Two hundred healthy adult volunteers, male and female, ages 18 to 60 years old were to be enrolled.

10.1.1.8 Inclusion Criteria

- Gender: male or female
- Ethnic origin: no restriction
- Age: between 18 and 60 years of age
- Body mass index: males; 19-30 $kg.m^2$; females: 19-32 kg/m^2
- Medical history without clinically relevant pathology as judged by the Investigator
- All physical examination parameters without signs of clinically relevant pathology as judged by the Investigator
- Computerized electrocardiogram recording (simultaneously recorded 12-leads) without signs of clinically relevant pathology as judged by the Investigator, in particular QTc (Bazett) < 430 (males) or <450 (females)
- All values for hematology, blood coagulation and fro clinical chemistry tests of blood and urine within the normal range or showing no clinically relevant deviation as judged by the Investigator. Transaminases and bilirubin should be < 1.5 times the upper limit of normal (ULN).
- Lung function tests with the normal range or showing no clinically relevant deviation as judged by the Investigator.
- Female subjects of childbearing potential must be practicing and effective method of contraception by oral contraceptive hormones or use of an intrauterine device. In addition, a barrier method (diaphragm, condoms or spermicidal) must be used during the eight-week study period. All women of childbearing potential must demonstrate a negative urine pregnancy test both at screening and at Day-1.
  All women are considered to be of childbearing potential unless they have:
  (1) not had a menstrual cycle for more than one year after menopause; or
  (2) had surgery to remove the uterus and/or both ovaries.
- All parameters will be determined within four weeks before the actual start of the study.
- Subject will have given written informed consent prior to his/her inclusion in the study and before any study-related activities will be carried out.
- Subjects taking part in the PK study and undergoing arterial and capillary blood gas analysis must have a positive Allen test during screening.

10.1.1.9 Exclusion Criteria

- Evidence of clinically relevant pathology or disease as judged by the Investigator
- Findings of acne or eczema during physical examination
- Mental handicap
- Legal incapacity or limited legal capacity

- And history of, or indication of, clinically important emotional, psychiatric or neurological illness or epilepsy as judged by the medial Investigator
- Known hypersensitivity to the study treatment, including vitamin B_{12}, or a constituent of the study treatment
- Any history of moderate or severe hypertension, hypotension or orthostatic hypotension
- Heart rate < 43 beats per minute
- Any history of bleeding disorder
- History of relevant drug and/or food allergies, e.g., anaphylactic, anaphylactoid reactions.
- Strict vegetarians
- Regular treatment with medications during three months prior to drug administration.
- Use of any prescription or non-prescription medication, including Vitamin C, multi-vitamin preparations and food supplements, except oral contraceptive hormones or hormonal replacement therapy, within 14 days prior to study drug administration and for the duration of the entire study.
- Short-term (400-2400 mg per os per day for up to 3 days) ibuprofen therapy will be accepted once during the duration of the eight-week study. Authorized treatments in case of intolerance of the infusion are mentioned in the protocol.
- Participation in a clinical study within 90 days prior to study drug administration
- Donation of blood within 90 days prior to study drug administration.
- Receipt of blood or plasma derivatives one year prior to study drug administration
- Smoking in subjects participating in the PK study only, due to logistical constraints.
- Any history of alcohol abuse or drug addiction
- Positive screen for drugs of abuse (opiate class, cocaine and metabolites, amphetamines' methamphetamines, cannabinoids, benzodiazepines, tricyclic antidepressants, methadone, barbiturates) and alcohol (urine test) at screening or on admission
- Positive screen for HBsAg, anti-HCV or anti-HIV 1 & 2.
- Consumption of abnormal quantities of coffee or tea (more than 5 cups, 750 mL, per day.
- The subject is a pregnant female or a breast-feeding mother or is planning a pregnancy during the course of the study
- Any disease, finding or condition, which in the Investigator's opinion would exclude the subject from the study.

10.1.1.10 Methods and Procedures

Subjects were to be initially screened and consent was to be obtained between two and 28 days prior to administration of study drug (Day -28 to -2). At that time, screening was to include a 12-lead ECG; serology for HBsAg, anti-HCV, and anti HIV 1&2; blood biochemistry, hematology, and coagulation tests; urinalysis, spirometry, pregnancy testing, when appropriate, for female subjects; and an Allen Test for subjects participating in the PK evaluation for the 5 and 10-g dose groups.

The day before study drug administration, subjects were to be hospitalized at which time they were to undergo screening to determine eligibility, which was to include recording of

medications, a complete physical examination, vital sign assessment, a 12-lead ECG, screening for drugs of abuse and alcohol, and, when appropriate, a pregnancy test. Randomization was to occur following the completion of all assessments.

Subjects were to be randomized to one of the four sequential dose groups described in the table below. The study drug, i.e., hydroxocobalamin (OH-Co) or saline placebo, was to be given as a single intravenous infusion of the duration indicated in the same table.

Table 21 Dosing groups and infusion durations

Dose Group [by grams of OH-Co]	Number of Subjects per Treatment Group		Duration of Infusion (min.)	Pharmacokinetic Population	
	Hydroxocobalamin	Saline		Male	Female
2.5 g	9	3	7.5	6	6
5 g	66	22	15	8	8
7.5 g	9	3	22	6	6
10 g	66	22	30	8	8

Prior to dosing on Day 1, the following were to be performed:

- Urinalysis
- 12-lead ECG (3 tracings with the 60-minute period before dosing)
- Vital signs (3 assessments with the 60-minute period before dosing)
- Monitoring by telemetry beginning at 1 hour prior to dosing
- Clinical laboratory assessments of blood chemistry, hematology, coagulation
- Spirometry
- Neurological assessments
- Adverse events assessment
- Local tolerability assessments
- Spot urine sampling for PK analysis before start of infusion

For subjects in each of the dosing groups who were to participate in the PK portion of the trial, blood was to have been drawn prior to dosing for baseline assessment, and, in the 5 and 10-g dose group subjects, additional blood was to have been collected for arterial and capillary blood gas measurements.

Study medication was to have been administered over the time period specified in the table above. A volume of saline equal to that of the hydroxocobalamin (each 2.5 g of freeze dried hydroxocobalamin was to have been diluted with 100 mL of normal saline) for each dose group was to have been administered as the placebo. To preserve initial double blinding, the containers with test drug were to have been wrapped to prevent observation of the red color of the hydroxocobalamin. Black tubing was to have been used to conceal the color of the infusate. Administration was performed through an independent physician who was not involved with any other study procedures.

After completion of the first dose group, an interim safety review of the group was to have taken place. The second dose group was to start after completion of the safety review for the first group provided no safety issues were identified. The same procedure was to have been followed for the subsequent dose groups.

Tolerability of the infusion rate was to have been assessed by the occurrence of significant adverse events including anaphylactoid reactions, cardiovascular intolerance (shortness of breath, chest tightness or pain, lightheadedness or dizziness) and gastrointestinal discomfort (nausea, vomiting, abdominal pain, or diarrhea). The occurrence of any combination of these symptoms in greater than 50% of the subjects in the group constituted grounds for abandonment of the infusion rate used for that group. (The proposed infusion rates were considered "rapid" but necessary to treat acute toxicity.) In the event that subjects were not able to tolerate the infusions at the rates specified in the table above, the Investigator was to have been permitted to restart the respective group with a new group of randomized subjects per dose and to extend the duration of infusion to 15 minutes for the 2.5-g dose group, 30 minutes for the 5-g dose group, 45 minutes for the 7.5-g dose group and 60 minutes for the 10-g dose group. In this case, the PK samples were to be collected at the alternative times specified in the table below; all other clinical assessments and PK samples were to have been performed as prespecified.

Table 22 PK sampling times based on tolerability of study drug infusions

Dose Group	PK sampling routine (initial or alternative)	Time of PK samples (minutes following start of infusion)		
		1st sample	2nd sample	3rd sample
2.5 g	Initial	4	7.5	N/A
	Alternative	5	10	15
5 g	Initial	5	10	15
	Alternative	10	20	30
7.5 g	Initial	5	10	22
	Alternative	10	20	45
10 g	Initial	10	20	30
	Alternative	20	40	60

The table below identifies the procedures that were to have been performed following initiation of study drug infusion and the times at which they were to have been performed.

Table 23 Safety assessments and their timing

Procedure	Time to be performed following start of study-drug infusion (all times are referenced to the completion of study drug infusion unless specified otherwise)
Vital Signs	q 5 min during infusion; then q 10 min for 2 hours; then at 3, 4, 8, and 12 hours.
12-lead ECG	at end of infusion; then q 30 minutes for 1 hour; then at 2, 4, 6, 8 and 12 hours
Telemetry	from 1 hour before dosing until approximately 6 hours
Chemistry, Hematology, and Coagulation Assessments	at 2, 4, and 12 hours
Spirometry	2 and 6 hours
Neurological Evaluations	at the end of the infusion and at 1, 2, 3, 4, 8 and 12 hours
Adverse Events	at the end of the infusion and at 0.5, 1, 2, 3, 4, 5, 6, 8 and 12 hours; spontaneously reported AE were to be recorded as they occurred
Local Tolerability Assessment	at end of infusion and at 2, 4 and 12 hours
Brief Physical Examination	at 2 hours

In addition to the evaluations described above, the first eight subjects randomized in the 5-g and 10-g dose groups were to have two PK samples collected at the end of the infusion and 10 minutes after the end of the infusion to document safety and tolerability. The timing of the remaining PK samples was specified in the protocol; they are examined in detail in the biopharmaceutical review.

The table below indicates the safety assessments that were to have been made on the days following the infusion of the study drug. Those subjects not participating in the PK part of the protocol were to have been released from the study center at the end of Day 3

Table 24 Safety assessments on the days following treatment with study drug

Assessment	Day 2	Day 3	Day 4 (1st ambulatory visit)	Day 8	Day 15	Day 28 (end of study)
Vital signs	X	X	X	X	X	X
Physical Exam	X	X		X	X	X
12-lead ECG	X	X	X	X	X	X
Chemistry Hematology and Coagulation	X	X	X	X	X	X
Urinalysis	X			X	X	X
Spirometry	X		X	X		X
Adverse Events	X	X	X	X	X	X
Local Tolerability	X		X	X		X

Subjects participating in the PK evaluations were to have additional blood sampling and urine collections performed during the follow-up sessions including a special session designated specifically for these subjects on Day 5 of the study.

In the event that pathological findings were noted post-treatment, the Investigator was to have provided follow-up of these findings until they resolved or could be otherwise explained as not related to the treatment.

10.1.1.11 Analysis Plan

The objective of the study was to assess safety and tolerability of four single intravenous doses of hydroxocobalamin compared to placebo during administration, immediately following administration and during a 4-week follow-up period.

The sample size selected was not based on a power calculation, as no hypothesis was being tested, rather it was considered sufficient to adequately reach the study objectives. No statistical tests were to be performed on the data. The safety parameters assessed were to be analyzed in a descriptive fashion.

10.1.1.12 Protocol Amendments and Changes in the Planned Analysis

The protocol was amended three times. The first amendment was made on September 7, 2004. It was primarily administrative in nature, but included the addition of two urine sample collections in the PK subgroups. The first additional urine sample was to be collected prior to dosing of study drug; the second was to be collected from 48 to 72 hours following the start of the test drug infusion. None of the changes made would be expected to impact significantly on the findings.

The second amendment was made on October 14, 2004. It was made to institute minor administrative changes and to comply with recommendations issued by the Ethics Committee overseeing the study regarding the replacement of subjects participating in the PK analysis subgroups who do not complete the study. Specifically, the amendment defined "non-completer" subjects as those who prematurely terminated the study due to other than study drug related reasons. Those who terminated the study up to 96 hours after the end of infusion of the study drug were to be replaced; those who terminated more than 96 hours after the end of the infusion were not to be replaced. The mechanism by which replacements were made is the subject of the biopharmaceutical review, but would not be expected to impact significantly on the study's safety and tolerability findings provided reasons for subject termination are appropriately captured and reported.

The third amendment was made on March 4, 2005. The changes included the following:

- The informed consent document was modified to include adverse event findings and laboratory parameter elevations noted in the study to date.
- The informed consent document was modified to allow an additional blood sample for genotyping experiments that would assess whether patients with a single nucleotide polymorphism at position -786 in the promoter of the *nos-3* gene were more susceptible to the blood pressure changes observed in subjects studied to date. It was speculated that the production of nitric oxide (NO) synthase, if altered by a mutation of the *nos-3* gene, would affect local levels of NO in the vascular walls and possibly render subjects more vulnerable to blood pressure changes with administration of hydroxocobalamin due to its ability to scavenge NO. Subjects who already completed the study were to be contacted and asked to participate in this additional testing.
- Subjects were to drink at least 1750 mL of water during the time period of immediately prior to infusion of study drug until 6 hours post-dose due to high urinary concentration of hydroxocobalamin observed in some subjects who received 5 g of the drug. In addition, two additional urine-sediment samples were to be evaluated at 6 and 12 hours post dosing.
- An additional β-hCG test was to be added to the blood work done at screening due to pregnancy in one subject that was not immediately noted secondary to a negative urine test.
- An additional blood pressure measurement at 2 minutes after the start of the infusion was added to the protocol due to the observed increase in blood pressure at the first planned assessment.

These changes would not be expected to adversely affect the study outcome; rather they would likely provide additional data to characterize the safety profile and safe use of hydroxocobalamin.

10.1.1.13 Study Conduct

10.1.1.13.1 Subject Disposition

In all, 586 subjects were screened, and 136 were randomized into the study. All but one of the randomized subjects received the scheduled dose and completed the study according to the

protocol. In one subject, the infusion was discontinued prematurely due to an allergic reaction. This subject was randomized to receive 10 g of study drug, but the infusion was stopped after 3.9 g had been administered over slightly less than 12 minutes.

A total of 200 healthy subjects were to have been enrolled; however, the study was terminated for tolerability reasons after only 24 of the anticipated 88 subjects in the 10-g dose group had received study drug.

10.1.1.13.2 Protocol Deviations

The following deviations were reported for the study:

1. In the 2.5-g dose group, there were to have been 12 subjects, including 6 males and 6 females. However one of the females dropped out of the study for personal reasons on Day 1 prior to study-drug treatment. She was replaced by an already recruited female subject who had to be excluded due to elevated blood pressure. As there were only male subjects available for substitution, the Sponsor elected to use this individual rather than delay the study. Thus, the 2.5-g dose group was comprised of 5 females and 7 males of whom, 2 males and 1 female received placebo and 5 males and 4 females received hydroxocobalamin.
2. Due to technical problems and resulting interruptions during the infusion, Subject 1010 (a female) who was to receive 2.5 g of hydroxocobalamin over 7.5 minutes, actually received the drug over 14 minutes. The longest delay in the infusion was 3 minutes and 50 seconds. Despite the delays, the entire volume of test drug was administered.
3. No alcohol test was administered to subjects who were examined prior to October 8, 2004. The Sponsor elected to allow these seven subjects to enroll without additional examination prior to Day -1; however, the alcohol test at admission on Day 1 was required to be negative.
4. Subject 2012 reported pregnancy on December 17, 2004. She had received a 5-g dose of hydroxocobalamin on November 15, 2004 following a negative urine pregnancy test. Her gynecologist estimated her to be in the fourth week of gestation at the time she received the study drug. The subject was followed until she delivered a healthy baby on b(6)
5. Paracetamol was administered to three subjects for the treatment of headache (subject no. 2010), common cold (subject no. 2086) and pain at the arterial cannula site (subject no. 4016) and as part of a combination medication to three subjects (nos. 1004, 2029, and 2064) for treatment of common cold. Acetylsalicylic acid alone was taken by three subjects for headache (nos. 2087 and 4020) and for common cold (no. 2071).
6. For the adverse events "redness of skin" (MedDRA preferred term "erythema") and "red colored urine" (MedDRA preferred term "chromaturia"), the original coding "severe" was replace by "intense" in the text, since the conditions did not interfere with usual daily activities.
7. Blood pressure measurements were to be taken at 2 minutes following the initiation of study drug infusion as per a protocol amendment. Four subjects did not have this measurement taken.

8. SGPT (ALT) was assessed by two different methods. The Sponsor decided that a clinically relevant deviation from normal ranges (2.5 times above the ULN) was only considered an adverse event if it was confirmed by both methods.

10.1.1.13.3 Protocol Termination

A marked increase in adverse events was observed with subjects in the 7.5-g dose group compared to the two lower-dose groups. At the 10-g dose, a second case of an allergic reaction occurred in one subject and required corrective treatment, in addition an increase in blood pressure lasting several days occurred in another subject. Also at the 10-g dose, there was an increase in the symptoms of chest discomfort, throat tightness, dry throat, dyspnea and cough. At this dose, an increase in injection site reactions was noted compared to the 5-g dose group. The Sponsor expressed concern that the benefit-risk ratio was inadequate to warrant further testing in healthy volunteers; the Division concurred, and the study was concluded prematurely.

10.1.1.14 Demographics/Group Comparability

All but one of the 136 subjects was Caucasian; the remaining subject was Asian. The subjects were almost evenly split between males and females, 51% and 49%, respectively. All subjects were healthy and ranged in age from 18 to 59 years.

10.1.1.15 Treatment Compliance

The study required a single intravenous administration of study drug that was initiated and supervised by a physician. Compliance was therefore 100%.

10.1.1.16 Unplanned Analyses

The statistical analyses were performed according to the amended study protocol. The amended analyses were designed to investigate the relationship of the safety results to pharmacokinetic data; they were planned and described before the database was locked.

10.1.1.17 Sponsor's Efficacy Results

Not applicable.

10.1.1.18 Sponsor's Safety Results

The results of this study are described and discussed in detail in Section 7 of this review.

10.1.1.19 Discussion of Safety Findings

This study was important as it identified the risks associated with administration of hydroxocobalamin to patients in whom there has been no exposure to cyanide or for whom more hydroxocobalamin is administered than is necessary to treat the cyanide exposure. Comments on the safety findings are included in Section 7.

10.1.1.20 Conclusions

This study demonstrated the overall safety for the 5-g dose of hydroxocobalamin in a non-cyanide exposed patient population. It suggests that the 10-g dose may be tolerated in cyanide-exposed patients who are suffering from the cardiovascular effects of cyanide poisoning. In addition to characterizing the pharmacokinetics of hydroxocobalamin, the study also provided a detailed summary of the interference generated by hydroxocobalamin on the measurement of clinical laboratory parameters.

