presence of nasal disease and nasal medications (in the clinical trial, one patient on Flonase for allergic rhinitis required a doubling of the (b) (4) dose). Also, the prescribing information for currently approved vitamin B<sub>12</sub> products reports that patients with renal or hepatic disease may require increased doses or more frequent administration of cyanocobalamin. Because of these considerations, all (b) (4) patients should have regular assessments of vitamin B<sub>12</sub> levels to assure long-term effectiveness (easily monitored using widely available clinical assays) and compliance with daily dosing. Patients with nasal pathology that may result in erratic vitamin B<sub>12</sub> absorption should not be prescribed (b) (4) and patients should not use (b) (4) within several hours of administering other intranasal drugs.

### 9.2 Recommendation on Regulatory Action

I recommend APPROVAL of this 505(b)(2) new drug application based on my clinical review of the efficacy and safety data.

### 9.3 Recommendation on Postmarketing Actions

None.

#### 9.3.1 Risk Management Activity

None.

#### 9.3.2 Required Phase 4 Commitments

None. The Sponsor requests a full waiver of pediatric studies, claiming that (b) (4) does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and that (b) (4) is not likely to be used in a substantial number of pediatric patients. Based on these considerations, a full waiver of pediatric studies is acceptable.

### 9.3.3 Other Phase 4 Requests

None.

### 9.4 Labeling Review

For the package insert, please see the separate Microsoft Word document that has my tracked changes with explanations (where applicable).

### 9.5 Comments to Applicant

None – except for my revisions to the proposed label.

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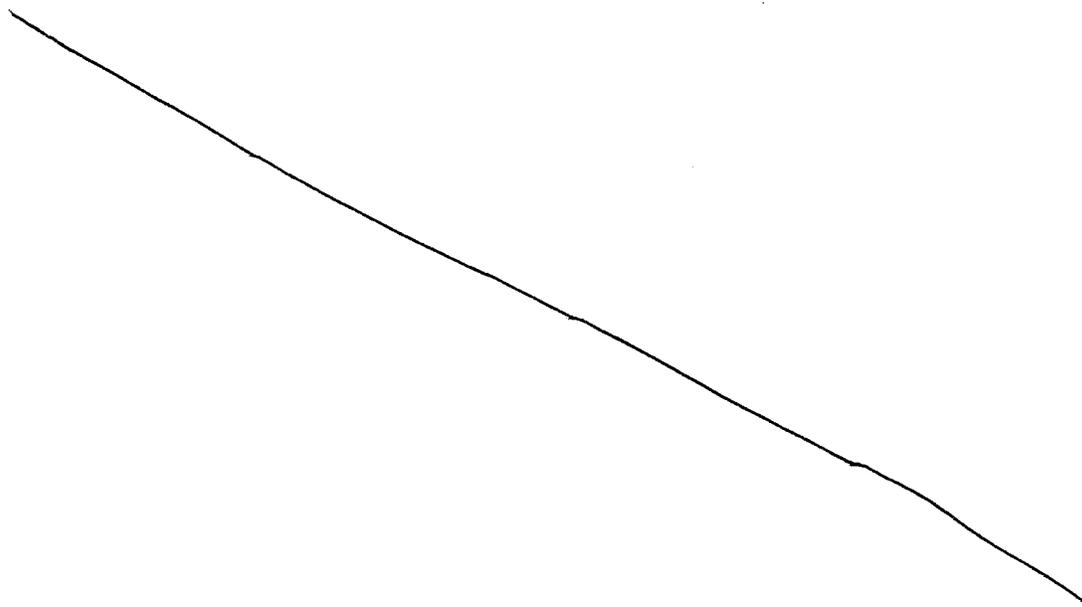
## 10 APPENDICES

### 10.1 Review of Individual Study Reports

Pivotal Study PR99-063 is reviewed in detail in Sections 6 and 7.

Below are the individual plots of vitamin B<sub>12</sub> levels by visit for Patients 501, 502, and 514. These patients had comparable vitamin B<sub>12</sub> levels at Visits 1 and 2, and relatively stable or slightly declining vitamin B<sub>12</sub> levels at Visits 3-6 (See Section 6.1.4).

**Figure 10.1. Vitamin B<sub>12</sub> levels by visit for Patient 501**



b(4)

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## 10.2 Line-by-Line Labeling Review

Please see the separate Microsoft Word document that has tracked changes with explanations (where applicable).

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