10.1.2 Baud-1 Study

"Baud-1 Study – Efficacy and safety of hydroxocobalamin in fire victims. Open-label, prospective study in 69 patients"

10.1.2.1 Overall Design and Summary of Findings

An earlier version of this study report served as the key clinical study to support the registration of Cyanokit in France in 1996.

10.1.2.2 Study Plan

This was an open-label study conducted in France between 1987 and 1994 involving adult smoke inhalation victims rescued by the Paris Fire Brigade and treated either at the site of the fire on in the hospital with a hydroxocobalamin infusion and admitted to the intensive care unit (ICU) of the ——————— b(6)

Patients were assessed at the scene prior to the administration of antidote, at the end of the infusion of hydroxocobalamin, on admission to the ICU, and on hospital days: Day 1, Day 2 and Day 3 in the ICU.

Data for patient records were more recently gathered in an effort to more thoroughly characterize the efficacy and safety results of this study. The information from the updated datasets is used in the report described herein and in a cardiovascular safety report described below in this review.

10.1.2.3 Objectives

> *Primary*: To evaluate the clinical efficacy of hydroxocobalamin in patients intoxicated by cyanide from smoke inhalation
>
> *Secondary*: To evaluate the safety of hydroxocobalamin in patients with suspected cyanide poisoning due to smoke inhalation.

10.1.2.4 Design

This was a prospective, open-label, uncontrolled, single-site study with subsequent retrospective collection of additional data from patient hospital records.

Due to the difficulty of administering a multi-component cyanide antidote, such as the Cyanide Antidote Kit, at the scene of a fire and because of the risks associated with methemoglobinemia secondary to the nitrites contained in such antidotes, the Investigator decided to conduct the study without a comparator.

10.1.2.5 Primary Efficacy Variable

Patient survival

10.1.2.6 Secondary Efficacy Variables

- Systolic and diastolic blood pressures measured at the accident scene, before and after hydroxocobalamin infusion and on admission to the ICU.
- Heart rate determined concomitantly with blood pressure.
- Neurological status (psycho-organic syndrome, coma) assessed on arrival of emergency medical services and at hospital discharge
- Response to hydroxocobalamin at the end of each infusion of 5.0-g dose (retrospectively evaluated by the Investigator): positive, negative, partial or unknown, based on blood pressure response, alterations in plasma lactate and neurological changes

10.1.2.7 Safety Variables

- Cyanide and carbon monoxide concentrations in the blood, on a blood sample obtained at the scene of the fire, on admission to the hospital (Day 0), and then on Days 1, 2, and 3 in the ICU
- Plasma lactate
- Creatinine
- Glycemia
- Total bilirubin
- Alkaline phosphatase
- Serum transaminases: aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
- Prothrombin index
- creatine phosphokinase (CK)
- complete blood count (CBC) including red blood cell count, hemoglobin, hematocrit, white blood cell count and differential, and platelet count
- presence or absence of rash, urticaria, edema, bronchospasm and anaphylactic shock
- (retrospectively) all adverse events and complications as found in fire or emergency medical services' reports and the patients' progress notes and discharge summaries from the ICU
- Any event reported by the Investigator as and adverse event r occurring within 7 days following hydroxocobalamin administration

10.1.2.8 Population

A total of 69 patients suffering from smoke inhalation and presumed cyanide poisoning were enrolled in the study and treated with hydroxocobalamin.

10.1.2.9 Inclusion Criteria

- Smoke inhalation victims examined at the accident scene by the medical emergency team of the Paris Fire Brigade
- Patients over 15 years of age
- Presence of soot in the mouth and expectoration
- Patients with altered neurological status characterized by either:
  - Impaired consciousness: coma, drowsiness, restlessness, transient loss of consciousness when found by the rescue workers, or
  - Disturbances of higher function (psycho-organic syndrome)a: confusion, slowness of thought
- Cyanide intoxication was confirmed retrospectively by assay of the sample taken at the accident scene before antidotal treatment.

10.1.2.10 Exclusion Criteria

- Children under 15 years of age
- Women who were obviously pregnant
- Multiple trauma victims
- Victims with at least second degree burns over 20% of body surface area and those with severe burns on the face and neck

10.1.2.11 Methods and Procedures

On discovery of a smoke-inhalation victim by the emergency medical team, an intravenous line was to have been established and blood samples were to have been taken for cyanide and carbon monoxide analyses. Oxygen was to be administered to all patients via mask or after intubation, by mechanical ventilation.

Each victim was to have been administered a hydroxocobalamin dose of 5 g as an infusion over 15 to 30 minutes. An additional one or two 5-g doses of hydroxocobalamin could be administered as needed if only a partial response was obtained. At the same time, supportive measures based on the patient's condition were to be instituted, e.g., volume replacement, assisted ventilation, administration of catecholamines, etc.

Blood pressure and heart rate were measured on discovery, prior to and after administration of OH-Co, and on hospital admission. On hospital admission, an arterial blood sample was taken for lactic acid assay.

Patient outcomes were to be determined based on demise during hospitalization, discharge of survivors from the hospital, and the neurological status of the patients at the time of their discharge.

10.1.2.12 Analysis Plan

Summary statistics were to be provided for demographics, hydroxocobalamin dosing parameters, clinical status at the time of presentation, and patient outcomes.

10.1.2.13 Protocol Amendments and Changes in the Planned Analysis

No protocol amendments were made.

10.1.2.14 Study Conduct

10.1.2.14.1 Subject Disposition

A total of 69 victims were rescued, treated and admitted to the hospital and evaluated.

10.1.2.14.2 Protocol Deviations

None were reported, although the study report stated that initially, the study protocol, approved by the ethics committee, included a control group of patients not treated with hydroxocobalamin; however, for ethical reasons at the outset of the study, the Paris Fire Brigade decided that all patient must be treated with hydroxocobalamin.

10.1.2.14.3 Protocol Termination

The protocol was designed to evaluate those patients brought to the Fernand Widal Hospital by the Paris Fire Brigade between 1987 and 1994 following treatment with hydroxocobalamin for suspected cyanide toxicity in association with smoke inhalation. In that regard, the study terminated as planned.

10.1.2.15 Demographics/Group Comparability

The 69 patients who were involved in the study included 36 (52%) women and 33 (48%) men. The patients ages ranged from 20-94 years old with a mean of 49.6 years (SD = 20 years). Fifteen patients (22%) were $\geq$ 65 years old, and of those, 10 (15%) were $\geq$ 75 years old. There were 26 patients (38%) who had suffered burns. At baseline, 42 patients (61%) had toxic blood levels of cyanide ($\geq$ 39 mmol/L); 57 (83%) had toxic blood levels of carbon monoxide ($\geq$ 1 mmol/L); and 66 (96%) had altered neurological status.

10.1.2.16 Treatment Compliance

Treatment was administered by rescuers. Compliance was thus assured.

10.1.2.17 Unplanned Analyses

At the request of the Division, the Sponsor attempted to retrieve additional data from available sources to compile the most thorough safety data base possible and to analyze the data in light of information from similar studies for an assessment of safety issues when hydroxocobalamin is used in the setting of suspected cyanide poisoning.

10.1.2.18 Sponsor's Efficacy Results

The Sponsor reported clinical outcomes as summarized in the table below.

Table 25 Clinical Outcomes for the Study

Clinical Outcome	Number of Patients (%)
Survival	50/69 (72%)
Death	19/69 (28%)
Causes of Death:	
Decerebration	13/19 (68%)
Septic Shock	5/19 (26%)
Hypoxemic Pneumonia	1/19 (5%)
Neurologic Symptoms:	
On Initial Examination	66/69 (96%)
Resolved	38/66 (58%)
Neuropsychiatric Sequelae at Discharge	9/66 (14%)
Patient Death	19/66 (29%)

Blood cyanide levels (BCN) were not available for 6 patients. The Sponsor indicated that BCN levels were not followed by repeated measurements because of the short half life (approximately 1 hour) in man. The range of the BCN for the 63 patients evaluated was 0 μmol/L -250 μmol/L with a median value of 52 μmol/L. The median age for these patients was 42.5 years and the range was 21 to 89 years. Nine of the patients were ≥ 65 years old, and six were ≥ 75 years of age. Eleven of these patients were noted to be in cardiac arrest when emergency personnel arrived at the scene of the fire.

The predefined threshold BCN levels for toxicity and potential lethality were 39 μmol/L and 100 μmol/L, respectively. [Note: a threshold of 40 μmol/L was used for review purposes to maintain consistency between studies. The numbers of patients classified into the different groups were

not affected by this nominal change.] Of the 60 patients who had documented BCN levels, 42 had toxic levels of cyanide, i.e., BCN ≥ 40 μmol/L, and of these, 28 (67%) survived. The survival rate was further subdivided as follows:

- 17 (74%) out of 23 patients with initial BCN ≥ 40 μmol/L and < 100 μmol/L survived
- 112 (58%) out of 19 patients with initial BCN concentrations ≥ 100 μmol/L survived

It was noted that all but one of the cyanide-poisoned patients also initially showed altered neurological status, which varied from impaired consciousness to coma. Following OH-Co treatment, the neurological symptoms resolved in 21 (50%) cases. Six patients were reported to suffer from neurological sequelae at the time of discharge.

The Sponsor also noted that in the subgroup of patients with documented cyanide poisoning, of the 14 deaths, nine patients died from decerebration. The unfavorable outcomes in these patients were strongly correlated with initial cardiac arrest and with severe neurological impairment.

As for the 21 patients with documented BCN levels < 40 μmol/L, 18 (86%) survived following hydroxocobalamin treatment. The median age for these patients was reported as 45 years with a range of 0 to 94 years. The median dose of hydroxocobalamin was 5 g with a median infusion time of 30 minutes. Neurological impairment was reported in 19 of the patients and resolved in 13. Three patients had neuropsychiatric sequelae at the time of hospital discharge which manifested as memory impairment and cerebellar syndrome in one, psychomotor retardation in another and was not specified in the third. There were three deaths in this subgroup including two from decerebration, both of which occurred in patients presenting at the scene of the fire with cardiac arrest.

10.1.2.19 Discussion of Efficacy Results

The study indicated that patients with toxic levels of both cyanide and carbon monoxide can survive when treated with hydroxocobalamin. It is impossible without a comparator arm to attribute the survival to hydroxocobalamin.

It was noted that the patients who presented with high blood cyanide levels and in cardiac arrest and later died did so 2-9 days after the fire. In addition, the circulatory status of each of these patients was restored (1 patient had missing data in this regard). All the patients who died presented with GCS=3 (1 patient had missing data in this regard).

Table 26 Summary of Efficacy Findings for the Study

Parameter	BCN ≥ 40 µmol/L					BCN < 40 µmol/L				
	BCO ≥ 1 mmol/L	BCO < 1 mmol/L	In Cardiac Arrest	Not in Cardiac Arrest	Group Summary	BCO ≥ 1 mmol/L	BCO < 1 mmol/L	In Cardiac Arrest	Not in Cardiac Arrest	Group Summary
Number of Patients	36	4	11	31	42	16	3	2	19	21
Median (Mean) CN level (µmol/L)	98 (121)	64 (64)	139 (141)	89 (102)	96 (112)	13 (11)	0 (6)	11 (11)	8 (9)	8.1 (9)
Range of CN levels (µmol/L)	40-250	41-87	40-239	41-250	40-250	0-27	0-19	0-21	0-27	0-27
Survival	24 (67%)	2 (50%)	2 (18%)	26 (84%)	28 (67%)	13 (81%)	3 (100%)	0 (0%)	18 (95%)	18 (86%)
Mean Dose of OH-Co (g)	5	5	5	5	5	5	5	5	5	5
Mean Infusion time (min)	32	28	20	35	31	31	63	30	36	32
Median (Mean) Age (y)	43 (50)	51 (52)	37 (45)	49 (51)	42 (50)	49 (48)	55 (51)	36 (36)	48 (49)	46 (50)
Age range (y)	21-89	25-82	25-83	21-89	21-89	20-94	31-68	33-38	20-94	20-94
Survivors Age ≥ 65	2/8	1/1	0/2	3/7	3/9	1/2	1/1	0/0	2/3	0
Survivors Age ≥ 75	1/5	1/1	0/2	2/5	2/6	1/2	0/0	0/0	1/2	0
Survivors without neurological sequelae	18 (75%)	2 (100%)	2 (100%)	20 (77%)	21 (75%)	10 (77%)	3 (100%)	0 (0%)	15 (83%)	3/19 (16%)

10.1.2.20 Discussion of Findings

The lack of a comparator makes a definitive statement about either the efficacy or safety of hydroxocobalamin in this patient population impossible. However, the survival of some of the subjects with blood cyanide levels in excess of 100 µmol/L suggests possible efficacy. Patients who presented in cardiac arrest had the least chance of survival. Hypertension associated with hydroxocobalamin use in these patients was not an issue as most patients were suffering from the hypotensive effects associate with cyanide poisoning.

10.1.2.21 Conclusions

This study provided some evidence suggestive that hydroxocobalamin given in a 5-g dose may enhance survival. The study did not identify any safety concerns that were not already noted from the safety and tolerability study in healthy volunteers.

10.1.3 Baud-2 Study

"Baud 2 – Retrospective study of use of hydroxocobalamin in smoke inhalation victims with suspected cyanide poisoning at the fire scene and hospital ICU"

10.1.3.1 Over Design and Summary of Findings

This was a retrospective data collection and analysis of patients who were treated with hydroxocobalamin (OH-Co) for suspected cyanide poisoning due to smoke inhalation between 1988 and 2004. A total of 61 patients who suffered from smoke inhalation were included in the study. The patients were treated with OH-Co either at the scene of the fire, on admission to the hospital, or at both sites.

The findings of this study, which lacked a comparator arm, suggested hydroxocobalamin provided a survival benefit without incurring significant risk when administered to patients exposed to lethal levels of cyanide. Of the 61 patients evaluated, 34 (56%) survived to hospital discharge

Overall, the adverse events were similar to those of subjects in the healthy volunteer study and included an intense red coloring of the skin and urine, and hypertension (moderate and transient).

10.1.3.2 Study Plan

This study utilized data collected retrospectively from patients who suffered smoke-inhalation injuries related to structural fires between 1988 and 2004. The treatment of the patients was not dictated by a predefined protocol. Data were collected from the medical records of the Department of Medical and Toxicological Critical Care at Fernand Widal and Lariboisière Hospitals in Paris, France. These records included firemen's reports, medical ambulatory emergency and first aid unit reports, and hospital records. A quality control review of the database was performed by the Sponsor that included variable definitions and conventions. Statistical analyses were performed to describe the outcomes.

10.1.3.3 Objectives

This study was to provide post-marketing safety and efficacy data surrounding the use of hydroxocobalamin as it is used by emergency medical service personnel in France.

10.1.3.4 Design

The design was open-label, retrospective, uncontrolled study designed to provide post-marketing safety and efficacy data surrounding the use of hydroxocobalamin as it is administered by emergency medical service personnel in France.

10.1.3.5 Primary Efficacy Variable

- Survival

10.1.3.6 Secondary Efficacy Variables

- Changes in neurological status (primarily based on the Glasgow Coma Score)
- Restoration of circulation in patients experiencing cardiac arrest
- Toxicology parameters

10.1.3.7 Safety Variables

- Adverse events reported within seven days following hydroxocobalamin administration
- Vital signs
- Clinical laboratory assessments
- Blood gases
- Electrocardiograms

10.1.3.8 Population

Adult patients who, between 1988 and 2004, were rescued from burning buildings and had signs or symptoms suggestive of cyanide toxicity were eligible for evaluation in this study.

10.1.3.9 Inclusion Criteria

- Adult smoke-inhalation victim
- Suspected acute cyanide poisoning
- Available hospital records related to treatment following rescue

10.1.3.10 Exclusion Criteria

- None

10.1.3.11 Methods and Procedures

Data collection covered the time period from the initial patient assessment at the scene of the fire through the resuscitative efforts made in the field and the patient's hospital course until the patient either died in the hospital or was discharged. Prospective patient follow-up was not performed.

The following information was sought from the available patient records:

- Demographic data including past medical history
- Circumstances of cyanide poisoning
- Pre-hospital examination by initial rescuers including
  - Presentation in cardiac arrest
  - Presenting Glasgow Coma Score (GCS) and neurological assessment
  - ECG at the fire scene
  - Toxicology evaluation
- Presence of soot in the airways
- Timing and dose for each hydroxocobalamin administration
- Use of additional medications and therapies
- In hospital treatments, medications, and evaluations
- Hospital outcome, i.e., death or discharge

When Coma Grades were used to describe the patient's level of consciousness instead of the GCS, the following conversion table was used to allow comparison of results from this study with others.

Table 27 Conversion of Coma Grade to GCS from NDA page 33 of Volume 35 in Module 5.

Coma Grade	Corresponding Glasgow Coma Score
Absence	15
Coma Grade 1	12
Coma Grade 2	7
Coma Grade 3	5
Coma Grade 4	3

10.1.3.12 Analysis Plan

Due to the nature of the study, only descriptive results were generated for all the collected variables without statistical testing.

10.1.3.13 Protocol Amendments and Changes in the Planned Analysis

None

10.1.3.14 Study Conduct

This was a retrospective study which lacked prospective follow-up of the participants, and as such, there were no protocol deviations or premature withdrawals; all 61 subjects received treatment; and the study was not subject to possible protocol termination. The results are based solely on the available data.

10.1.3.15 Demographics/Group Comparability

Data was available for 61 subjects during the protocol-specified study period. There were nearly equal numbers of males [n=30 (49%)] and females [n=31 (51%)]. The mean age of the patients was 54 years (range: 20-92 years) with missing age data for two patients. Seventeen (28%) of the patients were > 65 years old, and eight patients (13%) were > 75 years old. It was noted that none of the patients > 75 years old were found in cardiac arrest at the scene of the fire.

Of the 41 patients for whom there was weight information, it was noted that those who were found in cardiac arrest at the scene of the fire [n=8; 20%] were heavier than those who were not: 73 kg versus 64 kg, respectively.

There was little difference in the percentage of patients who had neurological symptoms at the scene of the fire based on whether or not they were found in cardiac arrest. Of those who were found in cardiac arrest, 82% had neurological symptoms; whereas, 84% of those not found in cardiac arrest were noted to have neurological symptoms.

10.1.3.16 Treatment Compliance

Treatment was administered by emergency rescue and hospital personnel; therefore, treatment compliance was assured.

10.1.3.17 Unplanned Analyses

As the study was retrospective in design, there were no unplanned analyses conducted.

10.1.3.18 Sponsor's Efficacy Results

The table below summarizes the survival findings based on the Sponsor's reported results.

Table 28 Summary of Efficacy Findings for the Baud-2 Study

Parameter	BCN ≥ 40 µmol/L					BCN < 40 µmol/L				
	BCO ≥ 1 mmol/L	BCO < 1 mmol/L	In Cardiac Arrest	Not in Cardiac Arrest	Group Summary	BCO ≥ 1 mmol/L	BCO < 1 mmol/L	In Cardiac Arrest	Not in Cardiac Arrest	Group Summary
Number of Patients	7	1	3	5	8	28	25	14	39	53
Median (Mean) CN level (µmol/L)	81 (104)	68 (68)	67 (89)	81 (106)	75 (99)	12 (15)	8 (12)	21 (22)	7 (11)	9 (14)
Range of CN levels (µmol/L)	47-165	N/A	47-154	62-165	47-165	3-38	4-29	9-38	3-30	3-38
Number in Cardiac Arrest	3	0	3	0	3	6	8	14	0	14
Survival	4 (57%)	1 (100%)	0 (0%)	5 (100%)	5 (63%)	14 (50%)	15 (60%)	1 (7%)	28 (72%)	29 (55%)
Mean Dose of OH-Co (g)	8.6	2.5	13.3	4.5	7.8	6.4	7.6	9.2	6.2	7.0
Mean Infusion time (min/1g of OH-Co)	22	Not known	27	6	22	6	14	18	5	10
Median (Mean) Age (y)	48 (51)	60 (60)	42 (39)	60 (60)	49 (53)	58 (55)	52 (55)	50 (51)	53 (56)	52 (51)
Age range (y)	29-79	N/A	29-48	50-79	29-79	20-87	22-92	22-73	20-92	20-92
Survivors Age ≥ 65	2/2	N/A	N/A	2/2	2/2	3/8	4/8	0/3	7/13	7/7
Survivors Age ≥ 75	1/1	N/A	N/A	1/1	1/1	2/4	1/3	0/2	2/7	2/2
Survivors without neurological sequelae	3 (75%)	1 (100%)	N/A	3 (60%)	3 (60%)	10 (71%)	9 (60%)	0 (0%)	19 (49%)	19 (66%)

Twenty-four patients (39%) died while hospitalized; 34 patients (56%) survived to hospital discharge. Death occurred, on average, six days following the fire.

Only one of the 17 patients (6%) who presented in cardiac arrest survived compared to 33 of the 44 patients (75%) who did not present in cardiac arrest and survived. Those who were found in cardiac arrest at the scene of the fire had their circulation restored by the time of hospital admission.

10.1.3.19 Discussion of Findings

As with the Baud-1 Study, this study indicated an increased survival rate occurred for patients who did not present in cardiac arrest compared with those who did. Also noted in this study was

survival in patients who presented with lethal blood levels of cyanide, which suggested a degree of efficacy for hydroxocobalamin use; however, the lack of a comparator arm makes this impossible to confirm. In this study, as in Baud-1, patients who presented in shock secondary to cardiac arrest were noted to have circulation restored as hydroxocobalamin was administered; hypertension was not an issue associated with hydroxocobalamin alone.

10.1.3.20 Conclusions

This study provides data suggestive of efficacy for hydroxocobalamin use in smoke-inhalation patients with exposure to lethal levels of cyanide. Efficacy cannot be confirmed, however, due to lack of a control arm in the study.

10.1.4 Baud-3 Study

"Treatment with hydroxocobalamin in severe acute cyanide poisoning by ingestion or inhalation"

10.1.4.1 Over Design and Summary of Findings

This study was conducted between 1988 and 2003 and consisted of the retrospective analysis of clinical cases involving patients poisoned by massive doses of cyanide which were either ingested or inhaled from sources other than fire. Patient laboratory assessments for the first three days of their hospital admission were evaluated, as was patient neurological status at the time of hospital discharge when applicable.

Despite limitations of the no-comparator, open-label design of the study and the use of alternative antidotes for cyanide poisoning in addition to hydroxocobalamin, the study raised no special concerns about patient safety and appeared to support the efficacy of Cyanokit for use in treating patients with lethal blood levels of cyanide. The study was unique among the human studies submitted to the NDA in that it evaluated patients whose exposure to cyanide was not due to smoke inhalation and, therefore, not part of a multi-toxin exposure, it evaluated patients with cyanide exposure by ingestion, and it evaluated safety and efficacy for a number of patients with blood cyanide levels well above lethal levels. In these regards, a 71% survival rate and the lack of neurological sequelae in 90% of the patients who survived their cyanide poisoning was highly suggestive of efficacy. Unfortunately, the use of additional cyanide antidotes in six patients confounds the ability to view the data as supportive of OH-Co efficacy more so than the limitations of study design alone.

10.1.4.2 Study Plan

In an effort to evaluate the efficacy and safety of hydroxocobalamin for treating cyanide poisoning due to causes other than smoke inhalation associated with fires, the Sponsor retrospectively analyzed data gathered from Fernand Widal and Lariboisière Hospitals in Paris, France.

10.1.4.3 Objectives

The objective of this study was to assess the efficacy and safety of hydroxocobalamin in patients with cyanide-only poisoning.

10.1.4.4 Design

The study was designed to provide information on the safety and efficacy of hydroxocobalamin as used in France for treating patients in settings of cyanide poisoning unrelated to fires. As such, the study was retrospective, open-label and uncontrolled. The treatment of subjects was not part of a predefined study protocol.

10.1.4.5 Primary Efficacy Variable

- Patient survival

10.1.4.6 Secondary Efficacy Variables

- Changes in neurological status
- Changes in vital signs

10.1.4.7 Safety Variables

- Adverse events
- Critical laboratory values
- Electrocardiographic changes

10.1.4.8 Population

The database consisted of all admissions to the toxicological intensive care units at Fernand Widal and Lariboisière Hospitals for the treatment of cyanide poisoning with hydroxocobalamin since the first use of hydroxocobalamin in these institutions in 1988 until 2003.

10.1.4.9 Inclusion Criteria

- Medial records of patients with a diagnosis of cyanide poisoning by ingestion or inhalation and treated with hydroxocobalamin were evaluated

10.1.4.10 Exclusion Criteria

- Cases involving smoke inhalation were excluded.

10.1.4.11 Methods and Procedures

Medial records of patients who met the inclusion and not the exclusion criteria were reviewed to find the following information:

- Patient demographics
- Circumstances of poisoning
- Clinical presentation
- Antidotal and supportive treatments provided from prehospital medical intervention until discharge
- Dose of hydroxocobalamin administered and time between poisoning and OH-Co treatment
- Critical laboratory values
- Neurological symptoms
- Glasgow Coma Score
- Vital signs
- Adverse events
- Duration of hospital stay and outcome

Medical records included reports from fire or emergency medical services, detailed patient progress notes, and discharge summaries from the ICU. Any untoward event that occurred within seven days following hydroxocobalamin administration was classified as an adverse event.

In cases where coma stages were reported instead of a Glasgow Coma Score (GCS), the coma stage was converted to a GCS based on the following table.

Table 29 Conversion from Coma Stage to Glasgow Coma Score

Coma Stage	Glasgow Coma Score
Absence	15
Coma Stage I	12
Coma Stage II	7
Coma Stage III	5
Coma Stage IV	3

10.1.4.12 Analysis Plan

Because of the retrospective non-comparative design of the study, all results were presented descriptively without any statistical testing.

10.1.4.13 Protocol Amendments and Changes in the Planned Analysis

As the study was retrospective, there were not protocol amendments, and no changes were made to the planned analyses.

10.1.4.14 Study Conduct

A total of 14 patients with cyanide poisoning by ingestion or inhalation were treated with hydroxocobalamin between the specified dates at the two hospitals. As the study was retrospective, there were no premature withdrawals or protocol violations, nor were there any protocol violations. The retrospective design also precluded protocol termination.

10.1.4.15 Demographics/Group Comparability

The table below provides the demographics for the 14 patients evaluated in this study. All but two of the patients were men; none of the patients were over 65 years of age. An attempted suicide was the most common circumstance surrounding the poisoning and generally involved ingestion of KCN.

Table 30 Patient demographics (taken from Table 11-2 on page 30 of Volume 43 in Module 5 of the NDA)

Patient ID	Age (years)	Gender	Type of Cyanide Exposure	Circumstances of Poisoning
136	25	Male	Potassium cyanide salt	Ingested in suicide attempt
137	28	Female	Potassium cyanide salt	Ingested in suicide attempt
138	51	Male	Potassium cyanide salt (suspected)	Suspected ingestion
139	27	Male	Potassium cyanide salt	Ingested in suicide attempt
141	32	Male	Potassium cyanide salt	Ingested in suicide attempt
142	52	Male	Potassium cyanide salt	Ingested in suicide attempt
143	39	Male	Potassium cyanide salt	Ingested in suicide attempt
144	32	Female	Potassium cyanide salt	Ingested in suicide attempt
145	64	Male	Potassium cyanide salt	Ingested in suicide attempt
146	38	Male	Cyanogen bromide	Inhaled in occupational accident
147	15	Male	Mercuric cyanide	Ingested in suicide attempt
148	44	Male	Potassium cyanide salt	Ingested in suicide attempt
152	40	Male	Acetonitrile	Ingested in suicide attempt
153	22	Male	Potassium cyanide salt	Ingested in suicide attempt

10.1.4.16 Treatment Compliance

The treatments were administered by emergency care personnel and hospital staff; therefore, treatment compliance was assured.

10.1.4.17 Unplanned Analyses

The nature of the study precluded unplanned analyses.

10.1.4.18 Sponsor's Efficacy Results

The table below summarizes the demographics, baseline characteristics and initial assessments including blood cyanide (BCN) levels and vital signs for the individual patients. Two of the patients presented in cardiac arrest; one had only respiratory arrest at the time clinical care was instituted. Of the patients for whom an initial blood-cyanide level was available, all but one had a level that was substantially greater than the lethal threshold of 100 µmol/L.

Table 31 Summary of patient exposures and initial assessments.

Patient Number	Age (years)	Gender	Initial BCN (µmol/L)	Initial Blood pressure (mmHg)	Initial Heart rate (bpm)	Initial Respiratory rate (bpm)	Initial GCS	OH-Co Dose (g)	Outcome
136	25	Male	125	150/90	100	--	15	5	Survived
137[1]	28	Female	154	110/60	120	8	12	10	Survived
138	51	Male	103	0/0	0	0	3	10	Survived
139	27	Male	150	95/50	110	3	3	20	Died Day 4 (shock)
141	32	Male	125	65/--	80	--	15	10	Survived
142	52	Male	158	200/120	110	25	15	5	Survived
143[1]	39	Male	238	120/70	90	14	12	10	Died Day 3 (brain death)
144[2]	32	Female	196	0/0	0	0	3	15	Died Day 4 (brain death)
145	64	Male	260	50/0	30	--	3	10	Died Day 10 (brain death)
146	38	Male	13	130/80	72	18	15	5	Survived
147[3]	15	Male	217	100/--	120	--	15	5	Survived
148[1]	44	Male	--	80/--	120	0	3	9	Survived
152[1]	40	Male	170	90/60	80	--	15	10	Survived
153	22	Male	--	115/80	140	20	15	5	Survived
Mean (SD)	36 (13)	n.a.	159 (54)	93 (54) 56 (40)	84 (45)	10 (10)	10 (6)	9 (4)	n.a.
Range	15-64	n.a.	0-200	0-200 0-120	0-140	0-25	3-15	5-20	n.a.

[1] Patient also received sodium thiosulfate as cyanide antidote therapy.

[2] Patient also received sodium thiosulfate and dicobalt edetate as cyanide antidote therapy.
[3] Patient also received dimercaprol (British anti-Lewisite [BAL]) and dimethyl-succinic acid as mercury antidote therapy.

The 10 patients (71%) who survived were discharged from the hospital. Of these, nine had no neurological impairments. The remaining patient (#138) had a post-anoxic encephalopathy with memory impairment. The Sponsor indicated that this patient was not treated with OH-Co for 12 hours after his discovery, and not before suffering a cardiac arrest to which his brain damage was attributed. The mean hospital stay for these patients was 13 days with a range of 2-56 days.

The four patients who died all suffered either cardiac arrest or respiratory arrest prior to OH-Co treatment. The time to death of these patients ranged from 4-12 days.

10.1.4.19 Sponsor's Safety Results

Twelve of the 14 patients experienced at least one adverse event. The most common ones included red coloring of the skin (n=3) and urine (n=5), hypertension (n=2), circulatory collapse (n=2).

Two serious adverse events were described, but not attributed by the Sponsor to OH-Co administration:

1. Patient #145 had labile blood pressure during his resuscitation which included swings form severe hypotension to severe hypertension. His severe hypertension occurred with his second infusion of OH-Co which was initiated after his catecholamine infusions were stopped. It was estimated he had received just over 400 mg of OH-Co when the hypertensive episode began. The Sponsor proposed that cerebral edema following the initial ischemic assault was a more likely cause of the blood pressure fluctuations.
2. Patient #137 was a 28-year old woman who was 18 weeks pregnant at the time she tried to commit suicide. Her medical history was significant for an extra-uterine pregnancy the year prior to admission, severe depression, and the suspicion that fetal demise had occurred with her current pregnancy. She was found convulsing and went into a coma when rescuers arrived. Her blood toxicology screen was positive for benzodiazepines. Her treatments included 10 g of OH-Co and two 8-g doses of sodium thiosulfate. Sonogram revealed a dead fetus. The Sponsor indicated that the fetal demise occurred prior to the suicide attempt and subsequent rescue efforts.

Hematology and coagulation parameters evaluated during the three days following hospital admission included changes outside the normal ranges for the means, notably for the white blood cell count and lymphocyte count, that did not follow a trend over the time period. The chemistry parameters were notable for increases in the means of creatinine, glucose, bilirubin, AST, ALT and CPK over the course of the three days following admission. Of these, the mean values for AST and ALT had returned to normal levels by Day 3. It should be noted that OH-Co can interfere with device measurements of all these parameters and discerning true variations from normal can be difficult at best. This is particularly relevant in this setting where it was not

known which devices were used by the laboratory and, therefore, an assessment of interference could not be made.

Nine patients had an ECG performed at the scene that was available for review. Four of these included normal findings; four were indicative of cardiac ischemia. In the hospital, ECGs were performed on 13 of the patients, some of whom had multiple ECGs performed. For the first hospital-recorded ECGs, 11 were read as normal, one indicated a rhythm disorder and another indicated a rhythm disorder plus myocardial ischemia. For the ten patients who had a second in-hospital ECG, seven were read as normal, and three indicated some type of rhythm disorder.

10.1.4.20 Discussion of Findings

Of the four studies evaluating Cyanokit in the setting of actual use, this is unique in several aspects: most patients were exposed to cyanide by ingestion rather than inhalation; the exposure was limited primarily to cyanide, i.e., the poisoning was not due to a combination of toxins as was often the case for the smoke-inhalation victims; the poisoning was not complicated by other acute injuries such as burns and trauma frequently associated with the smoke-inhalation studies; and the doses of cyanide to which patients were exposed were relatively large compared to those of the smoke-inhalation victims.

The lack of a comparator arm and the use of alternative antidotes in conjunction with the OH-Co for six of the patients make definitive statements regarding efficacy impossible. However the survival, without neurological sequelae, in patients exposed to relatively high levels of cyanide is suggestive of an efficacious effect of Cyanokit treatment. Specifically, of the 11 patients who had BCN $\geq$ 100 µmol/L, seven (64%) survived.

The safety findings were not inconsistent with those seen in the safety and tolerability study of OH-Co administered to healthy volunteers. However, the effects of the cyanide exposure, the use of additional antidotes, and the difficulty of assessing interference of OH-Co on laboratory chemistry measurements make discerning the impact of OH-Co on safety nearly impossible.

10.1.4.21 Conclusions

Although the limitations of the design of this study and the use of alternative cyanide antidotes in a significant number of patients preclude definitive conclusions, the results reinforce the observations suggestive of efficacy from the other Baud and Fortin studies without introducing any new safety concerns. Two impressive findings of this study were the survival of patients with blood cyanide levels which were considered lethal and the lack of neurological sequelae for 90% of the survivors.

10.1.5 Fortin Study

"Retrospective study of prehospital use of hydroxocobalamin in smoke inhalation victims with suspected cyanide poisoning: 8 years of experience of the Paris Fire Brigade"

10.1.5.1 Over Design and Summary of Findings

This was a retrospective study which utilized data collected from patients who suffered from smoke inhalation related to structural fires in Paris France between 1995 and 2003. Each patient was treated with hydroxocobalamin; however, the treatment was not part of a predefined protocol. The data used in this study came from the medical intervention reports of the Paris Fire Brigade and the hospital discharge summaries, when available.

The key findings of the study include the following:

1. A total of 84 (83%) of the patients survived until ICU admission; however, only 30% were know to survive to hospital discharge or transfer to other wards after discharge from the ICU.
2. Those patients presenting in cardiac arrest had the lowest survival rates, 10% in this study.
3. Of those patients who presented in shock or significant levels of hypotension, 75% showed improvement in hemodynamics with administration of OH-Co; the significance of which is uncertain without a comparator arm in the study.
4. The presence of soot in the airways was not associated with diminished survival. This contrasted with observations made in the Baud studies.
5. There was minimal change in the level of consciousness, as measured by Glasgow Coma Score, following administration of OH-Co. However the trend was toward an improvement.
6. Common adverse events included red color of the skin and urine and development of a rash following administration of OH-Co.
7. The possibility that two patients experienced cardiac arrest and one patient suffered respiratory distress in part because of the OH-Co infusion cannot be ruled out.

10.1.5.2 Study Plan

This study utilized data collected retrospectively from patients who suffered from smoke-inhalation injuries related to structural fires between 1995 and 2003. The treatment of the patients was not dictated by a predefined protocol. Data were collected from the records of the Paris Fire Brigade and the hospital which ultimately cared for the patients. A quality control review of the database, which included variable definitions and conventions, was performed by the Sponsor along with statistical analyses of the data.

10.1.5.3 Objectives

This study was conducted to describe the Paris Fire Brigade's experience with the prehospital use of hydroxocobalamin in the treatment of smoke-inhalation victims with suspected cyanide poisoning.

10.1.5.4 Design

This was an open-label, uncontrolled, retrospective study designed to provide data on the use of hydroxocobalamin by the Paris Fire Brigade between 1995 and 2003.

10.1.5.5 Primary Efficacy Variable

- Prehospital survival as documented by the number of patients hospitalized in intensive card unit ICU), i.e., the number of patients who survived until hospital admission

10.1.5.6 Secondary Efficacy Variables

- Hospital survival as described in the hospital discharge summaries
- Return of spontaneous circulation at the fire scene in patients with initial cardiac arrest
- Hemodynamic improvement (SBP > 90 mmHg) in patients with low blood pressure ($0 < SBP \leq 90$ mmHg) at the time of hydroxocobalamin administration
- Glasgow Coma Score (GCS) changes

10.1.5.7 Safety Variables

- Vital signs
- Adverse events: data were limited to the collection of events reported in medical reports.
- Electrocardiogram (ECG) findings: Since ECG interpretation was often missing, the ECG findings were classified into three categories: normal, ischemic disorders and rhythm and conduction disorders.
- Blood gases

10.1.5.8 Population

All adult and pediatric patients who, between 1995 and 2003, were rescued from burning buildings and had signs or symptoms suggestive of cyanide toxicity and were treated with hydroxocobalamin were eligible for evaluation in this study.

10.1.5.9 Inclusion Criteria

- Patients treated at the scene of a structural fire for presumed cyanide toxicity related to smoke inhalation
- Paris Fire Brigade reports were available detailing the patient's condition and the hydroxocobalamin treatment

10.1.5.10 Exclusion Criteria

- None

10.1.5.11 Methods and Procedures

Data collection for individual patients covered the time period from the initial patient assessment at the scene of the fire through the resuscitative efforts made in the field and the patient's hospital course until the patient either died in the hospital was discharged. No blood samples were taken for measurement of cyanide levels. Patient follow-up was not performed.

The following information was sought from the available patient records:

- Demographic data including past medical history
- Initial clinical status including assessments for cardiac arrest, shock, and neurological impairment
- Vital signs
- GCS
- Hydroxocobalamin administration
- ECG
- Blood gas analyses
- Concomitant medications administered
- Adverse events

10.1.5.12 Analysis Plan

Due to the nature of the study, only descriptive results were generated for all the collected variables without statistical testing.

10.1.5.13 Protocol Amendments and Changes in the Planned Analysis

None

10.1.5.14 Study Conduct

A total of 101 patients were identified for inclusion in the study. As the study was retrospective and lacked a prospective follow-up of the participants, there were no protocol deviations or premature withdrawals. All 101 of the subjects received treatment. The study was not subject to possible protocol termination due to the nature of its design. All results were based solely on the available data.

10.1.5.15 Demographics/Group Comparability

There were slightly more males than females in the study: 53 (53%) versus 48 (48%), respectively. In terms of the presenting clinical signs, males outnumbered females for those who presented in shock [3 (60%) versus 2 (40%)] and those who presented with neurological impairment [28 (61%) versus 18 (39%)]. Females outnumbered males, however, for those who presented in cardiac arrest: 23 (61%) versus 15 (40%).

The patient demographics for the entire study and for the different presenting-signs subgroups are shown in the table below.

Table 32 Demographics of the total population and clinical-signs subgroups (modified from Sponsor's table 11-4 on page 35 of Volume 40 in Module 5).

	Total Population N=101	Cardiac Arrest N=38	Shock N=5	Neurological Impairment N=46	No Predominant Sign N=12
Gender					
Female	48 (48%)	23 (61%)	2 (40%)	18 (39%)	5 (42%)
Male	53 (53%)	15 (40%)	3 (60%)	28 (61%)	7 (58%)
Age (years) Total population					
N	98	37	5	44	12
Mean	47	46	36	51	41
Range	2-88	2-87	23-55	11-88	24-68
Age (years) for Adults (≥ 19 y)					
N	90	31	5	42	12
Mean	51	54	36	53	41
Range	21-88	30-87	23-55	21-88	24-68
Age (years) for Children (< 19 y)					
N	8	6	0	2	0
Mean	6	4		13	
Range	2-14	2-5		11-14	

10.1.5.16 Treatment Compliance

Treatment was administered by emergency rescue and hospital personnel; therefore, treatment compliance was assured.

10.1.5.17 Unplanned Analyses

As the study was retrospective in design, there were no unplanned analyses conducted.

10.1.5.18 Sponsor's Efficacy Results

There were 17 patients who died at the scene of the fire; all were in cardiac arrest at the time rescuers arrived. The remaining 84 patients were admitted to the hospital where 25 died while in the ICU. Of the remaining 59 patients, 30 survived and were either discharged or transferred to another ward of the hospital; the hospital outcomes for the other 29 patients could not be determined due to lack of hospital summaries in the medical records.

A higher percentage of patients in the shock, neurological-impairment and no-predominant-sign subgroups survived following hospitalization in the ICU than did patients presenting in cardiac arrest: 3 patients (60%), 20 patients (44%), and 5 patients (42%), versus 2 patients (5%), respectively.

Death occurred on average four days following the fire. Patients presenting in cardiac arrest and shock died sooner than those presenting neurologically impaired or without predominant signs of poisoning: 2 and 3 days versus 15 and 9 days, respectively. Overall the leading cause of death was cardiac arrest (43%), followed by multiple organ failure (24%) and cerebral anoxia (24%).

Of the 38 patients who presented in cardiac arrest, 17 (45%) died on site whereas 21 (55%) had return of spontaneous circulation during the prehospital phase. However, most of the patients who had return of spontaneous circulation died within 1 to 8 days of ICU admission. Of the 21 patients, 17 (81%) died, 2 (10%) survived, and 2 (10%) had missing hospital outcomes.

Hemodynamic improvement was evaluated for patients with systolic blood pressures (SBP) of 0-90 mmHg prior, i.e., in shock, to administration of hydroxocobalamin. Improvement was defined by the Sponsor as at least a sing follow-up SBP > 90 mmHg. Of the 12 patients who qualified as having hemodynamic instability, 9 patients (75%) recovered normal blood pressure by 31 minutes (on average) after the start of hydroxocobalamin infusion; the remaining 3 patients did not recover.

The change in mean Glasgow Coma Scores (GCS) between the initial and final assessments was computed fro 52 patients. Values were not computed for the other 49 patients due to the use of sedation agents in 41 patients and missing final assessments for the remaining 8 patients. The mean initial GCS was 7.9 (S.D. = 5.4), and the mean final GCS was 8.5 (S.D. = 5.7), which yielded a difference of 0.6 on a scale from 3-15. Both numbers are consistent with values seen in patients with moderate to severe brain injury.

10.1.5.19 Significant Safety Findings Reported by the Sponsor

The Sponsor indicated that 13 adverse events were reported for 10 patients after hydroxocobalamin administration including the following:

- Five patients had pink or red coloration of skin or urine. One of these patients was also noted to have a blue colored kidney when it was removed for transplantation.
- One patient had a cutaneous rash. The patient also suffered from severe and extended burns and rhabdomyolysis. No mention was made of treatment for an allergic response. The patient died 19 days after the fire in a deep coma related to renal insufficiency.
- Two patients went into cardiac arrest that was assessed at the time as not related to the administration of hydroxocobalamin.
- One patient went into respiratory distress that was assessed as not related to hydroxocobalamin.

10.1.5.20 Discussion of Findings

The study is limited not only by the retrospective design and lack of a comparator, but also by the lack of data to assessing cyanide exposure. The presence or absence of soot in the airways may be used as a surrogate marker in an effort to distinguish between those patients who were more likely and those who were less likely to have inhaled toxic levels of cyanide (and other toxic agents). The table below summarizes the survival outcomes based on the parameters that appeared to be most relevant in the Baud studies for which pretreatment blood cyanide levels were available.

Table 33 Summary survival data for Fortin Study

	Soot present in airways			No soot in airways[1]		
	In Cardiac Arrest	Not in Cardiac Arrest	Total	In Cardiac Arrest	Not in Cardiac Arrest	Total
Evaluable Patients	19	53	72	19	10	29
Survival:[2]						
Overall	1 (5%)	25 (47%)	26 (36%)	1 (5%)	4 (40%)	5 (17%)
Age < 18 y	0/3 (0%)	0/2 (0%)	0/5 (0%)	0/4 (0%)	1/1 (100%)	1/5 (20%)
Age ≥ 18 y	1/16 (6%)	21/51 (41%)	26/67 (39%)	1/15 (7%)	3/8 (38%)	4/23 (17%)
Age ≥ 65 y	1/4 (25%)	4/9 (44%)	5/13 (38%)	1/4 (25%)	2/2 (100%)	3/6 (50%)
Age ≥ 75 y	1/4 (25%)	3/7 (43%)	4/11 (36%)	0/1 (0%)	1/1 (100%)	1/2 (50%)
Mean Dose of OH-Co (g)	6.3	4.9	4.8	4.0	4.4	4.3

[1] Includes patients for whom it was documented that no soot was present and those for whom there was no documentation and who, therefore, were assumed not to have been intubated.
[2] Includes only those patients who were know to survive until transferred out of the ICU.

The typical dose was 5 g for the adults although several received higher doses (none higher than 10 g), and some, including all the pediatric patients and nine adult patients, received smaller doses ranging from 1 to 3.5 g.

As was noted in the Baud smoke-inhalation studies, those patients presenting in cardiac arrest had the lowest survival rates. This was true regardless of the presence or absence of soot in the airway. Overall survival was greater for pediatric and elderly patients when no soot was present in the airways; however, the opposite was true for patients ages 18-65 years old. The significance of this result is questionable at best based on the limitations of the data and of the assumption that blood cyanide levels can be estimated by the presence of soot in the airways.

Without a comparator, it is also difficult to assess the safety findings. However the changes in skin and urine color and the development of a rash following OH-Co treatment initiation are consistent with the findings of the healthy volunteer study. The reports of two cardiac arrests and one episode of respiratory distress could be due to the injuries sustained from the fires and toxicity associated with smoke inhalation; however, the possibility that the patients were suffering from allergic reactions to the OH-Co which combined with their other injuries was sufficient to induce these adverse events cannot be ruled out.

10.1.5.21 Conclusions

Although the limitations of the design of the study and of the amounts and types of data collected preclude definitive conclusions, the results reinforce the efficacy observations from the Baud studies without introducing any new safety concerns. In particular, the lower survival rates for patients found in cardiac arrest, the improvement of hemodynamics following administration of OH-Co, the development of red colored skin and urine as well as a rash following initiation of the OH-Co infusion are consistent with the results from the Baud studies. The lack of a survival advantage when soot was not observed in the airways is not consistent with the Baud findings.

10.2 Line-by-Line Labeling Review

The proposed labeling submitted by the Sponsor, excluding the table of contents, is duplicated below. Recommended additions appear as underlined text; recommended deletions appear as strike-through text.

HIGHLIGHTS OF PRESCRIBING INFORMATION

b(4)

b(4)

14 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1

10.3 Adverse Events

The table below presents all the adverse event data for the four French studies (Baud 1, 2 and 3 and Fortin) and the safety and tolerability study conducted on healthy volunteers. It is copied from the Sponsor's adverse events table that was submitted by e-mail from Elliott Berger of EMD Pharmaceuticals, Inc. on October 13, 2006.

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ON ORIGINAL

Table 34 Listing of adverse events for all studies

Adverse Events	Combined French Experience					Healthy Volunteer Study				
	Missing	<5 g	≥5 - <10 g	≥10 - <15 g	≥15 g	Placebo	2.5 g	5 g	7.5 g	10 g
	N=9	N=22	N=166	N=39	N=9	N=34	N=9	N=66	N=9	N=18
Blood And Lymphatic System Disorders										
total	0	0	3(2)	6(15)	2(22)	0	0	0	0	0
agranulocytosis				1(3)						
anemia			1(1)							
blood disorder			2(1)							
disseminated intravascular coagulation				3(8)	2(22)					
leukocytosis				1(3)						
thrombocytopenia				1(3)						
Cardiac Disorders										
total	1(11)	1(5)	18(11)	11(28)	3(33)	0	1(11)	1(2)	0	0
atrial fibrillation			1(1)							
cardiac arrest			6(4)	5(13)	1(11)					
cardiac disorder			1(1)							
cardiac failure			1(1)	1(3)						
cardiac failure congestive	1(11)									
cardiac tamponade	1(11)									
cardio-respiratory arrest			1(1)							
cardiogenic shock			1(1)	1(3)	1(11)					
coronary artery insufficiency			1(1)							
cyanosis			1(1)							
extrasystoles				1(3)						
hypertrophic cardiomyopathy				1(3)						
myocardial infarction			1(1)	1(3)						
palpitations							1(11)			
sinus bradycardia		1(5)								
tachyarrhythmia			1(1)							
tachycardia		1(5)	4(2)	2(5)						
ventricular arrhythmia			1(1)							
ventricular extrasystoles			1(1)	1(3)				1(2)		
ventricular fibrillation			1(1)		1(11)					
Ear And Labyrinth Disorders										
total	0	0	1 (1)	0	1 (1)	0	0	0	0	0
ear hemorrhage			1 (1)		1 (1)					

Endocrine Disorders										
total	0	0	1(1)	0	1(11)	0	0	0	0	0
diabetes insipidus			1(1)		1(11)					
Eye Disorders										
total	1(11)	1(5)	17(10)	6(15)	0	0	0	2(3)	0	2(11)
conjunctival hemorrhage				1(3)						
conjunctival hyperemia	1(11)	1(5)	6(4)							
conjunctival irritation			1(1)							
conjunctivitis			5(3)	4(10)						
corneal edema			1(1)							
corneal ulcer			1(1)							
eye irritation			2(1)							1(6)
eye redness								2(3)		1(6)
eye swelling										1(6)
eyelid edema			1(1)							
keratitis				1(3)						
mydriasis			1(1)							
Gastrointestinal Disorders										
total	0	2(9)	12(7)	4(10)	1(11)	1(3)	1(11)	7(11)	4(44)	8(44)
abdominal discomfort								2(3)	2(22)	2(11)
abdominal distension				1(3)						
abdominal pain			1(1)							
abnormal feces										1(6)
acute abdomen		1(5)								
constipation			1(1)							
diarrhea			2(1)	1(3)						1(6)
dyspepsia									1(11)	
dysphagia			1(1)						1(11)	4(22)
fecaloma			1(1)							
flatulence			1(1)	1(3)	1(11)			1(2)		
frequent bowel movements										1(6)
gastric disorder										1(6)
gastric hemorrhage			1(1)							
gastritis			1(1)							
hematemesis			1(1)							
hematochezia										1(6)
loose stools								1(2)		

nausea			1(1)	1(3)		1(3)	1(11)	4(6)	2(22)	2(11)
pancreatitis acute		1(5)								
stomach discomfort										1(6)
vomiting			6(4)	1(3)			1(11)	2(3)	1(11)	
General Disorders And Administration Site Conditions										
total	1(11)	1(5)	13(8)	6(15)	3(33)	2(6)	1(11)	9(14)	3(33)	11(61)
asthenia	1(11)									
chest discomfort								3(5)		2(11)
crepitations			1(1)							
discomfort								1(2)	1(11)	
fatigue							1(11)			1(6)
feeling hot								1(2)		
feeling hot and cold								1(2)		
hyperthermia				2(5)						
hypothermia			5(3)	4(10)						
induration										1(6)
infusion site erythema								2(3)	3(33)	7(39)
infusion site induration										1(6)
infusion site pain										1(6)
infusion site swelling										1(6)
injection site erythema								2(3)		
injection site extravasation		1(5)								
multi-organ failure			1(1)		1(11)					
edema peripheral			1(1)			1(3)				2(11)
pyrexia			5(3)		2(22)					
rigors										1(6)
sensation of pressure						1(3)				
Hepatobiliary Disorders										
total	0	0	1(1)	1(3)	0	0	0	0	0	0
cytolytic hepatitis				1(3)						
hepatic failure			1(1)							
Immune System Disorders										
total	0	0	0	1(3)	0	0	0	0	0	0
drug hypersensitivity				1(3)						
Infections And Infestations										
total	1(11)	5(23)	39(23)	12(31)	2(22)	3(9)	2(22)	16(24)	6(67)	4(22)
acute sinusitis			1(1)							

bronchial infection	1(11)		1(1)							
bronchiolitis			1(1)							
bronchitis			3(2)							
bronchopneumonia			5(3)							
catheter bacteremia			1(1)							
catheter-related infection			1(1)							
catheter sepsis		1(5)								
cystitis										1(6)
gastroenteritis								1(2)		
herpes simplex										1(6)
laryngitis			2(1)	1(3)						
lung infection		2(9)	4(2)		1(11)					
nasopharyngitis						3(9)	2(22)	6(9)	2(22)	
pneumonia		1(5)								
pneumonia bacterial		1(5)	9(5)	5(13)						
pneumonia hemophilus			1(1)	1(3)						
pneumonia pneumococcal		1(5)	6(4)		1(11)					
pneumonia staphylococcal			1(1)	2(5)						
rash pustular								11(17)	4(44)	3(17)
sepsis			2(1)	3(8)						
septic shock			2(1)							
sinusitis			3(2)	3(8)						
tracheitis			2(1)							
urinary tract infection		1(5)	2(1)	1(3)						
urinary tract infection bacterial			3(2)							
Injury, Poisoning And Procedural Complications										
total	0	0	0	1(3)	0	0	0	0	0	1(6)
periorbital hematoma										1(6)
pulmonary edema post-fume inhalation				1(3)						
Investigations										
total	0	0	8(5)	3(8)	0	5(15)	3(33)	23(35)	8(89)	10(56)
blood amylase increased								1(2)		
blood bilirubin increased						1(3)				
blood creatine phosphokinase increased			1(1)				1(11)	1(2)	1(11)	1(6)
blood culture positive			1(1)							

blood glucose increased			1(1)							
blood phosphorus decreased						1(3)				
blood pressure decreased				1(3)		1(3)				
blood pressure diastolic increased								6(9)	5(56)	5(28)
blood pressure increased			1(1)	1(3)			2(22)	6(9)		
blood triglycerides increased										1(6)
c-reactive protein increased								4(6)	1(11)	1(6)
electrocardiogram repolarization abnormality				1(3)						
electroencephalogram abnormal			1(1)							
hemoglobin decreased						2(6)		2(3)		
heart rate increased			1(1)							
lymphocyte count decreased								6(9)	3(33)	3(17)
platelet count decreased			1(1)							
weight increased			1(1)							
white blood cell count decreased							1(11)			
Metabolism And Nutrition Disorders										
total	0	2(9)	27(16)	15(38)	3(33)	0	0	0	0	0
acidosis				1(3)						
dehydration					1(11)					
diabetes mellitus		1(5)	1(1)							
fluid retention				1(3)						
hypercreatininemia		1(5)	6(4)	7(18)	1(11)					
hyperglycemia		1(5)	17(10)	8(21)						
hyperkalemia			2(1)							
hyperlactacidemia			2(1)							
hypernatremia			3(2)	1(3)	1(11)					
hypokalemia			2(1)	2(5)						
hypovolemia			2(1)		1(11)					
lactic acidosis			1(1)							
metabolic acidosis			2(1)	2(5)						
sodium retention				1(3)						
Musculoskeletal And Connective Tissue Disorders										
total	0	0	3(2)	1(3)	1(11)	1(3)	0	2(3)	0	1(6)
arthralgia								1(2)		
back pain						1(3)		1(2)		
muscle cramp										1(6)

neck pain			1(1)							
rhabdomyolysis			2(1)	1(3)	1(11)					
Nervous System Disorders										
total	1(11)	2(9)	16(10)	4(10)	4(44)	3(9)	2(22)	7(11)	5(56)	7(39)
anoxic encephalopathy		2(9)	2(1)		1(11)					
apallic syndrome			1(1)							
aphasia			1(1)							
brain edema			1(1)		1(11)					
cerebellar syndrome			1(1)							
clonus			1(1)							
coma			3(2)		1(11)					
convulsion			3(2)	2(5)						
dizziness						1(3)		2(3)	1(11)	1(6)
encephalopathy			1(1)							
epilepsy			1(1)							
grand mal convulsion			1(1)							
headache	1(11)		1(1)			3(9)	2(22)	6(9)	5(56)	6(33)
memory impairment										1(6)
nervous system disorder				1(3)						
paresthesia						1(3)				
status epilepticus				1(3)						
subarachnoid hemorrhage					1(11)					
Pregnancy, Puerperium And Perinatal Conditions										
total	0	0	0	1(3)	0	0	0	0	0	0
intra-uterine death				1(3)						
Psychiatric Disorders										
total	0	0	10(6)	2(5)	0	0	0	2(3)	0	0
agitation			1(1)	2(5)						
alcohol withdrawal syndrome			1(1)							
anxiety			2(1)							
confusional state			2(1)							
depression			1(1)							
post-traumatic stress disorder			1(1)							
restlessness			4(2)					2(3)		
Renal And Urinary Disorders										
total	0	3(14)	25(15)	11(28)	4(44)	0	9(100)	66(100)	9(100)	18(100)
anuria				1(3)						

chromaturia		3(14)	16(10)	4(10)	2(22)		9(100)	66(100)	9(100)	18(100)
dysuria			1(1)					1(2)		1(6)
hemorrhage urinary tract			1(1)							
oliguria			1(1)	2(5)						
pollakiuria								2(3)		
renal disorder				1(3)						
renal failure			5(3)	2(5)	3(33)					
renal failure acute			1(1)	1(3)						
renal impairment			1(1)							
renal pain										1(6)
urine flow decreased			1(1)							
Reproductive System And Breast Disorders										
total	0	0	0	0	0	0	0	1(2)	0	0
dysmenorrhea								1(2)		
Respiratory, Thoracic And Mediastinal Disorders										
total	1(11)	2(9)	52(31)	14(36)	2(22)	1(3)	0	3(5)	2(2)	3(7)
acute respiratory distress syndrome		1(5)								
acute respiratory failure			2(1)							
asthma			1(1)							
bronchopneumopathy			3(2)							
bronchospasm			6(4)	1(3)						
cough						1(3)				2(11)
dry throat								1(2)		1(6)
dysphonia			9(5)							
dyspnea								1(2)	1(11)	
emphysema				1(3)						
epistaxis			1(1)					1(2)		
hypoxia		1(5)	26(16)	7(18)	1(11)					
laryngeal dyspnea			3(2)							
laryngeal edema			1(1)							
lung disorder		1(5)	4(2)	1(3)	1(11)					
obstructive airways disorder			2(1)							
pharyngolaryngeal pain								1(2)		
pleural effusion			1(1)							
pneumonia aspiration				1(3)						
pneumonitis			2(1)	1(3)						
pneumothorax	1(11)			1(3)						

pulmonary embolism			1(1)							
pulmonary edema	1(11)		2(1)	1(3)						
respiratory arrest				1(3)						
respiratory distress			1(1)							
respiratory failure			1(1)							
tachypnea			1(1)							
throat tightness								1(2)	2(22)	2(11)
wheezing			6(4)	1(3)						
Skin And Subcutaneous Tissue Disorders										
total	0	2(9)	9(5)	9(23)	1(11)	0	0	62(94)	9(100)	18(100)
dermatitis allergic				1(3)						
ecchymosis				1(3)						
erythema				2(5)				61(92)	9(100)	18(100)
exanthema										2(11)
face edema								1(2)		
generalized erythema			1(1)					1(2)		
hyperhydrosis									1(11)	
pruritus								1(2)	2(22)	3(17)
rash			1(1)					1(2)		
rash papular				1(3)						3(17)
rash pruritic								1(2)		
skin bleeding			1(1)							
skin discoloration		2(9)	6(4)	5(13)	1(11)					
urticaria								1(2)		
Vascular Disorders										
total	1(11)	2(9)	25(15)	15(38)	2(22)	2(6)	0	1(2)	0	1(6)
circulatory collapse	1(11)	1(5)	7(4)	4(10)						
hemodynamic instability			2(1)	2(5)	1(11)					
hot flush										1(6)
hypertension		1(5)	10(6)	3(8)						
hypotension			5(3)	2(5)						
lymphangitis		1(5)	5(3)	2(5)						
peripheral coldness						1(3)				
phlebitis			1(1)							
shock			2(1)	2(5)	1(11)					
thrombophlebitis						1(3)		1(2)		

thrombosis			1(1)							
venous thrombosis limb			1(1)	1(3)						

10.4 Information on Patient Deaths

The table below provides summary information for each of the patients who died in the Baud 1, Baud 2, Baud 3 and Fortin Studies. Narrative summaries for each of the deaths follow the table.

Table 35 Listing of deaths reported in clinical studies

Subject ID	OH-Co Dose (grams)	Sex	Age (years)	Initial cardiac arrest	Initial Glasgow Coma Score	Immediate cause of the death[1]	Day of death from time of OH-Co treatment (Day 1)
Baud1-12	10	F	70	Yes	3	Asystole	Day 3
Baud1-19	5	M	52	No	6	Septic shock	Day 6
Baud1-2	5	F	85	No	12	Septic shock	Day 6
Baud1-21	5	F	83	No	9	Septic shock	Day 26
Baud1-22	4	F	94	No	4	Septic shock	Day 4
Baud1-28	5	F	68	Yes	3	Therapy stopped	Day 4
Baud1-30	5	F	35	Yes	3	Therapy stopped	Day 4
Baud1-31	4	F	33	Yes	3	Therapy stopped	Day 8
Baud1-34	4	M	35	Yes	3	Refractory shock	Day 2
Baud1-35	5	M	44	Yes	3	Brain death	Day 5
Baud1-36	5	F	38	Yes	3	Electromechanical dissociation, asystole	Day 1
Baud1-48	5	M	89	No	12	Pneumonia	Day 13
Baud1-54	5	F	83	Yes	3	Brain death	Day 3
Baud1-55	5	F	31	Yes	3	Refractory shock	Day 4
Baud1-56	5	M	61	Yes	3	Cardiac arrest	Day 3
Baud1-59	5	F	25	Yes	3	Brain death	Day 9
Baud1-64	5	F	81	Yes	3	Brain death	Day 1
Baud1-67	5	F	66	No	15	Septic shock	Day 7
Baud1-9	5	M	33	Yes	3	Refractory cardiovascular shock	Day 2
Baud2-100	10	M	84	No	3	Hyperkalemia	Day 4
Baud2-101	5	M	51	No	12	Septic shock	Day 21
Baud2-103	10	M	61	Yes	3	Refractory shock	Day 1
Baud2-106	5	F	48	Yes	3	Brain death	Day 5
Baud2-108	10	F	73	Yes	3	Cardiac arrest	Day 2
Baud2-110	unknown	F	70	Yes	15	Multiple organ failure	Day 2
Baud2-113	15	M	41	Yes	3	Shock	Day 1
Baud2-115	15	M	54	Yes	3	Brain death (suspected)	Day 6
Baud2-122	5	M	45	Yes	3	Unknown	Day 26
Baud2-123	5	M	48	Yes	3	Brain death	Day 7
Baud2-124	5	M	68	No	6	Septic shock	Day 21
Baud2-127	10	F	87	No	15	Circulatory failure	Day 3
Baud2-128	5	F	92	No	10	Cardiac arrest	Day 3
Baud2-129	5	M	83	No	14	Cardiac shock	Day 9
Baud2-150	15	F	79	Yes	5	Asystole	Day 2
Baud2-156	10	F	42	Yes	3	Multiple organ failure	Day 2
Baud2-70	10	F	41	Yes	4	Brain death	Day 3
Baud2-71	10	F	65	Yes	4	Brain death	Day 1
Baud2-76	15	M	29	Yes	3	Cardiac arrest	Day 6
Baud2-79	5	F	59	No	14	Cardiac arrest	Day 7

Subject ID	OH-Co Dose (grams)	Sex	Age (years)	Initial cardiac arrest	Initial Glasgow Coma Score	Immediate cause of the death[1]	Day of death from time of OH-Co treatment (Day 1)
Baud2-83	10	F	57	Yes	3	Circulatory failure	Day 1
Baud2-85	5	F	?	No	12	Circulatory failure	Day 7
Baud2-87	12.5	F	27	No	5	Hemodynamic deterioration	Day 4
Baud2-93	5	M	31	Yes	15	Hemodynamic failure	Day 2
Baud3-139	20	M	27	No	3	Hemodynamic failure	Day 5
Baud3-143	10	M	39	Yes[2]	3	Brain death	Day 4
Baud3-144	15	F	32	Yes	3	Refractory shock	Day 4
Baud3-145	10	M	64	Yes[2]	3	Brain death (suspected)	Day 12
Fortin-332	10	F	52	Yes	3	Brain death	Day 1
Fortin-10013	5	M	55	No	3	Multiple organ failure	Day 2
Fortin-1079	5	M	37	Yes	3	Cardiac arrest	Day 1
Fortin-1101	unknown	M	30	Yes	3	Refractory shock	Day2
Fortin-12260	5	M	40	Yes	3	Cardiac arrest	Day 1
Fortin-12321	5	M	56	Yes	3	Cardiac arrest	Day 2
Fortin-15707	5	F	87	Yes	3	Cardiac arrest	Day 1
Fortin-16062	5	F	50	No	6	Multiple organ failure	Day 21
Fortin-18479	5	F	30	Yes	3	Cardiac arrest	Day 1
Fortin-18507	5	F	29	No	11	Multiple organ failure	Day 3
Fortin-18751	5	F	51	Yes	3	Multiple organ failure	Day 7
Fortin-18935	5	F	42	Yes	3	Discontinuation of therapy	Day 6
Fortin-19139	5	M	62	No	15	Multiple organ failure	Day 2
Fortin-19432	5	F	86	Yes	3	Discontinuation of therapy	Day 3
Fortin-19495	5	F	65	Yes	3	Cardiac arrest	Day 1
Fortin-19856	5	M	24	No	15	Septic shock	Day 9
Fortin-21601	5	M	40	Yes	3	Cardiac arrest	Day 1
Fortin-23976	5	M	60	Yes	3	Multiple organ failure	Day 2
Fortin-25382	5	F	37	Yes	3	Cardiac arrest	Day 1
Fortin-26303	1.5	F	5	Yes	3	Unknown	Day 1
Fortin-27311	1.5	M	4	Yes	3	Cardiac arrest	Day 1
Fortin-27606	5	M	47	Yes	3	Unknown	Day 1
Fortin-29391	5	F	79	Yes	3	Shock	Day 1
Fortin-29631	5	F	47	Yes	3	Cardiac arrest	Day 1
Fortin-3046	unknown	M	49	Yes	3	Cardiac arrest	Day 1
Fortin-3100	unknown	M	4	Yes	3	Cardiac arrest	Day 1
Fortin-3106	5	M	36	No	14	Cardiac arrest	Day 30
Fortin-31786	2.5	M	56	Yes	3	Cardiac arrest	Day 1
Fortin-31930	5	F	85	No	12	Unknown	Day 14
Fortin-32991	5	M	32	No	13	Multiple organ failure	Day 20
Fortin-33370	2.5	M	50	Yes	3	Cardiac arrest	Day 1
Fortin-4248	5	F	52	Yes	3	Multiple organ failure	Day 5
Fortin-4639	5	F	49	Yes	3	Brain death	Day 1
Fortin-5190	5	F	65	Yes	3	Cardio-circulatory arrest	Day 2
Fortin-5374	1.5	F	2	Yes	3	Cardiac arrest	Day 1
Fortin-5406	2.5	M	5	Yes	3	Cardiac arrest	Day 1
Fortin-643	1	F	2	Yes	3	Brain death	Day 2
Fortin-6922	10	F	47	Yes	3	Brain death	Day 3

Subject ID	OH-Co Dose (grams)	Sex	Age (years)	Initial cardiac arrest	Initial Glasgow Coma Score	Immediate cause of the death[1]	Day of death from time of OH-Co treatment (Day 1)
Fortin-748	5	F	46	Yes	3	Refractory shock	Day 8
Fortin-81	unknown	F	32	Yes	3	Cardiac arrest	Day 1
Fortin-9086	5	F	?	Yes	3	Cardiac arrest	Day 1
Fortin-9188	5	F	83	Yes	3	Cardiac arrest	Day 1

[1] Patients, who presented in cardiac arrest and for whom there was no evidence of successful resuscitation or restoration of circulation, and for whom there was no other Sponsor-attributed cause of death, were adjudicated by this reviewer to have died from cardiac arrest.

[2] Patient was not in cardiac arrest when rescue personnel arrived, but went into cardiac arrest prior to the administration of hydroxocobalamin.

Baud Study 1

Patient 2 was an 85 year old female who presented at the scene of the fire with a Glasgow Coma Score (GCS) = 12, BCN=42 µmol/L, BCO =1.97 mmol/L. She received a 5-g dose of hydroxocobalamin 15 minutes after the fire brigade was called and was transported to the hospital where she received normo- and hyperbaric oxygen therapy, mechanical ventilation, cardiac stimulants and electrolyte replacement. About two hours after her first dose of hydroxocobalamin, to which she did not respond, a second 5-g dose was administered. The second dose resulted in an increase in systolic blood pressure from 105 to 187 mmHg and a heart rate decrease from 110 to 83 bpm. Her hospital course was significant for ventricular extrasystoles, ECG repolarization abnormalities, hypertrophic cardiomyopathy (treated with dobutamine, dopamine and nicardipine), hypoxia (treated with normo- and hyperbaric oxygen therapy), erythema, and hyperglycemia (treated with insulin). The erythema and ECG abnormalities were thought to be possibly related to hydroxocobalamin treatment. She died five days after the fire from septic shock.

Patient 9 was a 22 year old man who was found at the scene of a fire. He presented in cardiac arrest with a GCS = 3, acidosis, a BCO = 2.8 mmol/L, and a BCN = 0 µmol/L. He was treated with a 5-g dose of hydroxocobalamin approximately 20 minutes following notification of the fire brigade. Additional therapy included normo- and hyperbaric oxygen therapy, mechanical ventilation, epinephrine, lidocaine, and sodium bicarbonate. The cardiac arrest responded to cardiopulmonary resuscitation and epinephrine. The hydroxocobalamin therapy was associated with a blood pressure of 130/70 mmHg and a heart rate of 83 bpm. Two hours and 20 minutes after resuscitative efforts began, he was transported to the hospital and received a second 5-g dose of hydroxocobalamin. His response to this dose was not recorded. While in the hospital, he experienced high serum creatinine (treated with intravenous fluids), hypothermia (treated with warming blankets), hypernatremia (treated with magnesium chloride), and cytolytic hepatitis. All these events were not thought to be related to hydroxocobalamin. He died in the ICU due to refractory cardiovascular shock the day after the fire (Day 2).

Patient 12 was a 70 year-old female patient was found at the scene of a fire in a coma (GCS=3) and in cardiac arrest. She also had a metabolic lactic acidosis at that time; her pretreatment BCN level was 120 µmol/L and her BCO was 4.68 mmol/L. She received a 10- g dose of hydroxocobalamin 1.5 hours after the fire brigade call. She also received normo- and hyperbaric oxygen therapy, mechanical ventilation, intravenous fluids, epinephrine, dobutamine, dopamine, and sodium bicarbonate. She did not respond to hydroxocobalamin; her blood pressure changed from 120/70 to 110/80 mmHg and her heart rate decreased from 80 to 75 bpm. While in the hospital, she experienced skin discoloration (considered to be related to hydroxocobalamin), and convulsions (treated with thiopental sodium and clomethiazole), high creatinine (treated with intravenous fluids and furosemide), diarrhea (treated with electrolyte replacement), hyperglycemia (treated with insulin), and hypokalemia (treated with potassium supplementation); all but the skin discoloration were considered not related to hydroxocobalamin. She died in the ICU on Day 3 due to asystole.

Patient 19 was a 52 year-old man who was found at the scene of a fire. He had a past history of neurofibromatosis and chronic obstructive airway disease. He was in a coma (GCS=6) and experiencing bronchospasm at the time rescuers arrived. The BCN level was 87 µmol/L and the BCO level was 0.31 mmol/L. He received a 5-g dose of hydroxocobalamin 40 minutes after the fire brigade call. He also received anticoagulant and antibiotic therapy, normobaric oxygen, salbutamol and theophylline. He did not respond to hydroxocobalamin; his heart rate (130 bpm) and blood pressure (140 mmHg systolic) did not change. While in the hospital, he experienced hypoxia (treated with ventilatory support, salbutamol, theophylline and furosemide), high creatinine (treated with IV fluids and furosemide), bacterial pneumonia (treated with cefalothin sodium and amikacin), hyperglycemia (treated with insulin), cardiac arrest (treated with cardiopulmonary resuscitation and epinephrine), and circulatory collapse (treated with dobutamine, epinephrine, norepinephrine and dopamine). All these events were considered not related to hydroxocobalamin. He died in the ICU due to septic shock on Day 6.

Patient 21 was an 83 year-old female patient who was found at the scene of a fire with a depressed level of consciousness (GCS=9) and metabolic acidosis; she had second and third degree burns on the face. The pretreatment BCN level was 114 µmol/L and BCO level was 5.6 mmol/L. She received a 5-g dose of hydroxocobalamin 23 minutes after the fire brigade call. She also received normo- and hyperbaric oxygen, mechanical ventilation, and sodium bicarbonate. Her apparent response to hydroxocobalamin was a decrease in blood pressure from 200/110 to 170/90 mmHg and a decrease in heart rate from 120 to 90 bpm. While in the hospital, she experienced chromaturia, considered related to hydroxocobalamin, and hypoxia (treated with mechanical ventilation), high creatinine (treated with IV fluids, dopamine, and furosemide), bacterial pneumonia (treated with oxacillin and gentamicin), urinary tract infection, conjunctival hyperemia (treated with artificial tears), hyperglycemia (treated with insulin), and lymphangitis, all considered not related to hydroxocobalamin. She died in the ICU due to septic shock on Day 26.

Patient 22 was a 94 year-old, bed-ridden, female patient who was found at the scene of a fire. She was in a coma (GCS=4) at that time. The pretreatment BCN level was 15.4 µmol/L and the BCO level was 1.29 mmol/L. She received a 4-g dose of hydroxocobalamin 23 minutes after the

fire brigade call. She also received normo- and hyperbaric oxygen and mechanical ventilation. Her response to hydroxocobalamin was an increase in systolic blood pressure from 150 to 180 mmHg, a decrease in heart rate from 120 to 83 bpm and an increase in GCS to 7. While in the hospital she experienced conjunctival hyperemia and skin discoloration (considered to be related to hydroxocobalamin) as well as hypertension (treated with nicardipine), high creatinine (treated with IV fluids, furosemide and dopamine), acute abdomen and hyperglycemia; all but the skin discoloration were considered unrelated to hydroxocobalamin. She died in the ICU due to septic shock on Day 4.

Patient 28 was a 68 year-old female patient who was found at the scene of a fire in cardiac arrest. She had a history of hypertension, cerebrovascular accident, and dementia. Her pretreatment BCN level was not recorded; however, her BCO level was 2.58 mmol/L. She received a 5-g dose of hydroxocobalamin 19 minutes after the fire brigade call. She also received normo- and hyperbaric oxygen, mechanical ventilation, epinephrine, dobutamine, external cardiac massage, and sodium bicarbonate. She received a second and third 5-g dose of hydroxocobalamin three and six minutes, respectively, following the first dose. She responded to the repeat dosing with spontaneous resumption of circulatory activity, disappearance of mydriasis and improvement of coma depth. While in the hospital she experienced hypoxia (treated with ventilatory support and normobaric oxygen), cardiogenic shock (treated with epinephrine,), high creatinine (treated with furosemide and intravenous fluids) and pneumococcal pneumonia (treated with cefalothin sodium and amikacin); all these events were considered unrelated to hydroxocobalamin. She died in the ICU due to withdrawal of therapy on Day 4.

Patient 30 was a 35 year-old female patient who was found at the scene of a fire in cardiac arrest, and with burns over 10% of her body. Her pretreatment BCN level was 40 µmol/L and her BCO level was 2.48 mmol/L. She received a 5-g dose of hydroxocobalamin 28 minutes after the fire brigade call. She also received normo- and hyperbaric oxygen, sodium thiosulfate, epinephrine, intravenous fluids, dopamine, and norepinephrine. She received a second 5-g dose of hydroxocobalamin six minutes after the first, to which she responded with improvement in blood pressure. While in the hospital she experienced erythema, considered possibly related to hydroxocobalamin, and hypoxia (treated with ventilatory support and normobaric oxygen), high creatinine (treated with furosemide), hyperglycemia (treated with insulin), and disseminated intravascular coagulation, all of which were considered unrelated to hydroxocobalamin. She died in the ICU on Day 4 due to withdrawal of therapy secondary to brain death.

Patient 31 was a 33 year-old female patient who was found in cardiac arrest at the scene of a fire. Her pretreatment BCN level was 238.5 µmol/L and her BCO level was 3.2 mmol/L. She received a 4-g dose of hydroxocobalamin 30 minutes after the fire brigade call. She also received mechanical ventilation, thiopental, mannitol, tetracosactide (cosyntropin) and hyperbaric oxygen. She had a partial response to hydroxocobalamin and received a second 4.0 g dose 50 minutes following the first. While in the hospital she experienced pleural effusion (treated with paracentesis) considered to be related to hydroxocobalamin, and clonus (treated with thiopental, ventilatory support, mannitol and tetracosactide (cosyntropin)), hypoxia (treated with ventilatory support and antibiotics), high creatinine (treated with furosemide and electrolyte

replacement), bacterial pneumonia (treated with cefotaxime and gentamicin), hypothermia (treated with warming blankets), hypernatremia (treated with electrolyte replacement), and increased CK, all of which were considered unrelated to hydroxocobalamin. She died in the ICU due to withdrawal of therapy secondary to brain death on Day 8.

Patient 34 was a 35 year-old male patient was found at the scene of a fire in cardiac arrest and with second-degree burns over 21 % of his body. The pretreatment BCN level was 138.5 µmol/L; the BCO level was 5 mmol/L. At the scene he received mechanical ventilation, normobaric oxygen, intravenous fluids, dobutamine and epinephrine. In the ICU he received a 4-g dose of hydroxocobalamin 2 hours 40 minutes after the fire brigade call. He received a second 5.0 g dose 3.5 hours after the first. His response to hydroxocobalamin was a systolic blood pressure increase from 35 to 145 mmHg. While in the hospital he experienced hypoxia (treated with intubation, ventilatory support and normobaric oxygen), high creatinine (treated with intravenous fluids and furosemide), hyperglycemia, and hypothermia, all of which were considered unrelated to hydroxocobalamin. He died in the ICU due to refractory shock on Day 2.

Patient 35 was a 44 year-old male patient was found in cardiac arrest at the scene of a fire. His pretreatment BCN level was 149 µmol/L, and his BCO was 3.5 mmol/L. He received a 5-g dose of hydroxocobalamin 20 minutes after the fire brigade call. He also received ventilatory support, normo- and hyperbaric oxygen, sodium bicarbonate, mannitol, and tetracosactide (a subunit of ACTH). His response to hydroxocobalamin was described as "positive." While in the hospital he was in coma with mydriasis (treated with ventilatory support, normo- and hyperbaric oxygen, mannitol, and tetracosactide), hypoxia (treated as above), lactic acidosis (treated with sodium bicarbonate, dopamine, and dobutamine), and hyperglycemia, all of which were considered unrelated to hydroxocobalamin. He died in the ICU due discontinuation of therapy secondary to brain death on Day 5.

Patient 36 was a 38 year-old female patient was found at the scene of a fire in cardiac arrest. She had a history of hypertension. The pretreatment BCN level was 21.1 µmol/L and her BCO level was 2.61 mmol/L. She received a 5-g dose of hydroxocobalamin 14 minutes after the fire brigade call. She also received ventilatory support, normo- and hyperbaric oxygen, epinephrine, sodium bicarbonate, external cardiac massage, and electrical defibrillation. She had a partial response to hydroxocobalamin and received a second 5-g dose of hydroxocobalamin two hours 20 minutes later, also with a partial response. While in the hospital she experienced hypoxia (treated with ventilatory support and normobaric oxygen), cardiac arrest (treated with external cardiac massage, dobutamine, isoproterenol and sodium bicarbonate), ventricular extrasystoles (treated with lidocaine), high creatinine (treated with iv fluids), hypothermia (treated with warming blankets), and hyperglycemia, all of which were considered unrelated to hydroxocobalamin. She died in the ICU on the Day 1 due to cardiac electromechanical dissociation.

Patient 48 was an 89 year-old male patient who was found at the scene of a fire conscious but confused and delirious. He had burns in the hair and scalp, and had mixed acidosis and clonus. His medical history included coronary artery disease, atrioventricular block and placement of a

cardiac pacemaker. His pretreatment BCN level was 96 µmol/L and his BCO level was 6.03 mmol/L. He received mechanical ventilation, hyperbaric oxygen, nifedipine, and theophylline at the scene. He was transported to hospital approximately two hours after the fire brigade call. He received a 5-g dose of hydroxocobalamin three hours after the call to the fire brigade and responded with an increase in blood pressure from 145/85 to 160/100 mmHg and a decrease in heart rate from 100 to 88 bpm. He received a second 5-g dose of hydroxocobalamin seven hours after the first. His blood pressure decreased from 160/100 to 115/65 mmHg, his heart rate decreased from 86 to 76 bpm, and the respiratory component of his mixed acidosis resolved. While in the hospital he experienced circulatory collapse (treated with intravenous fluids, epinephrine, dobutamine, dopamine and sodium bicarbonate), bacterial pneumonia and sepsis (treated with benzyl penicillin, metronidazole, ciprofloxacin, gentamicin and vancomycin), wheezing (treated with theophylline), and conjunctivitis (treated with picloxydine eye drops), all considered unrelated to hydroxocobalamin. He died in the ICU due to hypoxemic pneumonia on Day 13.

Patient 54 was an 83 year-old female patient who was found in cardiac arrest at the scene of a fire. Her pretreatment BCN level was 52 µmol/L, and her BCO level was 2.66 mmol/L. She received two 5-g doses of hydroxocobalamin as well as mechanical ventilation, normobaric oxygen and epinephrine at the scene of the fire and was transported to the hospital. While in the hospital she experienced skin discoloration, considered to be caused by hydroxocobalamin. No other adverse events were recorded. She died in the ICU due to refractory shock on Day 3.

Patient 55 was a 31 year-old female patient was found at the scene of a fire where she was in cardiac arrest and had first degree burns over 19% of her body. Her pretreatment BCN level was 208 µmol/L and her BCO level was 2.66 mmol/L. She received a 5-g dose of hydroxocobalamin 10 minutes after the fire brigade call. She received a second 5- g dose shortly thereafter. Her systolic blood pressure after second dose of hydroxocobalamin was 140 mmHg. She also received mechanical ventilation, mannitol, tetracosactide (cosyntropin), and hyperbaric oxygen. While in the hospital she experienced skin discoloration and decreased blood pressure (treated with epinephrine), during the second infusion of hydroxocobalamin, both events were considered to be possibly related to hydroxocobalamin. She also went into cardiogenic shock (treated with epinephrine), and had high creatinine (treated with intravenous fluids and furosemide) and ecchymosis, all considered unrelated to hydroxocobalamin. She died in the ICU due to refractory shock on Day 4.

Patient 56 was a 61 year-old male patient was found at the scene of a fire in cardiac arrest at that time. His pretreatment BCN level was 216 µmol/L and his BCO level was 4.68 mmol/L. He received two 5-g doses of hydroxocobalamin at the scene. After the hydroxocobalamin, his blood pressure at the scene was 80/40 mmHg. At the hospital, his blood pressure was 140/40 mmHg. Concomitant medications included a 5-mg epinephrine bolus followed by a1 mg/hr infusion and a 10 µg/kg/min dobutamine infusion started at the scene for 20 minutes. No associated ECG was reported. No adverse experiences were recorded. He died in the ICU due to cardiac arrest on Day 3.

Patient 59 was a 25 year-old female patient was found at the scene of a fire on 21 May 1988. She was in cardiac arrest with circulatory collapse at that time. The pretreatment BCN level was 84 µmol/L; the BCO level was 0.91 mmol/L. She received normo- and hyperbaric oxygen, mechanical ventilation, mannitol, IV fluids and isoproterenol at the scene. She was transported to hospital where she received a 5-g dose of hydroxocobalamin at one hour 52 minutes after the fire brigade call. While in the hospital she experienced hypoxia (treated with mechanical ventilation and oxygen), circulatory collapse (treated with iv fluids, dopamine, hydrocortisone), hyperglycemia (treated with insulin), hypokalemia (treated with potassium chloride) and diabetes insipidus (treated with electrolyte replacement and posterior pituitary lobe hormones), all considered unrelated to hydroxocobalamin. She died in the ICU due to discontinuation of therapy secondary to brain death on Day 9.

Patient 64 was an 81 year-old female patient who was found at the scene of a fire in cardiac arrest with circulatory collapse and had burns over 14% of her body. She had a medical history of chronic lymphocytic leukemia (treated with chlorambucil). The pretreatment BCN level was not recorded; however, the BCO level was 1.13 mmol/L. She received mechanical ventilation, dobutamine, epinephrine, and sodium bicarbonate at the scene. She was transported to hospital where she received a 5-g dose of hydroxocobalamin and responded with an increase in systolic blood pressure from 81 to 180 mmHg. Two hours late she received a second 5-g dose of hydroxocobalamin but the response unrecorded. While in the hospital she experienced hypoxia (treated with mechanical ventilation), high creatinine (treated with intravenous fluids), sepsis (treated with benzylpenicillin), and thrombocytopenia (treated with chlorambucil), all considered unrelated to hydroxocobalamin. She died due to cardiac arrest on the day of the fire.

Patient 67 was a 66 year-old female patient who was found confused and dysphonic at the scene of a fire. She had a medical history of hypertension. The pretreatment BCN level was 158 µmol/L and her BCO level was3.91 mmol/L. She received normo- and hyperbaric oxygen at the scene and was transported to hospital where she received a 5-g dose of hydroxocobalamin approximately 3 hours after the fire brigade call. She responded with normalization of blood pressure and improvement of level of consciousness. While in the hospital she experienced hypoxia (treated with mechanical ventilation, salbutamol, theophylline, almitrine and furosemide), tachycardia, hypotension (treated with theophylline), circulatory collapse (treated with dopamine, dobutamine, epinephrine, intravenous fluids, diuretics and lanatoside C), high creatinine (treated with furosemide and intravenous fluids), pneumococcal pneumonia (treated with cefotaxime, gentamicin and metronidazole) and conjunctivitis (treated with Flex-Care), all considered unrelated to hydroxocobalamin. She died in the ICU due to septic shock on Day 7.

Baud Study 2

Patient 70 was a 41 year-old female patient who was found at the scene of a fire in a grade 4 coma and cardiac arrest. Soot was found in her lower airways. She was given epinephrine (8 mg bolus followed by 19.5 mg/h infusion), dobutamine, thiopental sodium, sodium bicarbonate, and glucose at the scene. An hour later she was transported to hospital. In the ICU, she received a 10.0-g dose of hydroxocobalamin. The time between the fire brigade call and administration of

hydroxocobalamin was 121 minutes. Her ICU course was significant for the development of pulmonary edema. She died on Day 3 in the ICU due to brain death.

Patient 71 was a 65 year-old female patient who was found at the scene of a fire in a grade 4 coma and cardiac arrest with third degree burns over 65% of her body. She was given epinephrine 4 mg, dobutamine, and a 5-g dose of hydroxocobalamin. She was transported to hospital 2 hours after rescue efforts began. The time between the fire brigade call and administration of hydroxocobalamin was 35 minutes. She received a second 5-g dose of hydroxocobalamin in the ICU. She died in the ICU on Day 1 due to brain death.

Patient 76 was a 28 year-old male patient who was found at the scene of a fire in a grade 4 coma and cardiac arrest with second degree burns over < 1% of his body. Soot was found in his lower airways. He was given epinephrine l0 mg followed by a 1 mg/h infusion, magnesium sulfate, sodium bicarbonate, sodium lactate and a 5-g dose of hydroxocobalamin at the scene. He was transported to hospital an hour and 40 minutes after rescue efforts began. He received a 10-g dose of hydroxocobalamin in the ICU. While in the ICU, he experienced chromaturia, disseminated intravascular coagulation, renal failure, rhabdomyolysis, and ear hemorrhage. He died from cardiac arrest in the ICU on Day 6.

Patient 79 was a 58 year-old female patient who was found at the scene of a fire with second degree burns over a small area of her body and soot in her throat. She was given etomidate, atropine, midazolam, glucose, and a 5-g dose of hydroxocobalamin at the scene. She was transported to hospital an hour and ten minutes after rescue efforts began. While in the ICU, she experienced bronchopneumonia, an episode of cardiac arrest, hypertension, and anoxic encephalopathy. She died in the ICU on Day 7 due to the cardiac arrest.

Patient 83 was a 56 year-old female patient who was found at the scene of a fire in a grade 4 coma and cardiac arrest with second degree burns over < 1% of her body and soot in her throat. She was given epinephrine 4mg, sodium lactate, and hydroxocobalamin 5.0 g at the scene. The time between the fire brigade call and administration of hydroxocobalamin was 32 minutes. She was transported to hospital an hour and 15 minutes after rescuers arrived. She received another 5-g dose of hydroxocobalamin in the ICU. While in the ICU, she experienced anuria, hypotension, hypothermia, and metabolic acidosis. She died in the ICU due to circulatory failure on Day 1.

Patient 85 was a 94 year-old female patient who was found at the scene of a fire in a state of mental confusion with soot in her lower airways. She was given etomidate, midazolam, glucose, sodium lactate, and a 5-g dose of hydroxocobalamin. The time between the fire brigade call and administration of hydroxocobalamin was 82 minutes. She was transported to hospital an hour and a half after the rescuers arrived. While in the ICU, she experienced coma, lactic acidosis, an unspecified lung disorder, restlessness, hypokalemia, hypothermia, sepsis, hemodynamic instability, hyperglycemia, pulmonary edema, renal impairment, tachycardia and increased weight. She died in the ICU due to circulatory failure on Day 7.

Patient 87 was a 27 year-old female patient who was found at the scene of a fire in a grade 3 coma with soot in her throat. She was given etomidate, fentanyl, gelatin, and a 5-g dose of hydroxocobalamin at the scene and was transported to hospital an hour and a half after rescuers arrived. While in the ICU, she experienced pulmonary edema, disseminated intravascular coagulation, hyperthermia, oliguria, rhabdomyolysis, cardiac arrest, and hypotension. She died in the ICU due to hemodynamic deterioration on Day 4.

Patient 93 was a 30 year-old male patient who was found at the scene in cardiac arrest with a small area of second degree burn and soot in his lower airways. He was given epinephrine 5 mg, sodium lactate, and hydroxocobalamin 5.0 g at the scene. He was transported to hospital an hour and40 minutes after rescue efforts began. While in the ICU, he experienced convulsions, hypotension, pulmonary edema, and skin discoloration. He died in the ICU due to shock on the day of the fire.

Patient 100 was an 84 year-old male patient who was found at the scene of a fire in a coma with third degree burns over 7% of his body and soot in his lower airways. He was given sodium lactate, fentanyl, and hydroxocobalamin 5.0 g at the scene then was transported to hospital four hours and 45 minutes after rescuers arrived. While in the ICU, he received another 5-g dose of hydroxocobalamin 5.0 g dose and experienced hypothermia and oliguria. He died three days after the fire in the burn unit due to hyperkalemia.

Patient 101 was a 50 year-old male patient was found at the scene of a fire in a grade 1 coma with soot in his lower airways. He was given etomidate, midazolam, Ringer's solution, sodium bicarbonate, gelatin, and a 5-g dose of hydroxocobalamin. The time between the fire brigade call and administration of hydroxocobalamin was 28 minutes. He was transported to hospital at 13 minutes after rescuers arrived. While in the ICU, he experienced lung infection, circulatory collapse, acute sinusitis, hematemesis, renal failure, ventricular arrhythmia, and multi-organ failure. He died in the ICU on Day 21 due to septic shock.

Patient 103 was a 60 year-old male patient who was found at the scene of a fire in a grade 4 coma. He was given a bolus dose of epinephrine, 5 mg, followed by a 1.33 mg/h infusion, glucose, sodium chloride, and hydroxocobalamin 5.0 g at the scene. He was transported to hospital an hour and 13 minutes after rescue efforts were initiated. While in the ICU, he experienced abdominal distension, cardiac arrest, hyperglycemia, and renal failure. He died in the ICU on Day 1 due to refractory shock.

Patient 106 was a 47 year-old female patient who was found at the scene of a fire in a grade 3 coma and cardiac arrest with soot in her lower airways. She was given epinephrine 1 mg/h infusion, sodium bicarbonate, and hydroxocobalamin 5.0 g at the scene and was transported to hospital an hour and 15 minutes after rescue efforts were begun. She was given hydroxocobalamin 10.0 g in the ICU where she also experienced anoxic encephalopathy and pyrexia. She died in the ICU on Day 5 due to withdrawal of therapy secondary to brain death.

Patient 108 was a 73 year-old female patient was found at the scene of a fire in a grade 4 coma and cardiac arrest with third degree burns over 5% of her body. She was given epinephrine 13

mg followed by a 0.1 mg/h infusion, and hydroxocobalamin 10.0 g. The time between the fire brigade call and administration of hydroxocobalamin was 8 minutes. She was transported to hospital after one hour and 25 minutes. The only described adverse event in the ICU was flatulence. She died the next day (Day 2) in the ICU from cardiac arrest.

Patient 110 was a 70 year-old female patient who was found at the scene of a fire in cardiac arrest with second-degree burns on the face and right shoulder. She was given epinephrine (dose unknown) and hydroxocobalamin (dose unknown) at the scene. She was transported to hospital and while in the ICU she experienced congestive heart failure, cardiac tamponade, circulatory collapse, pneumothorax, and pulmonary edema. She died the following day, Day 2, from multiple organ failure.

Patient 113 was a 41 year-old male who was found at the scene of a fire in a coma and cardiac arrest with burns over 15% of his body. He was given epinephrine 29 mg followed by a 0.69 mg/h infusion, sodium lactate, and hydroxocobalamin 5.0 g at the scene. He was transported to hospital one and a half hours after the rescuers arrived. He received hydroxocobalamin 10.0 g in the ICU where he was noted to have experienced flatulence, renal failure, and ventricular fibrillation. He died later the same day in the ICU from shock.

Patient 115 was a 54 year-old male who was found at the scene of a fire in cardiac arrest. He was given an epinephrine infusion at 0.5 mg/h and hydroxocobalamin 10.0 g at the scene. He was transported to hospital where he received an additional 5.0 g hydroxocobalamin. While in the ICU he experienced brain edema, hemodynamic instability, lung infection, dehydration, and hypernatremia. He was discharged from the ICU on Day 5. He died three months later secondary to suspected brain death.

Patient 122 was a 45 year-old male who was found at the scene of a fire unconscious and in cardiac arrest. He had third degree burns over 2% of his body and soot was found in his lower airways on intubation. He was given etomidate, midazolam, fentanyl, and hydroxocobalamin 5.0 g at the scene. He was transported to hospital an hour after rescue efforts began. While in the ICU he experienced chromaturia, grand mal convulsions, and apallic syndrome. He died in the ICU from an unknown cause on Day 26.

Patient 123 was a 48 year-old male who was found at the scene of a fire in cardiac arrest and with third degree burns over < 10% of his body. On intubation, soot was found in his lower airways. He was given epinephrine 10 mg followed by a 1.17 mg/h infusion, etomidate, sodium bicarbonate, glucose, midazolam, and hydroxocobalamin 5.0 g at the scene. He was transported to hospital an hour and 50 minutes after rescuers arrived. While in the ICU, he experienced renal failure, abnormal electroencephalogram, brain edema, cardiac disorder (not described), and convulsions. He died in the ICU on Day 7 secondary to brain death.

Patient 124 was a 67 year-old male who was found at the scene of a fire unconscious and wounded. Soot was found in his lower airways on intubation. He was given lactated Ringer's solution at the scene and was transported to hospital an hour and 20 minutes after rescuers arrived. While in the ICU, he experienced circulatory collapse, ear hemorrhage, encephalopathy,

multiple organ failure, shock, chromaturia, ventricular fibrillation, heparin-induced thrombocytopenia, and a lung infection. He received 5.0 g hydroxocobalamin in the ICU. He died in the ICU from to septic shock on Day 21.

Patient 127 was an 86 year-old female who was found unconscious at the scene of a fire. On intubation, soot was found in her lower airways. She was given hydroxocobalamin 5.0 g at the scene and was transported to hospital an hour after rescuers arrived. She was given an additional 5-g dose of hydroxocobalamin ICU. While in the ICU, she experienced cardiac arrest and respiratory arrest. She died in the ICU from circulatory failure on Day 3.

Patient 128 was a 91 year-old female who was found at the scene of a fire in a coma and with second degree burns over 7% of her body. Soot was found in her throat at the time of intubation. She was given etomidate, sodium chloride, lactated Ringer's solution, midazolam, ketamine, and hydroxocobalamin 5.0 g. The time between the fire brigade call and administration of hydroxocobalamin was 29 minutes. She was transported to hospital two hours after rescue efforts began. While in the ICU, she experienced eyelid edema and "laryngeal dyspnea." She died in the ICU from cardiac arrest on Day 3.

Patient 129 was an 82 year-old male who was found at the scene of a fire in a state of mental confusion. Soot was noted in his lower airways. He was given aspirin, sodium lactate, sodium chloride, and hydroxocobalamin 5.0 g at the scene. He was transported to hospital at an unspecified time following onset of rescue efforts. While in the ICU, he experienced coronary artery insufficiency, coma and respiratory failure. He died in the ICU from cardiac shock on Day 9.

Patient 150 was a 79 year-old female who was found at the scene of a fire in a grade 3 coma. On intubation, soot was found in her lower airways. She was given epinephrine 10 mg, dobutamine, sodium bicarbonate, sodium lactate, and hydroxocobalamin 10.0 g at the scene. She was transported to hospital two hours and 10 minutes after rescuers arrived. At the hospital, she received an additional 5- g dose of hydroxocobalamin. While in the ICU, she experienced hypovolemia, multi-organ failure, and disseminated intravascular coagulation. She died in the ICU from cardiac arrest (asystole) Day 2.

Patient 156 was a 41 year-old female who was found at the scene of a fire comatose, in cardiac arrest, and with second and third degree burns over 30% of her body. She was given epinephrine 4mg followed by a 3 mg/h infusion, hydroxocobalamin 2.5 g, fentanyl, sodium chloride, and hetastarch at the scene. She was transported to hospital about 2 hours after rescuers arrived. In the ICU, she received a 7.5-g dose of hydroxocobalamin. While in the ICU, she experienced disseminated intravascular coagulation, hemodynamic instability, and myocardial infarction. She died in the ICU from multiple organ failure on Day 2.

Fortin Study

Patient 81 was a 32 year-old female who was found at the scene of a residential fire in cardiac arrest. She was administered hydroxocobalamin (dose unknown) and epinephrine (dose unknown). The time between the fire brigade call and administration of drugs was 16 minutes. She died at the scene from unspecified causes.

Patient 332 was a 52 year-old female who was found at the scene of a residential fire in cardiac arrest. Soot was found in her mouth. She was administered a 10.0-g dose of hydroxocobalamin and 15 mg epinephrine. The time between the fire brigade call and administration of drugs was 15 minutes. She was resuscitated but experienced ventricular and atrial fibrillation. She was transported to hospital 2 hours after rescuers arrived. She died the same day in the ICU from refractory cardiovascular shock secondary to cerebral anoxia. No adverse events were noted after hydroxocobalamin administration.

Patient 643 was a 2 year-old female who was found at the scene of a residential fire in cardiac arrest. Soot was found in her throat. She was administered 1.0 g hydroxocobalamin and 1 mg of epinephrine six minutes after rescuers arrived. The time between the fire brigade call and administration of drugs was 10 minutes. She was transported to hospital two hours after the rescuers arrived. She died on Day 2 due to discontinuation of therapy secondary to brain death. No adverse events were noted after hydroxocobalamin administration.

Patient 748 was a 46 year-old female who was found at the scene of a residential fire in cardiac arrest. Soot was found in her throat at the time of intubation. She was administered a 5.0-g dose of hydroxocobalamin and 6 mg epinephrine. The time between the fire brigade arrival and administration of drugs was 17 minutes. She was resuscitated and transported to hospital about two hours and 10 minutes after the rescuers arrived. She died in the ICU from refractory shock on Day 8. No adverse events were noted after hydroxocobalamin administration.

Patient 1079 was a 37 year-old male who was found at the scene of a residential fire in cardiac arrest. On intubation soot was found in the lower airways. He was administered a 5-g dose of hydroxocobalamin and 14 mg of epinephrine. The time between the fire brigade call and administration of drugs was 42 minutes. He died at the scene 35 minutes after the rescuers arrived.

Patient 1101 was a 30 year-old male who was found at the scene of a residential fire in cardiac arrest. He was administered hydroxocobalamin (dose unknown) and 3 mg epinephrine. He was resuscitated and transported to hospital three hours and 20 minutes after the medications were administered. He died in the ICU from refractory shock on Day 2. No adverse events were noted after hydroxocobalamin administration.

Patient 3046 was a 49 year-old male who was found at the scene of a residential fire in cardiac arrest. He was administered hydroxocobalamin (dose unknown) and epinephrine (dose unknown). He died at the scene of unspecified cause.

Patient 3100 was a 4 year-old male who was found at the scene of a residential fire in cardiac arrest. He was administered hydroxocobalamin (dose unknown) and epinephrine (dose unknown). The time between the fire brigade call and administration of drug was 15 minutes. He died at the scene of unspecified cause.

Patient 3106 was a 36 years old male without past medical history who was found at the scene of a fire conscious (GCS = 14) and agitated. He had burns covering 30% of body surface. Initial cardiovascular assessment indicated a regular rhythm with a pulse at 100 bpm, and blood pressure of 150/95 mmHg. Twenty minutes after rescuers arrived, the patient received lactated Ringers solution (a total of 3.5 L was administered at the scene of the fire), midazolam, fentanyl, and celocurine and was intubated and placed on mechanical ventilation. The patient had elevated blood pressure (160/100 mmHg) when a 5-g dose of hydroxocobalamin was administered 50 minutes after start of care based on agitation, transient bradycardia, the presence of soot in the airway, and generalized seizure despite sedation. Vital signs remained little changed 30 and 50 minutes after hydroxocobalamin with blood pressures of 150/90 mmHg and 160/100 mmHg, respectively. Upon admission to ICU 70 minutes after hydroxocobalamin administration, the blood pressure was 150/85 mmHg. The patient was noted to be hemodynamically stable without need for vasoactive drugs during his one-month hospital stay for surgical treatment of his burns including skin grafting. It was noted that diuretic treatment was instituted for fluid retention from Day 10 to Day 21. On Day 21 and Day 28, his hemodynamic status was described as stable without vasoactive drugs. On Day 29 the patient died from a cardiac arrest attributed to likely pulmonary embolism.

Patient 4248 was a 52 year-old female who was found at the scene of a residential fire in cardiac arrest. Soot was found in her mouth at the time of intubation. She had a history of psychiatric illness including attempted suicide with drugs. She was administered a 5-g dose of hydroxocobalamin and 6 mg epinephrine. The time between the fire brigade call and administration of the drugs was 10 minutes. She was transported to hospital one and a half hours after the rescuers arrived. She died in the ICU from multiple organ failure on Day5. No adverse events were noted after hydroxocobalamin administration.

Patient 4639 was a 49 year-old female who was found at the scene of a residential fire in cardiac arrest. Soot was found in the lower airways at the time of intubation. She was administered a 5-g dose of hydroxocobalamin and 1.5 mg of epinephrine. The time between the fire brigade call and administration of the drugs was 28 minutes. She was transported to hospital an hour after the rescuers arrived. She experienced gastric and cutaneous hemorrhages after hydroxocobalamin administration. She died in the ICU from cardiac arrest on Day 1.

Patient 5190 was a 65 year-old female who was found at the scene of a residential fire in cardiac arrest. She was administered 5.0 g hydroxocobalamin and 12 mg of epinephrine. The time between the fire brigade call and administration of the drugs was 71 minutes. She was transported to hospital two hours after the rescuers arrived. She died in the ICU from cardiac arrest on Day 2. No adverse events were noted after hydroxocobalamin administration.

Patient 5374 was a 2 year-old female who was found at the scene of a residential fire in cardiac arrest. She was administered a 1.5-g dose of hydroxocobalamin and 10 mg of epinephrine. The time between the fire brigade call and administration of the drugs was 33 minutes. She died at the scene 45 minutes after rescue efforts were initiated.

Patient 5406 was a 5 year-old male who was found at the scene of a residential fire in cardiac arrest. On intubation, soot was found in the lower airways. He was administered a 2.5-g dose of hydroxocobalamin and 3 mg of epinephrine. The time between the fire brigade call and administration of the drugs was 31 minutes. He died at the scene 55 minutes after the rescuers arrived.

Patient 6922 was a 47 year-old female victim of smoke inhalation who was found in cardiac arrest by rescuers. She had a medical history significant for neuropsychiatric disorders treated with carbamazepine, cyamemazine (a phenothiazine anxiolytic) and fluphenazine. She was resuscitated with 3mg of epinephrine and 2.5 g of hydroxocobalamin which restored her pulse to 74 bpm and blood pressure to 116/62 mmHg after 5 minutes. Fifteen minutes after hydroxocobalamin was started, she went into shock with blood pressure of 56/32 mmHg requiring further administration of 2.5 g hydroxocobalamin along with 50 mL of hydroxyethylamidon (a glucose polymer used for volume expansion). This second hydroxocobalamin treatment resulted in blood pressure increase to 81/45 mmHg and a pulse of 103 bpm 30 minutes after the infusion of hydroxocobalamin was started. Forty minutes after the initial hydroxocobalamin dose, a third dose of 2.5 g was given, concomitant to existing elevated blood pressure at 225/115 mmHg. During the next 10 minutes, blood pressure remained high (216/104 mmHg) but gradually decreased to 187/102 mmHg. A fourth administration of 2.5 g hydroxocobalamin started concomitantly with fentanyl and midazolam administration. On admission to the hospital, the blood pressure was 168/94 mmHg 70 minutes after hydroxocobalamin start and further decreased to 126/73 mmHg 2 hours after the first hydroxocobalamin infusion was begun. Firemen reported that hemodynamic stabilization was achieved with hydroxocobalamin. Over the next three days in hospital, reoccurrences of hemodynamic instability occurred requiring fluid administration and treatment with dopamine and norepinephrine. The patient died on Day 3 from cardiac arrest.

Patient 9086 was a female who was found at the scene of a residential fire in cardiac arrest. She was administered hydroxocobalamin (5.0 g) and epinephrine (9 mg) but died at the scene 45 minutes following the start of treatment.

Patient 9188 was an 83 year-old female who was found at the scene of a residential fire in cardiac arrest. She was administered hydroxocobalamin (5.0 g) and epinephrine (15 mg) but died at the scene 45 minutes after treatment was begun.

Patient 10013 was a 55 year-old male who was found at the scene of a residential fire in a state of neurological impairment. Soot was found in the lower airways. He was administered 5.0 g hydroxocobalamin at 09:30. The time between the fire brigade call and administration of hydroxocobalamin was 26 minutes. He was transported to a hospital 5.25 hours after

resuscitation was begun. He died in the ICU from multiple organ failure on Day 2. No AEs were noted after hydroxocobalamin administration.

Patient 12260 was a 40 year-old male who was found at the scene of a residential fire in cardiac arrest. He was administered hydroxocobalamin (5.0 g) and epinephrine (48 mg). The time between the fire brigade call and administration of the drugs was 6 minutes. He died at the scene 50 minutes following the start of resuscitation.

Patient 12321 was a 56 year-old man with a history of schizophrenia who was found at the scene of the fire in cardiac arrest. He was resuscitated with a 7-mg bolus of epinephrine and concomitant administration of 100 mL of "bicarbonates" and a 2.5-g dose of hydroxocobalamin. An epinephrine infusion at a rate of 1.5 to 2 mg/h was also instituted for the next 90 minutes. At time of resuscitation, the systolic blood pressure was below 60 mmHg. This remained unchanged with initial resuscitative efforts; therefore, the patient received another 2.5-g dose of hydroxocobalamin 15 minutes after the first. At the end of the second hydroxocobalamin infusion, the blood pressure was 80/40 mmHg. From this time point until hospital admission, two hours after initial resuscitation, the blood pressure remained between 90/60 mmHg and 140/110 mmHg. Upon hospital admission, the blood pressure was 110/60 mmHg and the cardiovascular examination was described as "normal." The patient died later that day from a second cardiac arrest.

Patient 15707 was an 87 year-old female who was found at the scene of a residential fire in cardiac arrest. Soot was found in her mouth at the time of intubation. She was administered hydroxocobalamin (5.0 g) and epinephrine (15 mg). The time between the fire brigade call and administration of the drugs was 14 minutes. She died at the scene after half an hour of resuscitative effort.

Patient 16062 was a 50 year-old female who was found at the scene of a residential fire in a state of "neurological impairment." Soot was found in her throat. She was administered 5.0 g hydroxocobalamin. The time between the fire brigade call and administration of the hydroxocobalamin was 38 minutes. She was transported to hospital an hour and 10 minutes after the rescuers arrived. She died in the ICU from multiple organ failure on Day 21. No adverse events were noted after the hydroxocobalamin administration.

Patient 18479 was a 30 year-old female who was found at the scene of a residential fire in cardiac arrest. Soot was found in her mouth at the time of intubation. She was administered hydroxocobalamin (5.0 g) and epinephrine (5 mg) with "rapid improvement of cardiac activity." The time between the fire brigade call and administration of the drugs was 20 minutes. She was transported to hospital an hour and 20 minutes after rescue efforts were initiated. She died from cardiac arrest in the ICU later the same day. No adverse events were noted after hydroxocobalamin administration.

Patient 18507 was a 29 year-old female who was found in shock at the scene of a residential fire. Soot was found in her mouth at the time of intubation. She was administered a 5-g dose of hydroxocobalamin. The time between the fire brigade call and administration of

hydroxocobalamin was 51 minutes. She was transported to hospital an hour and 45 minutes after rescuers arrived. She died in the ICU from multiple organ failure on Day 3. No adverse events were noted after hydroxocobalamin administration.

Patient 18751 was a 51 year-old female who was found at the scene of a residential fire in cardiac arrest. She was administered a 5-g dose of hydroxocobalamin and 5 mg of epinephrine. The time between the fire brigade call and administration of drugs was 21 minutes. Sibilant rales and respiratory distress were noted after hydroxocobalamin administration. She was transported to hospital after an hour and 20 minutes of resuscitation. She died in the ICU on from multiple organ failure on Day 7.

Patient 18935 was a 42 year-old female with no known past medical history who was found at the scene of a fire in cardiac arrest. She was resuscitated with mechanical ventilation and administration of two 3-mg boluses of epinephrine following which her heart went into ventricular fibrillation that returned spontaneously to sinus rhythm. Vital signs measured after resuscitation included a heart rate of 116 bpm and a blood pressure of 80/50 mmHg. Hydroxocobalamin was then administered as 2.5-g doses given twice over the next hour. Five minutes after the hydroxocobalamin infusion was started, the blood pressure was 115/70 mmHg, and increased to 200/110 at the end of the infusion (50 minutes after initiation). Her blood pressure was measured as 190/120 mmHg and 130.100 mmHg at 20 and 30 minutes, respectively, after the hydroxocobalamin infusion. It was noted that midazolam (10 mg) was also administered 30 minutes following the hydroxocobalamin infusion. On admission to the hospital, two and a half hours after rescue efforts were begun, the patient's blood pressure was 140/60 mmHg and her hemodynamic status was described as stable. Later that day, the patient became hypotensive (systolic blood pressure = 58 mmHg) requiring dopamine 10 to 12 µg/kg/min and 1 L of Elohes (a low molecular weight hydroxyethylstarch). Her hemodynamic status progressively deteriorated despite increases in dopamine doses to 20 µg/kg/min. She died later in the day from septic shock associated with cardio-vascular insufficiency.

Patient 19139 was a 62 year-old male who was found at the scene of a residential fire in a state of "neurological impairment." Soot was found in his lower airways at the time of intubation. He was administered a5- g dose of hydroxocobalamin. The time between the fire brigade call and administration of hydroxocobalamin was 14 minutes. He was transported to hospital an hour and 25 minutes after rescuers arrived. He died the next day (Day 2) in the ICU from multiple organ failure. No adverse events were noted after hydroxocobalamin administration.

Patient 19432 was an 86 year-old female who was found at the scene of a residential fire in cardiac arrest. On intubation, soot was found in her throat. She was administered a 5-g dose of hydroxocobalamin and 3 mg of epinephrine. The time between the fire brigade call and administration of drugs was 20 minutes. She was transported to hospital one hour and 35 minutes after the rescuers arrived. She died in the ICU on Day 3 from cardiac arrest. No adverse events were noted after hydroxocobalamin administration.

Patient 19495 was a 65 year-old female who was found at the scene of a residential fire in cardiac arrest. She was administered hydroxocobalamin (5.0 g) and epinephrine (3 mg). The

time between the fire brigade call and administration of the drugs was 21 minutes. She died at the scene after an hour and 20 minutes of rescue effort.

Patient 19856 was a 24 year-old male with untreated non-insulin-dependant diabetes who was found at the scene of a residential fire with burns over 50-55% of his body. Firemen found him conscious but "intoxicated" and agitated with a blood pressure of 150/80 mmHg and a normal cardiac auscultation. Thirty minutes after rescuers arrived, the patient was intubated following administration of etomidate, midazolam, celocurine, and fentanyl. Soot was found in the lower airways at the time of intubation. His blood pressure was relatively stable with systolic pressures in the 150-170 mmHg range. He was administered a 5-g dose of hydroxocobalamin approximately 30 minutes following intubation and 70 minutes following notification of the fire brigade. His blood pressure at 50 and 70 minutes following the start of the hydroxocobalamin infusion was noted to be 140 mmHg systolic. He was transported to hospital two hours and 20 minutes after rescue efforts began. He was noted to be hemodynamically stable on admission but hypothermic. The hyperthermia persisted through Day 4 after which he required hemodynamic support with intravenous fluids and dopamine and norepinephrine infusions. He died eight days after the fire (Day 9) from multiple organ failure secondary to septic shock.

Patient 21601 was a 40 year-old male who was found at the scene of a residential fire in cardiac arrest. He was administered hydroxocobalamin (5.0 g) and epinephrine (20 mg). The time between the fire brigade call and administration of hydroxocobalamin was 10 minutes. He died at the scene after 50 minutes of rescue effort.

Patient 23976 was a 60 year-old male with a past medical history significant for hypertension, myocardial infarction (2 years prior), and non-insulin-dependent diabetes. The patient was discovered at the scene of a fire in cardiac arrest and with severe burns covering > 50% of his body. Resuscitation with 3 mg of epinephrine restored a sinus rhythm and stable hemodynamic status. Then the patient was intubated, mechanically ventilated and administered a 5-g dose of hydroxocobalamin, and lactated Ringers solution. At time of hydroxocobalamin was started, 15 minutes after the rescuers arrived, the patient's blood pressure was 120/80 mmHg. Fifteen minutes after initiation of the hydroxocobalamin infusion, the patient suffered from a second cardiac arrest and was resuscitated with a bolus of 3 mg of epinephrine followed by a continuous infusion. Forty minutes after the hydroxocobalamin infusion was started, the patient's blood pressure was measured as 110/100 mmHg; the diastolic pressure normalized half an hour later at 80 mmHg. Upon hospital admission, two hours after rescue efforts began, the patient's blood pressure was 140/70 mmHg, and he was hemodynamically stable. Hospital discharge summary reported that the patient received another 5-g dose of hydroxocobalamin secondary to severe metabolic acidosis; there was no mention of cardiovascular or blood pressure problems at that time. The patient died on Day 1 from multiple organ failure associated with decerebration.

Patient 25382 was a 37 year-old female patient was found at the scene of a residential fire at 09:20 on [redacted] She was in cardiac arrest at that time. She was administered hydroxocobalamin (5.0 g) and epinephrine (40 mg) at 09:20. The time between the fire brigade call and administration of hydroxocobalamin was 8 minutes. She died at the scene at 10:20.

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Patient 26303 was a 5 year-old female who was found at the scene of a residential fire in cardiac arrest. She was administered hydroxocobalamin (1.5 g) and epinephrine (5 mg). The time between the fire brigade call and administration of hydroxocobalamin was 23 minutes. She was transported to hospital an hour and 45 minutes after rescue efforts began. She died in the ICU the same day from an unknown cause. No adverse events were noted after hydroxocobalamin administration.

Patient 27311 was a 4 year-old male who was found at the scene of a residential fire in cardiac arrest. Soot was found in his throat at the time of intubation. He was administered hydroxocobalamin (1.5 g) and epinephrine (1.75 mg) 12 minutes after the rescuers arrived. He died at the scene from unspecified causes an hour and seven minutes after rescue efforts began.

Patient 27606 was a 47 year-old male with no known medical history who was found at the scene of a fire in cardiac arrest. Initial resuscitation was successful with administration of a 2-mg bolus of epinephrine. He was intubated and an epinephrine infusion was started at 0.5 mg/h. In addition, 5 g of hydroxocobalamin, 300 mL of saline, and 300 mL of Elohes were administered. At time these drugs were started, the blood pressure was 119/78 and remained stable over the next 15 minutes. Thirty minutes after infusions were started, the epinephrine infusion rate was increased (for an unspecified reason) to 1 mg/hour with a concomitant blood pressure increase to 168/95 mmHg. Twenty minutes later, the blood pressure was 142/95 mmHg but another increase in the epinephrine infusion, to 1.5 mg/h, was required. The need for increased epinephrine infusion rates persisted for a period of 90 minutes at which point the patient arrived at the hospital. At that point the epinephrine infusion rate was 2.0 mg/h and the blood pressures were in the 140's/80-90's mmHg. Outcome information on the firemen report stated only that the patient died on Day 1; no additional information was available.

Patient 29391 was a 79 years old female with a past medical history significant for coronary disease and abdominal cancer. She was found at the scene of the fire in cardiac arrest. Resuscitation began with the administration of a 1-mg bolus of epinephrine which resulted in normal cardiac auscultation and atrial fibrillation. A dose of 2.5 g of hydroxocobalamin was started 12 minutes after arrival of the rescuers and was associated with a blood pressure of 170/90 mmHg. The blood pressure remained stable over the next 30 minutes, at which time, a second infusion of 2.5 g of hydroxocobalamin was started and lasted over 30 minutes. At the end of the second administration (50 minutes after the start of the first one), the patient's blood pressure was 160/80 mmHg. This was followed by a drop to 90/60 mmHg, which was treated with the administration of an epinephrine infusion at the rate of 0.1 mg/h, and which resulted in a return of blood pressure to previous values. The patient was admitted to hospital 95 minutes after fire start of hydroxocobalamin treatment with a systolic blood pressure of 139 mmHg and bradycardia with a pulse of 50 bpm. During the hospital stay the patient progressively worsened with occurrence of atrioventricular block (unspecified type), rhabdomyolysis, hyperkalemia and hypotension to 60/40 mmHg. The patient died 6 hours after admission from post anoxic coma, anuria, and cardiovascular collapse.

Patient 29631 was a 47 year-old female who was found at the scene of a residential fire in cardiac arrest. She was administered hydroxocobalamin (5.0 g) and epinephrine (15 mg). The

time between the fire brigade call and the administration of hydroxocobalamin was 20 minutes. She died at the scene of unspecified causes after 35 minutes of rescue efforts.

Patient 31786 was a 56 year-old male patient who was found at the scene of a residential fire in cardiac arrest. He was administered hydroxocobalamin (2.5 g) and epinephrine (10 mg). The time between the fire brigade call and administration of hydroxocobalamin was 14 minutes. He died at the scene of unspecified causes after 45 minutes of rescue efforts.

Patient 31930 was an 85 year-old female who was found at the scene of a residential fire in a state of "neurological impairment." She was intubated and soot was found in the lower airways. She was administered hydroxocobalamin (5.0 g). The time between the fire brigade call and administration of hydroxocobalamin was 8 minutes. She was transported to hospital an hour and 34 minutes after rescuers arrived. She died in the ICU from an unknown cause on Day 14. No adverse events were noted after hydroxocobalamin administration.

Patient 32991 was a 32 year-old male patient who was found at the scene of a residential fire in a state of "neurological impairment." He was administered 5.0 g hydroxocobalamin. A cutaneous rash was noted after hydroxocobalamin administration. The time between the fire brigade call and administration of hydroxocobalamin was 10 minutes. He was transported to hospital after more than two hours of rescue efforts. He died in the ICU on Day 20 from multiple organ failure.

Patient 33370 was a 50 year-old male who was found at the scene of a residential fire in cardiac arrest. Soot was found at an unspecified location in his airways following intubation. He was administered hydroxocobalamin (2.5 g) and epinephrine (1.1 mg). The time between the fire brigade call and administration of hydroxocobalamin was 15 minutes. He died on the scene after an hour and 35 minutes of rescue efforts.

Baud Study 3

Patient 139 was a 26 year-old student who ingested potassium cyanide in front of his girlfriend in a suicide attempt. Rescuers arrived about 20 minutes later and found the patient was in profound coma, with a Glasgow Coma Score (GCS) of 3, a respiratory rate of 3 breaths per minute, with ensuing respiratory arrest, a heart rate of 110 bpm and a blood pressure of 95/50 mmHg. He was intubated and ventilated with 100% oxygen. Hydroxocobalamin 5.0 g was administered over 10 minutes. A second dose of 5.0 g of hydroxocobalamin was given immediately after with a return of spontaneous ventilation. On arrival at the hospital two hours and 20 minutes following the cyanide ingestion, the patient remained intubated and unsedated. He had bilateral miosis and absent peripheral and Babinski reflexes. The GCS remained at 3. The heart rate was 108 bpm and the blood pressure had risen to 134/51 mmHg. The electrocardiogram showed prolonged QRS duration and T-wave inversions. Plasma lactate was 17.55 mmol/L. Two episodes of hypotension were reported. The patient was given two additional 5-g doses of hydroxocobalamin six hours apart with immediate increases in blood pressure each time. The initial blood cyanide level was 150 μmol/L (4 mg/L) [toxic ~80 μmol/L;

lethal ~100 µmol/L). Despite good early hemodynamic recovery, the patient remained in coma. Head CT and MRI revealed diffuse edema with tonsillar herniation and meningeal hemorrhage. The patient developed progressive decreases in blood pressure, despite norepinephrine support, and died on hospital Day 4.

Patient 143 was a 38 year-old male scientific researcher who drank the contents of a test tube containing cyanide. He was found in hypertonic coma by the fire department physician with a blood pressure of 120/70 mmHg and a heart rate of 90 bpm with a respiratory rate of 14 bpm. He was treated with oxygen by nasal cannula. He was described as stable during transport to the hospital, with the exception of a drop in heart rate to about 50 bpm. On admission, he was noted to be in Stage III coma with no reaction to painful stimuli, had a blood pressure of 50/10 mmHg, without palpable pulse and was apneic. He was intubated, mechanically ventilated, and treated with dobutamine, epinephrine, and dopamine to restore blood pressure; a 10-g dose of hydroxocobalamin was also given with a subsequent rise in blood pressure to 220/170 mmHg. It was note that his blood pressure soon return to 150/90 mmHg although the means by which this occurred were not documented, i.e., whether the change was spontaneous or drug induced. Despite correction of his hemodynamic status, the patient's neurological status continued to decline. Changes noted included bilateral mydriasis and opisthotonous. The initial blood cyanide level was confirmed at 238 µmol/L (6.2 mg/L), more than twice the reported lethal blood concentration, and the initial plasma lactate was 47.7 mmol/L. The lactate level dropped to 4.6 mmol/L after approximately 24 hours. The level of his coma progressed to Stage IV with a flat EEG. The patient died on hospital Day 3 secondary to brain death.

Patient 144 was a 32 year-old woman who took cyanide in a suicide attempt. She was found by emergency medical service personnel in cardiac arrest, with an estimated delay to cardio-pulmonary resuscitation (CPR) of 5 to 6 minutes. CPR was stared, the patient was intubated and ventilated and given 8 mg of epinephrine with a return of heart rate to 110 bpm (by monitor) but non-palpable pulse. A fluid bolus was administered and dobutamine and epinephrine infusions were started along with a 10-g dose of hydroxocobalamin. Sodium bicarbonate was also administered. Her systolic blood pressure became measurable at 90 mmHg and her heart rate was noted to be 120 bpm on admission to the hospital, an hour and 15 minutes following the arrival of the rescuers. She was in Stage IV coma with absent reflexes and no response to pain. Hospital treatment included gastric lavage and an additional 5-g dose of hydroxocobalamin at four hours and 15 minutes following initial rescue. The patient was also given an 8-g bolus dose of sodium thiosulfate 8.0 g followed by a continuous infusion for a total dose of 32.0 g of sodium thiosulfate over 2 days. One vial of dicobalt EDTA (300mg is the commercially available contents of one ampule) was administered the day after hospital admission. The initial blood cyanide level was 196 µmol/L (about 5.1 g/L). Two hours later, the blood cyanide was 89.2 µmol/L, dropping to 37.3 µmol/L and 13.1 µmol/L at two and half and nearly three and a half hours later, respectively. Despite initial hemodynamic recovery, the patient died on hospital Day 4 of refractory shock.

Patient 145 was a 64 year-old male who ingested a capsule of potassium cyanide in a suicide attempt. On arrival of the emergency personnel, the patient was awake, but his neurologic status rapidly declined as he became apneic and bradycardic with ventricular irritability. His systolic

blood pressure was measured as 50 mmHg, but dropped as low as 40 mmHg. His heart rate was 30 bpm. He was treated initially with isoproterenol, then atropine, with a subsequent increase in heart rate to about 70 bpm, the rate dropped again to less than 30 bpm at which point he was given a fluid bolus while en route to the hospital. Sodium bicarbonate was also administered. He was noted to have mydriasis, followed by miosis while en route. He suffered cardiac arrest during transport as well. On admission, the patient was in Stage III coma, with a blood pressure of 40/30 mmHg, and a heart rate of 72 bpm; he was intubated, and artificially ventilated. The blood cyanide was measured at 260 µmol/L (~ 6.8 mg/L) (more than twice the reported lethal level). The patient was given epinephrine and a 5-g dose of hydroxocobalamin with an immediate increase in blood pressure to 80/45 mmHg. While the epinephrine infusion was stopped, treatment was continued with another infusion of 5.0 g of hydroxocobalamin over 12 hours. Under continuous infusion of hydroxocobalamin, the blood pressure became temporarily elevated at 220/160 mmHg (6 hours following initial rescue efforts), requiring treatment with nitroglycerin and furosemide witch decreased the blood pressure to 160/100 mmHg over the next 30 minutes. Blood pressure of 75/55 mmHg and 90/60 mmHg were recorded 30 and ninety minutes later, respectively. The blood pressure eventually stabilized in the range of 130-140/70-80; however, despite the hemodynamic improvement, the patient died on hospital Day 10 of complications (unspecified) secondary to suspected brain death.

10.5 References

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I concur with this review.